UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-667 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-4149 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

Mitchell H. Cohen United States Courthouse
One John F. Gerry Plaza
Camden, New Jersey 08101
Monday, April 4, 2016

B E F O R E: THE HONORABLE JEROME B. SIMANDLE
CHIEF JUDGE
UNITED STATES DISTRICT JUDGE

Certified as true and correct as required by Title 28, U.S.C., Section 753.
/S/ Lisa Marcus, CCR, CRR, /S/ Theodore Formaroli, CCR, CRR, /S/ Karen Friedlander, CCR, CRR, /S/ Robert T. Tate, CCR, CRR, /S/ Carol Farrell, CCR, CRR

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-5144 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-335 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-5144 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-335 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-6893 (JBS/KMW)

-vs-

INNOPHARMA LICENSING, INC., et al.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-3240 (JBS/KMW)

-vs-

INNOPHARMA LICENSING, INC.,

Defendants.

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INDEX

EXHIBITS

DEPUTY CLERK: All rise.

THE COURT: Good morning.

Be seated.

Just a moment.

00:00 Welcome to everybody. We're here to commence the nonjury trial in Senju Pharmaceutical vs. Lupin and Senju Pharmaceutical vs. Innopharma, the Civil Action Numbers are 14-0667, 14-4149, 14-5144, 15-335, and also 14-6893, and 15-3240.

00:01 Let me ask trial counsel to please enter your appearances. Here I'm just asking for the appearances of those who are likely to speak during the course of the trial.

So let's begin with the plaintiffs.

MR. LIPSEY: Charles Lipsey, Finnegan, Henderson, for

00:01 the plaintiffs.

MR. DINER: Brian Diner, your Honor, Finnegan, Henderson, for the plaintiffs.

MR. HASFORD: Justin Hasford, your Honor, Finnegan, Henderson, also for the plaintiffs.

00:01 MS. LEBEIS: Jessica Lebeis of Finnegan, Henderson, also for the plaintiffs.

MR. SUKDUANG: Sanya Sukduang, your Honor, from Finnegan, Henderson, on behalf of plaintiffs.

MS. FUJIWARA: Chiaki Fujiwara for plaintiffs Senju,

00:02 et al., from Finnegan, Henderson.

THE COURT: I'm sorry, can you spell your name for me? Did you sign in?

MS. FUJIWARA: Chiaki Fujiwara.

THE COURT: Oh, yes. Thank you.

00:02 MS. CHUDEREWICZ: Melissa Chuderewicz from Pepper Hamilton on behalf of plaintiffs.

THE COURT: Next on behalf of Lupin.

MS. HOLLAND: Good morning, your Honor. Elizabeth Holland of Goodwin Proctor.

00:02 MR. PATUNAS: Good morning, your Honor. Michael Patunas, Patunas Tarantino.

MS. RAPALINO: Good morning, your Honor. Emily Rapalino of Goodwin Proctor.

MR. MARGOLIS: Good morning, your Honor.

00:02 Dan Margolis with Goodwin Proctor.

MS. DAUGHTRY: Natasha Daughtry of Goodwin Proctor.

THE COURT: And then on behalf of Innopharma.

MR. MUKERJEE: Deepro Mukerjee of Alston Bird, your Honor.

00:03 MR. SODERSTROM. Lance Soderstrom of Alston Bird, your Honor.

MR. MALIK: Jitendra Malik with Alston Bird, your Honor.

MR. CALMANN: Arnold Calmann from Saiber.

00:03 THE COURT: Good morning.

All right. Are there any questions about the logistics of trial before we begin? Did anything come up that requires my attention that would make you more comfortable to speak to it at this point in time?

00:03 MR. LIPSEY: Not for plaintiffs, your Honor.

MS. HOLLAND: Not for defendants, your Honor.

THE COURT: Okay. You'll recall that there were three motions in limine in which I reserved decision and I'd prefer not to take the time now to address them in an oral

00:04 Opinion, but I will either at the end of the day today or else tomorrow.

And there's one motion in limine by the plaintiff, which was actually the plaintiff's second motion in limine, it was to preclude evidence or argument that the plaintiff's

00:04 asserted patent claims are invalid as obvious based on plaintiff's internal documents and specifically identified non-prior art information. This was Docket Number 161. And I'm denying that motion. I'm denying that motion without prejudice to raise any specific objection and I'm doing so for

00:05 reasons that will be stated in the oral Opinion.

The defendants had two motions in limine. Their first motion in limine is to preclude evidence consistent with admissions in the patent specifications. This was at Docket Item 167 in the lead case. And that motion is also being

00:05 denied without prejudice. What's consistent and inconsistent

can only be determined on an item by item basis, and there's much in dispute about what is admitted and what's not admitted, quote, unquote, in the patent specifications. So I will, again, explain the reasons in an oral Opinion.

00:06 The third motion is the defendant's second motion in limine to preclude evidence of alleged unexpected results. This is Docket Item 169 in the lead case of 14-667. And that motion also is going to be denied. It's being denied because there's a very deep factual dispute about what's expected,

00:06 unexpected, the degrees of difference, and whether the unexpected result was a change in kind, all of that needs to be explored at trial. And, again, I'll flesh out these reasons in on oral Opinion.

Any questions so far?

00:06 MR. LIPSEY: Not for plaintiffs, your Honor.

THE COURT: Okay. There is also an appeal from Judge Williams' order regarding attorney/client privilege, and on that I would like to hear oral argument, not at this time because I know that it's unlikely you'd be prepared to do so

00:07 now. I would have the oral argument at some point tomorrow, if you need a day to decide who's going to argue it and collect your thoughts on that, and also to see if there's any way it can be worked out overnight.

Would you rather have it at 9:15 or at 4:30? I'm open

00:07 to either.

MS. HOLLAND: Either one is fine with Lupin, your Honor. Whatever is preferable to you.

MR. LIPSEY: If possible, 4:30. But, if not --

THE COURT: Okay.

00:08 MR. LIPSEY: -- whatever is convenient for the Court.

THE COURT: No, if there's a preference then for 4:30, then we'll do 4:30 tomorrow.

So 4:30 on Tuesday afternoon we will have oral argument on the defendant's appeal from Judge Williams' determination

00:08 recognizing the attorney/client privilege.

Before we leave that topic, I don't see that the issue of waiver is presented. In other words, there doesn't seem to have been a dispute presented to Judge Williams about the operation of the clawback provision that's been argued to me.

00:08 But since it wasn't presented to Judge Williams, at least not that I can tell from the papers, there's not a question here of whether the plaintiffs waived their privilege by producing the unredacted document and clawing it back six months later.

And also I don't believe that there is a question about

00:09 work product protection. Work product protection for these documents was not sought by the plaintiffs, Judge Williams recognized it and lumped it together with attorney/client privilege. I don't think that that's correct. If the plaintiffs raised attorney/client protection, then you can

00:09 point that out to me in the argument tomorrow. I didn't see

it anywhere in the papers. On its face it doesn't seem that the documents would qualify for work product protection. But the attorney/client privilege dispute is, of course, very much alive.

00:09 I hope that that focuses your arguments for tomorrow. Do you have any questions about what I'm asking you to address?

Okay. So are we ready to begin with opening statements.

00:10 MR. LIPSEY: We're ready, your Honor.

THE COURT: Okay. Then, Mr. Lipsey, you may proceed.

MR. LIPSEY: Okay. Thank you.

May it please the Court, I have some hard copy of my presentation, which I think the court reporter's might find

00:10 useful in the transcription, and perhaps the Court and the Court's clerk might find useful at some point.

May I approach?

THE COURT: Yes, please.

Thank you.

00:11 MR. LIPSEY: How many would you all like?

MS. HOLLAND: As many as you're offering.

MR. MUKERJEE: Charles, do you have any extra copies for Innopharma?

MR. LIPSEY: I have one.

00:11 MR. MUKERJEE: Thanks so much.

MR. LIPSEY: May it please the Court, the case is about the product Prolensa®, which is bromfenac ophthalmic solution .07 percent. The approved indication is for the treatment of postoperative inflammation and reduction of

00:12 ocular pain in patients who have undergone cataract surgery.

And the Court will be pleased to recall that while there are many patents in issue, we have agreed with the defendants that their right to market this product as a generic will stand or fall with the outcome on Claim 6 and 20

00:12 of the '431 patent, which, in essence, claim formulations in varying degrees of detail containing bromfenac sodium and about .02 percent tyloxapol. And that's what the case will largely be about.

THE COURT: I'm not disappointed that you narrowed

00:12 the dispute.

MR. LIPSEY: We suspected that might be the case. Nor are we disappointed either, your Honor.

We deal here with cataract surgery. And hopefully it's something we all don't have a lot of experience about.

00:12 We have Dr. Trattler who, unfortunately, can't be here till next week, but he can explain to us the details. But as you can see on the screen, what it involves, in essence, is cutting open the eye and removing the clouded natural lens and replacing that natural lens with an artificial one and then

00:13 allowing the patient to recuperate. And inflammation results

from that abuse of the eye, and we will hear that it's important to control that inflammation less there be some very serious adverse consequences. There's also pain associated, as you can imagine, with the incision and recovery.

00:13 And, as we all know, the eye is one of the most sensitive organs in the body to begin with. And when it's been surgically damaged, it's even more so. And the drugs that are used to treat this inflammation are administered, at least in the case of the product here, as drops directly into

00:13 the eye.

And so there are some complications and challenges in preparing such a formulation and our evidence will focus on these. These come largely out of the Ogawa patent, which is the principal piece of prior art.

00:14 You have to have a clinically effective ingredient.

The key is to get the ingredient to penetrate the eye to get to the tissues that need to be prevented from inflammation.

Maintenance in the eye of clinically effective

00:14 concentration is difficult because the surface area of the eye is quite small, the length of time the drug is actually in contact with the surface area is quite small, and so there's a challenge getting an adequate amount of drug into the eye.

Irritability, of course, is an issue in a surgically

00:14 compromised eye, stinging and burning principally, and most of

the evidence will focus on that.

And then there are questions of the stability of the formulation. We'll hear that making liquid formulations is a more difficult proposition than making a solid oral dosage

00:15 form. Things happen more readily when drugs are in solution, reactions can occur which don't normally occur when they're dry, they can occur more quickly, the various ingredients can interact with each other. And so life is difficult in the liquid formulation world and even more so in the ophthalmic

00:15 formulation world.

There are two kinds of stability that we'll be talking about. One is chemical stability and that is the active ingredient actually getting degraded and broken down into something that's not an active ingredient and there's several

00:15 reactions, chemical reactions by which that can occur. One we'll be talking about is oxidation. Another is hydrolysis.

And then there's the question of the physical stability of the formulation, and that tends to manifest itself by the formulation having a cloudy appearance when the ingredients

00:16 actually start to separate from each other. And there will be some testimony about that as well.

There is in the world of ophthalmic formulation a dizzying array of ingredients that can be contained or are available as options for inclusion. I've listed some of them

00:16 here on Slide 5 that I've extracted directly from the

documentary exhibits that will be coming into evidence. And these are categories, these are functional categories, and within each of those categories there are a very large number of different chemicals that are used in this regard. There
00:16 are entire books written describing each of the various chemical options and how they differ from each other and, indeed, they do differ from each other.

And we'll be guided through that morass by Dr. Robert Williams who is Ph.D. in pharmaceutics. He is the Johnson &
00:17 Johnson Centennial Chair at the University of Texas in Austin. He has more than 400 publications. His research focus is in development formulation and delivery of drugs. And, in essence, what we're going to hear from Dr. Williams is that the mantra, oh, that's routine experimentation, which most
00:17 defendants in cases like this advance and which the defendants here have advanced, is in the case of ophthalmic formulations is a gross oversimplification of what happens. The individual components can interact with each other in unpredictable ways and affect their properties in unpredictable ways, each drug
00:17 has to be considered based on its own unique properties. And, as he will say more eloquently than I, knowing the objective and getting there is often separated by trial and error, failures and frustration.

Now, there are also chemistry aspects to the case.
00:18 What we have on Slide 7 here are the structure of some of the

molecules that we'll be talking about. The ones on top are anti-inflammatory drugs and they are, more specifically, what are called in the trade nonsteroidal anti-inflammatory drugs. The initials N-S-A-I-D-S being amalgamated by people, and
00:18 probably by us at the trial, as NSAIDS. And when we refer to NSAIDS, that doesn't tell us what the structure of the molecule is, your Honor, it tells you what the therapeutic class is and that's to distinguish them from molecules which have been used before such as steroids. Steroids are very
00:18 powerful drugs that have a whole constellation of potentially adverse side effects and we are not talking about steroids.

Now, we will be led through this issue by Dr. Steve Davies who has a Ph.D. from the University of Oxford. He is the Waynflete professor of chemistry at the University of
00:19 Oxford. He's got 550 publications. And his research include organic and medicinal chemistry.

And the defendants were kind enough to share with us some of their slides, and I've used one here because it highlights I think what the difference in the proofs are going
00:19 to be, at least the difference in the focus of the proofs, and that is defendants' arguments and evidence largely will focus on these molecules as if they're fungible marbles or bowling balls all with this carboxylic acid group, which is the C, double-bond O, OH you see and which they have emphasized as
00:19 their theory of the case requires. And the fact of the matter

is our evidence will focus on the importance of structural differences elsewhere in the molecule, all of which need to be considered in assessing what can be expected of that molecule and what is unpredicted from that molecule.

00:20 And one of the concepts that Dr. Davies is going to teach us about, which is important here particularly in these aqueous systems, is the concept of hydrogen bonding. And this, when I tried to learn it in high school, escaped me completely until I realized that the water molecule looks like
00:20 Mickey Mouse. It's got a big oxygen atom, it's got two little hydrogen atoms, H_2O. But the hydrogen atoms are not equally spaced on the molecule, they're actually both on one side of the molecule and that causes one side of this molecule where the Mickey Mouse ears are to have a partial positive charge
00:20 and the end that has the big oxygen atom has a partial negative charge and that allows water when it is in the liquid form for those molecules to attract each other through hydrogen bonding, the slightly positive hydrogen atom being attracted to the slightly negative oxygen Mickey Mouse face.
00:21 And that's what makes water such a marvelous solvent, is those molecules actually stick together and that explains why the boiling point of water is as high as it is for such a small molecule.

And those same kinds of interactions can occur between
00:21 water and organic chemicals and, indeed, between different

organic chemicals because a number of the functional groups, which Dr. Davies is going to tell us about, have that same property of having a partial positive charge on one end and a partial negative charge on the other. An important one that
00:21 we'll see in a lot of these molecules is the carbonyl group, which is in the center here. And again, the oxygen that's hanging out in the space in the air has a partial negative, that's where the electrons like to be, as Dr. Davies will explain, the rest of the group has a partial positive charge.
00:21 And so when that is in an aqueous environment, the ears of Mickey Mouse, two of them actually, can associate themselves or become closely associated with that slightly negatively charged oxygen.

And the same thing happens with, expect in the opposite
00:22 direction, with the molecule or functional group known as a primary amine, which we have here on the right. And there -- now the hydrogen atoms there have a partial positive charge, the nitrogen has a partial negative charge, and so the face of Mickey Mouse can now associate with those positively charged
00:22 hydrogen atoms in that primary amine. And this hydrogen bonding that goes on can increase the solvation, the association of water solvent with these molecules, alter substantially their solubility, it can also alter the interaction with other excipients that may be in the drug
00:22 product, which also have slightly polar moieties.

And what Dr. Davies will teach us is that you now look at these molecules not like fungible bowling balls with acid groups but look at them as a whole. And he will show us that there are indeed different numbers of different types of and
00:23 different arrangements of these molecules that are capable of engaging in hydrogen bonding. And those are highlighted here in red.

And you can see that for bromfenac, which is the molecule we're interested in, as Dr. Davies will explain,
00:23 there are really more opportunities for hydrogen bonding with that molecule than for any of the others we're likely to discuss. And a particular feature of this molecule is that primary amine, that NH_2 group that's there, which is not shared by way of these other molecules.

00:23 While we have these up, there are two other molecules that we'll talk about. The one on the bottom is not really an NSAID at all but it has come into play because at one point earlier in the case the defendants were relying on it to suggest the invention was obvious. And then this nepafenac is
00:24 a horse of an entirely different color, you can see it doesn't have that carboxylic acid group at all. And, in fact, that molecule as it sits is not an active drug. In order to work, it has to be delivered into the eye and then enzymes in the eye actually will convert that into something that can operate
00:24 as an anti-inflammatory.

Something else we'll talk about are surfactants. And surfactants, as the word sounds, it's kind of a made up word. Surface active agent intends to refer, as we will hear, to molecules that could alter the surface tension of a liquid,
00:24 particularly water in our case. And the simplest and clearest example of a surfactant, just to get our feet wet, no pun intended, is soap or detergent. And we have here the simplified demonstrative exhibit. And the surfactants tend to have one end, it is water living, hydrophilic is the word you
00:25 may hear, and another end, it is oil loving, oleophilic or water hating, hydrophobic, and they can associate into these spherical, not always spherical, but these arrangements whereby the ends that like to be in water are near the water and other ends are all associated with each other and can hold
00:25 other molecules that are not readily soluble in water in that area. Just add soap or detergent can hold oil droplets that are not soluble in water, in solution in water so we can wash them away off the dishes.

Now, my diagram here, the ends that are water loving
00:25 need not necessarily be globular, they might look like tails, but they are nonetheless water loving. And the ends that are oil soluble need not look like tails, they might in fact be globules and some are in some of the molecules we'll see. But the concept is the same and Dr. Davies will explain that to
00:26 us.

And what he is particularly going to explain with surfactants is there is a large number of them, they vary from each other in structure and their properties are different and, therefore, what interactions, if any, they're going to
00:26 have with complex systems with many different components is unpredictable. And we don't really need to take Dr. Davies' word for that because right out of the documentary evidence that he has cited, we have the quote. And this particular article happens to have been cited in other patent cases that
00:26 have dealt with surfactant.

"The range of available surfactants is wide, and so, too, are the mechanisms of solubilization and the effects the surfactants have on the solubilized material. Examples are known of enhanced drug activity and of inactivation, of
00:27 increased stability, and instability; the interactions of the surfactants with components of the body must also be considered."

And the point is that's a complex and unpredictable world, which bears directly on the issue of obviousness, which
00:27 your Honor will have to decide.

Now, these are some of the -- these are models of some of the surfactants that we'll be talking about. And every time we draw one of these structural formula, we put a model on the board, it is our best effort, and scientists' best effort, a depiction of how the structures differ. Obviously

the molecules are minusculely small, they're flexible, they interact with their environment in complicated ways. But this is the best we can do to try to depict the differences.

The one on the left is polysorbate 80, that was the
00:27 surfactant that was in the closest prior art, which we'll see in a moment is the Ogawa patent that actually described bromfenac eyedrop. And the surfactant, which the inventors of the '431 patent discovered, had a whole cascade of benefits for use in the point of 2 percent concentration, is tyloxapol.
00:28 You can see it's structurally exceedingly different and we contend, and our evidence will show you, could not have predicted that molecule would have positive effects in a bromfenac formulation.

Some others that we will see are these octoxynol
00:28 molecules, which are structurally similar, at least in the globular end, which in this case happens to be the oil loving end, and they vary from each other simply in the length of the tail, which is the water-loving tail. The red atoms are oxygen atoms and the presence of the oxygen atoms in these
00:28 tails causes them to be associated easily with water, as Dr. Davies will explain, and as you can see from the structure of those molecules that they do not look like either polysorbate 80 or tyloxapol.

Now, there are also medical issues, as one might
00:29 imagine, with treating postsurgery inflammation in the eye.

We will be guided through those by Dr. Trattler, as I've said, who will be here next week. He has specialized in cornea and cataract surgery since 1997, been an investigator on nearly 70 clinical trials for ophthalmic products, including bromfenac. He conducts about 60 surgeries a month, and has actually used many of the drugs that are both in the prior art as well as Prolensa®, and will be here to tell us how important some of the differences between them are. And again, part of what he will tell us is also reflected in the prior art documentary evidence.

And there are two principal medical issues that come up, and the first is really captured here by Bowman which is one of the references they had originally cited to us. And Bowman points out that there are problems with these NSAID agents, and that is, that stinging and burning sensations are commonly experienced during the first few minutes after topical administration on the eye. Not only are patients who experience such stinging likely to avoid regularly taking their medication, they also receive less benefit from each application. Specifically, the stinging causes tearing which washes away the drug. Having physically removed a portion of the drug from the eye by tearing, the bioavailability of the drug is reduced.

So, the stinging and burning issue, which is somewhat downplayed, understandably, by the defendants, is an important

medical issue and will be the focus of some of our testimony.

There's a second issue that arises, and it too emerges from the prior art, and this is the Yanni publication. And in specific reference to the family of molecules to which bromfenac belongs, he points out that relatively high concentrations of these drugs are often needed to achieve corneal penetration rates sufficient to provide effective intraocular drug concentration. Such high drug concentrations are generally not desirable as they may provoke ocular irritation and discomfort, particularly in the surgically damaged eye.

That brings us really to the closest prior art, which is there was an original bromfenac formulation, and it was the subject of the Ogawa patent, which will be coming into evidence and much discussed by both parties. And Ogawa noted the problem right off the bat in referring to these molecules, that these molecules are unstable in an aqueous solution with the optimal pH range for the locally administrable therapeutic composition.

Now, pH refers to the acidity or alkalinity of the system. A pH of 7 is neutral; it's water. Numbers below 7 are acidic; numbers above 7 are alkaline. And it's an exponential scale, which means that when you go from 7 to 8 or from 8 to 9, that's a tenfold increase in alkalinity. So, we have to look at those numbers quite carefully. Even when they

are separated from each other by something like .5, that still is a threefold difference in terms of the alkalinity or acidity that you are dealing with, and we'll hear about that.

So, that was the problem that Ogawa acknowledged, and specifically what he found out was that when he made up these formulations with bromfenac and subjected them to long-term stability tests, he found these red insoluble matter in it, and we pointed out the sections in Ogawa where that's mentioned. And what you will hear in the testimony is that when there's a color change like that, that's almost always the indication of some kind of chemical degradation, and most particularly of an oxidative chemical reaction that results in that color change.

So, what Ogawa was concerned with was a chemical stability problem, not a physical stability problem. And we will see, as we go through the evidence, there are some patents that deal with chemical stability. Ogawa deals with the problem with this red junk showing up in his formulation, a chemical stability problem. Some of them deal with physical stability problems where the ingredients separate from each other and the formulation may become cloudy.

So, what did Ogawa do? Ogawa found out that if you include in this formulation polyvinylpyrrolidone, which in some of the documents is referred to as povidone, they are the same thing, and sodium sulfite, when those coexist with

bromfenac, then a change in appearance was not observed at all and the decomposition of compound was not observed either. It was found that the stability was remarkably enhanced. Thus, there can be successfully obtained a stable aqueous composition containing the compounds with his polyvinylpyrrolidone and sulfite.

Now, he noted nonetheless, and herein lies the rub with Ogawa, he noted nonetheless that the pH of the ophthalmic composition, according to the invention, has to be selected with due consideration paid to stability, on the one hand, and topical eye irritativity of the active ingredient on the other. And the question, of course, is where -- what was the best Ogawa could do with that formulation, and we have substantial evidence on that, and that is a formulation which I think at this point both sides acknowledge embodies the invention of Ogawa, was introduced into the market in Japan in 2000. It was described in a printed publication here, this *New Drugs in Japan* in 2001, and you can see that it's got the sodium sulfite, it has the povidone, which is polyvinylpyrrolidone, and we can see that the best they could do was a pH of 8 to 8.6. 8.3 is right in the middle of that range. And the problem was that when they took that formulation into the clinic in the clinical trials in Japan, and this is reflected in that same document, they got stinging and burning, which they acknowledged.

And we have substantial evidence about that property of these formulations, that same -- a formulation with those same ingredients was introduced in the United States as Xibrom®. You can see we now have more detailed information about the
00:35 pH. The pH was 8.3. And in the U.S. clinical trials for that product, that was a twice-a-day drug, administered two times a day, again, in the clinical trials, stinging and burning emerged.

There was then introduced a once-a-day form of that
00:36 same formulation, and when that was subjected to clinical trials, again, as we saw, that was called Bromday®, and when that went into its own clinical trials, still there was burning and stinging noted.

So, that then brings us to the contribution of the '431
00:36 patent which is, after all, the major focus of our attention here today. And the Sawa '431 patent tells us in part exactly what he's after. It is an object of the present invention to provide an aqueous liquid preparation of bromfenac which is stable within a pH range giving no irritation to the eyes.
00:37 And he tells us exactly what he did to get there. He has discovered that by adding tyloxapol to bromfenac, the aqueous solution becomes stable within a pH range giving no irritation to the eyes.

Now, as we said before, tyloxapol is a surfactant.
00:37 When you look back at the published Bronuck® formulation, you

can see that the surfactant used there was called polysorbate 80, and our evidence will show, your Honor, there wasn't a shred of evidence that the problem -- or there was any problem with Ogawa's formulation arising from the surfactant that
00:37 happened to be used. And I think we've already seen that the tyloxapol looks nothing like polysorbate 80.

And there was, in fact, a commercial product introduced embodying the Sawa '431 invention. It is called Prolensa®. It is the subject of this lawsuit. And there are some
00:38 important things to notice right off the bat, which is instead of .09 percent, they were able to reduce the amount of drug to .07 percent. Instead of a pH of 8.3, they were able to reduce the pH to 7.8. That's that .5 difference on the logarithmic scale which is about a factor of 3 in terms of the acidity.
00:38 And it had tyloxapol. And lo and behold, when that drug was carried into clinical trials in the United States, there is no reference to burning and stinging, the side effect having been effectively eliminated.

Now, we will see also that the scientists and doctors
00:38 who conducted those clinical trials published and commented upon the results of their studies. Defendants criticize this work saying, oh, Bausch & Lomb sponsored the clinical trial, but the fact remains, your Honor, these are distinguished doctors and scientists, and all of these publications appeared
00:39 in peer-reviewed journals. This particular one from Baklayan

is in the *Clinical Ophthalmology* peer-reviewed journal, points out the decrease in drug concentration arising from the change in pH, noting that it led to similar, and in the case of scleral tissue, increased penetration of ocular tissue studied
00:39 when compared to the .9 percent of pH 8.3. And that the lowering of pH increases the unionized fraction of drug, which can lead to enhanced corneal permeability. Additionally, the reduction of pH to a more physiological level could reduce the potential for discomfort and irritation.

So, that was the first problem that the prior art noted
00:39 about the discomfort and irritation, and then we will also see that Baklayan also noted --

THE COURT: Excuse me, Mr. Lipsey, before you do that, can you go back a slide to slide 37?
00:40 MR. LIPSEY: Certainly.

THE COURT: It mentions eye pain. Do we know that eye pain is different from irritation and --

MR. LIPSEY: The burning and stinging.

THE COURT: -- burning?
00:40 MR. LIPSEY: The burning and stinging is a distinctly identifiable side effect, as you can see in all the prior trials. And my understanding is that the FDA is the arbiter of what needs to be in as an adverse indication and what doesn't.
00:40 THE COURT: Can a patient discern that in the test?

MR. LIPSEY: The burning and stinging?

THE COURT: I have merely burning, I don't have eye pain, or vice versa?

MR. LIPSEY: Just from the fact that it's
00:40 differentiated throughout the other clinical trials, and since it is specifically called out in the prior art, the burning and stinging is a distinct feature, my assumption is yes. And I'm sure when we get Dr. Trattler here, we can ask him that.

THE COURT: Okay. That will be helpful. Thanks.
00:41 MR. LIPSEY: So, I won't burden the record. We've got publications from Dr. Walters in the peer-reviewed *Ophthalmology*, making more or less the same points. Dr. Silverstein in the peer-reviewed *Clinical Ophthalmology*, again pointing out those benefits. Dr. Rajpal in the peer-reviewed
00:41 journal *Patient Preference and Adherence*, again pointing out those benefits. And there is substantial evidence, which the Court will see, laying those benefits squarely at the feet of the use of .02 percent tyloxapol.

And what we have here on slide 43 is the original data
00:41 underlying Table 1 in the '431 patent, and the left-hand column is the test specimen using polysorbate. The columns on the right are various amounts of tyloxapol.

This test is being done at pH 7, which is a stringent test of stabilizing ability at lower pH. And what you can see
00:42 is that the surfactant used in Ogawa, there was basically half

of the material was destroyed after the four week test, whereas with .02 percent tyloxapol there was almost 90 percent still remaining.

And interesting trend emerged from that data, which you will hear testimony about, and that is, counter-intuitively, when you graph that data out and take a look at it, you see that the stability actually goes up as the concentration of tyloxapol goes down. To the extent the defendants contend that, well, it would be obvious to use low amounts, the reason people use low amounts is because they want to find the minimum amount that's still effective. In other words, everybody assumes a lot is good. The question is how little will still be just as good as a lot, and the evidence here shows exactly the opposite trend.

There is also evidence that tyloxapol at .02 percent provided such a significant increase in stability over polysorbate 80 that you didn't need to use the sodium sulfite that Ogawa had said was so important. And what we have here on slide 45 is some evidence comparing the Bronuck® formulation to the formulation with .02 percent tyloxapol that does not have that sulfite. Now, this test was done at a higher pH.

And then we have also the evidence which is actually embodied in Table 2 of the patent where, again, .02 percent tyloxapol formulations, again has a pH of about 8.15, all had

in excess of 90 percent of the drug remaining after that accelerated stability test of four weeks at 60 degrees C, and Ogawa himself points out in the patent that when you have more than 90 percent remaining, that's sufficient stability for eyedrops.

There are also benefits that flow from the .02 percent tyloxapol in terms of preservative efficacy that we will hear about. And this is the data actually embodied now in Table 3 of the patent and also in underlying documents interpreting the results.

Basically, the Ogawa formulation was perfectly good for Japan. It met the preservative efficacy standards for Japan. It met the standards for the United States. In internal research, which is not part of the prior art, they studied the question, they were going to go introduce it in Europe, and it turned out it didn't meet the European Pharmacopoeia standard, which is more stringent than the U.S. or the Japanese standard.

There are two parts to that standard. There's a part A which I understand to be the target or goal in terms of preventing microbial growth in the solution; and there's a somewhat laxer standard B which is a, for lack of a better word, acceptable standard. And you can see that the Ogawa formulation with .15 percent polysorbate didn't meet either, whereas that formulation with .02 percent tyloxapol, even

without the sulfite, passed them both. And interestingly, when you up the concentration of tyloxapol to .05 percent, while it passed the lesser standard B, it failed the more rigorous standard A.

So, that brings us really to the heart of our case, it being important to us for our evidence not just to snipe at whether defendants have met their burden of proof, and it is, indeed, their burden of proof on the issue of validity, but to really show the wonderful and unexpected cascade of benefits that flow from using .02 percent tyloxapol. We see that it permitted a reduction of pH from 8.3 to 7.8, which is more than a threefold difference; increased ocular penetration; reduced by 22 percent the amount of the active drug that needed to be used; effectively eliminated stinging and burning; reduction by eightfold of the surfactant load from .15 to .02; reduction of exposure of damaged ocular tissue to active drug and surfactant; improved patient compliance; increased preservative efficacy; and eliminated, if desired, the need to use the sulfite. And we will contend and our evidence will show that those are unexpected beneficial results, they are important, and that they could not have been predicted, and they highlight the unobviousness of using .02 percent tyloxapol.

Now, the argument will be made and has been made and I expect we will hear evidence that these don't matter, that the

reduction of burning and stinging isn't important. And what you will hear from Dr. Trattler is that burning and stinging matters to his patients, and since it is a compliance issue and you don't know who is going to have the compliance issue, and since there are consequences, potentially serious side effects that come from not taking the medicine, that it is important to absolutely minimize stinging and burning.

And there's also the objective indicator of the actions of these defendants themselves which I think speaks volumes, and that is, as we have here on slide 50, this is a report that's up on Lupin's website simply reporting a fact, and that is that the original bromfenac formulation, the Xibrom® and Bromday® formulation, is available for generic competition and, in fact, there are generics on the market. And our evidence will show that if they thought it didn't matter that those formulations were just as good, they could be on the market today with those formulations.

And what you will see is that's not what they want. They want to copy this formulation, and we contend that's because it's better, and they're not alone, you need look no further than the docket entrees in this court to see that there is a veritable who's who of the generic drug industry endeavoring to copy this product, and that they have, the defendants here have done so slavishly. They have copied it in every detail, even though the FDA regulations would have

allowed them to make some changes, which if they could have made and still have had the benefits, they could have avoided this suit conceivably altogether.

That brings us to the claims. There are two. A couple
00:49 of features of interest. They are dependent claims and so both parties have tried to construct them together with the claims that they depend from into one coherent body. The claim calls for an aqueous liquid preparation consisting essentially of, those are magic words in patent law meaning
00:49 excluding things that alter the basic and novel characteristics of the invention. The first component is bromfenac sodium; the second component is tyloxapol at about .02 percent for ophthalmic administration.

And interestingly here, because it will come up in some
00:49 of the evidence that we see, it excludes these quaternary ammonium stabilizers other than BAC and benzalkonium chloride, which is a widely used stabilizer and really is the focus of much of the defendants' evidence. And our claims all require that if there is such a molecule, that it be BAC.

00:50 The other claim, claim 20, is essentially what I guess would be called in this business a picture claim of the commercial formulation for Prolensa®. It has all the important ingredients, and again specifies tyloxapol having a concentration of about .02 percent.

00:50 And just so that we get oriented, taking a quick peek

at the prior art, the priority date for this patent application is January 21, 2003, and that's the dividing line between what's prior art and what isn't.

So, in the question of -- the issue here is
00:50 obviousness, and the challenge, as your Honor knows, and as we all know, the challenge in obviousness is trying to avoid the insidious effect of hindsight, it being almost impossible to fully divorce yourself from knowledge of what the inventor did in going back and reviewing the prior art, but it is important
00:51 to try to do that. But the way this case developed is the defendants did exactly the opposite.

Guided by what they knew the claim to be, they basically scoured the prior art looking for every reference they could find mentioning tyloxapol in connection with
00:51 eyedrops, and many of them had been asserted against us in one form or another, and as I understand it, while their opening is relatively narrow, they have not abandoned reliance on these, and so I will briefly take a look at them.

Basically, our case relies on the fact that the
00:51 totality of the prior art, not just little pieces of it which you might pick out and look at in isolation, really do not suggest or provide any likelihood of success or suggest you could get the benefits we get by substituting .02 percent tyloxapol into the formulations of Ogawa.

00:52 And just as a preliminary matter, their evidence will

try to create the impression that tyloxapol was commonly used for ophthalmic NSAID solutions and was, indeed, a household word in this field, but the fact of the matter is, I have on slide 57 all of the ophthalmic NSAID products containing
00:52 tyloxapol that were marketed as of 2003, and the short answer is there weren't any. They were not any.

Now, there were drugs. There was diclofenac, but it used a modified castor oil. There was ketorolac; it used something called octoxynol 9. There was bromfenac, it used
00:52 polysorbate 80.

And again defendants were kind enough to share with us one of their slides, and they have suggested here that, in fact, there were nine ophthalmic formulations using tyloxapol that had been approved by the FDA, and that we know that none
00:53 of those was an NSAID. And so the question will be asked what those are, and we expect the answer will be, oh, those are steroids and, oh, those are antibiotics and, oh, those are glaucoma drugs and not, oh, yes, those are NSAID solutions.

Now, something equally important from this document,
00:53 the heading here is missing for this right-hand column. That heading says potency range, and the range of the tyloxapol here is .05 to .1 percent, which is two-and-a-half to five times higher than what our claims specify.

So, what did the prior art actually suggest, and we'll
00:53 quickly run through these. The Yanni publication acknowledges

the '225 patent here is the Ogawa patent. He says, the '225 patent compounds are difficult to formulate in stable aqueous solutions. So what's the obvious thing to do? Yanni tells us. He says what's needed are additional agents. And that's
00:54 exactly what he did. He went out and he chemically modified those agents, and that was his invention. And what did he use them with? In his lone example, he used them with polysorbate 80.

We have Yasueda. Yasueda does mention, but apparently
00:54 never commercialized, a formulation with tyloxapol. But in what context, your Honor? And our evidence will bring this out in spades. The patent itself says that pranlukast, which is not even an NSAID, has very low water solubility, which makes it very difficult to prepare a useful aqueous liquid
00:54 pharmaceutical composition. And that's the problem that he is addressing here. And that problem simply does not exist with bromfenac sodium, which is the active ingredient in the Ogawa materials. As the *New Drugs in Japan* stated, it is freely soluble in water. There is no solubility issue with it at
00:55 all, so it is not even a candidate for whatever solutions it is that Yasueda happens to propose.

So, let's look more carefully at what you see Yasueda actually does propose. He says, you know, you can add a whole bunch of different excipients to my drugs, and he mentions
00:55 among them surfactants, and he says they can be nonionic,

cationic or anionic. Your Honor, that is the entire universe of surfactants. He goes on to mention specific ones. He mentions polysorbate 80, he mentions the modified castor oil that we heard about. Interestingly, he mentions tyloxapol. 00:55 He does not call it an ethoxylated octylphenol, which is what they will contend it is. He calls it a polyoxyethylene alkylphenyl formaldehyde condensate. It is a polymer that is made by reacting with formaldehyde. And he goes on and mentions a whole raft of other things including among others.

00:56 What he actually teaches is that tyloxapol isn't as good at solubilizing pranlukast as polysorbate 80. That's our slide 64. You can see that polysorbate 80 actually solubilized more of the drug than tyloxapol did. And when he actually went to make a test drug, a test medicine, what did 00:56 he use? He used polysorbate 80.

Now, he does have some examples where he just says here's a formulation, and even when he does that, he's got tyloxapol in there at 4 percent, which is 200 times the amount of tyloxapol in our formulation.

00:56 So, the bottom line is he may mention, you may have been able to search around and find a mention of tyloxapol with an eyedrop, but our evidence will show it doesn't suggest making the modification that we are claiming.

Sallmann is another reference they found that mentions 00:57 tyloxapol. But Sallmann actually highlights the

unpredictability in this art that our evidence will show. He found that simply by changing the salt of diclofenac from diclofenac sodium, which was the salt that had been commercialized, to diclofenac potassium, he got dramatic 00:57 difference in properties from a change as subtle and as simple as changing the salt. And, if anything, what that would suggest is possibly examining bromfenac potassium instead of bromfenac sodium. It does not suggest anything else with respect to bromfenac.

00:57 And when you look, apparently because he needed it for this potassium salt, the same way pranlukast needed it, he proposes using a solubilizer. And among the solubilizers, he does mention tyloxapol amongst a whole raft of others, including vitamin E derivatives, one called TPGS that we will 00:58 see later, but the most salient point is an especially preferred solubilizer is this Cremophor EL, a castor oil product.

When he does give illustrations of formulations with tyloxapol, he has massive amounts of cyclodextrin in there, 00:58 and you will hear evidence that cyclodextrin could be potentially troublesome for bromfenac sodium, which would be excluded by the "consisting essentially of" language.

And when he actually goes to make a medicine, what does he make? The evidence will show what he actually makes is one 00:58 with this Cremophor in it. That's in this Example 8, and it's

Example 8 that he actually does his in vivo testing with.

And then we come to what is apparently the centerpiece of defendants' case, and that is this published application of Fu. They call it EP 984. And Fu describes this issue that 00:59 some drugs with carboxylic acid groups can react with benzalkonium chloride to form a complex. And what his specific concern is, he's got this NSAID ketorolac, which we will see when we do it, and we had on the screen before, structurally quite different from bromfenac. And when he put 00:59 ketorolac BAC and polysorbate together, it became cloudy.

Now, that is a physical stability problem. And we know what it was that Fu did to measure that. He did a test where he mixed the ingredients up, and the solutions that remained clear are considered stable in this procedure. And what was 01:00 in the art about the formulations of bromfenac according to Ogawa as embodied in the Bronuck® formulation? The literature said those formulations were clear yellow. There was not a shred of evidence that the Ogawa formulations suffered from this problem. Therefore, not a shred of motivation to adopt 01:00 whatever solution it is that Fu suggests to solve it.

And, indeed, Ogawa itself, as we saw, said that with the use of polyvinylpyrrolidone and sodium sulfite you could make successfully stable formulations. There are, in fact, other examples in the literature of formulations that do not 01:00 have this problem that they characterize as universal.

There's one in Bowman with diclofenac solution that was stable with benzalkonium chloride.

And when we look at what Fu suggested doing, even if you want to look at it, even though there was no apparent 01:01 reason to need to, he says he adds an ethoxylated octylphenol. And they use this word a lot. And we'll have Dr. Davies explain to us what it means. He gives some examples including octoxynol 9, 12, 13, most preferably octoxynol 40.

And here is what those molecules look like. And 01:01 indeed, ethoxylated octylphenol, as matter of chemistry, refers to a material that has this single head group and then varying lengths of this oxygenated tail. Octoxynol 9 has nine repeating units, octoxynol 40 has 40. And tyloxapol is an entirely different animal made by the polymerization with 01:02 formaldehyde. And Dr. Davies will explain to us that tyloxapol is not an ethoxylated octylphenol, and, your Honor, that explains why Fu doesn't even mention it. He doesn't mention bromfenac, he doesn't mention tyloxapol. And what we have here is primary reliance of the defendants' evidence on a 01:02 reference that teaches a solution to a problem that the Ogawa products didn't have, using a material that the Fu publication does not describe.

And again, they have helpfully provided a slide which actually proves too much. This is the great danger in 01:02 demonstrative exhibits, of course. This is tyloxapol, the

chemical structure of it, and they have correctly noted that if all you had was this one strand here, you could call that an ethoxylated octylphenol. But when you engage in chemistry, to put these linking groups in, to join them together into
01:03 this long, long chain, you have taken it out of that category, as Dr. Davies will tell us.

They have also cited to us the Schott publication. This again, due to their courtesy, is one of their slides. They say that it's CMC, which I wish I remembered, critical
01:03 micelle concentration, which is the concentration which forms those little balls that we saw on the original slide. They said it's 4.4 times higher than octoxynol 9.

And what do they say that's good for? They say that's good in stabilizing emulsions, suspensions, ointments and
01:03 foams, and none of that is bromfenac liquid solution. And the bottom line, your Honor, is that whether that change would be good, bad or indifferent in a formulation of the Ogawa type with bromfenac is entirely unpredictable, as our experts will testify.

01:04 Q. Just to clean this up, Desai is -- mentions the same problem of these complexation issues, and what does he do? Again, the more obvious solution, your Honor, he says let's change the preservative. Let's put in this Polyquad® instead. And, as I noted at the outset, our claims exclude that. So
01:04 we're not even in the ballpark of Desai, since all of his

formulations include that.

What does he say? Like a lot of these publications, he's got a laundry list of things that could be in here. You can have comfort-enhancing agents, buffers, other
01:05 preservatives, tonicity agents, antioxidants, chelating agents, complexing agents, and surfactants. And he then gives a laundry list of surfactant. He's got tyloxapol in there, yes, but he's got the Cremophor that was so important in one of those other references. He's got the castor oil that was
01:05 important in another. He's got the polysorbates, which was Polysorbate 80. There is nothing in there suggesting any particular benefit in using tyloxapol.

And when you look at his example, what does he have? He's got no mention -- the drugs he mentions are not bromfenac
01:05 and the ingredients he mentions are not tyloxapol. They are, in fact, this Vitamin E material that we saw mentioned in the Sallmann reference.

And then they have the WO 13805 publication which, amongst us chickens, we've been calling the W 005 publication.
01:06 It's actually directed to a new therapeutic method. Doesn't purport to be inventing really any new drugs -- well, that's not quite true. He's got a new therapeutic method, and he's got a gigantic formula of compounds that he can use for it. And that gigantic formula includes acidic materials like
01:06 bromfenac. And for the compound ones, all he suggests using

is Polysorbate.

And he does have another material, that nepafenac molecule that we talked about at the outset, where he does suggest using tyloxapol. And, as we noted at the outset,
01:06 nepafenac is a horse of a different color. It is a prodrug; it is not itself an active ingredient. It is delivered into the eye and then converted into something that is active. And when that ultimately came to market, your Honor, it came to market not as a solution, like the Ogawa materials, but as a
01:06 suspension.

And, getting even further afield, the defendants have found a publication that describes treating cystic fibrosis with tyloxapol, specifically, to avoid damage caused by hypochlorous acid, and what they have glommed onto is that it
01:07 does that by inhibiting oxidation. The suggestion is made, well, you would have included tyloxapol in the Ogawa formulations as an antioxidant.

Before you even get to that, the tyloxapol amounts that are used here, 10 milligrams per milliliter, are 50 times the
01:07 concentration that we use in our invention. Well, it's a big number times. I'm being told I'm wrong. I think it's 50; he thinks it's 500. It's a lot more.

And, more importantly, it kind of misses the point. Ogawa already has an antioxidant in it. That sodium sulfite
01:07 that Ogawa added is an antioxidant. And so there is simply no

motivation to go add tyloxapol as another.

And, perhaps more importantly, the literature uniformly recognizes tyloxapol is not the recognized antioxidant in this field.

01:08 We saw the Sallmann reference they rely upon. He knows about tyloxapol. He calls it a solubilizer. When he gets down to antioxidants, he mentions entirely different molecules.

When we see the Yasueda publication, he knew about
01:08 tyloxapol. He calls it a surfactant. When he gets down to antioxidants, he mentions entirely different molecules.

And, frankly, your Honor, there is even an old, old, old publication from 1978 that suggests that, you know, this class of molecules that have these polyoxyl ethylene tails in
01:08 them, which would include both Polysorbate 80 and tyloxapol, they might actually undergo reactions that might actually generate things that are oxidizers, whereby, if anything, the message is mixed on these as antioxidants. And, in any event, that teaching in 1978 certainly didn't dissuade people from
01:09 using Polysorbate 80, as we saw in Ogawa, in the WO 13805 publication, in Yasueda, in Yanni, and in Desai.

So the bottom line, your Honor, is we feel that the evidence, in its entirety as a whole, without the aid of hindsight, simply does not suggest to a person of ordinary
01:09 skill in the art to use tyloxapol in the Ogawa-type

formulations; that, certainly not at .02 percent, certainly doesn't predict the cascade of benefits that flow from it. And our evidence will show that the defendants have failed to carry their burden of proof on the obviousness issue.

01:09 There is one more issue. They have an allegation of double patenting, obviousness-type double patenting. And this flows from the simple fact that the '431 patent being the first to issue was awarded, by statute, 604 days of patent term adjustment, under a statute that Congress passed to

01:10 accommodate United States patent owners in connection with the change from the 17-year-from-issue patent term to the 20-year-from-filing patent term that was needed to conform our system to the rest of the world. And that is a statutory right that Congress has granted.

01:10 And the evidence will show that the judge-made law of double patenting, whatever it might apply to, cannot be applied to abrogate a statutory right.

So, your Honor, you have been very patient. Thank you very much. We look forward to presenting our case. It

01:10 will be awhile until we get to the substance since I believe the defendants will go first, after we have a presentation about the patent and the products that are at issue.

THE COURT: Okay. Thank you very much.

Is there anyone who needs a break? No?

01:10 All right. Then Ms. Holland.

MS. HOLLAND: Good morning, your Honor. We are going to similarly pass out binders with the opening slides.

THE COURT: Thank you.

MS. HOLLAND: Before I start, your Honor, I would like

01:11 to introduce the Lupin representatives who are here in the courtroom today. First of all, Ms. Minaksi Bhatt, who is a Vice President of Intellectual Property at Lupin; and then Ms. Akanksha Kulcarni, who is in the IP Group in Lupin in Pune, India, who actually came in for the trial.

01:11 THE COURT: Welcome.

MS. HOLLAND: Your Honor, I would like to start by putting Prolensa®, the product that Mr. Lipsey talked about as an embodiment of the claims of the patent-in-suit here, in a little bit of context.

01:12 Bromfenac, you didn't hear about it from Mr. Lipsey, but this is actually a very old drug. It's been known for decades. Bromfenac, the active ingredient, was first used commercially in a product called Bronuck®, which was marketed in Japan in the year 2000.

01:12 Plaintiffs brought that Bronuck® formulation to the U.S. in 2005, marketed under the name of Xibrom®. Xibrom® is the exact same formulation as Bronuck®.

In 2010, plaintiffs put the Bromday® product on the market. Bromday®, again, has the same formulation as

01:12 Bronuck®, same formulation as Xibrom®, but it's marketed as

a twice -- was marketed, I should say, as a twice -- a once-a-day product, whereas Bronuck® and Xibrom® were twice-a-day products.

At the same time that plaintiffs put Bromday® on the

01:13 market, they discontinued the Xibrom® product, and you'll hear a little bit more about this during Mr. Mukerjee's presentation, his opening, after I'm done.

In 2013, plaintiffs put the Prolensa® product on the market, the product that we are here to talk about at this

01:13 trial. It is essentially the same formulation as what came before it as Bronuck®, as Xibrom®, as Bromday®, with the simple substitution of tyloxapol for Polysorbate 80.

Now, I heard Mr. Lipsey in his opening say that, well, there are the generics, you know, on the market. What

01:13 are they really complaining about? But the simple fact is that when plaintiffs put Prolensa® on the market, they discontinued Bromday®. So the fact that there may be a generic to Bromday® really has no commercial meaning because there is no product on the market for it to be generic to.

01:14 There is no substitution that can take place if there is no brand products on the market.

Let me now turn to the claims that are at issue here in this case, and, as Mr. Lipsey said, the essential parts of these claims are they're all formulation claims, and they have

01:14 the active ingredient bromfenac sodium, the inactive

ingredient tyloxapol, and the inactive ingredient benzalkonium chloride. Now, this is Slide 3.

Slide 4, you see the Claim 20 formulation. Again, you see the active bromfenac; you see the inactives tyloxapol and

01:14 benzalkonium chloride; along with additional list of excipients.

What I want to point out here, your Honor, when you look at these claims, what you see is that there are no limitations in these claims as to pH. Mr. Lipsey talked a lot

01:15 this morning about how the pH of Prolensa® is lower than the pH of the products that had come on the market before it and how there is, I think, to quote him, a cascade flowing of benefits from that. But the simple fact is that's nowhere in the claims here.

01:15 So the claims, for example, cover the Prolensa® product with its pH of 7.8, but they also would cover a formulation with a pH of 8.3, which is the pH of the prior bromfenac products that had been on the market.

Because any benefit coming from pH, if there is any,

01:15 is not commensurate with the scope of the claims, as a matter of law, it can't be considered as an unexpected result.

With that background, I'm now going to turn to the substantive arguments about Claim 6 and Claim 20 being obvious over the prior art.

01:16 I'm going to be addressing defendants' case-in-chief

on invalidity, and then Mr. Mukerjee, InnoPharma's counsel, is going to address a rebuttal's case on secondary considerations.

Our case-in-chief is going to be presented by our formulation expert, Professor Jayne Lawrence, and Professor Lawrence is in the courtroom this morning, Your Honor.

THE COURT: Welcome.

MS. HOLLAND: Professor Lawrence is a Professor of Biophysical Pharmaceutics at Kings College in London. At the same time, she holds an appointment as chief scientist of the Royal Pharmaceutical Society. She is a well-known expert in formulation and drug delivery, and, importantly, collaborates with pharmaceutical companies on ophthalmic formulations.

So, of all the experts you've heard about this morning, your Honor, Professor Lawrence has the right experience and the right expertise to address the issues in this case, which are not chemistry issues. These are not chemistry patents. These are formulation patents, and, particularly, formulation of ophthalmic compositions.

So, as Professor Lawrence will explain, the claimed formulations here are nearly identical, very, very close to the prior art bromfenac formulations.

And what I have on Slide 7, on the left column, you see the formulation of the '225 patent, Example 6. '225 patent was referred to as Ogawa by Mr. Lipsey.

And sorry about that, your Honor, but we've tended to refer to these by numbers and plaintiffs have tended to refer to them by names, but it's -- the '225 and Ogawa are one and the same.

Example 6 of the Ogawa patent -- and Mr. Lipsey agreed with this in his direct examination -- is the formulation of the Bronuck®, Xibrom®, and Bromday® products.

On the right you see the formulation of Claim 20 of the '431 patent, the patent-in-suit in this case. It's the formulation of the Prolensa® product.

And as you see, the difference, the sole difference between the two is that the prior art formulation has Polysorbate 80 and the '431 patent has tyloxapol.

You may notice in the columns, there are some wording differences. So, the '225 patent says borax, whereas the '431 patent says sodium tetraborate. But there is no dispute here that those are one and the same, and that the only difference is between Polysorbate 80 and tyloxapol.

THE COURT: So the '431 -- I'm sorry. The Prolensa® manifestation contains sodium sulfite?

MS. HOLLAND: It does.

THE COURT: I thought that Mr. Lipsey had said it does not.

MS. HOLLAND: He -- yes, I was confused about that as well, your Honor. It certainly contains sodium sulfite. I

believe what Mr. Lipsey said is that potentially, you could find a formulation that doesn't, but that's not what happens here. The claims here do have the sodium sulfite.

MR. LIPSEY: The point I made on that chart was, if desired, you could eliminate the sulfite.

THE COURT: I see.

MR. LIPSEY: I did not mean to imply it was not there.

MS. HOLLAND: Apparently, it either wasn't desired or wasn't -- or plaintiffs weren't able to do it, because it is in the Prolensa® product.

Can we put up -- Mr. Cort, can we put up one of the demonstratives that Mr. Lipsey used this morning? It's PDX1-4.

Your Honor, Mr. Lipsey this morning started out his presentation by talking about all these challenges that he called -- as he called them, in topical ophthalmic formulation, but when you look at the list, the inventors of the patents-in-suit in this case didn't have any of those challenges because they had all been resolved by the prior art, Ogawa '225 patent, and the commercial products that were the embodiment of the inventions in that patent.

Those products -- Bronuck®, Xibrom®, Bromday® -- they were all safe and effective ophthalmic compositions. They were clinically effective active ingredients. They had the

appropriate ocular penetration. They maintained that penetration in the eye. To the extent there was any irritability, stinging, burning, it was at a very, very extremely low level. And this is something Mr. Mukerjee is going to get into a bit later in his presentation. And they -- and they were chemically and physically stable at the pH of 8.3 that existed -- in which they went on the market.

Let's concentrate a little bit more then on Polysorbate 80 and tyloxapol. As you can see on Slide 8, these are both referred to as nonionic surfactants. A surfactant is a surface-active agent. It's a common type of excipient or inactive ingredient that's used in pharmaceutical formulations. And while they can have different -- while surfactants can have different types of functions, they can function, and one important function is as solubilizers, and solubilizers are, as the name sounds, agents that increase solubility. And both Polysorbate 80 and tyloxapol were known in the prior art as solubilizers.

When they're referred to non- -- as nonionic surfactants, nonionic refers to them having no electrical charge, no positive or negative charge. They are neutral molecules.

So why are solubilizers, Polysorbate 80 or tyloxapol, why are they used in bromfenac formulations? Well, Dr. Lawrence is going to explain that this is based on the

interaction between the active ingredient, bromfenac sodium, and the inactive ingredient, benzalkonium chloride.

Here on Slide 10, you see benzalkonium chloride is sometimes referred to as BAC, by shorthand. You'll hear that
01:22 a lot in this trial. It's a preservative, and it's a very widely used preservative, as Mr. Lipsey acknowledged this morning, very widely used preservative in ophthalmic formulations. It prevents microbial growth.

And, as Mr. Lipsey said, the eye is one of the most
01:23 sensitive organs in the body. You have to be very careful about microbial growth.

You can imagine when you have a multi-use eyedropper or container and you're taking them out, putting it in your eye, putting it back in, there is a good chance for microbial
01:23 growth. So it's really important to include a strong preservative in the ophthalmic solutions, and that is why BAC is used so commonly, because it's an excellent preservative.

THE COURT: Maybe it doesn't matter, but in practice, are these administered with a dropper or are they administered
01:23 with kind of a sealed little bottle?

MS. HOLLAND: These formulations are multi use. When you have the multi-use formulation, they are in a little bottle like, like Prolensa® is. Then it's with an eyedropper. There are formulations on the market that are those single-use
01:23 vials. But the ones that are the eyedropper type must have a

preservative in them to combat any microbial growth.

As you heard from Mr. Lipsey, bromfenac is an NSAID, a nonsteroidal anti-inflammatory drug. It's also referred to as an acidic NSAID. The reason for that -- and if you look on
01:24 Slide 11, it's clear, this is the structure of bromfenac.

If you look at the left-hand portion, you'll see, in green, a piece of the molecule that's known as a carboxyl group. The carboxyl group on bromfenac is what gives it its acidic name. And bromfenac is just one of a whole class of
01:24 NSAIDs that are called acidic NSAIDs.

As you can see on Slide 11, while the structures may differ a bit from each other, the key point is that they all have that carboxyl group. That's shown in green on each of these molecules.
01:25 And, your Honor, sometimes you may see that in, either during testimony or in the prior art, as a COOH group. That's the same thing as a carboxyl group. And this is really the key to the issue between bromfenac and BAC when they go into solution.
01:25 So now on Slide 12, what I've displayed here is bromfenac. Again, the upper right-hand corner, circled in green on that molecule, you'll see a carboxyl group.

When bromfenac goes into solution, the positive H, hydrogen, is separated from the molecule, and it's left with a
01:26 negative charge, as you can see there, next to the oxygen or

the "O" on the left-hand side of the molecule. So we refer to that as an anionic compound, anionic having the negative charge.

If you look now at the BAC molecule, which is the lower
01:26 left-hand portion of the screen, you'll see that it is -- has the negatively charged chlorine and the positively charged nitrogen. And BAC is referred to as a cationic compound, having the positive charge.

And you'll see, your Honor, when the BAC and the
01:26 bromfenac -- the cationic and the anionic compounds go into solution, when they go into solution, what you're left with is the bromfenac with a negative charge and the BAC with a positive charge. And, as you may remember from high school or college chemistry, the negative charge is attracted to the
01:27 positive charge. What happens is they come together and form a complex, and this is the root of the problem. As you can see, they are no longer these separate molecules; they're one complex of the BAC and the bromfenac together with each other. This is an insoluble complex. In other words, it doesn't mix
01:27 in with the rest of the solution.

And if you look on Slide 12, it kind of -- the kind of little white dots in the beaker there are meant to show these little complexes that exist in the solution, when they are -- the NSAID and the BAC come together in the complexation.
01:28 Now, there are really two problems with this. The

first is you lose some of the effect of the active ingredient because the active ingredient that's part of the insoluble complex is not available to do its job of -- as an NSAID. You also lose some of the activity of the BAC, the preservative,
01:28 because, again, it's not available to do its job as a preservative. And this was a well-known issue in the prior art as I'll show you in a moment; NSAIDs and BACs come together in solution, they form these complexes, and it affects both the efficacy and the preservative efficacy.
01:28 Now, what I have up on Slide 13 is an excerpt from the '431 patent itself. It's in the background art section of the '431 patent specification, which is a section of a patent that covers what's in the prior art.

Mr. Lipsey said a couple of things this morning
01:29 relevant to this slide. First of all, he said that the '431 patent -- we claim that the '431 patent was solving a problem that didn't exist. Well, as you see, your Honor, the '431 patent inventors acknowledged that this problem exists in the prior -- existed in the prior art.
01:29 As they say right there in the patent specification, "benzalkonium chloride is a widely used preservative in ophthalmic solutions." Mr. Lipsey agreed with that this morning. Then they say, "However, benzalkonium chloride and other quaternary ammonium compounds are generally considered
01:29 to be incompatible with ophthalmic compositions of drugs with

acidic groups, such as nonsteroidal anti-inflammatory drugs.

And, as you see, your Honor, this is known about the class of acidic NSAIDs in general. This was a problem that was widely known among formulators in the art to exist between
01:30 any of the NSAIDs on this class of acidic NSAIDs and BAC.

And, just as I explained a minute ago, your Honor, what the inventors of the patent said in their patent is that these preservatives, in other words, BAC, lose their ability to function as they form complexes with the charged drug
01:30 compounds.

So, contrary to what Mr. Lipsey said, the inventors were clearly aware of this problem and clearly were concerned about it in terms of bromfenac ophthalmic compositions.

Mr. Lipsey also said that defendants say that all
01:31 these acidic NSAIDs are fungible but that plaintiffs focus on the differences.

Well, I submit, your Honor, it's not that defendants say they're fungible. When you look at the prior art, they're treated as a class. None of the prior-art references you're
01:31 going to see today make any distinction by structure of the NSAID as to whether or not it would be expected to form a complex with BAC.

On Slide 14, I listed just some of the references in the prior art that make it clear that the NSAID BAC problem,
01:31 complex section problem, was well known as of 2003. And as

you see, these references, again, they're not talking about specific NSAID compounds and saying that the problem only applies to ketorolac or it only applies to diclofenac. These acidic NSAIDs are being handled as a class.

01:31 Benzalkonium chloride is generally considered to be incompatible with NSAIDs. NSAIDs tend to form insoluble complexes with benzalkonium chloride. Acidic drugs with carboxyl groups tend to form insoluble complexes with BAC. Benzalkonium chloride is considered to be incompatible with
01:32 anionic drugs. As we saw earlier, your Honor, bromfenac is an anionic drug, and they form insoluble compounds, and on and on.

So the suggestion that the formulators or the authors of the prior art reference in any way understood this to be
01:32 something that was specific to one or two particular NSAIDs is simply incorrect and inconsistent with the prior art.

Now, you heard from Mr. Lipsey that one of the key prior art references here is the EP 984 reference. And the reason this is so key is because it provided the solution to
01:32 this NSAID BAC complexation problem.

As you can see, on Slide 15, the EP 984 reference identified the problem here. Anti-inflammatory solutions of NSAIDs are incompatible with BAC due to the fact that the carboxyl group forms a complex with the BAC, rendering the
01:33 preservative less available to serve its function and reducing

the activity of the active ingredient, just as I said a minute ago.

Two problems: One is the preservative is not able to perform its function; second problem, the active reduces its
01:33 activity because it becomes part of the complex.

The solution provided by the EP 984 reference was to include, as you can see in the bottom portion of Slide 15, the solution, as you can see it in Claim 1, was to include within the formulation a stabilizing amount of nonionic ethoxylated
01:34 octylphenol surfactant.

I know you've heard that term already from Mr. Lipsey this morning. And Mr. Lipsey actually was kind enough to put our slide up on there to show you exactly why tyloxapol is an ethoxylated octylphenol.

01:34 But before I get there, I want to show you one more teaching from the EP 984 patent, which is on Slide 16.

On Slide 16, you see Example 5 of EP 984. And what Example 5 shows is testing that was conducted comparing Octoxynol 40, the ethoxylated octylphenol compound, with Tween
01:34 80. Tween 80 is another name for Polysorbate 80. That's not something that's in dispute.

And what EP 984 showed was that when you used octoxynol 40, the ethoxylated octylphenol compound, and you substituted it for Polysorbate 80, the solutions remained clear under all
01:35 the test conditions.

When you look at the Polysorbate 80 column in the middle, what you'll see is that the solutions were either turbid or very turbid, meaning that these insoluble complexes had formed into the solution and made them cloudy.

01:35 So the EP 984 reference tells the person of ordinary skill in the art, as Professor Lawrence is going to explain, that if you have concerns about -- with a problem of complexation between an NSAID and BAC, substitute in an ethoxylated octylphenol surfactant for Polysorbate 80 and you
01:36 can clear up the complexation issue.

On the subject of whether tyloxapol is an ethoxylated octylphenol, as you can see on Slide 17, and as Professor Lawrence is going to explain, tyloxapol has this octylphenol portion along with the ethoxylated portion and they are simply
01:36 strung together, but they have that octylphenol portion and the ethoxylated portion, and they would be considered, by persons of ordinary skill in the art, by formulators, as ethoxylated octylphenol compounds.

Professor Lawrence is going to explain that there
01:37 were only two ethoxylated octylphenol surfactants that were approved for ophthalmic use in the FDA Inactive Ingredient Guide as of 2003. And this is on Slide 18.

And this is absolutely critical, your Honor. If you're a formulator, not a chemist like Dr. Davies, but somebody who
01:37 is actually working in the field of formulation, what you know

is that you want to use inactive ingredients that are already listed in the FDA's Inactive Ingredient Guide. The guide tells you which inactive ingredients have previously been used in pharmaceutical products; and it actually goes down to tell you that they are used in ophthalmic products.

So although Mr. Lipsey said that there were a large -- that Dr. Davies, the organic chemist, is going to tell us that there were a large number of choices of surfactants, formulators know that that's simply not the case. You are going to be looking for something that was already listed in the Inactive Ingredient Guide.

And, as you can see here, the only two ethoxylated octylphenol surfactants that have been listed are tyloxapol and Octoxynol. Tyloxapol had been used nine times versus one time for Octoxynol.

So, once the formulator understands that they want to use an ethoxylated octylphenol as taught by the '984 patent, and as Dr. Lawrence will explain, there were two choices, Octoxynol 40 and tyloxapol, the prior art Schott reference actually gives a little bit more information on making -- to the formulator as when they're making their choice between these two ethoxylated octylphenols.

Schott says the fact that the CMC, the critical micelle concentration, is 4.4 times smaller than Octoxynol is an advantage. Why is it an advantage? Because you can use

surfactants at a lower level without compromising the effectiveness. So there is a teaching there in the Schott reference that tyloxapol could potentially be used at a lower level in a formulation than octoxynol because it has 4.4 times smaller critical micelle concentration. And, again, this will be explained by Professor Lawrence.

THE COURT: Now, back on Slide 18 for a moment. That's your prior one, okay?

MS. HOLLAND: Yes.

THE COURT: You see the potencies or concentrations of the tyloxapol. Mr. Lipsey argued that those are two-and-a-half to five times more than the 0.02 percent that was the breakthrough. Is your witness going to be speaking to whether that distinction matters?

MS. HOLLAND: Yes, your Honor. And what you'll hear is that when an active -- when an inactive ingredient is listed in the inactive ingredient guide, you'll hear it referred to as the IIG. When it's listed in the IIG, it gives you the percentage that it had previously been used in other ophthalmic compositions.

And if you want to go higher than that percentage, it may be an issue because you'd have to perform additional toxicity, toxicological testing, to confirm the safety. But if you're going below the use that had come previously, there really isn't any issue. You don't have to perform any extra

testing. And at that point it's just a matter of routine optimization for the formulator, as Dr. Lawrence is going to explain.

So, your Honor, what do plaintiffs say here? What did Mr. Lipsey say this morning?

You heard that they are going to put an organic chemist on the stand and rely on his testimony to show, basically, why the chemistry in this case, according to him, is very complicated. But the simple fact is this is not a case about chemistry. These patents are about formulations. The right expert to tell you what would be obvious to a formulator is a formulator.

But, as you saw in the examples for the prior art about NSAID BAC complexation, while an organic chemist may tell you there are a lot of differences in these molecules, a formulator, like Professor Lawrence -- and the formulators in the prior art acknowledge that they treat them as a class.

And if you look on Slide 20, perhaps there is no better evidence of that than from a treatise called Remington's, which formulators refer to as the bible of pharmaceutical science. It's the key reference that formulators rely on when they're looking to formulate a compound.

And this is from Remington's, the edition that was in use as of 2003. What you see is there is an entry for

quaternary ammonium compounds, and benzalkonium chloride is noted as being a typical quaternary ammonium compound and by far the most common preservative used in ophthalmic preparations. Over 65 percent of these formulations are preserved with benzalkonium chloride. So, clearly, a person of ordinary skill in the art knows they want to use benzalkonium chloride. It's a very effective preservative. It's in 65 percent of ophthalmic formulations.

What else does the person of ordinary skill in the art know, according to Remington's?

Well, as you see on the second blowout for Remington's, as a cationic surface active material of high molecular weight, it is not compatible with anionic compounds. Again, as a class, it is not compatible with anionic compounds. Anionic, as we saw earlier, negatively charged compounds like bromfenac.

So what does that mean to the formulator? How did they deal with that issue? They want to use the BAC but they know that it's not compatible with acidic NSAIDs like bromfenac.

Well, what Remington says is, given the alternative, it would be preferable to modify a formulation to remove the incompatibility rather than include a compatible but less effective preservative.

In other words, formulator, what you should be doing,

use BAC in your -- in your ophthalmic formulation. You don't want to include something less effective, but just modify the formulation to remove the incompatibility.

And as we saw, the '984 patent already told the formulator exactly how to do that -- using ethoxylated octylphenol compounds, problem solved.

Now, as I said a moment ago, this is a case about formulation science. It's not about chemistry. It's not about showing how molecules are really complicated. But to the extent that Dr. Davies is going to be discussing some of the chemistry to try to show how complicated it is, we will be presenting testimony from Dr. Clayton Heathcock. You can see his credentials on DDX-121. He's a really preeminent organic chemist in the U.S. He's the Emeritus Professor at the University of California Berkeley. He's former Dean of the College of Chemistry. He wrote one of the classic undergraduate textbooks on organic chemistry, *Introduction to Organic Chemistry*, and he's been the editor of many very prestigious journals in field -- *Journal of Organic Chemistry* and *Organic Syntheses*.

So he will be testifying to rebut some of the chemistry issues that Dr. Davies may bring up in his testimony.

THE COURT: I imagine a lot of tears were spilled over his organic chemistry tests by undergraduates, including my roommates who were premed.

MS. HOLLAND: Well, yes, your Honor, I bet if you asked them, that would be exactly the case.

And one thing in particular that Dr. Heathcock is going to point out in his testimony, coming back again to this point of acidic NSAID, is that, yes, the structures may be a little different; however, the important part is that they have this carboxyl group that loses the proton, that loses the hydrogen in solution, makes it negative, and it becomes attracted to the BAC. That's the important part of the molecule for these purposes.

And as you can see, the flurbiprofen, the diclofenac, the ketorolac -- these are all the specific compounds that were mentioned in the references that Mr. Lipsey was talking about -- they don't have the same structure as each other. They also differ from each other. But it didn't matter because the important part of the molecule was that left-hand part, that carboxyl group. It made them all behave the same way in solution and be attracted to the BAC molecule.

THE COURT: Does that really make sense, though, chemically? Because the other structures are different. They have different ions that are available to -- to interact.

MS. HOLLAND: Yes, but what you'll hear, Your Honor, is that the specific reaction that occurs between BAC and these acidic NSAIDs is the reaction that occurs at that point at the carboxyl group. That's what was -- that's what all

those prior art references are referring to, when they say acidic NSAIDs generally form complexes with BAC or it's well-known that they form complexes with BAC. That's the reaction that's being referred to. So even though they are different from each other, they all undergo the same reaction with BAC.

One other thing I wanted to address, Your Honor, is that one of the things Mr. Lipsey said was that the solubilities of these different acidic NSAIDs are different from each other, and that, you know, that may be the case, but we're not talking about the solubility here of the acidic NSAID. We're talking about the solubility of the complex, of the acidic NSAID attached to the BAC, and that is different from the solubility of any of these particular NSAIDs if they were just on their own in solution.

In terms of the percentage of tyloxapol in the '431 patent formulations that Mr. Lipsey talked about this morning, this -- as Dr. Lawrence is going to explain, this is really just a matter of routine optimization for the formulator. As Your Honor pointed out earlier, there was a range of tyloxapol used in the prior products, in the IIG, that might be a starting point for the formulator, but the formulator is going to do routine optimization, test a few different concentrations, see what works.

The formulator, a person of ordinary skill in the art

would know that there were a known range of concentrations for ethoxylated octylphenol surfactants. As you can see on Slide 24, the EP '984 reference gave a range of concentrations for its surfactant against the ethoxylated octylphenol surfactants ranging from .001 to 1. The .02 falls squarely within that range.

We also know that tyloxapol had been used in NSAID BAC formulations at a range of concentrations. This is from the '913 patent, it says the concentration of the solubilizer is tyloxapol in that case, is from 0.1 to 5,000 times the concentration of the actives. So again, you can use tyloxapol in a range of concentrations and that's really the bread and butter of the formulator, what they do every day at work is figure out the right concentration for these inactive ingredients in the particular formulation that they're working on.

And then you'll hear from Professor Lawrence that general pharmaceutical principles dictate using the lowest amount of surfactant that is compatible with a stable formulation. So in other words, if you saw that prior formulation at .05, but you think your formulation could go a bit lower than that, that's what formulators do, they figure out the proper concentration of the inactive ingredients to make a stable formulation.

So just to sum up on obviousness, Your Honor, this is

on Slide 28, a person of ordinary skill in the art, a formulator working on ophthalmic formulations, has the '225 patent, Example 6, as a starting point. The person of ordinary skill in the art would know that that's the
01:51 formulation of Bronuck, not on the market in the U.S., but a marketed product in Japan.

If you want to improve the physical stability of that product, the prior art says that there could be a complexation problem between the bromfenac and the BAC. EP '984 says, I
01:51 can solve that problem by replacing the polysorbate 80 with the ethoxylated octylphenol surfactant. There were only two that could potentially be used at that time by formulators. There was octoxynol 40 and there was tyloxapol. The shot reference gives some preference to tyloxapol, because of the
01:51 lower CMC value.

And then, all that would be left to do by routine optimization is to tweak the formulation until you get to the appropriate tyloxapol concentration, and that's it, Your Honor. That is the patent in this case, which is obvious in
01:52 view of the prior art.

Now, before Mr. Mukarjee gets up, I'm just going to touch on another issue in the case which is obviousness-type double patenting. Mr. Lipsey spoke about that a bit at the end of his presentation. Obviousness-type double patenting is
01:52 a judiciously-created doctrine that's meant to prevent

timewise extension of a patent monopoly. It prevents patentees from patenting the same invention or obvious variance of the same invention one time after another, and by doing that, getting longer and longer patent terms for
01:52 essentially the same invention.

And as Mr. Lipsey noted this morning, the '431 patent has a longer patent term, a couple of years longer than the other patents that had previously been at issue in this case, the '290 patent and the '131 patent. But as Professor
01:53 Lawrence will explain, the '431 patent Claim 20 and Claim 6, they are essentially -- essentially obvious variants of the claims in the '131 and '290 patents, and, in fact, I didn't hear Mr. Lipsey dispute that fact this morning. He talked about the patent term adjustment, but he didn't at any point
01:53 say that if the doctrine of obviousness-type double patenting applies here that the claims of the '431 wouldn't, in fact, have been obvious over the claims of the '131 and the '290 patent.

So in sum, Professor Lawrence will explain to the Court
01:53 that Claims 6 and 20 of the '431 patent are invalid, both for obviousness and for obviousness-type double patenting.

Mr. Mukarjee, InnoPharma's counsel, Your Honor, is now going to address some of the secondary considerations you heard about from Mr. Lipsey, unless you have any other
01:54 questions.

THE COURT: No, I don't at this time, Ms. Holland, thank you very much.

MS. HOLLAND: Thank you.

THE COURT: Okay. Mr. Mukarjee.
01:54 MR. MUKARJEE: Good morning, Your Honor. And thank you, Elizabeth.

Your Honor, as we had stated in the trial logistics conference about two weeks ago, I'm going to do my best to keep my comments relatively brief, and what I'd like to focus
01:54 my time on is to discuss the purported secondary considerations that plaintiffs are alleging in response to or in rebuttal to the obviousness case that defendants will be putting forth at trial.

Now, as was just stated by my co-counsel, we believe
01:54 that the evidence will show that Claims 6 and 20 of the '431 patent are obvious in light of certain key references, but certainly, in light of two key pieces of prior art, namely -- and here, Your Honor, I'm going to try to bridge the gap between the way plaintiffs and Lupin refer to the prior art,
01:55 but they are obvious in light of the Ogawa '225 patent and the Fu EP '984 patent.

Now, as Ms. Holland covered in detail, among other things, Ogawa generally provides bromfenac in an ophthalmic solution. And Fu, also among other things, discloses the
01:55 ethoxylated octylphenol surfactant like tyloxapol in the

concentrations outlined in the claims at issue.

Taken together, the -- that combination, the combination of at least those two references, disclosed each and every limitation of the claims at issue.
01:55 Now, the strength of defendant's argument is further demonstrated by InnoPharma's successful petition to institute an interparty's review of Claims 6 and 20 of the '431 patent and for these reasons, we believe --

MR. LIPSEY: Excuse me, Your Honor, I'm not sure
01:56 that's admissible in evidence. I think it's a non-final agency decision. I don't mean to interrupt and I apologize, I hate it when people do it to me, but just for the record, I want to lodge that.

THE COURT: Right. All right. The objection is
01:56 noted. Has there been any word from the --

MR. MUKARJEE: For the PTAB? Yeah. Your Honor, thank you for asking that question. Actually, as soon as I finish up at trial here with you, my team and I are heading to the PTAB because we have our final argument on April 19th to
01:56 specifically argue with respect to the validity of all of the claims of the '431 patent, obviously, then including Claims 6 and 20.

And Mr. Lipsey, while I appreciate what you just said, you'll also recall that in our meet and confer yesterday, we
01:57 both discussed that openings are not evidence, per se. So

it's -- it just provides some context.

But regardless, for these reasons, Your Honor, we believe the prior art will evidence that the claims at issue are invalid.

01:57 Now, Your Honor, we heard from Mr. Lipsey this morning and it is apparent that among other things, plaintiffs intend to rely on purported secondary considerations to try to rebut defendant's obviousness case. Now, up until late last week, plaintiffs maintained that the so-called commercial success of 01:57 Prolensa rebutted the obviousness of Claims 6 and 20. It now appears that plaintiffs will not be calling their economist, Mr. Jarosz, whose opinions were directed to this notion of purported commercial success. But be that as it may, plaintiffs continue to allege other secondary considerations, 01:57 namely, industry acclaim, copying and unexpected results.

Your Honor, the evidence will show that like commercial success before it, none of the secondary considerations can rebut the obviousness of Claims 6 and 20, and if I may, even though I know plaintiffs are not calling Mr. Jarosz at trial, 01:58 it certainly seems as if, under the guise of at least copying an industry acclaim and certainly through the testimony of their experts, Drs. Trattler and Williams, plaintiffs are still alleging that Prolensa is a success and they are still alleging that Prolensa is an improvement over existing 01:58 therapies.

It is that latter point that I'd like to address first because, Your Honor, the evidence will show that Prolensa is not being prescribed because it is this improvement over existing therapies as Mr. Lipsey has alleged.

01:58 In fact, defendants will show that it's not an improvement at all, rather, what really explains why Prolensa is prescribed is essentially because of two key things. One, a general familiarity with the bromfenac compound. A compound which, Your Honor, has been known for almost four decades.

01:59 And the second reason is because of a campaign by plaintiffs to extend their exclusivity by making minor and in some instances no formulation changes to solutions containing bromfenac.

Now, let's take a closer look at that particular point 01:59 and Ms. Holland actually alluded to it as well.

So, Your Honor, I've put up on the screen DDX-131 and this slide is in some ways a recap of one of the slides Ms. Holland touched on earlier, and it shows a timeline relating to a number of different bromfenac products that 01:59 plaintiffs have marketed and discontinued over the past decade, and you will note the first date on the left, and again, I believe Ms. Holland mentioned this, it's -- May 2000 is when plaintiffs launched their first bromfenac product, Bronuck, in Japan. Plaintiffs then launched the identical 02:00 product under the name Xibrom in the United States in March of

2005.

Now, Xibrom, which was introduced in March 2005 was covered under the Ogawa '225 patent that Ms. Holland and Mr. Lipsey spoke about in detail and that I noted in the 02:00 beginning of my opening. And that patent, the Ogawa '225 patent expired in 2009.

Now, why am I mentioning the expiry data? Well, up until 2009, Xibrom enjoyed patent exclusivity, and so up until that time, it was not necessarily amenable to generic 02:01 competition or generic substitution.

Now, obviously, it being plaintiff's own patent, plaintiffs were acutely aware that the Ogawa patent was expiring in 2009. Now Xibrom is in the market, 2009 comes, the Ogawa patent expires. Xibrom is now amenable or 02:01 susceptible to generic substitution, generic competition.

So what do plaintiffs do? Well, in December of 2009, plaintiffs file a supplemental NDA for Bromday, and as Ms. Holland indicated, Bromday and Xibrom, Your Honor, are identical formulations, they are the same. The only 02:01 difference between Xibrom and Bromday is with respect to a change in indication. Xibrom was indicated for twice daily administration, whereas Bromday was indicated for once-a-day administration. That is it. From a formulation perspective, no difference. The only change: Twice-a-day versus 02:02 once-a-day.

For that change, for that change of indication, Bromday was afforded a three-year regulatory exclusivity. So they submit -- plaintiffs submit their supplemental NDA in December 2009; in October 2010, Bromday is approved.

02:02 Now, keep in mind between 2009 and 2010 now, Xibrom is susceptible to generic substitution. So what do plaintiffs do? Well, not three months after Bromday is approved in February of 2011, they discontinue Xibrom. Now, why do I make mention of that? Well, by discontinuing Xibrom, what 02:02 plaintiffs were effectively able to do was to stop any automatic generic substitution of that drug.

Up until that point, it would have been automatically substituted for the generic, but by discontinuing, by discontinuing the reference listed drug, in this case, Xibrom, 02:03 that was no longer possible. And so what plaintiffs were able to assure is really the only real bromfenac product in the market would then be Bromday, which now had this regulatory exclusivity for another three years which went out all the way to 2013. So now they've prevented generic competition on 02:03 Xibrom. And now Bromday's on the market.

Well, they're obviously also aware of the October 2013 date. And so as that date is approaching, in June of 2012, they file the NDA for Prolensa, and Prolensa is approved in April of 2013. Now Prolensa, just like they did with respect 02:04 to Xibrom, because they recognized that Bromday was soon to be

susceptible to generic substitution, what plaintiffs did was once again, just four months after Prolensa gets approval, they discontinue Bromday once again. Again, ensuring that now their second follow-on product Bromday would also not be susceptible to generic substitution.

Now, Your Honor, neither Xibrom nor Bromday were ever discontinued for safety and efficacy reasons. They were discontinued solely for this particular purpose. They were discontinued such that plaintiff's market exclusivity could continue far longer than the 2009 expiry date of Ogawa. And that, Your Honor, is the context.

That, Your Honor, is the story of why Prolensa is even in the marketplace. It is not because of all these incremental benefits that Mr. Lipsey alludes to. It is not because Prolensa is a great pharmaceutical discovery or formulation. It's not because Prolensa is even an incremental advancement over the prior product. It is simply to maintain this market exclusivity for as long as possible, an exclusivity that should have ended in 2009.

Now, Your Honor, plaintiffs don't exactly run away from this. They openly and publicly acknowledge it. In fact, actually one thing to note, in August of 2013, Your Honor, they discontinue Bromday. In that very same month, in Valeant's quarter of -- Q2 results earnings call, both the CFO and CEO of Valeant not only acknowledged this particular

mechanism or strategy, but they actually embrace it. Howard Bradley Schiller, the CFO of Valeant stated on the earnings call again at the exact time that Bromday was being discontinued and in the case of Bromday and Lotemax suspension, new products have already been launched to sustain these franchises. We would expect to be able to implement life cycle management programs to extend the lives of other franchises as well.

And J. Michael Pearson, Valeant's CEO, stated: For each of our products that are coming off patent, we are working on life cycle management products that we can introduce before the patent expires.

This is the real motivation for why Prolensa is in the marketplace. It is not because of any purported success or improvement over prior formulations that plaintiffs are now alleging as purported secondary considerations.

Now, against this backdrop, let's take a look at plaintiff's allegations that Prolensa has inured industry acclaim. Now, I know Mr. Lipsey didn't mention as part of his opening, industry acclaim, but industry acclaim is set forth in their pretrial order and industry acclaim is set forth in their expert reports.

The key point there, Your Honor, is that any acclaim that there is in the record comes from plaintiffs themselves. As I've highlighted on the slide, the articles that

plaintiff's expert, Dr. Trattler -- Dr. Trattler relies on in support of his opinion were sponsored by plaintiffs.

Incidentally, Your Honor, they don't actually even give Prolensa much acclaim. What the articles actually state is that Prolensa has similar safety and efficacy profiles. It's not lauding the virtues of Prolensa. So even in articles sponsored by plaintiffs themselves, they are not lauding that this is a better or -- a better treatment than Xibrom or Bromday, or that it was an improvement over Xibrom and Bromday. They're just saying it's safe and efficacious.

Now, with respect to the allegation of copying, I did take note of Mr. Lipsey's slide where he had listed all of the generic filers, and I believe he stated that this in some way shows that what a great product Prolensa is.

Well, Your Honor, Your Honor is well aware that this is an ANDA litigation. Any evidence of copying by defendants is nothing more than defendants simply complying with FDA regulations requiring that the ANDA product be bioequivalent to the referenced drug. And in fact, Your Honor, the Federal Circuit has expressly recognized that this is not probative of nonobviousness, and I've put it up in the slide.

The Federal Circuit has stated evidence of copying in the ANDA convex is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval. And it says *Bayer Healthcare versus Watson Pharmaceuticals,* 713 F

3rd 1369.

Your Honor, defendants couldn't agree more. This is an ANDA litigation. Of course, there are bioequivalency requirements, and evidence of copying does nothing to rescue the claims from being obvious.

THE COURT: Wasn't the point somewhat different on copying, I thought, that if there's really no difference between Prolensa and its predecessor Bromday, that nothing prevents the defendants from coming out with generic Bromday and as long as it doesn't infringe Prolensa, then you're fine.

MR. MUKARJEE: But this is an ANDA litigation and this is a separate ANDA litigation, Your Honor. And, you know, that notion -- the fact of the matter is, that there are -- part of plaintiff's strategy was also to file scattershot patent applications, so I don't necessarily find that too compelling. But also, there is no generic substitution right now for Bromday, because they discontinued Bromday in the marketplace. So...

THE COURT: There wouldn't be a listed substitution, but your client's laboratory could formulate the generic version of Bromday and sell it, couldn't it?

MR. MUKARJEE: But there's no incentive for a generic or any other, really, pharmaceutical company to do that because the automatic substitution, Your Honor, is what's -- what's really needed. That's the driving force. If, if a

doctor has to write down in -- with that level of specificity, I think effectively, there would be nothing -- there would be nothing to sell. And, in fact, if you even looked at what happened to their prior predecessor product sales, like Bromday and Xibrom during the short period of time when they introduced the follow-on product, it went to nothing, it went to zero. And the same thing here would be the case, too.

So there would be absolutely no incentive for my client or really any generic filer to be doing that because that automatic substitution is important.

THE COURT: And so you would say it's not evidence that there's a dime's worth of difference between Bromday and Prolensa.

MR. MUKARJEE: Correct, Your Honor, that is exactly right, that is exactly right.

THE COURT: Even if you did generic Bromday and gave it a jazzy name?

MR. MUKARJEE: Without -- without that automatic substitution, the jazzy name wouldn't do my client or any of the other generic filer clients any good.

THE COURT: Why not? You could advertise it, you could have doctors go on TV and --

MR. MUKARJEE: In the generic industry, Your Honor, that automatic substitution is one of the driving forces, the driving economic forces, or at least the incentive and that's

the whole point. I mean, if you really look at it, that's the whole point of even the Hatch-Waxman Act, right, it's to introduce these lower price drugs. The whole concept of the automatic substitution is really an outgrowth of that, it's an outgrowth of the fact that the doctor can write this and then you can get that.

THE COURT: Doesn't that prove the point of my question? That if your argument is right, nothing prevents you from introducing that very drug today. You may not enjoy the commercial success of borrowing off of Prolensa's name.

MR. MUKARJEE: Right.

THE COURT: But you would have the substance available on the market at any price that you wanted to set, you know, within the market, and the patients would have the benefit of what you say is everything Prolensa has. You just wouldn't be able to borrow off the Prolensa name, you know, at that point.

MR. MUKARJEE: But, but, economically, with Prolensa -- with Prolensa in the marketplace, so let's -- with Prolensa in the marketplace, as the reference-labeled drug out there, and -- and a generic coming in on a discontinued drug that's out there, even albeit with a jazzy name, I don't see how those two would even really be able to effectively be, you know, comparable certainly in the marketplace. I don't --

THE COURT: Does ANDA promote comparability, or does

it promote, you know, the notion that you make a pharmaceutical breakthrough, you have protection for a limited period of time, and then it goes into the public domain in an orderly way.

MR. MUKARJEE: Right. And that's the way exactly it should, actually, you know, go. But that is exactly what that slide that I was going through kind of goes to show, right? Xibrom came off patent in 2009, and they knew that, and as a result of that, they filed their supplemental NDA and had the same formulation Bromday, changed the indication and was now able to extend the exclusivity for another three years, even though it was the exact same formulation as Bromday. And the same almost can be said with Prolensa, right? They knew the 2013 date was coming to an end. What did they do in 2012? They filed the NDA for Prolensa and four months after they introduced Prolensa into the marketplace, during that interim time, plaintiffs, what are they doing? Their pharmaceutical reps are all over the country promoting Prolensa in favor of Bromday, so that they can now move the Bromday position, so to speak, over to Prolensa.

And once that -- once that actually occurs, they discontinue Bromday, and, therefore, now, inoculate themselves from the automatic substitution with respect to Bromday.

THE COURT: No, I understand your argument.

MR. LIPSEY: Excuse me, Your Honor. I've sat very

patiently listening to this. We had a dispute over what was going to be in here. This sounds very much like an allegation of either unfair competition or antitrust violation, that is unpled, that is unmeritorious and utterly irrelevant to the technical patent issues in this case, and I would like to note my objection to the entire statement to the extent it did not deal with alleged lack of meaning of our articles, as really irrelevant to the patent issues in the case, and quite detrimental to my client and we would move to strike it, Your Honor.

MR. MUKARJEE: Your Honor, the prolonged conversation was an outgrowth of the colloquy between the Court and myself. The slide, the intro slide that I talked about was to also give context. Mr. Lipsey has extolled the virtues of Prolensa and that because of the improvements of Prolensa over prior formulations, that is why physicians are prescribing Prolensa. Well, the fact is that that's not correct, and just as Mr. Lipsey gave context in his view of the facts, as to the history of the development of Prolensa, defendants have, I'm sorry to say, an alternate view and a different story, and that is exactly the manner in which I presented it to you.

THE COURT: All right. I'm going to consider the argument for the limited purpose for which I believe it was originally offered, which is to attempt to demonstrate that the plaintiffs have not made a dramatic change in Prolensa,

and that it allegedly is ---
MR. MUKARJEE: Continuing, yeah.
THE COURT: -- a continuing marketing strategy, and much of our discussion was in response to my question about
02:16 copying, and asking you to comment on the point that Mr. Lipsey had made that if the defendants really believed in their position, why don't they just market their version of Bromday.
MR. MUKARJEE: Thank you, Your Honor, yes.
02:17 Finally, Your Honor, then moving on, finally, I'd like to address plaintiff's allegations of unexpected results. Throughout the course of this litigation, plaintiffs have contended -- throughout the course of this litigation, Your Honor, plaintiffs have contended that tyloxapol purportedly
02:17 has some unexpected stabilizing effect on bromfenac, and I believe that Mr. Lipsey said that this stabilizing effect leads to a wonderful cascade of benefits.
But as discussed by Ms. Holland in detail, one of ordinary skill in the art would know that tyloxapol would have
02:17 this stabilizing effect. And the purported benefits that were outlined in I believe your -- Mr. Lipsey's Slide 49 would naturally have flown from this effect.
Could we queue up Slide 49? Okay.
Your Honor, this was plaintiff's Slide 49 and in fact,
02:18 you will see that while the slide is entitled, benefits

flowing from the use of .02 percent tyloxapol, the evidence will show that getting to .02 percent is simply the result of routine experimentation.
THE COURT: Point 02.
02:18 MR. MUKARJEE: Point 02 percent, I'm sorry, Your Honor. And further, the vast majority of the so-called benefits listed in Slide 49 to the extent they even exist, Your Honor, would be attributable to Prolensa's pH.
Now, before I go into Prolensa's pH profile, I'll also
02:18 just add that Mr. Lipsey here has included increased preservative efficacy as one of the wonderful cascade of benefits, and I don't believe that either claims -- either of the claims at issue have any notion of preservative efficacy. In fact, as Mr. Lipsey had noted and I think Your Honor had
02:19 even noted, we narrowed the issues in this case. So any claims that dealt with preservative efficacy are no longer at issue at this trial. But be that as it may, as I said --
THE COURT: Aren't you saying because they are not covered by dependent Claim 6 or 20?
02:19 MR. MUKARJEE: They are not covered by Claim 6 or 20, Your Honor, the entire notion of preservative efficacy is not there.
But again, be that as it may, the vast majority of these benefits that are listed in Slide 49 is actually, if
02:19 they even exist, would have been attributable to Prolensa's pH

profile, but Your Honor, the problem with that -- could we go to the next slide?
The problem with that, is that Prolensa's pH profile which has been given so much accolade, was actually disclosed
02:19 in the prior art. So Prolensa has a target pH of 7.8 and the prior art, namely the Ogawa '225 patent actually discloses a preferred range of pH 7.5 to 8.4 and in fact, I believe Mr. Lipsey's slide, PDX-1-24 was a slide where he discussed the pH and there was a certain portion that was blown up.
02:20 Well, the exact line right under that blowup portion was what I have quoted here in this slide, that it discloses a preferred pH range of 7.5 to 8.5. So Prolensa's target pH of 7.8 is squarely within the actual disclosed or preferred range that the prior art Ogawa has listed.
02:20 So there may be, you know, exalting of the virtues of Prolensa's pH but that pH was well-known.
And, Your Honor, if you're looking at plaintiff's slide deck, if you go to PDX-1-24, there's a blowup, I believe, that plaintiffs highlighted, and I know that the remainder of the
02:21 patent is in very, very small print, but I can tell you that literally the next line gives the preferred pH range. And if -- Elizabeth, do you have a copy of the patent?
THE COURT: Well, I'm sure it will be discussed.
MR. MUKARJEE: It's there, Your Honor, that I assure
02:21 you. So in any event --

THE COURT: The print is smaller than small.
MR. MUKARJEE: I won't ask why it's created that small on that slide, but in any event, so whatever the virtues are with respect to Prolensa's pH and whatever benefits flow
02:21 from that pH, well, that was already disclosed. The pH profile was already well-known, and further as Ms. Holland stated earlier, the asserted claims, again, much like preservative efficacy, Your Honor, the asserted Claims 6 and 20 are not directed to any particular pH range.
02:21 And while Mr. Lipsey also spoke about Prolensa absolutely minimizing stinging and burning, although I believe in the slide, the exact verbiage was that it effectively eliminates stinging and burning. Stinging and burning had effectively been eliminated by Xibrom already, Your Honor.
02:22 We heard quite a bit about stinging and burning, but I've put up on the slide, Your Honor, there was a study done on Xibrom, actually, and that study showed that 1.4 percent of treated individuals may have experienced burning and stinging with Xibrom. 1.4 percent. 98.6 percent of the population
02:22 experienced no burning or stinging. And any reduction by Prolensa in burning -- burning and stinging for at least, at most, I should say, that insignificant percentage of the population has no bearing on the obviousness determination.
THE COURT: What's the date of this source?
02:23 MR. MUKARJEE: Your Honor, I will get that for you

because I can't read the date on the slide.
Your Honor, do you mind if, just at a break, I can provide --
THE COURT: Aha, you used very small print.
02:23 (Laughter.)
MR. MUKARJEE: Yes. Well, actually, this --
THE COURT: Okay. It's --
MR. MUKARJEE: I'll get it for Your Honor.
But again --
02:23 THE COURT: Would the date matter?
MR. MUKARJEE: Would the date matter on this? No.
THE COURT: Certainly it would have more weight if it was before 2003, wouldn't it?
MR. MUKARJEE: But the whole notion -- ultimately,
02:23 the point of the study was, well, did people complain -- you know, one of the things they looked at was with Xibrom, was there burning and stinging? There was one of plaintiff's main points, that Prolensa reduced the burning and stinging.
Well -- and according to the slide, they effectively
02:23 eliminated burning and stinging. But Xibrom, according to this study alone, says that only 1.4 percent of treated individuals, at most 1.4 percent of treated individuals, even experienced burning and stinging. That is effective elimination of burning and stinging.
02:24 And as to your point on the date, Your Honor, I will

get you that date. But I'm not sure that the date would necessarily matter, because the study itself is just analyzing whether or not Xibrom actually resulted in burning and stinging, and that is actually one of the so-called unexpected
02:24 benefits that plaintiffs purport or allege.
And as Your Honor knows, secondary consideration evidence doesn't necessarily have to be prior art. So if they are alleging that, hey, Prolensa is so much better than Xibrom and it reduces this burning and stinging, with respect to
02:24 secondary considerations, I can come in with evidence showing that, well, that's not exactly true. In fact, people who were treated with Xibrom were not experiencing burning and stinging anyway.
And in any event, Your Honor, defendant's expert,
02:25 Dr. Cykiert will testify that it is impossible to completely eliminate burning and stinging, which might be the reason why Mr. Lipsey in the opening said absolutely minimizing, instead of effectively eliminating, because as Dr. Cykiert puts it, some patients will always experience some degree of transient
02:25 burning and stinging.
And moreover, Your Honor, and this, to me is very probative, the record will show that plaintiffs -- while plaintiffs allege these purported benefits, they never once, not one time compared Prolensa with Xibrom. They never once
02:25 compared Prolensa with Bromday in a head-to-head comparison.

You would think that if we are extolling the virtues of Prolensa, there would be some comparison, Prolensa versus Xibrom, Prolensa versus Bromday, but that never happened. Instead, what actually happened was -- any analysis that was
02:26 ever done was Prolensa versus placebo and the reason that that analysis was done was to simply show that it had the same safety and efficacy, as, guess what? Xibrom and Bromday. That was it. No head-to-head comparison whatsoever, and defendant's expert, Dr. Prausnitz and Dr. Cykiert will testify
02:26 to the probative value of that fact. They will testify as to what it means, also the fact that they did not put in any head-to-head comparison.
Now, Dr. Cykiert will also testify that as a prescribing physician, an ophthalmic surgeon, Prolensa is no
02:26 different from Xibrom or Bromday and, therefore, Your Honor, at trial, plaintiff's reliance on Drs. Trattler and Williams will be shown to be unfounded, and in fact, we believe, Your Honor, that the evidence will show that their opinions related to unexpected results are conjecture and based on anecdotal
02:27 evidence.
For these reasons, Your Honor, defendants submit that Claims 6 and 20 of the '431 patent are obvious in light of -- at least, the Ogawa '225 patent and the Fu EP '984 patent.
Moreover, the evidence will show that Claims 6 and 20
02:27 are duplicative of other of plaintiff's patent claims, and

finally, Your Honor, the evidence will show that none of plaintiff's purported secondary considerations hold any weight against defendant's strong prima facie case of obviousness.
Your Honor, the claims are invalid, and we look forward
02:27 to presenting our evidence at this trial. Thank you.
THE COURT: All right, thank you. And Mr. Lipsey.
MR. LIPSEY: May I utter three sentences before we break for lunch?
THE COURT: Yes, of course.
02:27 MR. LIPSEY: The point I made is that the formulations of Ogawa that are set out there and that are embodied in Bronuck, had no stability problem, based on this reaction between BAC and the active ingredient. They were clear, they were acknowledged to be stable and commercially
02:28 acceptable. There was no problem of the sort that they found for ketorolac in food, and, therefore, the food solution, even if you could translate it from ketorolac to bromfenac was on its face unnecessary.
Second, the pH matters. The whole point of that
02:28 evidence that I showed you when you tried to operate at pH 7, you couldn't get to the low pHs with the Ogawa formulations and that was what the great value of adding tyloxapol was. And lastly, just as a matter of patent law, so we don't get too far off the beam here, positive attributes that flow from
02:29 the invention as claimed are perfectly relevant evidence of

unexpected results and patentability.

If you have a drug that's claimed as a chemical compound and it cures cancer, the fact that it has that property is perfectly acceptable evidence.

02:29 When you have a formulation that allows you to operate at a lower pH than the prior art could get to, that's perfectly acceptable evidence. When you have a formulation which allows you to attain stability that was lower or better than you -- preservative efficacy that was lower and better

02:29 than what you could with the formula -- former formulation, perfectly acceptable evidence. And I just wouldn't want the trial to go forward at least with the perception that there wasn't at least an issue about whether that material was relevant to patentability.

02:29 Thank you very much, Your Honor. The Court has been very patient and I will not --

THE COURT: Do you agree that pH is not part of Claims 6 and 20?

MR. LIPSEY: The formulation that is claimed in 6 and

02:30 20 can be formulated at a lower pH than the formulations that are described in Ogawa, and that difference is a important attribute of those formulations, which bears directly on its patentability. Need not -- this comes up all the time, people say, well, you've had unexpected result as it was cited in the

02:30 claims. The cases are legion. It doesn't have to be recited

in the claims, it has to flow naturally from what is in the claim.

MS. HOLLAND: Your Honor, if I could just respond to that for a moment.

02:30 THE COURT: Okay.

MS. HOLLAND: The way we know that that's not correct is that there were a legion of claims in this case with specific pH limitations that they've dropped. So it's not like there were never any claims here with pH limitations and

02:30 so Mr. Lipsey is saying, well, it doesn't really matter.

There were actually claims here that covered the pH of Prolensa that are no longer being asserted in this case. So we know that there's something about the pH that's different from the general claim. If the pH is a dependent claim, it

02:31 necessarily means that the independent claim is broader and includes not only the pH in the dependent claims, but any pH.

MR. MUKARJEE: And that's precisely right, and that's also the same point with preservative efficacy. There was a whole host of claims that actually had preservative efficacy

02:31 requirements and those claims were dropped. And so Ms. Holland is exactly right, there were actual claims at issue here that had pH, that had a pH range and those were dropped.

But to answer your question, Your Honor, Claims 6 and 20 do not have a pH limitation.

02:31 MR. LIPSEY: The reason --

MS. HOLLAND: Your Honor, I just note --

THE COURT: Just a moment. Mr. Lipsey.

MR. LIPSEY: The reason they were dropped is because it was unnecessary to assert those claims in order to assert

02:31 the patentability deriving from this capability. All it would have done was require us to engage in a whole lengthy stream of additional infringement proof that would have lengthened this trial into something really absurd, and that's the reason those are dropped.

02:32 And the fact that those features may have been explicitly recited in other claims does not mean it's not an attribute that flows naturally from what is recited in these, and that's the standard.

THE COURT: All right. We're only at the beginning

02:32 of the trial.

(Laughter.)

THE COURT: This is something that the parties will have ample chance to explore and to brief, and we will see which legion of cases marches into the courtroom.

02:32 Let's take a break, then, and I think the first witness is going to be actually for the plaintiff.

MR. LIPSEY: Yes, it will be Dr. Williams.

THE COURT: All right. So let's take a break for 15 minutes and then we will resume.

02:32 MR. MUKARJEE: Thank you, Your Honor.

THE COURT: Oh, it's 12 already? Do you want to take a lunch break at this time instead?

MR. HASFORD: Sure.

THE COURT: Why don't we break for lunch from now

02:32 until 1:15.

(LUNCHEON RECESS; 12:05 p.m.)

(Afternoon Session)

(Open Court)

DEPUTY CLERK: All rise.

03:43 THE COURT: Be seated, please.

Good afternoon. Let's proceed.

MR. HASFORD: Good afternoon.

Yes, your Honor. Justin Hasford on behalf of plaintiffs. May we approach to distribute binders for the

03:43 next witness?

THE COURT: Sure.

MR. HASFORD: Our next witness we'll be calling Dr. Robert O. Williams, III.

THE COURT: Okay. Dr. Williams, please come up to

03:43 the witness stand.

(**ROBERT O. WILLIAMS, III**, HAVING BEEN DULY SWORN AS A WITNESS, TESTIFIED AS FOLLOWS:)

(DIRECT EXAMINATION OF ROBERT O. WILLIAMS, III, BY MR. HASFORD)

03:44 DEPUTY CLERK: Thank you. You can be seated, sir.

Please speak into the microphone.
THE COURT: I think you just broke your opponent's back.
MR. HASFORD: I apologize, your Honor.
03:44 MS. HOLLAND: I'm going to assume it was unintentional.
MR. HASFORD: I agree.
May we proceed, your Honor?
THE COURT: Yes.
BY MR. HASFORD:
Q. Good afternoon, Dr. Williams.
A. Good afternoon.
Q. Would you please state your address for the record?
A. My address is 2305A West Lake Drive, that's in Austin,
03:45 **Texas.**
Q. Where are you presently employed?
A. I'm employed at the University of Texas at Austin, College of Pharmacy.
Q. What is your current position at the UT Austin, College
03:45 of Pharmacy?
A. Currently I am the Johnson & Johnson Centennial Chair of Pharmaceutics. I also have an appointment as the division head of the Division of Pharmaceutics.
Q. How long have you been a faculty member at the University
03:45 of Texas?

A. I have been a faculty member since 1995.
Q. Would you please describe the faculty positions that you have held at the University of Texas?
A. Yes, when I started in 1995, I was assistant professor.
03:45 **And through the years I went up in rank to associate professor with tenure and then professor went with tenure.**
Q. Are you currently the division head of the Division of Pharmaceutics?
A. Yes, I am.
03:45 Q. In what field do you specialize?
A. I specialize in the field of pharmaceutics of design and development of drug delivery systems and their characterization.
Q. Does that encompass the design, evaluation, and
03:46 formulation of drug products?
A. Yes, it does.
Q. For how long have you worked in that field?
A. Since approximately 1986.
Q. Would you please turn to PTX-165 in your binder and
03:46 identify that document?
A. I need a binder.
MR. HASFORD: Oh, I apologize.
THE WITNESS: Thank you.
So PTX-165 is a copy of my curriculum vitae.
BY MR. HASFORD:

Q. Does your curriculum vitae accurately reflect your work experience?
A. Yes, it does.
Q. Would you please describe your educational background
03:46 following your graduation from high school?
A. Yes. So following high school, I earned a Bachelor of Science degree in biology from Texas A & M University with special honors. I then earned a Bachelor of Science degree in pharmacy from the University of Texas at Austin with honors.
03:47 **And then I received my Ph.D. degree from the University of Texas at Austin.**
Q. Are you a licensed pharmacist?
A. I am, yes.
Q. What is your understanding as a licensed pharmacist of
03:47 the purpose of the FDA approved package insert that accompanies a marketed drug product?
A. My understanding as a pharmacist is the purpose of the label is to convey directions on the approved product that were approved by FDA.
03:47 Q. What, if any, adverse event information is included in the FDA approved package insert that accompanies a marketed drug product?
MS. HOLLAND: I'm going to object to this, your Honor. As per the conversation we had at the pretrial
03:47 conference and the Order that followed, this is supposed to be

restricted to background on the patent and the products. Now I believe we're getting to opinions on what is in the label on adverse event.
MR. HASFORD: If I could respond, your Honor. We are
03:48 restricting it to background on the patents and the products, necessarily the product is accompanied in its marketed form by package insert. I'm merely asking Dr. Williams a background question about what type of adverse event generally is included in the FDA approved package insert.
03:48 THE COURT: All right. I understand. It's only for background and it's just a question or two.
BY MR. HASFORD:
Q. Do you need me to repeat the question, doctor?
A. Yes.
03:48 Q. What, if any, adverse event information is included in the FDA approved package insert that accompanies a marketed drug product?
A. In the product label there is a section on adverse events that were approved by FDA.
03:48 Q. You testified that you have a Ph.D. in pharmaceutics. What did you do after completing your Ph.D.?
A. Following completion of my Ph.D., I worked in the pharmaceutics industry for about nine years.
Q. At what companies in the pharmaceutics industry did you
03:49 work?

A. I worked at, first of all, at Eli Lilly & Company where I was responsible for development of liquid and solid dosage forms. I then worked at a company called Duramed Pharmaceutics, again I was responsible for development of liquid and solid and semisolid dosage forms. And then I worked at a company called Rhone-Poulenc Rorer, which is now a part of Sanofi, and at that time I worked on development of liquids and semisolids and inhaled products, as well as solid pharmaceutical dosage forms.

Q. Did your work in the pharmaceutical industry include formulation work on aqueous liquid preparations?

A. Yes.

Q. Have you founded or cofounded any pharmaceutical companies?

A. Yes, I have.

Q. What were those?

A. I cofounded a company called PharmaForm in 1996, which was a development services company that did product development and analytical development for a variety of pharmaceutical companies around the world. And then I cofounded a company called Enavail, which was a service company that specialized in particle engineering for a variety of different platform technologies.

Q. What courses have you taught at the University of Texas at Austin?

A. So I teach several courses to the PharmD students, so these are in their first professional year. I teach a course called pharmaceutics, which is generally a course on dosage form, design dosage form just generally. To graduate students I teach four courses, there's three graduate courses that are in -- that cover various aspects of dosage form development, characterization, and manufacturing science. And then I teach a forth course that deals with pharmaceutical entrepreneurship.

Q. Have you conducted any research?

A. I have, yes.

Q. Would you please describe your research?

A. So my research generally involves the development of liquid, semisolid, and solid dosage forms, it could be administered by a variety of routes of administration.

Q. Has your research encompassed work on aqueous liquid preparations?

A. Yes.

Q. Have you published any research articles?

A. I have.

Q. Approximately how many research articles have you published?

A. I have published approximately 400 peer reviewed papers, books, book chapters, abstracts during the course of my career.

Q. Are your publications listed on your curriculum vitae?

A. Yes, they are.

Q. Have you received any honors or awards in connection with your work?

A. I have, yes.

Q. Would you please briefly describe those?

A. Yes. I was elected Fellow of the American Association of Pharmaceutical Scientists. I was also elected Fellow of the American Institute of Medical and Biological Engineering. And then I received our university's highest award for teaching, which is called the Sheffield award.

Q. Have you served as an editor for any scientific journals?

A. I have, yes.

Q. What journals?

A. So from 2000 to 2014, I was editor and chief of a Taylor and Francis Journal called Drug Development and Industrial Pharmacy. And then beginning late 2014 to present I'm the editor and chief of a journal called AAPS PharmSciTech, it's all one word, which is the association -- it's the American Association of Pharmaceutical Scientists, it's one of their three official publications.

Q. Have you consulted for both innovator pharmaceutical companies and generic pharmaceutical companies?

A. Yes, I have.

Q. Have you previously been approved by the court in this

case as an expert in the field of the design, the evaluation, and formulation of drug products encompassing pharmaceutical formulation and pharmaceutical development?

A. My understanding is I was, yes.

MR. HASFORD: Your Honor, at this time plaintiffs offer Dr. Williams as an expert in the field of the design, evaluation, and formulation of drug products encompassing pharmaceutical formulation and pharmaceutical development.

THE COURT: Any objection or do you wish to *voir dire*?

MS. HOLLAND: No, your Honor.

THE COURT: Okay. The Court will recognize Dr. Williams as an expert in the fields in which he's offered.

MR. HASFORD: Thank you.

MR. MUKERJEE: Your Honor, may I ask one logistical question? Can we perhaps make it such that -- I don't want a situation where every time there's an objection made necessarily that Innopharma would have to stand up and say same objection or vice versa, so perhaps we could, just for simplicity, make it if one defendant makes an objection, unless otherwise noted the objection carries for both defendants. Would that work with your Honor?

THE COURT: Okay. Do the plaintiffs have any objection?

MR. HASFORD: We have no objection to that, your

Honor.

THE COURT: All right. So it will be understood that if an attorney for either defendant makes an objection, that it will be deemed an objection by all defendants. Unless for some reason you wish to distinguish yourself from their objection and not assert it, in which case you'll have to rise and say so.

MR. MUKERJEE: Correct, your Honor. And, again, my apologies for interrupting.

BY MR. HASFORD:

Q. Let's now discuss the patent-in-suit. Would you please turn to JTX-1 in your binder and identify that document?

THE COURT: Excuse me, are you offering his curriculum vitae into evidence?

MR. HASFORD: Oh, I'll be offering all these into evidence. As your Honor will recall --

THE COURT: That's right, at the end.

MR. HASFORD: -- we will offer it at the end.

THE WITNESS: So JTX-1 is a copy of U.S. Patent 8,129,431.

BY MR. HASFORD:

Q. If I refer to U.S. Patent No. 8,129,431 as the '431 patent, will you understand what I mean?

A. **Yes.**

Q. Did you review the '431 patent in connection with your

opinions in this case?

A. **Yes, I did.**

Q. Would you now please turn to JTX-6 in your binder and identify that document?

A. **JTX-6 is a copy of the prosecution history for the '431 patent.**

Q. Did you review the prosecution history of the '431 patent in connection with your opinions in this case?

A. **Yes, I did.**

Q. Please turn back in your binder to JTX-1, which is the '431 patent. What is the title of the '431 patent?

A. **The title of the '431 patent is Aqueous Liquid Preparation Containing 2-amino-3-(4 bromobenzoyl)phenylacetic acid.**

Q. By what other name is 2-amino-3-(4 bromobenzoyl)phenylacetic acid known?

A. **That's known as bromfenac.**

Q. Who are the named inventors of the '431 patent?

A. **The named inventors are Shirou Sawa and Shuhei Fujita.**

Q. Who is the assignee of the '431 patent?

A. **The assignee is Senju Pharmaceutical Company.**

Q. Based on your review of the '431 patent, did you develop an opinion as to the qualifications of a person of ordinary skill in the art would have with respect to that patent?

A. **Yes, I did.**

Q. Have you prepared a demonstrative of your opinion with respect to the qualifications of a person of ordinary skill in the art?

A. **I did.**

Q. Let me direct your attention to PTD-2-1 on the screen. What is your opinion regarding a person of ordinary skill in the art with respect to the '431 patent?

A. **So in my opinion a person of ordinary skill in the art would have a bachelors -- at least a bachelors degree in the fields of pharmaceutical chemistry, chemistry, or a related discipline, with about three to five years of work experience in the area or a comparable level of education and training and alternatively a comparable level of overall experience in designing, evaluating and/or administering pharmaceutical formulations obtained by some combination of education such as, for example, a degree in medicine with work experience.**

Q. Please turn back in your binder to JTX-1, which is the '431 patent. Let me direct your attention again to the paper bearing Bates No. PROL followed by a sting of zeros and then 2, it's the face of the '431 patent. In particular let me direct your attention to the left-hand column under the heading Foreign Application Priority Date. Do you see that it say the Japanese Patent Application No. 2003-12427 was filed on January 21, 2003?

A. **I see that, yes.**

Q. Were you at least a person of ordinary skill in the art of the '431 patent as of January 21, 2003, according to the definition that you just gave?

A. **Yes, I was.**

Q. On what date did the '431 patent issue?

A. **The date of the patent is March 6, 2012.**

Q. Let me direct your attention to Column 1 of the '431 patent, it's on the next page, and in particular to the section entitled Background Art. Specifically let me direct your attention to the first paragraph of that section in Column 1 from Lines 24 to 47. What does the chemical structure in Column 1 of the '431 patent depict?

A. **The patent refers to the chemical structure as being bromfenac.**

Q. What type of drug is bromfenac?

A. **The patent states in -- well, it's a nonsteroidal anti-inflammatory agent it states in Line 40.**

Q. Is nonsteroidal anti-inflammatory drug also abbreviated NSAID?

A. **Yes, it is.**

Q. According to the paragraph in Column 1, Lines 24 to 47 of the specification of the '431 patent, against what conditions is bromfenac effective?

A. **So the patent states, really starting about Line 40, says, "they," and it's referring to bromfenac and salts or**

hydrates of bromfenac. It says, "they are effective against inflammatory diseases of anterior or posterior segment of the eye such as blepharitis, conjunctivitis, scleritis, and postoperative inflammation in the field of ophthalmology."

04:00 Q. Let me direct your attention to the bottom of the paragraph and in particular to Lines 44 to 45 in Column 1 of the '431 patent. Does the '431 patent indicate whether or not bromfenac had ever been used previously in eyedrops?

A. Yes, it does. It states that bromfenac as a "sodium salt has been used in the form of eyedrops." And then it cites to a 2001 New Drugs in Japan article.

Q. Would you please turn to JTX-210 in your binder and identify that document?

A. JTX-210 is a certified translation of the article New Drugs in Japan article.

Q. Is that the same article cited in Column 1 of the '431 patent?

A. It is, yes.

Q. Did you review JTX-210 in connection with your opinions in this case?

A. I did, yes.

Q. Let me direct your attention to the page in JTX-210 bearing Bates Number PROL 0364735. In particular let me direct your attention to the middle row of the box toward the top of the page. I apologize the Bates number should be 732.

What product does JTX-210 disclose?

A. JTX-210 discloses here Bronuck® Ophthalmic Solution and Bronuck®.

Q. Let me direct your attention to the box in the right hand column of the page in JTX-210 bearing Bates No. PROL 0364732, in particular let me direct your attention to the second row of the box entitled Additives and specifically to additive polysorbate 80. What is polysorbate 80?

A. Polysorbate 80 is a type of surfactant, nonionic surfactant.

Q. What is a surfactant?

A. A surfactant is a molecule that reduces interfacial tension between two phases, generally used as a wetting agent or solubilizer depending on the use.

Q. Is a surfactant a compound similar to a soap?

A. Yes.

Q. Does it help things dissolve in water that might otherwise not be soluble?

A. It could, yes.

Q. What's a nonionic surfactant?

A. A nonionic means that it's a neutral charge, it's not positive or negative but it's neutral when dissolved.

Q. By further way of background were bromfenac products containing polysorbate 80 ever introduced into the United States market?

A. They were, yes.

Q. What bromfenac products containing polysorbate 80 were introduced into the United States market?

A. As we heard this morning, it was Xibrom® and Bromday®.

Q. Is it your understanding that the Xibrom® was introduced in 2005?

A. It is, yes.

Q. Is it your understanding that Bromday® is was introduced in 2010?

A. Yes.

Q. Please turn back in your binder to JTX-1, which is the '431 patent, let me direct your attention to Column 1, Lines 48 to 53. What, if anything, does this paragraph of the '431 patent disclose about the polysorbate 80 containing eyedrop formulations of bromfenac that we just discussed?

A. So in this passage in the '431 patent, this is referring, it's says, "the eyedrop as mentioned above is designed to stabilize bromfenac by means of adding a water soluble polymer," and as an example, polyvinylpyrrolidone or polyvinyl alcohol, "and a sulfite." And it mentions sodium sulfite or petroleum sulfite and it reference or cites what's been referred to this morning as the '225 Ogawa patent for that statement.

Q. Would you please turn to JTX-147 in your binder and identify that document?

A. JTX-147 is a copy of U.S. patent 4,910,225.

Q. Is JTX-147 the same United States Patent 4,910,225 that's cited in Column 1, Lines 48 to 53, of the '431 patent?

A. It is, yes.

Q. Who is the first named inventor of JTX-147?

A. Ogawa is the first named inventor.

Q. If I refer to JTX-147 as the '225 patent or Ogawa patent, will you understand what I mean?

A. Yes.

Q. Did you review the Ogawa patent in connection with your opinions in this case?

A. I did, yes.

Q. Who are the assignees of the Ogawa patent?

A. The assignees of the Ogawa patent is Senju Pharmaceutical and A.H. Robbins Company.

Q. Please turn back in your binder to JTX-1, which is the '431 patent. Let me direct your attention to Column 2 of the '431 patent and in particular to the section entitled Disclosure of the Invention. Specifically let me direct your attention to the first paragraph of that section in Column 2, Lines 14 through 22. According to the specification of the '431 patent, what was an object of the invention?

A. So it's stated here an object of the intention was an aqueous liquid preparation that comprises bromfenac, which is stable within a pH range giving no irritation to eyes, and

when a preservative is included in that aqueous liquid preparation such as benzalkonium chloride, the preservative effect does not substantially deteriorate over time.

Q. You mentioned benzalkonium chloride. What is benzalkonium chloride?

A. Benzalkonium chloride is an example of a cationic surfactant.

Q. Is benzalkonium chloride also a type of preservative?

A. It is, yes.

Q. Is benzalkonium chloride a quaternary ammonium salt?

A. Yes.

Q. Is benzalkonium chloride commonly abbreviated BAC, BAK, or BKC?

A. It is in the literature, yes.

Q. Let me direct your attention to Column 2, Lines 34 to 47, of the '431 patent. According to the specification, how did the inventors achieve the objective?

A. So, as described here, the inventors found that by adding what they call an alkyl aryl polyether alcohol type polymer, and the example is tyloxapol, or another type of excipient called polyethylene glycol fatty acid ester, such as polyethylene glycol monostearate, to that aqueous liquid preparation containing bromfenac, that aqueous liquid solution becomes stable within pH range giving no irritation to eyes. And it notes that the change in bromfenac over time can be

inhibited. And, furthermore, when the aqueous solution contains a preservative, that that preservative effect is maintained for a long period of time.

Q. You mentioned tyloxapol. What is tyloxapol?

A. Tyloxapol is an example of a nonionic surfactant.

Q. Let me direct your attention to the portion of the '431 patent from Column 4, Line 65, to Column 5, Line 15, and in particular to the chemical structure in Column 5. What does the chemical structure in Column 5 of the '431 patent depict?

A. The chemical structure of the patent states that it's tyloxapol.

Q. Are tyloxapol and polysorbate 80 the same or different nonionic surfactants?

A. They're different.

Q. Was tyloxapol used in any of the Bronuck®, Xibrom®, or Bromday® formulations?

A. No.

Q. What nonionic surfactant was used in the Bronuck®, Bromday®, and Xibrom® formulations?

A. That would be polysorbate 80.

Q. Let me direct your attention back to Column 2, Lines 34 through 47, of the '431 patent. At Column 2, Lines 43 through 44 of the '431 patent states that the change of the bromfenac over time can inhibited. What does this mean?

A. So to the person of ordinary skill in the art, when the

patent states that the change in bromfenac over time can be inhibited, it's talking about chemical degradation, so inhibition of chemical degradation of bromfenac.

Q. Column 2, Lines 46 through 47, of the '431 patent states that the preservative effect of said preservative can be inhibited for a long period of time. What does this mean?

A. So what this means to a person of ordinary skill in the art is that the deterioration, so the decrease in the preservative effect, the preservative that's being used is inhibited for a long period of time. So, in other words, that aqueous liquid solution maintains its ability to be preserved.

Q. What is preservative effect or preservative efficacy?

A. So that's understood by a person of ordinary skill in the art to refer to the ability of a liquid to not support microbial growth over its shelf life.

Q. Let me direct your attention back to the entirety of the paragraph at Column 2, Lines 34 for 47, of the '431 patent. What were the inventors finding, if anything, from the use of tyloxapol in bromfenac ophthalmic solutions?

A. Based on this, a person of ordinary skill in the art would understand that the patentees found that when tyloxapol is included with bromfenac in this aqueous liquid solution, that it becomes stable within pH range, chemically stable giving no irritation to the eyes and that it's able to maintain its preservative effect if there's a preservative

present.

Q. After the '431 patent issued, was a bromfenac product containing tyloxapol that embodied the '431 patent introduced into the United States market?

A. There was one, yes.

Q. What bromfenac product containing tyloxapol was introduced into the United States market after the '431 patent issued?

A. That's Prolensa®.

Q. Did that happened in 2013?

A. Yes.

Q. Prior to 2003, to your knowledge was tyloxapol ever used as a stabilizer in ophthalmic solutions to increase chemical stability?

A. Not to my knowledge, no.

Q. Prior to 2003, to your knowledge was tyloxapol ever used as a stabilizer in ophthalmic solutions to increase preservative efficacy?

A. Not to my knowledge, no.

Q. Prior to 2003, to your knowledge was tyloxapol ever used in a marketed ophthalmic solution of a nonsteroidal anti-inflammatory drug?

A. Not to my knowledge, no.

Q. Let me direct your attention to Column 6, Lines 11 through 31, of the '431 patent and in particular Lines 11 to

13. What other types of excipients may be included in the tyloxapol containing formulation of bromfenac of the '431 patent?

A. So in that passage a person of ordinary skill in the art would understand that the liquid, aqueous liquid solution could also contain various additives and it mentions isotonics, buffers, thickeners, stabilizers, chelating agents, pH controlling agents, perfumes, and the like can be appropriately added.

Q. The '431 patent refers to isotonic. What is isotonic?

A. An isotonic agent is one that's added to a liquid solution to maintain the same osmotic pressure to the tissue that it's being applied to or in contact with.

Q. Why is it important to maintain the same osmotic pressure between the aqueous liquid eyedrop preparation and the fluid in the eye?

MS. HOLLAND: Your Honor, I have an objection again. I think we are veering into expert testimony here. I think the question was the purpose of isotonic substance in the patent.

MR. HASFORD: I think that's background.

THE COURT: I'll sustain the objection.

MS. HOLLAND: Thank you.

BY MR. HASFORD:

Q. What are some examples of isotonics that may be included

in the bromfenac formulations of the '431 patent?

A. Examples for isotonics include sodium chloride, potassium chloride, glycerin, mannitol, sorbitol, boric acid, glucose, propylene glycol, and it says the like.

Q. The '431 patent also refers to buffers. What are some examples of buffers that may be included in the bromfenac formulations of the '431 patent?

A. Examples of buffer include phosphate buffer, a borate buffer, citrate buffer, tartrate buffer, acetate buffer, boric acid, borax, amino acids, and the like.

Q. The '431 patent also refers to thickness. What are some examples of thickness that may be included in the bromfenac formulations of the '431 patent?

A. Thickness listed in the '431 patent include polyvinylpyrrolidone, carboxymethylcellulose, carboxypropyl cellulose, hydroxymethyl cellulous, hydroxypropyl cellulose, hydroxypropylmethylcellulous, polyvinyl alcohol, sodium polyacrylate, and the like.

Q. The '431 patent refers to polyvinylpyrrolidone. Is polyvinylpyrrolidone also referred to as povidone or PVP?

A. It is in the literature, yes.

Q. The '431 patent also refers to stabilizers. What is an example -- actually let me direct your attention to Column 6, Lines 25 through 26, of the '431 patent. What is an example of stabilizers that is used in bromfenac formulations of the

'431 patent?

A. Stabilizers include sodium sulfite as an example of sulfites.

Q. The '431 patent also refers to chelating agents. What are some examples of chelating agents that may be included in the bromfenac formulations of the '431 patent?

A. Chelating agents include sodium edetate, sodium citrate, condensed sodium, phosphate, and the like.

Q. The '431 patent also refers to pH controlling agents. What are some of the examples of pH controlling agents that may be included in the bromfenac formulations of the '431 patent?

A. PH controlling agents include hydrochloric acid, sodium hydroxide, phosphoric acid, acetic acid, and the like.

Q. Let me direct your attention to Column 6, Line 39 through 41, of the '431 patent, what pH ranges are set forth for the bromfenac formulations of the '431 patent?

A. The pH range described in Column 6 is about 6 to 9 and then it says preferably 7 to 9, especially about 7.5 to 8.5.

Q. Let me direct your attention to Experimental Example 1 of the '431 patent, which is at Column 7, Line 7, through Column 8, Line 2. What does Experimental Example 1 of the '431 patent report?

A. Experimental Example 1 reports a stability test for bromfenac sodium and it compares different examples of the

invention to a Comparison Example 1.

Q. Is it your understanding that Experimental Example 1 of the '431 patent reports the results of chemical stability testing conducted on bromfenac ophthalmic solutions?

A. The person of ordinary skill in the art seeing the results in Table 1 would understand this is chemical stability.

Q. What storage conditions were used in Experimental Example 1 of the '431 patent?

A. The experimental conditions are stability is at 60 degrees C for four weeks.

Q. What is the significance, if anything, of the use of storage condition of 60 degrees Celsius for four weeks in Experimental Example 1 of the '431 patent?

A. A person of ordinary skill in the art --

MS. HOLLAND: I'm going to object again. This is opinion testimony. I'll tell you, your Honor, it's in this section of Dr. Williams' report that talks about unexpected results. So I think it's more appropriate to have this testimony when Dr. Williams gets up to testify again and it's appropriate to talk about unexpected results.

MR. HASFORD: We're doing this as background, your Honor. I think it appropriate for him to explain what the '431 patent teaches on these items.

THE COURT: All right. I'll permit it.

BY MR. HASFORD:
Q. Shall I re-ask the question?
A. **No. Thank you. So, a person of ordinary skill in the art would understand, when these aqueous liquid solutions are stored at 60 degrees C for four weeks, that that is a condition of what's referred to as accelerated stability conditions.**
Q. At what pH are the formulations that are used in experimental example 1 of the '431 patent formulated?
A. **Each of the four liquids are noted at pH 7.**
Q. What is the significance, if anything, of the fact that the formulations that are used in experimental example 1 of the '431 patent were formulated at pH 7?
A. **The significance is that at pH 7 bromfenac is, as shown in the '225 Ogawa patent, bromfenac is susceptible to chemical degradation.**
Q. Does this better allow the relative chemical stability of the formulations to be measured?
A. **It does, yes.**
Q. Do the results in experimental example 1 relate to the '431 patent's teaching --
MR. MUKERJEE: Your Honor, I have to object to that. This is now clearly going into expert testimony territory.
THE COURT: I think so, and the last question was also quite leading. Describing the patent is different from

saying why are these things --
MR. MUKERJEE: Significant.
THE COURT: -- significant for a step forward. There will be a point in the case, of course, where the plaintiff will be able to put on that case. I'll sustain the objection.
MR. MUKERJEE: Thank you, your Honor.
BY MR. HASFORD:
Q. Do the results in experimental example 1 relate to the '431 patent's teaching that tyloxapol chemically stabilized bromfenac in the aqueous liquid preparations of the '431 patent?
MR. MUKERJEE: Same objection.
MR. HASFORD: I think I can ask whether they relate to that, your Honor.
THE COURT: All right. I'll permit it.
THE WITNESS: The results do support the combination of bromfenac sodium and tyloxapol in samples A-01, 2 and 3.
BY MR. HASFORD:
Q. Let's discuss these results further. First let me direct your attention to Table 1 of the '431 patent which is at column 7, lines 40 through 55. What are the components of the formulation of comparison example 1 used in experimental example 1 of the '431 patent?
A. **The components of comparison example 1 include bromfenac sodium, boric acid, benzalkonium chloride, polysorbate 80, and**

then it's added to a final volume with sterile purified water.
Q. What amounts of the components are present in the formulation of comparison example 1 of experimental example 1 of the '431 patent?
A. **Bromfenac sodium is present at .1 grams per hundred ml. Boric acid is at 1.5 grams per hundred ml. Benzalkonium chloride is at .005 grams per hundred ml. Polysorbate 80 is at 0.15 grams per hundred ml. And then the final volume is added up to 100 mls with sterile purified water.**
Q. Was polysorbate 80, which is used in comparison example 1, also used in the Bronuck, Xibrom® and Bromday® formulations?
A. **Yes.**
Q. What remaining percent of bromfenac was measured in the formulation of comparison example 1 in experimental example 1 of the '431 patent after storage at 60 degrees Celsius for four weeks?
A. **The remaining rate reported as 51.3 percent.**
Q. What are the components of formulation A-02 in experimental example 1 of the '431 patent?
A. **The components of A-02 are bromfenac sodium, boric acid, benzalkonium chloride, tyloxapol, and then sterile purified water to add up to volume.**
Q. What amounts of the components are present in formulation A-02 of experimental example 1 of the '431 patent?

A. **A-02 contains .1 grams per hundred mls of bromfenac sodium, contains boric acid at 1.5 grams per hundred ml, contains benzalkonium chloride at .005 grams per hundred ml, contains tyloxapol at 0.15 grams per hundred ml, and then the final is added up to volume with sterile purified water.**
Q. How does formulation A-02 differ from the formulation of comparison example 1 in experimental example 1 of the '431 patent?
A. **The two, the comparison example 1 and formulation A-02 differ in the polysorbate 80 as contained in comparison example 1 and tyloxapol as contained in formulation A-02.**
Q. Are all the other components the same?
A. **Yes.**
Q. What remaining percent of bromfenac was measured in formulation A-02 in experimental example 1 of the '431 patent after storage at 60 degrees Celsius for four weeks?
A. **The remaining rate of bromfenac sodium is 73.8 percent.**
Q. What are the components of formulation A-03 in experimental example 1 of the '431 patent?
A. **A-03 has bromfenac sodium, boric acid, benzalkonium chloride, tyloxapol and sterile purified water.**
Q. What amounts of the components are present in formulation A-03 of experimental example 1 of the '431 patent?
A. **The amounts are bromfenac sodium at .1 grams per hundred ml, boric acid at 1.5 grams per hundred ml, benzalkonium**

chloride at .005 grams per hundred ml, tyloxapol is .02 grams per hundred ml, and then the final volume is added up with sterile purified water to 100 mls.

Q. How does formulation A-03 differ from the formulation of comparison example 1 in experimental example 1 of the '431 patent?

A. It differs in it contains -- A-03 contains tyloxapol whereas comparison example 1 contains polysorbate 80.

Q. Are all the other formulation components the same?

A. They are, yes.

Q. How does formulation A-03 differ from formulation A-02 in experimental example 1 of the '431 patent?

A. A-02 and A-03 are the same except for the amounts of tyloxapol; A-03 having less, .02 grams compared to 0.15 grams tyloxapol in formulation A-02.

Q. What remaining percent of bromfenac was measured in formulation A-03 in experimental example 1 of the '431 patent after storage at 60 degrees Celsius for four weeks?

A. The remaining percent of bromfenac is 89.6 percent.

Q. How, if at all, do the results of experimental example 1 of the '431 patent relate to the '431 patent's teaching that tyloxapol chemically stabilized bromfenac?

A. A-02 and A-03 with the presence of tyloxapol, you have a higher bromfenac chemical amount, potency, compared to comparison example 1 with polysorbate 80.

Q. And how did the remaining rates compare between formulation A-02 with .15 weight per volume percent tyloxapol versus formulation A-03 with 0.02 weight per volume percent tyloxapol?

A. So, from Table 1 the A-03 with .02 grams per hundred ml of tyloxapol is 89.6, so it's a much greater amount of bromfenac potency compared to with the higher amount of tyloxapol.

Q. Let me direct your attention to the passage beneath Table 1 of the '431 patent at column 7, and in particular to the sentence beginning at line 59 beginning "As is apparent." What, if any, conclusion is drawn in the '431 patent from the data in experimental example 1?

A. So, here the patent states that based on the data, the stability test that was conducted at pH 7 at 60 degrees C stored for four weeks, the bromfenac in the eyedrops was stable in the order of tyloxapol-containing, was more stable than the polyoxyl 40 stearate-containing liquid, which both of those were more stable than the polysorbate 80-containing preparation.

Q. Let me direct your attention to the next sentence of the '431 patent at column 7 beginning at line 65. What, if any, further conclusion is drawn in the '431 patent from the data in experimental example 1?

A. Here the patent states that with respect to the A-02 and

A-03 from Table 1, that bromfenac made with .02 weight percent of tyloxapol is more stable with regards to the bromfenac content than the .15 weight percent tyloxapol containing A-02 liquid preparation.

Q. Let me now direct your attention to experimental example 2 of the '431 patent, which is at column 8, lines 5 through 49. What does experimental example 2 of the '431 patent report?

A. So, Table 2 reports stability tests for different liquid formulations, either containing tyloxapol or containing polyoxyl 40 stearate.

Q. At approximately what pH are the formulations that are used in experimental example 2 of the '431 patent formulated?

A. The pH of these formulations is generally like 8.15 to 8.19.

Q. Do the results in experimental example 2 relate to the '431 patent's teaching that tyloxapol chemically stabilized bromfenac in the aqueous liquid preparations of the '431 patent?

A. Yes.

Q. Let's discuss these results further. First let me direct your attention to Table 2, which is in column 8 of the '431 patent. What are the components of formulation A-04 in experimental example 2 of the '431 patent?

A. So, formula A-04 contains bromfenac sodium, boric acid,

borax, benzalkonium chloride, tyloxapol, polyvinylpyrrolidone, specifically K-30 grade, sodium edetate, and then the formula can contain either sodium hydroxide -- well, could contain sodium hydroxide sufficient to adjust the pH to the 8.17, and then the final volume is made up with sterile purified water to 100 ml.

Q. What amounts of the components are present in formulation A-04 of experimental example 2 of the '431 patent?

A. Bromfenac sodium is present at .1 grams, boric acid at 1.1 grams, borax at 1.1 grams, benzalkonium chloride at .005 grams, tyloxapol at .02 grams, polyvinylpyrrolidone is at 2.0 grams, sodium edetate is at .02 grams, and then the -- the sodium hydroxide could be used to adjust the pH, and then that total volume is added up to 100 mls using sterile purified water.

Q. What remaining percent of bromfenac was measured in formulation A-04 in experimental example 2 of the '431 patent after storage at 60 degrees Celsius for four weeks?

A. That's 92.6 percent.

Q. What are the components of formulation A-05 in experimental example 2 of the '431 patent?

A. Formulation A-05 contains bromfenac sodium, boric acid, borax, benzalkonium chloride, tyloxapol, polyvinylpyrrolidone, K-30, sodium edetate, may contain sodium hydroxide to adjust the pH, and then that is -- sterile water -- sorry, sterile

purified water is used to adjust the final volume.
Q. What amounts of the components are present in formulation A-05 of experimental example 2 of the '431 patent?
A. The bromfenac sodium lists .1 gram, boric acid, 1.1 gram, borax, 1.1 gram, benzalkonium chloride, .005 gram, tyloxapol .05 gram, polyvinylpyrrolidone, 2 gram, sodium edetate, .02 gram, and then it may contain sodium hydroxide to adjust the pH, and then the final volume is added up with sterile purified water to 100 mls.
Q. What remaining percent of bromfenac was measured in formulation A-05 in experimental example 2 of the '431 patent after storage at 60 degrees Celsius for four weeks?
A. 90.9 percent.
Q. What are the components of formulation A-06 in experimental example 2 of the '431 patent?
A. A-06 contains bromfenac sodium, boric acid, borax, benzalkonium chloride, tyloxapol, polyvinylpyrrolidone, sodium edetate, it may contain sodium hydroxide to adjust the pH, and sterile purified water to adjust the final volume to 100 ml.
Q. What amounts of the components are present in formulation A-06 of experimental example 2 of the '431 patent?
A. Bromfenac sodium is at 0.1 gram, boric acid at 1.1 gram, borax at 1.1 gram, benzalkonium chloride at .005 gram, tyloxapol at .03 gram, polyvinylpyrrolidone at 2 gram, sodium edetate at .02 gram, and then sodium hydroxide may be used to

adjust the final pH, and the final volume is added up with sterile purified water.
Q. What remaining percent of bromfenac was measured in formulation A-06 in experimental example 2 of the '431 patent after storage at 60 degrees Celsius for four weeks?
A. It's 92.0 percent.
Q. How do formulations A-04, A-05 and A-06 of the '431 patent differ?
A. They differ in the amount of tyloxapol that's present in each of the aqueous liquid solutions.
Q. Otherwise, are they all the same?
A. They are, yes.
Q. How, if at all, do the results of experimental example 2 of the '431 patent relate to the '431 patent's teaching that tyloxapol chemically stabilized bromfenac?
A. So, it was shown by the potency value the remaining rate of bromfenac sodium when tyloxapol is used in this aqueous liquid solution, it shows that the remaining rate is at the values that it's at, in the low 90 percents.
Q. Do any of the formulations of experimental example 2 of the '431 patent use sodium sulfite?
A. No.
Q. Let me direct your attention to the passage beneath Table 2 of the '431 patent at column 8, and in particular to the sentence at line 43 beginning "As is apparent." What, if any,

conclusion is drawn in the '431 patent from the data in experimental example 2?
A. So, what's stated here in the patent is that based on the stability data or the potency of bromfenac in Table 2, the bromfenac potency in the compositions containing tyloxapol at .02, .03, and .05 weight percent is not less than 90 percent after storage at 60 degrees C for four weeks, and it states, the patent states that this indicates that those compositions have sufficient stability for eyedrops.
Q. Let me now direct your attention to experimental example 3. Actually -- yes, experimental example 3 of the '431 patent. It's going to be at column 8, line 51, through column 10, line 50. What does experimental example 3 of the '431 patent report?
A. So, experimental example 3 takes A-04, A-05 and A-07 from experimental example 2 and performs preservative effectiveness testing on them, and that's what's reported.
Q. Do the results in experimental example 3 relate to the '431 patent's teaching that tyloxapol contributes to maintaining the preservative efficacy of the aqueous liquid preparations of the '431 patent?
A. It does, yes.
Q. Was the testing in experimental example 3 of the '431 patent conducted according to European Pharmacopeia criteria?
A. Yes, according to EP criteria A and B.

Q. By way of background, is it your understanding that the European Pharmacopeia is a standard reference used in connection with drug formulation?
A. It is, yes.
Q. Generally speaking, what is the purpose of preservative efficacy testing using European Pharmacopeia criteria?
A. So, the preservative efficacy testing is a test that's done to show the ability of that liquid to maintain its ability to act as a preservative, maintain sterility.
Q. In maintaining sterility are you referring to antimicrobial stability?
A. Yes.
Q. Is there also a separate U.S. Pharmacopeia?
A. There is, yes.
Q. Do you understand that the U.S. Pharmacopeia has different preservative efficacy standards from the European Pharmacopeia?
A. Yes.
Q. Do you understand that the preservative efficacy standards of the European Pharmacopeia are more demanding than the preservative efficacy standards of the U.S. Pharmacopeia?
A. Yes.
MR. MUKERJEE: Your Honor, I'm going to object to this. I don't understand what preservative efficacy has anything to do with the trial. As we had indicated even in

the opening, none of the claims require any preservative efficacy. So, even from a background perspective, I don't quite understand it.

MR. HASFORD: Your Honor, it's a property of the claim formulation. The Federal Circuit has repeatedly said that properties of the claim formulation are relevant. They're set forth in the background of the patent. We're merely doing background at this point.

MR. MUKERJEE: Even those claims that even have pharmacopeia requirements were European Pharmacopeia requirements. So, as to whether or not U.S. Pharmacopeia requirements are more stringent or less stringent, I still fail to see any relevance of that, particularly in light of the way we have streamlined this case.

MR. HASFORD: Your Honor, it is purely background. Their expert does not dispute that the U.S. Pharmacopeia standards are less demanding than the European Pharmacopeia standards. Again, it's just by way of background to set forth what the European Pharmacopeia is that's being testified about.

MR. MUKERJEE: And therein lies my problem. He's referencing expert testimony right now, and again, the whole point of this is just background information.

MR. HASFORD: I'm merely pointing out, your Honor, that their expert has not disputed this.

THE COURT: Well, if it is pointing out areas that are not in dispute, it might be helpful in framing what we are talking about in this '431 patent, so I'll permit it.

BY MR. HASFORD:

Q. Let me direct your attention to Table 3-1 and Table 3-2 in experimental example 3 of the '431 patent which are in columns 9 and 10. What does Table 3-1 of the '431 patent report?

A. Table 3-1 reports the results of this preservative efficacy test for formulation A-04 from experimental example 2.

Q. What does Table 3-2 of the '431 patent report?

A. Likewise, Table 3-2 reports the same for formulation A-05 from experimental example 2.

Q. Let me direct your attention to column 9, lines 47 to 51 of the '431 patent. According to the '431 patent, what conclusions were drawn as to whether formulation A-04 satisfied the European Pharmacopeia preservative efficacy standards?

A. So, the '431 patent states that based on the results presented in Tables 3-1, which was A-04, that composition A-04 was found to be compatible with EP criteria A.

Q. Do you understand that formulation A-04 also satisfied the EP criteria B standard?

A. Yes.

Q. According to the '431 patent, what conclusions were drawn as to whether formulation A-05 satisfied the European Pharmacopeia preservative efficacy standards?

A. So, the patent states that A-05 was found to be compatible with EP criteria B.

Q. Do you understand that the European Pharmacopeia criteria A standard is more demanding than the European Pharmacopeia B standard?

A. Yes.

Q. How, if at all, do the results of experimental example 3 of the '431 patent relate to the '431 patent's teaching that tyloxapol contributes to maintaining the preservative efficacy of the aqueous liquid preparations of the '431 patent?

A. So, the findings of the '431 patent as exemplified by the results in experimental example 3 show that over the course of this, of the samples stored at 60 degrees C for four weeks, these compositions maintain their ability to have preservative efficacy.

Q. Let me direct your attention to the claims of the '431 patent which begin at column 11. In reviewing the '431 patent, did you also consider the claims listed in columns 11 to 14?

A. I did, yes.

Q. Did you gain an understanding of what is claimed, generally speaking, in the '431 patent?

A. Yes.

Q. What is your understanding of what is claimed, generally speaking, in the '431 patent?

MS. HOLLAND: Objection, your Honor. There is no such thing claimed, generally speaking. Claims define the scope of the protected invention, and we can't look at them as a general matter. And in addition, there are only two of them that are actually still in the case.

MR. HASFORD: I think he can provide his general understanding of what the patent sets forth, your Honor.

THE COURT: No, I'll sustain the objection. I think the question could be reformulated. He's giving very detailed explanations of what the patent means, and so I don't think a general one is called for.

MR. HASFORD: I'll go to the two patents that are currently at issue in this trial.

BY MR. HASFORD:

Q. Let me direct your attention to claim 6, and that's at column 12. Do you understand that claim 6 depends from claim 4 which further depends from claim 3 which further depends from independent claim 1?

A. Yes.

Q. Have you prepared a demonstrative showing the elements of claim 6 in its independent form?

A. I have.

Q. Let me direct your attention to PTD 2-2 on the screen.
To what is claim 6 of the '431 patent directed?
A. So, claim 6, as I have written here, in its independent form, is directed to an aqueous liquid preparation that
04:42 **consists essentially of bromfenac sodium from about .05 to about .2 weight percent, and tyloxapol having a concentration of about .02 weight percent, wherein said liquid preparation is formulated for ophthalmic administration, and when a quaternary ammonium compound is included in said liquid**
04:43 **preparation, the quaternary ammonium compound is benzalkonium chloride.**
Q. Let's now turn to claim 20 of the '431 patent, which is at column 14. Do you understand that claim 20 depends from claim 19 which further depends from independent claim 18?
04:43 **A. Yes.**
Q. Have you prepared a demonstrative showing the elements of claim 20 in its independent form?
A. Yes, I have.
Q. Let me direct your attention to PTD 2-3 on the screen.
04:43 To what is claim 20 of the '431 patent directed?
A. So, claim 20, as I have shown here, and it's written in its independent form, is an aqueous liquid preparation consisting essentially of bromfenac sodium from about .01 to about .5 weight percent, tyloxapol at a concentration of about
04:44 **.02 weight percent, boric acid, sodium tetraborate, EDTA**

sodium salt, benzalkonium chloride, polyvinylpyrrolidone, sodium sulfite, and that liquid preparation is formulated for ophthalmic administration, and wherein benzalkonium chloride is the only quaternary ammonium compound which is included in
04:44 **that liquid solution.**
Q. What is the active pharmaceutical ingredient in the formulation of claim 20 of the '431 patent?
A. It's bromfenac sodium.
Q. Are the remaining ingredients of the formulation of claim
04:44 20 of the '431 patent also called excipients?
A. Yes.
Q. Let's now turn to plaintiff's Prolensa® product. Is Prolensa® an embodiment of the aqueous liquid preparations of claims 6 and 20 of the '431 patent?
04:45 **A. It is, yes.**
Q. Have you reviewed the FDA approved package insert for Prolensa®?
A. Yes.
Q. Would you please turn to PTX-745 in your binder and
04:45 identify that document.
A. PTX-745 is a copy of the Prolensa® package insert from the NDA.
Q. And when you say NDA, do you understand PTX-745 to be the version of the package insert that the FDA approved in the new
04:45 drug application for Prolensa®?

A. That's my understanding.
Q. Would you please turn to JTX-22 in your binder and identify that document.
A. JTX-22 is a copy of the Prolensa® package insert that's
04:45 **actually included with the product.**
Q. Was this ultimately placed in the packaging with the marketed Prolensa® product?
A. Yes.
Q. Do you understand that PTX-745 and JTX-22 are
04:46 substantively identical?
A. That's my understanding.
Q. Looking at JTX-22, let me direct your attention to the indications and usage section within the full prescribing information section on the first page of the Prolensa® package
04:46 insert. According to the Prolensa® package insert, what is the FDA approved indication for Prolensa®?
A. It says Prolensa® .07 percent is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.
04:46 Q. Let me direct your attention to the dosage and administration section within the full prescribing information section on the first page of the Prolensa® package insert. According to the Prolensa® package insert, how is Prolensa® administered for ophthalmic use?
04:46 **A. According to the package insert, it says one drop of**

Prolensa® should be applied to the affected eye once daily beginning one day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.
04:47 Q. Let me direct your attention to the adverse reactions section within the full prescribing information section on the first page of the Prolensa® package insert. According to the Prolensa® package insert, is Prolensa® associated with adverse reactions of burning and stinging?
04:47 **A. That's not listed on the package insert.**
Q. Have you reviewed the formulation of Prolensa® as set forth in the FDA approved new drug application for Prolensa®?
A. I have, yes.
Q. Would you please turn to PTX-120 in your binder and
04:47 identify that document.
A. PTX-120 is an excerpt from the NDA for Prolensa®.
Q. Let me direct your attention to the page of PTX-120 bearing Bates number PROL0002267, and in particular to Table 1 on that page. What does Table 1 in PTX-120 show?
04:48 **A. Table 1 shows the composition of Prolensa®, of bromfenac ophthalmic solution .07 percent, which is Prolensa®.**
Q. What is the active pharmaceutical ingredient in Prolensa®?
A. That is bromfenac sodium sesquihydrate.
04:48 Q. What is the amount of bromfenac sodium sesquihydrate in

Prolensa®?
A. It lists .0805 grams per hundred ml.
Q. And is it your understanding that that is equivalent to .07 weight per volume percent bromfenac free acid?
04:48 **A. Yes, and that's footnoted as footnote 1 to Table 1.**
Q. Does Prolensa@ contain tyloxapol?
A. Yes.
Q. What is the function of tyloxapol in Prolensa®?
A. It's as a stabilizer.
04:48 Q. What amount of tyloxapol is included in Prolensa® as a stabilizer?
A. It lists .02 grams per hundred ml, so .02 percent by weight.
Q. Does Prolensa® contain benzalkonium chloride?
04:49 **A. Yes.**
Q. What is the function of benzalkonium chloride in Prolensa®?
A. It is listed as a preservative.
Q. What amount of benzalkonium chloride is included in
04:49 Prolensa® as a preservative?
A. It is at .005 grams per hundred ml.
Q. Is benzalkonium chloride the only quaternary ammonium compound included in Prolensa®?
A. It is, yes.
04:49 Q. What other excipients are included in Prolensa®?

A. In addition to those three, it has boric acid, sodium borate, sodium sulfite, edetate disodium, povidone, which is also known as polyvinylpyrrolidone, sodium hydroxide, that can be added to adjust the final pH, and then purified water to
04:50 **add up to volume.**
Q. What are the functions of these other excipients that are included in Prolensa®?
A. The boric acid and sodium borate act as buffering agents. It states sodium sulfite is a stabilizer, edetate disodium it
04:50 **lists as a chelating agent, povidone it lists as a stabilizer, and then sodium hydroxide to adjust the pH of the solution.**
Q. What are the amounts of these other excipients that are included in Prolensa®?
A. Boric acid is at 1.4 weight percent. Sodium borate is
04:50 **at .74 weight percent. Sodium sulfite is at .2 weight percent. Edetate disodium is at .02 weight percent. Povidone is at 1 percent. And then sodium hydroxide, it can be used just to adjust the final pH.**
Q. What is the pH of Prolensa®?
04:51 **A. It states here it's -- the final pH, it's made to pH 7.8.**
Q. Upon review of the new drug application and the package insert for Prolensa®, do you understand that Prolensa® is an embodiment of the aqueous liquid preparations of Claims 6 and 20 of the '431 patent?
04:51 **A. I do, yes.**

Q. Are you aware of any opinion to the contrary offered by any of defendants' experts?
A. I'm not.
Q. Let's now turn to Lupin's generic bromfenac ophthalmic
04:51 solution.
Have you reviewed the proposed package insert for Lupin's generic bromfenac ophthalmic solution?
A. I have, yes.
Q. Would you please turn to PTX-127 in your binder and
04:51 identify that document.
A. PTX-127 is a copy of the package insert for Lupin's generic bromfenac ophthalmic solution.
Q. Please turn back to PTX-745 which is the Prolensa® package insert.
04:52 How similar are Lupin's proposed package insert for its generic bromfenac ophthalmic solution and the Prolensa® package insert?
A. They're very similar.
MS. HOLLAND: Objection, Your Honor. This is not
04:52 background anymore. I believe that goes to their copying case, if I could hazard a guess about what this is related to. But there is certainly no reason to compare the two marketed products. This is supposed to be a background about the patent and a description of the product.
04:52 MR. HASFORD: It's simply a background to indicate,

your Honor, that the Lupin proposed package insert is essentially identical to the Prolensa® package insert so that we don't have to go through, you know, the entirety, for example, of all the formulation components.
04:52 THE COURT: I'm going to sustain the objection. I think the purpose of this limited testimony was to explain the patent itself, to give the plaintiffs the first opportunity to introduce the concepts of the patent rather than to preview the arguments that the plaintiffs are going to be making later
04:53 in the case.
MR. HASFORD: And as I understand Your Honor's ruling in the -- from the call that the parties had with your Honor approximately a week ago, your Honor will permit us to provide factual information about the products, which includes Lupin's
04:53 product; is that correct?
THE COURT: The products I believe were meant to be Prolensa®, the plaintiffs' products. What does the order say? I don't have a copy in front of me.
MR. HASFORD: So, your Honor, this is Docket 221.
04:53 And your Honor's statement is with respect to Item 5, the order of proof, plaintiffs will be permitted to go first and presentations shall be limited to background testimony on the claim subject matter of the '431 patent and the products at issue. We understood that to mean both Prolensa® and Lupin's
04:54 generic -- Lupin's and InnoPharma's generic bromfenac

ophthalmic solution. And we certainly didn't get any objections yesterday when we disclosed these documents to counsel for the defendants. So we believe that --

MS. HOLLAND: Your Honor --

04:54 MR. HASFORD: -- that's their understanding as well.

MS. HOLLAND: -- what this formulation is. I don't think we have to spend another, you know, half hour of the Court's time on this. Why don't we try to do that tonight and we can come back with a stip tomorrow instead of having to go

04:54 through this.

MR. HASFORD: Well, your Honor --

MS. HOLLAND: There is a stip on infringement in any event so I'm not sure --

THE COURT: It's not an infringement case, and so the

04:54 products at issue are not the defendants' products, are they?

MR. HASFORD: Well, the defendants have certainly stipulated that those products infringe. We merely had planned to go through that for background purposes, your Honor.

04:54 MR. MUKERJEE: Your Honor --

THE COURT: I don't think it's necessary. I detect that there is really no dispute about your characterization of the defendants' products, and so the witness wouldn't have to take the time to go through that. But this was meant to be an

04:55 introduction to the '431 patent. Perhaps I shouldn't have

used the plural form of "products."

MR. MUKERJEE: And, your Honor, in looking at Mr. Hasford's binder, I think they intend on asking the same type of question on InnoPharma, so to the extent that

04:55 Mr. Hasford does, I assume your sustaining of Ms. Holland's objection applies to them also.

THE COURT: Well, do you also agree with what Ms. Holland said, that there is no dispute that the product of InnoPharma is identical to the Prolensa® product?

04:55 MR. MUKERJEE: I -- I agree that there is a stipulation on infringement on file, and I also agree that the issue of infringement is no longer an issue at trial, and so, therefore, there really is no relevance to that. And so, just as your Honor sustained the objection that Ms. Holland put

04:55 forth, I'm just asking that to the extent Mr. Hasford asks the identical question again with respect to InnoPharma, that the objection be sustained there as well.

MR. HASFORD: Your Honor, what I would do then is I would offer Lupin's and InnoPharma's infringement stipulations

04:56 on Claims 6 and 20 of the '431 patent into evidence.

MR. MUKERJEE: Evidence with respect to what? The stipulation speaks for itself.

MR. HASFORD: I don't believe that the stipulation has yet been signed by your Honor, so I'm offering it in

04:56 evidence so we don't have to prove this all up.

THE COURT: I wasn't aware there is a signature space on there for me. But it's been filed with the Court, hasn't it, the stipulation?

MR. HASFORD: I believe it has, your Honor. And I

04:56 apologize if we forgot to include a signature space for your Honor.

THE COURT: No, but there is no doubt now, is there, about what the stipulation is?

MR. HASFORD: We don't believe there is, your Honor.

04:56 THE COURT: Okay. Do you agree, Mr. Mukerjee?

MR. MUKERJEE: Yes, Your Honor.

THE COURT: All right. That's like a constitutional document. It frames the rest of the trial. I don't think it has to be entered into evidence.

04:57 MR. HASFORD: All right. We understand.

THE COURT: If there is a dispute that comes up where it becomes necessary for some reason, then you can offer it, but at this point it is of record.

MR. HASFORD: Well, your Honor, then we have no

04:57 further questions at this time.

We would offer PTX-165, JTX-1, JTX-6, JTX-210, JTX-147, PTX-745, JTX-22, and PTX-120 into evidence.

MS. HOLLAND: I don't -- your Honor, I don't believe they were all actually used in the testimony.

04:57 MR. HASFORD: I believe that those -- those

particular ones I believe were. I didn't include the -- your -- Lupin's proposed package insert or InnoPharma's. PTX- -- I can go through them.

THE COURT: I think you've used everything in the

04:57 book --

MR. HASFORD: Up through PTX-120, including PTX-120. We obviously -- given your Honor's ruling on the objection, we won't be using PTX-127 and up.

THE COURT: All right. Is there any objection to any

04:58 of those documents? And I will recite them again.

MS. HOLLAND: No objection.

MR. MUKERJEE: No, Your Honor.

THE COURT: Okay. The following then are received into evidence: JTX-001, JTX-006, JTX-210, JTX-147, PTX-745,

04:58 JTX-22, and PTX-120.

(PLAINTIFF EXHIBITS JTX-001, JTX-006, JTX-210, JTX-147, PTX-745, JTX-22, and PTX-120 WERE RECEIVED IN EVIDENCE.)

MR. HASFORD: And I believe PTX-165 which was Dr. Williams' curriculum vitae, your Honor.

04:59 THE COURT: Oh, yes. The very first. PTX-165 is also received into evidence.

(PLAINTIFF EXHIBIT PTX-165 WAS RECEIVED IN EVIDENCE.)

MR. HASFORD: Your Honor, plaintiffs also offer PDX2-1, PDX2 -- sorry -- PTD2-1 -- is it PDX? Okay. PDX2-1,

04:59 PDX2-2, and PDX2-3 as demonstrative exhibits.

THE COURT: Well, by their nature, demonstrative exhibits are not received into evidence and the evidence will be his testimony. He read those exhibits and he can be cross-examined on what he testified to. But demonstratives are not evidence themselves.

MR. HASFORD: We would only be offering them to the Court as demonstratives, your Honor.

THE COURT: Okay. You can retain them and if they're helpful in your closing arguments or with some other witness, you can use them, but they are not themselves evidence. His testimony will be the evidence on this.

MR. HASFORD: Thank you, your Honor.

THE COURT: Is there cross-examination?

MS. HOLLAND: There is, Your Honor.

MR. HASFORD: And briefly, your Honor, we understand that your Honor would prefer the non-bound versions of the exhibits? We have those here.

THE COURT: Let's pause for a minute. With regard to each witness, the parties are going to be offering packets or bundles, and the same exhibit probably may be used with many different witnesses. Is that same exhibit then going to appear in each and every bundle, for instance, the '431 patent?

MS. HOLLAND: It likely will, because each witness will need to look at the patent as part of their testimony.

THE COURT: Okay. And you've put your patents together so I'm not going to displace that. I don't know how many copies of the same document I need to receive, but I can sort that out. I think that's probably the easier thing.

And so I'm okay with the binders. Everything is included and I don't need a second set.

MR. HASFORD: All right.

THE COURT: Is there any reason why the -- you know, the paper version of the binder version might be more useful?

MR. HASFORD: We had purely understood that the paper version was your Honor's preference, but if your Honor is fine with the binder version, you're certainly -- that's fine with us.

THE COURT: Well, to me, the binder version is a paper version.

MS. HOLLAND: Your Honor, may I suggest, it might be easier for the Court if at the end of trial, once we know what exhibits have actually been admitted, that we must make binders of those for the Court so it won't be repetitious?

THE COURT: Yes, I think by the time of closing arguments that having one set of exhibits will be helpful. And each day, I'd encourage you to compare notes with Marnie Maccariella as to what's actually been admitted into evidence, make sure that our bookkeeping compares with yours. Okay?

MR. HASFORD: All right.

MS. HOLLAND: (Nods head.)

THE COURT: All right. Okay. Cross-examination.

(CROSS EXAMINATION OF ROBERT O. WILLIAMS, III BY MS. HOLLAND:)

Q. Good afternoon, Dr. Williams.

A. **Hi, Ms. Holland.**

MS. HOLLAND: We are going to be handing up binders with the cross-examination exhibits.

BY MS. HOLLAND:

Q. Dr. Williams, you were asked about the disclosure of the invention section of the '431 patent which is JTX-1. Do you recall that?

A. **Yes.**

Q. And you testified that tyloxapol was inhibiting the chemical degradation of the bromfenac formulation; is that correct?

A. **Based on the results shown in Table 2 and Table 3 of experimental Example 1 and experimental Example 2, that was the conclusion, yes.**

Q. Well, my question was a little different.

So, you're saying that the purpose of the tyloxapol in the formulation was to prevent chemical degradation; is that right?

A. **Well, I said that was an object of the invention.**

Q. Okay. So, let's go back to that disclosure of the invention section, and, again, it's Column 2 of JTX-1 which is

the '431 patent. And the paragraph you pointed to starts at Column 2, Line 34, and it goes down through Column 2, Line 49. Are you there?

A. **Yes.**

Q. Okay. Now, that paragraph actually does not use the words "chemical degradation," correct?

A. **As I stated, that paragraph in Line 43 uses change of the bromfenac over time can be inhibited, which, in my opinion, that's understood to be chemical degradation of bromfenac.**

Q. All right. But my question is a little different.

Did you see the words "chemical degradation" anywhere in the '431 patent? Those words.

A. **The words "chemical degradation," no. But that --**

Q. That was my question. Thank you.

A. **-- Table 1 or Table 2 is --**

MR. HASFORD: Whoa. Your Honor, she's cutting him off. He's entitled to explain his answer.

THE COURT: Well, I think it's a "yes" or "no" question that's being asked, Doctor, is whether the words "chemical degradation" appear anywhere in the '431 patent, to the best of your knowledge.

THE WITNESS: Okay. Thank you. I don't see them, no, those two words.

BY MS. HOLLAND:

Q. And, likewise, the words "chemical stability" don't

appear anywhere -- anywhere in the '431 patent, correct? Those words.

A. I don't believe they do.

Q. Now, there is another type of stability called physical stability, correct?

A. Yes.

Q. And, in your opinion, physical stability refers to whether the formulation's appearance changes over time; is that right?

A. That's true, yes.

Q. For example, if a formulation becomes cloudy or turbid, you would consider that a problem of a physical stability rather than chemical stability, correct?

A. Turbid. And yes, that's true.

Q. Now, you also talked about the background art section of the '431 patent, so I'd like to focus your attention back there now. But I actually want to talk about a part of the background art section that you didn't talk about in your direct examination. So let me refer you to Column 1, starting at Line 62, and then the paragraph goes over to Column 2, Line 3. Do you see that?

A. Yes.

Q. And do you see there that what's written in the patent is that "benzalkonium chloride is a widely used preservative in ophthalmic solutions"?

A. The quote, yes.

Q. Okay. And then it says, "However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal anti-inflammatory drugs." Do you see that?

A. Yes.

Q. And it says, "These preservatives, referring to BAC, lose their ability to function as they form complexes with the charged drug compounds." Do you see that?

A. Yes.

Q. So that paragraph describes a phenomenon where drugs with acidic groups like NSAIDs form complexes with BAC, correct?

A. Well, that describes that that could happen, because it uses the word "generally considered." So I think that would be understood by a person of ordinary skill in the art to mean -- or be understood that that could happen, but you have to figure out if it's happening or not with data.

Q. Okay. But the '431 patent does acknowledge that that phenomenon of NSAID complexation with BAC can happen, correct?

A. Well, they're quoting from this Japanese 35 -- or 2954356 patent, and I mean, that it says generally considered, so it -- it recognizes that that could happen.

Q. Now, if -- if an NSAID forms a complex with BAC, is that a problem with physical stability or chemical stability?

A. From my experience, it's a problem with physical stability.

Q. All right. Now, bromfenac is an NSAID with an acidic group, right?

A. Bromfenac has a carboxylic acid group.

Q. Do you consider that an acidic group?

A. Yes.

Q. Okay. So if bromfenac forms complexes with BAC, if that happened, that would be a problem of physical stability, correct?

MR. HASFORD: Objection, Your Honor. Assumes facts not in evidence. That sounds like this is getting into the type of opinion testimony that Ms. Holland objected to when we were doing direct exam with Dr. Williams.

MS. HOLLAND: May I address that, your Honor?

THE COURT: Yes.

MS. HOLLAND: Dr. Williams gave testimony that in his opinion, when the patent says stability, it refers to chemical stability. I'm entitled to probe whether it really refers to chemical stability or not or if that's the way a person of ordinary skill in the art would really understand it. It's about what the patent means.

THE COURT: I hesitate to let you probe his understanding of everything in this patent --

MS. HOLLAND: I'm not going to.

THE COURT: -- because that's what the rest of the case is going to be about. If there is something that he testified to on direct that you feel needs cross-examination, I'll permit it.

MS. HOLLAND: Your Honor, what he testified to on direct, and I wrote it down to make sure that I would stay within the scope of the direct, was that the patent shows that tyloxapol was used to combat chemical degradation. I'm cross-examining him on that issue.

THE COURT: All right. I'll permit it.

BY MS. HOLLAND:

Q. So the question was: If bromfenac formed complexes with BAC, would that be a problem of physical stability or chemical stability? If that happens.

A. Well, if that happens and it's -- and the complex is not soluble, then it will precipitate, so it would be a physical stability, from my experience.

Q. Do you agree that tyloxapol is included in the claimed formulations to address the problem of bromfenac forming complexes with BAC?

A. I mean, what I understand from the patent is that tyloxapol is included to inhibit chemical degradation of bromfenac, and that in that process, however it's working, which I don't understand exactly how it works, but that the preservative efficacy when a quaternary ammonium preservative

like benzalkonium chloride is also used, that it maintains the preservative efficacy over some shelf life.

Q. Let me try my question again because maybe you didn't understand it.

My question is about tyloxapol. Do you agree that tyloxapol is included in the '431 patent to address issues of physical stability of bromfenac formulations?

A. No.

Q. And it's your view that tyloxapol is not included to address the problem of bromfenac forming complexes with BAC; is that correct?

A. Say that again, please.

Q. Yes. Do you agree that tyloxapol is included in the claimed formulations of the '431 patent to address the problem of bromfenac forming complexes with BAC?

A. No. I don't -- I don't think it is, no.

Q. Now, you testified that -- I'm just trying to find your quote.

You testified that tyloxapol was not used as a chemical stabilizer as of 2003, right?

A. Yeah. There was more to the question that I answered, but that was part of it. I think it was for NSAIDs. I can't quite remember the question but --

Q. Well, was tyloxapol used as a chemical stabilizer as of 2003?

A. It -- I'm not aware of where it was.

Q. But it was used as a physical stabilizer as of 2003, correct?

A. Tyloxapol?

Q. Yes.

A. For suspensions or emulsions or -- I believe it was.

Q. Now, did you make any effort to determine why the inventors actually included tyloxapol in their formulations that are in the '431 patent?

MR. HASFORD: Objection, Your Honor. Again, this goes beyond the background of the patent. It goes to an issue of what was in the inventors' mind. It certainly bears nothing on obviousness, and it's just not an issue in this case, and it's improper for at least those reasons.

MS. HOLLAND: Your Honor, Dr. Williams gave testimony that the tyloxapol was included for chemical degradation purposes. I'm entitled to explore whether that's, in fact, accurate. Just because they don't put an inventor on the stand doesn't mean they can shield everything that the inventors did.

MR. HASFORD: Your Honor --

MS. HOLLAND: That contradicts the expert's testimony.

MR. HASFORD: And, your Honor, he was testifying as to the background of what's presented in this patent. He's

not testifying as to what the background was, of what may have been in the inventor's mind, which is irrelevant in an obviousness case in any event. The Federal Circuit has said that over and over and over again.

THE COURT: Well, I think part of this issue has to do with the function that this witness is serving at this point in the trial.

As I understood the proffer by the plaintiffs and as I understood their direct examination, the witness was to be speaking as if he were the patent. He's explaining himself. This is what the patent is, this is what these words mean, this is what the references to prior art contain, and so on. I don't believe that the witness is being asked, well, what's his personal opinion about whether this all makes sense or whether it's good science or whether he agrees or disagrees with the patent. My understanding was in introducing the patent, quote, unquote, Professor Williams' role was a limited one, which is explaining what the patent means from the view point of the patent.

MS. HOLLAND: That's all I'm asking, Your Honor. I want to understand.

THE COURT: No, I think you're asking a different question. Excuse me.

MS. HOLLAND: Yes.

THE COURT: The question that you're asking is what

did the inventors have in their mind, and did he do research on what the inventors did. Now, he did testify that he reviewed the prosecution history. I'll permit questions about that.

MS. HOLLAND: Your Honor, he also testified about the function of each of the components of the formulation.

MR. HASFORD: Your Honor, that drew an objection. When the -- when I asked about the functions in the patent of the components, Ms. Holland jumped up and objected.

MS. HOLLAND: There was an exhibit up on the screen that showed the function of tyloxapol and it said stabilizer.

MR. HASFORD: And that was in the new drug application, Your Honor. That was for the commercialized product. We wouldn't have any objection to Ms. Holland doing cross-examination about that particular document.

The point here, she's trying to get into, as Your Honor noted, what was in the inventors' mind, it's not relevant, and it shouldn't be permitted here because it's additionally beyond the scope of what he testified to on direct exam.

MS. HOLLAND: May I be permitted one more attempt at this, Your Honor?

THE COURT: Yes, I was going to say, perhaps if the question could be reformulated to something other than the inventors' mind.

MS. HOLLAND: Well, let's do it this way. Let's

start from --

THE COURT: In other words, the patent itself expresses what its purpose was. What were the objects. I think it mentions three of them.

05:15 MS. HOLLAND: So here's the issue, Your Honor. The patent uses the word, "stability." Dr. Williams gets on the stand and says, well, of course, it's talking about chemical degradation, but I need to be able to probe whether that was really the object of the invention here. If the inventors

05:15 think they were trying to do something else, then plaintiffs don't bring the inventors to trial and then plaintiffs can say whatever they want about what the object of the invention is.

THE COURT: Just a moment. Ms. Holland.

MS. HOLLAND: That permits plaintiffs to basically

05:16 put a witness on the stand, not show him what the inventors actually said, and have him give opinions that are clearly contradicted by what the inventors' own documents say. I should be able to probe that.

THE COURT: Well, you will, throughout the trial, but

05:16 again, with an introductory witness, you can ask him about his testimony on direct, and if some of the testimony came in without objection, as to what he discerned as the purposes, then I'll permit you to question him about that. But I do think that overall, the scope of the direct and the cross was

05:16 to explain to me what the patent is saying, what brought it

about, what it does, what it doesn't do. Okay?

MS. HOLLAND: All right. So let me go to a different question, then.

BY MS. HOLLAND:

05:16 Q. Dr. Williams, you testified that Prolensa is an embodiment of these asserted claims, correct?

A. Yes.

Q. And, in fact, you put up a section of the new drug application on the screen to show what the function of each of

05:17 the excipients is in the claimed formulation, right?

A. Well, there was a page from the Prolensa NDA table that one of the columns listed what the NDA stated was a function of the excipients along with the amount used in Prolensa.

Q. And you're aware that there are other sections of the NDA

05:17 that give a more robust description of what the functions of the different ingredients are in the Prolensa product, right?

A. You would have to show me. I'm --

Q. All right. Let's look at PTX-125A, and this is an excerpt of the NDA for Prolensa, Section 2.3.2.

05:17 MR. HASFORD: Your Honor, I'm going to object. It's beyond the scope of direct. We didn't go into this document on direct. If she wants to ask about the document in the NDA that we discussed on direct, we're fine with that, but this is clearly beyond the scope of direct.

05:17 THE COURT: No, I'll permit it. It's

cross-examination as to another section of the same document.

BY MS. HOLLAND:

Q. All right. Are you open to that section, Doctor? It should be in your binder.

05:18 **A. I didn't get a binder.**

Q. I apologize about that.

A. No worries. Thank you.

Q. Let's go to the first page of the document, please.

A. I'm sorry, this is --

05:18 Q. This is a section of the NDA for Prolensa.

THE COURT: What's the last document in the binder?

MS. HOLLAND: 125A.

THE WITNESS: Thank you.

BY MS. HOLLAND:

05:18 Q. And you see it's entitled pharmaceutical development.

Do you see that?

A. Yes.

Q. Okay. And if you go to Page 2 point -- I'm sorry, if you go to Page 7 of 16, maybe that's the easiest way to look at

05:18 it.

And I want to focus your attention on the third paragraph from the bottom of the page.

A. Okay.

Q. And in specific, I want you to look at the -- let's start

05:19 with the first sentence of that paragraph and this again is

talking about the function of tyloxapol in Prolensa, which you testified is the embodiment of the claims in this case.

And what it says is, tyloxapol acts as a solubilizing agent to prevent interaction between benzalkonium chloride and

05:19 bromfenac sodium.

Do you see that?

A. I do.

Q. Does that change your view on why tyloxapol was included in the claimed formulations?

05:19 **A. I mean, not according to my reading of the patent. I see what this says, but...**

Q. Let's go back to JTX-1. I want to go to Column 6 of the '431 patent. And if you look at Line 11 through the end of that paragraph, that's a paragraph you testified about on

05:20 direct, correct?

A. Yes.

Q. Okay. Now, you said that this paragraph talks about additives that could be put into the claimed formulations, right?

05:20 **A. Yes.**

Q. Okay. I just want to confirm that the patent characterized those as conventional additives, correct?

A. The patent on Line 12, Column 6 says conventional various additives.

05:20 Q. Okay. Now, you said that these could be added to the

form -- to the formulations of the claims in suit here, however, most of them are not actually part of those claims, correct?

A. I'm sorry? I don't understand.

Q. Are all of the additives listed in the paragraph we've been looking at requirements of the claims in this case?

A. Requirements of the claim? I don't believe so, no.

Q. Let's turn to Column 7 and the experimental examples that you looked at during your direct examination.

You looked at Experimental Example 1 and you testified that the testing there was done with a pH of 7, correct?

A. Yes.

Q. And then you looked at Example 2 and you said the pH was done at a test -- in the testing at about 8.2, correct?

A. I didn't say that, no.

Q. Well, what is the pH?

A. I think I said it was about 8.13 to 8.19, something in that range.

Q. Okay. The patent doesn't have any testing at a pH of 7.8, correct?

A. Well, I mean, the -- Table 1 is at pH 7 and Table 2 ranges within the range I just said, like 8.13 to 8.19.

Q. So the answer to my question is no, there is no testing in the patent at 7.8, is that right?

A. Not that I see.

Q. And that's the pH of Prolensa, correct?

A. Yes.

Q. Let's go back to Table 1 then and I want you to look at the formulation and the components in Table 1.

The formulations in Table 1 don't contain sodium sulfite or povidone, right?

A. That's true, they don't.

Q. And I think you testified that sodium sulfite and povidone, the patent says -- well, let me withdraw that.

You testified that the function of sodium sulfite and povidone in Prolensa was stabilizers, correct?

A. Well, that's what the page from the NDA, that table I was looking at, that's what it stated. And it's also in Column 6 as how the patent characterizes stabilizers -- or sorry, characterizes sodium sulfite as stabilizers.

Q. So those stabilizers are missing from the formulations that were tested in Experimental Example 1, right?

A. Well, polyvinyl povidone and sodium sulfite are not in the compositions of the formulas made in Table 1.

Q. And you would expect the remaining rate percentages in Table 1 to be different had they actually included sodium sulfite or povidone, correct?

A. I don't know. I'd have to test it. I mean, based on what the '225 Ogawa says with adding PVV and sodium sulfite, I mean, Experimental Example 1 may be better.

Q. But you believe it's going to affect the rate of degradation, right?

A. Well, I -- probably in a positive way, if they are included.

Q. Right. So the rate of degradation in Table 1 will be different if the examples actually include sodium sulfite and povidone which, of course, are in Claim 20 of the '431 patent, right?

A. I mean, they may be.

Q. Now, let's look at Experimental Example 2.

That Table 2 does not contain any data for compositions containing polysorbate 80, right?

A. That's true.

Q. So there's no comparison in Table 2 between compositions with polysorbate 80 and compositions with tyloxapol, right?

A. That's true.

Q. Now, if you look at the tyloxapol compositions, you testified on direct that they have three different amounts of tyloxapol. The A-04 has .02, correct?

A. Yes.

Q. A-05 has .05, correct?

A. That's true.

Q. And A-06 has .03, correct?

A. Yes.

Q. And in the test, in Table 2, in the '431 patent, all of

those formulations have greater than 90 percent remaining rate of bromfenac after the testing, correct?

A. Those three do, yes.

Q. Okay. So formulas with any of those three amounts of tyloxapol are stable pharmaceutical formulations, right?

A. Well, they're all -- the chemical potency of bromfenac is all of -- it's -- A-04 is 92.6 percent, A-05 is 90.9 percent and A-06 is 92 percent.

Q. You looked at the package insert for Prolensa. Do you recall that?

A. Yes.

Q. That's JTX-23, I believe.

MS. HOLLAND: Can we see that, please.

THE WITNESS: I think it's -- I have JTX-22.

BY MS. HOLLAND:

Q. I think it's comparable. We can use 22. That's fine. And I'd like to look at the adverse reaction section and that's a section you looked at in your direct examination, right?

A. Yes.

MR. HASFORD: I apologize. I think we might have a binder problem here because I have JTX-23 in my binder.

MS. HOLLAND: I have it in mine as well, but Dr. Williams said he testified about the version that's JTX-22, so it doesn't matter to me which one we use. I think

you've established that they were the same.

MR. HASFORD: I think we used JTX--- let me just check my outline real quick. We used PTX-745 and JTX-22, unfortunately.

05:27 MS. HOLLAND: All right. Why don't we just use JTX-22.

BY MS. HOLLAND:

Q. Is that the Prolensa label?

A. Yes.

05:27 Q. Okay. That's what we want.

Let's look at the adverse reaction section and this is something you testified about on direct, correct?

A. Yes.

Q. Okay. And you said that there was no burning or stinging

05:27 listed in the adverse reaction section, right?

A. It's not listed there, that's true.

Q. Okay. But that section only reports adverse reactions that occurred in three percent or greater of patients, right?

A. That's what it says.

05:28 Q. Okay. So it could be that up to three percent of patients in the clinical trials did experience burning and stinging, right?

MR. HASFORD: Objection, Your Honor. Calls for speculation.

05:28 THE COURT: I'll permit it.

THE WITNESS: I don't know.

BY MS. HOLLAND:

Q. Do you know what percentage of patients experience burning and stinging in the Xibrom or Bromday clinical trials?

05:28 **A. The percent, I don't.**

Q. Do you know if it was over or under three percent?

A. I know it's listed in there, in the comparable section in their package insert, but I don't know what percent.

Q. You don't know if it's over or under three percent, do

05:28 you?

A. I do not.

Q. You talked about the pH specification of Prolensa in your direct testimony, correct?

A. Yes.

05:28 Q. And you had -- well, let's put up your demonstrative that had slides -- I'm sorry, that had Claim 6.

This is your slide that you -- to show the elements of Claim 6 of the '431 patent, correct?

A. Yes.

05:29 Q. None of these elements have any requirement as to a specific pH, correct?

A. Well, I mean, it's formulated for ophthalmic administration, so I mean, there is some pH component but a specific pH range is not described in Claim 6.

05:29 Q. And 8.3 would be a pH for an ophthalmic formulation,

right? That was the pH of Bronuck and Xibrom and Bromday, right?

A. It could be.

MS. HOLLAND: Let's see Slide 20.

BY MS. HOLLAND:

Q. And again, can you confirm that Claim -- I'm sorry, I said Slide 20. I actually meant to say Claim 20.

Can you confirm in Claim 20 similarly that there's no requirement for a specific pH for the formulation?

05:30 **A. Yeah, I mean, I have the same opinion. It says formulated for ophthalmic administration. So pH is part of it. But there is no specific pH range that is a limitation in Claim 20.**

Q. But again, a pH of 8.3, as in the previous bromfenac

05:30 products, would be suitable for ophthalmic administration, right?

A. It could be.

Q. They were approved products, right?

A. They were approved products that had a pH of about 8.3.

05:30 **So that pH could be.**

Q. Now, let me ask you about the preservative efficacy testimony that you gave.

Do you also agree that the two asserted claims in this case have no limitations as to preservative efficacy?

05:31 **A. Again, it's like a specific pH range. It says formulated**

for ophthalmic administration, so a sterility is a component of that. So preservative efficacy, but as Claim 6 or Claim 20 are written, there's no specific limitation regarding preservative efficacy.

05:31 Q. And you agree that for a product marketed in the U.S., if it met the U.S. Pharmacopeia for preservative efficacy, that would be good enough to market the product, right?

A. From my experience, that's true.

MS. HOLLAND: I have nothing further, Your Honor.

05:31 THE COURT: All right, thank you. Any further cross by Mr. Mukarjee?

MR. MUKARJEE: No, Your Honor.

THE COURT: All right. Any redirect?

MR. HASFORD: Just a brief bit of redirect, Your

05:31 Honor.

THE COURT: All right.

(REDIRECT EXAMINATION OF DR. WILLIAMS BY MR. HASFORD:)

Q. Dr. Williams, would you please turn back to JTX-1 in your binder, which is the '431 patent, and take a look at

05:32 Experimental Examples 1 and 2 which are on Columns 7 and 8 respectively.

A. Okay.

Q. Do you remember when Ms. Holland asked you on cross whether there was a specific example in Experimental

05:32 Examples 1 or 2 that disclosed pH 7.8 which is the pH of

Prolensa?
A. **Yes.**
Q. Okay. Turn, if you would, back to Column 2 of the '431 patent. I apologize, Column 6 of the '431 patent.
05:32 Let me direct your attention to Column 6, Lines 39 through 41 of the '431 patent.
It states: The pH of the aqueous liquid preparation of the present invention is adjusted to about 6 to 9, preferably about 7 to 9, especially about 7.5 to 8.5.
05:33 Do all of those ranges encompass pH 7.8 at which Prolensa was formulated?
A. **They do, yes.**
MR. HASFORD: Nothing further, Your Honor.
MS. HOLLAND: Your Honor, I would just like to put PTX-125A into evidence.
05:33 THE COURT: Okay. Any objection?
MR. HASFORD: No objection, Your Honor.
THE COURT: Okay. Very well. PTX-125A, which is the entire --
05:33 MS. HOLLAND: It's just the excerpt that's in the binder. It's not the entire NDA.
THE COURT: Right. The excerpt from the NDA for Prolensa will be received into evidence.
(DEFENDANT EXHIBIT PTX-125A WAS RECEIVED IN EVIDENCE)
05:33 THE COURT: Is this a good time for a break?

MR. HASFORD: Yes, Your Honor.
THE COURT: Okay. Let's take about a 10, 15-minute break.
MR. LIPSEY: Your Honor, is the witness excused?
05:34 THE COURT: Yes.
MR. LIPSEY: Okay.
THE COURT: You don't have to file for a writ.
(RECESS TAKEN; 3:07 p.m.)
THE COURT: Be seated, please. All right.
06:02 You may proceed.
MS. RAPALINO: Good afternoon, Your Honor. Emily Rapalino from Goodwin Proctor on behalf of the Lupin defendants.
The defendants call as their first witness in our case
06:02 in chief, Professor Jayne Lawrence.
THE COURT: Okay. Professor, please come to the witness stand.
THE DEPUTY CLERK: Can you place your left hand on the Bible and raise your right hand.
06:02 (**MARGARET JAYNE LAWRENCE**, having been duly sworn as a witness, testified as follows:)
THE DEPUTY CLERK: Can you please state your name, ma'am, and spell your first and last name, please.
THE WITNESS: Margaret Jayne Lawrence. That's
06:02 Margaret, M-A-R-G-A-R-E-T, Jayne with a Y, and Lawrence,

L-A-W-R-E-N-C-E.
THE DEPUTY CLERK: Thank you. You can be seated.
MS. RAPALINO: Your Honor, may we approach with the witness binders?
06:03 THE COURT: Yes, of course.
THE DEPUTY CLERK: Thank you.
(VOIR DIRE EXAMINATION OF MARGARET JAYNE LAWRENCE BY MS. RAPALINO:)
Q. Good afternoon, Professor Lawrence.
06:03 A. **Good afternoon.**
Q. Where do you live?
A. **I live in a place called Ashford, Middlesex, which is near London in the U.K.**
Q. Are you employed?
06:03 A. **Yes, I am. I have a full-time position as a full tenured professor at King's College, London, where I'm a professor of biophysical pharmaceutics, and I'm also on the 50 percent secondment at the Royal Pharmaceutical Society where I'm the chief scientist.**
06:04 Q. Are you affiliated with a particular group in connection with your appointment at King's College, London?
A. **Yes, I am. I'm head of the pharmaceutical biophysics group.**
Q. What is the pharmaceutical biophysics group?
06:04 A. **It's a group of about six academics and associated**

post-doctoral fellows, Ph.D. students who are concerned with understanding drugs and drug delivery systems at the molecular level, using a range of advanced analytical tools.
Q. You used the term, "drug delivery systems."
06:04 What does this mean?
A. **Yes. This is the way in which drugs are administered to a patient basically in the form of a medicine and this obviously includes pharmaceutical formulation.**
Q. How long have you held your position at King's College,
06:04 London?
A. **Since 2002.**
Q. Generally speaking, what are your academic responsibilities as head of the biophysics group?
A. **I have research, teaching and administrative**
06:05 **responsibilities.**
Q. With respect to your research, what is the general subject of your research?
A. **It's -- it's generally on drug delivery systems which obviously includes pharmaceutical formulation and a particular**
06:05 **interest of mine is increasing the solubility of poorly water soluble drugs.**
Q. What do you mean by a poorly water soluble drug?
A. **This is a drug that doesn't freely dissolve in water.**
Q. In terms of your teaching responsibilities at King's
06:05 College, what classes have you taught over the course of your

career?
A. I've taught many over the course of my career. I currently teach first-year classes looking at pharmaceutical formulation, in particular formulation of aqueous formulations, creams, suspensions, emulsions. I also teach a class on bioavailability and this is basically to do with how drugs are absorbed in the body.
Q. What kinds of formulations do the classes that you teach cover?
A. I cover non- -- I cover oral formulations and nonoral formulations, which cover ophthalmic preparations.
Q. You also mentioned that in addition to your appointment at King's College, London, you're also the chief scientist of the Royal Pharmaceutical Society.
Can you describe that role?
A. Yes, certainly. In this role, I have an efficacy role for pharmaceutical science. This may involve me talking to the media, talking to other professional bodies with mutual interest. Interacting with the government at a high level, and also Department of Health.
Q. You mentioned that you talk to the media.
Can you give us a little bit more detail about what you do in that role?
A. Yes, in my role at the Royal Pharmaceutical Society, I'm often called upon by national TV stations, such as the BBC to

give a view on matters of pharmaceutical importance.
Q. Could you turn in the witness binder that you have in front of you to DTX-442.
What is DTX-442?
A. This is my curriculum vitae.
Q. Did you prepare this document?
A. Yes, I did.
Q. Does it accurately reflect your education and experience?
A. Yes, it does.
Q. Let's talk for a moment about your educational background.
Where did you go to university?
A. I did my pharmacy degree at Liverpool Polytechnic in Liverpool. After that, I spent a year undertaking professional training to become a registered pharmacist, that involved working six months in the community pharmacy or retail pharmacy, as it was known there, and in the pharmaceutical industry. After that, I started a Ph.D. in the pharmacy department at Manchester University.
Q. What year did you obtain your Ph.D.?
A. 1985.
Q. What was the subject of your research for your Ph.D.?
A. It was concerned with synthesizing novel surfactants and characterizing them using physical chemistry.
Q. We've heard a little bit about surfactants already, but

can you briefly describe what surfactants are?
A. Yes. They're quite unique molecules in that they have a part -- a part of the molecule that is soluble in water and a part of the molecule that is insoluble in water and as a consequence, they have a range of properties that are very advantageous for pharmaceutical formulation.
Q. Could you give us an example of a property that's advantageous for pharmaceutical formulation?
A. Yes. Surfactants are often used to increase the solubility of poorly water soluble drugs and this is one of my interests.
Q. Do the formulations of the '431 patent in this case contain a surfactant?
A. Yes, they do. They contain the surfactant tyloxapol.
Q. You said that your Ph.D. was in the department of pharmacy at Manchester University, but did your Ph.D. research involve any chemistry?
A. Yes, it did. It involved me making a number of novel new surfactants and then I characterized them using physical chemical techniques.
Q. What did you do after you received your Ph.D.?
A. Well, it was actually before I received my Ph.D. At the end of my second year of Ph.D., I was fortunate enough to be awarded an academic position at King's College, London, and I've been there ever since.

Q. Have you followed the literature over the course of your career related to pharmaceutical formulation?
A. Yes, I have.
Q. Have you had any experience working in the pharmaceutical industry over the course of your career?
A. Yes, I have. In addition to the six months I spent while I was training to be a pharmacist, I've also spent the six months sabbatical working in Glaxo Group Research or GSK as they are known now. I've also undertaken consultancies for industry. I've undertaken research projects and I'm a member of the Industrial Pharmacy Forum which is the U.K. group being industrial pharmacists.
Q. Have you had any experience working with ophthalmic drugs over the course of your career?
A. Yes, I have. I've -- I've undertaken consultancies for pharmaceutical industry evaluating ophthalmic products.
Q. And can you explain, just in a general way, what kind of work you did in connection with those consultancies on ophthalmic products?
A. Yes. I was looking at the effect of the surfactants on the formulation.
Q. Now we've heard that bromfenac, the drug at issue in this case, is a nonsteroidal anti-inflammatory drug or NSAID.
Have you worked with any NSAID formulations over your career?

A. **Yes. Well, I haven't worked with bromfenac, I've worked with a number of nonsteroidal anti-inflammatory drugs.**
Q. And what kind of work have you done with NSAIDS?
A. **I've been particularly interested in seeing how they interact, basically complex, with ingredients in the formulation.**
Q. Have you been active in any professional organizations over the course of your career?
A. **Yes, I have, lots.**
Q. If we look at -- back at DTX-442 in your binder, is that activity reflected at Pages 2 to 4 of your CV?
A. **Yes, it is.**
Q. Directing your attention to Pages 3 and 4, can you give us a couple of examples of professional organizations with which you've been involved?
A. **Certainly. I'm currently chair of the Academy of Pharmaceutical Sciences, which is a professional body in the U.K. representing pharmaceutical sciences, and I'm also chair of the Formulation of Pharmaceutical Technology Special Interest Group of the International Pharmaceutical Federation, which is a federation that promotes pharmacy and pharmaceutical sciences at a high level on the international arena.**
Q. Have you had any involvement with regulatory authorities over your career?

A. **Yes, I have.**
Q. Can you describe that involvement?
A. **Certainly. I was a member of the Task and Finish Group of the European Medicine Agency which is the equivalent of the FDA, and I was involved in preparing a reflection paper on micellar injectables.**
Q. What is a reflection paper?
A. **This is a paper that represents the state of the art in terms of use of -- in this case, micelles for injectable formulations and how to characterize them.**
Q. Have you had any other involvement with regulatory authorities?
A. **Yes, I have. In my role with the Pharmaceutical Society, I meet on a fairly regular basis with the MHRA, which is the English equivalent of the FDA, and we meet to discuss matters of mutual interest.**
Q. Have you published in your field?
A. **Yes, I have.**
Q. About how many publications do you have?
A. **I have over 124 papers, in addition, obviously book chapters, reviews and conference abstracts, et cetera.**
Q. What's the general subject matter of your publications?
A. **It's basically drug delivery using surfactants to increase -- improve the delivery of drugs.**
Q. Have you had a role in any journals over the course of

your career?
A. **Yes. In addition to being a reviewer, I was on the editorial board of Journal -- Journal of Pharmaceutical Sciences, and quite a while ago, I was actually on the editorial board of Drug Development and Industrial Pharmacy.**
Q. Have you won any awards in connection with your work?
A. **Yes, I have.**
Q. If I could direct your attention to Page 1 of DTX-442, can you tell us about a couple of your more recent awards?
A. **Yes. In 2012, I was awarded an eminent fellowship of the Academy of Pharmaceutical Sciences for my leadership in pharmaceutical science, leadership and research.**
Q. How many such awards are given?
A. **It's less than 25 at the moment.**
Q. Can you give us another example of a recent award?
A. **Certainly. I was given -- awarded in 2013, a faculty fellowship from the Royal of Pharmaceutical Society, again for my leadership in research in pharmaceutical science.**

MS. RAPALINO: Defendants offer Professor Lawrence as an expert in pharmaceutical formulation and drug delivery.

MR. HASFORD: No objection as to those two fields, Your Honor.

THE COURT: Okay. Very well. The Court will recognize Professor Lawrence as an expert in those fields.

MS. RAPALINO: Thank you, your Honor.

BY MS. RAPALINO:
Q. Professor Lawrence, before we talk about the substance of your opinions in this case, I'd like to talk about some of the background science that's relevant here. Have you prepared a slide that reflects the topics that you're going to cover by way of scientific background?
A. **Yes, I have.**
Q. With reference to your slide, could you briefly review the topics that you plan to cover?
A. **I briefly intend to cover pharmaceutical formulation of ophthalmic products.**

After I've done that, I'll talk about nonsteroidal anti-inflammatories or NSAIDS, in particular the NSAID bromfenac.

After that, I'll have a discussion of quaternary ammonium compounds and in particular benzalkonium chloride, which I describe as BAC.

And, finally, I'll finish off with the discussion about surfactants and in particular surfactant tyloxapol.

Q. Very generally, beginning with the first topic that you're going to cover, what is the scientific field that's relevant to the '431 patent-in-suit?
A. **The scientific field that's relevant to the patents-in-suit is pharmaceutical formulation and in the particular formulation of ophthalmic products.**

Q. Can you describe generally what ophthalmic formulation is?
A. Yes. Basically it's making of a medicine, it's mixing the drug with various other inactive ingredients to make a product that could be administered to the patient.
Q. How would a pharmaceutical formulator as of 2003 go about making an ophthalmic solution formulation product?
A. Well, first of all, they have to have active ingredients. And once they had an active ingredient, as they're going to be formulating an ophthalmic product, they would actually know there's a range of inactive ingredients to select from, these would be well-known to the formulator and they'd be chosen specifically to perform different types of functions.
Q. And how does the formulator go about choosing the inactive ingredients to use in a particular formulation?
A. Well, basically literature gives guidance to this. So, for example, there'd be textbooks such as -- or handbooks such a Remington Pharmaceutical Excipient Handbook. There's the FDA an active ingredient guide. And there'd also be literature on similar products and that would be consulted as well.
Q. And how does the formulator, generally speaking, go about choosing the amounts of the inactive ingredient?
A. Yes, they look at the literature, consult the literature and see what range of ingredients was actually acceptable for

use in the type of product that they're interested in and, in particular, they'd consult the inactive guide of the FDA to see what was acceptable for formulation purposes.
Q. And once they had a starting point from the literature, what would the formulator then do to select the amount of the inactive ingredient?
A. Once they had selected a range, what they would look at is making preparation that contain that range of material to effectively optimize that amount of material and they would normally try to select the lowest concentration of that ingredient that was appropriate to produce a stable formulation.
Q. How many options were available to the formulator as of 2003 in terms of acceptable excipients to use in an ophthalmic solution product?
A. Very few.
Q. Why were there very few excipients that were available?
A. When you're going to be formulating product, you don't want to use an inactive ingredient, anything that hasn't already obtain regulatory approval.
Q. Why is that?
A. If it hasn't obtained regulatory approval, you would have to undertake some range of toxicity studies, which are effectively slightly less small versions of clinical trials, to prove that the excipient is actually safe for use. And, of

course, that costs a lot of money and companies aren't interested in doing that sort of thing.
Q. Have you ever published anything discussing the formulators' preference for previously approved ingredients?
A. Yes, I have.
Q. Can you turn in your binder, please, to JTX-45? Can you identify for us what JTX-45 is?
A. This is a review I published in a journal called Chemical Society Reviews in 1994 on surfactant systems they use in drug delivery.
Q. Did you say anything in this review about the limited number of excipients available to a formulator?
A. Yes, I did.
Q. Can you tell us what you said?
A. Yes. I basically explained what I've just explained to you and said that there's obviously understandable reluctance of a pharmaceutical company to actually go into full scale toxicity tests to prove, in this case because I'm talking about surfactants, a new surfactant was safe for drug delivery purposes. I stated that in 1994 it was about ten million pounds, and it's obviously going to be greater now, and, as a consequence of this, formulators only tend to look for ingredients that are recognized as safe.
Q. And can you point us to where in JTX-45 you see that statement?

A. Yes, certainly. It's on JTX-45.6 on the left-hand column under the Choice of Surfactants.
Q. Is there other literature that discusses the limited number of options for pharmaceutical ingredients that were specifically available for ophthalmic formulations as of 20003?
A. Yes, there is.
Q. Can you give us an example of another piece of literature?
A. There's a piece of literature would be Remington's, which is a handbook for pharmaceutical formulators and is sometimes known as the bible of formulation.
Q. Let's look in your binder at DKT-15. What is DKT-15?
A. This is an extract from the 20th edition of Remington: The Science and Practice of Pharmacy, this is the edition from 2000, which would have been the one formulators would have used for this present case.
Q. What does Remington say about the number of excipients available to formulate an ophthalmic solution product?
A. Yes. On DTX-015.4 on the left-hand side of the page under Additives it says, "The use of various additives in ophthalmic solution is permissible; however, the choices are very few."
Q. Would a pharmaceutical formulator as of January 2003 have known which were the few pharmaceutical excipients that had

been previously approved by FDA for use in ophthalmic solution?

A. Yes. They would have done and they would have -- to obtain this information they would have consulted with the appropriate FDA inactive ingredients guide.

Q. Can you tell us, just generally, what is the FDA inactive ingredients guide?

A. It's a listing of all excipients that are currently contained in pharmaceutical formulations that have been approved by the FDA, it lists the type of formulation and the amount of excipients or the range of excipient that is used and also the number of formulations it's contained in.

Q. Can you turn in your binder to DTK-196. What is DTX-196?

A. This is the FDA inactive guide from 1996, 1997.

Q. Okay. Now, once a pharmaceutical formulator decides that an ingredient is appropriate for inclusion in his or her ophthalmic formulation, can you just explain generally how the formulator goes about determining the right amount of that excipient to use?

A. Yes, they would undergo a process, which I've entitled here as Pharmaceutical Principles. They would use the range of concentration of that excipient that is reported in prior formulations. They would then prepare the formulations using a range of concentrations. Test those formulations to ensure that they're appropriate for their use and were stable and use

the lowest concentration possible to obtain a stable formulation.

Q. And is there a name for that process that formulators use?

A. Yes, it would be called routine optimization.

Q. And generally how does an optimization process work?

A. It's generally a systematic process in which the formulator will come up with a series of formulations containing different concentrations of the inactive ingredients, prepare the formulation and test them for the attributes that they're interested in.

Q. You mentioned earlier that the formulator is interested in using the lowest possible amount of the inactive ingredient that will be compatible with a stable formulation. Why is the formulator interested in the lowest possible amount of the inactive ingredient?

A. It's mainly in terms of toxicity because in every inactive ingredient, if used in too high concentrations, can exhibit some toxicity. So the formulator tries to use the lowest concentration that will give them a stable formulation to ensure the least toxicity possible.

Q. Okay. Let's move on to the next section of your background science tutorial.

And can you tell us, before we do that, just generally, the ingredients, the basic ingredients in the formulations

claimed in the '431 patent?

A. The basic ingredients in the '431 patent are, for nonsteroidal anti-inflammatory bromfenac, the quaternary ammonium compound is the surfactant tyloxapol.

Q. Let's start with bromfenac. We heard a little bit about this from Professor Williams so I don't want to belabor it, but can you tell us generally what the class of compounds is that bromfenac belongs to?

A. Yes, certainly. Bromfenac is an example of what's known as a nonsteroidal anti-inflammatory drug or NSAID for short.

Q. And, generally speaking, what are NSAIDS used for?

A. NSAIDS are used to treat inflammation of various types.

Q. Is there anything notable about the chemical structure of the subclass of NSAIDS to which bromfenac belongs?

A. Yes. Bromfenac belongs to a subset of NSAIDS that are called the acidic NSAIDS because they all contain an acidic or carboxyl group.

Q. Okay. Have you prepared a demonstrative showing -- demonstrating that carboxyl or carboxylic group?

A. Yes, I have.

Q. Can you point out DTX-210 where the carboxylic acid group is in bromfenac?

A. I have put up two examples of nonsteroidal anti-inflammatories, the one on the left being bromfenac, and in both cases the acidic group is on the left-hand side of the

molecule as you look at it. It's consists of a carbon, which you can't see, but that's basically at the joint between the two solid lines and the equal sign and oxygen and an OH group, which consists also of oxygen and OH.

Q. And have you prepared a demonstrative to show what happens when compounds like bromfenac are put in solution at the pH that's relevant for ophthalmic formulations?

A. Yes, I have.

Q. Can you walk us through what happens in your demonstrative?

A. Certainly.

MR. HASFORD: I'll object, your Honor, to the extent this is going into chemistry. Dr. Lawrence is not qualified here as a expert in chemistry. I'll object on that basis.

MS. RAPALINO: Your Honor, this is squarely within the scope of Professor Lawrence's expert report. And at least her opening report Paragraph 66, she testified that her Ph.D. research in pharmaceutical formulation involved several aspects of chemistry. And she's just testifying about the very, very basic chemistry that's involved in ionization of these compounds at a pH that a formulator would be most concerned with when preparing an ophthalmic solution.

MR. HASFORD: Your Honor, she has neither been offered nor qualified as an expert in chemistry. They have a chemist of Dr. Heathcock, this information could conceivably

have been in his report. Regardless of whether it happens to be in her report she's simply not an expert in chemistry. That's the basis or our objection.

THE COURT: Can you perhaps ask a few clarifying or qualifying questions to establish her expertise in this level of chemistry?

MS. RAPALINO: Yes.

BY MS. RAPALINO:

Q. Professor Lawrence, are you familiar with the chemistry, acid chemistry that's involved in the formulation of NSAIDS compounds in solution?

A. Yes, I am.

Q. And have you studied that over the course of your career?

A. Yes, I have. And to formulate medicines you have to understand basic chemistry.

Q. Thank you.

Can you then describe for us the basic chemistry that's involved in placing an NSAID expound like bromfenac into solution at the pH that's relevant for ophthalmic formulations?

THE COURT: Before you answer, are you satisfied with the foundation that's been laid?

MR. HASFORD: I think we're satisfied, your Honor, as long as she doesn't try to go into actual organic or medicinal chemistry opinions, which would be potentially something that

their chemist Dr. Heathcock would be doing.

MS. RAPALINO: We have no intention of doing that because this case is about pharmaceutical formulation and we're going to stick with the chemistry relevant for formulation.

THE COURT: Okay.

MR. HASFORD: They've argued, your Honor, in fact they argued in their opening statement chemistry is not an issue in this case. It seems improper for them to try to get that on through their formulation expert.

MS. RAPALINO: And to be fair, are --

THE COURT: Basic chemistry is relevant here and I'll permit it. And I recognize the expert as also embracing the field of chemistry of NSAIDS.

MS. RAPALINO: Thank you, your Honor.

BY MS. RAPALINO:

Q. Professor Lawrence, I'm just going to repeat that question one more time.

Could you walk us through the demonstrative that demonstrates what happens to bromfenac and other NSAIDS like it when it's put in solution at the pH that's relevant for ophthalmic solution products?

A. At the pH that's relevant for the products we're talking about today, what will happen is the hydrogen ion, which is indicated by the H and the plus, will disassociate from the

rest of the carboxylic group living in carboxylate iron, which will be negatively charged in solution.

Q. Is there another word for the negatively charged ion?

A. Yes, there is, it's called an anion.

Q. Were NSAIDS approved for any ophthalmic indications as of 2003?

A. Yes, they were. In 2003 they were used for postoperative inflammation, cystoid macular edema after cataract surgery and symptoms of allergic conjunctivitis.

Q. Is there any pre-2003 literature that discusses the use of NSAIDS in ophthalmic formulations as of that time?

A. Yes, there is.

Q. Can you turn in your binder to DTK-109, please. And once you're there, can you identify what DTK-109 is?

A. Yes. This is a chapter from a volume called New Drugs in Ophthalmology, and the particular chapter of interest is edited by Allan J. Flach and it's from -- I'm trying to find the year. I'm sorry. From 1996.

Q. What does this chapter by Allan Flach say about the NSAID drug and indications that were approved as of 2003?

A. On DTK-109.6 at the top of the page it points out that the flurbiprofen, suprofen, ketorolac, and diclofenac had been approved by the FDA for ophthalmic use.

Q. Okay. We heard a little bit about this this morning so we won't belabor this either. Was bromfenac marketed anywhere

as of 2003?

A. Yes, it was.

Q. Where was bromfenac marketed?'

A. Bromfenac was marketed in Japan as of 2000.

Q. And what was the name of that product?

A. The product was called Bronuck®.

Q. Has bromfenac been marketed in the United States under any name?

A. Yes, it has, it was marketed in 2005 as a once -- I'm sorry, twice daily formulation known as Xibrom® and this formulation was identical to the Bronuck® formulation.

Q. Has it been marketed in the United States under any other name?

A. Yes, in 2010 Xibrom® replaced Bromday® and this was now a once daily formulation.

THE COURT: Excuse me. Isn't it the other way around, Bromday® replaced Xibrom®?

THE WITNESS: I'm sorry, did I say it wrong, your Honor?

THE COURT: Perhaps. You could correct the record.

THE WITNESS: Thank you.

BY MS. RAPALINO:

Q. Was Bromday® marketed under any other name besides Xibrom® in the U.S.?

A. Yes, in 2010 Bromday® replaced Xibrom® as a once daily

preparation.
Q. And how is bromfenac marketed in the United States now?
A. **In 2013 Prolensa® replaced Bromday®, which is a slightly different formulation than the previous formulations. This** 06:34 **formulation is used for postoperative inflammation and reduction of ocular pain after cataract surgery.**
Q. Okay. Now, that we've talked about bromfenac and NSAIDS, let's move to benzalkonium chloride, the next ingredient you said was in the claimed formulations. What is benzalkonium 06:35 chloride used for?
A. **Benzalkonium chloride, or BAC, is a widely used preservative in ophthalmic preparations.**
Q. Is there anything notable about the chemical structure of benzalkonium chloride?
06:35 A. **This slide here shows the structure of benzalkonium chloride. As can be seen on the right-hand side, there's a long carbon chain that's indicated by the zigzags. On the left-hand side there's a benzene ring which is a lozenge-like structure, and in the center is a nitrogen which in solution** 06:35 **is positively charged.**
Q. And is there another name for a positively charged compound?
A. **Yes, a cation.**
Q. And just to be clear is benzalkonium chloride a single 06:35 compound?

A. **No, it's a mixture of compounds. The carbon chain length, which is shown on the right-hand side here as C12, varies between 8 and 18.**
Q. Now, why are antimicrobial preservatives like 06:36 benzalkonium chloride used in ophthalmic products at all?
A. **They are particularly important when that product is a multidose formulation because every time the patient opens the bottle to use it, there's a chance that that formulation might get contaminated, for example, with microbes such as fungi or** 06:36 **bacteria, and obviously, if that happens, there's no preservative, they can grow, and then they can contaminate the patient's eye when it is used next time.**
Q. How common was the use of benzalkonium chloride as a preservative in ophthalmic solution products as of 2003?
06:36 A. **It was very widely used.**
Q. Is there any literature that talks about how common it was, how common benzalkonium chloride was in ophthalmic products?
A. **Yes, there is. Remington's refers to this.**
06:36 Q. Okay. Can you remind us briefly, what was Remington's?
A. **Certainly. Remington's is a handbook of pharmaceutical formulation and what I referred to earlier as almost like a bible for formulators.**
Q. So, let's look back at Remington's at DTX-15 in your 06:37 binder. What does Remington's say about the prevalence of the

use of benzalkonium chloride in ophthalmic formulations?
A. **On DTX-015.5, on the left-hand column under quaternary ammonium compounds, it states that benzalkonium chloride is a typical quaternary ammonium compound and is by far the most** 06:37 **common preservative used in ophthalmic preparations. And it goes on to say it was used in over 65 percent of all commercial ophthalmic preparations.**
Q. As of 2003, were there any known disadvantages to benzalkonium chloride?
06:37 A. **Yes, there were.**
Q. What were those known disadvantages?
A. **One of the disadvantages, you had to be careful of the concentration of benzalkonium chloride you use because too high a concentration was known to be toxic to the eye, which** 06:38 **obviously is a bad property. And in addition, benzalkonium chloride was known to interact with negatively charged compounds.**
Q. Does Remington's say anything about that problem, that latter problem?
06:38 A. **Yes, it does.**
Q. What does Remington's say?
A. **On the same page, in the same paragraph, it states that as a cationic material of high molecular weight, in other words, that's benzalkonium chloride, it's not compatible with** 06:38 **unionic compounds.**

Q. Did formulators as of 2003 avoid using benzalkonium chloride because of these known problems?
A. **No, they did not.**
Q. Does Remington's say anything about the approach to be 06:38 taken?
A. **Yes, it does. Also, in the same paragraph, obviously on the same page, it states that given the alternative, it would be preferable to modify a formulation to remove the incompatibility rather than include a compatible but less** 06:39 **effective preservative.**
Q. Okay. Let's move on now to your discussion of surfactants and tyloxapol. Can you remind us just very briefly what a surfactant is?
A. **Yes. Surfactants are unique compounds in that they** 06:39 **consist of a region that likes water, in other words, it's water soluble, and a region that dislikes water and is water-insoluble, and as a consequence, these properties -- I'm sorry, yes, the consequence of these properties are particularly advantageous in pharmaceutical formulation.**
06:39 Q. Let's talk specifically about tyloxapol. What is tyloxapol?
A. **First of all, tyloxapol is a nonionic surfactant. That means when it is dissolved in solution, it's electrically neutral, it carries no charge.**
06:40 Q. And what class of nonionic surfactants does tyloxapol

belong to?
A. Tyloxapol is an ethoxylated octylphenol surfactant.
Q. Can you explain what you mean by ethoxylated?
A. Yes, I can. If we look at the very schematic representation on the slide, you can see on the right hand of the slide I have marked a portion in yellow. This is the ethoxylated portion of the molecule and this is the water soluble part of the molecule.
Q. And what do you mean when you say that it is an octylphenol surfactant?
A. An octylphenol surfactant, if we look at now the blue highlighted -- I'm sorry, can I just have a drink?
THE COURT: Sure.
THE WITNESS: Sorry. Sorry. If we look at the blue portion that's highlighted with the benzene ring, the lozenge structure and the branch chain, that's an octylphenol region of the surfactant and that's the region of surfactant that doesn't dissolve in water, is water-insoluble.
BY MS. RAPALINO:
Q. Is tyloxapol a single compound?
A. No, it's not. It's a mixture of compounds. It consists of different chain lengths of the ethoxylated portion and different numbers of ethoxylate -- and oxy phenol groups in the molecule.
Q. As of 2003, were there other surfactants within the class

of ethoxylated octylphenol surfactants?
A. There were a large number, but there were only two that were suitable for use in ophthalmic preparations.
Q. Why do you say there were only two that were suitable for use in ophthalmic preparation?
A. There were only two octylphenol surfactants, octylphenol ethoxylated surfactants that were actually listed in the FDA Inactive Ingredient Guide.
Q. What were those two ethoxylated octylphenol surfactants that were listed in the FDA Inactive Ingredient Guide as previously approved surfactants?
A. For ophthalmic use, there was tyloxapol and octanol 40.
Q. Okay. Professor Lawrence, now that we've covered some of that background science, let's turn to your opinions in this case. Can you tell us briefly what issues you were asked to consider with respect to claims 6 and 20 of the '431 patent?
A. Yes. Firstly, I was asked to consider whether claims 6 and 20 of the '431 patent would have been obvious to a person of ordinary skill in the art as of January 2003 in view of that prior art for obviousness. And for obviousness type double patenting, I was asked to consider whether claims 6 and 20 of the '431 patent were obvious in view of claim 7 of the '290 patent and claim 6 of the '131 patent.
Q. With respect to the first issue, the obviousness issue you were asked to consider, were you asked to look at the

prior art as of a particular date?
A. Yes, I was, and that date was January 2003.
Q. What type of prior art generally did you review?
A. I reviewed the patent literature, scientific journals, and reference handbooks and textbooks.
Q. After forming your opinions in this case, did you review any other documents besides the publicly available literature?
A. Yes. Only after I formed my opinion in this case, I reviewed Senju's internal documents, and I reviewed these to see whether or not they agreed with my opinions, which they did.
MR. HASFORD: I'll object, your Honor, and move to strike. The review of Senju's internal documents has already been taken off the table by agreement of the parties. It is certainly not proper to any kind of obviousness case per Federal Circuit case law.
MS. RAPALINO: Your Honor, as Professor Lawrence just testified, she did not rely on her review of any internal documents in support of her obviousness opinion. She simply reviewed those documents after forming her opinion to determine whether or not they were consistent with her opinion, and there is Federal Circuit case law directly on point that supports the use of a patentee's internal documents for that very purpose, just to show that it is consistent with the expert's opinion about the state of the knowledge in the

art as of the time that the invention was made.
MR. HASFORD: We disagree with that characterization, your Honor. The statute itself says "patentability shall not be negative by the manner in which the invention is made." That's straight out of 35, U.S.C., Section 103. She shouldn't be testifying about internal documents if she is not relying on them in connection with an obviousness case, and she cannot by statute.
THE COURT: Well, could it be clarified, because I didn't get that from her testimony, that the witness is not relying on the internal documents as a basis for her opinion?
MS. RAPALINO: I can clarify that with the witness.
THE COURT: All right.
BY MS. RAPALINO:
Q. Professor Lawrence, have you relied on the internal Senju documents in support of your obviousness opinion?
A. No, I definitely didn't rely on those documents in support of my obviousness opinion.
MR. HASFORD: And I'll object and move to strike the last portion of that statement, your Honor. If she is not relying on them as relevant to her obviousness opinion, there's no need and no reason for her to testify about them and they shouldn't come in.
MS. RAPALINO: Your Honor, again, the threshold for relevance here under 402 is a liberal one, and the fact that

they are not the direct support for her obviousness opinion does not render those documents irrelevant to the issues. They are still relevant as making more likely than not her opinions in this case which she arrived at independently of her review of those internal documents.

MR. HASFORD: We disagree entirely with the statement about the liberality or alleged liberality of Federal Rule 402. The fact is they are not relevant to an obviousness case. The statute says so, the Federal Circuit case law says so. She has disclaimed any reliance on those in connection with her obviousness opinion. She should not be permitted to testify about them, your Honor.

MS. RAPALINO: If I could, there is a Federal Circuit case again directly on point. It's the *Thomas & Betts Corp. V. Litton Systems, Inc.* Case at 720 F.2d 1572. This is a Fed Circuit 1983 case holding that a plaintiff's internal studies, although they were not technically prior art, were proper -- can be properly used as indicators of the level of ordinary skill in the art to which the invention pertained and were admissible as evidence.

MR. HASFORD: And I'm not aware that that case has been cited anywhere, your Honor, in their case law statement, in the joint pretrial order. Even if it has, it sound like it's a case, even if counsel's characterization of it is correct, from well over 30 years ago and it is not consistent

with the statute, if that's how she is describing it.

MS. RAPALINO: The case that -- the case --

THE COURT: Excuse me. It was cited in connection with one of the motions in limine, and it did provide an example consistent with what counsel has argued, that I do recall.

MR. HASFORD: Well, your Honor, so I'm looking at what's in the joint pretrial order here. I apologize, your Honor. So, regardless of whether they cited it in their motion in limine, the reality is, the statute is as I presented it to you. There are also other Federal Circuit cases, for example, *Life Techs v. Clontech*, 224 F.3d 1320, 1325, Federal Circuit 2000, specifically stating, "the path that leads an inventor to the invention is expressly made irrelevant to patentability by statute."

And then *Otsuka Pharmaceutical Company v. Sandoz*, which is actually a case that opposing counsel, Ms. Holland, was involved with and I was involved with, your Honor, 678 F.3d 1280, 1296, Federal Circuit 2012, essentially says the same thing.

MS. RAPALINO: And, your Honor, if I could just address those two cases briefly, starting with the *Otsuka* case. In the *Otsuka* case, what the Court actually held was that obviousness couldn't be based on the inventor's internal path to development, but the Court did not preclude -- did not

exclude that evidence at trial. In fact, accepted that evidence and just found that it was -- that that wasn't -- that that evidence wasn't sufficient, was not a sufficient basis to support obviousness.

And, again, here we're not trying to use plaintiff's internal documents to support our obviousness position. It's merely to show that their internal documents are consistent with what Professor Lawrence will present is the state -- was the state-of-the-art as of January 2003.

With respect to the *Life Technologies v. Clontech* case, that case is not about Rule 402 at all. It is about whether prior art was material and should have been submitted to the Patent Office, which is an entirely different analysis and a different standard from Rule 402 relevance.

MR. HASFORD: And I believe I have some clarification on the case law that defendant cited, your Honor. So, there, the Federal circuit has at times approved the use of unpublished internal documents only for the limited purpose of ascertaining the level of ordinary skill in the art, and that's the *Thomas & Betts* case that they cited, held that internal documents were "properly used as indicators of the level of ordinary skill in the art to which the invention pertained."

And so for that limited purpose they were allowed, but the defendants here are trying to take the next step, your

Honor, and use internal documents to make or confirm conclusions about the teachings of the prior art, and that is expressly prohibited by statute. That's expressly prohibited by the portion of the patent statute that says "patentability shall not be negative by the manner in which the invention was made." That's 35, U.S.C., Section 103.

And that's also confirmed by other cases, and, in fact, there's a case out of the Fed Circuit *In re Omeprazole Patent Litigation*, it's an unpublished case, but it's at 84 Fed Appendix 76, 81, and it's Fed Circuit 2003. And it says, "GenPharm reads too much into *Thomas & Betts* because, unlike here, the document at issue in that case received additional support in the form of testimony about the state-of-the-art at the time of the publication."

In other words, they can't take the next step and try to use these internal documents as evidence of or even as confirmatory of their obviousness case.

MS. RAPALINO: And again, your Honor, I would submit that we're planning to offer this evidence for precisely the purpose that it was offered in *Thomas & Betts*. This is purely to offer testimony that indicates the level of ordinary skill in the art to which the invention pertained, which includes the person of ordinary skill in the art's understanding of what the prior art taught at that time.

THE COURT: Well, is the -- just a moment. Is the

witness offering it for that purpose? I understand *Thomas & Betts* permits it where it is evidence that indicates the ordinary skill in the art as of that time. Is that the purpose? Because I thought a moment ago you said that the
06:51 purpose was it is confirmatory of the witness's opinions.

MS. RAPALINO: Well, I think that to the extent that the witness's opinions, part of the obviousness analysis is an analysis of the level of skill in the art, and based on that level of skill in the art, the scope of the prior art and how
06:52 that art would have been understood, that the documents from plaintiff's internal files are confirmatory of those opinions, which go precisely to the issue of the level of skill in the art.

THE COURT: I'm going to grant -- I'm going to
06:52 sustain the objection in part and overrule it in part. I will permit it to be offered for a limited purpose, and the limited purpose is as an indicator of the ordinary skill in the art that existed at that time. I'll sustain the objection and not receive the opinion -- I'm sorry, not receive the testimony
06:52 about internal documents to the extent that they are offered as confirmation of this witness's opinion that she has developed for the trial. And so in that way I think that the *Thomas & Betts* precedent is honored and that the witness will be permitted to testify.

06:53 MS. RAPALINO: Your Honor, if I just may quote one

more quote from the *Thomas & Betts* case. The Federal Circuit there permitted this internal data, internal criteria as evidence of what would have been within the knowledge of one of ordinary skill in the art. And so thus, the criteria,
06:53 though not technically prior art, were in effect properly used as indicators of the level of ordinary skill in the art.

So, again, that level of ordinary skill in the art includes, includes the information regarding the knowledge of one of ordinary skill in the art, what would have been within
06:53 the knowledge of a person of ordinary skill in the art.

MR. HASFORD: We disagree here, your Honor. What they're trying to do is they're trying to take this very limited exception, to the extent there really even is an exception, and try to swallow the whole with it and
06:54 effectively backdoor this information in violation of the statute. 35, U.S.C., Section 103 is clear on its face, and that's the basis for our objection.

THE COURT: Well, it is an indicator of the ordinary skill in the art. If it is offered for that purpose, then
06:54 it's admissible, is it not?

MR. HASFORD: Under *Thomas & Betts*, they accepted it for that limited purpose, but it is certainly not available to confirm or to support her underlying obviousness opinions.

THE COURT: That's what I ruled five minutes ago. I
06:54 sustained your objection to that extent, and I don't think

that Ms. Rapalino has argued something to the contrary. So, I'll permit it to that limited extent.

MS. RAPALINO: Thank you, your Honor.

THE COURT: And we only have a few more minutes this
06:54 afternoon in any event.

MS. RAPALINO: Okay. We're about to launch into sort of the details of the obviousness opinion, and if it makes sense, we could just start with that first thing in the morning.

06:54 MR. HASFORD: We're fine with that, your Honor.

THE COURT: Okay. Then let's conclude for today, and the witness is excused for the day. Thank you very much. Don't forget to come back tomorrow morning.

MS. RAPALINO: May I ask a point of clarification
06:55 regarding your Honor's practices? I understand the general rule with the witness is so long as they are still on direct, we can confer with the witness. Is there anything we should know about your Honor's practice with respect to that?

THE COURT: Thanks for asking, because we should
06:55 speak now about sequestration of witnesses. I notice that it is in the pretrial order and that all sides have agreed that there should be sequestration of witnesses until they have finished testifying. Is that right?

MS. RAPALINO: I think what the pretrial order says
06:55 is that there's sequestration of fact witnesses. As it turns

out, neither party has called any fact witnesses, which I think renders that provision in the pretrial order moot.

THE COURT: Okay. So, there's no fact witnesses in the trial even from the -- from the plaintiffs?

06:55 MR. HASFORD: We're not calling any fact witnesses, your Honor. We're only calling experts.

THE COURT: All right. Then the sequestration would not apply to experts. Experts can be present and enjoy the entire trial.

06:56 And so now you asked about the rule of not conferring during cross-examination, and that is, I think, the standard, that when you have a witness on the stand who is under cross-examination by your adversary, that during breaks and even during the overnight, you're not permitted to confer with
06:56 them for the purpose of rehabilitating their testimony. Of course, you are permitted on redirect to ask any questions that you want, but they can't be pre-coached while your witness is on cross. Is that a clear formulation for both sides?

06:56 MR. HASFORD: It is for us, your Honor.

MS. RAPALINO: It is for us, your Honor. Thank you.

MR. MUKERJEE: Yes, your Honor.

THE COURT: All right. Anything else?

MR. HASFORD: Nothing from plaintiffs, your Honor.

06:56 THE COURT: Okay. Very well, then we will adjourn to

tomorrow morning at 9:30.

MS. RAPALINO: Thank you.

(Proceedings concluded at 4:29 p.m.)

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, -vs-

CIVIL ACTION NUMBER: 14-667 (JBS/KMW)

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, -vs-

CIVIL ACTION NUMBER: 14-4149 (JBS/KMW)

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

Mitchell H. Cohen United States Courthouse
One John F. Gerry Plaza
Camden, New Jersey 08101
Tuesday, April 5, 2016

B E F O R E: THE HONORABLE JEROME B. SIMANDLE
CHIEF JUDGE
UNITED STATES DISTRICT JUDGE

Certified as true and correct as required by Title 28, U.S.C., Section 753.
/S/ Lisa Marcus, CCR, CRR, /S/ Karen Friedlander, CCR, CRR, /S/ Robert T. Tate, CCR, CRR, /S/ Carol Farrell, CCR, CRR

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, -vs-

CIVIL ACTION NUMBER: 14-5144 (JBS/KMW)

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, -vs-

CIVIL ACTION NUMBER: 15-335 (JBS/KMW)

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, -vs-

CIVIL ACTION NUMBER: 14-5144 (JBS/KMW)

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, -vs-

CIVIL ACTION NUMBER: 15-335 (JBS/KMW)

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, -vs-

CIVIL ACTION NUMBER: 14-6893 (JBS/KMW)

INNOPHARMA LICENSING, INC., et al.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, -vs-

CIVIL ACTION NUMBER: 15-3240 (JBS/KMW)

INNOPHARMA LICENSING, INC.,

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INDEX

EXHIBITS

(In open court at 9:31 a.m.)

THE DEPUTY COURT CLERK: All rise.

00:00 THE COURT: Be seated, please. Good morning.

00:00 Good morning.

00:00 THE WITNESS: Good morning.

00:00 THE COURT: Are we ready to resume?

00:00 MR. HASFORD: Plaintiffs are ready, your Honor.

00:00 MS. RAPALINO: Yes, your Honor.

00:00 THE COURT: Okay. Then go ahead.

00:00 MS. RAPALINO: Thank you.

(DIRECT EXAMINATION OF PROFESSOR LAWRENCE BY MS. RAPALINO:)

00:00 **Q.** Good morning, Professor Lawrence.

00:00 **A. Good morning.**

00:00 **Q.** When we left off yesterday we were about to talk about your obviousness opinion. Have you applied any particular framework in determining whether the asserted claims of the '431 patent are obvious?

00:00 **A. Yes, I have.**

00:00 **Q.** Have you set forth that framework in a demonstrative?

00:00 **A. Yes, I have. It's DDX2-21. What I did was considered the qualifications of a person of ordinary skill in the art, the scope of the prior art, differences between the prior art and the claims, and determined whether the claims were obvious in view of the prior art; and in particular, whether the person of ordinary skill in the art would have been motivated**

to make and use the formulations of the asserted claims and have had a reasonable expectation of success upon doing so.

Q. Now, you used the term "person of ordinary skill in the art." Have you considered what the qualifications and level of skill of the person of ordinary skill in the art would be?

A. Yes, I have.

Q. What were the qualifications of the person of ordinary skill in the art as of 2003?

A. As of 2003, a person of ordinary skill in the art would have had a Ph.D. in pharmaceutical science and training and experience in the research and development of pharmaceuticals.

Q. Are you aware that Professor Williams has offered a different opinion, a different definition for the person of ordinary skill in the art?

A. Yes, I am.

Q. Generally speaking, can you just remind us what his definition was?

A. Yes. That a person of ordinary skill in the art as of January 2003 will have a bachelor's degree in pharmaceutical chemistry, chemistry or related discipline, and about three to five years work experience or comparable level of education and training.

Q. Do you agree with the definition that Professor Williams offered?

A. No, I don't. I think it's very broad and I'm rather

surprised it doesn't actually list pharmaceutical science in that list. And, for example, it would include someone with degree of chemistry working in the agrochemical industry, which is obviously not appropriate in a case like this.

Q. Would you agree that a pharmaceutical formulator would consult a chemist or an organic chemist on issues of pharmaceutical formulation?

A. It wouldn't actually dawn on me as a pharmaceutical formulator to consult a pharmaceutical chemist, certainly on this type of issues that we are discussing here, such as complexation.

Q. Why wouldn't you consult an organic chemist on those issues?

A. Because this type of information is well known by -- would have been well known by a person of ordinary skill in the art at the time.

Q. Can you summarize what conclusions you reached concerning the obviousness of the asserted claims?

A. Yes. It's my opinion that claims 6 and 20 of the '431 patent are obvious over the '225 patent and in view of EP 984.

Q. And can you explain in a little bit more detail the basis for that opinion?

A. Certainly. A person of ordinary skill in the art would have started with Example 6 of the '225 patent, and actually replaced the polysorbate with tyloxapol and, by routine

optimization, ended up with the concentrations that are present in the '431 patent.

Q. Okay. Let's start with claim 20 of the '431 patent. Have you prepared a slide showing claim 20 rewritten in independent form?

A. Yes, I have.

Q. Okay. Is that at DDX2-25?

A. Yes, it is.

Q. What does claim 20 of the '431 patent cover?

A. It's directed towards the preparation of a liquid aqueous formulation and is intended for ophthalmic use and contains bromfenac sodium, tyloxapol, and a range of other ingredients, including benzalkonium chloride.

Q. And now you also mentioned that this is obvious over the '225 patent. Could you turn in your binder to JTX-147? Are you there?

A. I am.

Q. Is this the '225 patent you are referring to?

A. Yes, it is.

Q. What does Example 6 of the '225 patent disclose?

A. It discloses an aqueous ophthalmic preparation containing bromfenac sodium, polysorbate, benzalkonium chloride, and the same range of other ingredients.

Q. Now, you said it discloses bromfenac sodium. Where do you see that in Example 6 of the '225 patent?

A. The long chemical name on lines 2 -- 1 and 2 of the ingredient list is bromfenac sodium.

Q. Have you prepared a slide comparing claim 20 of the '431 patent in suit to Example 6 of the prior art '225 patent?

A. Yes, I have.

Q. Is that DTX2-27?

A. Yes, it is. On the left-hand side, I have reproduced Example 6 of '225 patent while on the right-hand side there's claim 20 of the '431 patent.

Q. And can you explain how the Example 6 of the '225 patent compares to claim 20 of the '431 patent?

A. Yes. As I have just said, both are directed towards aqueous liquid preparations for ophthalmic administration.

Q. Is that what you have highlighted here?

A. Yes. That's highlighted in yellow on the slide. Both contain bromfenac sodium. Both contain boric acid. Both contain borax or, as it is sometimes known, sodium tetraborate.

Q. Are those two compounds the same?

A. They are indeed, yes. They both contain either disodium edetate or EDTA sodium salt, which both parties have agreed for the purposes of this case are the same thing.

Q. How else are they similar?

A. They both contain benzalkonium chloride. They both contain polyvinylpyrrolidone, which is sometimes known as

povidone, and they both contain sodium sulfite.
Q. How do the amounts, the amount of sodium bromfenac in Example 6 of the '225 patent, how does that compare to the range of concentrations for bromfenac sodium in claim 20 of the '431 patent?
A. **Yes. Example 6 of the '225 patent states sodium bromfenac is present at .1 gram in a hundred ml which is .1 percent, and as you can see, .1 percent falls within the concentration range claim for bromfenac in claim 20 of the '431 patent.**
Q. Now, before we delve more deeply into your obviousness opinion, let's take a step back and talk about the scope of the prior art. Did you review prior art literature that reflected the scope of the art with respect to formulation of ophthalmic NSAID products as of 2003?
A. **Yes, I did.**
Q. What type of references did you consider?
A. **I considered the patent literature and scientific papers, handbooks, textbooks from the time.**
Q. Have you organized those references in any way for purposes of your presentation today?
A. **Yes, I have.**
Q. Can you explain how you organized them?
A. **Yes. This is explained on DTX-29. I've grouped the prior art into three groups. Group A deals with bromfenac and**

the fact that its usefulness as an NSAID in ophthalmic preparations was known as of January 2003. The second group, which I have called group B, deals with the preservative benzalkonium chloride showing that it was widely known as was its compatibility with NSAIDs. And finally, group C, which deals with the prior art around the use of ethoxylated octylphenol surfactants and how they were used to solve the complexation problem with BAC, and tyloxapol's use in ophthalmic solutions at the time was known.
Q. Okay. Let's start with your group A references. What prior art references did you put into the category of group A?
A. **I have put in four references. They are *New Drugs in Japan* from 2001, which is JTX-210, Hara from 2000, which is DTX-110, U.S. patent number 4,910,225 from 1990, which is JTX-147, and U.S. patent number 5,475,034 from 1995, which is JTX-168.**
Q. And can you remind us just at a general level what these references teach?
A. **Yes, certainly. Taken together, these references teach that the usefulness of bromfenac as an NSAID in ophthalmic preparations was known at the time.**
Q. Let's talk about each of those references in turn. Could you turn in your binder to JTX-210, please? What is JTX-210?
A. **This is an extract from *New Drugs in Japan* from 2001.**
Q. What does this *New Drugs in Japan* reference, JTX-210,

teach about bromfenac sodium?
A. **Yes. JTX-210.4, an extract of which is reproduced on the slide DDX2-31, states that bromfenac sodium was the active ingredient of Bronuck and was a new NSAID drug.**
Q. Does *New Drugs in Japan* say anything about when Bronuck was approved?
A. **Yes, it does. On the same page, further down, it states this was approved in Japan as of March 2000 and for use for a variety of inflammation conditions of the eye.**
Q. Does the *New Drugs in Japan* reference, JTX-210, say anything about the formulation of Bronuck?
A. **Yes, it does. It lists the ingredients of the formulation of Bronuck, stating that it contains 1 milligram per ml of the sodium hydrate salt, and as other ingredients contain boric acid, borax, sodium sulfite, sodium edetate, povidone, which is obviously polyvinylpyrrolidone, polysorbate 80, and benzalkonium chloride.**
Q. Generally speaking, what would a person of ordinary skill in the art understand from the *New Drugs in Japan* reference?
A. **They would have understood that bromfenac was a new drug that was useful to treat various inflammation conditions in the eye, and that it was on the market in Japan being approved of -- as of March 2000, and would also know the ingredients the formulation contained.**
Q. Let's move on to the next reference in your group A.

Could you turn in your binder to DTX-110, please? What is DTX-110?
A. **This is an extract from a book Clinics & Drug Therapy from 2000. Specifically, it is an evaluation of new drugs by clinicians and that new drug is bromfenac sodium hydrate, and it's written by Hara.**
Q. What does the Hara reference teach about the indications for bromfenac?
A. **On DTX-110.2 on the first column, it states that bromfenac sodium hydrate was developed to treat a range of inflammatory conditions of the eye.**
Q. Does the Hara reference teach anything about how bromfenac compares to other NSAIDs?
A. **Yes, it does. It specifically compares it with three other NSAID drugs on the market, pranoprofen, indomethacin and diclofenac sodium.**
Q. What does the Hara reference conclude about that comparison?
A. **On DTX-110.2 -- sorry. On DTX-110.3, under the section entitled Conclusion, it states that this drug, in other words, bromfenac, shows superior efficacy in treating anterior eye inflammation and postoperative inflammation.**
Q. And did you say that's under the section entitled Comments?
A. **Sorry, did I -- yes, Comments.**

00:14 Q. Okay. Let's look now at the next reference in group A.
00:14 Could you turn in your binder to JTX-147? Are you there?
00:15 **A. Yes.**
00:15 Q. Okay. And can you just remind us what JTX-147 is?
00:15 **A. This is U.S. patent number 4,910,225 from the 20th of**
00:15 **March, 1990, and this is what I've been referring to as the**
00:15 **'225 patent.**
00:15 Q. Generally speaking, what is the '225 patent directed to?
00:15 **A. It's concerned with preparing formulations for**
00:15 **ophthalmic -- predominantly for ophthalmic use of the**
00:15 **nonsteroidal antiinflammatory bromfenac.**
00:15 Q. Can you remind us, is there a specific example from the
00:15 '225 patent that is particularly relevant here?
00:15 **A. Yes, there is. That is on JTX-147.6 and is Example 6.**
00:15 Q. Why is Example 6 particularly relevant to a person of
00:16 ordinary skill in the art?
00:16 **A. As you can see on DDX2-33, the list of ingredients on**
00:16 **Example 6 of the '225 patent is identical to the list of**
00:16 **ingredients in the Bronuck formulation I showed you a few**
00:16 **minutes ago.**
00:16 Q. Let's move on to the last reference in your group A. Can
00:16 you turn in your binder, please, to JTX-168? What is JTX-168?
00:16 **A. This is U.S. patent number 5,475,034 from December the**
00:16 **12th, 1995, and I've been referring -- I refer to this as the**
00:16 **'034 patent.**

00:16 Q. What does the '034 patent teach about the activity of
00:16 bromfenac compared to other NSAIDs?
00:16 **A. On Table 1, which is produced on JTX-168.9, there's a**
00:17 **table showing the results of a range of antiinflammatory**
00:17 **agents, some of which have been synthesized specifically for**
00:17 **this study. So, it compares the results in a range, in a**
00:17 **range of in vivo and in vitro tests.**
00:17 Q. Okay. And what do -- so, can you explain just by
00:17 reference to the table what kind of data you see represented
00:17 here?
00:17 **A. Yes. What you can see is in columns 4 and 5, there's**
00:17 **results of in vitro data, whereas in columns 6 and 7, this is**
00:17 **in vivo data, while column 1 lists the range of compounds that**
00:17 **are being tested. I've highlighted bromfenac and another well**
00:18 **known nonsteroidal antiinflammatory diclofenac.**
00:18 Q. And what do the data for bromfenac and diclofenac teach
00:18 about the activity of bromfenac?
00:18 **A. They show that bromfenac in the tests is either better**
00:18 **than or at least comparable to the results obtained with**
00:18 **diclofenac.**
00:18 Q. What did the authors of the patent, the '034 patent
00:18 conclude about the activity?
00:18 **A. On page JTX-168.8, under the section entitled Results at**
00:18 **the bottom of the first paragraph, they state similar results**
00:18 **were obtained with the reference compound, diclofenac. And**

00:18 **then this is a significant bit. It states that diclofenac was**
00:18 **somewhat less effective both in vitro and in vivo than the**
00:19 **chloro or bromo substituted 2-amino-3-benzoylbenzeneacetic**
00:19 **acids.**
00:19 Q. And which compound in Table 1 is the bromo substituted
00:19 2-amino-3-benzoylbenzeneacetic acids?
00:19 **A. That would be bromfenac.**
00:19 Q. And so what would a person of ordinary skill in the art
00:19 understand from that conclusion in the patent?
00:19 **A. They would understand that bromfenac demonstrated a good**
00:19 **level of activity, better than or comparable to diclofenac,**
00:19 **and think it would have been an interesting drug to look at**
00:19 **formulating.**
00:19 Q. Are you aware that plaintiff's experts have argued that
00:19 this '034 patent showed that bromfenac was not as good as
00:19 diclofenac?
00:19 **A. Yes, I am.**
00:19 Q. Do you agree with that?
00:19 **A. No. I think they probably misread the results in this**
00:20 **patent.**
00:20 Q. Can you summarize for us then what the references in
00:20 group A taken together would have taught to the person of
00:20 ordinary skill in the art?
00:20 **A. Firstly, that bromfenac was known to be marketed,**
00:20 **marketed as a commercial formulation in Japan. In addition,**

00:20 **bromfenac was known to be more effective for some indications**
00:20 **than other nonsteroidal antiinflammatories, that the**
00:20 **ingredients of the marketed formulation were known, and that**
00:20 **marketed formulation contained bromfenac, benzalkonium**
00:20 **chloride and polysorbate 80.**
00:20 Q. Okay. Let's move on to the references in group B. Can
00:20 you just tell us which references you have put into the group
00:20 B category?
00:20 **A. Yes, I have. They are U.S. patent number 5,558,876 from**
00:20 **1996, which is JTX-201, patent WO 94/15597 from 1994, which is**
00:21 **JTX-207, U.S. patent number 5,603,929 from 1997, which is**
00:21 **JTX-061, and Remington's from 2000, which is DTX-15.**
00:21 Q. And just in a general way, what do the references in
00:21 group B teach to the person of ordinary skill in the art?
00:21 **A. Firstly, that the preservative benzalkonium chloride was**
00:21 **widely used and its incompatibility between nonsteroidal**
00:21 **antiinflammatory drugs and benzalkonium chloride was known at**
00:21 **the time.**
00:21 Q. Let's look at your first reference in group B. Could you
00:21 turn in your binder, please, to JTX-201? What is JTX-201?
00:22 **A. This is U.S. patent number 5,558,876 from the 24th of**
00:22 **September, 1996.**
00:22 Q. And generally what is the '876 patent directed to?
00:22 **A. This is directed towards the development of an ophthalmic**
00:22 **formulation of acidic drugs.**

00:22 Q. Does the '876 patent say anything about what happens to NSAID drugs with benzalkonium chloride in a formulation?
00:22 **A. Yes. DDX2-37 reproduces an extract from JTX-201.3, which states that the drugs tend to form insoluble complexes with quaternary ammonium preservatives such as benzalkonium chloride.**
00:23 Q. And the drugs referred to in that statement, which drugs is that referring to?
00:23 **A. These are referring to -- I'm sorry, these are referring to nonsteroidal antiinflammatory drugs.**
00:23 Q. And so what does this reference teach the person of ordinary skill in the art about what happens to NSAIDs and benzalkonium chloride in solution?
00:23 **A. It tells us there's an interaction between the benzalkonium chloride and the nonsteroidal antiinflammatory such that an insoluble complex is formed.**
00:23 Q. Have you prepared a demonstrative to show how that complexation between an NSAID and benzalkonium chloride occurs?
00:23 **A. Yes, I have.**
00:23 Q. Is that at DDX2-38?
00:23 **A. Yes, it is.**
00:23 Q. Can you walk us through this demonstrative?
00:23 **A. Certainly. On the top right-hand side we have a nonsteroidal antiinflammatory. As I indicated yesterday, the**

00:24 **carboxylic acid group is on the left-hand side of the molecule and that is highlighted in green. When that's in solution, the proton will dissociate from the rest of the molecule, leaving a negatively charged anion in solution.**
00:24 **Dealing now with the benzalkonium chloride, which you can see at the bottom just above the beaker, this has, as you can see, a positive charge and a negative charge. In solution, the chloride ion would dissociate from the rest of the benzalkonium chloride leaving a positively charged cationic molecule, both the hydrogen and chloride ions would go into solution, and then the negatively charged anionic drug would be attracted to the positive charge on the benzalkonium chloride, as I've shown here, and you can see now there's a big -- there's a complex between that NSAID and the benzalkonium chloride. There's no charge on that. It is effectively neutral, because the two charges have neutralized each other, so we have a very large water-insoluble complex resulting, which I've tried to show by the white dots in the beaker.**
00:25 Q. Okay. Let's look at the next reference in your group B set of references. Could you turn in your binder to JTX-207?
00:25 **A. Yes.**
00:25 Q. What is JTX-207?
00:25 **A. This is WO 94/15597, publication date 21st of July, 1984.**
00:25 Q. I think you may have misspoken. Did you mean 1994?

00:25 **A. I'm sorry, 1994, yes.**
00:25 Q. And generally speaking, what is the WO 597 reference
00:26 directed to?
00:26 **A. This is a preparation of ophthalmic -- it's a preparation of ophthalmic formulations comprising of another related benzalkonium chloride preservative.**
00:26 THE COURT: Excuse me. May I interrupt? What's the
00:26 notation WO stand for?
00:26 MS. RAPALINO: Are you asking me?
00:26 THE COURT: Well, maybe the witness.
00:26 THE WITNESS: It's the world patent, isn't it? So,
00:26 international patent.
00:26 THE COURT: I'm sorry, can you repeat that?
00:26 THE DEFENDANT: World patent.
00:26 THE COURT: Okay. Thank you.
00:26 MS. RAPALINO: An international patent application.
00:26 BY MS. RAPALINO:
00:26 Q. Does the WO 597 international patent application say
00:26 anything about preservatives generally in ophthalmic
00:26 solutions?
00:26 **A. Yes, it does. On page JTX-207.3, I've highlighted an**
00:27 **extract on the slide, and it states that ophthalmic**
00:27 **formulations must be, if they're intended for a multidose**
00:27 **regime, be preserved with an effective antimicrobial agent.**
00:27 Q. Does it say anything about benzalkonium chloride in

00:27 particular in ophthalmic solutions?
00:27 **A. Yes, it does. On JTX-207.4 at the top of the page, it states that benzalkonium chloride, which is a quaternary ammonium compound, has been widely used in ophthalmic preparations. However, it is known to be incompatible with anionic drugs forming insoluble compounds which can turn the solution cloudy.**
00:27 Q. Does the WO 597 patent say anything about how that
00:28 complexation with anionic drugs and benzalkonium chloride
00:28 occurs?
00:28 **A. Yes, it does. On the same page, it goes on to say that many acidic drugs carry a negative charge in solution at the relevant pH, and that benzalkonium chloride is positively charged, and because of this negative acidic anionic drug and this positive cationic preservative, you get an ion pair forming, just as I've tried to illustrate a moment ago, and that this ion pair is insoluble and precipitates out to solution.**
00:29 Q. Let's move on to the next reference in group B. Could
00:29 you turn in your binder, please, to JTX-61? Generally
00:29 speaking -- well, first of all, what is JTX-61?
00:29 **A. It's U.S. patent number 5,603,929 from the 18th of February, 1997.**
00:29 Q. Generally speaking, what does the '929 patent deal with?
00:29 **A. It talks about forming ophthalmic preparations that are**

00:29 **preserved using a polymeric quaternary ammonium compound.**
00:29 Q. Does the '929 patent say anything about formulating
00:29 NSAIDs with benzalkonium chloride?
00:29 **A. Yes, it does. On JTX-061.2, which I've highlighted an**
00:30 **extract on the first column halfway down, it states again that**
00:30 **benzalkonium chloride is a widely used preservative, and again**
00:30 **goes on to state that it's considered incompatible with acidic**
00:30 **drugs such as nonsteroidal antiinflammatory agents, and that**
00:30 **when they interact, the preservative loses its ability to**
00:30 **function.**
00:30 Q. And why does it say it loses its ability to function?
00:30 **A. Because when the complex is taken out of solution, it's**
00:30 **no longer available to exert its preservative properties.**
00:30 Q. Okay. Let's look next at your final reference in group
00:30 B. Could you turn to DTX-15 and briefly remind us what DTX-15
00:30 is?
00:31 **A. Certainly. This is the 20th edition of Remington Science**
00:31 **and Practice of Pharmacy, which, as I said yesterday, which is**
00:31 **a widely used reference book by pharmaceutical formulators.**
00:31 Q. Can you remind us again just briefly what Remington's
00:31 says about benzalkonium chloride?
00:31 **A. Certainly. On DTX-015.5, under quaternary ammonium**
00:31 **compounds, it states once again that benzalkonium chloride is**
00:31 **by far the most commonly used preservative in ophthalmic**
00:31 **preparations, and states over 65 percent of commercial**

00:31 **ophthalmic products are preserved at that time with**
00:31 **benzalkonium chloride.**
00:31 Q. And can you remind us, does Remington's say anything
00:31 about the problems with benzalkonium chloride?
00:31 **A. Yes. It goes on to say just below that, as a cationic**
00:32 **surface active material of high molecular weight, in other**
00:32 **words, we're talking about benzalkonium chloride, it is not**
00:32 **compatible with anionic compounds.**
00:32 Q. Does Remington's suggest that formulators avoid
00:32 benzalkonium chloride because of that complexation problem?
00:32 **A. No, not at all. In the same paragraph, at the end of the**
00:32 **paragraph, it is stated that given the alternative, it would**
00:32 **be preferable to modify a formulation to remove the**
00:32 **incompatibility rather than include a compatible but less**
00:32 **effective preservative.**
00:32 Q. Other than the four references you have listed on this
00:32 slide, are there any other references that show that it was
00:32 well known to the person of ordinary skill in the art as of
00:32 January 2003 that acidic drugs like NSAIDs formed insoluble
00:32 complexes with benzalkonium chloride?
00:33 **A. Yes, there's lots of prior art from that time.**
00:33 Q. Does the '431 patent-in-suit say anything about the
00:33 formation of complexes between NSAIDs and benzalkonium
00:33 chloride?
00:33 **A. Yes, it does.**

00:33 Q. Could we turn then to JTX-1, which is the '431
00:33 patent-in-suit? Looking at the background art section of the
00:33 '431 patent, what does the patent-in-suit say about what was
00:33 known in the prior art about complexation between NSAIDs and
00:33 benzalkonium chloride?
00:33 **A. Yes. On JTX-001.3, the bottom of the first column on the**
00:33 **background art, it states that benzalkonium chloride is a**
00:33 **widely used preservative and is considered incompatible with**
00:33 **acidic drugs, and in particular, or such as, nonsteroidal**
00:34 **antiinflammatories, and as a consequences -- as a consequence**
00:34 **of the interaction, what happens is the preservative becomes**
00:34 **less effective and loses its ability to function as a**
00:34 **preservative.**
00:34 Q. Can you summarize for us, generally speaking, what your
00:34 group B references would have taught to the person of ordinary
00:34 skill in the art as of 2003?
00:34 **A. Certainly. Taken together, the references say that**
00:34 **benzalkonium chloride is the most widely used preservative in**
00:34 **ophthalmic preparations. It was well known that benzalkonium**
00:34 **chloride was incompatible with anionic negatively charged**
00:34 **acidic drugs such as the NSAIDs, that the complexation between**
00:34 **benzalkonium chloride and the NSAID led to the formation of**
00:34 **insoluble precipitates, and that left less preservative in**
00:35 **solution to exert its preservative effect, and it was also**
00:35 **preferable to resolve the incompatibility rather than use a**

00:35 **less effective alternative preservative to benzalkonium**
00:35 **chloride.**
00:35 Q. Thank you. Let's move on now to your group C references,
00:35 and can you just tell us which references you have placed in
00:35 the category of group C?
00:35 **A. Yes, I can. That is European patent number 0 306 984**
00:35 **from 1984, which I have termed the 984 patent, which is**
00:35 **JTX-209; a reference from Schott in 1998 from -- as a**
00:35 **scientific article, and it's JTX-199; and U.S. patent number**
00:35 **5,891,913 from 1999 which is JTX-071.**
00:36 Q. Okay. Let's -- before we move to the first reference,
00:36 can you tell us just generally what the references in group C
00:36 taught to the person of ordinary skill in the art?
00:36 **A. These references deal with the prior art that states that**
00:36 **the ethoxylated octylphenol surfactants could solve the**
00:36 **problem of the complexation between a nonsteroidal**
00:36 **antiinflammatory and BAC, and furthermore, the use of**
00:36 **tyloxapol in ophthalmic preparations was known.**
00:36 Q. Let's go to the first reference in group C. Can you turn
00:36 in your binder, please, to JTX-209? What is JTX-209?
00:36 **A. This is the European patent number 0 306 984 from the**
00:36 **15th of March, 1989.**
00:37 Q. Generally speaking, what does the EP -- is it okay if I
00:37 call that the EP 984 patent?
00:37 **A. Yes, it is.**

Q. Generally speaking, what does the EP 984 patent say about the problem of NSAID benzalkonium chloride complexation?

MR. HASFORD: I'd just like to object for the record, your Honor. I believe that JTX-209 is not actually a patent. It looks like it is a European patent application. I just wanted to get that on the record.

THE COURT: Is that correct?

MS. RAPALINO: It is a patent application. It is a published patent application.

THE COURT: All right. Is the witness aware of that?

THE WITNESS: I am. My mistake. I should have said that.

THE COURT: Okay. Very well. Let's continue.

Q. Generally speaking, what is the EP 984 patent application directed to?

A. It's directed to forming -- or the preparation of ophthalmic preparations that are -- that contain negatively-charged drug, in particular, NSAIDs, that are effectively preserved.

Q. And what does the EP 984 patent application say about complexation TWEEN nonsteroidal anti-inflammatory drugs and benzalkonium chloride?

A. Yes, on JTX-209.2, on the first page, near the top of the page, it points out, when it's talking about a particular patent, which is abbreviated as '13151 patents, that while the

formulation is efficacious, and these are formulations containing benzalkonium chloride, an insoluble complex is found to form between the NSAID and the BAC. And as a result, the formulations became cloudy or turbid and did not have the stability designed for shelf life for a commercial formulation.

Q. Does the EP 984 patent application say anything else about the effect of this complexation between NSAIDs and benzalkonium chloride?

A. Yes, it does. Further down the page, again, states that benzalkonium chloride is a widely-used preservative, and is considered to be the preservative of choice, and that it is -- sorry. Beg your pardon. And that it is incompatible with anionic drugs forming insoluble complexes, which cause the solution to be cloudy and turbid.

And it goes on to say that one of the consequences of this is that it can decrease the pharmaceutical activity of the anionic drug, because that drug is now precipitated and is no longer in solution to exert its activity.

Q. And does the EP 984 patent -- excuse me one minute. Does the EP 984 patent application say anything about the effect of this complexation on benzalkonium chloride?

A. Yes, it does. Slightly further down the page in the section I've highlighted in yellow, it explains what the cause of the compatibility is, which is the COOH group, in other

words, the anionic carboxylic group, and the carboxylic acid group, and it forms a complex with the benzalkonium chloride; and thereby renders the preservative less available to serve its function and also, as it said before, reduces the activity of the active ingredients.

Q. Now, generally, what is the solution given by the EP 984 patent application for this problem of NSAID benzalkonium chloride complexation?

A. As I've shown on DDX-2-48 under the claims, it states that the solution to this problem is that all -- a solution to the problem is a nonionic ethoxylated octylphenol surfactant.

Q. Does the EP 984 patent application say anything about the use of polysorbate 80 in connection with this problem?

A. Yes, it does. On Page JTX209.9, under Example 5, it produces a table, which talks about Tween 80, which in effect is polysorbate -- it's another name for polysorbate 80.

Q. Can you describe what you see in the table in Example 5 of the EP 984 patent application?

A. Yes, this table is reporting an experiment between an NSAID drug, benzalkonium chloride, and nonionic surfactants, and it's a physical stability test, and it explains how the solution appeared after various time periods and under storage at various temperatures.

Q. And which nonionic surfactants are being compared in this table, in Example 5 of EP 984?

A. I've highlighted the data for Tween 80, which as I've explained a moment ago, is polysorbate 80, and the ethoxylated octylphenol surfactant Octoxynol 40.

Q. What does the table demonstrate are the results of that comparison between the use of Tween 80, or polysorbate 80 on the one hand, and the ethoxylated octylphenol surfactant on the other?

A. What is significant from the results shown in table -- in Example 5 is, all the results under the two columns dealing with Octoxynol 40 show that the solutions were clear, no matter how long they were stored for and at what temperature, whereas the data for polysorbate 80 or Tween 80 shows that most of the solutions became turbid or cloudy at storage at various temperature conditions.

Q. What does a turbid or cloudy solution suggest to the person of ordinary skill in the art?

A. It suggests that there's a complex being formed between the benzalkonium chloride and the nonsteroidal anti-inflammatory drug, and that precipitates its turning the solution cloudy.

Q. So then what would a person of skill in the art understand about which of these nonionic surfactants is preferable, in terms of avoiding the complexation between NSAIDs and benzalkonium chloride?

A. From the data shown in Example 5, a person of ordinary

00:44 skill in the art would have seen that Octoxynol 40, the
00:44 ethoxylated octylphenol surfactant, was superior over Tween 80
00:44 or polysorbate 80.
00:44 Q. Let's look at the next reference in group C. If you
00:44 could turn in your binder, please, to JTX199. What is JTX199?
00:45 A. This is a scientific article from the *Journal of Colloid*
00:45 *and Interface Science* in 1998, and it's authored by Hans
00:45 Schott.
00:45 Q. Generally speaking, what does this article by Schott --
00:45 what is it about?
00:45 A. It's comparing the properties of two ethoxylated
00:45 octylphenol surfactants, octoxynol 9 and tyloxapol.
00:45 Q. What does the Schott reference conclude about the
00:45 properties of tyloxapol?
00:45 A. On Page JTX199.6, at the top of the section -- in the
00:45 first paragraph of the section entitled Conclusions, it states
00:46 that from a practical point of view, the critical micelle
00:46 concentration of tyloxapol is just over four times smaller
00:46 than that of Octoxynol 9 on a waiting weight basis. This is
00:46 an advantage for the pharmaceutical formulation -- advantage
00:46 for formulation.
00:46 Q. Can you explain why a lower critical micelle
00:46 concentration is an advantage?
00:46 A. Certainly. The critical micelle concentration is a
00:46 concentration of surfactants at which micelles start to form,

00:46 and the lower that concentration, it means you have to add
00:46 less surfactant into the formulation to form micelles.
00:46 Q. Let's look now at the last reference in your group C.
00:46 Could you turn in your binder, please, to JTX71. What is
00:47 JTX71?
00:47 A. Yes. This is U.S. Patent No. 5,891,913 from the 6th of
00:47 April, 1999.
00:47 Q. Generally speaking, what is the '913 patent directed to?
00:47 A. It's directed towards the preparation of ophthalmic and
00:47 aural compositions, but in particular, ophthalmic compositions
00:47 contained in the nonsteroidal anti-inflammatory diclofenac
00:47 potassium.
00:47 Q. Does the '913 patent say anything about tyloxapol?
00:47 A. Yes, it does. On Page JTX071.3, it states that tyloxapol
00:47 is a preferred solubilizer?
00:47 Q. Is solubilizer another name for a surfactant?
00:48 A. Yes, it is.
00:48 Q. Are there any examples in the '913 patent of the use of
00:48 tyloxapol in a formulation of a nonsteroidal anti-inflammatory
00:48 drug with benzalkonium chloride?
00:48 A. Yes, there is. Example 15 on Page JTX071.7 shows it
00:48 being used in an eye drop formulation.
00:48 Q. Does the '913 patent say anything about any aspect of the
00:48 stability of the formulations described in the '913 patent?
00:48 A. Yes, it does. On the same page, JTX071.7, just further

00:48 up the page, it states a little bit about the use of the
00:49 European Pharmacopeia to look at the preservation activity of
00:49 the formulation.
00:49 Q. And what do you mean by "preservation activity of the
00:49 formulation"?
00:49 A. This is a test to assess how effective the formulation is
00:49 at -- preserving the product under challenge to various types
00:49 of antimicrobial agents.
00:49 Q. Does the '913 patent say anything about the amount of
00:49 tyloxapol that should be used in formulations of NSAIDs with
00:49 benzalkonium chloride?
00:49 A. Yes, it does. On Page -- the top of Page JTX071.4, it
00:49 states that the concentration of solubilizer, in other words,
00:49 surfactant ranges from .1 to 5,000 times the concentration of
00:50 the active ingredients.
00:50 Q. And given the amount of active ingredient or diclofenac
00:50 in Example 15 of the '913 patent, what would that translate
00:50 into in terms of a lower concentration range for tyloxapol?
00:50 A. The lowest concentration would be 0.01 weighting volume
00:50 percent of tyloxapol.
00:50 Q. Had tyloxapol ever been used in an approved ophthalmic
00:50 pharmaceutical product as of 2003?
00:50 A. Yes, it had.
00:50 Q. How would the person of ordinary skill in the art know
00:50 that?

00:50 A. To determine whether or not it had been used in
00:50 ophthalmic preparation, they would consult the FDA inactive
00:50 ingredients guide.
00:50 Q. Okay. So let's turn to the FDA inactive ingredient guide
00:51 at DTX-196. Can you explain what the FDA inactive ingredient
00:51 guide says about the use of tyloxapol?
00:51 A. Yes. Under -- on Page DTX-196, 158, there is a listing
00:51 for tyloxapol, and it states that tyloxapol at the time had
00:51 been used both in ophthalmic solutions and ophthalmic
00:51 suspensions. For solutions -- sorry. Is it five solutions,
00:51 four suspensions. It also states the range of concentrations
00:51 at which tyloxapol had been used at.
00:51 Q. Okay. Before we move on to talking about your
00:51 obviousness opinions in more detail, can you just summarize
00:51 for us, generally, what your references in group C would have
00:51 taught to the person of ordinary skill in the art?
00:51 A. They would have taught that replacing polysorbate with an
00:51 ethoxylated octylphenol surfactant removed the problem with
00:52 the complexation between the nonsteroidal anti-inflammatory in
00:52 BAC, that tyloxapol is an example of an ethoxylated
00:52 octylphenol surfactant and that it had been used in previous
00:52 products.
00:52 Furthermore, tyloxapol has a number of favorable
00:52 properties in terms of pharmaceutical formulation, and
00:52 tyloxapol had previously been used in ophthalmic formulations

with an NSAID and benzalkonium chloride.

Q. Okay. Now that we've talked about the scope of the prior art, let's talk about your specific obviousness opinion in this case.

If we can put up again on DDX-2-57, Claim 20 of the '431 patent as rewritten in independent form. What -- can you remind us, what is your opinion about whether Claim 20 of the '431 patent would have been obvious to a person of ordinary skill in the art as of January 2003?

A. It's my opinion that Claim 20 of the '431 patent would have been obvious to person of ordinary skill in the art, as of January 2003.

Q. Do you have a slide summarizing the basis for your opinion that Claim 20 is obvious?

A. Yes, I do. It's my -- opinion --

MR. HASFORD: And I'll just object, Your Honor. I mean, it appears that she's literally reading opinions off of these slides. I'm not sure that's proper in the context of this witness giving obviousness opinions.

THE COURT: I'll permit it.

MS. RAPALINO: Your Honor, the slide is just there as a memory aid and it's -- she has formed these opinions independent of any slides that have been created, and she's simply using them as a guide, and as a guide also for the Court so the Court can see her opinions in writing while she

-- while she expresses those opinions.

And I would also just -- I disagree that she's just reading off of slides. She's offering her opinion, as a professor often does, guided by a PowerPoint presentation. But her opinions are her own.

THE COURT: I understand the point of the objection, that the witness can't just sit here and read slides that have been prepared in a way that may or may not have been her own hand that created them. She can be cross-examined, certainly without the benefit of slides, as to any of her testimony. And it's not meant to be a memory test, but rather to fix what is and what is not her opinion.

But I'll permit it. I mean, I don't know about anyone else, but I find the material very dense. I find these slides helpful, and the witness's explanation, you know, is her testimony. So I'll permit it.

MS. RAPALINO: Thank you, Your Honor.

BY MS. RAPALINO:

Q. Professor Lawrence, can you summarize the basis for your opinion that Claim 20 of the '431 patent would have been obvious to a person of ordinary skill in the art as of January 2003?

A. Yes, certainly. It's my opinion that it would have been obvious to a person of ordinary skill in the art because they would have been aware of formulation in the Example 6 in the

'225 patent, and it would have also been aware that the ingredients in Example 6 of the '225 patent are, in fact, the same as those in the Bronuck formulation that was marketed in Japan.

They would have also been aware there was this problem of complexation between benzalkonium chloride and a nonsteroidal anti-inflammatory, and that this could have been overcome by the use of tyloxapol, and once they decided to use tyloxapol would, by routine optimization, have come up with the concentration of tyloxapol that's contained in examples -- in the '431 patent Claim 20.

Q. Let's start with the first part of that. That the person of ordinary skill in the art would have been aware of Example 6 of the '225 patent as a starting point. Can you remind us what '225 patent Example 6 covers?

A. Yes, certainly. It deals with an aqueous liquid preparation intended for ophthalmic use that contained bromfenac, benzalkonium chloride, polysorbate 80 and a range of other ingredients.

Q. Why would the person of ordinary skill in the art focus specifically on Example 6 of the '225 patent as the starting point?

A. Okay. Well, they would have been aware that bromfenac had showed some advantages, in terms of its use as a nonsteroid anti-inflammatory over other nonsteroid

anti-inflammatories, and they would have got this from the Hara reference from 2000 and the 034 reference from 1995.

They would also be aware that Bronuck was a marketed formulation in Japan as of 2000, and again, this would have been from the Hara reference of 2000, and new drugs in Japan from 2001, and they would have finally been aware that the same ingredients were in Example 6 of '225 patent, as were in the Bronuck formulation, and they would have got this from the '225 patent from 1990 and new drugs in Japan from 2001.

Q. Can you remind us how Example 6 of the '225 patent compares to Claim 20 of the '431 patent?

A. Yes. The next slide here compares claims -- Example 6 of '225 patent which Claim 20 of the '431 patent, and as you can see by what I've highlighted in blue, they are virtually identical.

Q. What is the difference between Example 6 of the '225 patent and Claim 20 of the '431 patent?

A. Yeah, the only difference is in the type of nonionic surfactant that was used in the formulation. Claim 6 of the '255 preparation contained polysorbate 80, whereas Claim 20 of the '431 patent contains tyloxapol.

Q. Other than the nonionic surfactant, how did the -- how does the list of ingredients in Example 6 of '225 patent compare to the list of ingredients in Claim 20 of the '431 patent?

00:58 A. **They are identical.**
00:58 Q. Now, you said that it would have been obvious to a person
00:58 of ordinary skill in the art to replace the polysorbate 80 in
00:58 Example 6 with tyloxapol. But if the Bronuck formulation that
00:58 is an embodiment of Example 6 was already a sufficiently
00:58 stable product to have been marketed, why would the person of
00:58 ordinary skill in the art have had a motivation to change that
00:58 formulation?
00:58 A. **There's two reasons. A pharmaceutical formulator will**
00:58 **always look at producing the most stable formulation. So one**
00:58 **of the things they would have done was to see whether they**
00:58 **could improve the stability, and coupled with that, there was**
00:58 **the knowledge that there was a problem with benzalkonium**
00:58 **chloride and nonsteroid anti-inflammatories, so they would**
00:59 **have ensured that the surfactant was suitable to overcome that**
00:59 **problem.**
00:59 Q. Now, once the person of ordinary skill in the art decides
00:59 to replace the polysorbate 80 in Example 6 of the '225 patent,
00:59 why would the person of ordinary skill in the art have focused
00:59 on tyloxapol as the solution to that problem of complexation?
00:59 A. **They would have been aware of the information contained**
00:59 **in patent -- in EP 984, from 1989, that ethoxylated**
00:59 **surfactants overcome the problem of complexation, and**
00:59 **obviously was being aware of the facts of the problems of**
00:59 **complexation in the first case. Then they would have known**

00:59 **that tyloxapol was only one of two ethoxylated octylphenol**
01:00 **surfactants that had been approved for use in ophthalmic**
01:00 **formulations, and they would have known that from a variety of**
01:00 **sources, and as a consequence, they would have focused on**
01:00 **tyloxapol.**
01:00 Q. Now, you also testified that a person of ordinary skill
01:00 in the art would have conducted routine optimization to
01:00 determine the amount of tyloxapol. Can you just remind us
01:00 what routine optimization is?
01:00 A. **Yes. As I said before, a formulator will have a range of**
01:00 **concentrations over which they would expect to use ingredients**
01:00 **in the formulation. In order to find the most appropriate**
01:00 **formulation that contained the least amount of that**
01:00 **ingredient, they would go through a process where they made a**
01:00 **number of formulations, tested those formulations and selected**
01:00 **the one that had the optimal properties, again, with the least**
01:01 **amount of ingredient presence.**
01:01 Q. Is that a process that a formulator uses on a regular
01:01 basis?
01:01 A. **Yes, it is. It's routine optimization.**
01:01 Q. In this situation, how would the person of ordinary skill
01:01 in the art have gone about doing that routine optimization
01:01 process?
01:01 A. **Okay. A person of ordinary skill in the art would have**
01:01 **known that there's a range of concentrations over which to use**

01:01 **the ethoxylated octylphenol surfactants, and they would have**
01:01 **known that from EP 984.**
01:01 **They would have also known that tyloxapol had been used**
01:01 **in NSAID/BAC formulations itself at a range of concentrations,**
01:01 **and that would have been obtainable from the '913 patent from**
01:01 **1999 and the FDA inactive ingredients guide, and then they**
01:01 **would have followed, as I've explained before, these general**
01:02 **pharmaceutical principles, optimized the amounts of surfactant**
01:02 **to obtain the formulation that contained the lowest**
01:02 **concentration that ensured stability.**
01:02 Q. You testified that there was a known range of
01:02 concentrations for ethoxylated octylphenol surfactants in EP
01:02 984. Could you turn back to that patent application at
01:02 JTX209? What range of ethoxylated octylphenol surfactant does
01:02 the EP 984 patent application disclose?
01:02 A. **Firstly, there's two tables to look at. The first table**
01:02 **is on JTX209.4, which lists the range of surfactant, which is**
01:02 **highlighted in yellow, as being from 0.001 to 1 weight in**
01:03 **volume percent.**
01:03 Q. And then are there specific examples of specific
01:03 concentrations of ethoxylated octylphenol surfactant in EP
01:03 984?
01:03 A. **Yeah, the patent then goes on to use some specific**
01:03 **formulations. So the table under Example 5, which I showed**
01:03 **you before, under Octoxynol 40, states two concentrations of**

01:03 **0.004 and 0.02 percent.**
01:03 Q. Now, when tyloxapol has been -- I'm sorry. When
01:03 polysorbate 80 has been replaced by tyloxapol in Example 6 of
01:03 the '225 patent, how does the list of ingredients in that
01:03 modified Example 6 compare to the list of ingredients in Claim
01:03 20 of the '431 patent?
01:04 A. **In this case, that list of ingredients would be**
01:04 **identical.**
01:04 Q. Have you considered whether the modified Example 6
01:04 formulation, where polysorbate 80 is replaced with tyloxapol,
01:04 would have consisted essentially of the ingredients recited in
01:04 Claim 20?
01:04 A. **Yes, I have.**
01:04 Q. Can you remind us, what does the phrase "consisting
01:04 essentially of" mean in this case?
01:04 A. **Yes, consisting essentially of means including the listed**
01:04 **ingredients and, in addition, any unlisted ingredients,**
01:04 **assuming they don't affect -- materially affect the basic and**
01:04 **novel characteristics of the claimed preparation.**
01:04 Q. Would the modified Example 6 formulation, where -- again,
01:04 where polysorbate 80 has been replaced with tyloxapol have
01:04 consisted essentially of the recited ingredients in Claim 20
01:04 of the '431 patent in light of that definition?
01:04 A. **Yes, it would.**
01:04 Q. Why do you say that?

01:04 A. **Because it contains basically the same ingredients.**
01:05 Q. Okay.
01:05 A. **Exactly the same ingredients.**
01:05 Q. Thank you.
01:05 Now, you've been discussing the obviousness of Claim 20
01:05 of the '431 patent. Have you also considered the obviousness
01:05 of Claim 6 of the '431 patent that's been asserted here?
01:05 A. **Yes, I have.**
01:05 Q. And with reference to slide DDX-2-72, can you explain
01:05 what Claim 6 of the '431 patent covers when it's rewritten to
01:05 include all of its limitations?
01:05 A. **Yes. Claim 6 of the '431 patent covers an aqueous liquid**
01:05 **preparation containing bromfenac sodium and tyloxapol and when**
01:05 **a quaternary ammonium compound is present, that quaternary**
01:05 **ammonium compound is benzalkonium chloride.**
01:05 Q. And how does Claim 6 compare to Claim 20 of the '431
01:05 patent that we were just discussing?
01:05 A. **The two claims are obviously very simple -- similar.**
01:06 **Claim 6 requires only bromfenac sodium and tyloxapol to be**
01:06 **present without specifying all of the additional ingredients**
01:06 **of Claim 20, while Claim 6 also specifies a slightly narrower**
01:06 **concentration range for bromfenac sodium.**
01:06 Q. What did you conclude about whether Claim 6 of the '431
01:06 patent would have been obvious to a person of ordinary skill
01:06 in the art as of January 2003?

01:06 A. **For the same reasons as I concluded for Claim -- for**
01:06 **similar reasons that I included for -- concluded for Claim 20,**
01:06 **I concluded that Claim 6 of the '431 patent would have been**
01:06 **obvious.**
01:06 Q. Can you just briefly explain those reasons?
01:06 A. **Certainly. As I've said before, a person of ordinary**
01:06 **skill in the art would have started with Example 6 of the '225**
01:06 **patent, and would have also been aware that the ingredients in**
01:06 **Claim -- Example 6 of '225 patent are identical of those in**
01:07 **the marketed formulation in Japan of Bronuck.**
01:07 **They would have been motivated to replace the**
01:07 **polysorbate with tyloxapol because of the anticipated problems**
01:07 **with complexation between the nonsteroidal anti-inflammatory**
01:07 **and benzalkonium chloride, and once they had replaced**
01:07 **tyloxapol, they would have undergone the process of routine**
01:07 **optimization to obtain the concentration of tyloxapol that is**
01:07 **present in the claims.**
01:07 Q. You testified that Claim 6 has a slightly narrower
01:07 concentration range for bromfenac sodium as compared to Claim
01:07 20. Would the narrower concentration range in Claim 6 have
01:07 rendered that claim nonobvious?
01:07 A. **No, it wouldn't, because the concentration of bromfenac**
01:07 **sodium in Example 6 of the '225 patent is included in the**
01:08 **narrower concentration range of Claim 6 of the '431 patent.**
01:08 Q. Okay. Now, you also mentioned that Claim 6 required --

01:08 requires only that bromfenac sodium and tyloxapol rather than
01:08 all of the ingredients required by Claim 20 of the '431
01:08 patent, does that modified Example 6 formulation that we
01:08 talked about, where polysorbate 80 is replaced with tyloxapol,
01:08 consist essentially of bromfenac sodium and tyloxapol?
01:08 A. **Yes, it does.**
01:08 Q. Why do you say that?
01:08 A. **Because all the other added ingredients, I wouldn't**
01:08 **expect them to materially affect the basic and novel**
01:08 **characteristics of the formulation.**
01:08 Q. What do you mean by that?
01:08 A. **I wouldn't expect them to detrimentally affect the**
01:08 **stability of the preparation.**
01:09 Q. Are any of those ingredients unusual ingredients in an
01:09 ophthalmic solution product?
01:09 A. **No, they're all very standard ingredients in an**
01:09 **ophthalmic product.**
01:09 Q. Would a person of ordinary skill in the art have had a
01:09 reasonable expectation of success in making a formulation of
01:09 bromfenac, tyloxapol, and benzalkonium chloride for ophthalmic
01:09 use?
01:09 A. **It's my opinion that they would, yes.**
01:09 Q. Why would they have that reasonable expectation?
01:09 A. **Well, the person of ordinary skill in the art would be**
01:09 **aware that bromfenac sodium, tyloxapol and benzalkonium**

01:09 **chloride were all suitable for ophthalmic administration for**
01:09 **many of the reasons I've explained before, from -- with**
01:09 **reference to EP 984, they would understand that tyloxapol**
01:09 **would overcome the problem of the formation of complexes**
01:09 **between the nonsteroidal anti-inflammatory and benzalkonium**
01:10 **chloride.**
01:10 Q. Now, earlier, you testified about a number of references
01:10 that you put into categories, group A, group B, group C. Did
01:10 you mean to suggest that it was necessary to combine all of
01:10 those references to support your obviousness opinion?
01:10 A. **No, I did not.**
01:10 Q. How many references did you combine to find the claims
01:10 obvious?
01:10 A. **Only two. That would be Example 6 of the '225 patent and**
01:10 **EP 984.**
01:10 Q. If you combine just those two references to support your
01:10 obviousness opinion, why did you discuss the other references?
01:10 A. **I wanted to show -- to give evidence of the body of**
01:10 **knowledge that was available to a person of ordinary skill in**
01:10 **the art at the time.**
01:10 Q. Did you discuss every reference that was available to a
01:10 person of ordinary skill in the art at the time that would
01:10 have taught those teachings from group A, B and C?
01:10 A. **No, there's a number of -- there's quite a lot more**
01:10 **references that would have supported what I've said.**

Q. Okay. Now that we've talked about why Claim 6 and 20 of the '431 patent are obvious. Let's talk about your obviousness-type double patenting opinion.

Was there a particular framework that you used to analyze obviousness-type double patenting?

A. Yes, there is, and this is detailed on DTX-2-77. So I compared the claims of the patents-in-suit with other claim -- other patents. I determined whether there was any differences between those claims, and whether there was any differences between the claims, whether they were to be obvious to a person of ordinary skill in the art over the prior arts.

Q. And in doing -- in applying that framework here, what was the analysis that you did?

A. In particular, I compared Claim 60 and 20 of the '431 patent with Claim 6 of the '290 patent -- I'm sorry, Claim 7 of the '290 patent and Claim 6 of the '131 patent to determine whether those differences would have been obvious to a person of ordinary skill in the art.

Q. And just -- I think you may have misspoken. Which claims of the '431 patent did you compare?

A. Claim 6 and Claim 20.

Q. Okay. Could you turn in your binder to JTX2. And was this the '290 patent that you're referring to for that comparison?

A. Yes, it is.

Q. And could you also turn to JTX3 in your binder.

A. Yes.

Q. Is this the '131 patent that you referred to in doing your comparison?

A. Yes, it is.

Q. What did you conclude about obviousness-type double patenting?

A. It's my -- my opinion that Claims 6 and 20 of the '431 patent would have been obvious to a person of ordinary skill over Claim 7 of the '290 patent and Claim 6 of the '131 patent.

Q. Okay. Let's start with Claim 20 of the '431 patent compared to Claim 7 of the '290 patent. Have you prepared a slide showing that comparison?

A. Yes, I have. It's on DDX-2-80. On the left-hand side I've reproduced the Claim 20 of the '431 patent; on the right-hand side, Claim 20 of the -- I'm sorry, Claim 7 of the '290 patent.

Q. Which elements of Claim 7 of the '290 patent and Claim 20 of the '431 patent are the same?

A. I've indicated those elements of the claims that are the same in blue on the slide now.

Q. And what are those elements?

A. Both are directed towards a stable aqueous liquid -- sorry. Both directed towards an aqueous liquid preparation

intended for ophthalmic administration, that contains bromfenac sodium, contains tyloxapol, it contains -- they both contain boric acid, sodium tetraborate, EDTA sodium salt, benzalkonium chloride, polyvinyl pyrrolidone, and sodium sulfite.

Q. Are there other elements of the two claims that are similar?

A. Yes, there are -- there are, and I've highlighted these in green now on the slide.

Q. What's the -- can you -- can you walk us through which elements here are similar?

A. Yes, I can. In Claim 7 of the '290 patent, it states a stable formulation, whereas there's no such claim or statement in Claim 20 of the '431 patent, which means that Claim 20 of the '431 patent contained -- could be at both the stable and unstable preparation, and as a consequence, Claim 7 of the '290 patent is a subset of Claim 20 of the '431 patent.

Q. What other elements did you find were similar as between Claim 7 of the '290 patent and Claim 20 of the '431 patent?

A. With respect to the concentration of bromfenac sodium, Claim 7 of the '290 patent states the concentration of bromfenac sodium from about 0.02 to about .1 weight in volume percent, whereas Claim 20 of the '431 patent states a concentration of about 0.01 to about .5 weight in volume percent. As a consequence, Claim 70 -- 7 of the '290 patent

is a subset of Claim 20 of the '431 patent.

Q. And what was the other limitation as between Claim 7 of the '290 patent and Claim 20 of the '431 patent that you found similar?

A. In Claim 7 of the '290 patent, it states that bromfenac sodium must be the sole active ingredient, whereas there's no such limitation in Claim 20 of the '431 patents, which means that Claim 20 of the '431 patent can contain bromfenac sodium alone or an additional active ingredient, and as a consequence, Claim 7 of the '290 patent is a subset of Claim 20 of the '431 patent.

Q. Did you identify any differences between Claim 7 of the '290 patent and Claim 20 of the '431 patent?

A. Yes, I did, just two.

Q. What was the first difference that you identified?

A. The first difference is in the concentration of tyloxapol where Claim 7 of the '290 patent states it must be present as an amount sufficient to stabilize bromfenac sodium, where Claim 20 of the '431 patent states a concentration of about .0, .002 weight in volume percent.

Q. Would the .02 weight per volume percent concentration of tyloxapol in Claim 20 of the '431 patent have been obvious in view of the limitation on the amount of tyloxapol specified in Claim 7 of the '290 patent?

A. Yes, it was. A person of ordinary skill in the art

preparing a formulation under Claim 7 of the '290 patent would undergo routine optimization and then end up with a concentration of 0.02 weight in volume percent stated in Claim 20 of the '431 patent.

Q. What was the other difference that you identified between Claim 7 of the '290 patent and Claim 20 of the '431 patent?

A. Yes. Claim 20 of the '431 patent stated when benzalkonium chloride is the only quaternary ammonium chloride included in the formulation, and there was no such limitation in Claim 7 of the '290 patent.

Q. Would it have been obvious to a person of ordinary skill in the art to include benzalkonium chloride as the only quaternary ammonium compound in the formulation?

A. Yes. Firstly, it's the only listed benzalkonium chloride in the formulation and besides, it's the most commonly used preservative.

Q. What did you mean when you said it's the only listed benzalkonium chloride, what did you mean?

A. It's the only benzalkonium chloride, it's the only preservative listed in Claim 7 of the '290 patent.

Q. Okay. What conclusion then did you reach regarding whether Claim 20 of the '431 patent would be obvious in view of Claim 7 of the '290 patent?

A. It's my opinion that the person of ordinary skill in the art would have found that Claim 20 of the '431 patent was

obvious in light of Claim 7 of the '290 patent.

Q. Okay. Let's move on now to a comparison of Claim 6 of the '431 patent-in-suit to Claim 7 of the '290 patent. Did you prepare a slide showing that comparison?

A. Yes, I did, and this is on the next slide here. On the left-hand side again is the '431 patent, in this case Claim 6, and on the right-hand side is Claim 7 of the '290 patent.

Q. Which elements of Claim 6 of the '431 patent are the same as the elements of Claim 7 of the '290 patent?

A. Again, I've listed the similar elements of the claim in blue on the slide.

Q. And can you just recite for us for the record what those elements are?

A. Okay. Both claims are directed towards an aqueous liquid preparation that is intended for ophthalmic use that consists essentially of bromfenac sodium and tyloxapol.

Q. Are there other elements of the two claims that are similar?

A. Yes, there are. And again, I have highlighted the similar claims in green.

Q. Okay. And can you briefly summarize for us the elements that are similar as between these two claims, and why they're similar?

A. As before, Claim 7 has the limitation that the formulation must be -- Claim 7 of the '290 patent has a

limitation that the formulation must be stable, whereas there's no such limitation in Claim 6 of the '431 patent, which, as I said before, can include a stable and unstable preparation and, as a consequence, Claim 7 of the '290 patent is a subset of Claim 6 of the '431 patent.

Q. What other limitations are similar between Claim 7 of the '290 patent and Claim 6 of the '431 patent?

A. Claim 7 of the '290 patent lists extra ingredients of boric acid, sodium tetraborate, EDTA sodium salt, benzalkonium chloride, polyvinylpyrrolidone, and sodium sulfite where there are no such extra ingredients listed in Claim 6 of the '431 patent, which means that Claim 6 of the '431 patent may or may not contain these ingredients and, as a consequence, Claim 7 of the '290 patent is a subset of Claim 6 of the '431 patent.

Q. And what is the next element of Claim 7 of the '290 patent that you found similar to Claim 6 of the '431 patent?

A. Yes. Claim 7 of the '290 patent states that bromfenac sodium is an active ingredient, whereas Claim 6 of the '431 patent has no such limitation, which means it may contain only bromfenac sodium or there may be additional active ingredients, which then makes Claim 7 of the '290 patent a subset of Claim 6 of the '431 patent.

Q. And what's the final limitation between the two claims, Claim 7 of the '290 patent and Claim 6 of the '431 patent that you found similar?

A. Yes, Claim 6 of the '431 patent states that when a quaternary ammonium is included, that quaternary ammonium must be benzalkonium chloride. And, as you can see, Claim 7 of the '290 patent explicitly lists the preservative benzalkonium chloride making it a subset of Claim 6 of the '431 patent.

Q. Let's talk about any differences. Did you identify any differences between Claim 7 of the '290 patent and Claim 6 of the '431 patent?

A. Yes, I did, there were two.

Q. What was the first difference you identified?

A. Claim 7 of the '290 patent contains bromfenac sodium at a concentration from about 0.02 to about .1 weight in volume percent whereas Claim 6 of the '431 patent contains bromfenac sodium at a concentration of about 0.05 to about .2 weight in volume percent.

Q. Would the concentration range in Claim 6 of the '431 patent of .05 to about .2 weight in volume percent have been obvious to a person of ordinary skill in the art in view of the concentration range for bromfenac sodium specified in Claim 7 of the '290 patent?

A. Yes, they would because they're overlapping ranges. And, in addition, the composition of bromfenac sodium in Example 6 of the '225 patent is actually included in both of those concentration ranges.

Q. What's the second difference you identified between Claim

7 of the '290 patent and Claim 6 of the '431 patent?
A. Yes. Claim 7 of the '290 patent states that when tyloxapol is present in an amount sufficient to stabilize the bromfenac sodium, whereas Claim 6 of the '431 patent states that tyloxapol is present at a concentration of about 0.02 volume percent.
Q. Would the concentration of tyloxapol of about 0.02 weight by volume percent in Claim 6 of the '431 patent have been obvious to a person of ordinary skill in the art in view of the limitation on tyloxapol in Claim 7 of the '290 patent?
A. Yes, it would. A person of ordinary skill preparing a formulation under Claim 7 of the '290 patent would by routine optimization of the concentration range of tyloxapol end with the concentration range stated in Claim 6 of the '431 patent.
Q. What then did you conclude about whether Claim 6 of the '431 patent would have been obvious in view of Claim 7 of the '290 patent?
A. It's my opinion that Claim 6 of the '431 patent would have been obvious over Claim 7 of the '290 patent.
Q. Did you do the same analysis comparing Claim 6 and 20 of the '431 patent to Claim 6 of the '131 patent?
A. Yes, I did.
Q. And without subjecting anyone in the courtroom to recitation of all of the similarities and differences between those claims, what did you conclude in light of that

comparison of Claim 6 and 20 of the '431 patent to Claim 6 of the '131 patent about whether the asserted claims of the '431 patent would have been obvious in view of Claim 6 of the '131 patent?
A. Okay. By performing a similar analysis -- and I've shown on this slide here on DDX2-88 Claim 6 and 20 of the '431 patent and Claim 6 of the '131 patent. As I said, by performing a similar analysis it is my opinion that Claim 6 and 20 of the '431 patent are obvious over Claim 6 of the '131 patent.
Q. And in terms of the comparison that you did between Claim 6 and 20 of the '431 patent and Claim 6 of the '131 patent, how did that comparison compare to the analysis you did comparing the asserted claims to Claim 7 of the '290 patent?
A. The analysis that I underwent to arrive at my conclusion was for the Claim 6 and 20 of the '431 patent over Claim 6 of the '131 patent was very similar to the analysis I performed for Claim 6 of the '290 patent.
Q. Did you mean to say Claim 7 of the '290 patent?
A. Sorry. Claim 7 of the '290 patent, yes.
Q. There are a lot of patent numbers and claim numbers to remember here.
Okay. Turning to a different topic, is there anything unexpected about the improved stability or preservative efficacy of a bromfenac/benzalkonium chloride formulation that

includes tyloxapol in place of polysorbate 80?
A. It's my opinion that there's absolutely nothing unexpected about the improved stability and preservative activity from use of tyloxapol.
Q. Can you explain why?
A. A person of ordinary skill in the art would have expected tyloxapol to overcome the problem between the complexation of BAC and benzalkonium chloride and, as a consequence, both increase the amount of active ingredient in solution and the amount of benzalkonium chloride in solution, and the increase in benzalkonium chloride would result in improved preservation of the formulation.
Q. Is there anything in the prior art that supports that expectation that tyloxapol would have this effect on the formulation?
A. Yes, there is.
Q. What is that?
A. If we go to EP '984, which is JTX-209, on JTX-209.2 I've taken an extract from towards the bottom of the page which explains that the incompatibility between benzalkonium chloride and a nonsteroidal anti-inflammatory is due to the presence of this acidic carboxyl group which is described here COOH and that's -- this complexation means that benzalkonium chloride is less effective to exert its preservative activity by overcoming that complexation. A person of ordinary skill

in the art would have expected the formulation to exhibit better preservative efficacy.
Q. And what does the EP '984 patent suggest about the expectation with respect to the activity of the drug itself?
A. The same patent says that there should be an increased activity of the drug in solution, so you would expect it, the drug itself to be more effective as well.
Q. Is there anything unexpected about the fact that a smaller amount of tyloxapol at .02 percent would provide greater stability as compared to a higher amount of polysorbate 80 at .15 percent?
A. No, there isn't.
Q. Why not?
A. Again, if we refer to EP '984, this suggested that low levels of the ethoxylated octylphenols were effective as overcoming the problem of complexation between BAC and the NSAIDS and a person of ordinary still would look, as I've explained, at reducing the concentration of tyloxapol to have a formulation containing the least amount of tyloxapol that was compatible with it being a stable formulation.
Q. Now, earlier you mentioned that you had reviewed some of plaintiff's internal documents regarding the development of the formulation that became Prolensa®.
MR. HASFORD: At this point, your Honor, we're going to object. The defendant served revised slides on us last

night after your Honor sustained our objection that in part directed to the use of internal documents. Defendants served revised slides on us last night, stated that they would change these slides that they were using from the alleged internal -- or the internal documents allegedly do not support non-obviousness or allegedly confirmed non-obviousness in that they would change that to these documents that are relevant to level of skill in the art. Well, that's not anywhere in any of Dr. Lawrence's expert reports. And we lodged this objection with defendants yesterday. We met and conferred about it last night. Actually this morning they agreed to withdraw that. So we ask that your Honor enforce that agreement between the parties.

MS. RAPALINO: So I'm going to disagree in part with what Mr. Hasford said. They objected to our revised slide that we served yesterday and we agreed to withdraw the slide and not use it for purposes of this testimony.

Per your Honor's ruling of yesterday, we do still intend to present evidence from Professor Lawrence on plaintiff's internal documents and how they reflect the level of ordinary skill in the art. And this testimony is within the scope of Professor Lawrence's expert report beginning at, I believe it begins at Paragraph 733 of Professor Lawrence's opening expert report.

But perhaps Mr. Hasford would agree to reserve his

objection until he hears what the testimony is.

MR. HASFORD: No, your Honor. She doesn't have anything in her expert reports about level of skill in the art with respect to these documents, it's nowhere in her expert reports.

THE COURT: All right. I don't believe I have a copy of that report. Do I?

MS. RAPALINO: We can hand up a copy to the Court. May I approach?

THE COURT: Yes, please.

Thank you.

MR. HASFORD: Do you have a copy for us?

MS. RAPALINO: Just give us a moment, your Honor, to get extra copies of that opening report.

Mr. Hasford, you do not have a copy?

MR. HASFORD: I don't.

And, your Honor, I direct you to the heading on Page 218 above Paragraph 733, it's actually above Paragraph 731, it says, "documents produced by plaintiffs are consistent with my opinions regarding obviousness." Doesn't say anything about level of skill in the art.

MS. RAPALINO: Your Honor, if I could just direct your attention to the paragraphs that follow, in particular to statements that are consistent with testimony that plaintiff's documents are consistent with the level of skill in the art.

As just one example, in Paragraph 734 she discusses an internal document and concludes that the rapid identification of an optimization tyloxapol --

MR. HASFORD: Actually, your Honor, I've got to object to this. I object to her reading this document into the record. These are sensitive Senju internal documents. She's trying to make an argument to read these into the record and I have to object to that and move to strike.

THE COURT: I think that there is a problem with Paragraph 733, which attracted me to it a moment ago because it has to do with how quickly the discovery was made, and there's case law that says that the inventor's time line can't be used against him to support that it was all obvious.

MS. RAPALINO: So that's part of Paragraph 733. But then towards the end of that paragraph she explained how -- what was done by the inventors in this case supports the expectation of a person of ordinary skill in the art.

THE COURT: I'm going to sustain the objection to Paragraph 733 at least.

MS. RAPALINO: Okay.

THE COURT: I can cite cases, if we need to, but I think that the parties ought to be in agreement that this is one of the purposes that the federal circuit is pretty clear that prior -- that the inventor's own workbooks, especially the time line and how rapid it was that this invention came

about, cannot be used to prove obviousness.

MS. RAPALINO: Okay. And I will limit the testimony so we avoid anything about the time line and how rapid it was. Again, it will just be testimony supporting what the person of skill in the art would have known at the time, how it's consistent with what a person of skill in the art would have known.

MR. HASFORD: That's our problem, your Honor. There's absolutely nothing in Dr. Lawrence's expert report that states this is what the level of ordinary skill in the art is based on plaintiff's internal documents. That's our objection, there's nothing in any of her expert reports about that.

MS. RAPALINO: If I could, this testimony will be limited to testimony about the fact that based on the level of skill in the art, a person of skill in the art would have known how to conduct routine optimization. And it's just for that limited point about the level of skill in the art allowing for routine optimization as reflected in the plaintiff's documents.

MR. HASFORD: Your Honor, counsel isn't even responding to my objection. The objection here is that this information is not in Dr. Lawrence's reports anywhere, it's objectionable for that reason.

MS. RAPALINO: Right. I'm pointing again to

Paragraph 734, the last sentence.

MR. HASFORD: That does not go, your Honor, to the level of skill in the art. That goes to an alleged identification, a rapid -- alleged rapid identification of something.

THE COURT: I'll sustain the objection as to 734 for essentially the same reasons. Now, in sustaining the objections, I'm sustaining it with respect to the defendant's direct case and it will depend also on what's brought up on cross-examination. If, for instance -- well, I don't want to give examples in the witness' presence. But there could be a line of cross-examination that might open the door to the witness being able to testify that such steps were so routine they were present here, they were present in the literature, I would permit that probably. But, otherwise, I'm seeking to uphold the principle that the inventor's own notes can't be used -- cannot be used to show that the invention was obvious to a POSA just because it happened to be obvious to the inventor, or happened to occur to the inventor, I should say.

MS. RAPALINO: Okay.

THE COURT: Very well.

BY MS. RAPALINO:

Q. Professor Lawrence, did you review the testimony of the inventors about their development of formulations that are the subject of the '431 patent?

MR. HASFORD: Same objection, your Honor.

THE COURT: I'll permit it.

You can answer.

THE WITNESS: Okay.

Yes, I did.

BY MS. RAPALINO:

Q. Did anything strike you about the testimony that you reviewed about their formulation?

A. Yes, it did. It was very striking that the inventors remembered very little of the process --

MR. HASFORD: Objection, your Honor. Not relevant to anything in the case. Move to strike.

THE COURT: Is it in her expert report?

MR. HASFORD: I'm not sure that it is.

MS. RAPALINO: It is, your Honor. It's in her reply expert report at Paragraph 13, and I can hand up a copy of that.

MR. HASFORD: Your Honor, if it's in a reply expert report, I don't think it belongs here. And it's not relevant to any issue in the case, in any event.

MS. RAPALINO: May I approach to hand up the report?

THE COURT: Certainly.

MR. HASFORD: Do you have a copy for us?

Thanks.

THE COURT: Is there a paragraph that we should be --

MR. HASFORD: It's Paragraph 13, your Honor.

The basis for our objection is Dr. Lawrence isn't here to opine on the reasons why the inventors did or did not do something. As your Honor will see, in Paragraph 13, this plainly goes to the same issue, it's talking about this work that the inventors did and characterizing it in some way. That's our objection.

MS. RAPALINO: This is really quite different in that here I'm asking for Professor Lawrence's experience as a formulator and what that experience as a formulator suggests about memory or lack of memory about a formulation process.

MR. HASFORD: That's ridiculous, your Honor. This -- again, it's just an attempt to backdoor in the information from Mr. Sawa and Mr. Jujita, the inventors. It goes to no issue in the case. She's not here to testify about what lack of memory may or may not mean to a formulation scientist or what the inventors did here. It's not relevant to the issue in the case.

MS. RAPALINO: Plaintiffs put the testimony of the inventors at issue in the case, they brought their inventors for deposition but shielded them from testimony at trial.

MR. HASFORD: That's not --

THE COURT: Just a moment. You keep cutting off your adversary.

MR. HASFORD: I apologize.

THE COURT: Do you realize that?

Please continue.

MS. RAPALINO: This is, again, another instance of this pattern of shielding their internal documents, shielding their inventors from cross-examination at trial and we feel this testimony is in evidence through the deposition designations. And without the benefit of the inventors here to cross-examine them about their own testimony, we're entitled to have an expert opine about what that testimony means to a formulator and an expert in this field.

THE COURT: So there are excerpts of the inventors' depositions that are going to be offered as part of the case?

MR. HASFORD: Yes.

MS. RAPALINO: Yes, your Honor, in our deposition designations.

THE COURT: All right. And those have already been identified?

MS. RAPALINO: They've been identified in the pretrial order. The parties reached an agreement which I -- and I believe that it was raised with the Court in a call prior to trial that we would submit those deposition designations, perhaps in some reduced form, after the close of trial so that we'd have an opportunity to cull them down somewhat based on the testimony that came in at trial, but they are designated in the pretrial order at the moment.

THE COURT: Okay. I'll permit the expert to testify with regard to the anticipated testimony of the inventors. Since the parties have identified excerpts of the inventors' depositions that are going to be used as trial testimony, the expert is permitted to comment upon the testimony as long as it's within the scope of her report, and that would include this reply report and as long as it's not ruled out as evidence under any of the rules of obviousness. In this case, because they would be trial witnesses, albeit not live, commenting upon their testimony, I believe, is within her right, and due notice has been given to the plaintiffs. The comment here has to do not with the work that they performed but rather with their recollection of it. And it's the, allegedly, inability to recollect as if they were testifying at trial that, as a formulator herself, she finds striking. I find that that's probative and that it doesn't intrude into the forbidden area that's been staked out and so the objection's overruled. But it itself depends upon offering the underlying testimony that she's commenting on as if the witnesses were present and testifying in this case.

Is there any clarification needed of the ruling?

MS. RAPALINO: No, your Honor.

MR. HASFORD: Well, our only question, your Honor, is would this be going to level of skill in the art? Because it clearly can't go toward the underlying obviousness issues.

MS. RAPALINO: And, your Honor, if I may, as your Honor pointed out, this is not a matter of using their formulation process or those internal documents in support of an obviousness position. This is a matter of a formulator commenting on memory or lack of memory and what that suggests about the nature of that project. And, again, I believe it does not run afoul of the rule that plaintiffs -- the inventors' own path to the invention not be used to support obviousness, this is not about their path, this is about their memory or lack thereof.

THE COURT: I'm going to admit it into evidence. It's a nonjury case and what weight, if any, it receives will have to be determined in the future. But I find that it is at least relevant and probative of the issues before me that sufficient notice has been given of it in the expert report and that it doesn't intrude into the undue questioning of the path that they followed.

MS. RAPALINO: Okay.

BY MS. RAPALINO:

Q. Professor Lawrence, what struck you about the testimony of the inventors that you reviewed about their formulation work?

A. I was particularly struck by how little the inventors could actually remember their formulation process.

Q. Was there anything in particular that was striking about

that lack of memory?

A. As a formulator myself, if I had a particular challenge or difficult problem to overcome, I would remember that. I tend to forget the things that are fairly routine and easy to solve.

Q. Okay. My final question, Professor Lawrence.

Based on your review of all of the prior art, what did you conclude about whether Claim 6 and 20 of the '431 patent would have been obvious to a person of ordinary skill in the art?

A. It's my opinion that Claims 6 and 20 of the '431 patent would have been obvious to somebody of ordinary skill in the art.

MS. RAPALINO: I pass the witness.

Thank you, Professor Lawrence.

THE COURT: Let's take a break before cross-examination. Let's take about 15 minutes and we'll resume at 11:30.

(Brief Recess.)

DEPUTY CLERK: All rise.

THE COURT: Be seated, please.

Okay. Cross-examination.

MS. RAPALINO: Your Honor, before we do the cross-examination, I neglected to move into evidence the exhibits that Professor Lawrence talked about. Could I read

that?

THE COURT: Okay. Just a minute.

Okay. Have you reviewed these with opposing counsel? Is there any objection to any of them?

MS. RAPALINO: We disclosed the exhibits prior to Professor Lawrence's testimony and we resolved any objection to them.

THE COURT: Okay. Very well. Then please slowly read into the record the exhibits that you're moving.

MS. RAPALINO: JTX-2, JTX-3, JTX-45, JTX-61, JTX-71, JTX-168, JTX-199, JTX-201, JTX-207, DTX-15, DTX-109, DTX-110, DTX-196, and DTX-442. And I believe that yesterday three exhibits that Professor Lawrence discussed had already been moved into evidence, and those are JTX-1, JTX-147, and JTX-210.

THE COURT: Okay. Any objection?

MR. HASFORD: No objection, your Honor.

THE COURT: Okay. Very well. Then each of those will be received into evidence?

(JOINT EXHIBITS JTX-2, JTX-3, JTX-45, JTX-61, JTX-71, JTX-168, JTX-199, JTX-201, JTX-207, DTX-15, DTX-109, DTX-110, DTX-196, and DTX-442 WERE RECEIVED IN EVIDENCE)

THE COURT: Mr. Hasford, you may proceed.

MR. HASFORD: Thank you, your Honor.

May we approach and distribute binders?

THE COURT: Yes.

Let me make an offer to counsel on both sides, that if, because you have a lot of materials, it would be easier to examine from your counsel table, you can do that. You don't necessarily have to use the podium if things just don't fit. I'm sorry it's not a larger podium. But it's up to you.

MR. HASFORD: Thank you, your Honor. I'll try to use the podium and see how it goes.

May I proceed, your Honor?

THE COURT: Yes.

(CROSS-EXAMINATION OF JAYNE LAWRENCE BY MR. HASFORD:)

Q. Good morning, Dr. Lawrence.

A. Good morning.

Q. You testified on direct exam about motivation to select and modify Example 6 of the Ogawa patent. Do you remember that?

A. I do.

Q. Yet in your opinion, to the extent there was even any need in the art for the claim formulations of the '431 patent, you would state that that need would have been met by the disclosures of the Ogawa patent and the Hara reference, each of which in your view purports to describe stable ophthalmic formulations. Correct?

A. I'm sorry, you're going to have to slow it down. Can you repeat it, please?

Q. Certainly.

In your opinion, to the extent there was even any need in the art for the claimed formulations of the '431 patent, you would state that that need would have been met by the disclosures of the Ogawa patent and the Hara reference, each of which in your view purports to describe stable ophthalmic formulations, correct?

A. I believe that's an extract from one of my reports, but I would like to look at the context it's put in.

Q. Doctor, do you remember testifying under oath in a deposition in this case?

A. Yes, I do.

MR. HASFORD: Let's pull up Dr. Lawrence's deposition transcript from February 29, 2016, and let's go to Page 139, Lines 12 through 20.

MS. RAPALINO: Objection, your Honor.

THE COURT: Sustained. It hasn't been established that there's inconsistency. If you can get an answer from the witness that is consistent with her prior dep, then I will permit the dep to be used. And I think she asked for a copy of her materials so that she could look at it.

MR. HASFORD: Certainly. I'm happy to provide those. Do we have a copy of Dr. Lawrence's opening report?

THE COURT: I have an extra one.

THE WITNESS: Thank you very much.

THE COURT: You can borrow mine.

THE WITNESS: Could you direct me to the page, please?

BY MR. HASFORD:

Q. Certainly. Let's go to Paragraph 727.

A. And would --

Q. We may have to go to the next page on the screen, it's going to be at the top of Page 217.

And let me direct your attention to that first full sentence. You state: To the extent there was even any need for the claimed bromfenac ophthalmic formulations claimed in the asserted claims of the asserted patents, it is my opinion that that need would have been met by the disclosures of the '225 patent and Hara, each of which purport to describe stable ophthalmic bromfenac formulations.

You wrote that in your expert report, correct?

A. Yes, in the context that Senju couldn't demonstrate there had been a long felt need for the formulations.

Q. You in fact wrote that sentence in your expert report, correct?

A. But in a particular context.

Q. Did you or did you not write that sentence in your expert report, doctor?

A. I wrote the sentence in the context that Senju cannot demonstrate long felt need, yes.

Q. I'll ask you once again.

Did you write that exact statement in your expert report?

A. I wrote -- I can see where I wrote in my report as part of a longer sentence, yes.

Q. In fact it is your opinion that any need in the art for an aqueous preparation of an NSAID formulated with benzalkonium chloride for ophthalmic administration was already meet by aqueous ophthalmic formulations of NSAIDS known as of January 21, 2003, correct?

A. I am sorry, but I feel that's taking that out of context.

Q. I'm simply asking you.

It is your opinion that any need in the art for an aqueous liquid preparation of an NSAID formulated with benzalkonium chloride for ophthalmic administration was already met by aqueous ophthalmic formulations of NSAIDS known as of January 21, 2003, correct?

A. Of course there's preparation been allowed at this time on to the Japanese market, so obviously had sufficient stability for that particular market.

Q. You also testified on direct exam about modifying formulations to remove incompatibility issues with benzalkonium chloride. Do you remember that?

A. Yes, I do.

Q. Your opinions on modifying a formulation to remove any

incompatibility issues with benzalkonium chloride are based on pure hindsight, correct?

A. No, they're not.

Q. Take a look at your deposition transcript.

MR. HASFORD: Let's go to her deposition transcript of February 29th at Page 125, Line 13, and let's bring it up also on the next page as well.

BY MR. HASFORD:

Q. Okay. So starting at Line 13 -- let me know when you're there.

A. Sorry, I'm not --

MS. RAPALINO: Your Honor, I'm going to object to this as improper impeachment. What she said is not relevant to her testimony here and it is not inconsistent with what she just said.

MR. HASFORD: It's absolutely relevant to the testimony, your Honor, because, as the federal circuit has pointed out time and again, a hindsight analysis of obviousness is entirely improper. And it's entirely inconsistent with her testimony because I asked her this question at her deposition and she admitted that she in fact used hindsight.

MS. RAPALINO: That's not at all what she admitted. And I suppose we can let the testimony be read in and it will be clear from the testimony that she was not at all talking

about providing a hindsight analysis.

MR. HASFORD: Well, let's read the testimony in.

THE COURT: Well, just a moment. Looks like my Line 13 doesn't match up what's in my book. Line 13 just contains the words "to 8.5."

MR. HASFORD: Let's see, is there -- perhaps your Honor has a bad copy. Would you like a different one? I can hand this up.

THE COURT: Can I hand you what I'm looking at?

MR. HASFORD: Certainly.

THE COURT: 125, Line 13. Is there a different pagination maybe? I'm sorry, there's different dates. I didn't realize that.

MR. HASFORD: Yes.

THE COURT: Okay. You can proceed. I'll permit it.

MR. HASFORD: Thank you, your Honor.

BY MR. HASFORD:

Q. I asked you a question:

QUESTION: Is it still your opinion that a person of ordinary skill in the art would have found it preferable to modify a formulation or remove any incompatibility issues with benzalkonium chloride?

And then there was an objection.

And then you answered:

ANSWER: May I ask, are you talking in 2016 would I

have formulated to use it now or are you talking with my hindsight looking back to 2003?

And I asked a question:

QUESTION: Let's start with your hindsight looking back to 2003.

There was another objection.

And you answered:

ANSWER: Yes.

That was your testimony, wasn't it, doctor?

A. Well I -- okay. While I read --

Q. Was that your testimony, doctor?

A. While I read the word "hindsight" there, it wasn't meant in the context that you've interpreted it as and that was very clear from my testimony. Any opinions I've made are stated with an expert -- as a person of ordinary skill in the art in 2003.

Q. You never qualified your testimony in any way at your deposition, did you, doctor?

A. That was obviously not the appropriate word to use, but that is not what's been done in this particular case as is clear from my evidence.

Q. You never qualified your testimony at your deposition, did you, doctor?

A. I obviously said that word, it's in the text.

Q. You also testified on direct exam about the Ogawa '225

patent. Let's take a look at the Ogawa '225 patent, which is JTX-147 in your binder. Let me direct your attention to Example 6.

Are you there, doctor?

A. Yes, I am.

Q. The Ogawa '225 patent itself characterizes the Example 6 formulation as stable. And in your view the inclusion of tyloxapol instead of polysorbate 80 in an identical formulation would be expected to have no material effect on stability, correct?

A. Yes, in my understanding of what I understand by the word "material effect on stability."

Q. Let's -- you can put that document aside.

Let's discuss the way in which you went about preparing your obviousness opinions in this case. The first document you considered in connection with your opinions in this case was the '431 patent, correct?

A. Yes, that is correct.

Q. You obtained the documents that you considered in connection with your opinions in this case from defendant's counsel, correct?

A. As I've explained before, the initial documents were provided by the counsel, yes.

Q. In formulating your obviousness opinions you believe it is important to know the goal you were trying to reach because

you need to understand what you require from the formulation, correct?
A. Could you repeat that, please?
Q. Certainly.
In formulating your obviousness opinions you believe it is important to know the goal you were trying to reach because you need to understand what you require from the formulation, correct?
A. I wouldn't quite put it like that but, yeah.
Q. Let's take a look at your deposition transcript then, February 29th at Page 248.
MS. RAPALINO: Objection, your Honor. I believe the witness gave -- answered the question yes.
MR. HASFORD: I believe she said she wouldn't quite put it like that, so I would like to show where she answered this question at her deposition.
THE COURT: I'll permit it.
BY MR. HASFORD:
Q. Let's look at 248, Line 9. And I asked you:
"QUESTION: In formulating your obviousness opinions, why do you believe it is important to know the goal you are trying to reach?"
And then there was an objection, and you answered:
"If you're preparing a formulation, you need to understand what you require from that formulation."

And that was your testimony, wasn't it, Doctor?
A. Yes.
And can you just repeat the question you asked me, please?
Q. I believe you've answered my question, actually.
Let's now discuss formulation issues. You testified on direct exam about formulation of ophthalmic products including stability testing. Do you remember that?
A. Yes, I do.
Q. You would characterize stability testing as a very large area, and the tests you would perform and how you would perform them would depend upon the formulation you were looking at and the intended purpose, correct?
A. My recollection of the large area is in relation to the number of liquid preparations rather than stability.
Q. Let's take a look at your deposition transcript of September 4th, so it's going to be the first one in your binder. And let's take a look at Page 41, and let me direct your attention to Line 8. Tell me when you're there.
A. I'm there.
Q. I asked you:
"QUESTION: How did you conduct stability testing on aqueous liquid preparations?"
Then there was an objection.
Then you answered: "I repeat my answer. Stability

testing is a very large area. The tests you performed and how I perform them would depend upon the formulation I was looking at and the purpose, the intended purpose."
That was your testimony, wasn't it, Doctor?
A. The "very large area" referred to the liquids -- number of liquid preparations.
Q. That was the exact question that I asked and the exact answer you gave, correct?
MS. RAPALINO: Objection, Your Honor. Improper impeachment. This is entirely consistent with the answer the witness just gave about the large area being the number of preparations.
THE COURT: Okay. Just a moment.
Well, I don't see anything in the deposition answer about a large number of preparations. Is it there?
MS. RAPALINO: I believe her answer was that it would depend upon the formulation I was looking at and the purpose, the intended purpose, the implication of which is that the large area means that it depends on the number of preparations, the large number of preparations.
THE COURT: I'll permit it. I think it's arguably there, but I'll permit it.
BY MR. HASFORD:
Q. The exact question I asked you, Doctor, was:
"QUESTION: How did you conduct stability testing on

aqueous liquid preparations?"
And the exact answer you gave was:
"I repeat my answer. Stability testing is a very large area. The tests you performed and how I perform them would depend upon the formulation I was looking at and the purpose, the intended purpose?"
Correct?
A. In the context of a large number of aqueous preparations, yes.
Q. You didn't qualify your testimony in any way at your deposition, did you?
A. Well, it was in the context of the questions you're asking me.
Q. You didn't qualify your testimony in any way at your deposition, did you, Doctor?
A. Well, I thought the questions qualified it.
Q. You didn't qualify your testimony in any way at your deposition, did you?
THE COURT: You're being argumentative now.
MR. HASFORD: Okay. The point is made.
BY MR. HASFORD:
Q. In order to determine whether it is possible to successfully formulate a drug as a medicine, it is essential to determine the drug's basic physicochemical properties, including its water solubility, its partitioning between oil

and water, and its behavior in different pH environments, correct?
A. I've stated that, yes.
Q. You do not know the oil and water partition coefficient of bromfenac, correct?
A. I -- I have a value for it, but that was not available, to my understanding, back in 2003.
Q. Once a potential drug candidate has been identified, its fated behavior in the body have to be assessed before a decision can be made whether it is possible to develop the molecule into a safe, effective medicine, correct?
A. Yes. And that would be done, as I've stated, in preformulation studies as an early stage of development rather than a stage of pharmaceutical formulation we're talking about here.
Q. Let me actually direct you to your -- the middle transcript which is February 16th, and it's going to be at Line 73. Sorry. Page 73, Line 6 through 15. I apologize. Page 273, 273.
THE COURT: 273?
MR. HASFORD: Yes. Wait a minute. Oh, oh. Lines 3 through 9, sorry. So it's going to be the February 16th transcript, Page 73 is correct, Lines 3 through 9. 73.
MS. RAPALINO: Your Honor, again, I'm going to object as improper impeachment. The witness answered the question in

the affirmative when it was just asked of her, and so I don't see any inconsistency here between what was in her deposition testimony and the answer she gave here today.
MR. HASFORD: Well, your Honor, I believe she tried to qualify her answer by saying that it only applied to free formulation. She certainly did not qualify that answer when she gave it in her deposition.
MS. RAPALINO: And, again, there is nothing inconsistent about an affirmative answer that offers more context here to the deposition answer that was given several months ago.
MR. HASFORD: I would disagree, Your Honor, if she's trying to qualify it.
THE COURT: I'll permit it if the question would have embraced the answer that she gives today. If the deposition question would have embraced today's answer and what she said at her dep was materially different, then I'll permit it.
MR. HASFORD: So I asked you, Doctor:
"QUESTION: Once a potential drug candidate has been identified, its fate and behavior in the body have to be assessed before a decision can be made whether it is possible to develop the molecule into a safe, effective medicine, correct?"
There was an objection.
And you answered: "That's correct."

That was your testimony, wasn't it, Doctor?
A. And I stand by it's correct in as far as it goes, but you have to put it into context.
Q. You didn't qualify your testimony in any way at your deposition, did you, Doctor?
A. I think we discussed that later on, in another deposition.
Q. At this deposition, when I asked you that question, you gave me the exact answer, "That's correct," didn't you?
A. I just agreed to that.
Q. Okay. A successful drug requires a balance to be struck between potency and selectivity in its pharmacokinetic properties, correct?
A. Correct.
Q. In particular, the drug's physicochemical, pharmacokinetic, pharmacodynamic, and toxicological properties all have to be established, correct?
A. That is correct, yes.
Q. You have no understanding of the pharmacokinetic properties of any aqueous liquid preparations of bromfenac, correct?
A. That is correct, yes.
Q. You have no understanding of the pharmacodynamic properties of any aqueous liquid preparations of bromfenac, correct?

A. That is what I've said, yes.
Q. You have no understanding of the toxicological properties of any formulation of bromfenac, correct?
A. Yes, I see that.
Q. Taking a drug molecule from concept through formulation, clinical trials, manufacture, and the strict regulatory process to its ultimate use as a medicine by the patient is an expensive, complex, and lengthy process with a great many hurdles at which a potential drug may fail, correct?
A. Yes, I've said that previously.
Q. Once a lead compound has been identified, a decision has to be made as to whether it is possible to develop the molecule into a safe, effective medicine, correct?
A. Yes, that is correct.
Q. To do this, the compound's physicochemical properties, as well as its fate and behavior in the body all have to be assessed, correct?
A. In the context of the development process, yes.
Q. Particular attention is given to the efficacy and toxicity of a lead compound, as these are the main reasons for failure of a compound to progress beyond this stage, correct?
A. That is correct, yes.
Q. You testified earlier that you have no understanding of the toxicological properties of any formulation of bromfenac, correct?

A. Well, that is correct, but it is -- it doesn't follow on from the previous statements that you've made.

Q. Just to be clear, you have no understanding of the toxicological properties of any formulation of bromfenac, correct?

A. That is correct in as far as it goes, yes.

Q. There can be considerable challenges encountered in the preparation of an appropriate formulation or delivery form of a drug, with the formulation being used for preclinical studies unlikely to be the formulation used in man, correct?

A. If you're dealing with a brand new drug which is what all this is dealing with, yes, you are correct.

Q. The physical and chemical properties of aqueous liquid preparations for ophthalmic use depend upon the drug being used and the drug dose, correct?

A. That is a correct statement, yes.

Q. Those would be factors in determining the formulation that would be prepared, correct?

A. That is a correct statement as far as it goes, yes.

Q. A formulator developing an ophthalmic solution as of 2003 had to consider variables including efficacy, comfort to the patient, extent of absorption of solution into the eye, and shelf life, correct?

A. As would any formulator preparing something for market, yes.

Q. Efficacy of a formulation is determined by form, for example, free acid, free base, or salt, and the amount of the one or more active ingredients, and also requires a careful balance of excipients, correct?

A. These statements are correct but you've got to be careful not to take them out of context.

Q. For example, pH modulators such as sodium hydroxide are used to keep the pH as close to possible to the pH of natural tears, between 6.5 and 7.6, which ensures comfort and may aid in absorption, correct?

A. I have made that statement, yes.

Q. In your opinion, some of the considerable challenges encountered in the preparation of an appropriate ophthalmic formulation include the dose, dosing frequency, physicochemical properties of the drug, how those properties are affected by the likely excipients to be added to the formulation, the effective temperature on the formulation, the pH of the formulation because that may affect the stability of the drug, how the drug is likely to be degraded, what is the best formulation, and what is the best solvent to add, correct?

MS. RAPALINO: Objection, compound, your Honor. There is a lot in that question.

THE COURT: Well, if the witness understands the question and can answer it, then you may. If you would like

it broken down into its components, then just say so.

THE WITNESS: I would like it reread because I did lose what was being said.

THE COURT: All right. Then I will sustain the objection as a compound question.

MR. HASFORD: I will repeat it.

BY MR. HASFORD:

Q. One of the considerable formulation challenges encountered in the preparation of an appropriate ophthalmic formulation is the dose, correct?

A. Perhaps -- yes. Perhaps you could direct me to where I actually wrote that in my report. It might be easier.

Q. I will direct you to your deposition testimony, in fact.

Take a look at your first transcript which is --

A. Can I not see where I wrote it in the report in the context in which it was said? No?

Q. You testified about it at your degradation. I'll show you that.

A. Okay.

Q. Turn in your first deposition transcript, which is the September 4th, 2005, transcript, and please turn to Page 271. And let me direct your attention to Line 9. Actually, let me direct your attention to Line 2. And I'm going to read you from Page 271, Line 2, through 272, Line 10.

A. I believe we also discussed this in deposition in

February 2000 -- 29th, as well.

Q. Well, let me read you your testimony here. I said:

"QUESTION: Take a look at the section on Page 14 entitled 'Formulation Challenges.' In the first sentence, you state, 'There can be considerable challenges encountered in the preparation of an appropriate formulation or delivery form of a drug, with the formulation being used for preclinical studies unlikely to be the formulation used in man.'"

And then I asked you: "What are some of the considerable challenges encountered in the preparation of an appropriate ophthalmic formulation?"

Then there was an objection.

I said, "You may answer."

You said: "I believe I've already answered this question earlier."

Then I asked, "Could you summarize them, please?"

And then you testified, "There would be -- what you would need to understand" was -- "what you would need to understand, what the dose was, the dosing frequency, physicochemical properties of the drug, how those properties are affected by the likely excipients that you're going to add to the formulation, the effect of temperature on that formulation. I think pH is obviously included in there as well because that may be -- may affect the stability of the drug, how it's likely to be degraded, what's the best

formulation, what's the best solvent you're going to add."

Then I asked:

"QUESTION: Anything else?"

You answer: "I think I've given a reasonable start."

And that was your testimony, wasn't it, Doctor?

A. Well, I said that in testimony. You have to appreciate that they are -- although it seems like a long list, they are not challenges to somebody doing pharmaceutical formulation, particularly of a drug whose properties are known.

Q. You never qualified your testimony in any way at your deposition, did you, Doctor?

A. I did in a later deposition.

Q. In your opinion, comfort, extent of absorption, and shelf life of a formulation are controlled by the excipients, correct?

A. I have said that, yes, in the context of what I wrote.

Q. There are many examples of complex problems encountered in the art of the patents-in-suit, including multiple types of stability, viscosity, and avoidance of eye irritation, among other things, correct?

A. It would be helpful if you could direct me to where I wrote that, please.

Q. I'll direct you to where you testified about it. It's back to your September 4th deposition transcript.

A. Yeah.

Q. And if you'll turn to Page 140.

MS. RAPALINO: Objection, your Honor. I'm just going to object to a line of questions that's simply a recitation of her deposition testimony. If there is a reason for using this for impeachment, that's another story, but this just appears to be an attempt to get her deposition testimony into the record.

MR. HASFORD: Your Honor, she asked me to point her to where she provided this opinion.

THE COURT: That's correct. Mr. Hasford is correct, and I'll permit it because the witness did ask to be referred. These are long questions, and they're not offered for impeachment at this point, but, rather, to refresh the witness's recollection about --

MS. RAPALINO: Okay. I don't have a problem pointing the witness to the place in the deposition transcript. It's just the recitation of the testimony by counsel into the record that I'm objecting to. So, if it's just to orient the witness to the testimony, that's fine, and then he can ask a question, not based on the testimony itself -- not reading testimony itself.

MR. HASFORD: Well, I'm happy, once Dr. Lawrence has reread the testimony, to ask the question again, your Honor.

THE COURT: Well, again, it's not impermissible for counsel to read from the deposition in formulating his

question. His questions are not evidence. And it's the witness's answer that's going to determine the content of the evidence. And so I'll permit it.

The only thing is if there is going to be a lot of questions that have multiple factors in them, like Dr. Lawrence's answers do, they really ought to be broken down into component parts.

MR. HASFORD: I'll try to do a better job of that, your Honor.

BY MR. HASFORD:

Q. So, on Page 140 of your deposition transcript, I asked you:

"QUESTION: How complex are the types of problems encountered in the art of the patents-in-suit?

Then there was an objection.

And then you answered: "I could list some examples of formulations that are encountered."

And then I asked:

"QUESTION: Please do."

Then you answered: "If it's a solution formulation, it's important that there are no large particulate contaminants in the formulation. If it's a suspension formulation, it's important that the particles or the suspension are small enough and not too large. That could be a problem due to poor stability of the formulation, so that's

an example of a type of problem encountered."

Then I asked you:

"QUESTION: Are there any other examples?"

You answered: "One very practical problem is getting the formulation viscous enough to stay in the eye but not too viscous to come out of the eyedrop bottle, for example."

Then I asked:

"QUESTION: Are there any other examples?"

Then you answered: "We spoke about stability in respect to particulates, but there might be stability in the container that you choose to put the formulation in. There might be problems once you -- there is two types of stability. There's the shelf-life stability, and then there's the stability once the formulation is opened, and they may be -- opened and in use, and they may be different, and that is something else that you need to consider. You need to make sure you're not introducing anything damaging that's going to irritate into the eye."

Then I asked:

"QUESTION: Are there any other examples?"

And you answered: "I'm sure there are, but they are the ones that I can think of at the moment."

That was your testimony, Doctor, wasn't it?

A. Well, that's my testimony. These problems are just bread and butter for a pharmaceutical formulator.

02:39 Q. When I asked you how complex are the types of problems
02:39 encountered in the art of the patents-in-suit, you provided me
02:39 a page and a half worth of testimony, correct?
02:39 **A. As I explained, these are just standard problems for a**
02:39 **pharmaceutical formulator.**
02:39 Q. You never characterized them as "standard" at your
02:39 deposition, did you, Doctor?
02:40 **A. While I don't see the word "standard" there, it looks**
02:40 **like it's a long list. What I'm just saying, you've got to**
02:40 **put it into context with the pharmaceutical formulator.**
02:40 Q. There are a large number of different possible ways to
02:40 formulate aqueous liquid preparations of NSAIDs, depending on
02:40 the dose, correct?
02:40 **A. In as far as it goes, it's correct.**
02:40 Q. There are a large number of different possible ways to
02:40 formulate aqueous liquid preparations of NSAIDs, depending on
02:40 the route of administration, correct?
02:40 **A. In as far as it goes, it's correct, yes.**
02:40 Q. There are a large number of different possible ways to
02:40 formulate aqueous liquid preparations of NSAIDs, depending on
02:40 whether you want a salt or a free acid or base, correct?
02:40 **A. In as far as it goes, yes.**
02:40 Q. As of 2003, the search was still ongoing for technologies
02:41 to overcome the solubility and permeability problems
02:41 encountered with the formulation of drugs as medicines,

02:41 correct?
02:41 **A. And that is still the case today.**
02:41 Q. Let's now discuss your opinions on NSAIDs. In your own
02:41 words, quite a lot of different NSAIDs are known to exist,
02:41 correct?
02:41 **A. Yes, but as I've stated, very few of them are used as**
02:41 **medicines themselves.**
02:41 Q. Take a look, if you would, at your September 4th
02:41 deposition transcript, and let me direct your attention to
02:41 Page 157 and to Line 7.
02:41 The exact question I asked you was: "How many
02:41 different NSAIDs are known to exist?"
02:41 And the exact answer you gave was: "Quite a lot."
02:41 Correct?
02:42 **A. That is true. But that's not inconsistent with the**
02:42 **answer I've just given.**
02:42 Q. You didn't qualify your testimony at your deposition, did
02:42 you, Doctor?
02:42 **A. I'm explaining that there is a lot -- I'm quite happy to**
02:42 **say there is quite a lot of NSAIDs, but very few of them have**
02:42 **been developed into medicines, that's all.**
02:42 Q. In fact, in your own words, the range of potential drug
02:42 molecules is enormous, correct?
02:42 **A. The range of any chemical space is enormous, yes.**
02:42 Q. Different NSAIDs having different chemical structures

02:42 possess different physical and chemical properties, correct?
02:42 **A. I think that's got to be a qualified statement.**
02:42 Q. Take a look, if you would, at your February 16th
02:42 transcript. And let me direct your attention to Page 85, and,
02:42 in particular, to Lines 15 through 18. Tell me when you're
02:43 there.
02:43 MS. RAPALINO: Your Honor, I would ask that further
02:43 context be provided for this question, going onto 86, Lines 3
02:43 through -- Lines 1 through 4.
02:43 MR. HASFORD: I think the exact question is Page 85,
02:43 Lines 15 through 18, your Honor.
02:43 MS. RAPALINO: Again, I'm just asking for some more
02:43 context be provided in the transcript to that question.
02:43 MR. HASFORD: If she would like me to read that
02:43 additional line into the record, I don't have any problem with
02:43 doing that.
02:43 THE COURT: Okay.
02:43 MR. HASFORD: The exact question is here so --
02:43 THE COURT: I'll permit it as completeness.
02:43 MR. HASFORD: Okay.
02:43 BY MR. HASFORD:
02:43 Q. So, Doctor, I asked you: "Different NSAIDs having
02:43 different structures possess different physical and chemical
02:43 properties, correct?"
02:43 And you answered, "Correct."

02:43 Do you see that?
02:43 **A. Yes. And that's in the context of the previous**
02:43 **statement, as I said, while there is a large number of**
02:43 **potential drugs, not all of them will be developed as**
02:43 **medicines.**
02:43 Q. And then on the next page, what Ms. Rapalino asked me to
02:44 ask, to read in, is starting on Page 86, Line 1, I asked you:
02:44 "QUESTION: Diclofenac and bromfenac have different
02:44 chemical structures, correct?"
02:44 And you answered, "Yes, but they also have a lot of
02:44 similarities."
02:44 And then I asked you:
02:44 "QUESTION: Diclofenac and bromfenac, in fact, have
02:44 different chemical structures, correct?"
02:44 And then there was an objection.
02:44 And you answered, "They won't have the same name, if
02:44 they're the same chemical structure."
02:44 That was your testimony, wasn't it, Doctor?
02:44 **A. That's what's on the page, yes.**
02:44 Q. Bromfenac and indomethacin also have different chemical
02:44 structures, correct?
02:44 **A. While they're not identical, as I've explained before,**
02:44 **they have lots of similarities.**
02:44 Q. Take a look at this same deposition transcript on Page
02:44 89, and let me direct your attention to Line 6.

I asked you: "Indomethacin and bromfenac have different chemical structures, correct?"

And you answered, "They do."

That was your testimony, wasn't it, Doctor?

MS. RAPALINO: Again, I just lodge an objection as improper impeachment. What she said was entirely consistent with that answer in the deposition.

MR. HASFORD: She didn't say it in the qualifying manner in which she said it here, Your Honor.

THE COURT: I'll permit it.

BY MR. HASFORD:

Q. Do you need me to ask the question again, Doctor?

A. No, I don't.

Q. Was that your testimony?

A. That's what's on the page, yes.

Q. Bromfenac and ketorolac have different chemical structures, correct?

A. Yes. And, as I said in that section of testimony, while they are not identical structures, or else they would have the same name, they have a number of similarities.

Q. Bromfenac and suprofen have different chemical structures, correct?

A. Yes, but they also have similarities in their properties.

Q. Bromfenac and flurbiprofen have different chemical structures, correct?

A. It's the same answer as I've just given.

Q. I'll ask it again so we're clear.

Bromfenac and flurbiprofen have different chemical structures, correct?

A. Yes, they do, but they have similarities in their properties.

Q. Let's now discuss your opinions on surfactants.

The number of different nonionic surfactants that are known to exist is, in your own words, as many as you want in your brain, correct?

A. Theoretically, as I've said, yes, it is possible to have as much and as many as you like to make.

Q. The number of possible surfactant structures, in your words, is absolutely huge, correct?

A. Yes, but the reality of the numbers that actually exist in practice is very small.

Q. Take a look, if you would, at your September 4th deposition transcript, and it's going to be at Page 309, Line 18, through 310, Line 6. And you had just asked me to repeat the question and so I said, "Certainly." Then I asked you, "Is it true that surfactants display diverse structures in aqueous environments depending on their concentration, the temperature, pH, and the presence of other species in the system?"

Then there was an objection.

And you answered: "It is vague. You have to remember the number of surfactant structures possible is absolutely huge. So, if you take surfactants as a whole, ionic, cationic, anionic, zwitterionic, nonionic, that statement will be true."

That was your testimony, wasn't it, Doctor?

MS. RAPALINO: Objection as for completeness. It's sort of an unusual case where the deposition was really in three parts, and if we go to the February 29th deposition, Page 213 -- 212 to 213, and we could pull that up as well for completeness.

MR. HASFORD: Yeah, your Honor, if all she's trying to do here is point to a prior consistent statement, I believe she's entitled to do that on redirect, so I don't think that's proper at this stage.

THE COURT: That's correct. What's permitted at this stage is to better understand the question that was asked on September 4th.

BY MR. HASFORD:

Q. So that was your testimony, correct, Doctor?

A. Yes. And the word "possible" is an important word in that sentence.

Q. There are a wide variety of equilibrium surfactant structures -- let me strike that and try again.

There are a wide variety of equilibrium surfactant

systems that can be used in aqueous drug formulations, correct?

A. Yes, but the case we're talking about is just micelles -- micelles.

Q. Is it correct that there are a wide variety of equilibrium surfactant systems that can be used in aqueous drug formulations?

A. I believe I said it's yes, but there is only one that's of relevance here.

Q. Take a look, if you would, at your September 4th deposition transcript again, and let's turn to Page 291, and, in particular, to Lines 17 through 22. I asked you:

"QUESTION: Is it fair to say that there are a wide variety of equilibrium surfactant systems that can be used in aqueous drug formulations?"

There was an objection.

And you answered, "Potentially there are, yes."

That was your testimony, wasn't it, Doctor?

A. I haven't denied that.

Q. There are a wide variety of nonequilibrium surfactant systems that can be used in aqueous drug formulations, correct?

A. As a statement goes, that's correct, but irrelevant here.

Q. Let me point you back to your deposition testimony. Page 292 in the September 4th deposition, and let me point you to

Line 1.
I asked, "Take a look, if you would, at Table 3. Is it fair to say that there are a wide variety of nonequilibrium surfactant systems that can be used in aqueous drug formulations?"
A. I have agreed with that sentence.
MR. HASFORD: May I continue, your Honor?
THE COURT: I find the witness to not offer inconsistent testimony. She did agree. She's just saying it's irrelevant to the issues that bring us to trial.
MR. HASFORD: Okay.
BY MR. HASFORD:
Q. There are, in your words, a plethora of stable surfactants in water, correct?
A. A plethora of stable surfactants in water.
Q. There are, in your words --
A. In what context was that said, please?
Q. Well, let me point you to your deposition transcript, the September 4th deposition.
A. It doesn't sound like a very good answer.
Q. At Page 86, and Line 1. I asked:
"QUESTION: What if they wanted to use it in a stable aqueous liquid preparation, what characterization would they do?"
Then there was an objection.

And you answered, "There's a plethora of stable -- of surfactants in water. So it would depend upon the aggregation state, the formulation state."
And that was your testimony, wasn't it, Doctor?
MS. RAPALINO: Objection, Your Honor. I'm not sure that that testimony was consistent or inconsistent. I just don't think that there is any way to compare that testimony to what -- the answer that the witness just gave.
MR. HASFORD: Well, I think her volunteered testimony there was that there were a plethora of stable surfactants in water.
MS. RAPALINO: No, I believe that's a misreading of the transcript, your Honor.
THE COURT: Well, the witness asked in what context was that said, and counsel directed Dr. Lawrence to her dep.
Having reread your dep, does that help you to answer the question?
THE WITNESS: I obviously said that, but I'd actually need to read further back because of the line of questioning that was going on.
THE COURT: All right. I'll permit you to dial back a few pages if you need to to refresh your recollection of the context.
THE WITNESS: That's helpful. Thank you.
(Pause)

THE WITNESS: That was a vague answer because the line of questioning was very vague.
MR. HASFORD: Your Honor, I note that it's almost 12:30. Would this be a good time for a lunch break or would your Honor prefer that I continue?
THE COURT: This is fine, and so let's break for lunch and resume at 1:30, and have a pleasant lunch.
MR. HASFORD: Thank you, your Honor.
(A luncheon recess was taken at 12:25 p.m.)
(In open court at 1:37 p.m.)
THE DEPUTY COURT CLERK: All rise.
THE COURT: Be seated, please. Good afternoon. And you may resume.
MR. HASFORD: Thank you, your Honor.
BY MR. HASFORD:
Q. Good afternoon, Dr. Lawrence.
A. Good afternoon.
Q. As of 2000, it was understood in the art that the drug solubilizing capacity of most of the commonly used surfactants was too low to be of widespread practical use, correct?
A. I'm sorry. Can you repeat that? It's my fault.
Q. I certainly will. As of 2000, it was understood in the art that the drug solubilizing capacity of most of the commonly used surfactants was too low to be of widespread practical use, correct?

A. I noted that in a paper I wrote in 1994, yes.
Q. Let's now discuss your opinions regarding polysorbate 80 versus tyloxapol. First, the sodium salt of bromfenac is a water-soluble hydrophilic drug, correct?
A. That's what I understand from the literature, yes.
Q. Polysorbate 80 is a nonionic surfactant, correct?
A. Yes.
Q. Tyloxapol is a nonionic surfactant, correct?
A. This is correct, yes.
Q. A solution containing tyloxapol and water where water is in the greater proportion would be considered an aqueous surfactant system, correct?
A. That is correct, yes.
Q. The prior art, in fact, the prior art that you authored in a peer-reviewed academic journal teaches that there is no use trying to increase the solubility of a water soluble hydrophilic drug in an aqueous-based surfactant system, correct?
A. Yes, I've said that, yes.
Q. Determining how the physical and chemical properties of tyloxapol would affect aqueous liquid preparations of NSAIDs that contain tyloxapol would, in your words, very much require looking on a case-by-case basis, correct?
A. Well, there would be some general similarities, but yes, you would look at the particulars on a case-by-case basis,

yes.
Q. An understanding of the interaction between surfactants and drugs is quite complex, correct?
A. **Again, you can make some generalities, but you would have to look on a case-by-case basis, yes.**
Q. Polysorbate 80 and tyloxapol have different chemical structures, correct?
A. **Yes, they have some differences, yes.**
Q. Different nonionic surfactants having -- let me strike that and try again.
Different nonionic surfactants have different chemical and physical properties because the structure of the surfactants can vary so the hydrophobic/hydrophilic balance can vary, correct?
A. **Could you repeat that, please? Sorry.**
Q. Certainly. Different nonionic surfactants have different chemical and physical properties because the structure of the surfactants can vary so the hydrophobic/hydrophilic balance can vary, correct?
A. **The last bit of that sentence doesn't make sense in the context I think of what you are saying, but different surfactants may behave in different ways, that is certainly correct.**
Q. Take a look, if you would, at your deposition transcript of September 4th, and let me direct your attention to page 76,

line 21, through page 77, line 6.
I asked you, question, "Why do different nonionic surfactants have different chemical and physical properties?"
Then there was an objection.
And I said, you may answer.
And then you answered, "Because the structure of the surfactants can vary, so the balance between the hydrophobic and the hydrophilic can vary."
There was your testimony, wasn't it, Doctor?
A. **I see that sentence, and that sentence as it's stated there is correct.**
Q. In fact, different physical and chemical properties that different nonionic surfactants possess in aqueous liquid preparations depend on the structures of the surfactants, correct?
A. **That is correct, yes.**
Q. Let's now discuss your opinions -- actually, before I get to that, let me ask you something different. Tests would need to be conducted for a person of ordinary skill in the art to determine whether the same amount of two different nonionic surfactants having different chemical structures would be expected to have the same stabilizing effect in an aqueous liquid preparation of a nonsteroidal antiinflammatory drug, correct?
A. **That is correct, because you need to understand how many**

molecules you are adding if there are different molecular weights.
Q. And that is because, in your words, it would be very unexpected to have the same behavior in the same way, correct?
A. **It would be very unexpected to have --**
Q. In your words, it would be very unexpected to have the same behavior in the same way, correct?
MS. RAPALINO: Objection. That strikes me as a very vague question.
MR. HASFORD: Well, let me ask it this way.
THE COURT: All right.
BY MR. HASFORD:
Q. In your words, it would be very unexpected for two different nonionic surfactants to have the same behavior in the same way, correct?
A. **Two different nonionic surfactants, it would depend on the variability of the structure, how far apart they were in the structure obviously, sorry, in terms of the structure.**
Q. Let me direct you to your second deposition transcript, which is your February 16th deposition transcript, and in particular to page 199, line 14, through 200, line 2.
I asked you, question, "Tests would need to be conducted for a person of ordinary skill in the art to determine whether the same amount of two different nonionic surfactants having different chemical structures would be

expected to have the same stabilizing effect in an aqueous liquid preparation of a nonsteroidal antiinflammatory drug, correct?"
And then there was an objection, and you answered, "It would be very unexpected to have the same behavior in the same way, so, yes, of course experiments would be needed."
That was your testimony, wasn't it?
MS. RAPALINO: Again, I'm going to lodge an objection here. There was an objection on the record to the form of the question which was quite vague and remains vague.
MR. HASFORD: I believe she answered the question in her deposition with no problem, your Honor.
MS. RAPALINO: She was required to answer the question at the deposition.
THE COURT: You preserved your answer to form of the question at the dep. Let me reread it.
I'll overrule the objection. It seems like a specific question and the witness gave a responsive answer.
BY MR. HASFORD:
Q. That was your testimony, wasn't it, Doctor?
A. **I see that in answer to your question, yes.**
Q. No tests were conducted in the Fu EP 984 reference comparing tyloxapol to octoxynol 40, correct?
A. **That is correct, yes.**
Q. Let's now discuss your opinions on benzalkonium chloride.

You testified on direct exam about what you called complexes with benzalkonium chloride. Do you remember that?
A. Yes, I do.
Q. Yet, to your knowledge, the solubility of any complex between bromfenac and benzalkonium chloride is not reported in any reference, correct?
A. I haven't seen it. It doesn't mean it obviously doesn't exist.
Q. In fact, it is your view that the benzalkonium chloride would not materially affect the basic and novel properties of the claimed aqueous liquid preparations of the '431 patent, correct?
A. That is correct, yes.
Q. You testified on direct exam about the solubility of complexes with benzalkonium chloride. Yet, with respect to aqueous liquid preparations, the concepts of stability and solubility are not synonymous at all, correct?
A. I'm sorry. Can you repeat that question?
Q. Certainly. I'll break it apart into two questions.
You testified on direct exam about the solubility of what you called complexes with benzalkonium chloride. Do you remember that?
A. Yes, I do.
Q. With respect to aqueous liquid preparations, the concepts of stability and solubility are, in your words, not synonymous

at all, correct?
A. They're not synonymous, but obviously if something is a complex, it then causes a physical instability.
Q. Take a look, if you would, at your first deposition transcript. It's going to be the September 14th transcript -- or September 4th transcript, rather. And let me direct your attention to page 43, line 22, through page 44, line 5.
I asked you, question, "How does the concept of stability differ from the concept of solubility with respect to aqueous liquid preparations?"
And there was an objection.
And you answered, "They are not synonymous at all."
That was your testimony, correct?
A. Yes, that is correct. I see that.
Q. You testified on direct exam that benzalkonium chloride becomes toxic to the eye at what you called high levels. Do you remember that?
A. Yes, I do.
Q. You are not even aware of the level at which benzalkonium chloride becomes toxic to the eye, correct?
A. It's outside the concentration range recommended in ophthalmic preparations.
Q. Take a look --
A. I don't remember the exact figure, no.
Q. Let's now discuss pH. Xibrom® and Bromday® were

formulated at a specific pH of 8.3, correct?
A. That's what the information tells me, yes.
Q. Prolensa® was formulated at a pH of 7.8, correct?
A. Again, that's what the literature says, yes.
Q. When developing an aqueous ophthalmic formulation, ideally the pH of the formulation should be 7.4, the same as tear fluid, correct?
A. That's the ideal to be achieved if you can, of course.
Q. The pH of an ophthalmic formulation is important to stability, comfort, and bioavailability, correct?
A. That is correct, yes.
Q. pH is measured on a logarithmic scale rather than a linear scale, correct?
A. That is correct, yes.
Q. On a linear scale, Xibrom® and Bromday® are over three times more alkaline than Prolensa®, correct?
A. Yes, they have about the alkalinity of seawater.
Q. Let's now discuss your opinions on the category A references you cited referring to bromfenac. First let's turn to the Ogawa '225 patent which is JTX-147 in your binder. Are you there, Doctor?
A. Yes, I am.
Q. To be clear, you have neither stated nor suggested that the Ogawa '225 patent teaches the formation of a complex between bromfenac and benzalkonium chloride, correct?

A. Beg your pardon? I have not stated that, no, but I -- no, I have not, but I think it probably was obvious to a person of ordinary skill in the art that that might be the case.
Q. Take a look at your deposition transcript, February 29th, the last one. Let me direct your attention to page 186, line 22, through 187, line 5.
And I asked you, question, "To be clear, you have neither stated nor suggested that the Ogawa '225 patent teaches the formation of a complex between bromfenac and benzalkonium chloride, correct?"
A. Yes, that's correct.
Q. And you answered, "Correct, that's what I say in -- yes."
A. I see that.
Q. The Ogawa '225 patent identified the formulations of Examples 6, 7 and 8.
A. Sorry. Can I just sort out this?
Q. Oh, of course.
A. Sorry. I've got too many...
Q. And if you would, go ahead and turn to Examples 6, 7 and 8 which I believe are in column 10 of the Ogawa '225 patent.
A. Okay. I'm there now.
Q. You are familiar with Examples 6, 7 and 8, correct?
A. Yes, I am.
Q. The Ogawa '225 patent identified the formulations of

Examples 6, 7 and 8 as not forming red insoluble matters and described them as stable, excellent for a long period of time, correct?

A. That's what it says, yes.

Q. The formulations of Examples 6, 7 and 8 of the Ogawa '225 patent did not have any problems with instability or degradation, correct?

A. Not under the conditions of the test they were tested under, no.

Q. In your view, the Ogawa '225 patent solved bromfenac's stability problem by showing that under the conditions of Examples 6, 7 and 8, the formulations were stable, correct?

A. It certainly showed there was no red precipitate, correct.

Q. Example 6 of the Ogawa '225 patent teaches the known ability of sodium sulfite to stabilize ophthalmic preparations, correct?

A. Correct.

Q. In fact, the Ogawa '225 patent discloses that the stability of ophthalmic formulations containing carboxyl group containing NSAIDs and benzalkonium chloride can be improved by including both sodium sulfite and polyvinylpyrrolidone, correct?

A. It teaches that, yes.

Q. Let's now turn to your opinions regarding Bronuck and the

reference you referred to as the *New Drugs in Japan* reference. First --

A. Would you tell me what reference that's at, please.

Q. Let me ask you a question regarding Bronuck first, if I may. Is that okay?

A. Yes.

Q. You would agree that in order for Bronuck to be marketed in Japan, undoubtedly the producers had to demonstrate to the regulatory authority that the formulation had sufficient stability, correct?

A. To the Japanese regulator authority, of course.

Q. Now, please turn to the *New Drugs in Japan* reference, which is JTX-210 in your binder. You testified about JTX-210 on direct exam. Do you remember that?

A. Yes, I do.

Q. Let me direct your attention to the page bearing Bates number PROL0364732, and in particular to the third line of the top table.

A. Yes, I see that.

Q. The *New Drugs in Japan* reference describes the Bronuck formulation, correct?

A. Yes, it does.

Q. Let me direct your attention to the table in the right-hand column entitled Composition/Properties, and in particular, let me direct your attention to the row that says

color. The *New Drugs in Japan* reference describes the Bronuck formulation as clear yellow, correct?

A. That is correct.

Q. The *New Drugs in Japan* reference nowhere mentions any precipitate or cloudiness in the Bronuck formulation, correct?

A. I believe it doesn't, no.

Q. It is your position that Xibrom® is an embodiment of the Ogawa patent, correct?

A. That is correct, yes.

Q. Is it your understanding that the Ogawa patent is listed on the face of the Xibrom® package insert?

A. I'm sorry. I can't answer that question.

MR. HASFORD: May I hand up an exhibit, your Honor?

THE COURT: Yes.

THE WITNESS: Thank you.

MR. HASFORD: For the record, I have handed the witness plaintiff's trial Exhibit PTX-749. It is a one-page document that bears Bates number PROL0167921.

BY MR. HASFORD:

Q. Let me refresh your recollection, Doctor. Please turn or please look at PTX-749, and specifically let me direct your attention to the lower right-hand column where it says U.S. patent number 4,910,225. Do you see that?

A. Yes, I do.

Q. Do you agree that the Ogawa patent is listed on the face

of the Xibrom® package insert which is PTX-749?

A. Just one moment. I can't find the right page here. Sorry.

Q. I believe it is Exhibit 147.

A. Found it, found it, sorry.

Q. You found it. Do you need me to re-ask the question?

A. No, that's fine. The number is the same, yes.

Q. You may put that document aside.

Let's now turn to the Yanni '034 patent, which is JTX-168 in your binder. In particular, please turn to column 1 of the Yanni '034 patent and let me direct your attention to line 60. Are you there, Doctor?

A. Yes, I am.

Q. The Yanni '034 patent states that the full antiinflammatory potential of benzoylphenylacetic acids has not been approached due to their generally slow rate of penetration through the cornea, correct?

A. That is correct.

Q. Bromfenac is a benzoylphenylacetic acid, correct?

A. That is correct.

Q. Let me direct your attention to the next sentence of the Yanni '034 patent at column 1, line 63. The Yanni '034 patent teaches that relatively high concentrations of benzoylphenylacetic acids are often needed to achieve corneal penetration rates sufficient to provide effective intraocular

drug concentrations, correct?
A. That is correct.
Q. Let me direct your attention to the next sentence of the Yanni '034 patent at column 1, line 66. The Yanni '034 patent teaches that such high drug concentrations are generally not desirable as they may provoke ocular irritation and discomfort, correct?
A. I see that.
Q. Let me direct your attention to column 14, lines 42 through 45 of the Yanni '034 patent. The Yanni '034 patent states that although the in vitro potency was clearly enhanced by halogenation of the 4-position of the benzoyl ring of the 2-amino-3-benzoylbenzeneacetic acid, there was little evidence for such a structure related effect in vivo. Do you see that?
A. That is correct, and the reason for my comments about bromfenac.
Q. Bromfenac, in fact, is halogenated with a bromine atom at the 4-position of the benzoyl ring of 2-amino-3-benzoylbenzeneacetic acid, correct?
A. That is correct, and there is a reason for my comments earlier about it showing some benefit in the same as for others.
Q. Let me direct your attention to the last paragraph in column 14 of the Yanni '034 patent. The Yanni '034 patent states, "Conversion of the free carboxylic acid functional

group of bromfenac to an ethyl ester (compound 14) also resulted in a greater than 3 orders of magnitude decline in in vitro cyclooxygenase inhibitory activity. However, when tested for topical ocular antiinflammatory activity, the ethyl ester showed significant inhibitory activity by reducing plasma protein extravasation into the aqueous humor by 60 percent." Do you see that?
A. I'm hesitating to answer because, although I see that wording, my understanding of the table is different.
Q. I'm just asking you --
A. The results in the table are different. It shows no real difference in the table.
Q. I'm just asking you if you see what the Yanni patent has disclosed in column 14 starting at that bottom paragraph starting at approximately line 55. Do you see that?
A. I see that statement, yes.
Q. The ethyl ester of bromfenac is a different chemical compound from bromfenac, correct?
A. That is correct, yes.
Q. You would agree that the Yanni '034 patent describes ophthalmic formulations of bromfenac derivatives and esters, correct?
A. Sorry. Could you repeat that?
Q. Certainly. You would agree that the Yanni '034 patent describes ophthalmic formulations of bromfenac derivatives and

esters, correct?
A. It gives some very simple formulations, but that's not what the patent is directed to.
Q. Okay. Let me direct you to your deposition transcript. This is going to be the middle one, the February 16th deposition transcript. And in particular, let me direct your attention to page 239, line 3, through 239, line 12.
And I asked you, question, "Well, you state in your declaration that in 1995 Yanni described an ophthalmic formulation of bromfenac derivatives and esters. Do you see that?"
And you answered, "Well, I thought there was something I read in column 16. He gave example formulations. I'm sorry. Whether -- the statement he described an ophthalmic formulation of bromfenac derivatives and esters, I believe is true. He talks about under 16, column 16."
That was your testimony, wasn't it, Doctor?
A. Yes, and I'm sorry, I thought you just said the same thing, sorry.
Q. The claimed formulations of the '431 patent do not use bromfenac derivatives and esters, do they?
A. The claim formulations of '431 patent, no, they do not.
Q. In your opinion, the Yanni '034 patent teaches that to achieve penetration, high concentrations of bromfenac might be needed, and the Yanni '034 patent uses this as a starting

point for formulation with esters and amides, correct?
A. They use that, yes, they use that for their starting point, that's correct.
Q. In fact, in your opinion, the Yanni '034 patent uses bromfenac as a jumping off point to develop other drugs such as amfenac formulations, correct?
A. They use it to explore the preparation of other drugs.
Q. Let's take a look at Table 1 of the Yanni '034 patent which you discussed on direct exam. In particular, let me direct your attention to the results in Table 1 of the in vivo aqueous humor PGE2 accumulation assay, which are disclosed in the second to last column. Bromfenac exhibited 98 percent inhibition while compound number 7, compound number 8, and compound number 9 also exhibited 98 percent inhibition in this assay, and the 4-chloro amfenac compound exhibited 99 percent inhibition in this assay, correct?
A. Yes, I'd say they are all effective at inhibiting the enzyme.
Q. Looking at Table 1 of the Yanni '034 patent, let me direct your attention to the results of the in vivo paracentesis protein extravasation assay, which are disclosed in the last column. Bromfenac exhibited 62 percent inhibition, while compound number 16 also exhibited 62 percent inhibition, compound number 15 exhibited 64 percent inhibition, compound number 9 exhibited 65 percent inhibition,

and the 4-chloro amfenac compound exhibited 72 percent inhibition in this assay, correct?

A. I see that, yes.

Q. The Yanni '034 patent does not teach the use of tyloxapol, correct?

A. No, it does not.

Q. Let me now direct your attention to the Hara reference, which is DTX-110 in your binder. In particular, let me direct your attention to the page bearing Bates number --

A. 110, sorry.

Q. Oh, I apologize. Let me know when you're there.

A. I've got there now.

Q. Let me direct your attention to the page bearing Bates number PROL0079164, and specifically to the first sentence of the last paragraph of the right-hand column beginning "diclofenac sodium." You testified on direct exam about various comparisons involving bromfenac in the Hara reference. Do you remember that?

A. Yes, I do.

Q. The Hara reference explains that diclofenac shows superior antiinflammatory efficacy following cataract surgery, correct?

A. You stated it was -- I'm sorry, please make the statement again, because I'm trying to read and listen to what you say at the same time.

Q. Certainly. Take a look at that first sentence and tell me when you're ready.

A. Could you ask the question?

Q. Certainly. The Hara reference explains that diclofenac shows superior antiinflammatory efficacy following cataract surgery, correct?

A. I think it's a little bit more specific than that.

Q. In what way?

A. It suggests that it's treating anterior ocular segment information following cataract surgery, that's all.

Q. Let me direct your attention to the next page bearing Bates number PROL0079165, and in particular to the top paragraph of the right-hand column. The Hara reference warns that based on deaths from oral administration of bromfenac sodium, that the drug is meant to be used for less than one month, correct?

A. I see that, yes.

Q. Please look at the previous page of the Hara reference, again bearing Bates number PROL0079164, and let me direct your attention to the upper portion of the left-hand column. The Hara reference discloses Bronuck ophthalmic solution, correct?

A. Sorry. I'm lost where you're directing me.

Q. I apologize. It might be easier to look on the screen. You can look right underneath the box.

A. Okay.

Q. When you're there, I'll ask you the question again.

A. Okay. Thank you.

Q. The Hara reference discloses Bronuck ophthalmic solution, correct?

A. That is correct, yes.

Q. Please look back at the last page of the Hara reference bearing Bates number PROL0079165. Let me direct your attention to the subheading Tips in using the drug, and in particular to the first paragraph.

A. Yes.

Q. The Hara reference describes the Bronuck formulation as a clear yellow solution, correct?

A. That is -- I see that, yes.

Q. The Hara reference nowhere mentions any precipitate or cloudiness in the Bronuck formulation, correct?

A. That is correct, yes.

Q. The Hara reference does not teach the use of tyloxapol, correct?

A. That is correct. It's looking at the evaluation of the drug.

Q. Okay. Let's now discuss your opinions on the category B references you cited referring to benzalkonium chloride. First let's turn to the Desai '929 patent which is JTX-061 in your binder. Let me know when you're there.

A. I've got there.

Q. The only two nonsteroidal antiinflammatory drugs exemplified in the Desai '929 patent are sodium diclofenac and suprofen, correct?

A. That is correct. While that's correct, it does specify bromfenac in the detailed description of the invention.

Q. Let's take a look at your deposition transcript, and in particular, the February 29th, the third one. In that transcript let's take a look at page 103, and in particular lines 2 through 10.

I asked you, question, "What are the two nonsteroidal antiinflammatory drugs exemplified in the Desai patent?"

You answered, "Sodium diclofenac and sodium suprofen I think it's meant to be. It's a mistake, though, it's a spelling mistake. My eyes --"

And then I asked you, question, "Are they sodium diclofenac and suprofen?"

And you answered, "Yes."

That was your testimony, correct?

A. Exemplified, yes.

Q. The only nonionic surfactant exemplified in the Desai '929 patent for which data are provided is vitamin E TPGS, correct? Do you need me to repeat the question, Doctor?

A. No, no. Again, my answer is the same, yes, it is the only one exemplified, but it is mentioned in the detailed description of the invention.

Q. The Desai '929 patent does not teach the use of tyloxapol in any specific example formulation, correct?
A. Not in an example formulation, no.
Q. The Desai '929 patent does not disclose any data for any formulations containing benzalkonium chloride, correct?
A. That is correct, yes.
Q. In fact, the Desai '929 patent teaches that the most preferred polymeric quaternary ammonium compound is polyquaternium 1, correct?
A. That's what the patent is directed towards, yes.
Q. You are not familiar with the chemical structure of Polyquad, such as polyquaternium 1, correct?
A. I didn't remember the precise structure, no.
Q. The Desai '929 patent discloses, in your opinion, storage stable preserved ophthalmic compositions, correct?
A. That is correct, yes.
Q. The formulations disclosed in the Desai '929 patent, in fact, did not have any stability problems, correct?
A. Sorry.
Q. The formulations disclosed in the Desai '929 patent, in fact, did not have any stability problems, correct?
A. That's my reading in the patent, yes.
Q. Claims 6 and 20 of the '431 patent specify benzalkonium chloride as the only permissible quaternary ammonium compound, correct?

A. That is correct, yes.
Q. Let's now discuss the Desai '876 patent which is JTX-201 in your binder.
A. Okay.
Q. Are you there?
A. Yes, I am.
Q. The Desai '876 patent does not teach the use of tyloxapol, correct?
A. That is correct, yes.
Q. The Desai '876 patent uses vitamin E or vitamin E TPGS as a surfactant, correct?
A. Yes, in combination with caffeine, yes.
Q. The formulations disclosed in the Desai '876 patent did not have any stability problems, correct?
A. That is my understanding of the patent, yes.
Q. Let's now discuss the Wong reference, which is JTX-207 in your binder. Let me know when you're there.
A. I'm there.
Q. The Wong reference teaches the use of flurbiprofen and does not teach the use of bromfenac, correct?
A. Specifically, it teaches flurbiprofen, although it's directed towards nonsteroidal antiinflammatories.
Q. The Wong reference does not teach the use of tyloxapol, correct?
A. No, it does not teach the use of tyloxapol.

Q. The Wong reference teaches lauralkonium chloride, correct?
A. Which is a component of benzalkonium chloride, yes.
Q. The approach that the Wong reference took is different from the approach that the inventors of the '431 patent took when formulating the claimed aqueous liquid preparations of that patent, correct?
A. Yes, it is.
Q. Turn, if you would, to the Remington reference, which is DTX-015 in your binder, and actually this is a portion of the Remington reference about which you testified on direct exam, correct?
A. Just one moment, please.
Q. Certainly.
A. Yes, it is.
Q. Let me direct your attention to the page bearing Bates number DTX-015.5.
A. Yes.
Q. In particular, let me direct your attention to the last sentence of the paragraph beginning with the subheading Quaternary Ammonium Compounds. It states, "Given the alternative, it would be preferable to modify a formulation to remove the incompatibility, rather than include a compatible but less effective preservative." You testified about this sentence on direct exam. Do you remember that?

A. Yes, I do.
Q. In fact, you would agree that an aqueous liquid preparation of bromfenac could have sufficient preservative efficacy as an eyedrop without containing benzalkonium chloride if it contained a different preservative, correct?
A. I'd like to see where I said that, please.
Q. Take a look, if you would, at your first deposition transcript, the September 4th transcript, and in particular let me direct your attention to page 132, line 17, through 133, Line 2.
And I asked you, question, "My question is a little different. Could an aqueous liquid preparation of bromfenac have sufficient preservative efficacy as an eyedrop without containing benzalkonium chloride?"
Then there was an objection.
And you answered, "The simple answer, which sounds a bit facetious, is if you had a different preservative, of course."
That was your testimony, wasn't it, Doctor?
A. I can't find that. Sorry.
Q. It's page 132.
A. Okay. Right. Okay.
Q. I'll ask it again. 132, line 17, tell me when you're there.
So I asked you a question. My question is a little

different. Could an aqueous liquid preparation of bromfenac have sufficient preservative efficacy as an eye drop without containing benzalkonium chloride? There was an objection, and you answered: The simple answer, which sounds a bit facetious, is if you had a different preservative, of course.

That was your testimony, wasn't it, Doctor?

A. While that statement is correct, it would be an un-preferred -- it wouldn't be the preferred solution to the problem.

Q. You never qualified your testimony at your deposition, did you, Doctor?

A. I wouldn't have to look back now at everything to check that.

Q. You don't remember qualifying your testimony?

A. Not without reading the text.

Q. Let's now discuss the category C references you cited discussing certain surfactants. First, let's turn to the Sallmann '913 patent, which is JTX-071 in your binder.

A. Yes, I'm there.

Q. The Sallmann '913 patent, in your opinion, does not show any real data from anything, correct?

A. It shows no real data from anywhere.

Q. Yet you would admit that every formulator would rely on biological data in making formulation decisions, correct?

A. Biological data is important in deciding which particular

drug to formulate, and once that decision is made, you would not then expect a pattern of formulations of biological data.

Q. Take a look, if you would, at your February 29th deposition transcript, and in particular, Page 41, Line 6, through 13. Are you there?

A. Yes.

Q. I asked you a question --

MS. RAPALINO: I have an objection. I'm just going to make a completeness objection. This line of questioning goes on through the bottom of Page 41.

MR. HASFORD: We will get to those remaining questions.

MS. RAPALINO: I'm sorry, but I'm just asking that they -- for completeness for this question, that he show the rest of it, of the transcript through Page 41.

MR. HASFORD: Your Honor, if I may, I intend to ask her about whether a formulator will rely on chemical and physical stability data, that's what it goes to, and we will go there if there is a need.

THE COURT: Okay. That's fine.

BY MR. HASFORD:

Q. I asked you a question: Have you ever relied on biological data in making formulation decisions?

Then there was an objection, and I said: You may answer.

And you said: I believe every formulator will be aware of certain biological data when they are formulated, yes.

That was your testimony, wasn't it, Doctor?

A. While that statement is correct and I stand by it, I think it's being taken -- I think it's being misunderstood. You wouldn't formulate an un -- biological data in a formulation patent.

Q. You never qualified your testimony at your deposition, did you, Doctor?

A. I didn't believe it would be used like this.

Q. You would admit that every formulator would rely on chemical stability data in making formulation decisions, correct?

A. Of course. They would want a stable formulation.

Q. You would admit that every formulator would rely on physical stability data in making formulation decisions, correct?

A. Again, if they want a stable formulation, yes.

Q. The Sallmann '913 patent does not teach the use of bromfenac, correct?

A. No, it's directed towards a related nonsteroidal anti-inflammatory.

Q. The Sallmann '913 patent discloses the superiority of diclofenac potassium over diclofenac sodium, correct?

A. Can you direct me to where it says that?

Q. Actually, let me direct you to your deposition testimony where you testified about this. In particular, it's in your February 16th transcript, and actually --

A. I only want to see where it was in the patent.

Q. Well, first, first, let me direct you to --

MS. RAPALINO: I'm sorry, is he withdrawing -- are you withdrawing your previous question?

BY MR. HASFORD:

Q. Well, actually, let me withdraw my previous question. I'm going to re-ask the earlier setup question.

Doctor, the Sallmann '913 patent does not teach the use of bromfenac, correct?

A. That is correct. It is related to nonsteroidals.

Q. Okay. The Sallmann '913 patent discloses the superiority of diclofenac potassium over diclofenac sodium, correct?

MS. RAPALINO: I'm just going to object. I think that Professor Lawrence asked it to be pointed to that statement in the patent in response to this question when it was previously asked.

MR. HASFORD: Well, the statement is in her deposition transcript. She's welcome to review as much of the patent as she needs.

MS. RAPALINO: I don't think the question was about the deposition transcript, it was about the '913 patent.

MR. HASFORD: The deposition testimony, I would

represent to Your Honor, will support the answer that I'm seeking from her.

THE COURT: Well, the pending question is whether the '913 patent supports the use of -- or discloses the use of bromfenac.

MR. HASFORD: Well, the pending question now, she confirmed that it does not teach the use of bromfenac. The pending question now is the Sallmann '913 patent discloses the superiority of diclofenac potassium over diclofenac sodium, correct?

THE COURT: All right. And so Dr Lawrence may answer it based on the patent.

A. There was a statement that has been demonstrated that, for example, the ocular penetration of diclofenac potassium is much superior in comparison to the corresponding diclofenac sodium.

Q. Let me direct your attention to the claims of the Sallmann '913 patent. All of the claims of the Sallmann '913 patent are directed to formulations of diclofenac potassium, correct?

A. It states that, yes.

Q. Potassium salts and sodium salts are different salts, correct?

A. They are different salts, correct.

Q. You testified on direct exam about Example 15 of the

Sallmann '913 patent. Let's take a look at it. Example 15 of the Sallmann '913 patent discloses a formulation of diclofenac potassium, correct?

A. That is correct, yes.

Q. The Sallmann '913 patent provides many other examples besides Example 15, correct?

A. It contains a good number of examples, yes.

Q. Let me direct your attention to Column 5, Lines 39 through 40 of the Sallmann '913 patent.

A. Column 5?

Q. Column 5, Lines 39 through 40, where it begins: Preferred preservatives.

A. Yes, I can see that.

Q. The Sallmann '913 patent names cetrimide, benzalkonium chloride, benzoxonium chloride, and parabens as preferred preservatives with none being especially preferred, correct?

A. In the section you've highlighted, I agree.

Q. Let me direct your attention to Column 5, Lines 62 through 63 of the Sallmann '913 patent. Let me know when you're there.

A. Yes, go on.

Q. The Sallmann '913 patent teaches cyclodextrin as a stabilizer, correct?

A. Such as, yes.

Q. Let me direct your attention to Column 4, Line 64 of the

Sallmann '913 patent. Are you there?

A. I am there, yes.

Q. The Sallmann '913 patent teaches the use of tyloxapol as a solubilizer, not a stabilizer, correct?

A. It uses the word "solubilizer," yes.

Q. The approach that the Sallmann '913 patent took is different from the approach that the inventors of the '431 patent took, when formulating the claimed aqueous liquid preparations of that patent, correct?

A. In the -- I can see they've used different excipients to solve the problem, yes.

Q. Let's now turn to the Fu EP '984 reference?

A. Which is where, please?

Q. We're looking for the exhibit number. I apologize. It's JTX-209 in your binder.

A. Okay.

Q. In particular, let me direct your attention to Example 5, about which you testified on direct exam. Specifically, I'd like to direct your attention in Example 5 to the first sentence, which begins, physical stability. Are you there?

A. I am there, yes.

Q. The Fu reference teaches physical stability not overcoming chemical degradation, correct?

A. This is -- this is dealing with physical stability, yes.

Q. You would agree that the two different stability issues

described in the Ogawa '225 patent and the Fu EP 984 reference are two different problems, and a person of ordinary skill in the art would not conflate them, correct?

A. Chemical stability is obviously different than physical stability, that's correct, yes.

Q. The Fu EP 984 reference discusses one specific example of an NSAID, which is ketorolac tromethamine, not bromfenac, correct?

A. But the patent is directed towards nonsteroidal anti-inflammatories, but yes, the examples only mention ketorolac.

Q. The most preferred nonionic surfactant used in the EP 984 Fu reference is Octoxynol 40, correct?

A. I think it actually says preferred example, but they do say the preferred surfactant is Octoxynol 40.

Q. Octoxynol 40 and tyloxapol are different chemical compounds, correct?

A. That is correct, but they belong to the same class of compounds.

Q. Let's take a look at your deposition transcript. February 16th, and in particular, Page 159, Line 21, through 160, Line 2. I asked you:

Question: Octoxynol 40 and tyloxapol are not identical, correct?

And there was an objection, and you answered: They're

not identical.
That was your testimony, wasn't it, Doctor?
MS. RAPALINO: Objection. Improper impeachment, and her testimony is entirely consistent here.
THE COURT: Sustained. It's not inconsistent.
BY MR. HASFORD:
Q. Let's now turn to Example 5 again of the Fu EP 984 reference. Example 5 of the Fu EP 984 reference discloses six ketorolac formulations, correct?
A. Yes, that is correct.
Q. The ketorolac formulations of Example 5 of the Fu EP 984 reference contain Octoxynol 40, polysorbate 80 or Merge 52, correct?
A. I see that, yes.
Q. The Fu EP 984 reference does not disclose the pH of the formulations of Example 5, correct?
A. Well, the Fu reference doesn't disclose the pH. All the other examples are adjusted to pH 7.4 plus or minus .4. So you would expect possibly.
Q. Well, let's take a look at your February 29th deposition transcript, and in particular, Page 96, Line 6 through 14. And I asked you --
MS. RAPALINO: Again, Your Honor, I'm just going to object as improper impeachment, as with most of these, is her testimony here is entirely consistent with what she said at

the deposition.
MR. HASFORD: Well, this testimony is not entirely consistent at all, Your Honor. She just testified that it would be possible to tell, and at her deposition she testified that it would not be possible to tell. I think the transcript will show that.
MS. RAPALINO: I believe that's a mischaracterization of her testimony here. And again, she testified that it doesn't disclose the pH but all other examples are adjusted to pH 7.4 plus or minus .4, so you would expect possibly.
MR. HASFORD: And she certainly didn't --
THE COURT: It's possibly inconsistent.
BY MR. HASFORD:
Q. Doctor, I asked you:
Question: Do the formulations of Example 5 of the FU EP 984 reference have the same pH as all of the claimed formulations of the patents-in-suit?
And there was an objection, and then you answered: It is not possible to tell what the pH of the formulations are, because it's not recorded in the table.
That was your testimony, wasn't it, Doctor?
MS. RAPALINO: Objection. Right now, the claims at issue in the patents-in-suit have no pH limitations, and so this testimony has no relevance to the claims that are at issue and is not directed to the same topic that counsel is

asking about here today, which are claims 6 and 20, with no pH limitations.
MR. HASFORD: The question is still highly relevant, Your Honor. As Mr. Lipsey explained in opening, the compositions and their properties are one and the same according to controlling Federal Circuit precedent and it goes towards her opinions as to Fu.
THE COURT: Yeah, I'm not prepared to rule out pH as being a relevant property here.
MS. RAPALINO: It's not so much that the pH is irrelevant in this case. It's that the question that he's attempting to impeach with, refers to the pH of the claims and there is no claim -- there are no pH limitations in the claims that Professor Lawrence is testifying about today.
THE COURT: Oh, okay. That's different.
MR. HASFORD: Notwithstanding the question itself referred to the pH of the claims, Your Honor, she's -- the question itself went to the pH of the formulations of Example 5 in Fu, and that's exactly what her testimony went to. So that question would be applicable whether it specified the claims of the patents-in-suit or not.
THE COURT: No, the question has become irrelevant, the deposition question, because it's indexing it to the same pH as all of the claimed formulations of the patents-in-suit, and we're down to two claims with no pH limitations. So I'll

sustain the objection.
I'm sorry, I didn't understand it the first time.
MR. HASFORD: Let's now turn --
THE COURT: I'm sorry, let me explain one thing. Maybe it's obvious. I'm not saying pH has somehow become irrelevant in the case. I'm just saying this particular question, which refers to pH, is in the claimed formulations that are in suit has become irrelevant.
MR. HASFORD: I understand, Your Honor, certainly.
THE COURT: Okay.
BY MR. HASFORD:
Q. Let's now turn to the Schott reference, which is JTX-199 in your binder. In particular, let me direct your attention to the conclusions section on JTX-199.6 about what you testified on direct exam. Specifically, let me direct your attention to the first paragraph, and in particular, to the first sentence, where the Schott reference states that it is discussing stabilizing emulsions, suspensions, ointments and foams. Do you see that?
A. I see that, yes.
Q. Emulsions, suspensions, ointments and foams are different from solutions, such as the aqueous liquid preparations of the '431 patent, correct?
A. That is correct, yes.
Q. The Schott reference does not teach Octoxynol 40,

correct?
A. It doesn't deal with Octoxynol 40, no.
Q. And you can put the Schott reference aside.
I'd like to direct your attention now to DTX-196 in your binder, about what you testified on direct exam. And in particular, let me direct your attention to the Page DTX-196.93. Let me direct your attention to the entry for Octoxynol 40, ophthalmic solution. Do you see that?
A. I see that, yes.
Q. As of the date of DTX-196, only one ophthalmic solution containing Octoxynol 40 had been approved by the FDA, correct?
A. There was only one formulation listed in the active ingredients list of this date, that is correct.
Q. As of the date of DTX-196, the only ophthalmic solution containing Octoxynol 40 that had been approved by the FDA was Acular, correct?
A. I don't have the composition of Acular in front of me, so I can't confirm that.
Q. Let's turn now to DTX-196.158. And let me direct your attention to the entry for tyloxapol ophthalmic solution toward the bottom of that page. Do you see that?
A. I see that, yes.
Q. None of the ophthalmic solution formulations containing tyloxapol that are identified in DTX-196 is an ophthalmic NSAID, correct?

A. I don't have the information to be able to answer that question.
Q. Let's take a look at the right-hand column that says potency range. Do you remember testifying about those entries for tyloxapol ophthalmic solution on direct exam?
A. I do.
Q. The potency range for tyloxapol in the ophthalmic solutions identified in DTX-196 is a potency range, not a toxicity range, correct?
A. It's the range of concentrations at which that excipient is used in the formulations.
Q. You may put that document aside.
You testified on direct exam that Remington's is, in your words, the Bible. Do you remember that?
A. For pharmaceutical formulators.
Q. You also acknowledged that a formulator, as of 2003, would have looked to a different handbook, the *Handbook of Pharmaceutical Excipients*, correct?
A. That's one of the reference sources they would have used, correct.
Q. You are aware, in fact, that the third edition of the *Handbook of Pharmaceutical Excipients* published in 2000, correct?
A. I believe it will be the third edition. I don't know. Can't remember.

Q. In fact, you have relied on the 2000 edition of the *Handbook of Pharmaceutical Excipients* in connection with your opinions in this case, correct?
A. That is correct, yes.
Q. In 2003, a person of ordinary skill in the art would have considered the *Handbook of Pharmaceutical Excipients* an important reference for formulating an aqueous liquid preparation, correct?
A. That would have been one of the reference sources. There are others, obviously.
Q. In fact, in 2003, a person of ordinary skill in the art definitely would have looked to the *Handbook of Pharmaceutical Excipients* when formulating an aqueous liquid preparation, correct?
A. As I've said, it's definitely one of the books they would have used, be one of them.
Q. You, in fact, have written monographs in the *Handbook of Pharmaceutical Excipients* on surfactants, correct?
A. That is correct, yes.
Q. The 2000 edition of the *Handbook of Pharmaceutical Excipients* nowhere discloses tyloxapol, correct?
A. That is correct, yes.
Q. The 2000 edition of the *Handbook of Pharmaceutical Excipients* nowhere discloses any Octoxynol, correct?
A. That is correct.

Q. Let's discuss your opinions on obviousness-type double patenting. Do you remember testifying about that on direct exam?
A. Yes, I do.
Q. Let's bring up DDX-220 on the screen.
You testified that Claim 6 and 20 of the '431 patent are, in your opinion, obvious over Claims 7 of the '290 patent and Claim 6 of the '131 patent, correct?
A. Yes, I did.
Q. Let's bring up DDX-280, if we could. 8-0.
Claim 7 of the '290 patent and Claim 6 of the '131 patent both include the phrase "consisting essentially of," correct?
A. That is correct.
Q. You understand that the phrase "consisting essentially of" means that Claim 7 of the '290 patent and Claim 6 of the '131 patent are open to additional un-recited elements, so long as they do not affect the basic and novel properties of the claimed aqueous liquid preparations, correct?
A. That's my understanding, yes.
Q. You do not know, however, whether the aqueous liquid preparations of Claim 7 of the '290 patent and Claim 6 of the '131 patent could include other quaternary ammonium preservatives besides benzalkonium chloride, correct?
A. Sorry, could you slow down when you say that, please.

Q. Certainly. You do not know whether the aqueous liquid preparations of Claim 7 of the '290 patent and Claim 6 of the '131 patent could include other quaternary ammonium preservatives besides benzalkonium chloride, correct?

A. I don't understand what you mean by the way you phrased the question.

MS. RAPALINO: I'm just going to object in that it's compound and it's a complicated question, and if he could just break that down and perhaps direct the witness to the claims you're referring to.

MR. HASFORD: Certainly. Yeah, I can direct the claims.

BY MR. HASFORD:

Q. So let's look at -- let's look at Claim 7 of the '290 patent, and you see the phrase "consisting essentially of" there. Do you see that?

A. Yes, I do.

Q. And you testified that it's your understanding that the phrase "consisting essentially of" means that Claim 7 of the '290 patent is open to additional un-recited elements, so long as they do not materially affect the basic and novel properties of the claimed aqueous liquid preparations, correct?

A. Yes, I did.

Q. You do not know, however, whether the aqueous liquid

preparation of Claim 7 of the '290 patent could include other quaternary ammonium compounds besides benzalkonium chloride that is recited in that claim, correct?

A. I'm sorry, I really don't understand the question you're asking me, that I don't understand or I don't know?

Q. Do you know whether --

A. I don't know -- what did you say? Sorry.

Q. Let me ask it this way.

A. Yeah.

Q. Could the aqueous liquid preparation of Claim 7 of the '290 patent include other quaternary ammonium preservatives besides benzalkonium chloride?

A. It is my understanding that Claim 7 of '290 patent could do.

Q. Is that the same for Claim 131 of the -- sorry. Claim 6 of the '131 patent?

A. I'd have to see the claim.

Q. Okay. Let's take a look at the claim. Let's bring up Claim 6 of the '131 patent. I think it's on one of her slides.

MR. BAIRD: Can you give me a little more.

MR. HASFORD: Let's go through her slides. I don't have it in my... It looks like DDX-2-88.

BY MR. HASFORD:

Q. Claim 6 of the '131 patent includes the transition

phrase, "consisting essentially of." Do you see that?

A. I see that, yes.

Q. Could the aqueous liquid preparation of Claim 6 of the '131 patent include other quaternary ammonium compounds besides benzalkonium chloride?

A. It's my understanding that they could, as long as it didn't affect -- materially affect the basic and novel characteristics of the formulation.

Q. Thank you, Doctor.

Let's switch gears here.

MR. HASFORD: Actually, would this be a good time for a break, Your Honor?

THE COURT: Sure. Okay. Let's take about a 10-minute break.

(RECESS TAKEN; 2:51 p.m.)

THE DEPUTY CLERK: All rise.

(OPEN COURT; 3:06 p.m.)

THE COURT: Be seated, please. Are we ready to continue?

MR. HASFORD: Yes, Your Honor. I will be passing up one exhibit. I want to revisit the witness's testimony with respect to DTX-196, Your Honor. May I approach?

THE COURT: Yes.

MR. HASFORD: Thank you.

THE COURT: You're welcome.

BY MR. HASFORD:

Q. Doctor, let me direct your attention back to DTX-196 and then I'm going to ask you a quick question regarding PTX-265.

A. I'm sorry, DTX-196?

Q. DTX-196.

A. Okay.

Q. And in particular, Page -- let me direct your attention, Doctor, to DTX-196, and in particular, Page DTX-196.93.

Before the break, do you recall me asking you, as of the date of DTX-196, the only ophthalmic solution containing octoxynol that had been approved by the FDA was Acular, and you testified that you were uncertain. Do you remember that?

A. Yes, I do.

Q. Well, for the record, I've handed you PTX-265, which is a copy of the Acular package insert, that bears Bates numbers PROL0332429 through PROL0332439. And in particular, let me direct your attention to the front page and the paragraph right above the subheading, Clinical Pharmacology.

A. Okay.

Q. Does PTX-265 refresh your recollection that Acular contains Octoxynol 40?

A. I don't remember seeing this insert before, but certainly, that's what this page would indicate.

Q. Do you now agree that as of the date of DTX-196, the only ophthalmic solution containing Octoxynol 40 that had been

approved by the FDA was Acular?
A. Well, that would be the assumption, based on the information you've given me.
Q. You understand that Acular is the commercial embodiment of the Fu EP 984 reference, correct?
A. No, I did not.
Q. The innovators of Acular sought and obtained approval of a surfactant that had not been previously listed in DTX-196, correct?
A. I really don't have the information to definitely say one way or another.
Q. You may put those documents aside.
Look again at DTX-196.93, at the Octoxynol 40 ophthalmic solution line.
A. Okay.
Q. Is it fair to say that a company sought and obtained approval of a surfactant in Octoxynol 40 that had not been previously listed in DTX-196?
A. I would be making judgments on things I don't have enough information to make judgments. I can agree with you, there is only one -- apparently one compound that's listed, and you've just shown me this, but I really don't know enough information to necessarily put the two things together.
Q. Well, aside from the Acular package insert, let me just direct your attention to DTX-196.93 at the number 1 that

corresponds to Octoxynol 40 ophthalmic solution. Do you see that?
A. Yes, I do.
Q. Is it fair to say that based on the number one in that line, that one innovator sought and obtained FDA approval of a surfactant that had not been previously listed in the FDA's inactive ingredient guide?
A. I don't think I could say that on the information I have here.
Q. Why don't you think you have enough information?
A. I don't know whether it was listed in, for example, the U.S.P. Pharmacopoeia at the time, and it got some sort of acceptability for that. So I'm sorry, I don't have that information.
Q. Prior to the one approval for Octoxynol 40 that is identified in DTX-196.93, would there have been any approvals identified for Octoxynol 40 ophthalmic solution in the FDA's inactive ingredient guide?
A. My hesitation to you is, I don't know when the first date this was started. So, for example -- and the earliest formulations from a quick scan go back to 1980 -- 1997. So it would depend when the guide was started, to be able to answer that.
Q. You don't know that information?
A. No, I don't know that information.

Q. You can put that document aside.
A. Okay.
THE COURT: Excuse me. May I ask for clarification? On this DTX-196, isn't it a January 1996 document on Page DTX-196.3?
MR. HASFORD: It looks like the date on the front page of the document, Your Honor, says 06-09-98, and I'm just getting that based on DTX-196.1.
THE COURT: Well, I think that's the cover letter.
MR. HASFORD: Oh, okay.
THE COURT: But the document itself on Page 3. See where it says January, 1996?
THE WITNESS: Yes.
MR. HASFORD: Yes, I see that.
THE COURT: Would that have been the date of this publication, then?
MR. HASFORD: I would assume, but I -- I don't know. This is something that defendants provided.
THE COURT: And so what it says is what was going on, in terms of approvals by January of 1996?
MR. HASFORD: That's what I understand it to be, Your Honor.
THE COURT: All right.
MR. HASFORD: The point --
THE COURT: Is that Dr Lawrence's understanding?

THE WITNESS: That's my understanding, yes.
THE COURT: Okay. Thank you.
BY MR. HASFORD:
Q. Doctor, as of 1996, and 2003, there was one FDA-approved ophthalmic solution containing Octoxynol 40, correct?
A. Can you confirm to me what year Acular was first on the U.S. market?
Q. Well, let's take a look at the package insert, DTX-265 that I gave you.
MR. HASFORD: May I hand up another document, Your Honor?
THE COURT: Yes, of course.
THE WITNESS: Thank you.
MR. HASFORD: I have two copies of this one.
THE WITNESS: Because the copyright is on 2001 for this.
BY MR. HASFORD:
Q. Right. But let me direct your attention -- so for the record, this is PTX-295, which bears Bates No. PROL0081123 through 27, and let me direct your attention to the entry for Acular, which begins at PROL0081126 through 27, and then in particular, to the middle column, on PROL0081127.
A. I'm afraid I can't read it on the copy I've been given.
Q. Our graphics assistant will highlight it on the screen for you.

THE COURT: We're all going to need eye drops soon.
(Laughter.)
MR. HASFORD: I apologize, Your Honor. Since the print is so poor, we will just -- we will put this document aside for now.
BY MR. HASFORD:
Q. Let's discuss your qualifications, Doctor. You testified on direct exam about chemistry issues, yet you have never been qualified by any court or by the U.S. Patent and Trademark Office as an expert in chemistry, correct?
A. That is correct, yes.
Q. You are not an expert in medicinal chemistry, correct?
A. No, I'm not an expert in medicinal chemistry.
Q. You are not an expert in organic chemistry, correct?
A. No, although my laboratory routinely synthesizes novel compounds, so I have some experience in synthetic chemistry.
Q. Take a look, if you would, at your deposition transcript, your February 29th deposition transcript. This is going to be Page 24, lines 15 through 20. I asked you.
Question: Have you ever held yourself out to the public as an expert in organic chemistry?
MS. RAPALINO: Objection, Your Honor. Again, this is improper impeachment. This is a different question that was asked at her deposition.
MR. HASFORD: I believe she tried to say that she had

expertise based on this laboratory work, where she testified at her deposition she's never held herself out as an expert in organic chemistry, Your Honor.
MS. RAPALINO: Right. I think that the question of whether you held yourself out to the general public as an expert is different from whether you have expertise in a particular area.
MR. HASFORD: I think naturally, Your Honor, if you had expertise in that area you would hold yourself out as such.
THE COURT: Well, I'm going to sustain the objection. I thought the pending question was, have you ever been qualified as an expert in organic chemistry, and her answer was no.
BY MR. HASFORD:
Q. You are not an expert in pharmacology, correct?
A. That is correct.
Q. You are not an expert in ophthalmology, correct?
A. That is correct.
Q. You have never led any clinical testing on a pharmaceutical product, correct?
A. That is correct, yes.
Q. You've also never designed any clinical testing on a pharmaceutical product, correct?
A. That is correct, yes.

Q. You have never conducted any research on any bromfenac product, correct?
A. That is correct, yes.
Q. You have never formulated any bromfenac product, correct?
A. That is correct, yes.
Q. You have never formulated any marketed drug product, correct?
A. No, not a marketed drug product, no.
Q. You have never formulated any product for treating an inflammatory disease of the eye, correct?
A. Not a marketed product.
Q. You have never formulated any product at all for treating an inflammatory disease of the eye, correct?
A. Sorry, I've never formulated any product at all.
Q. That's my question. You have never formulated any product at all for treating an inflammatory disease of the eye, correct?
A. If you mean a product that got to market, no, I have not.
Q. I mean any product whether it got to market or not.
A. I've done some consultation for pharmaceutical companies.
Q. You have never formulated any product for treating an inflammatory disease of the eye, correct?
A. I have made potential products for treating with steroids.
Q. Let's take a look at your February 16th deposition

transcript. Let me direct your attention to Page 35, Lines 14 through 18. I asked you:
QUESTION: You have never formulated any product for treating an inflammatory disease of the eye, correct?
There was an objection.
And you answered:
ANSWER: Correct.
That was your testimony, wasn't it, doctor?
MS. RAPALINO: Objection, your Honor. I ask for completeness, the question and answer before that need to be included in the record.
THE COURT: Okay. Can you read that, too, please?
MR. HASFORD: Certainly.
BY MR. HASFORD:
Q. QUESTION: You have never formulated any marketed drug product, correct?
ANSWER: Correct.
A. I understood that question to be referring to something not to market, which is why I asked you to clarify just now.
Q. You didn't ask me to clarify at your deposition, did you, doctor?
A. It was straight after a marketed product so I assumed you meant the same thing.
Q. The exact question I asked you was:
QUESTION: You have never formulated any product for

treating an inflammatory disease of the eye, correct?
And the exact answer you gave me was:
ANSWER: Correct.
Isn't that correct?
A. A product in my opinion is something that gets -- gets to market.
Q. Aside from your work in this case, you have never consulted for any party regarding any bromfenac product, correct?
A. That is correct, yes.
Q. You never conducted any bench testing in connection with your opinions in this case, correct?
A. That is correct, yes.
Q. You testified on direct exam about medical issues regarding bromfenac, yet you do not practice medicine, correct?
A. I don't know what, other than it was used for a particular medical use I mentioned.
Q. You do not practice medicine, correct?
A. No, I do not practice medicine.
Q. You have never prescribed medication to a patient, correct?
A. No, I don't prescribe medication, I'm not a medic.
Q. You have not dispensed a medication to a patient in the last 20 years, correct?

A. That is correct, yes.
Q. You have never dispensed any bromfenac product to a patient, correct?
A. That is correct, yes.
Q. You have never founded or cofounded a pharmaceutical services company, correct?
A. What do you mean pharmaceutical services?
Q. Do you understand my question?
A. I would like you to define what you meant by pharmaceutical services, please.
Q. Well, let me go to your deposition transcript of February 16th.
MS. RAPALINO: Objection. I don't believe that there's a question pending at the moment.
MR. HASFORD: Well, she asked me -- she told me that she didn't understand it, your Honor, but she understood it at her deposition so I'd like to direct her to her testimony there.
THE COURT: I'll permit it.
BY MR. HASFORD:
Q. Take a look if you would at Page 35, Lines 20 through 22, I asked --
A. I was just clarifying what you meant by pharmaceutical services.
Q. I asked you:

QUESTION: You have never founded or cofounded a pharmaceutical services company, correct?
And you answered:
ANSWER: Correct.
That was your testimony, wasn't it, doctor?
A. I see that.
Q. You testified on direct exam about regulatory requirements, yet you have never been qualified by any court or anybody as an expert in regulatory law, correct?
A. No, I have not been qualified.
Q. You have never consulted for any party on any issue of FDA regulatory law, correct?
A. On FDA regulatory law? That is correct, yes.
Q. You are not a named inventor on any U.S. patents or patent applications, correct?
A. Not on U.S. patent applications, no.
Q. You only ever filed two non-U.S. patent applications, correct?
A. That is correct, yes.
Q. You have never filed a patent application dealing with the use of bromfenac in a pharmaceutical formulation, correct?
A. That is correct, yes.
Q. You have never filed a patent application dealing with the use of tyloxapol in a pharmaceutical formulation, correct?
A. That is correct, yes.

Q. You have never filed a patent application dealing with the use of benzalkonium chloride in a pharmaceutical formulation, correct?
A. That is correct, yes.
Q. You have never filed a patent application dealing with formulating a stable aqueous liquid preparation, correct?
A. That is correct, yes.
Q. I'd like to conclude with questions regarding your proposed definition of a person of ordinary skill in the art.
You did not cite anything in support of your proposed definition of a person of ordinary skill in the art of the '431 patent, correct?
A. That is correct, yes.
Q. In proposing your definition of a person of ordinary skill in the art, you did not consider the definitions that any other experts have provided in other cases, did you?
A. Not at the time; I have subsequently done so.
Q. In proposing your definition of a person of ordinary skill in the art, you did not consider the definition that any courts have adopted in other cases, correct?
A. Not at the time, no.
MS. RAPALINO: I object on the ground of relevance to what other courts in other cases about other patents, what that has to do with the definition of the person of ordinary skill in the art here.

MR. HASFORD: I think --

THE COURT: Well, in terms of what she consulted with I'll permit it.

BY MR. HASFORD:

Q. I will ask the question again.

In proposing your definition of a person of ordinary skill in the art, you did not consider the definition that any courts have adopted in other cases, correct?

A. **No, I used my knowledge at the time.**

MR. HASFORD: Nothing further at this point, your Honor.

THE COURT: Okay. Thank you.

Redirect?

MS. RAPALINO: Yes, your Honor.

(REDIRECT EXAMINATION OF JAYNE LAWRENCE BY MR. RAPALINO:)

Q. Good afternoon, Professor Lawrence. Nice to see you again.

A. **Good afternoon.**

Q. Do you recall in the cross-examination Mr. Hasford asked you about some deposition testimony where you used the word hindsight in answering a question?

A. **Yes, I did.**

Q. Can you explain what you meant by hindsight?

A. **What I meant was just putting myself back into that particular period.**

Q. And what particular period did you put yourself back into to do your obviousness analysis in this case?

A. **January 2003.**

Q. Do you recall that Mr. Hasford also asked you some questions about whether substituting tyloxapol into Example 6 of the '225 patent would have had a material effect on stability?

A. **Yes, I do.**

Q. And do you recall that you testified that it would have no effect, no material effect on stability?

A. **Yes, I do.**

Q. Can you explain what you meant by a material effect?

A. **Yes, I meant it would have no detrimental effect on the novel and basic properties, characteristics of the formulation.**

Q. Okay. Now, Mr. Hasford also asked you some questions based on one of your publications where he quoted your publication as saying that there's no using a surfactant to increase the solubility of an already water soluble drug. Do you remember that?

A. **Yes, I do.**

Q. And then he asked you whether the sodium salt of bromfenac was water soluble. Do you remember that?

A. **Yes, I do.**

Q. Is the issue that we're dealing with in this case the

issue of solubilizing the sodium salt of bromfenac?

A. **No, it is not.**

Q. What is the issue that -- what is the problem to be addressed by adding a surfactant in this case?

A. **The problem that the addition of surfactants solves is overcoming this complexation between benzalkonium chloride and sodium bromfenac, it doesn't need the soluble the sodium bromfenac in that process.**

Q. Do you recall that you were also asked a number of questions about issues that a formulator needs to consider in developing a new drug product?

A. **Yes, I do.**

Q. For example, you were asked about considering the issue of the efficacy of a drug. Do you remember that?

A. **Yes, I do.**

Q. Was bromfenac already a marketed product as of the relevant date here, January 2003?

A. **Yes, it was, it was well known to be.**

Q. So did a formulator need to consider issues of efficacy in connection with bromfenac as of that date?

A. **No, it didn't, that would have been done in the preclinical, pre-formulation work.**

Q. Likewise, Mr. Hasford also mentioned comfort to the eye as another consideration that a formulator would need to consider. Given that bromfenac was already a marketed product

as of 2003, would comfort to the eye be a particular issue or challenge that the formulator would need to consider?

A. **It wouldn't be a particular challenge, no.**

Q. Now, Mr. Hasford also mentioned during your cross that there were other considerations -- you testified there were other considerations that a formulator might consider in developing a new drug product, and one of them includes safety. Do you remember that?

A. **I do.**

Q. And again, in light of what was known about bromfenac in 2003, would safety have you been a particular issue or challenge for a formulator?

A. **No, it would not. Many of those conditions are important during development of a new drug, not the formulation of an already established drug.**

Q. Okay. And do you recall that you testified similarly that some other considerations that a formulator would consider would be having sufficient viscosity to stay in the eye, container stability, route of administration -- and route of administration?

A. **Yes, I do.**

Q. And were any of those particular issues or challenges for bromfenac given what was known as of January 2003?

A. **No, they were not, it would have been routine for a formulator at that stage.**

Q. Now, do you recall that Mr. Hasford pointed you to the Ogawa '225 patent?
A. **Yes, I do.**
Q. And that was JTX-147. Do you remember that?
A. **I don't remember the numbers.**
Q. Do you recall that you offered testimony about Example 6 of the '225 patent?
A. **Yes, I do.**
Q. And Mr. Hasford asked you about whether there was any report in the '225 patent of any problem of cloudiness or complexation. Do you remember that?
A. **Yes, I do.**
Q. And I believe that your testimony was that there was no report but it would have been obvious to a person of ordinary skill in the art why there was no complexation reported. Do you remember that?
A. **Yes, I do.**
Q. In light of the ingredients of Example 6 of the '225 patent, what would a person of skill in the art understand about why there was no complexation in Example 6?
A. **They would have been aware of the problems of complexation between benzalkonium chloride and bromfenac and realized that the surfactant polysorbate 80 was there to overcome those problems. If it wasn't there to overcome the problems, there would be no reason for adding that surfactant**

into the formulation.
Q. Okay. Thank you.
Now, do you also remember that Mr. Hasford pointed you to JTX-168, which is the '034 patent?
A. **Yes, I do.**
Q. And specifically he pointed you to Table 1 in the '034 patent. Do you remember that?
A. **Yes, I do.**
Q. And he had you compare results comparing bromfenac to various numbered compounds in that table. Do you remember that?
A. **Yes, I do.**
Q. Were any of those numbers compounds in patent marketed pharmaceutical products as of 2003?
A. **No, they were not.**
Q. And given the option of formulating a product that had already been a marketed product and had gone through safety and efficacy clinical trials as compared to starting from scratch with a new compound that hadn't yet been approved, what would be the preference of the pharmaceutical formulator?
A. **A formulator would always go with something that already received approval. If not, they would have to put the new drug through very expensive clinical trials.**
Q. Now, Mr. Hasford also pointed you to what he characterized as other approaches taken to the problem of

complexation. Do you remember that?
A. **Yes, I do.**
Q. Specifically he asked you about the '929 patent, which uses a preservative Polyquad in place of benzalkonium chloride. Do you remember that?
A. **Yes, I do.**
Q. Would a person of ordinary skill in the art have been motivated to replace benzalkonium chloride with Polyquad to solve the problem of complexation between an NSAID and benzalkonium chloride?
A. **No, it wouldn't have been the preferred approach, they would have looked at modifying the formulation of benzalkonium chloride.**
Q. How would a person of ordinary skill in the art know that was the preferred approach?
A. **Can I look at the patent number?**
Q. Maybe I can direct your attention to DTX-15.
A. **There was two reasons why I think they wouldn't have used the Polyquad approach, because there was far less experience with the use of Polyquad, and coupled with the fact that Remington suggests that it's always better to use the most favored preservative, which is benzalkonium chloride, rather than use a less favored preservative.**
MS. RAPALINO: Can I have one moment, your Honor?
THE COURT: Yes.

(Brief pause.)
MS. RAPALINO: Okay. I have no further questions, your Honor.
I just want to take care of one housekeeping matter. When I read the list of exhibits to be moved into evidence with Professor Lawrence's testimony, I inadvertently omitted JTX-209.
THE COURT: And which document is that?
MS. RAPALINO: It is the EP '984 patent.
THE COURT: Okay. Any objection to that being received into evidence?
MR. HASFORD: No objection, your Honor.
THE COURT: Okay. JTX-209 is received into evidence.
(JOINT EXHIBIT JTX-209 WAS RECEIVED IN EVIDENCE)
THE COURT: Any short follow-up within the scope of redirect?
MR. HASFORD: We've got no recross, your Honor.
We have the same housekeeping issue, we want to make sure all the exhibits we used on cross are entered. I have PTX-265, PTX-295, and I think there may have been another one, PTX -- the Xibrom® package insert.
THE COURT: 749?
MS. LEBIS: It's Bates No. PROL 0167921.
THE COURT: 0167921. I don't think it was qualified. Did the witness lay a foundation for this as something she

recognizes or is there any objection?

MS. RAPALINO: There is an objection. I don't think there was any foundation laid for this document.

MR. HASFORD: Well, I don't believe there was. So she testified that the package insert included the same U.S. patent number as Ogawa, so she matched that up and confirmed in fact the Ogawa patent is listed on that package insert, your Honor, I believe that does lay the foundation.

MS. RAPALINO: Can I just ask for clarification which exhibit you're talking about?

THE COURT: This one page Xibrom® package insert.

MS. RAPALINO: Yeah, again, I don't think there was any foundation laid. It was just purely a matter of her reading whether there was a patent number on the document.

MR. HASFORD: Well, counsel didn't object at the time, your Honor, we have argued that that objection is waived then. I was able -- I asked the witness questions about the document.

THE COURT: You asked her what's printed on this piece of paper and she said what she said in terms of the patent being listed, but I think she said that she hadn't seen this before. So there may be another way to get it in, or perhaps the parties can stipulate when the defense has an opportunity to look at this, but through this witness there's an objection to foundation. I'll give you another opportunity

to lay a foundation with Dr. Lawrence.

MR. HASFORD: May I, your Honor?

THE COURT: Sure. I apologize, what was the PTX number again?

MR. HASFORD: 749.

THE COURT: Thank you.

(RECROSS-EXAMINATION OF JAYNE LAWRENCE BY MR. HASFORD:)

Q. Doctor, do you recognize PTX-749 as a copy of the package insert for Xibrom®?

A. I've never seen it until today.

Q. Do you have any reason to believe that PTX-749 is not a copy of the package insert for Xibrom®?

A. I have no view either way.

Q. You've relied on package inserts in connection with your opinions in this case, doctor, correct?

A. I really haven't seen this one before, that's all I can say.

Q. Again, you've relied on package inserts in connection with your opinions in this case, correct?

A. I would have to check, but probably.

Q. Does PTX-749 look like the type of packaging insert you would have relied on in connection with your opinions in this case?

A. I guess so. I don't know.

MS. RAPALINO: Your Honor, maybe I can short-circuit

this. I don't think we're going to have an objection to the exhibit, we have all just seen it for the first time during the cross-examination, if we could have some time, we might be able to arrive at a stipulation to enter it into evidence.

THE COURT: Okay. The reason I think that's the better way to do it, the witness hasn't laid a foundation, she can't say it is, she can't say it isn't, and that's understandable.

Also, this particular document's marked confidential. With a package insert it couldn't be confidential, could it?

MR. HASFORD: Yeah, if it's a public package insert with that confidentiality designation, it might have been put there inadvertently. I'm not sure.

THE COURT: The parties can track this down if it remains in dispute.

But let me deal with the two documents that you have moved in. You moved in PTX-265 and PTX-295.

MR. HASFORD: Correct.

THE COURT: And is there any objection to those or do you need to consult?

MS. RAPALINO: I believe that they suffer from the same issue. For PTX-265 I also believe that the witness testified she hadn't seen that before. And I don't even believe that 295, I don't think there was any testimony elicited on PTX-295.

THE COURT: That's correct. PTX-295, there is no testimony, that was the PDR 54th addition.

MR. HASFORD: Maybe we can reach another agreement with counsel on those because I don't believe there should be any legitimate dispute, these are what they purport to be, your Honor. But we're happy to take care of that on the side with counsel.

THE COURT: Okay. Actually the Acular® one might well be incomplete because it seems to start with Page 4.

MR. HASFORD: Oh, your Honor, I think that's how the FDA starts their numbering with any package inserts, at least that's what we've seen.

THE COURT: Do they charge for the first three pages?

MR. HASFORD: I hope not, your Honor.

THE COURT: Do counsel have any other questions? Because I may have one or two questions for the witness.

MR. HASFORD: I have no recross, your Honor.

THE COURT: So for now 265 and 295 are not received into evidence, PTX-265 and 295.

Now, throughout the trial I may ask a question here and there, it's permitted by the Rules of Evidence. But it's also permitted to counsel that you have a right to object and for me to rule at sidebar on any objection before the witness answers. So don't be reluctant to object if you feel I might be asking a question that is not comporting with the Rules of

Evidence or what's relevant in the case. And I won't be offended in the least, that's what the rules provide.

My question, doctor, is about your definition of a person ordinarily skilled in the arts. Where does your definition -- well, could you repeat for me your definition of a person ordinarily skilled in the arts -- a person of ordinary skill in the art as it applies to this case?

THE WITNESS: Certainly. I used, based on my experience of working with pharmaceutical companies and being aware of the people who did formulation within these companies, they were generally Ph.D.s in pharmaceutical sciences, often pharmacists, but often pharmaceutical scientists as well, and they will have a year or two -- a year -- a few years of experience, and that's how I arrived at the definition from my own experience.

THE COURT: There's already been some testimony that a person with a bachelor's degree and experience could well be a POSA. Do you agree or disagree with that?

THE WITNESS: I think it would have been unusual for somebody without a Ph.D. to be in that position. Although, obviously, if they had sufficient experience, that would compensate it for that. But I do have a problem with their definition of pharmaceutical chemist, chemist, I think that would have been very unusual.

THE COURT: How does pharmaceutical science differ

from pharmaceutical chemistry?

THE WITNESS: That's a good question. Pharmaceutical chemists tend to go and work in the medicinal chemistry side of the industry, they'd be looking at preparing new drug molecules. Pharmaceutical science, you're correct, your Honor, does include pharmaceutical chemistry, but I'm talking about pharmaceutical science related to formulation.

THE COURT: And so the formulators are the pharmaceutical scientists in your view?

THE WITNESS: Yes.

THE COURT: Doesn't that set a very high bar for the persons who are deemed to have such skill here?

THE WITNESS: I took that from my experience. And, in fact, Professor Williams had that experience when he went into working in formulation himself, he had a Ph.D.

THE COURT: And he didn't work in formulation, as far as you know, before that date?

THE WITNESS: He's obviously better to qualify, but that's what his CV seemed to indicate.

THE COURT: All right. Are there any follow-up questions as to my questions? Beginning first with the defendant who called the witness.

MS. RAPALINO: No, your Honor, no questions.

THE COURT: Plaintiff?

MR. HASFORD: None from plaintiff, your Honor.

THE COURT: Okay. And, Dr. Lawrence, I think we've reached the end of your testimony and you may step down.

Is Dr. Lawrence excused to return or is she --

MS. RAPALINO: She's going to be returning for our rebuttal case, but for now she is excused.

THE COURT: So, doctor, you may step down. Thank you very much.

THE WITNESS: Thank you.

(Witness Excused.)

THE COURT: Do you need five minutes to set up for the next witness or are you ready to go?

MR. DINER: Just a couple of minutes to set up, your Honor, and we're ready to go.

MR. HASFORD: Well, we would request clarification from the defendants whether they concluded their case in chief.

MS. HOLLAND: Your Honor, this is the last live witness. However, as you know, there are deposition designations, those are not going to go into the record until the end of trial, so we -- you know, we can't rest at this point until all the evidence is in, I would say, but this is our last live witness.

THE COURT: Okay. So all that awaits is the deposition designations?

MS. HOLLAND: Correct, in our case in chief. We

expect to put on a rebuttal case.

THE COURT: What I don't want to see is a couple days down the road that your real case emerges as a rebuttal case.

MS. HOLLAND: No, certainly not, your Honor. Dr. Lawrence's testimony was essentially the evidence we're putting in on our obviousness and obviousness-type double patenting together with the deposition designations. The rebuttal case will go to issues of secondary considerations, which plaintiffs have the burden on, so they're going to go first on that and we will be replying to that.

THE COURT: Is that the parties' understanding?

MR. HASFORD: Well, this was part of our concern, your Honor, is that they would be holding back part of their case in chief and trying to put it on in their rebuttal case. If they're stipulating now before your Honor that they won't do that, then that's one thing, but that was our concern all along. I guess the question arises, since they have no further live witnesses, that a Rule 52 motion would be appropriate at this point.

THE COURT: I believe it would not be because I haven't seen the deposition excerpts yet that are also part of their case. Normally a Rule 52 at the point where a party rests is fine. I think the short answer is the defendant actually is not resting yet. But also they have called their last live witness, unless somebody fits the category of

rebuttal.

MR. HASFORD: Respectfully, your Honor, would your Honor sustain an objection to the extent they attempt to put in additional evidence toward their case in chief during their rebuttal case that they should have properly put in their case in chief here?

THE COURT: I don't think I can rule *a priori*. It's like any rebuttal situation, it has to be judged on its own circumstances. I think there's at least two rules about rebuttal, A, the same witness can't be called to give the same testimony that they did before and just in a louder voice and, B, that if a witness who properly is part of the party's direct case could have testified but wasn't called, then the reason for calling that witness has to be something that happened in the opponent's case that requires rebuttal and wasn't anticipated,

MS. HOLLAND: Your Honor, maybe I can -- I think there's some veiled language here that maybe we should just air out.

So we put Dr. Lawrence on, she's our witness on our case in chief. We have Dr. Heathcock who is a chemist, his report came in in rebuttal to Dr. Davies' report, so he's a rebuttal witness based on the -- based on the order of the expert reports that went in. And to the extent Mr. Hasford was trying to preview that, I just wanted to make sure that we

were clear with your Honor, that Dr. Heathcock is rebutting Dr. Davies' opinions on organic chemistry.

MR. HASFORD: I would ask your Honor that Dr. Davies served a reply report to Dr. Heathcock's rebuttal report. There was some disagreement between the parties as to whether that reply report was proper. Plaintiff moved to strike it but then per agreement with the parties -- or defendants moved, rather, to strike it. Per agreement of the parties defendants withdrew that motion. So we would respectfully request the opportunity to reply to anything new that they put on through Dr. Heathcock or anything from the other witnesses that would have been properly in their case in chief.

MS. HOLLAND: Your Honor, I think we -- we withdrew it as part of a larger deal on withdrawing a lot of motions. And the phone conference that we had pretrial, I believe I asked the specific question about the order and you said plaintiffs will go first and third and that defendants would go second and forth, and that's what we understood the order to be.

THE COURT: Yeah. And the fourth would be to rebut new evidence that comes in --

MS. HOLLAND: Yes.

THE COURT: -- in the third stage.

MS. HOLLAND: Correct.

THE COURT: And the question we can probably resolve

right now is whether Dr. Heathcock's testimony would be seen by the plaintiffs as being proper rebuttal to Dr. Davies. I assume Dr. Davies will testify, and then within the field of organic chemistry Dr. Heathcock will say this is why we don't agree with Dr. Davies.

MS. HOLLAND: Exactly, your Honor.

MR. MUKERJEE: That's exactly right.

MR. HASFORD: Except it's our view, your Honor, that that testimony as to the organic chemistry issue should have come in in defendant's case in chief, and that's exactly why Dr. Davies provided the reply report to Dr. Heathcock.

THE COURT: Well, I can see why it hasn't. I mean, the defendants don't see this as an organic chemistry case.

MS. HOLLAND: Correct, your Honor.

MR. MUKERJEE: That is correct, your Honor.

MS. HOLLAND: That's why he's not in our case in chief. That's why Dr. Heathcock only came into the case at all, to rebut Dr. Davies, that's his sole function in the case.

MR. MUKERJEE: Right.

THE COURT: No, I think this makes sense. And everybody is on notice what Dr. Heathcock's rebuttal testimony is apt to be, since he has served the reports and they deal with Dr. Davies' reports. Everybody knows Dr. Davies' position with regard to what Dr. Heathcock is going to say,

too, because Dr. Davies does have a reply report that has been served upon the defendants. It's just that there won't be a fifth stage of the case, whatever Dr. Davies wants to say, including whatever he anticipates is needed to rebut Dr. Heathcock, he'll have to say in this, call it stage three. I think that that's fair to both sides and it won't unduly prolong the trial.

MS. HOLLAND: We agree, your Honor.

MR. MUKERJEE: We agree.

THE COURT: Is that okay?

MR. HASFORD: We can see how it goes, your Honor, but in principle that may work.

THE COURT: I'll take that as a yes.

Well, it's like all things at trial, no one can guarantee exactly what is going to happen in the trial. If the circumstances change substantially, then I'll revisit this situation.

MR. HASFORD: Thank you.

THE COURT: But I think that the defendants are putting their cards on the table about what they anticipate.

Is there any other live witness you anticipate for rebuttal?

MS. HOLLAND: Yes, there are, your Honor. There's Dr. Trat -- I'm sorry. Dr. Trattler is going to be plaintiff's medical doctor witness. We're going to be

rebutting that with Dr. Cykiert. As well, we have Dr. Pranlukast, who is also addressing secondary consideration issues.

THE COURT: And that's because on secondary considerations, that's the plaintiffs' --

MS. HOLLAND: Burden.

THE COURT: So I think that part makes sense.

MR. HASFORD: Just to be clear, your Honor, plaintiffs don't technically bear any burden with respect to defendants' defenses, so it's merely their own to place evidence on secondary considerations to further show that the invention in fact was not obvious.

MS. HOLLAND: What I mean, your Honor, is there's nothing to reply to until plaintiffs put on their case. We don't have to put on any evidence on secondary considerations, it's only in the nature of providing anything plaintiffs put on.

MR. MUKERJEE: Correct.

THE COURT: Yes, I'm sorry, I didn't mean to suggest the plaintiffs had the burden on that.

But there's nothing to rebut on secondary considerations until the plaintiffs put something on, so that makes sense to me as proper rebuttal.

MR. MUKERJEE: That's correct. And that's in keeping, your Honor, with what you ordered for the

presentation of proofs at trial, the last thing it says, defendants shall present their evidence regarding lack of -- defendants shall present -- last present their evidence regarding lack of secondary considerations.

THE COURT: And on the medical, is Dr. Cykiert a proper rebuttal witness to Dr. Trattler?

MS. HOLLAND: Yes, Dr. Trattler is also on secondary considerations, so it's the same issue as Dr. Prausnitz. We'll rebutting whatever evidence comes in on secondary considerations offered by plaintiffs in the third stage.

THE COURT: Okay. So there is actually a lot more live testimony to go from the defendants. It's just not part of your direct case.

MS. HOLLAND: Correct. And I don't believe these are going to be long witnesses.

THE COURT: All right.

MR. HASFORD: But that's our concern.

THE COURT: Well, they won't be longer than 13 hours.

MS. HOLLAND: Your Honor, we are planning on keeping to 13 hours, and we are assuming that plaintiffs are as well.

THE COURT: Okay. And, you know, by tomorrow afternoon, we can talk more about the time and how we're doing.

Okay. So, again, this roadmap, this blueprint makes sense to me.

And the plaintiff is resting its direct case, except for the deposition excerpts which, by agreement of the parties --

MR. HASFORD: Did you mean defendants, your Honor?

THE COURT: I'm sorry. The defendants are resting except for the deposition excerpts.

MS. HOLLAND: Yes. And the exhibits that come in with the deposition excerpts.

THE COURT: All right. So I think that a Rule 52 motion would be premature.

MR. HASFORD: May we reserve on it?

THE COURT: And you can -- well, you have a placeholder.

MR. HASFORD: Thank you, your Honor.

THE COURT: You've mentioned it and I've determined that it's premature. But, in any event, when all the evidence is in, you can argue the motion.

MR. HASFORD: Thank you, your Honor.

THE COURT: All right. What shall we do next then, this afternoon? Is it time for the plaintiff's witness?

MR. HASFORD: Well, the question, your Honor, is whether, given the hour, we have the privilege issue that needs to be resolved, whether it makes sense for Dr. Davies to come on for just a short period of time and then have to go back off the stand or whether it makes more sense for your

Honor to adjudicate or at least hear the argument.

THE COURT: Well, why don't we get started, and then we'll end about 4:30, and I think the argument will be short on the privilege issue. I should say that I don't think either side should take more than five or seven minutes in its argument on the privilege issue.

(Pause)

THE COURT: Okay. Shall we proceed?

MR. DINER: Yes, Your Honor.

May it please the Court, Bryan Diner on behalf of the plaintiffs.

And, your Honor, in opening our rebuttal case, we would like to call Dr. Stephen G. Davies.

THE COURT: Dr. Davies, please come to the witness stand.

THE DEPUTY CLERK: Sir, can you please place your left hand on the Bible and raise your right hand.

(**STEPHEN GRAHAM DAVIES**, HAVING BEEN DULY SWORN/AFFIRMED, TESTIFIED AS FOLLOWS:)

THE WITNESS: I do.

THE DEPUTY CLERK: Please state your name, sir, and spell your first and last name for the record, please.

THE WITNESS: Stephen Graham Davies, S-T-E-P-H-E-N D-A-V-I-E-S.

THE DEPUTY CLERK: I-E-S?

THE WITNESS: That's correct.

THE DEPUTY CLERK: Thank you, sir. You can be seated. Please speak into the microphone.

(DIRECT EXAMINATION OF STEPHEN GRAHAM DAVIES BY MR. DINER:)

Q. Good afternoon, Dr. Davies. Would you please state your address for the record.

A. **My address is 7 Apsley Road, Oxford, UK.**

Q. And where are you presently employed?

A. **At the University of Oxford.**

Q. And what is your current position at the University of Oxford, Dr. Davies?

A. **I am the Waynflete Professor of Organic Chemistry.**

Q. And how long have you been a faculty member at the University of Oxford?

A. **I joined the faculty in 1980, so 36 years.**

Q. Would you please describe the faculty positions that you have held at the University of Oxford.

A. **So, I was first appointed as a University Lecturer which is a tenure-track position, equivalent to an assistant professorship in the U.S., I guess.**

Two years later, I gained tenure on the work we had done at that stage.

I then stayed with the title University Lecturer, that's a peculiarity of Oxford, but I was appointed Professor in the mid-'90s, if not a bit before then, and then was

appointed to the Waynflete Chair ten years ago.

Q. Is the Waynflete Chair a professorship chair?

A. **It is, yes.**

Q. And what is the significance of becoming the Waynflete Professor?

A. **The Waynflete Chair is the only named chair in organic chemistry at Oxford. It's one of the oldest chairs in the UK, if not in the world. And it's a great privilege to hold it.**

Q. And what, if any, departments within Oxford do you chair?

A. **So, Oxford University Chemistry Department is one of the largest in the world, and I was chairman of the whole department for five years up until about five or six years ago.**

Q. In what fields, Dr. Davies, do you specialize in?

A. **I'm a chemist, and within that, I specialize in organic chemistry, but in all its aspects, and then within organic chemistry, I specialize in synthesis, stereochemistry, medicinal chemistry.**

Q. Have you ever worked with carboxylic-acid-containing compounds as part of the work that you've done in chemistry?

A. **I think throughout my career I've worked with carboxylic acids.**

Q. And have you worked with aqueous solutions of carboxylic-containing compounds?

A. **That is standard chemistry you have to do if you work**

with carboxylic acids.

Q. For how long have you worked in the fields that you mentioned previously?

A. **We started since I started my independent work, and then we built up expertise in those areas over the time, so that would be since about 1978.**

Q. Do you have a doctorate degree?

A. **I do, yes.**

Q. Okay. And when did you obtain that?

A. **I obtained that in 1976.**

Q. And how, if at all, has your work continued to the present day? The work in the chemistry and that you do at Oxford.

A. **Well, we're still a very active group, working across the fields I have mentioned to you. It goes on.**

Q. Would you -- let me hand you your binder. Please, would you turn to PTX-160.

A. **Yes.**

Q. And can you identify that document for us?

A. **That is my curriculum vitae.**

Q. And does your C.V. accurately reflect your educational work experience?

A. **I believe so, yes.**

Q. Would you briefly describe your educational background following your graduation from high school?

A. **So, I went to the University of Oxford in 1973 to study for a B.A. in chemistry. It's a four-year course, so I received my B.A. in 19 -- so I went in 1969. I got my B.A. in 1973, after a four-year course.**

And then I stayed on for my D.Phil., which is equivalent to a Ph.D., and I received that two years later in 1975.

I then received a competitive research fellowship that allowed me to go and work with anybody I chose. I chose to stay in Oxford, but moved from organic chemistry to inorganic chemistry in order to learn applications of metals and other inorganic compounds to organic chemistry. That was a two-year position, so that took me to 1977, when I received -- gained another competitive research fellowship, a N.A.T.O. fellowship, which I took to Paris to work with Professor Sir Derek Barton on natural product chemistry, again trying to broaden my research experience.

And after one year there, I gave that up because I was offered a tenure-track position in the French Scientific Civil Service, and I held that position for two years before coming back, being invited back to Oxford on the faculty there.

Q. What, if any, degrees did you obtain while you were in Paris?

A. **I received in 1980 a second doctoral degree from the University of Paris.**

Q. And in what area of science was that?
A. **It was in organic chemistry.**
Q. And what did you do then after you came back from Paris? I think you were starting to mention that.
A. **So, I set up an independent research career. I started off as a University Lecturer, and then I've moved up from a tenure-track to a tenure position to a professorship now to the main chair of an inorganic -- in organic chemistry.**
Q. And, now, would you please briefly describe your research work since 1980?
A. **It's been in all aspects of chemistry, focussing on organic chemistry, so we have a lot of collaborations across other departments in the university and other parts of chemistry. It's all to do with how to make organic compounds, how do you control their structure and their shape, and how those compounds can be applied to biological systems and to the development of drugs.**
Q. Do you also teach at the University of Oxford?
A. **Since I think 1976, I've taught at the University of Oxford, apart from the three years I was in Paris, but I've been on the faculty and teaching on the faculty since 1980. In the last ten years, my contract says I don't have to teach anymore, but I choose to do a full teaching load.**
Q. And what is it that you teach?
A. **To undergraduates, in a tutorial based system, I teach**

the whole of organic chemistry. In terms of to the -- to -- in terms of lecture courses, I can only teach the first course in organic chemistry that they receive at the University of Oxford; in fact, they get their first lecture from me. And I also teach a course on aromatic and heteroaromatic and pharmaceutical chemistry.
Q. Do you teach about hydrogen bonding as part of your courses that you teach at Oxford?
A. **It's part of the very start of their career, so since I give them their first course, I certainly do.**
Q. And is hydrogen bonding an aspect or a type of chemistry?
A. **It's chemistry, yes, absolutely. It's a fundamental part of chemistry.**
Q. Now, were you in the courtroom yesterday listening to the defendants' opening statement?
A. **I was, yes.**
Q. Do you recall that the defendants gave a PowerPoint presentation about the theory of how NSAIDs would allegedly complex with BAC, benzalkonium chloride?
A. **I saw that, yes.**
Q. Could we put up -- before we get to the document I was going to introduce, let me ask a few more questions.
I want to go back to your graduate program that you work within and with the students at Oxford. Do you work with graduate students at Oxford?

A. **I do, yes. Over the years, I've supervised more than -- well over a hundred doctoral students have come through my group and graduated.**
Q. And, Dr. Davies, have you founded or cofounded any companies in the pharmaceutical area?
A. **I have, yes. They're listed in my curriculum vitae, on the third page of that. I've been founding companies since 1992. And there's six or seven or more different companies that are listed there.**
Q. And what do some of these companies do in terms of the work or research that they do?
A. **Well, the first company I founded was Oxford Asymmetry in 1992; it's a limited company. That was a service company to the pharmaceutical industry. It was there to provide synthetic methods and, in particular, ways to make single-handed molecules to improve drugs for the pharmaceutical industry.**
And in 1995, I founded a company called Oxford Diversity Limited, another service-type company for the pharmaceutical and the agrochemical industries, where we made libraries of very large numbers, up to a million single compounds for biological evaluation by pharmaceutical companies.
I founded in 2000 -- and so those two would be drawn together to a company called Oxford Asymmetry International,

PLC, so it's a public company. At that stage, that was in 1998, we sold it in 2000. It's still going. It's a large contract research organization these days.
2003, I founded a company called VASTox, which is now called Summit Corporation, which is -- started off as a novel way to screen molecules for biological properties, drug-like properties. Currently, it's called -- it's Summit Corporation, which is listed on the London Exchange and on NASDAQ, and that has -- that is a drug -- drug discovery and development company, has two compounds going through the drug development process. One is in Phase 2; the other one is in Phase 3. The one in Phase 2 is for an orphan disease called Duchenne muscular dystrophy. And the other one is a novel completely selective antibiotic against clostridium difficile.
Most recently, I founded a company called OxStem Limited, which is looking at regenerative medicine, how do you develop drugs for controlling cells within the body to self repair in disease states.
Q. What, if any, honors or awards have you received in connection with your work?
A. **As I also listed on my C.V., so there is -- over the years, there is a significant list of awards for the work we have been doing.**
Q. Okay. There is an award on your C.V. called the Perkin Medal. Do you see that?

A. It's the Perkin Prize and Medal, yes, for organic chemistry.

Q. What is that?

A. That's given by the Royal Society of Chemistry, London. It's their most prestigious organic chemistry award. It's basically a lifetime achievement award.

Q. And what, if any, scientific journals have you served as an editor on?

A. I have been editor on a number of journals. In fact, I founded a journal in 1990 called *Tetrahedon: Asymmetry*. I became the editor in chief at that time, and I'm still the editor in chief.

I'm also on the board of the *Tetrahedon* publications, which is a set of journals of which *Tetrahedon: Asymmetry* is one, but the others are *Tetrahedon, Tetrahedon Letters, Bioorganic & Medicinal Chemistry*, and *Bioorganic Chemistry Letters*. And I have been on the editorial board of another -- a number of others journals, as well.

Q. Would you please turn to plaintiff's trial Exhibit 632 in your binder and identify that document?

A. That is my list of publications.

Q. And does your list of publications accurately reflect your published research articles?

A. Well, it goes up to 568. But since the time this was produced, I would have published four or five more papers.

MR. DINER: Your Honor, plaintiffs would like to proffer Dr. Davies as an expert in the field of chemistry.

THE COURT: Any objection?

MS. HOLLAND: I don't have an objection to his expertise in chemistry.

We obviously have an objection to the relevance of his expertise to this case. I would be happy to voir dire on that, your Honor, but I'm also happy to ask those questions later.

THE COURT: All right. Perhaps save them for cross and see what ground is covered on direct.

MS. HOLLAND: Okay. Yes.

THE COURT: All right. Then I'll certainly recognize Dr. Davies as an expert in chemistry.

BY MR. DINER:

Q. Dr. Davies, let's discuss the patent-in-suit for a moment.

Would you please turn to JTX-001 in your binder, and identify that document.

A. This is U.S. Patent 8,129,431.

Q. And if I refer to the U.S. Patent 8,129,431 as the '431 patent, will you understand what I mean?

A. Yes.

Q. Okay. Did you review the '431 patent in connection with your opinions in this case?

A. I did, yes.

Q. And if you could please turn to Columns 11 through 14 of the '431 patent, let me know when you're there.

A. I'm there.

Q. Did you review the claims at the end in Columns 11 through 14 of the '431 patent in connection with the opinions that you've offered in this case?

A. I reviewed the whole patent, including the claims, yes.

Q. Did you gain a general understanding, Dr. Davies, of what is claimed in the '431 patent?

A. Yes, I did.

Q. And what is your general understanding of what is claimed in the '431 patent?

MS. HOLLAND: Objection, Your Honor. This is the same objection I raised earlier. I mean, to speak about what's generally claimed is problematic. Generally disclosed in the specification is a different question, but the claims are very particular and you can't speak about them in generalities.

MR. DINER: Your Honor, he can talk about what the elements are in the claim, and I am only going to ask him as for Claim 6, for example, can you describe generally what is covered by Claim 6 of the '431 patent.

THE COURT: Well, it's the same problem.

By way of introduction, I'll permit it, but the

claims are what the claims are.

And so what's the pending question again?

BY MR. DINER:

Q. As to Claim 6, Dr. Davies, what is your general understanding of what that claim covers in the '431 patent?

A. Liquid aqueous preparation of bromfenac and tyloxapol for ophthalmic use.

MS. HOLLAND: This is actually outside the scope of his expert report, your Honor, believe it or not. Dr. Davies really didn't look at -- didn't discuss anything about the patents in depth. He just went right into the chemistry. There is nothing in the expert report that talks about Claims 6 or 20.

MR. DINER: Well, your Honor, Dr. Davies was deposed on his opinions and there was discussion in his deposition as to the claims and what they generally cover. He offered testimony on that. It should come as no surprise at this point, and it's just introductory. We're going to be getting into the chemistry in a second, your Honor.

MS. HOLLAND: Your Honor, Dr. Davies actually testified at his deposition that he did not look at the patents in detail. That was his question. So I'm therefore going to continue objecting to Dr. Davies giving any kind of detailed testimony about the patents. It's not in the report, and at his deposition he said he did not review the patents in

detail.

THE COURT: All right. I think I've just sustained the objection. If it's not in the report and the deposition didn't have detailed testimony on it, he said he had not reviewed the patents to prepare his report, then I'll sustain it.

MR. DINER: Actually, your Honor, he did say that he considered the patents. He didn't review them in detail is what he said at his deposition, but he did consider the patents in an overall sense and has a view as to, in an overall sense, what the patents are directed to.

MS. HOLLAND: Your Honor, again, it's not in the report. He gave specific testimony at his deposition that he wasn't here to talk about the patents. He doesn't know what they say in detail. He's only talking about the chemistry. That appears over and over in the deposition. And I'm happy to hand it up and show it to you, but I don't think there will be disagreement on that.

THE COURT: Well, his testimony is going to be about the chemistry.

MR. DINER: That's right.

THE COURT: If it's necessary to ask a question or two about how it relates to why we're all here, I'll permit it, but --

MR. DINER: Okay.

THE COURT: In other words, it will be by way of directing me to which terms and so forth he is addressing as a chemist.

MR. DINER: Okay. Fair enough.

BY MR. DINER:

Q. Now, Dr. Davies, did you hear Dr. Lawrence testify earlier about certain NSAIDs, bromfenac, diclofenac, ketorolac, and flurbiprofen?

A. I did, yes.

Q. Did you hear Dr. Lawrence testify that because each of bromfenac, diclofenac, ketorolac and flurbiprofen possess a carboxylic acid group, that they would be expected to behave similarly in solution?

A. I heard that, yes.

Q. Do each of bromfenac, ketorolac, diclofenac and flurbiprofen include a carboxylic acid group?

A. They do as one of other groups in each of them, yes.

Q. And did you also hear Dr. Lawrence testify regarding the preservative benzalkonium chloride?

A. I did, yes.

Q. Did you hear Dr. Lawrence testify that because each of bromfenac, diclofenac, ketorolac and flurbiprofen possess a carboxylic acid group, they would be expected to interact in solution with benzalkonium chloride and form a complex?

A. I heard that, yes.

Q. I'd like to turn now to defendant's Exhibit DDX1-12. I believe, Dr. Davies, this is also in the leaflet of your binder there.

Now, do you recall during the opening statement that you testified to earlier that you were present at, that this slide was presented by defendants during their opening?

A. Yes, I saw it.

Q. And in this slide, is it reporting an alleged complexation occurring as between an NSAID, which happens to be bromfenac, and an ion of benzalkonium chloride in solution?

A. That's what it is supposed to show.

Q. Okay. And was it your understanding that as defendants rolled this slide, because I believe it was an animated slide, that when they formed the complex, they caused a precipitate to develop in solution?

A. That's what was said.

Q. Dr. Davies, can you tell us if that process, if it, indeed, is true, that they come together and form a complex, is a matter of chemistry?

MS. HOLLAND: I don't -- that is not in the expert report. I'm not sure I understand the question. So maybe if the question were rephrased, I could --

MR. DINER: Well, he's talked about in his expert reports about the likelihood of things precipitating in the context of the complexation issue.

THE COURT: I'll permit it. If you would like to repeat the question.

BY MR. DINER:

Q. Dr. Davies, as we see in DDX1-12, the coming together of the NSAID here identified as bromfenac with an ion of benzalkonium chloride to form a complex, is that complexation a matter of chemistry in your view?

A. That sort of process, if it were to happen, is chemistry. That's what chemistry is, as is the solution and precipitation. It's all chemistry.

Q. And was it your understanding that defendant's position here is that the complexation is the reason or motivation for how they are looking at the various pieces of prior art?

A. I heard that, yes.

Q. Okay. Now, going back to the testimony offered by Dr. Lawrence, did you understand that it was her opinion that a person of ordinary skill in the art would expect that bromfenac to form an insoluble precipitate with benzalkonium chloride in solution and precipitate out?

A. That's what she said.

Q. Do you agree with that?

A. I don't agree with that, no.

Q. Why is that?

A. I've not seen any evidence to suggest that would happen.

Q. Dr. Davies, in your opinion, when one is considering

whether something like this would occur, what would the person of ordinary skill in the art look at in terms of the molecules that are involved in a complexation reaction like this?

A. You would have to look at the whole molecule, whole molecules or ions being involved, you have to look at all of the functional groups that are in those molecules, and you have to look at the effects that would keep molecules in solution or cause them to precipitate.

Q. And what else would you look at in terms of the molecules that are in solution as to whether they would or would not precipitate?

A. You can't actually tell them until you do an experiment, but you can compare molecules and you can look at whether they are ionized, whether they form hydrogen bonds, what the polarity of the various groups are, what the distribution of the groups are, and what the shapes of the molecules are.

Q. And as between the compounds, the NSAIDs that we were mentioning before, bromfenac, diclofenac, ketorolac, flurbiprofen, do you have an understanding of whether those compounds are structurally similar or dissimilar?

A. The molecules contain different functional groups, different heteroatoms placed in different positions. In a person of ordinary skill's view, I think that would be -- they are certainly different molecules.

Q. And so what are some of the functional properties that

the differences you just testified to in structure can give rise to?

A. Different hydrogen bonding abilities, different solubilities, different molecular weights, a whole variety of different properties, physical and chemical.

Q. You mentioned hydrogen bonding a moment ago. What in particular is hydrogen bonding, generally speaking?

A. It's the interaction -- it normally occurs where you can put up hydrogen atom in-between two heteroatoms, which a heteroatom being an oxygen or a nitrogen most commonly, and it forms an additional bond that gives you stability.

Q. Have you prepared a demonstrative to assist the Court with your testimony in this regard?

A. I have, yes.

Q. Would you please describe this demonstrative in the context of hydrogen bonding.

A. Certainly. So, to illustrate hydrogen bonding, I picked a very simple molecule, water, which is H_2O, which I've drawn on the top left of the screen. It has a hydrogen -- two hydrogens bound to an oxygen atom.

Q. May I interrupt you for a moment?

MR. DINER: Your Honor, may I approach the witness and hand him a pointer?

THE COURT: Sure.

MR. DINER: I think it will assist the Court. Oh,

you have one there. Okay. Thank you.

THE WITNESS: I've drawn the oxygen atom in red as a red ball and the two hydrogens are the gray spheres. Water has a molecular weight of 18, and at that molecular weight, normally one might expect it to be a gas, but we all know that water is a liquid, and the reason water is a liquid is the water molecules are held together by what are called hydrogen bonds, and the hydrogen -- so I've tried to illustrate that on the bottom left here. And the hydrogen bond occurs when you put a hydrogen, say that one, in-between that oxygen and that oxygen, whenever a hydrogen ends up between two heteroatoms, oxygen in this case, you get an extra bonding. This water molecule essentially bonds to the other water molecule. That water molecule bonds to that water molecule. So, you end up with a chain of one molecule bonding to another, bonding to another, bonding to another, and those bonds stabilize the molecule, stabilize it so it is now a liquid holding those water molecules together.

BY MR. DINER:

Q. Are those hydrogen bonds strong bonds?

A. They are strong hydrogen bonds, yes, strong bonds.

Q. And what is the implication of those bonds being strong bonds?

A. That you have to put energy in to break them and to split the water molecules apart. So, for example, you have to

put -- you have to put energy into water, liquid water, in order to make it steam. That is breaking hydrogen bonds.

Q. Please continue with your description or your explanation.

A. So, these types of hydrogen bonds are one of the most important reasons why molecules dissolve in water. And I picked two functional groups in organic chemistry to illustrate that. One is a carbonyl group, which is this structure on the top row in the middle. It has a carbon atom bound to two other parts of the molecule, and the double bond illustrated by those two vertical lines connect the carbon to the oxygen atom shown in red.

Q. Dr. Davies, may I interrupt a second? The carbonyl group that you have drawn here, is that a basic chemical moiety?

A. It's one of the most common chemical functional groups.

Q. And as a chemical functional group or moiety, does that exist on the product bromfenac?

A. It does, yes.

Q. Please continue.

A. So, this is an oxygen atom. When it dissolves in water, when this molecule dissolves in water, if it dissolves, it dissolves because a water molecule can put a hydrogen, one of these hydrogens between its own oxygen and the oxygen of the carbonyl and form a hydrogen bond. Likewise, another molecule of water can form a second hydrogen bond to that oxygen atom.

And those two bonds as shown in the middle structure on the bottom, those two hydrogen, strong hydrogen bonds are what's helped keep the molecule in solution.

Another common functional group is an amine. I've drawn a primary amine, a nitrogen bound to two hydrogens on the top right here. And this can also hydrogen bond, this type of functional group, it can hydrogen bond, but in the other way because the two hydrogens are nitrogen already. Then what happens now when it dissolves is water puts an oxygen atom in a line, oxygen, hydrogen, nitrogen on the left-hand one to form a strong hydrogen bond, so when this primary amine with the two hydrogens, a nitrogen dissolves in water, a water molecule forms a strong hydrogen bond to the hydrogen on the left by placing its oxygen in a line from between the oxygen, the hydrogen and the nitrogen. So, you have two heteroatoms, oxygen and nitrogen this time with a hydrogen in the middle.

It can do exactly the same on the right-hand side. Another water molecule comes up, forms a strong hydrogen bond to the hydrogen on the right. There's oxygen, hydrogen, nitrogen now. That's the hydrogen bond. And that bonding holds that type of structure, that type of functional group in water, in aqueous solution.

Q. Now, the primary amine functional group that you were just referring to on the right portion on the slide, is that

also a chemical functional group that exists on bromfenac?

A. **It is indeed.**

Q. And so how, if at all, does this hydrogen bonding impact the solvation of an anion such as bromfenac in solution?

A. **Well, the more hydrogen bonds that a molecule or an ion can form, the more solvated it will be and the more soluble it will be and the less likely it will be to precipitate out of solution with anything else or, indeed, on its own.**

MR. DINER: I think it's close to 4:30, your Honor. I think this would be a good breaking point.

THE COURT: It's a good time to break for the day then, and so we will adjourn the trial portion until tomorrow morning at 9:30. And why don't we take about a five-minute break, and then we will resume for the oral argument on the appeal motion. Okay?

(Recess at 4:35 p.m.).

THE DEPUTY CLERK: All rise.

(OPEN COURT; 4:45 p.m.)

THE COURT: Be seated, please. Okay. I'd like to convene oral argument upon the motion by Lupin and InnoPharma appealing from Magistrate Judge Williams, February 10th, 2016, discovery order. This is Docket Item No. 70 in the -- I think in the lead case. But it applies to all -- all cases.

And so this is the defendant's motion. I've read your papers, I have a few questions, and who will argue the case?

MS. DAUGHTREY: Good afternoon, Your Honor, Natasha Daughtrey from Goodwin Proctor on behalf of the Lupin and defendants. And so as Your Honor stated, we are appealing Judge Magistrate Williams's order and request that the Court order the plaintiffs to produce unredacted copies of these two scientific reports or, at the very least, Your Honor, we would request that the Court review these quite short documents in camera, which is what we believe is appropriate in the circumstances such as this where the issue of privilege is contested.

THE COURT: And I think the document that was presented for in-camera inspection was not these reports, was it? Wasn't it just the unredacted transcript of the deposition?

MS. DAUGHTREY: So, Your Honor, I think at the time that we originally did this briefing, we didn't have agreement with the plaintiffs on certified English translations of Japanese documents, and so I have -- they're on our DTX list. They were in the pretrial order. I can give you the copies of the actual document, which I think will facilitate your decision here.

THE COURT: Well, it might. But wouldn't it have facilitated Judge Williams's decision? You're asking me to review what you presented to her and what she decided.

MS. DAUGHTREY: Yes, we offered, I believe on the

teleconference, to send these documents to Judge Williams, and she -- at that time, she requested that the plaintiff provide the declaration from Ms. Kashida, and it might make -- that might make sense why she didn't have the documents because in her order, she just said if Ms. Kashida's declaration falls within the Bates range of the documents, you know, then I find it privileged. But she didn't have the documents in front of her, you're correct.

She did have the portions of the unredacted transcript, which I believe conveyed the -- some of the information that was redacted, but it did not -- she did not have the full, you know -- she did not have the full context for the documents, because at that time, we didn't have certified translations or an agreement with plaintiffs on that, and if we had been allowed to conduct full briefing in front of Judge Williams, we would have been happy to have provided it to her at that time. But we weren't and, you know, she issued her decision and so here we are.

THE COURT: All right. As to the transcript, are you seeking that I should inspect it in camera, the unredacted transcript of the deposition?

MS. DAUGHTREY: Well, yes, you can review the unredacted transcript, which I believe is part of the briefing to Magistrate Judge Williams. But it would give you context to view that in addition to the DTXs. They are on our DTX

list. I have copies of them here. I can hand them up to Your Honor. They are redacted, but viewing, I think, Mr. Sawa's testimony about these documents, Ms. Kashida's declaration, which I believe Your Honor already has, and the documents, it would be an easy task for Your Honor to review them in camera and make a decision on this.

THE COURT: Because the redactions in the -- in the documents are what was read into the record of the deposition, at least most of them, I guess?

MS. DAUGHTREY: I believe it's partially or all of it, yes, that's correct.

THE COURT: Now I know the existence of that, but I've not inspected it, because I didn't think it would be appropriate in reviewing something that wasn't inspected below. I think one of the arguments or one of the issues today is, that you've raised is, whether it was an abuse of discretion for the Magistrate Judge not to have inspected the documents that you presented. So I've not inspected them. I'm putting myself into the position that existed at that time in determining, with the appropriate standard of review, whether Judge Williams erred.

MS. DAUGHTREY: Yes, we understand. And like I said, we requested her to review these in camera and she declined and asked for the declaration and then issued her order without reviewing the documents.

THE COURT: Now, is that within the Judge's discretion to obtain a sworn statement from the -- the attorney with actual knowledge of the communication?

MS. DAUGHTREY: Your Honor, I think in a lot of these cases, a declaration from an attorney or the recipient of legal advice is used to establish the privilege. However, in this case, the scientific reports at issue, they're not a communication between Ms. Kashida and Mr. Sawa, they are a report authored by Mr. Sawa. There's no evidence and I don't think plaintiffs have made any evidence that this report was ever forwarded to an attorney or anyone in the legal department, and it's a scientific report, and so while Ms. Kashida may very well be able to say that she provided certain factual information to Mr. Sawa, she cannot -- she did not establish in her declaration that Mr. Sawa didn't also obtain that information from a nonlawyer or, you know, any number of people, and unfortunately, at his deposition, Mr. Sawa was completely unable to recall really anything about these statements, and so given that, we really can't determine, plaintiffs haven't demonstrated what the source, the true source of the information is in Mr. Sawa's scientific report. From our view of the case law, it just doesn't satisfy the standards for privilege.

THE COURT: Was Sawa asked whether he communicated with the attorney?

MS. DAUGHTREY: No, and I can -- well, I think you already have the transcript. He was asked, did you write this document? Yes. Is that your signature? Yes. Do you recognize it? Yes.

When asked about the specific contested statements, he didn't recall why he wrote it. He was asked if he had any reason to disagree with the statements and he said, I don't know, and at that time, as Your Honor will recall, there was no allegation that the information was privileged at all and so we wouldn't have had a reason to probe whether that information came from an attorney.

It was only -- I think it was close to an hour later that the documents were clawed back, and at that point, it was under the claim of privilege, without any explanation further. And then I think it was six weeks later that plaintiff first stated that the alleged privileged information came from Ms. Kashida and she was present at the entire deposition when all of this questioning occurred.

THE COURT: And so neither party really staked out Sawa's factual testimony about whether he did or didn't confer with the attorney?

MS. DAUGHTREY: No, and I mean, he couldn't recall the specific statements, so I would -- I think that establishes that he didn't know where the information came from. But we were never -- we did not specifically ask him,

you know, did this statement come from an attorney or specifically Ms. Kashida or someone else. We didn't -- at the time, we didn't think that they would be claiming privilege over it because it had been produced and questions had been asked about it.

THE COURT: Is there a reason that Judge Williams should not have trusted the certification from Ms. Kashida?

MS. DAUGHTREY: So if you look at the certification from Ms. Kashida, it -- really, there's one paragraph that's two sentences that deals with this specific document at issue, and she says that -- do you have a copy of it, Your Honor? Would you like me to pass one up?

THE COURT: I do. It's Exhibit D to the -- to the February 25th submission. I have it.

MS. DAUGHTREY: Okay. So if you see in Paragraph 4, she says: I provided Shirou Sawa, a researcher, with certain legal advice which was redacted from these two scientific reports for the purposes of submitting -- and the project -- that's the project name on these scientific reports for planning documents and summary reports.

Now, even if we assume that Ms. Kashida recalls from ten years ago telling Mr. Sawa the allegedly privileged information, that doesn't mean that the only source of the information was from an attorney and therefore privileged. Mr. Sawa could have learned this information from anyone, any

number of people, and more importantly here, Your Honor, the information is purely factual business information and the case law is quite clear that even if you're getting information from an attorney, it isn't privileged if it relates to, you know, business strategies or commercial aspects. And, you know, and if Your Honor would conduct an in-camera review, I think it would be immediately apparent that this is business as opposed to legal advice.

And as a further point, even assuming what Ms. Kashida says is true and accurate, facts obtained from a third party that you then convey to your client is not protected by the privilege unless you're, you know, providing further legal analysis of it.

And I know plaintiff in their briefing, apparently maybe recognizing that this issue of normal attorney/client privilege does not apply, have asserted that the common interest privilege would apply. But as you can see from Ms. Kashida's declaration, she doesn't say that she received this information as part of a joint or common interest with ISDA, an attorney at ISDA. She doesn't talk about that at all and so -- and that's required for the common interest privilege to apply, and furthermore the common interest privilege does not apply if it's the conveyance of commercial information.

THE COURT: Her declaration doesn't mention ISDA at

all, does it?

MS. DAUGHTREY: It does not.

THE COURT: And she was a Senju Pharmaceutical legal department attorney?

MS. DAUGHTREY: That's correct. And the redacted portions of the documents, and I can hand them to Your Honor, around them, it talks about that this is related to ISDA's stability testing or, you know, testing of a product obtained from ISDA. The context of the document makes it clear that this is something -- the unredacted portions of the document make it clear that this is something related to ISDA, which is a third party.

So, Your Honor, really, it boils down to, from the defendant's point of view, Ms. Kashida possibly received business information from a third party, told it to Mr. Sawa. Who knows if anyone else told it to Mr. Sawa. He put it in a scientific report and that's just not privileged. That's factual commercial information.

And I think, Your Honor, particularly relevant here, the Union Carbide case which we've cited in our briefing, there's a sentence -- couple sentences in there, and this is on Page 1047 of the *Union Carbide v Dow Chemical* case which is 619 F. Supp. 1036, and that's a District of Delaware case.

The Court said: The application of privilege in patent litigation represents particular problems. Often patent

attorneys perform not only the legal functions of preparing and prosecuting patent applications, but evaluate the business ramifications of the company's patent position, as well. And the Court goes on to say: The latter, it's just not privileged. It's business ramifications.

It might, you know, be cloaked in the idea that has some legal aspect to it, but it's ultimately factual business information from a third party in this case.

THE COURT: All right. I don't think I have any other questions at this time.

MS. DAUGHTREY: Thank you, Your Honor.

THE COURT: Thank you. Mr. Lipsey?

MR. LIPSEY: Sure, Your Honor. I mean, the fact of the matter is that there was a procedure set forth for dealing with this, there was plenty of time to deal with it. There was a lot of paper exchanged. If they had wanted to put something more before the Magistrate Judge, they could have done that. They chose not to. And unless we are down to the point that the Magistrate Judge must always conduct an in-camera review, the procedure which she followed is one that is reasonably commonly followed in the circumstances of asking for a declaration from the legal representative involved, and it was provided, and the statement was made that the section that was redacted embodied legal advice that had been given to Mr. Sawa.

THE COURT: Well, were the defendants really free to send whatever they wanted to the Magistrate Judge? You've raised objections that the defendants violated the discovery confidentiality order by using what they did.

MR. LIPSEY: They could have sent the unredacted document, which they did not do. At least, I didn't see it in the pleadings.

THE COURT: The unredacted document is what you are claiming privilege for in --

MR. LIPSEY: Oh, I misspoke. I misspoke. They could have sent the redacted document. They did not is my understanding. I think the only thing --

THE COURT: But they say the translation didn't exist at that time.

MR. LIPSEY: I'm told they had -- they had a translation of the deposition. We did not, is my understanding, thus, the confusion over what was in the document, which was then promptly clawed back.

THE COURT: Now, you're the party asserting the privilege, of course. Do you agree that you have the burden of establishing the privilege?

MR. LIPSEY: I think I have the burden of establishing it within reason. I think I do not have the burden of proving the negative and excluding all other possible sources for the information. We have here a

declaration from the involved legal professional, that the material that's in there embodied legal advice that she had given. The document in which it appears, while it is a technical report, it appears in the introduction of a sort where material relating to matters that are not specifically scientific that are embodied in the report might well appear.

And short of standing up here and telling you what's in the redacted portion, which, A, I can't do because we don't want to waive the privilege and, B, as a matter of principle, I think that what they really want you to do is they just want you to read the document. This is not a circumstance in which they really have a quarrel with the claim of privilege or what's been said about it.

They had it, they saw it and they want Your Honor to see it and they've done --

THE COURT: Well, isn't that something that should give me pause? This is an unusual circumstance. They had the document for six months. They prepared to examine on it. There was no attorney/client privilege asserted at the deposition, as far as I'm aware.

MR. LIPSEY: I think we clawed it back immediately.

THE COURT: It was clawed back based on privilege, right?

MR. LIPSEY: Correct.

THE COURT: I don't know that it was announced that

this is attorney/client privileged information that they could have then asked Mr. Sawa about.

It became the basis of the clawback, I believe.

MR. LIPSEY: I was not at the deposition. I understand from my colleagues, that that was the basis on which they clawed the document back.

MS. DAUGHTREY: Your Honor, I think -- I think Mr. Margolis was taking the deposition. He asked Mr. Hasford what is the basis for the privilege. Mr. Hasford said, privilege, I'm not going to explain it anymore. So we had no way to move forward and probe that and they had clawed the document back at that point and asked us to immediately destroy all copies.

So we wouldn't have been able to go through this process and establish with Mr. Sawa, and plaintiffs could have submitted a declaration from Mr. Sawa if there would have been any evidence to support their claim here.

MR. LIPSEY: They already got the testimony from Mr. Sawa that he didn't recall the event. There isn't any testimony from Mr. Sawa. They know that.

THE COURT: So there's no support from Mr. Sawa for the proposition that this is privileged. Is that --

MR. LIPSEY: There is no recollection of Mr. Sawa. There is -- it is in a place in the document where a communication from counsel in an otherwise technical document

might reasonably appear. It has been sworn by the Japanese benrishi that it, in fact, embodies legal advice that she did, in fact, give and it -- short of having an in-camera inspection, I don't know what more I can say about it. And unless the Magistrate Judge was required to have conducted an in-camera inspection, which I don't believe the law requires, I don't think -- I guess -- let me just briefly touch on some things that were said several times in the papers.

And that is, they say they want this because it undermines plaintiff's contentions that the patents-in-suit were developed to make needed improvements on its prior formulations. The document in question is dated in 2006. The patent application was filed fully and completely in January of 2003. It doesn't even bare on why the work was done that's in the patent that was done much earlier and filed much earlier.

So I have no doubt that they want to use it. I -- I don't believe there's been established any basis for reversing the Magistrate Judge here. The procedure that was used is the one that is customarily used, or at least not infrequently used, and we would ask Your Honor to affirm the Magistrate Judge.

THE COURT: And so, are you -- are you arguing that the document itself is irrelevant, and that should end the -- end the inquiry? Because it comes after the formulation of

the -- after the application for the '431 patent?

MR. LIPSEY: I am arguing that in addition to the fact that an adequate demonstration of privilege was made. In other words, it cannot, because of its sequence in timing and as they say, its subject matter relate to what the purpose of the work that was embodied in the patent was.

THE COURT: And also Ms. Kashida did not come on board until 2006, and so I assume that it's not based upon her prior experience with the earlier application.

MR. LIPSEY: Correct, Your Honor, she --

THE COURT: Now, should I accept her conclusion or should Judge Williams have accepted her conclusion that this is legal advice as opposed to business chatter?

MR. LIPSEY: I believe it was within the discretion of the trial Judge to accept that. Not trial Judge, the Magistrate to accept that. And unless, as we say, it is to be a matter of routine that the Magistrate Judge is required to conduct an in-camera review, I think that we need to -- to honor that discretion.

THE COURT: Normally, this would be a very easy call for me, and I would tend to agree with you. There are different ways of handling such a privilege dispute. What gives me pause here is that the defendants actually know the contents and they're characterizing it as business information, and they're saying that if it had been inspected,

it would have become obvious that it was business information, that there's not some legal issue that this scientist, Mr. Sawa, is addressing. It's not authored by a lawyer, but rather, it's in his scientific report.

MR. LIPSEY: Your Honor, I have wrestled since you announced you wanted to discuss this, with how I can communicate to you some information about the nature of the communication without being accused of waiving the privilege, and without my own statement being offered into evidence against my client. I can't think of a way to do that, other than to say that -- that the text does reference patent matters, as the benrishi said.

THE COURT: Well, patents are also part of the business, aren't they? How much are we going to spend to develop, you know, further research or how much -- how much effort are we going to put into this particular product line where we have Patents A, B and C. Those are business decisions, aren't they?

MR. LIPSEY: I think I can fairly tell you without waiving the privilege, because I can tell you what's not in there and there's nothing about money in there. There's nothing about expense. Hypothetically, as you've given me a hypothetical, hypothetically, if a lawyer were to opine about what was covered by a patent, that would be legal advice. If the lawyer were to opine about what's covered by a pending

application, that would be legal advice.

These are things that patent lawyers would legitimately communicate to their -- their clients, and the fact that Mr. Sawa didn't recall where the information came from doesn't change it from being the kind of information in my hypothetical -- well, in the hypothetical, that's the sort of thing that might well be included in things like that. There are lots of explanations for this document that are benign. I'm not suggesting, and I understand Your Honor's point, you know, that sometimes, there is a, you know, a commingling of things that are clearly patent and a commingling of things that you could argue are more strategic. When they are inextricably intertwined, the privilege attaches, and all I can do by way of hypothetical is to say that there are situations of that nature where the privilege would properly apply, as described by the witness.

THE COURT: Well, I do feel a little left out because everybody in this courtroom but me knows what it says.

(Laughter.)

THE COURT: It's hard to decide this, imagining what it might say when your adversaries, who are honorable attorneys that said they've read it, it was in their hands for six months and they're characterizing it one way and you're characterizing it a different way, and I'm reviewing a decision of a Judge who didn't read it.

MR. LIPSEY: I mean, if I may, Your Honor, my understanding of what happens when there's been an inadvertent production, is the proceeding is supposed to proceed as if nobody had seen it. Because frankly, using what you have learned from what you saw in order to gain access to it is improper. And some of these statements skate perilously close to the line. So I think for that reason, it should not be treated as a special situation. It should be treated as a garden-variety situation where a dispute has arisen and that the Magistrate has taken steps that the Magistrate deemed appropriate for ascertaining the applicability of the privilege, and that the Magistrate's discretion in that regard should be sustained.

THE COURT: I assume there's no dispute by either side that a benrishi legal advice is subject to the same protection as if she were an attorney and that the choice of law here is U.S. laws of attorney/client privilege and not Japanese law?

MR. LIPSEY: I believe the *East Side* case dealt with the fact that there is a privilege recognized for benrishi in Japan and that the U.S. law is that such privileges are recognized. Excuse me.

THE COURT: Do you agree, Ms. Daughtrey?

MS. DAUGHTREY: I agree, if the privilege meets all of the other requirements, for example, if it's not factual,

business information, if it was a communication between the attorney and the client and if it wasn't just a third party's recitation of facts to a benrishi who then tells it to a scientist.

THE COURT: If Ms. Kashida's certification is held up to the -- to those standards, is there an element that's missing?

MS. DAUGHTREY: Yes. Well, you can see on their face, Your Honor, that it's not an e-mail between Ms. Kashida and Mr. Sawa, and I think when you alluded to the fact that this is an unusual situation, that's what you meant. Most of the time attorney/client privilege is claimed, it's a communication between an attorney and a client. And here, this is a scientific report that Mr. Sawa offered. There's no evidence that, you know, it was drafted by Ms. Kashida or Mr. Sawa sent it to Ms. Kashida. It's just his document and so their only claim of privilege really rests on that this redaction -- redacted information came from Ms. Kashida, and that that's the communication.

But in circumstances such as that, the case law has held, there's kind of a higher standard for demonstrating that it's an attorney/client communication and you have to demonstrate that the communication from the attorney to the client would not have occurred but for the need for the client to obtain legal advice. And you don't see anything in Ms.

Kashida's declaration about that.

And I can tell you the case law that discusses that issue, if you'd like, it's the *HPD v. Clorox* case, 202 FRD 410 414. That's a District of New Jersey case. And so, you know, I think Your Honor, while an in-camera review may not always be necessary, in a unique circumstance such as this where there's no objective indicia -- I hate to use that word in a patent case -- but there's no indicia on the face of the document that it's privileged, and the parties contest it, like you said, defendants characterize this as factual information, plaintiffs argue Ms. Kashida's statement that it is legal advice. In-camera review would be wholly appropriate and very easy to resolve the dispute.

And in terms of the in-camera review, the matter of *Grand Jury* 603 F. 2d. 469 is a Third Circuit case, 1979 -- oh, I'm sorry, I misstated that, it's *United Coal v. Powell*, 839 F. 2d. 958 Third Circuit 1987.

The Court stated the proper procedure when there's a dispute such as this regarding privilege is in-camera inspection.

MR. LIPSEY: That is too slippery a slope, Your Honor. The fact of the matter is, we have sworn testimony that the statement embodies legal advice from a company lawyer to a company employee. It is embodied in the writing of the company employee which went at least to his director of

applied R and D laboratory, who is also a signatory on the document. The conduit theory makes quite clear that the, you know, communication of legal advice from one person personifying the client to another personifying the client is a perfectly legitimate thing to do.

The Third Circuit case *In Re Teleglobe* that we cited, I think makes clear that the privilege applies to any communication that satisfies the following elements. It must be a communication made between privileged persons in confidence for the purpose of obtaining and providing legal assistance for the client, and it is described as such by Ms. Kashida and the idea that it is then embodied in a report that goes at least to Mr. Sawa's supervisor does not cause it not to be privileged. There is nothing suspicious about that transaction.

THE COURT: I assume Mr. Sawa doesn't say in the redacted information: A lawyer told me that, da-da, da-da...

MR. LIPSEY: I can tell you without waiving a privilege that it doesn't say that. I can tell you that it is the type of information that routinely comes from patent lawyers.

MS. DAUGHTREY: And, Your Honor, information that is publicly available, even if it's conveyed by an attorney would not be privileged. And so even in a hypothetical situation that Mr. Lipsey is referring to, if the information is

otherwise publicly available, it wouldn't be privileged.

For example, if -- for example, if an attorney told someone that a package insert, you know, document reflected that that product was covered by a certain patent, well, the package insert is publicly available, so you wouldn't be able to shield that information by having an attorney convey those facts.

MR. LIPSEY: If it's publicly available --

THE COURT: But if -- if you're aware of public information that covers this same ground, why don't you just use that and you can forget about penetrating the privilege?

MS. DAUGHTREY: So it's my understanding that their claim of privilege partially relates to public information. Not all of -- not all of the redacted information is public, but I think their claim of privilege relates to information from a third party that was publicly available, and they're trying to protect their business motivations for some of their research and development.

MR. LIPSEY: Six years after -- three years after the patent was filed. The argument is, it's relevant to why the invention was made. A document that's written three years later cannot possibly bear on that issue.

MS. DAUGHTREY: Your Honor, I think you'd agree that you can memorialize later motivations from previously. So -- and it would also be relevant to secondary considerations

which can be past the priority date here.

THE COURT: All right. I don't want the dispute to drag on throughout the trial, because if the information is discoverable, this is the time to make that decision. I think under the circumstances, that in order to properly determine the appeal, I should make an in-camera inspection of the documents, that is, of the reports with the Bates numbers, which I don't have, and of the unredacted transcript, which is part of the sealed record and which I can have access to.

The reason that I'm saying that and why I'm not persuaded at the moment, that for closing the -- or refusing the in-camera inspection is proper, is the following: The circumstances that are known don't -- they comprise a thin record. The party that seeks to protect the attorney/client privilege has almost no facts that would support it, other than the benrishi certification. Her certification doesn't contain facts. It doesn't really say when she had this communication, who she communicated to, and it also characterizes her communication as legal advice without giving a context or an explanation for why it was legal advice, other than that she is the patent attorney. But I don't want to sell short this certification.

MR. LIPSEY: May I suggest, Your Honor, if that's the procedure to be followed, that maybe the appropriate thing is for us to scamper over to the Magistrate Judge and let her do

it, just because the consequence, if she concludes it's privileged, as Your Honor knows as they always say in these cases, there's no way to unring the bell, and Your Honor is the trial Judge.

MS. DAUGHTREY: Your Honor, given the timing, where we are right now, I think it would be quite easy, and I'm sure Your Honor would be able to give -- firewall any information that he sees, that the other -- even if he decides against the defendants and that really, you know, I haven't seen any Third Circuit law or anywhere saying that in-camera review is not appropriate just because you're, you know, the Judge, you know, deciding this matter at this time. I think we could short-circuit all of this.

THE COURT: That's correct. I have to rule all the time on what's admissible and what's not and see that evidence even if it's not admissible.

I think because we're well into the trial that remanding it for *in camera* inspection with the prospect of a subsequent appeal by either side as to the result of that, we just don't have time for it, unfortunately.

MR. LIPSEY: That's fair enough, your Honor.

THE COURT: Okay. And so why don't we make a record of what it is that you're asking me to -- show it to Mr. Lipsey first and make sure that he agrees that this --

MS. DAUGHTRY: Well, we don't have -- we destroyed

all the unredacted copies. You mean the redacted Bates numbers?

THE COURT: Actually, I need the unredacted Bates numbers.

MS. DAUGHTRY: We requested --

THE COURT: Are you saying I don't, because if I take what you're giving me and review the unredacted transcript, that I'll have the information about what's been redacted?

MS. DAUGHTRY: I think it would be easier, your Honor, if you just take the unredacted scientific reports that are the subject of the dispute. And plaintiffs have it. We actually asked them to bring it a couple days ago and they said -- they have never responded. But they could just give that to your Honor and that would be -- I can go over the Bates just to confirm with Mr. Lipsey these are the correct Bates numbers because the redacted version has the same Bates as the originals, it just has an R at the end. So --

THE COURT: All right. Is that acceptable, Mr. Lipsey? Do you have the unredacted versions?

MR. LIPSEY: I think I do. I know what I have -- do I have the unredacted ones?

MS. DAUGHTRY: If you'd like me to, I can read into the record and show Mr. Lipsey the pages I'm referring to.

So this is defendant's exhibit list 32 and the Bates numbers are PROL 0075077 through PROL 0075088, that's one of

the documents.

And the other document is DTX-031 and the Bates on that are PROL 0075073 through PROL 0075076.

Does that sound right?

MR. LIPSEY: Those sound like the right numbers, your Honor.

THE COURT: So I guess what I'm requesting is those documents in unredacted form that I would receive *in camera* and retain under seal and inspect hopefully overnight. And then if there's a need for further argument, I'll ask you, and, otherwise, I'll rule in due course probably tomorrow.

MS. DAUGHTRY: Thank you, your Honor.

MR. LIPSEY: Your Honor, what I do have in my hand are the redacted copies and I have individual copies of the two redacted pages so that the two together will constitute the unredacted document if that facilitates your Honor's review more promptly.

THE COURT: Okay. As long as it adds up to what I mentioned.

MS. DAUGHTRY: Well, your Honor, I just want to make sure I understand. So what they produced to us ultimately was a certified translation with a redaction box over it, so we've never seen what they're certified translation of the unredacted information is. And I think, if I understand Mr. Lipsey right, he'll be -- I think it would make more sense

for you to review the entire document so you can have context what's contained within it in addition to just the redacted page. So if they have this English, you know, translation just with the redacted box removed and if we could -- well, we can't see it so I hope their translation is good. So that would be fine if they gave you the entire document.

MR. LIPSEY: If I can take just a minute, I might be able to do that.

THE COURT: Okay. Thank you, sir.

MR. LIPSEY: Okay. I assume it will be sufficient to provide the translation without the Japanese document.

MS. DAUGHTRY: Unless your Honor speaks Japanese, I think that's fine.

And would your Honor also like the unredacted transcript, or can your Honor get that?

THE COURT: I have that.

MS. DAUGHTRY: Okay.

THE COURT: That's filed under seal with the Court.

MS. DAUGHTRY: Okay. Great.

MR. LIPSEY: Your Honor, I have copies of the unredacted translation of the document PROL 0075073 through 76 and of PROL 0075077 through 88, will that suffice?

THE COURT: Okay. Very well. If you can --

MR. LIPSEY: Would you like me to mark the things that have been redacted?

07:58 THE COURT: Yeah, that's right, how else would I --
07:58 MS. DAUGHTRY: I can give you a copy of the redacted
07:58 version.
07:58 MR. LIPSEY: I have that as well. I have it as well.
07:58 THE COURT: Mr. Lipsey, I'll ask you to mark what
07:58 you're giving me, the unredacted versions, as Exhibit C-1 and
07:58 C-2 just to make a record of what I'm receiving under Court
07:58 Exhibit 1 and 2.
07:58 MR. LIPSEY: I'll just write C-1.
07:59 THE COURT: C-1 and perhaps add today's date, which
07:59 is April 5th, and mark the second one C-2.
07:59 MS. DAUGHTRY: Can you tell me which ones you're
07:59 marking as well?
07:59 MR. LIPSEY: I'm marking the one ending 073 as C-2
07:59 and the one ending 077 C-1.
07:59 MS. DAUGHTRY: Thank you.
07:59 MR. LIPSEY: And the redacted versions bear
07:59 production exhibits DTX-032 and DTX-031. And I will hand
07:59 those four copies to the Court.
07:59 THE COURT: Okay. Very good.
07:59 MR. LIPSEY: And I will be happy to answer any
08:00 questions your Honor may have as to the nature of the patent
08:00 question if and when the time comes.
08:00 THE COURT: Okay. Very well. So with that, I'll
08:00 close this hearing. I'll reserve decision on the appeal.

08:00 And is there anything else for this evening?
08:00 MR. LIPSEY: Not for us, your Honor.
08:00 MS. DAUGHTRY: Not for defendants, your Honor.
08:00 THE COURT: Thank you very much. We're adjourned
08:00 until tomorrow morning at 9:30.
08:00 MR. LIPSEY: Thank you.
08:00 (Proceedings Concluded)

B

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-667 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-4149 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

Mitchell H. Cohen United States Courthouse
One John F. Gerry Plaza
Camden, New Jersey 08101
Wednesday, April 6, 2016

B E F O R E: THE HONORABLE JEROME B. SIMANDLE
CHIEF JUDGE
UNITED STATES DISTRICT JUDGE

Certified as true and correct as required by Title 28, U.S.C., Section 753.
/S/ Lisa Marcus, CCR, CRR, /S/ Karen Friedlander, CCR, CRR, /S/ Robert T. Tate, CCR, CRR, /S/ Carol Farrell, CCR, CRR

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-5144 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-335 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-5144 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-335 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-6893 (JBS/KMW)

-vs-

INNOPHARMA LICENSING, INC., et al.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-3240 (JBS/KMW)

-vs-

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INDEX

EXHIBITS

DEPUTY CLERK: All rise.

THE COURT: Be seated, please.

Okay. Good morning, everybody.

Before we resume our witness, I just wanted to at least announce my decision with regard to the appeal from Judge Williams' determination regarding attorney/client privilege. And when we have time, I'll place the oral Opinion upon the record.

But the summary is simply that I conducted the *in camera* inspection of the documents. I found that the attorney/client privilege does apply to the excerpts that had been redacted and so the claim of attorney/client privilege is being sustained. I find that it contains legal advice from the benrishi which was given for purposes of legal advice upon the patent itself, and which was being transmitted internally. And so, therefore, it's protected as the memorialization of an attorney/client communication rather than mere business advice that happens to come from an attorney.

And so for these reasons I agree with the finding below that the privilege applies but have undertaken and have the benefit of the *in camera* review and also the additional legal research. And I'll enter a written Order to this effect.

Are there any questions?

MR. DINER: None from plaintiffs, your Honor.

THE COURT: All right. And I thank counsel for your

hard work on both sides on this issue.

Good morning. Are we ready to proceed?

MR. DINER: Yes, your Honor.

THE COURT: Okay.

00:20 MR. DINER: May it please the Court, your Honor, I would like to approach the bench, I have some demonstrative slides I would like to present to the witness and Court.

THE COURT: Yes.

(**STEPHEN G. DAVIES,** HAVING BEEN PREVIOUSLY SWORN AS A WITNESS, TESTIFIED AS FOLLOWS:)

(DIRECT EXAMINATION OF STEPHEN G. DAVIES BY MR. DINER:)

Q. Good morning, Dr. Davies.

A. Good morning.

Q. Do you recall yesterday when we concluded for the day we

00:21 were talking hydrogen bonding?

A. Yes.

Q. Okay. I would like to transition into the impact and effect of hydrogen bonding on the NSAIDS that are the subject of this case. Let's start with bromfenac and diclofenac.

00:21 Do you have an opinion as to whether bromfenac and diclofenac are structurally dissimilar?

A. They have a different set of functional groups that are dispersed differently around the molecule and they have different interactions of those functional groups, so they are

00:21 **dissimilar molecules.**

Q. And have you prepared a demonstrative to assist the Court in your testimony in this regard?

A. I have, yes.

Q. Will you take a look at PDX3-2 and can you please explain

00:22 how this demonstrative shows the structural differences between bromfenac and diclofenac.

A. So what I've shown on this demonstrative is the chemical structure in two dimensions of bromfenac on the left and diclofenac on the right and I've shown the functional groups

00:22 **as shown by the letters.**

So bromfenac on the left has a primary amine group, which is the nitrogen, the N, bonded to two hydrogens, so it's the NH_2 group. Whereas diclofenac has a secondary amine that is a nitrogen bonded to just one hydrogen.

00:22 **Bromfenac has a 4-bromobenzoyl group, which is this bromine here, that's the whole unit there, including the carbonyl oxygen, is the 4-bromobenzoyl group and it's attached adjacent to the NH_2, whereas diclofenac has a 2,5-dichlorophenyl, which is this unit here, the Cl's are the**

00:23 **chlorine. The phenyl is the six membered ring with the two chlorine atoms attached, and that is attached directly to the NH group.**

And as we can see, the bromfenac has the carbonyl, that's a carbon with a double bump to the oxygen, a carbonyl

00:23 **group, whereas diclofenac does not have such a group.**

Q. So these structural differences that you've just pointed out, how would they impact the chemical or functional properties of the compounds?

A. The chemical and functional properties of any compound

00:24 **depends on all the functional groups, how they interact with one another, how they interact in the environment in which they are.**

Q. Have you prepared a demonstrative to assist the Court in this regard?

00:24 **A. I have, yes.**

Q. Could we go to PDX3-3?

A. What I've shown on this demonstrative the same structures of bromfenac and diclofenac and I've highlighted by putting them inside red circles the functional groups that will form

00:24 **strong hydrogen bonds to water as a solvent. Both of the compounds have a carboxylic acid at the pH we're dealing with in ophthalmic preparations, these will be ionized to a carboxylate anion but they'll be the same, they'll both be strongly hydrogen bonded.**

00:25 **But bromfenac, in addition to that, has an NH_2, as we saw yesterday, that will strongly hydrogen bond to water, and the carbonyl group that will also strongly hydrogen bond to water. Whereas diclofenac only has one NH group, the secondary amine that can hydrogen bond in addition to the**

00:25 **carboxylate to water.**

Q. And what is the implication of the hydrogen bonding, as you've described here, to the NSAIDS solvation in an aqueous formation?

A. Well, there're more hydrogen bonds so the molecule, the

00:25 **more strong hydrogen bonds in particular, that any molecule or anion can form to water as the solvent the stronger the solvation will be and the more stable that anion will be in solution.**

Q. And what impact will it have on the solubility of that

00:25 product in solution?

A. Well, it will mean that any salts that are formed -- could be formed of these anions, the more solvated the anion, the more soluble the salt will be, the less likely it will be to precipitate.

00:26 Q. And does bromfenac have more hydrogen bonding sites than diclofenac?

A. As you can see from where I placed the red balls, bromfenac has more hydrogen bonds, strong hydrogen bonding sites than diclofenac.

00:26 Q. And would one of ordinary skill in the art understand that that would make bromfenac more soluble than diclofenac?

A. They would expect that to be the result, yes.

Q. And would bromfenac's better solubility impact -- or how would bromfenac's better solubility impact whether bromfenac

00:26 would precipitate with the cation in solution and come out of

solution?

A. If it's more -- if the anion is more solvated, then it will be less likely to precipitate out of solution with any cation.

Q. And as between bromfenac on the one hand and diclofenac on the other hand, what would one of ordinary skill in the art expect about whether bromfenac would precipitate out of solution by interacting with the cation compared to diclofenac?

A. They would expect the bromfenac salt -- bromfenac salts to be less likely to precipitate out than diclofenac salts.

Q. Okay. Dr. Davies, can you turn to JTX-210 in your binder and identify that document, please?

A. This is New Drugs in Japan 2001.

Q. Okay. Now, let me direct your attention to Page 6 of JTX-210.

A. Okay.

Q. You there?

What's the structure that is illustrated in the left-hand column on Page 6 of JTX-210?

A. It's the sodium salt of bromfenac as a half hydrate.

Q. And would you be so kind to read into the record the text just below the formula for bromfenac all the way down to, but before the word "packaging."

A. It says, "Properties: Bromfenac Sodium Hydrate is an

odorless crystalline powder of yellow-orange color. It is freely soluble in water, soluble in methanol, slightly soluble in ethanol anhydride, and practically insoluble in acetonitrile or ether."

Q. And would one of ordinary skill in the art in view of this passage in JTX-210 understand that bromfenac was freely soluble in water?

A. Absolutely. That's what it says so that's what it means.

Q. Okay. In generating PDX3-3 did you use information for the summary that you presented in those slides from PTX-187, PTX-180, PTX-193, PTX-321, and PTX-188?

A. I did, yes.

Q. Okay. Dr. Davies, have you had an opportunity to consider the structural differences between bromfenac and ketorolac?

A. I have, yes.

Q. And have you prepared a demonstrative to assist the Court in your testimony in this regard?

A. I have, yes.

Q. Can we turn then to PDX3-4. And can you describe how this demonstrative illustrates the differences between bromfenac and ketorolac?

A. So again, I've drawn the structure of bromfenac in two dimensions on the left-hand side and the structure of ketorolac in two dimensions on the right-hand side. And I put

in the functional groups. And what we see the bromfenac has a primary amine group, that is this NH_2 group, whereas ketorolac has a tertiary amine, no hydrogens on that nitrogen.

Bromfenac has a 4-bromobenzoyl group, which is this unit here, attached to the -- adjacent to the NH_2, whereas ketorolac has a simple benzoyl group on the aromatic pyrrole ring, which is this five membered ring here.

Bromfenac is an aniline, so aniline is this NH_2 attached to the phenyl ring, six membered ring with three carbon carbon double bonds, whereas ketorolac does not have that grouping.

Q. And would one skilled in the art expect that these structural differences that you just pointed out would impact the functional chemical properties of bromfenac versus ketorolac?

A. The functional properties of any molecule depends on the number and distribution of the functional groups and heteroatoms within the molecule.

Q. Have you prepared a slide -- a demonstrative to support your opinion in this regard?

A. I have, yes.

Q. If we can go to PDX3-5. Can you explain how this demonstrative supports your opinion?

A. So what I have shown, again, here is the structures of bromfenac and ketorolac, ketorolac on the right. And I've

highlighted the groups, the functional groups that will form strong hydrogen bonds in red circles. And bromfenac, as before, has the carboxylate, I've drawn it as a carboxylic acid but in solution it would be the carboxylate ion, the carboxylate ion, which can hydrogen bond strongly to water. It has the NH_2 and that can strongly hydrogen bond to water. It has the carbonyl oxygen that can strongly hydrogen bond to water.

Ketorolac has the carboxylate group but only a carbonyl group on the left in the red circle that can also hydrogen bond to water.

Q. And how, if at all, do these differences in hydrogen bonding sites impact how bromfenac would behave in solution compared to ketorolac?

A. Well, the more strongly hydrogen bonding sites the molecule or ion, anion has, the more soluble -- the more solvated it will be in solution.

Q. And would bromfenac, if it was better solvated, be expected to interact with an ion in solution and precipitate out to a lesser extent compared to ketorolac?

A. Well, that's the fault of any particular atom salts, any particular cations, because a bromfenac anion will be more solvated, it will be more likely to stay in solution and not precipitate out than the ketorolac anion.

Q. Okay. In preparing PDX3-5 did you use information from

PTX-187, PTX-180, PTX-193, PTX-321 and PTX-188?
A. **I did, yes.**
Q. Dr. Davies, have you had an opportunity to consider the structural differences as between bromfenac and flurbiprofen?
00:34 A. **I have, yes.**
Q. Have you prepared a demonstrative in this regard to assist the Court with your testimony?
A. **I have, yes.**
Q. Okay. Let's take a look at PDX3-6, and can you explain
00:34 this demonstrative for the Court, please?
A. **So again, I've drawn the structure of bromfenac in two dimensions on the left-hand side and flurbiprofen on the right-hand side. Bromfenac has a primary amine group, this NH_2 group, whereas flurbiprofen has no amino group, no**
00:35 **nitrogen atom in that molecule.**

Bromfenac has a 4-bromobenzoyl group attached adjacent to the NH_2. So this is this unit here. That's the 4-bromo. The benzoyl means there's the carbonyl group attached. Whereas flurbiprofen has a fluorine in the same position.
00:35 **Bromfenac has a phenylacetic acid derivative, that's this side chain here, whereas flurbiprofen is derived from phenylpropionic acid and has an extra methyl group attached to the carboxylic acid, which is this right here, that is the propionic acid unit as shown on the right.**
00:36 **Bromfenac has a hydrogen distal to the acetic acid**

residue, that is in this position, whereas flurbiprofen has a phenyl group, that is that phenyl group there distal to that on there. And it is a biphenyl derivative. So there's two phenyl groups attached to each, that's called a biphenyl
00:36 **group.**
Q. And would one skilled in the art expect these structural differences would impact the functional and chemical property of the NSAIDS that you're discussing on this demonstrative?
A. **As before, the functional properties and the physical**
00:36 **properties of a molecule depend on the number and distribution and type of the functional groups in any molecule or ion.**
Q. And have you prepared a demonstrative in that regard to assist the Court with your testimony?
A. **I have, yes.**
00:36 Q. So let's turn to PDX3-7. And can you explain how this demonstrative illustrates the differences in hydrogen bonding between the two molecules?
A. **So again, I've drawn bromfenac in two dimensions on the left and flurbiprofen on the right and I've highlighted again**
00:37 **the strong hydrogen bonding groups with red circles.**

Bromfenac acid or anion, anion in the case of pH's we're dealing with, has the carboxylate that can strongly hydrogen bond to water, NH_2 group, and the carboxyl group, all of which will strongly hydrogen bond to the water solvent.
00:37 **Flurbiprofen, on the other hand, only has the**

carboxylic acid or the carboxylate group that can hydrogen bond to the water solvent, has no other functional groups that will form strong hydrogen bonds to water as a solvent.
Q. And how, if at all, do the differences in hydrogen
00:37 bonding impact how bromfenac will behave in solution compared to flurbiprofen?
A. **The more strongly hydrogen bonding sites you have, the more solvated the carboxylate anion will be and the more stable it will be in solution.**
00:38 Q. And when you refer to being more stable in solution, what does that mean in terms of solubility in solution?
A. **It means that the water is bonding to this -- to the bromfenac anion strongly, it will hold it in solution, it will stop -- making it less likely for any salt to precipitate.**
00:38 **Flurbiprofen, for example, only has the carboxylate that's solvated, it's going to be more likely to precipitate from solution if you observe that effect.**
Q. Okay. If the skilled person saw a precipitation in a solution containing, for example, ketorolac, benzalkonium
00:38 chloride, and other ionic excipients, could that person draw a conclusion what the precipitate was?
A. **No, they would not be able to. So can you specify -- can you repeat the question?**
Q. Sure. If a skilled person saw a precipitation in a
00:39 solution containing, for example, the ketorolac, benzalkonium

chloride, and other ionic excipients, could that person draw a conclusion what the precipitate was?
A. **No, they would not be able to draw a conclusion.**
Q. Why not?
00:39 A. **Because the only way you can tell what a precipitate is made up of would be isolate that precipitate and do a chemical analysis on that precipitate to find what the constituents are. And if you had a solution that contains many ions, you won't get to tell what is in the precipitate until you've gone**
00:39 **done a full analysis, you can't assume anything.**
Q. Dr. Davies, in generating PDX3-7 did you use information from PTX-187, PTX-180, PTX-193, PTX-321 and PTX-188?
A. **I did, yes.**
Q. Thank you. Now, Dr. Davies, did you hear testimony
00:40 yesterday from Dr. Lawrence about various nonionic surfactants including polysorbate 80, tyloxapol, and octoxynol 40?
A. **Yes.**
Q. Are you aware that defendants here are taking the position that the nonionic surfactants polysorbate 80 and
00:40 tyloxapol could be used interchangeably in formulation and would be expected to behave similarly?
A. **I understand that's their view, yes.**
Q. Do you agree with the defendants?
A. **I do not, no.**
00:40 Q. And why not?

A. **Because those materials have very different structures and the structural properties, physical chemical properties of molecules depend on the structure and the distribution and the shape of molecules, you can't take different molecules and say** 00:41 **you can just interchange them.**

Q. Okay. Have you prepared a demonstrative in this regard to assist the Court in understanding your opinions?

A. **I have, yes.**

Q. So we now go to PDX3-8, and can you explain what this 00:41 demonstrative shows?

A. **So I've shown on the left the structure of polysorbate 80 and on the right a structure of tyloxapol. The structure of tyloxapol has the unit I've shown in between the two vertical lines, brackets, has that repeated seven times. There's not** 00:42 **room to put the whole structure on the slide but that is repeated seven times with that carbon in there. And so you can see how structurally different these molecules are.**

Q. Can I just ask you a question? You're referring to the repeating unit identified by the small N.

00:42 A. **That's correct.**

Q. Do you see that?

The hexagonal moiety, chemical moiety there, is that a phenyl group?

A. **That is a phenyl group, yes. The six membered ring with** 00:42 **the three double bonds is a phenyl group.**

Q. What is that, just for understanding purposes --

THE COURT: Excuse me --

BY MR. DINER:

Q. -- what is that line that comes up?

THE COURT: May I interrupt?

I lost which small N you're referring to.

THE WITNESS: There's two brackets, your Honor.

THE COURT: Okay.

THE WITNESS: And then there's a small N on the right 00:43 indicating that's a repeating unit. And then I've defined N underneath as N equals seven of those.

THE COURT: Very well. Thank you.

BY MR. DINER:

Q. Now, the question I have for you, Dr. Davies, is to the 00:43 right of that phenyl group in this repeating unit we're talking about, you see how that line comes up to a peak and it comes down?

A. **Yes.**

Q. What is that peak? What does that peak illustrate?

00:43 A. **That is -- whenever you see a line in organic chemistry that has no letters on it, it means that carbon atom is on each end of that line. And all of the -- carbon always has four bonds. So if you look at the left-hand end here, there's a line to the right which goes up to a carbon, that is the** 00:43 **point of the zigzag if you like, and then there are three**

other bonds, three other lines attached to it, double bond to the top left and a vertical line to the bottom, so that's three more, that's four bonds in all. Carbon likes to form four bonds. This peak here is a carbon atom with two 00:44 **hydrogens on it. There's two other bonds with carbon carbon, that we've just been talking about, to the phenyl ring. And then the line to the right going down is to another carbon here, so that's two bonds. The other two are bond to hydrogen, that's CH_2 unit, an extra carbon, if you like, or** 00:44 **HCH_2.**

Q. I think I may have interrupted you while you were going through your explanation on the chemical differences between them. Have you finished discussing the full demonstrative in terms of the differences?

00:44 A. **I was in the middle.**

Q. Okay.

A. **So what you see on the -- while we are on tyloxapol, you can see there's this octyl chain on the bottom, which has no functional groups, no heteroatoms involved in it. And then** 00:45 **you have this chain along the top which has an oxygen that is bound to the top carbon of the phenyl group and then a bond from the O to a point which is a CH_2 group, another CH_2 group, and then another oxygen. And that unit CH_2, CH_2O is in brackets because that repeats eight to ten times on each of** 00:45 **the groups, such groups in tyloxapol.**

In polysorbate 80 you have to the right-hand side this long zigzag, which is a lot of carbon atoms bound to each other, each bond to hydrogen atoms with this carbonyl group here attached to now a chain, another chain of oxygen CH_2, CH_2 00:45 **repeat units and then to this unit here, this central part, which allows three branches to come off. Again, each of those has repeating units of oxygen carbon carbon. And so there's one chain there, another chain, a second chain bottom right, and a third chain bottom left.**

00:46 **So polysorbate 80 has a long single non-polar linear tail, which is this unit here to the right, and a triply-branched polar head group, which is this unit here, this chain, this chain, this chain.**

Polysorbate 80 has three hydroxyls in its polar head 00:46 **group, one, two, and three on the end of those three branches, whereas tyloxapol has seven hydroxyls, one, this hydroxyl on the end, one on each of the seven head groups.**

In polysorbate 80 the non-polar tail consists of a hydrocarbon chain, this unit here, whereas the many tails of 00:47 **tyloxapol are a combination of aromatic rings, the phenyl group, and hydrocarbon chains, this is this group at the bottom with no functional atoms attached.**

Q. Now, does this polysorbate 80 and tyloxapol exist in three dimensions?

00:47 A. **They do, yes.**

552

Q. And have you prepared a demonstrative to explain how they appear in three dimensions to assist the Court?
A. I have, yes.
Q. Can we go to PDX3-10? And can you explain what this demonstrative shows?
A. This shows three dimensional structures of polysorbate 80 and tyloxapol to illustrate what I was explaining on the previous demonstrative.
For polysorbate 80 you see the single hydrocarbon chain in grey on the bottom. The grey colors show the CH_2 groups, there are no functional atoms in that part. This was the chain of the repeating, they're called methylene octy groups, CH_2 CH_2 O, that goes up to the head group of three branches, which is shown at the top. At the end of each of those branches is an oxygen atom which is bound to a hydrogen that is the hydroxy group. And all the way through these chains I've colored the oxygens in the repeat units, the ethyleneoxy repeat groups in red so it's easy to see.
Tyloxapol, on the other hand, has a broad based hydrocarbon unit at the bottom, again, shown in grey. And then seven of these tails that come off that have these repeat units of CH_2 CH_2 and O. And then the end of each of those, the top, is the oxygen that has a hydrogen, which is the hydroxy group, seven of them up there. So this is a very different three dimensional structure to the polysorbate 80 on the left.

553

Tyloxapol's got a completely different shape and functionality.
Q. So given the differences in two dimensions and three dimension as shown, would a person of ordinary skill in the art expect that polysorbate 80 and tyloxapol would have different chemical and functional properties?
A. They would definitely expect them to have different chemical, physical chemical, chemical properties, yes.
Q. And have you prepared a demonstrative to explain your opinions in this regard to the Court?
A. I have, yes.
Q. Can you explain what this demonstrative shows.
I'm sorry about that. Can we please turn to PDX3-9?
A. I'm there, yes.
Q. And can you explain what PDX3-9 shows?
A. This compares polysorbate 80 with tyloxapol, which are the two structures we were looking at a moment ago. The molecular weight of polysorbate 80 is 1310, whereas the molecular weight of tyloxapol is 4500. The critical micelle concentration, CMC, for polysorbate 80 is .010 millimol and the corresponding CMC for tyloxapol is .018 millimol.
Q. Dr. Davies, does a surfactant CMC impact its ability to solubilize a compound?
A. It does, yes, as does its structure. Both of those will impact on whether something will be solubilized or not.

554

Q. Let me direct your attention to PTX-181 in your binder and --
A. Okay.
Q. Before we go to PTX-181, can we return to PDX3-9.
And, Dr. Davies, in generating PDX3-9 did you use for information in preparing that PTX-181, PTX-190, JTX-199, and PTX-201?
A. I did, yes.
Q. Okay. Before we leave this demonstrative, could you explain a little bit what is meant by CMC?
A. That is the concentration of which -- above which the surfactant will produce, start to form micelles, which are aggregates of the surfactant in solution. And millimol is a thousandth of a mole, the mole being the molecular weight in a liter of water.
Q. Okay. And for the reasons you stated previously, one skilled in the art would expect the CMC to impact a surfactant's ability to solubilize a compound?
A. That's correct, yes.
Q. Now, let's go to PTX-181 in your binder. And would you please identify this document?
A. This is a book called Surfactant Systems, Their Chemistry, Pharmacology, and Biology, by Attwood and Florence from 1983.
Q. Okay. And have you reviewed PTX-181 in connection with

555

your opinions in this case?
A. I have, yes.
Q. Okay. Let me draw your attention to Page 343 of PTX-181 and in particular table 6.23(a).
A. I have it, yes.
Q. Thank you. What, if anything, does table 6.23(a) show about the differences in solubilizing ability between polysorbates?
A. Well, the table shows us the first four entries, the surfactants polysorbate 20, polysorbate 40, polysorbate 60, and polysorbate 80. And what the table is showing is how well a vitamin A palmitate is dissolved in a 20 percent aqueous solution of those surfactants and the amount that is dissolved in the right hand column under the MAC, that is the mols of vitamin per mol of surfactant. You can see very different values for those polysorbates, polysorbate 20 dissolves .15 mols of vitamin per mols of surfactant, polysorbate 40 dissolves .54, whereas polysorbate 60 .67, and polysorbate 80 .68 per mol of surfactant.
Q. And so what would the person of ordinary skill in the art glean about the differences, if any, as to the solubilizing ability of the polysorbates that you just discussed?
A. The polysorbate compounds, surfactants have different abilities to solubilize compounds, in this case salts.
Q. And what does Table 6.23(a) in PTX-181 say to the skilled

person about the predictability of activity among surfactants?

MS. HOLLAND: Objection, your Honor. That's not in the expert report.

MR. DINER: I believe it is, your Honor, at Dr. Davies' responsive report at Paragraph 64 where he discusses the Attwood textbook and the differences in solubility.

MS. HOLLAND: There's nothing about predictability, your Honor. All it says -- I can hand it up if you want. There's nothing about whether -- this would lead to any kind of predictability or not. That's not in there. That's not in the paragraph you were just pointed to.

MR. DINER: The whole discussion in this part of his expert report is with regard to the interchangeability, interchangeability implicitly is about --

MS. HOLLAND: May I hand up the report, your Honor?

THE COURT: Just a moment.

MR. DINER: It says even when there are differences in solubilizing the ability of the polysorbate that they are different and it goes into the changeability issue, and that's what is exactly in his expert report. So this is relevant about the interchangeability and the predictability of your activity is relevant to what he's testifying to now and what is in his expert report.

MS. HOLLAND: Your Honor, just so I can put a fine

point on this, he did testify -- I'm sorry. The expert report does contain some information about this table, but it's an entirely separate opinion to give about whether you can draw conclusions about predictability from the table, that's not in the expert report. The factual information about what's on the table, that's fine. Whether or not it tells somebody about predictability, that's not an opinion that's previously been offered.

MR. DINER: And, your Honor, I would disagree with that. What it says is even among polysorbates there's differences in solubilizing ability and it's in the context of the interchangeability issue that was addressed by Dr. Davies in response to Dr. Lawrence's --

THE COURT: Well, could the pending question be rephrased in terms of interchangeability? If he gave an opinion as to interchangeability, then I'll permit that. If he's not giving one as to predictability, then I have to sustain the objection. I may be able to infer one from the other, I don't know, I'm not a chemist.

MS. HOLLAND: Your Honor, just to be clear, I don't have any objection as long as the testimony is what's in the expert report, so...

MR. DINER: I'll rephrase the question, Your Honor.

THE COURT: Very well.

BY MR. DINER:

Q. So, Dr. Davies, based on the information that is in Table 6.23A, would a person of ordinary skill in the art expect that these differences would lead to significant different functional and chemical properties with regard to the ability of the polysorbates to solubilize other compounds?

A. Yes, you can see that they have -- they are having a different effect in their solubilizing ability on this -- in this example.

Q. Now, Dr. Davies, do you have an opinion as to the structural differences between Octoxynol 9, Octoxynol 40 and tyloxapol?

A. I do, yes.

Q. And have you prepared a demonstrative in this regard to assist the Court with your opinion?

A. I have.

Q. Now, let's turn to PT -- PDX 3-11, and can you explain to the Court what this demonstrative shows?

A. What I've shown on this demonstrative is the structure on the left of Octoxynol 9, and the structure on the right of tyloxapol, and Octoxynol 9, I've shown nine, the nine repeating units of the ethoxy group, which is this OCH2, CH2, OCH2, CH2, et cetera, and likewise for tyloxapol. And you can see that on the left that tyloxapol -- I'm sorry, on the left, that Octoxynol 9 has a single head group with a phenyl and the octyl unit and then a long chain, one single long chain of the

ethoxylated part, whereas tyloxapol has a very different structure.

It has seven of these groups, the phenyl and the hydrocarbon unit along the bottom as drawn. It had -- they're each connected by a CH2 group which is shown by the red ball and then out of -- off of those, each of those is the tail or the ethoxylated tail. So overall, there are seven of these tails coming off. They're structurally very different compounds.

Q. Now, I noticed that Octoxynol 40 is not depicted on this demonstrative. Why is that?

A. I've not shown Octoxynol 40 on this one because it's -- it's a very big molecule. If I drew Octoxynol 40 on this molecule -- on this demonstrative, you wouldn't be able to see properly either of these two. It would be -- it would draw the slide, the demonstrative.

Q. Now, the -- the red balls that you have indicated there, what are they highlighting in terms of what exists there in the molecules of tyloxapol?

A. They -- they're showing an extra carbon between each of the aryl groups, a CH2 group that is linking adjacent phenyl groups. It comes from a reaction from -- with formaldehyde in order to put those in. It's a linker atom or group.

Q. And how do they get there again?

A. You have to copolymerize in a chemical reaction a

molecule like Octoxynol 9 with formaldehyde and acid under specific conditions.

Q. And that produces what?

A. That will produce molecules like this, like tyloxapol.

01:03 Q. Would one of ordinary skill in the art consider tyloxapol to be structurally different from Octoxynol 9 and Octoxynol 40?

A. Absolutely. You will have different physical properties to Octoxynol 9.

01:03 Q. The question was actually first, would one of ordinary skill in the art consider tyloxapol to be structurally different from Octoxynol 9 and Octoxynol 40?

A. Absolutely, yes.

Q. Okay.

01:03 **A. Very different. It's very different because they have completely different shapes and structures. You can see, this is a long head group with multi-tails against Octoxynol 9, which has a single head group and one tail. Octoxynol 40 would be very similar -- would be similar to Octoxynol 9. Not**

01:04 **very similar, it would be similar in the sense that it's got the same head group, but a very much longer tail.**

Q. What about those methylene groups that you described before? Do they exist in Octoxynol 9 or Octoxynol 40?

A. They do not, no. They're added extra to each of the

01:04 **phenyl groups when you go from Octoxynol 9 to tyloxapol.**

Q. And to one of ordinary skill in the art, does that constitute a contribution to the structural differences as between tyloxapol on the one hand and Octoxynol 9 and Octoxynol 40 on the other hand?

01:05 **A. Absolutely, it would -- changes the structure, changes the shapes that can be adopted, changes the molecule greatly.**

Q. Now, did you hear defendant's counsel state during her opening that tyloxapol is simply strung together?

A. I did, yes.

01:05 Q. Dr. Davies, is it really that simple?

A. Absolutely not. If they are simply strung together, I don't quite understand that concept in chemistry, but if they are simply strung together, the CH2s shown by balls would not be there. The electronic properties of such a conceptual

01:05 **molecule would be extremely -- very different to this type of molecule, the types of shapes that would be likely adopted would be very different. It's a concept you cannot apply to tyloxapol in reference to Octoxynol 9.**

Q. Okay. Now, do Octoxynol 9, Octoxynol 40 and tyloxapol

01:06 have three-dimensional structures?

A. They do, yes.

Q. And have you prepared a demonstrative to assist the Court in this regard with your testimony?

A. I have, yes.

01:06 Q. Could we go to PDX 3-12?

A. Okay.

Q. And can you explain what this demonstrative shows?

A. So what I've shown on the left-hand side is Octoxynol 9, which has its single hydrophobic, greasy if you like, head

01:06 **group with its single chain of nine repeating units, ethylene oxy or ethoxy groups that come up here with the single OH group at the top.**

Next to it, I've shown Octoxynol 40 which has the same sized head group at the bottom in gray and a very much longer

01:07 **single chain coming out of that head group, and then tyloxapol is on the right, that has the broad base of the head group shown in gray, and the seven tails coming out with the oxygens on them, which is the seven ethylene oxy side chains.**

Q. Dr. Davies, would these structural differences that you

01:07 just explained impact the functional chemical properties of Octoxynol 9, Octoxynol 40 and tyloxapol?

A. They will, indeed, yes.

Q. And how so?

A. Because the shape -- the properties depend on the shape

01:07 **and the distribution of the functional groups and any molecule.**

Q. And have you prepared a demonstrative in support of your opinion in this regard?

A. I have, yes.

01:08 Q. And can we go to PDX 3-13? And can you explain this

demonstrative to the Court?

A. This compares Octoxynol 9, Octoxynol 40 and tyloxapol, in terms of the molecular weight, which is 625 for Octoxynol 9, 1966 for Octoxynol 40 and 4500 for tyloxapol, and also

01:08 **compares a critical micelle concentration, the CMC, which for Octoxynol 9 is .24 millimolar, for Octoxynol 40 is 0.810 millimolar and for tyloxapol is .018 millimolar.**

Q. Okay. And what if anything would a person of ordinary skill in the art expect regarding the solubilizing abilities

01:09 of Octoxynol 40, Octoxynol 9 and tyloxapol given their structural differences?

A. They would expect them to be different.

Q. And when you say -- what would you expect to be different? Or what would the person of ordinary skill in the

01:09 art have expected to be different?

A. The solubilizing ability of each of those would be expected to be different from the others.

Q. Thank you. In -- in generating PDX 3-13, Dr. Davies, did you use information from PTX-190, JTX199 and PTX-201?

01:09 **A. I did, yes.**

Q. Now, Dr. Davies, given the structural and functional differences among NSAIDs that you explained and given the structural and functional differences among the surfactants that you explained, what could one of ordinary skill in the

01:09 art reasonably expect with regard to a precipitate or whether

a precipitate will form in a given system if both the NSAID and the surfactant were changed?

A. Well, if you -- as I've indicated, you can't predict what will happen --

01:10 MS. HOLLAND: Your Honor, I'm sorry -- sorry to interrupt, Dr. Davies. But I was looking for that in the expert report and I didn't see it.

MR. DINER: I can tell you exactly where it is, Elizabeth.

01:10 MS. HOLLAND: Okay. Thank you.

MR. DINER: It's at Paragraph 57 and 58 at least of his responsive expert report. And if you also look at reply report, Paragraph 21, it's there as well.

MS. HOLLAND: Can I hear the question again? I

01:10 apologize, but...

MR. DINER: No worries, no worries.

BY MR. DINER:

Q. Given the structural and functional differences among the NSAIDs that you explained and given the structural and

01:10 functional differences among the surfactants that you've just explained, could one of ordinary skill in the art reasonably predict if a precipitate will form in a given system if both an NSAID and a surfactant were changed?

MS. HOLLAND: So my objection, Your Honor, is that

01:11 the paragraphs we were pointed to don't say anything about

surfactants and I think the question was complex in that way, it included both surfactants and NSAIDs.

MR. DINER: And if we go, Your Honor, to reply report at Paragraph 21, it brings it together in conjunction with

01:11 Paragraphs 57 and 58 of the responsive report.

BY MR. DINER:

Q. It says in Paragraph 21, with regard to surfactants, a person of ordinary skill in the art would not expect all ethoxylated octylphenols to be interchangable. With only data

01:12 provided for Octoxynol 40, a person of skill in the art would not have drawn any conclusions of interchangeability for different Octoxynol -- ethoxylated octylphenols, let alone for alleging solubilizing NSAIDs, slash, BAC complexes, and then --

01:12 MS. HOLLAND: No, I'm sorry. I just -- that was a different -- what you just read was a different question than what you asked, so I don't have a problem if you ask that question.

MR. DINER: Well, no, but I'm stringing it together

01:12 with what is also in Paragraphs 57 and 58.

MS. HOLLAND: I understand, but Dr. Davies didn't string it together in his report. That would be a new opinion, then.

MR. DINER: No, I don't believe so.

01:13 It says, in Paragraph 58, in any given system, there is

accordingly no way to predict whether an individual NSAID anion will form an insoluable salt with BAC cation without experimentation. And in the bottom, it says, indeed, salt formation will depend on the interaction of all ions in

01:13 solution and their solvation, including the surfactants, including those from the NSAID salt and those from separate and distinct benzalkonium chloride salts.

So together, what we have here is an opinion from Dr. Davies that it wouldn't -- that in any given system, you can't

01:13 predict what's going to happen as between -- especially when you change one surfactant or you change the NSAID.

MS. HOLLAND: Your Honor, I don't have any objection to questions for each of these points separately. My problem is trying to string them together in a way that Dr. Davies

01:13 never did in his own opinions in his report. That's more of an argument, and I'm sure plaintiffs will argue that later.

But in terms of the opinions, there are separate opinions in different places and I don't have a problem with plaintiffs asking it in that way.

01:14 THE COURT: Well, are you saying that the way that Dr. Davies laid it out in his two reports, that he addressed the issues separately for NSAIDs and surfactants and their predictability?

MR. DINER: Yes, and then in the responsive report,

01:14 in Paragraph 58, he talks about in any given system, you can't

just change the surfactant -- sorry, the NSAID, and expect that, you know, what may have happened in a prior system is going to carry forward into the next system, and then in Paragraph 21 of his report, he's also talking about that same

01:14 concept in the context of the surfactants.

THE COURT: All right. Well, I think it logically follows if you can't predict for one change, you certainly can't predict for two. I'll permit it.

MR. DINER: Okay.

BY MR. DINER:

Q. Would you like the question read back?

A. Yes, please.

Q. Given the structural and functional differences among the NSAIDs and given the structural and functional differences

01:15 among the surfactants, could one of ordinary skill reasonably predict if a precipitate will form in a given system if both the NSAID and the surfactant were changed?

A. They would not -- a person of ordinary skill would not be able to do that, because if you change the surfactant, you

01:15 **can't predict. If you change the NSAIDs, you can't predict, and if you change both, you'll have no chance.**

Q. Thank you. Can we now turn to JTX147 and take a look at that in your binder, and if you could be so kind, identify that document, please.

01:16 **A. This is U.S. Patent 4,910,225.**

Q. And who is the first named inventor on this patent?
A. **Ogawa.**
Q.
And if I refer to U.S. Patent No. 4,910,225 as the
01:16 Ogawa patent, will you understand what I mean?
A. **Yes.**
Q. Okay. And did you review the Ogawa patent in connection with your opinions in this case?
A. **I did, yes.**
01:16 Q. And --
THE COURT: Excuse me. Can I ask you to pull the mic a little closer? You are soft spoken, sir.
THE WITNESS: Sorry.
THE COURT: We need to pick up your voice a little
01:16 better. Thank you.
MR. DINER: Thank you, Your Honor.
BY MR. DINER:
Q. What, generally speaking, is the Ogawa patent directed to?
01:16 A. **Bromfenac ophthalmic preparations.**
Q. Okay. Now, Dr. Davies, are you aware that defendants are relying on general statements in the prior art that NSAIDs complex with benzalkonium chloride to argue that bromfenac would precipitate with benzalkonium chloride?
01:17 A. **Yes.**

Q. What, if anything, does the Ogawa patent disclose that would convey to one of ordinary skill in the art that bromfenac complexes with benzalkonium chloride?
A. **I haven't found any evidence within Ogawa to suggest that**
01:17 **it does.**
Q. Now, let's turn to Ogawa Example 6 at Column 10.
A. **I have it, yes.**
Q. Okay. Can you tell us in Ogawa Example 6, the chemical name there that begins with the word, "sodium." What is that
01:18 compound?
A. **That is the sodium sulfite of bromfenac.**
Q. Okay. And just for the record, could you read in the rest of the ingredients in that formulation?
A. **There's also boric acid, borax, disodium edetate,**
01:18 **benzalkonium chloride, polysorbate 80, polyvinyl pyrrolidone, sodium sulfite and then sterile purified water.**
Q. And what is the pH that is identified there?
A. **It's pH 8.**
Q. Okay. Now, let me direct your attention to Column 10,
01:18 Lines 49 to 57. And would you please read that passage into the record.
A. **The following (Table 11) are the residue and appearance of the compositions in Examples 6 to 8 after four weeks at 60 degrees centigrade.**
01:19 **As shown in Table 11, it was found that changes in**

appearances of the compositions were not observed at all and the decomposition of the compound was not -- almost observed, the aqueous compositions being stable, excellent for a long period of time.
01:19 Q. What would this passage in Ogawa convey to a person of ordinary skill in the art about the stability of the formulation of Ogawa Example 6?
A. **That for a period, for a long period of time, it was excellent.**
01:19 Q. And are you also aware that defendants have taken the position that a person of ordinary skill in the art would expect that bromfenac and benzalkonium chloride in Example 6 of Ogawa would complex and form an insoluble salt?
A. **This is showing that they do not do that, they do not**
01:20 **form an insoluble salt. So a person of ordinary skill would understand that.**
Q. Would understand what, I'm sorry?
A. **That they do not form an insoluble salt.**
Q. Thank you. Now, could we go to JTX209 in your binder and
01:20 if you can be so kind, to identify that document, please.
A. **This is European Patent Application 0 306 984.**
Q. And if I refer to JTX209 as the Fu patent application or the Fu reference -- I'll strike that.
Let me -- would you tell us please first on the front
01:21 page of JTX209, who is the first named inventor?

A. **Roger Fu.**
Q. Okay. So if I refer to JTX209 as the Fu reference or the Fu patent application, will you understand what I mean?
A. **Yes, I will.**
01:21 Q. Okay. Have you considered the Fu patent in connection with your opinions in this case?
A. **I have, yes.**
Q. What is the Fu patent primarily directed to?
A. **Ophthalmic preparations for ketorolac.**
01:21 Q. Okay. And previously, do you recall we just talked about the structural and functional differences between Octoxynol 9, Octoxynol 40 and tyloxapol?
A. **Yes.**
Q. Okay. Does the Fu patent reference disclose tyloxapol?
01:21 A. **It does not, no.**
Q. Please refer to Page 5, Line 21 of the Fu reference.
MR. DINER: I think it's actually further down. The paragraph beginning with nonionic surfactants.
Can you come over a little bit so I can see the line
01:22 number?
MR. BAIRD: Yeah.
MR. DINER: So for the record, I'd like to refer the witness to Page 5, Line 24 of the Fu patent reference. And in particular, can you highlight the long chemical name,
01:24 octylphenoxypoly-(ethylene -- all the way through ethanol.

BY MR. DINER:

Q. And Dr. Davies, do you see in Line 24, which has been highlighted as octylphenoxypoly-(ethyleneoxy)ethanol?

A. **I see that, yes.**

01:23 MR. DINER: Okay. Now, can we also, on this slide, pull up PDX 3-11. Can we get them together?

MR. BAIRD: One second. That's the best I could do.

MR. DINER: Okay. And can you hone in on the paragraph that we were looking at where it begins nonionic

01:23 surfactants? Yeah, that's good. Thank you.

BY MR. DINER:

Q. Can you see that roughly -- Dr. Davies, also, there's a monitor in front of you.

A. **Okay.**

01:24 Q. If you want to look more closely.

A. **I've got it, yes.**

Q. Okay. Thank you. Dr. Davies, is tyloxapol an octylphenoxypoly-(ethyleneoxy)ethanol?

A. **Yes.**

01:24 Q. How large of a class of compounds are the octylphenoxypoly-(ethyleneoxy)ethanols?

A. **There are huge numbers of -- a number of such compounds, so the class is enormous.**

Q. Okay. And what are the surfactants that are specifically

01:24 disclosed in Fu?

A. **Fu discloses Octoxynol 9, Octoxynol 12, Octoxynol 13 and Octoxynol 40.**

Q. And just for the record, are you reading that from Page 5, Lines 26 through 28, approximately?

01:25 A. **26 to 27.**

THE COURT: Excuse me, Mr. Diner, can I ask you just to spell this very long term for the record, because I'm confident our court reporters won't have it in their dictionary.

01:25 MR. DINER: Okay. Sure. It's O-C-T-Y-L-P-H-E-N-O-X-Y-P-O-L-Y, dash open paren, E-T-H-Y-L-E-N-E-O-X-Y, close paren, E-T-H-A-N-O-L-S.

THE COURT: Thank you.

MR. DINER: You're welcome. Thank you for asking.

BY MR. DINER:

Q. So I think the question that we left off with was what are the surfactants specified, and I believe you answered that.

What did the surfactants or what do those compounds,

01:26 surfactants in Fu look like?

A. **They -- if we look at the demonstrative at the top, they look like -- well, one of them is Octoxynol 9. The others are similar structures in the sense that they have the same head group but the tail has a different length. So the ethyleneoxy**

01:26 **units, which are the CH2, CH2O units in the tail, there are**

nine of them in Octoxynol 9, 12 in Octoxynol 40 -- 12, 13 in Octoxynol 13 and 40 in Octoxynol 40.

Q. Okay. Does tyloxapol look like any of the specifically identified compounds in Fu?

01:26 A. **No. It has a completely different structure, as you can see between Octoxynol 9 and Octoxynol 40 on the top demonstrative.**

Q. Now, let me ask you, is Octoxynol 9 an ethoxylated octylphenol?

01:27 A. **Technically, no, because they're not -- octylphenol requires a hydroxy group on the phenyl ring. And this phenyl ring in Octoxynol 9 does not have a hydroxy group.**

Q. Okay. And is your opinion -- your opinion in that regard the same with respect to tyloxapol?

01:27 A. **The same applies. It's technically, it's not an octylphenol compound, because there's no OH group on any of the phenyl, seven phenyl rings in tyloxapol. However, Fu has characterized all of these compounds as ethoxylated octylphenol compounds, as his way of describing them. But**

01:28 **technically, they're not phenols.**

Q. Okay. Thank you, Dr. Davies.

Now, let me direct your attention to Page 2 of the Fu patent reference, and in particular, Lines 33 through 36.

Are you there?

01:28 A. **Yes, yes.**

Q. Okay. Can you read that passage into the record, beginning with the word, "however?"

A. **However, BAC has typically been considered to be incompatible with anionic drugs, e.g., salicylates or**

01:28 **nitrates, et cetera, forming insoluble complexes which cause the solution to become cloudy or turbid. Such a complex between the anionic drug and benzalkonium chloride can cause a decrease in the pharmaceutical activity of the anionic drug.**

Q. Okay. How would a person of ordinary skill in the art

01:29 interpret this statement in light of the -- as it appears in the Fu patent reference?

MS. HOLLAND: Objection, Your Honor. That opinion is -- as far as I know, not in any of the expert reports.

MR. DINER: That's incorrect, Your Honor. It's all

01:29 over his expert report, in terms of areas in which he discusses the Fu patent reference in the general statement, as to whether or not complexation would take place.

MS. HOLLAND: I'm sorry, can you point me to something?

01:29 MR. DINER: Yeah, from -- if you take a look at Paragraph 12 of Dr. Davies's reply report and in particular, Footnote 3. Right. So he's addressing Dr. Heathcock's statement that -- Dr. Heathcock cites to Fu to argue that a number of poly -- a number of phenol acetic acid derivatives

01:30 NSAIDs were known as of 2003 to complex with BAC and

precipitate from solution.

And then he goes on to say, however, as discussed in my opening report, however, Fu discloses formulations containing the specific NSAID ketorolac trimethamine, non-NSAIDs
01:30 generally or bromfenac in particular with BAC, and then it goes on to say, Fu does not establish that ketorolac and BAC form a precipitate as Fu does not test the disclosed turbid ketorolac formulations to determine the chemical makeup of the precipitate.
01:30 So it's in the context of that statement and what is taking place in Example 5 of Fu, to address the issue as to whether or not the complexation actually does take place. And his report addresses that in numerous places.

MS. HOLLAND: Your Honor, there's a -- the Footnote 3
01:31 that you were directed to deals with the specific question about this patent application -- this patent and ketorolac. This statement about BAC and how the person of ordinary skill in the art would understand that statement, that's not in the expert report.
01:31 This is a -- this, and many other patents have general statements about the fact that NSAIDs as a class, acetic NSAIDs don't form -- I'm sorry, will form complexes with BAC. I think Dr. Davies's point in his report is that the one NSAID that's typified, I would say, in this patent, is ketorolac.
01:31 So that testimony, I don't have any objection to.

THE COURT: Okay. Can you repeat the pending question, Mr. Diner.

MR. DINER: The question was: How -- so he read the passage from the Fu patent application into the reference, and
01:32 the question was -- or into the record -- how would a person of ordinary skill in the art interpret this statement in light of the Fu reference?

THE COURT: Just a moment.

Well, was there any comment in any of Dr. Davies's
01:32 reports regarding this passage in Fu?

MR. DINER: It was in the context of Fu as a whole when he was looking at Example 5 and talking about the precipitate that formed there, and whether or not it was, in fact, a precipitate resulting from the NSAID with benzalkonium
01:33 chloride, which is tied effectively to the statement at the very beginning of the patent, because the patent says that when NSAIDs come together with benzalkonium chloride, they will precipitate, and so his -- the report was directed to why that may not be the case.
01:33 THE COURT: All right. And I regard this as necessarily included within his expressed opinion, even though it's not -- it's not evident in so many words, but it is something he reviewed, it's something that he opined upon, and it's -- if I am interpreting what you're asking, an example of
01:33 why he doesn't get from the Fu patent application the concept

that the defendants are citing it for.

MR. DINER: Correct, your Honor. Thank you.

THE COURT: I'll permit it.

MR. DINER: Okay.

01:34 MS. HOLLAND: Can I just express one more thing on this topic, your Honor?

THE COURT: Sure.

MS. HOLLAND: I'm concerned here in general because there has been a lot that's been said and I anticipate will be
01:34 said addressing opinions about statements like this in the prior art that are very general statements that would apply to any NSAID.

There is no opinion in Dr. Davies's report about those types of statements. There just isn't. He
01:34 addresses very, very narrow issues within these patents, and I think that there is a lack of notice here to the extent that it's going to be Dr. Davies, for example, versus Dr. Williams who addresses these things. I mean, we couldn't have asked him about these opinions at his deposition if they weren't in
01:34 his report.

MR. DINER: But you did actually ask him about them in his deposition. And, in fact, it all goes to, as you acknowledged, your Honor, the idea of whether or not these are general statements which he was directing his testimony to in
01:35 his expert -- or his expert report to in the context of five,

but in the context of the whole patent is, well, do they really form a precipitate and how do you know from looking at the full context of the patent? So that was the whole thrust of his expert report in trying to address this complexation
01:35 issue as raised by the defendants. And even defendants' expert, Dr. Heathcock, recognized that in his -- in his report back to Dr. Davies, which he responded to, and, as I indicated, Dr. Davies was deposed for a very long time on these exact statements in all of the references and, of
01:35 course, they -- as a result, they would have had knowledge of that, and it's in his reports as well.

THE COURT: All right. No, I --

MS. HOLLAND: Your Honor, my understanding at Rule 26 is that you have to give particularized notice of the
01:35 opinions. It's not enough to say that it was the thrust of his report, it just isn't, under the rules. And I understand what your ruling was, your Honor, but I just wanted to make a short record on this, because Dr. Davies is veering outside of the opinions he gave as a chemist in this case and seems to be
01:36 addressing things that maybe a formulator would be looking at and he wasn't --

MR. DINER: I would --

THE COURT: Well, the subject of precipitates is part of his opinion. The Fu report itself is part of his opinion.
01:36 Here is a statement in the Fu report that may be general, and

it I think would be a question of what weight, if any, should be given to his opinion, but I don't see it as being outside of the expression of his opinions that have been described upon the record. It's not like he's pulling Fu off some shelf somewhere and for the first time referencing it or even taking issue with its statements about the likelihood of the precipitate being formed.

MS. HOLLAND: I understand, Your Honor.

THE COURT: I haven't read all of these depositions or reports, but I don't hear you in disagreement with the fact that this is one of the major areas of Dr. Davies's opinions in this case, is whether a precipitate was known or not known to have been formed.

And, also, you have the opportunity to address these opinions, if they are striking you as new or as amplifications of something that you hadn't heard before, then you do have the opportunity to cross-examine him on it, and also to introduce rebuttal testimony that would, if an expert agrees with your thesis, contradict what he's testifying to.

MS. HOLLAND: Okay, your Honor. Thank you.

THE COURT: Okay.

BY MR. DINER:

Q. Okay. So, would you like the question read back?

A. Yes.

Q. How would a person of ordinary skill in the art interpret

this statement from the Fu patent application?

A. It's a very general statement in the introductory part to the patent. It gives no experimental evidence to say that -- to show that any precipitate will form between any particular NSAID and BAC. And they would look at the patent as a whole to see if there was any evidence within the patent to see if such a precipitate occurred in this case.

Q. And when you reviewed the patent, did you see any evidence that a precipitate formed that was a precipitate of benzalkonium chloride and ketorolac?

A. I found no evidence at all, no.

Q. Now, are you aware that defendants are taking the position that the general statement that we just referred to in Fu is applicable to bromfenac formulations in Ogawa?

A. I believe that's true, yes.

Q. And how, if at all, does this statement that you read from Page 2 of Fu inform one skilled in the art about whether bromfenac will precipitate with benzalkonium chloride?

A. It doesn't inform a person of ordinary skill at all. The only examples in this one are salicylates or nitrates, and bromfenac is neither of those.

Q. Okay. Now, please take a look at Examples 2 and 3 on Page 7 and 8 of Fu.

A. I'm there, yes.

Q. Okay. Would one of ordinary skill in the art understand

that Examples 2 and 3 are formulations that are representative of the Fu invention?

A. Yes.

Q. Do Examples 2 and 3 contain the same ingredients?

A. They do, yes.

Q. What are those ingredients?

A. Ketorolac promethazine, BAC, which is benzalkonium chloride, Octoxynol 40, EDTA disodium, and sodium chloride.

Q. Do they differ in the amount of Octoxynol 40?

A. They do.

Q. And what are the amounts for Octoxynol 40 in each of the examples?

A. So, in Example 2, the amount of Octoxynol 40 is .02 percent weight per volume. In Example 3, the amount of Octoxynol 40 is .004 percent weight per volume.

Q. Thank you.

I would like to direct your attention now to Page 9 of Fu, and, in particular, Example 5.

A. Yes.

Q. Are you there?

A. I'm there.

Q. What is being tested in Example 5 of Fu?

A. The physical stability of formulations of the present invention, so Fu's invention.

Q. And what is the NSAID that's being used in these

formulations?

A. Ketorolac.

Q. And what surfactants are compared in Example 5?

A. Octoxynol 40, Tween 80, which is Polysorbate 80, and Myrj 52.

Q. Okay. And the Octoxynol 40 formulations, is it your understanding that those are the formulations of the Fu invention?

A. That's what it says, yes.

Q. And what is the amount of Octoxynol 40 used in the first identified formulation of the Fu invention?

A. .004 percent.

Q. Does that correspond to Fu's Example 3?

A. It does, yes.

Q. And what is the amount of Octoxynol 40 used in the second identified formulation of the Fu invention?

A. .02.

Q. Does that correspond to Fu's Example 2?

A. It does, yes.

Q. Would the skilled person have reasonably understood, reading this, that the Octoxynol 40 formulations in Fu, Example 5, correspond to Fu's Examples 2 and 3?

A. Yes, he would, yes.

Q. For comparison purposes, would the skilled person have expected that the comparative examples with Polysorbate 80 and

Myrj 52 to have contained the same ingredients as Fu's Example -- Examples 2 and 3 except for surfactants -- except for the surfactants?

MS. HOLLAND: Your Honor, I'm going to object to that. I don't believe this is in his report.

MR. DINER: Your Honor, his report is directed to Example 5 on the idea of what, if anything, could be understood from the precipitate that is disclosed in there. And it's in that context where we're just laying foundation to help him explain what he has already said in his expert report which is that you don't know what that precipitate is until you test it. And what we're doing is just going through the foundation for the Court's benefit to understand what the example is about, what the examples were that were compared, such that when he comes to his testimony, it makes sense. So it's foundation and informational for the Court, and I don't think it's confusing or prejudicial to any of the parties.

THE COURT: Did his report mention Example 5?

MR. DINER: Yes, your Honor.

MS. HOLLAND: The report did not compare Example 5 to Examples 2 and 3 or make any assessment of whether the same inactive ingredients would be present for Tween 80 and Myrj 52.

MR. DINER: Your Honor, it references --

THE COURT: Well, he can be cross-examined on that.

I think it's, again, within the scope of his report. I'll permit it.

BY MR. DINER:

Q. Now, let me direct your attention to Lines 34 through 36 of Example 5.

A. 34 to 36, yes.

Q. Yes, thank you.

Would you please read that highlighted portion of the Fu patent application into the record.

A. "The presence of turbidity suggested the inability to solubilize a precipitate formation between ketorolac moiety and benzalkonium chloride."

Q. What would this passage convey to one of ordinary skill in the art?

A. That the authors don't know what the precipitate is, because it says "suggested." They haven't done an experiment to find out, to isolate or to analyze what the precipitate is, so it could be something other than that; otherwise, if they thought -- if they knew it was that, they would say it is.

Q. Okay. And what could it be other than that?

A. Well, these preparations contain --

MS. HOLLAND: Objection, your Honor. This specific question was asked at the deposition, and Dr. Davies did not have an answer as to what an alternative explanation could be.

MR. DINER: I disagree, your Honor. What he said in

his deposition is that you could not tell exactly what it is unless you did testing.

MS. HOLLAND: That's not --

MR. DINER: But what he said -- no, because telling means to know exactly what it is. And what he said clearly in his report and in his testimony, you don't know without experimentation, and in his deposition response he said you could not tell without testing. Obviously, it leaves open the possibility that it's something else based on the fact that you can't tell that it's the complex allegedly between bromfenac -- or ketorolac and benzalkonium chloride.

THE COURT: Well, I'll sustain the objection. It's a different question. You're asking today "what could it be" rather than "can you tell."

BY MR. DINER:

Q. Okay. Dr. Davies, did you hear Dr. Lawrence testify about Example 5 of Fu that a person of ordinary skill in the art would use 0.02 weight per volume percent tyloxapol in formulations of bromfenac based on the disclosure of a 0.02 weight percent Octoxynol 40 in Fu?

A. Yes.

Q. Do you agree with Dr. Lawrence?

A. I do not, no.

Q. And why not?

A. Because those two surfactants have -- have different

structures, and you can't substitute one for another, just like that, so you can't -- the amount you put into one preparation has no meaning on another preparation with a different surfactant.

Q. Dr. Davies, what, if anything, does Fu teach with regard to bromfenac?

A. Nothing at all. Bromfenac is not -- there are no experiments for bromfenac.

MR. DINER: Your Honor, I'm at a point where I think it may be actually a good point for a short bio break. Would that be okay?

THE COURT: Okay. So let's break for about ten minutes until 11:15.

MR. DINER: Okay be, thank you.

(A recess was taken at 11:05 a.m.)

THE COURT: Okay. Be seated, please.

Before we begin, there is a matter that was brought to my attention where the parties had written to Judge Williams, and I wanted to see if that's still a live dispute or not. March 25th, there was an issue raised about defendant Lupin's designation of Ms. Kulkarni, and then there was a response by Mr. Patunas on March 28th. Has that been resolved?

MS. HOLLAND: I don't think it's been resolved, your Honor, but, actually, Mrs. Kulkarni is in court and she's only

had access to what's been going on in open court, so I don't think there is an issue anymore. I think it's moot.

MR. HASFORD: So, respectfully, your Honor, from the plaintiff's view, we don't have any problem with Ms. Kulkarni being in open court and hearing what's here. The issue was providing other confidential documents of plaintiffs to Ms. Kulkarni. If plaintiffs will represent they are not going to do that, then we have no issue.

MS. HOLLAND: Yeah, at this point, your Honor, I think it's moot. I think it's just what -- Ms. Kulkarni is here and this is the record now and that's all we'll be sharing with her.

MR. HASFORD: If I may, your Honor, just so the record is clear, will counsel for defendants stipulate that they or represent that they will not provide any of plaintiff's confidential documents that we have produced in connection with this litigation that were not used in this court proceeding to Ms. Kulkarni?

MS. HOLLAND: Yes, we can stipulate.

MR. HASFORD: Then we're fine, Your Honor.

THE COURT: Okay, fine.

And, for the record, Kulkarni is spelled K-U-L-K-A-R-N-I.

And I'll just make note that this is moot, and Judge Williams and I need not concern ourselves with it.

Okay. Thank you. So let's resume.

MR. DINER: Thank you, your Honor.

BY MR. DINER:

Q. Dr. Davies, before the break, do you recall we were discussing the Fu patent reference, in particular, the Example 5 from that document?

A. **Yes.**

Q. To be clear, would a person of ordinary skill in the art be able to determine what the precipitate is in Example 5 of the Fu patent reference?

A. **They would not because there is no description of that precipitate being isolated and then analyzed.**

Q. Thank you.

Now, I would like to go to JTX-043, and would you please turn to that document in your binder and identify it for the record, please.

A. **This is U.S. Patent 6,265,444.**

Q. Okay. And I'll just refer to this using defendants' nomenclature as the '444 patent. If I do so, will you understand what I mean?

A. **I will, yes.**

Q. Okay. Have you reviewed the '444 patent in connection with your opinions in this case?

A. **I have, yes.**

Q. Let me direct your attention to Column 7 of the 444

patent, and, in particular, Lines 55 through 61.

A. **I'm there.**

Q. Okay. Would you mind reading that portion of the '444 patent into the record, please.

A. **"It should be noted that BAK was found to be unexpectedly compatible with diclofenac in the present ophthalmic composition. While the reasons for this are not entirely clear, and without wishing to be bound by any theory, the presence of the divalent cation is believed to prevent the BAK from complexing the diclofenac out of the system."**

Q. How, if at all, does this portion of the '444 patent that you just read support your opinions in this case?

A. **This says they had no problem with that precipitate of diclofenac, an NSAID, with benzalkonium chloride.**

Q. Okay. And how, if at all, does this statement at Column 7, Lines 54 to 61 of the '444 patent impact how a person of ordinary skill in the art would understand the applicability of all NSAIDs -- of the general statement that NSAIDs and benzalkonium chloride allegedly complex?

A. **This obviously does not fall within that category. It shows that all NSAIDs do not complex with BAK and come out of solution.**

Q. Okay. Can we please turn to your binder, JTX-057, and, again, would you please identify this document for the record?

A. **This is U.S. Patent 5,597,560.**

Q. Okay. And so I'll refer to that as the '560 patent. Is that okay with you?

A. **That's fine.**

Q. Okay. Have you reviewed the '560 patent in connection with your opinions in this case?

A. **I have, yes.**

Q. And now let me direct your attention to Column 6 of the '560 patent, and, particularly, the comparative Example C starting at Line 55, and continuing on to Column 7 through Line 20 of the '560 patent.

A. **I'm there.**

Q. What is this comparative test that is -- what is the comparative test that is being done here?

A. **So, this experiment or this set of experiments is, first of all, taking a formulation that uses -- that contains diclofenac, Tobramycin, and benzalkonium chloride as amongst the ingredients, and then takes some -- does some control, two control experiments, where the formulations were paired, the first one with sodium diclofenac as the active ingredient, so without the tobramycin, and the second one with tobramycin and without the diclofenac, and then looks at the stability of those formulations. And samples from those three formulations were stored at 4 degrees and 22 degrees, and a precipitate was looked for.**

Q. And what were the results that were reported?

A. What was found was that at 41 degrees -- 41 days, sorry, at 4 degrees Centigrade, the formulation with both diclofenac and tobramycin developed a precipitate, while the other two control experiments, the one with diclofenac without tobramycin and one with tobramycin without diclofenac did not develop precipitates.

Q. And what, if any, analysis was done here to make that determination?

A. In this experiment, the authors of the patent did exactly what I've been saying previously, in that they isolated the precipitate and analyzed what was made up of the -- in the precipitate. And they found, on analysis, the precipitate was from diclofenac and tobramycin. So what is precipitating out is diclofenac and tobramycin in the solid form, whereas the solution that contained diclofenac and the benzalkonium chloride remained clear and didn't precipitate, and the tobramycin alone, without the diclofenac with benzalkonium chloride, that didn't precipitate.

Q. Okay. How, if at all, does this portion of the '560 patent and this comparative experiment support your opinions in this case?

A. It shows that even if you see a precipitate, you mustn't make any assumptions and that the only way of knowing what is in that precipitate is to separate it, analyze it, and find out what the components are.

Q. And, once again, did this -- did all the formulations of the comparative example that you just discussed contain at least diclofenac and benzalkonium chloride? Sorry. Strike that.

Did the formulations that were tested contain benzalkonium chloride?

A. They did, yes.

Q. Okay. What does this example from the '560 patent teach the person of ordinary skill in the art about whether NSAIDs and benzalkonium chloride will precipitate?

A. This shows that the NSAID diclofenac does not precipitate with benzalkonium chloride.

Q. And, based on what we've just seen in the '560 patent, is Dr. Lawrence's general opinion that NSAIDs form a complex and will precipitate with benzalkonium chloride accurate?

A. I've not -- we've been through some examples where that does not happen. I've not seen any examples where it does.

Q. Okay. Now, is benzalkonium chloride a quaternary ammonium compound?

A. It is, yes.

Q. What does the skilled person understand about the solubility of salts of quaternary ammonium compounds, if anything?

A. They would understand that they are soluble.

Q. Okay.

A. In water. So they are used in -- as reagents, passive reagents in chemistry to act as water-cooled phase transfer agents, which means they're soluble in both organic solvents and water.

Q. Would you please turn in your binder -- (pause)

MR. DINER: Your Honor, may I ask the witness if he has a particular document in his binder?

THE COURT: Of course.

MR. DINER: Do you have PDX-199 in your binder?

THE WITNESS: Yes.

THE COURT: PTX, right?

MR. DINER: Yeah, PTX-199. Do you have it, your Honor?

THE COURT: Yes.

MR. DINER: Okay.

BY MR. DINER:

Q. Well, Dr. Davies, at least can you identify PTX-199, please, for the record?

A. This is an extract from an organic textbook called *Introduction to Organic Chemistry*, Third Edition, by Streitwieser and Heathcock.

Q. Now, you mentioned Heathcock. I think it's pronounced Heathcock. And is that the same Dr. Heathcock that is serving as defendants' expert in this case?

A. I believe so, yes, since the first name and the initial

look the same.

Q. Can I direct your attention to Page 697 of this document? PTX-199.

A. Yes.

Q. And I'm sorry, I misspoke. It's 696. I apologize.

And will you read into the record -- well, will you read into the record the paragraph beginning with "such compounds" around the middle of Page 696?

A. "Such compounds which have four alkyl groups replacing the four hydrogens of the ammonium ion are called quaternary ammonium compounds. Since they are ionic, they are generally water soluble and have fairly high melting points. They often decompose at the melting point."

Q. And if you would, please, at Page 697, would you also read the first sentence of the first full paragraph into the record?

A. "To understand what has happened, we need to recognize that although the quaternary ammonium compound is a salt soluble in water, it also has a large organic group and has solubility in organic solvents as an ion pair."

Q. Okay. And so, based on those two passages that you read into the record, would one of ordinary skill in the art be of the view or understanding that quaternary ammonium compounds are water soluble?

A. They would, yes.

Q. Okay. And, once again, benzalkonium chloride is a quaternary ammonium compound?
A. It is, yes.
Q. Okay.
MR. DINER: Your Honor, I have no further questions. I would like to at this time read in --
(Pause)
MR. DINER: Oh, I apologize.
BY MR. DINER:
Q. The last question, Dr. Davies.
Did you hear Dr. Williams' statement on Monday of his view of the level of ordinary skill in the art?
A. I did, yes.
Q. How does that definition relate to the level of ordinary skill that you have applied in expressing your opinions in this case?
MS. HOLLAND: Your Honor, Dr. Davies didn't put the level of ordinary skill in the art in his --
(Pause)
MR. DINER: It's Paragraph 11 of his responsive report.
MS. HOLLAND: I'm sorry. Were you suggesting that it was the same thing that Dr. Williams said?
MR. DINER: The first paragraph.
MS. HOLLAND: The first paragraph of Dr. Williams --

MR. DINER: Right. And what he has as his expert report.
BY MR. DINER:
Q. So the question is: Does that definition relate to the level -- I'm sorry.
How does that definition relate to the level of ordinary skill you have applied in expressing your opinions in this case?
A. I believe my definition is the same as Dr. Williams'.
Q. And have you applied that definition in connection with opinions in this case?
A. I have, yes.
MR. DINER: Okay. I think that was our last question for Dr. Davies, and so if I will -- if I may, your Honor, I would just like move into evidence the documents that we went through today.
THE COURT: Okay. Would you like to read that list into the record and then I'll see if there is any objection? Some, of course, are already in evidence.
MR. DINER: Yeah.
THE COURT: But are there new ones?
MR. DINER: There certainly are, but I don't know which ones are the new ones and which ones are the old ones. I think we talked yesterday that we would just bring them in and then we'll sort it out later. Is that okay?

THE COURT: Well, if there is any dispute, I would rather handle it now with the witness on the stand.
Ms. Holland, do you know?
MS. HOLLAND: Yeah, we have objections, your Honor. Do you recall that there were certain demonstratives that were shown that the witness testified about and then there was like a general conclusory statement at the end of, you know, which documents did you look at to put together this demonstrative. And so to the extent that those individual documents are going to be submitted into evidence, there was no particularized testimony about them. We don't even know where in the documents that the testimony came from that was -- the information, I should say, came from that was in the slides. And I can tell you those are PTX-187 --
THE COURT: Well, I know what you're referring to. I think on three occasions he gave the source for his --
MS. HOLLAND: Yeah.
THE COURT: -- demonstratives, and it was kind of a string cite of documents that are on the exhibit list.
MR. DINER: Correct.
THE COURT: All right. Are those documents being offered at this time?
MR. DINER: I was going to, your Honor, yes.
THE COURT: Are they admissible since he merely relied on them but didn't qualify any of them as, for

instance, learned treatises or something else that would be admissible?
MR. DINER: They were certainly prior art, your Honor. And I think --
THE COURT: Well, all I have is a bunch of numbers as to those sources. Some of the sources themselves may be in evidence. But for those that aren't, I'd have to sustain the objection.
He's disclosed what he relied on, but that doesn't make those sources somehow admissible without the laying of a foundation.
MR. DINER: Okay. Can I have one second, your Honor?
(Pause)
MR. DINER: Okay, your Honor, then with regard to the exhibits that we were just discussing from the demonstratives, we will pass on that and we will just go and read in the other exhibits that the witness has qualified.
THE COURT: All right. So do you want to do that after lunch maybe? Or are you ready to do it now?
MR. DINER: I can do it right now, won't take very long.
THE COURT: No, very well, if you're prepared to do it.
MR. DINER: Yeah. No, I am. I'm ready.
THE COURT: Okay, fine. So read into evidence at

this time the exhibit numbers that you are seeking to have considered as evidence.

MR. DINER: Okay. PTX-199, PTX-160, PTX-632, JTX-001, JTX-210, PTX-181, JTX-147, JTX-071, JTX-209, JTX-043, JTX-057.

MS. HOLLAND: Your Honor, may we reserve on this right now and then just come back after lunch, after we have had a chance to look at these, and I'll let you know whether we have any objections?

THE COURT: That's fine.

MS. HOLLAND: Thank you.

THE COURT: All right. And so those are on the table, and then we'll take care of it after lunch to see if there is any objection as to those documents.

All right. Are we ready for cross-examination?

MS. HOLLAND: Yes, Your Honor.

THE COURT: Okay, Ms. Holland, you may proceed.

(CROSS EXAMINATION OF DR. DAVIES BY MS. HOLLAND:)

Q. Good morning, Dr. Davies.

A. Good morning.

Q. Are you aware that this case concerns pharmaceutical formulations?

A. Yes.

Q. And you're aware that in particular those formulations are ophthalmic formulations, right?

A. That's correct.

Q. You are not a pharmaceutical formulator; is that right?

A. I am not, no.

Q. And you've never been part of a team formulating an ophthalmic formulation, correct?

A. I have not, no.

Q. You've never been involved in selection of excipients or inactive ingredients to be used in a pharmaceutical formulation, right?

A. I've been involved in a team that's --

Q. Well, let me try again. You have never been involved in the selection of ingredients for a pharmaceutical formulation, correct?

A. Selection of ingredients, that's correct.

Q. And your opinions in this case are from the point of view of an organic chemist, right?

A. From the point of view an organic chemist, medicinal chemist.

Q. Okay. Now, you testified about whether bromfenac would be expected to form insoluble complexes with BAC. Do you recall that?

A. Yes.

Q. Okay. You've never done work with any -- with bromfenac, correct?

A. I have not worked with bromfenac.

Q. And, in fact, you have never done research on any NSAID; is that right?

A. Not that I recall. We may have done in the 560 plus publications, but I don't recall having done so.

Q. And how many of those 560 plus publications deal with pharmaceutical formulation?

A. I don't believe any of them do.

Q. Okay. Now, you have also never used BAC in a pharmaceutical formulation, correct?

A. We haven't worked on pharmaceutical formulations, so that's correct.

Q. Okay. And you don't recall -- let me withdraw that question.

You don't recall working with BAC at all, correct?

A. We've worked with quaternary ammonium salts similar to BAC, but I don't recall working with BAC directly.

Q. You also testified about whether a person of ordinary skill in the art would understand tyloxapol and polysorbate 80 to be interchangeable, right?

A. That's correct, yes.

Q. And you've never worked with tyloxapol, right?

A. I have not, no.

Q. And you've also never worked with polysorbate 80, correct?

A. Not as far as I remember.

Q. You also provided testimony comparing tyloxapol with octoxynol 40, right?

A. That's correct.

Q. And you have never worked with octoxynol 40 either, right?

A. I have not worked with those particular compounds. We work with many compounds and understand their structures.

Q. Now, you testified that ethoxylated octylphenols constitute a huge class of compounds, right?

A. That's correct.

Q. Okay. And that was based on your knowledge of organic chemistry; is that right?

A. Yes, I suppose so, yes.

Q. Now, is it correct that octoxynol 40 is an ethoxylated octylphenol compound?

A. Can you repeat the question, please?

Q. Yes. Octoxynol 40 is an ethoxylated octylphenol compound, correct?

A. Strictly, it's not, but under Fu's classification, it is.

Q. All right. Well, let's -- I think you should have a copy of your deposition transcript in your binder.

MS. HOLLAND: Did we hand out the cross binders yet? Okay. Sorry. Let's get those.

BY MS. HOLLAND:

Q. Now, I believe you should have your deposition transcript

in your binder. Did you find it, Dr. Davies?
A. Yes.
Q. Okay. Would you turn to page 145, please.
MR. DINER: Your Honor, before we get going on this,
02:34 I think that the impeachment that Ms. Holland is about to embark upon is improper. I think he's already just agreed with her in the context of Fu of what octoxynol 40 can be.
MS. HOLLAND: Well, I didn't ask in the context of Fu, your Honor. That's the issue. I asked generally. So, I
02:34 think it's proper impeachment once you take a look at it.
THE COURT: All right. Before I see what the text of the dep says, I can't rule on whether it's inconsistent. I mean, is there an agreement that he is withdrawing certain testimony?
02:34 MR. DINER: No, your Honor. I'm just thinking that he, when he answered her question about whether or not ethoxylated -- octoxynol 40 is an ethoxylated octylphenol, he said no, not strictly, but it is according to Fu and how Fu defines things. And I think what she is going to do in terms
02:35 of her impeachment is just ask him what it is in terms of the octoxynol 40 that was disclosed in Fu.
MS. HOLLAND: Your Honor, if I may just do the impeachment, and if there's an issue with it, so -- I'm going show everybody the -- your Honor, I'll direct you and the
02:35 witness to the testimony. It's at page 145, lines 3 to 5.

THE COURT: Okay. I'll permit it.
MR. DINER: If I may, your Honor, I just would ask for completeness purposes that Ms. Holland also ask the witness the questions that follow which will bring into
02:35 context the Fu reference.
MS. HOLLAND: I don't see anything that would make that particular Q and A complete, completer, more complete, I should say, by reading anything more in.
MR. DINER: Line 6 and all that.
02:36 MS. HOLLAND: That's a separate question I asked.
THE COURT: I agree with Ms. Holland, that wouldn't be completeness material. It could be asked on redirect, but I don't see that it's qualifying the answer that's given on line 5 because it seems to be a different topic.
02:36 BY MS. HOLLAND:
Q. So, Dr. Davies, I'm directing you to your deposition testimony, page 145, lines 3 to 5. Were you asked at your deposition, "Octoxynol 40 is an ethoxylated octylphenol compound, right?"
02:36 And did you provide the answer, "Yes"?
A. I did, yes.
Q. Now, you have also referred to octoxynol 40 as a polyethoxylated octylphenol surfactant, right?
A. Where do I say that?
02:36 Q. I'm just asking you, do you agree that octoxynol 40 can

also be referred to as a polyethoxylated octylphenol surfactant?
A. As a polyethoxylated?
Q. Octylphenol surfactant.
02:37 **A. Under Fu's definition, yes. I'm happy to call it that.**
Q. When you say you are happy to call it that, do you mean you agree?
A. That it's not an ethoxylated phenol. It's a -- it's where you're putting the poly. So, if you show me the
02:37 **reference --**
Q. Let me direct you to your deposition testimony then at line -- page 192, please.
A. Yes.
Q. And I'll direct you to line 13.
02:38 **A. Of 192?**
Q. Yes. And just for now, I'm showing it to you to refresh your recollection that is it -- in your view, can octoxynol 40 be referred to as a polyethoxylated octylphenol surfactant?
MR. DINER: Your Honor, I'm not sure which reference
02:38 she's pointing to. She's talking about column 4, starting at lines 32, and I'm not sure that we have context of where we're talking about.
THE COURT: All right. Can you supply that? Is that the Fu patent?
02:38 MS. HOLLAND: This is --

MR. DINER: It's a different Fu patent other than the one that we've been talking about.
MS. HOLLAND: It's the '493 patent.
THE COURT: Okay. Well --
02:39 MS. HOLLAND: Do you want me to -- my question was just more of a definitional one.
THE COURT: Maybe ask the question without reference to this aspect of the transcript, if it's not the Fu patent that he was talking about.
02:39 MS. HOLLAND: Sure, your Honor.
BY MS. HOLLAND:
Q. My question is, are ethoxylated octylphenol and polyethoxylated octylphenol, do they refer to the same thing?
A. They do. If you put the phenol in the name, in terms of
02:39 **the name, if you put the phenol in the name strictly, it's not true, but Fu introduced to the system the easier way to call them, which is to call them the ethoxylated phenols. That's where it comes from.**
Q. Thank you. And you agree that tyloxapol is in the family
02:40 of polyethoxylated octylphenol surfactants, correct?
A. It's part of a huge family of such compounds, yes.
Q. Now, you said just again that ethoxylated octylphenol compounds are a huge family. Do you know whether a formulator would have considered the possible ethoxylated octylphenol
02:40 compounds to be used in an ophthalmic formulation to be among

a huge family as of 2003?
A. **Well, I think they could consider using anything in an ophthalmic formulation. They would have to get it approved, of course.**
02:40 Q. How many ethoxylated octylphenol compounds were approved for ophthalmic formulations as of 2003?
A. **I haven't done that analysis.**
Q. You didn't attempt to determine that before providing your opinions in this case?
02:41 A. **I don't think it was relevant to my opinions in this case.**
Q. Let me move on to something else then. You testified that there was no evidence in the Ogawa '225 patent that bromfenac and BAC form a precipitate. Do you recall that
02:41 testimony?
A. **Yes.**
Q. Example 6 of Ogawa contains polysorbate 80, correct?
A. **Can you --**
Q. Why don't we -- is it in the cross binder? It's JTX-147.
02:42 And we'll put it up on the screen as well, but I'm going to refer you to Example 6, which is in JTX-147, it's in your binder, and you can find it at column 10.
A. **Yes.**
Q. So, my question again was, does Example 6 of Ogawa
02:42 contain polysorbate 80?

A. **It's listed there, yes.**
Q. Do you know what polysorbate 80 is?
A. **It's -- I went through the structure earlier. It's sorbitan with the long chain and the three groups on it, and**
02:43 **80 will mean there's 80 of the ethoxylated units.**
Q. So, that's what it means to an organic chemist, but to a formulator, what is the function of polysorbate 80?
A. **I believe it has a number of functions.**
Q. Is one of them as a solubilizer?
02:43 A. **It's one of several functions it could have.**
Q. Are you aware that polysorbate 80 as of 2003 had been used as a physical stabilizer?
A. **I don't recall. I'd have to look through all of that.**
Q. I'm sorry. I couldn't hear you.
02:43 A. **Sorry. I don't recall. But I've seen that. I'd have to look.**
Q. You didn't investigate that issue before forming your opinions in this case?
A. **I just don't recall.**
02:43 Q. Do you know the function of polysorbate 80 in the '225 formulation?
A. **I don't believe it's listed.**
Q. Okay. Well, do you know if a formulator, when they see polysorbate 80 in a formulation, would understand what the
02:44 function is?

A. **Well, since there are several, I believe there are several possible functions, and one is not listed, you'd have to ask a formulator, but I don't think -- I don't know how they would if it's not listed.**
02:44 Q. Did you attempt to find out what the function of polysorbate 80 was in the '225 formulation?
A. **I don't know how I would do that.**
Q. Now, did you consider that polysorbate 80 might be present to prevent complexation of bromfenac and BAC?
02:44 A. **I don't -- I would have no way of telling. What I can tell is that this is a stable solution, this is -- whether it contains both bromfenac sodium and BAC and doesn't form a precipitate.**
Q. My question was a little different. Did you think about
02:44 the possible functions of polysorbate 80 in this formulation of Example 6 in the '225?
A. **What we have is -- I don't think I needed to consider that because what we have here is an example of a stable solution that contains both sodium bromfenac and BAC.**
02:45 Q. Okay. So, is the answer to my question that you did not consider the possible functions of polysorbate 80 in the formulation?
A. **Well, I would have looked at the list of ingredients in general, but what I took out from it was that it contains the**
02:45 **two species, sodium bromfenac and BAC, and that there was no**

precipitate, it was stable. I can't tell why it's stable. It's stable.
Q. Is one possibility for the reason it's stable is that it contains polysorbate 80; is that a possibility?
02:46 A. **Well, it's an ingredient in there. The solution as a whole is stable. Any of the ingredients could be doing anything.**
Q. So, in your view, it is at least possible as a matter of chemistry that polysorbate 80 is performing the function in
02:46 the '225 Example 6 of preventing complexation of bromfenac and BAC; is that right?
A. **Well, in terms of chemistry, these are systems. You have everything in there and you can't say any one component does a particular thing. It would be all the components together**
02:46 **producing the system in which material is dissolved.**
Q. When you look at the list of excipients in Example 6 of the Ogawa '225 patent, is there anything else on that list that would prevent physical complexation other than polysorbate 80? And if you don't know, you can just tell me
02:46 you don't know.
A. **Well, I don't understand the concept of preventing complex formation. If the ions are perfectly happy in solution and to be staying in solution, it's not a case of preventing complex formation. It just doesn't happen.**
02:47 Q. So --

THE COURT: If there's happy ions?

(Laughter.)

THE WITNESS: If they're happy ions to be in solution with water molecules around them, why would they form complexes?

BY MS. HOLLAND:

Q. All right. Let me probe that a little bit. So, we've seen several references where at least the authors of the references say that complexes form between NSAIDs and BAC. I understand you disagree with them, but you have at least seen several references where those statements are made, right?

A. There are several references where they speculate that might be happening, yes.

Q. And you agree that purely as a matter of chemistry, there can be a salt formed between the plus charge of the benzalkonium ion and the minus charge of the NSAID in solution, right?

A. If you dissolve a salt in solution, in a solvent, you form a solution that has plus and minus charges, but again, it's a system. So, whatever the minus species, however many there are, are floating around in a lot of water molecules with a lot of equivalent number of plus species, whatever they are and whatever makeup they are, you have to look at the whole formulation to see. They don't suddenly say we're going to grab -- one is going to grab another.

Q. Let me try my question again because I appreciate that chemistry lesson, but my question I believe was a little different, so let me see if I can explain it better. Do you agree as a matter of chemistry that it is potentially possible for a salt to form between benzalkonium chloride and an acetic NSAID in solution?

A. In chemistry terms that doesn't have a meaning. It is already a salt. You have a salt when you have plus and minus charges. It is already a salt. If it is dissolved, you have a mixture of possibly -- it's a mixture of salts, if you want to look at it. Once you have dissolved ions into solution, they don't remember who they came in with. You end up with a mixture of minuses and a mixture of pluses floating around that come and interact occasionally and go apart again.

Q. All right, well -- I'm sorry, I didn't mean to interrupt. Are you done?

A. If they stay in solution, then they keep moving around.

Q. All right. I'm going to try this one more time. Do you agree as matter of chemistry that a salt could form between the plus charge of a benzalkonium ion and the minus charge of an NSAID compound at pHs relevant to ophthalmic solutions?

A. As soon as you dissolve the ions in solution, it is a salt form in solution.

Q. I'm going to direct you to your deposition testimony, page 184, lines 3 to 13. So, at your deposition, Doctor, were

you asked, "So, potentially, a salt could form between the plus charge of the benzalkonium ion and the minus charge of an NSAID compound at pHs relevant to ophthalmic solutions?"

There was an objection.

Your answer, "It's a theoretical possibility, but without evidence, you don't know it's going to happen."

Was that the question and answer?

MR. DINER: Objection. I don't think that what Ms. Holland is offering is inconsistent with how he just responded a moment ago.

THE COURT: No, I'll permit it. His trial testimony doesn't offer that it may be a theoretical possibility. So, I'll permit it.

THE WITNESS: I'm just looking at the context.

MS. HOLLAND: There's no question and answer on the table anymore.

THE COURT: No, the witness didn't answer your question.

MS. HOLLAND: Oh, I'm sorry, your Honor. I thought there was -- that he had.

THE COURT: The tail end of your question was was that the question and answer? I assume the answer is yes.

THE WITNESS: Yes.

THE COURT: That's what's on the paper, and you can ask the next question.

MS. HOLLAND: Thank you, your Honor.

BY MS. HOLLAND:

Q. Now, in your testimony about Example 6 of the '225, and let's put that back up again, you said that the stability was excellent, correct?

A. Well, I'm quoting from the words underneath Example 8.

Q. And Example 6 of the '225 patent is at pH of 8, correct?

A. That's correct.

Q. Do you know whether pH has an effect on the stability of a pharmaceutical formulation?

A. I'm sure it does in some cases, yes.

Q. Okay. Do you know whether the stability of this particular formulation would still be excellent at a pH of 7?

A. Sorry. Can you repeat that question?

Q. Sure. Do you know whether the stability of Example 6 of Ogawa would still be excellent if it were at a pH of 7?

A. I don't believe he does that experiment, so I can't tell.

Q. You showed the Court several three dimensional structures during your direct testimony.

A. Yes.

Q. Do you recall that?

A. Yes.

MS. HOLLAND: Could we put one of those examples up on the screen? Can you tell me which PDX it is? PDX3-10.

BY MS. HOLLAND:

Q. All right. And those three dimensional structures as you testified were meant to show that the compounds look different from each other, right?

A. That's correct.

Q. Now, those images, they represent structures of the molecules in the gas phase, correct?

A. They are generated from a program that cannot put the solvent there, so yes.

Q. So, those are in the gas phase, but you understand that the formulations in this case are aqueous solutions, right?

A. I do, yes.

Q. And your 3D images don't show what the molecules would look like in an aqueous solution, right?

A. We have no way of telling what they would look like directly in solution, but a common use of these types of programs to generate 3D images, when we can get information about what they look like from the gas phase calculation to the solution, very often they are a very close correlation.

Q. You didn't mean to suggest to the Court that what you put up on the screen here are how the molecules would look like in the aqueous solutions relevant to this case, right?

A. No. These things are mobile. I can't show them moving around. But you have to take one static view, and however they move around, you're not going to be able to turn polysorbate 80 on the left into the structure on the right.

You have to take a snapshot.

Q. But these are a snapshot in the gas phase, not in an aqueous solution, right?

A. The calculation is done in a gas phase, but an organic chemist's experience would be that this does translate in most cases to the aqueous or any other solvent base.

Q. I'd like to turn to your testimony on the 984, EP 984, which is JTX-209. Can you open up to that reference, please, in your binder?

A. I have it. I have it.

Q. Okay. And you see that the title of this particular patent application on the first page of JTX-209 is preservative system for ophthalmic formulations. Do you see that?

A. I see that, yes.

Q. So, you agree that this particular reference is directed to the field of pharmaceutical formulations, right?

A. Yes.

Q. And you pointed out this sentence on page 2 of the EP 984 at paragraph 40 -- I'm sorry, at line 40 on page 2.

MS. HOLLAND: Can we blow that up, please?

BY MS. HOLLAND:

Q. And that statement here in this pharmaceutical formulation reference is that, "As in the case with other ophthalmic drugs that contain a COOH group, antiinflammatory

solutions of NSAIDs for ocular use have proven to be incompatible with quaternary ammonium compounds such as BAC." Do you see that?

A. That's what it says.

Q. Okay. Now, do you know one way or the other whether formulators as of 2003 generally considered it to be common knowledge that antiinflammatory solutions of NSAIDs with COOH groups were generally incompatible with BAC?

A. I don't know how I'd know what a formulator would know. I read this type of general statement in the introduction to a number of patents and papers, and no, it doesn't provide any evidence that it will happen in any case or any particular case.

Q. Okay. So, well, let's look at the next sentence then. "This incompatibility is due to the fact that the COOH group can form a complex with the quaternary ammonium compounds, rendering the preservative less available to serve its function, and reducing the activity of the active ingredient." Do you see that?

A. Yes.

Q. And you understand that, at least in this reference, this pharmaceutical formulation reference, it is being stated as a general proposition that the incompatibility is due to the interaction between the COOH group of the NSAID with the -- with BAC that renders the BAC less available to serve its

function and reduces the activity of the NSAID. Do you see that?

A. That's what it says.

Q. Okay. Now, that particular sentence doesn't say that whether or not the NSAID is going to form a complex with BAC depends in some way upon the chemical structure of the acetic NSAID, does it?

A. That doesn't state that, but the chemical structure would depend on whether it would form what they term here as a complex, and it doesn't -- I don't think it says that it would have to precipitate out either. So, if it stayed in solution, you wouldn't reduce the amount of the active ingredient.

Q. All right. But just getting back to my question, my question was, does this paragraph say anything about the formation of the complex being dependent in any way on the structure of the NSAID?

A. No. But a person of ordinary skill would know that forming any complex depends on the structure of the two compounds coming together or ions coming together.

Q. Okay. And it also doesn't say whether or not the ability to form a complex between an NSAID and a BAC depends -- and BAC depends upon the solubility of the NSAID, does it?

A. It doesn't say that, but if they formed a complex in solution, they would -- it would be temporary and they would solvate apart and join up with something else and come back

together.
Q. But this reference doesn't say that, does it?
A. **It doesn't say that, no.**
Q. And it doesn't mention hydrogen bonding, correct?
03:01 A. **Those are very basic parts of chemical knowledge that students learn in their first term in any chemistry course.**
Q. It doesn't say that whether or not the NSAID will form a complex with BAC depends upon its hydrogen bonding abilities?
A. **It doesn't say that.**
03:01 Q. Now, you said this reference is directed to ketorolac, right?
A. **Yes.**
Q. And you pointed the Court to Examples 2 and 3, correct?
A. **Yes.**
03:01 Q. Now, would you go to page 4, please. This is a part that you didn't direct the Court to, but I want to look at it anyway. Why don't we go to page 4.
A. **Yes.**
Q. There's a table on lines 30 to 40. I'm actually going to
03:02 look first at line 29. It says, "In a preferred ophthalmic NSAID solution, the ingredients are combined in the following proportions." Do you see that?
A. **I do, yes.**
Q. Okay. And what is the first ingredient on that table?
03:02 A. **It says NSAID.**

Q. Right. It's not particular to any particular NSAID; is that right?
A. **It just says NSAID.**
Q. And then if you look at the next table, it says another
03:02 preferred ophthalmic NSAID solution, and again it's a generic NSAID, correct?
A. **Well, it uses the term "NSAID." It doesn't say one in particular or every NSAID. A person of ordinary skill would read the rest of the patent to see what was being referred to.**
03:02 Q. In these particular tables, there's no reference to the formulations being applicable to any particular NSAID, correct?
A. **In these general tables, it doesn't specify one or all or some.**
03:03 Q. And then if you go -- why don't we look at claim 1 on page 11.
MS. HOLLAND: Can we put that up on the screen? Thank you. Maybe a little larger. Is that possible? Thank you. Maybe it's me. Okay.
BY MS. HOLLAND:
Q. If you look at claim 1, it says, "An ophthalmic NSAID formulation comprising an NSAID in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic ethoxylated octylphenol
03:03 surfactant, and an aqueous vehicle." Do you see that?

A. **Yes.**
Q. So, the claims of this patent are not directed specifically to ketorolac, right?
MR. DINER: Your Honor, I'd like to just insert an
03:04 objection for the record. These are claims, and what is in a claim is not necessarily an interpretation of what is in the specification and what one of ordinary skill in the art typically looks to.
THE COURT: So, you're asking the question be
03:04 rephrased to speak only to this claim?
MR. DINER: Well, I'm just saying that the -- that the claim refers to NSAID, but that is a claim, and claims are directed to lawyers whereas the specifications are directed to people of ordinary skill in the art. And it doesn't really
03:04 matter what a claim says to a skilled person. It matters what's in the spec.
THE COURT: All right. Just a moment.
MR. DINER: And moreover, your Honor --
THE COURT: If the witness is aware of the claims of
03:04 this patent, he can answer the pending question, which is, "So, the claims of the patent are not directed specifically to ketorolac?" I'll permit it.
THE WITNESS: Some of the claims are.
BY MS. HOLLAND:
03:05 Q. Okay. But claim 1 is general and would apply to any

NSAID, correct?
A. **I don't know that. That's a legal conclusion I don't have the expertise to make.**
Q. And while we're on claim 1, you will see that it refers
03:05 generally to nonionic ethoxylated octylphenol surfactants. Do you see that?
A. **Yes.**
Q. It doesn't name any specific nonionic ethoxylated octylphenol compound in that claim, right?
03:05 A. **It doesn't name any, but a person of ordinary skill would look at the whole patent, read the whole patent to find out what was being referred to.**
Q. Let's go to Example 5, which you discussed in your testimony.
03:06 A. **Okay.**
Q. And I believe you said that this Example 5 shows results of testing of three ketorolac-benzalkonium chloride formulations, right?
A. **I think it actually involves six.**
03:06 Q. Correct, they had different concentrations. Thank you. Thank you for that correction.
Okay. But there were three different surfactants that were being evaluated, right?
A. **That's correct.**
03:06 Q. And do you understand that the purpose of this experiment

was to determine whether or not these three surfactants would help in keeping the solution clear rather than turbid, right?

A. Well, they were looking to see whether the formulations that include those different surfactants stayed clear, yes.

03:07 Q. And more specifically, if you look at the third paragraph under Example 5, it tells exactly what this experiment was intended to do. It says, "Three surfactants were evaluated for their ability to dissolve the ketorolac-benzalkonium chloride complex and maintain a physically clear solution over an extended period of time." Do you see that?

A. That's correct, yes.

Q. Do you at least agree that that was the purpose of this experiment?

A. That's what it says, yes.

03:07 Q. Now, you said earlier I believe in your testimony that when you looked at Example 5, it suggested -- it suggested to you that the authors really didn't know what was causing this turbidity in the solution. Was that your testimony?

A. It says the word "suggested." It doesn't say "is."

03:08 Q. Okay. But when you look at the paragraph I just pointed to you, it says that they were "being evaluated for their ability to dissolve the ketorolac-benzalkonium chloride complex." Do you see that?

A. Yes.

03:08 Q. Does that indicate to you that the authors believed there

was a ketorolac-benzalkonium chloride complex?

A. No.

Q. All right. And when you look at Example 5, do you agree that it was the octoxynol 40 that was able to keep these

03:08 solutions clear?

A. That's what the table says.

Q. You also said in your direct testimony, looking at this same table, you commented on Dr. Lawrence's testimony that a formulator would have looked at the .02 percent octoxynol 40

03:09 and used that as a starting point for tyloxapol formulation. Do you recall that?

A. No.

Q. You don't recall that testimony of yours about Dr. Lawrence relying on the .02 percent?

03:09 **A. I remember Dr. Lawrence saying that, yes.**

Q. Yes. Okay. And you said that's not right because they have different structures, right?

A. I can't remember my exact words, but I think I went on to say you can't swap amounts with surfactants.

03:09 Q. And that's because they have different structures. That was your testimony, right?

A. Yes.

Q. Okay. Now, you don't know if a formulator looking at this would, in fact, use .02 percent octoxynol 40 for --

03:10 withdrawn.

You don't know whether a formulator would use .02 percent for a tyloxapol solution given that it had been used at that percentage for octoxynol 40 in the 984 patent, right?

A. Well, I can see that there would be no reason for the

03:10 **formulator to believe that that would work, and so a formulator would do the normal experimental procedures they use to determine what would be, if any, the best formulation, which would mean a whole set of experiments under different concentrations.**

03:10 Q. Right. I want to turn to the '560 patent, which you also talked about in direct testimony, JTX-57.

A. I have it.

Q. Sorry. It's a big binder. I'm going to try to fit it up here.

03:11 Now, the '560 patent that you testified about -- sorry about that.

The '560 patent has an additional statement in it that you didn't testify about earlier, and I'd like to take a look at that. If you go to column 8.

03:12 **A. Yes.**

Q. And then at line 63.

A. 63?

Q. Yes, in column 8.

A. Yes.

03:12 Q. I'd like to look at that last sentence. It says, "The

discovered conditions also permit including in the formulation quaternary ammonium compounds as preservatives, since these same conditions also inhibit the unacceptable interaction between diclofenac and the quaternary ammonium compounds." Do

03:12 you see that?

A. That's what it says.

Q. Okay. And a quaternary ammonium compound again, BAC would be an example of that, correct?

A. BAC would be an example of that.

03:12 Q. Okay. And this paragraph is telling the formulator that including BAC as a preservative can be used to inhibit unacceptable interaction between diclofenac -- well, I'm sorry. Let me start that again.

This sentence is telling the formulator that there is a

03:13 way to inhibit the unacceptable interactions between diclofenac and BAC, right?

A. Well, it is saying that you can include the quaternary ammonium compound. That's the thing relating back to the control experiment that was done where diclofenac was included

03:13 **with the quaternary ammonium salt and they didn't see a precipitate. It doesn't say that you would ever get a precipitate under those conditions.**

Q. But again, this patent acknowledges, as others that we've looked at have, that there was a general understanding that

03:14 there was an interaction between acetic NSAIDs and BAC,

correct?
A. It is making that type of statement, but for which there is no experimental evidence that I've seen in the prior art.
Q. Just to be clear, your opinions in this case are not that
03:14 these interactions don't exist or can't exist. It's that you haven't seen experimental evidence of them existing, correct?
A. Not in the prior art, no, I haven't, no.
Q. Let's go to the '444 patent which is JTX-43. You also testified about this patent on your direct examination?
03:15 **A. Which is the number?**
Q. JTX-43.
A. 43?
Q. Yes.
A. I have it.
03:15 Q. And you did testify about this patent as well in your direct examination, correct?
A. Yes.
Q. All right. Let's look at column 2, lines 34 to 39. Actually, I'm going to look at the sentence that starts on 36.
03:15 It says, "Conventional broad spectrum." Do you see that?
A. I do.
Q. And it says, "Conventional broad spectrum antimicrobial agents like BAC tend to interact with the nonsteroidal antiinflammatory agents over time and thereby reduce the
03:16 efficacy of the medication." Do you see that?

A. It says that, but it is including the word "tend" which means it may or may not.
Q. But the authors are acknowledging that a phenomenon exists of NSAIDs complexing with BAC, right?
03:16 **A. Well, they are making a speculative comment in the introductory part of a patent for which I have not seen any experimental evidence.**
Q. So, you think all the authors of these prior art references in the area of pharmaceutical formulation, they
03:16 were all just speculating that this complexation exists?
A. Well, since they don't seem to see any evidence that it happens in their cases, it looks like speculation to me.
Q. Okay. And again, this is a reference in the field of pharmaceutical formulation, right?
03:16 **A. It wouldn't matter where it is.**
Q. No, but my question was different. You agree that this is a reference in the field of pharmaceutical formulation?
A. Right, but it's dealing with chemistry.
Q. Is this a reference in the field of ophthalmic
03:17 formulations?
A. Which is part of chemistry.
Q. Do you have a problem answering my question?
A. It is, yes.
Q. Is this a reference in the field of ophthalmic
03:17 formulations?

A. It is, yes.
Q. Okay. Now, you pointed out column 7, line 55, you pointed to a sentence that said, "It should be noted that BAC was found to be unexpectedly compatible with diclofenac in the
03:17 present ophthalmic composition." Do you see that?
A. Can you remind me of the line, please?
Q. Yeah, I apologize for that. It is column 7, line, I think it's 54. This is something you had -- or 55. It's something you pointed to in your direct examination.
03:18 **A. Oh, yes, sorry. I have it, yes.**
Q. All right. So, again, that sentence says that, "it should be noted that BAK was found to be unexpectedly compatible with bromfenac in the present ophthalmic composition." Do you see that?
03:18 **A. Yes, that's what it says here.**
Q. So does that suggest to you that it is expected that it would be incompatible?
A. That's one way you could interpret it. But it's another one of those speculative expect or not. I haven't seen any
03:18 **evidence that it happens.**
Q. And again, in that particular reference that you cited earlier, there's no statements in here that say that the interaction between BAK and the NSAID in any way depends on structure, isn't that right?
03:19 **A. That would be in the general knowledge of either a**

formulator or the chemist or whoever is reading the patent.
Q. Okay.
A. So the person of ordinary skill in the art.
Q. I had a bit of a different question; just answer this
03:19 question.
My question was isn't it correct that nowhere in this patent is there any mention of the complexation issue having anything to do with the structure of the particular NSAID.
A. I don't believe there is, no.
03:19 MS. HOLLAND: Your Honor, would you mind if we broke now for lunch? It's 12:40.
THE COURT: All right. That's fine.
MS. HOLLAND: Thank you.
THE COURT: So let's break until 1:40. And remember that this afternoon, this is the day when I have to end court a little bit early, 3:45. Okay?
MS. HOLLAND: Yes, your Honor.
(Luncheon Recess)
DEPUTY CLERK: All rise.
04:32 THE COURT: Be seated, please.
Sorry I'm a bit late, but stuff happens during the lunch hour in other cases and so that detained me. But we're ready to go.
MS. HOLLAND: Thank you, your Honor.
04:32 May I begin?

THE COURT: Yes.
BY MR. HOLLAND:
Q. Dr. Davies, I'd like to look at one of the demonstratives you put up this morning, I think it's Slide 13. Yes. Thank you.
So this slide was a comparison of octoxynol 9, octoxynol 40, and tyloxapol, correct?
A. **Yes.**
Q. And you compared them in terms of molecular weight as well as critical micelle concentration, correct?
A. **That's correct.**
Q. You have never personally done any experiments to assess critical micelle concentration, right?
A. **I have not, no.**
Q. Okay. Now, when you look at the critical micelle concentrations of octoxynol 9, octoxynol 40, and tyloxapol, they differ from each other, right?
A. **That's correct.**
Q. And a critical micelle concentration is a property of a surfactant, right?
A. **It is, yes.**
Q. Okay. And the lower the critical micelle concentration is, the less surfactant you have to use in a particular system in order for it to be able to solubilize in that system, correct?

A. **It depends on whether you're talking about molecules or grams.**
Q. So let's look. You did it in terms of moles, right?
A. **That's correct.**
Q. Okay. And that's what a chemist would do, right?
A. **I think both are acceptable by anybody.**
Q. Okay. And you've seen it -- you've seen formulation documents look at it in terms of grams, right?
A. **I have, yes.**
Q. So if you look at it in terms of moles, you see that of the three tyloxapol has the lowest critical micelle concentration, right?
A. **That's correct.**
Q. It's also correct even if look at it in terms of grams, tyloxapol has the lowest critical micelle concentration, right?
A. **I can't remember the calculation.**
Q. Well, let's talk about that for a second. So in order to figure that out, you would multiply -- so let's look at octoxynol 90 for example. So 625 grams per mole is the same as .625 grams per millimol, right?
A. **Yes.**
Q. So if you multiple the .625 grams per millimol times .24 millimol per liter that you use as the critical micelle concentration, that gives you the CMC in grams per liter,

right?
A. **That's correct, yes.**
Q. Okay. And that would be the same calculation for each of the octoxynol 9, octoxynol 40, and tyloxapol, right?
A. **Yes.**
Q. Any. Now, have you done that calculation before?
A. **A long time ago.**
Q. Okay. So do you recall after you did that calculation, that tyloxapol has the lowest CMC even in terms of grams per liter?
A. **I don't recall that, no.**
Q. Okay. But that's a simple matter of arithmetic, right? We would just have to multiple, as we said before, grams per millimol times the CMC in millimol to get the grams per liter, right?
A. **That's correct, yes.**
Q. Just so the record is clear, I actually have a calculator. So why don't we do the math so that we can just confirm that tyloxapol has the lowest CMC of those three in terms of grams per liter as well.
A. **Okay.**
Q. Are you up for that?
A. **Yes.**
MS. HOLLAND: May I approach the witness, your Honor?
THE COURT: Yes.

BY MR. HOLLAND:
Q. Okay. So let's start with the octoxynol 9, I think we had agreed that you'd multiple .625 times .24 to get the CMC in grams per liter, right?
A. **Yes.**
Q. And what do you get after that calculation?
A. **.15.**
Q. .15?
A. **Yes.**
Q. And then for octoxynol 40 what do you get?
A. **1.59.**
Q. Okay. Thank you.
And let's, finally, do the calculation for tyloxapol.
A. **.081.**
Q. Okay. So now you agree with me that of the three nonionic surfactants that you listed on your slide, octoxynol 9, octoxynol 40, and tyloxapol, tyloxapol has the lowest CMC both in terms of millimol and in terms of grams per liter, correct?
A. **Yes.**
Q. And that is information that would have been available to the person of ordinary skill in the art, right?
A. **That's true. We just worked it out.**
Q. Okay. I'd like to put something up on the screen. I apologize, I'm not sure if these are in the plaintiff binders

or not, but let's see. Thank you.

So what I've done here, doctor, is I've simply taken the structures for flurbiprofen, ketorolac, and diclofenac that were in your expert reports and just put them up on the
04:40 screen. You confirm those are the correct structures, right?

A. Yes.

Q. And these compounds all have different structures, right?

A. They do, yes.

Q. Okay. The thing they have in common is the COOH carboxyl
04:40 group, right?

A. They're all acids, carboxylic acids.

Q. They're all what we've been calling acidic NSAIDS, right?

A. They are acidic NSAIDS, yes.

Q. And these are three acidic NSAIDS that have been
04:40 particularly exemplified in the prior art references that talked about complexation, correct?

A. They're the ones we've been discussing, yes.

Q. Now, even though these three compounds all have different structures other than the carboxyl group, the COH group, they
04:41 all were reported as forming a complex with BAC, correct?

A. I don't believe any of them reported forming a complex with BAC.

Q. I know you don't -- I know you don't think there was experimental evidence, but do you recall in your direct
04:41 testimony talking about those three compounds being ones that

appeared in the prior art references that had brought up the issue of complexation?

A. Well, the general statement was in the introductory part of the papers -- of the patents.

04:41 Q. Okay.

A. But there were no -- the complexation was not seen in the -- or was not evidenced in the examples of those patents.

Q. All right. I think I understand what you're saying. Let me ask it again just to make sure.

04:42 What you're saying is we've looked at patents that had these three different acidic NSAIDS in them, that had general statements that these NSAIDS would form complexes with BAC, but you saw no evidence in those patents of the complexes forming, is that right?

04:42 **A. I don't think I said would.**

MR. DINER: It's outside the scope of his direct testimony with regard to flurbiprofen.

MR. HOLLAND: Oh. I apologize.

Did you not talk about -- he did talk about it.

04:42 MR. DINER: Not a reference. That reference to flurbiprofen, that was your question.

BY MR. HOLLAND:

Q. All right. So let's look at the ketorolac and diclofenac then. That's fine. Ketorolac and diclofenac again are acidic
04:42 NSAIDS, right?

A. Yes.

Q. They both have different structures other than the COOH carboxyl group, right?

A. Yes.

04:42 Q. And both of them appear in references where there are general statements about complexation between NSAIDS and BAC, right?

A. Whether they be, yes.

Q. Okay. Do you recall that flurbiprofen was an Example 4
04:43 of EP '984, one of the references that you brought up on your direct examination?

A. I recall that, but I don't think there was any data to do with any experiment to do with it.

Q. Can we look at the '929 patent, JTX-61? It should be in
04:44 your case binder.

A. Oh, the cross binder.

Q. And I'd like to turn to Column 1.

THE COURT: Excuse me, I need to interrupt because my monitor is not picking up the feed.

04:44 DEPUTY CLERK: I'm going to shut it down and bring it back up.

(Realtime Malfunction)

THE COURT: We're back on board.

MS. HOLLAND: Thank you.

BY MR. HOLLAND:

Q. All right. So we had been looking at JTX-61, this is the '929 patent. And then I believe I asked you to read Column 1 starting at Line 27. You see there's a paragraph that begins "benzalkonium chloride is a widely used preservative in
04:49 ophthalmic solution?"

A. Yes.

Q. You there?

The next sentence says "benzalkonium chloride and other quaternary ammonium compounds are generally considered to be
04:49 incompatible with ophthalmic composition of drugs with acidic groups such as nonsteroidal anti-inflammatory drugs, NSAIDS." Do you see that?

A. That's what it says.

Q. So this particular reference talks about it as a general
04:49 proposition that benzalkonium chloride and acidic NSAIDS are considered to be incompatible. Do you see that?

A. It's what it says. Generally could be taken to mean not always or sometimes.

Q. Okay. Now again, in this reference, the '929 patent,
04:50 there's absolutely no statement that the tendency of an acidic NSAID to form a complex with BAC has anything to do with the specific structure of the acidic NSAID, correct?

A. It doesn't say it, but it's what a person of ordinary skill would understand.

04:50 Q. All right. Let's turn to JTX-207, this is WO 597.

A. **Okay.**
Q. Again, this is a reference in the field of ophthalmic compositions, correct?
A. **Yes.**
04:50 Q. And just to be clear, if you turn back to JTX-61 for a moment, the one we just looked at, the '929 patent, that was also a reference in the field of ophthalmic compositions, correct?
A. **That's what it says in the title, yes.**
04:51 Q. Thank you.
So let's go back then to JTX-207. Would you turn to Page 2 of the reference, it has JTX-207.4 on the bottom.
A. **Yes.**
Q. At the top of the page we again see the statement that
04:51 we've seen many times before, "benzalkonium chloride has been widely used in ophthalmic solutions." Do you see that?
A. **Yes, I see that.**
Q. Okay. And then this reference says that it was "well-known that benzalkonium chloride was incompatible with
04:51 anion drugs forming insoluble compounds which caused the solution to turn cloudy." Do you see that?
A. **It says it is considered.**
Q. Bromfenac is an anion drug, correct?
A. **Bromfenac is an acidic compound that forms anions when**
04:52 **it's in solution at a pH that we're talking about, yes.**

Q. Yes. But you understand that bromfenac would fall within the meaning of anion drugs in this paragraph, right?
A. **Yes.**
Q. And again, there's no mention in this reference of the
04:52 tendency of the NSAID to form a complex with BAC having anything to do with the structure of the particular NSAID, right?
A. **I wouldn't expect there to be. It's such a basic part of chemistry.**
04:52 Q. So you agree with me it's not there in the reference, right?
A. **I can't see it there.**
Q. Okay. Would you turn to JTX-158, the '113 patent?
A. **Okay.**
04:53 Q. And this is another reference in the field of ophthalmic formulations, right?
A. **I can't see it in the title but --**
Q. Let's look at Column 1 of this reference. Again, it says at line -- let's see, 31, "benzalkonium chloride is a
04:53 quaternary ammonium compound which has been widely used in ophthalmic solutions." Do you see that?
A. **Yes.**
Q. Again we see the statement that it was well-known that it was incompatible with anion drugs. Do you see that?
04:54 A. **It says it's considered incompatible.**

Q. It says it was well-known that it was considered incompatible, right?
A. **Yes.**
Q. Okay. And this is another reference where there is no
04:54 qualification on that general statement in terms of the specific structure of any particular NSAID, right?
A. **But it's a general reference in the introductory part to a patent. I wouldn't expect there to be a reference because it's such a basic part of chemistry.**
04:54 Q. Now, so -- all right. Now, have you heard of a reference called Remington's?
A. **Yes.**
Q. Okay. That's a reference that's in the field of pharmaceutical formulation, right?
04:54 A. **Yes.**
Q. And is that -- do you understand that to be a well-known reference in the field of ophthalmic formulation?
A. **I believe it is well-known, yes.**
Q. All right. Can we look at DTX-15, please?
04:55 A. **Sorry. 15?**
Q. Yes, that should be in your cross binder.
A. **Okay. I have it.**
Q. Would you go to page DTX15.5, please. And you'll see there a section of Remington's that called quaternary ammonium
04:55 compounds. Do you see that?

A. **Yes.**
Q. And the first sentence of Remington says that "BAC is by far the most common preservative used in ophthalmic formulations." Do you see that?
04:56 A. **Yes.**
Q. And then the next sentence says that "over 65 percent of commercial ophthalmic products are preserved with BAC." Do you see that?
A. **Yes.**
04:56 Q. And then if you look two sentences later, what Remington's tells the formulator is that "as a cationic surface acts as material of high molecular weight, it is not compatible with anion compounds." Do you see that? Do you see that statement?
04:56 A. **Sorry, where did you point me to?**
Q. I think it's six lines down from the top of the paragraph. It's highlighted actually if you want to look up on the screen if that's easier.
A. **That's what it says there.**
04:56 Q. Okay. And Remington's makes a broad statement that the incompatibility issue applies to anion compounds, right?
A. **That's true, it does so here. But elsewhere in Remington under benzalkonium chloride it says the incompatibility is at certain concentrations.**
04:57 Q. Okay. So why don't we look here first. Okay? So right

here it says that it's incompatible with anion compounds, right?

A. It doesn't say under what circumstances it's incompatible. It doesn't say under all circumstances.

04:57 Q. Does this tell -- does this section tell the formulator that BAC is incompatible with anion compounds?

A. That's what it says, but it doesn't say under which circumstances.

Q. All right. And this is a text that is used by

04:58 formulators, right?

A. I believe so, yes.

Q. Now, you looked at several references here that contained what you called, I think, general statements about acidic NSAIDS being incompatible with BAC, right?

04:58 **A. Yes.**

Q. All right. Does that indicate to you that as of 2003, pharmaceutical formulators generally believed that acidic NSAIDS were incompatible with BAC?

A. It says some were, some of the references that I've seen

04:58 **are by the same authors or the same inventors.**

Q. Now, a person of ordinary skill in the art in 2003, they're confronted with all these references that say there's a problem here or potential problem between acidic NSAIDS and BACs. Is it your opinion that the person of ordinary skill in

04:58 the art would simply disregard the statements in those

references?

A. I think they do what any scientist would do, do an experiment and find out whether their set of conditions presented a problem or not.

04:59 Q. So in your view a person of ordinary skill in the art looking to formulate bromfenac in 2003 aware of this literature would at least test to see if bromfenac formed a complex with BAC, right?

A. If they were interested in making a formulation that

04:59 **included it, they would do an experiment, yes.**

Q. And if they had done the experiment, they would have seen that bromfenac in fact does form complexes with BAC, isn't that correct?

A. I don't know that, no.

04:59 Q. Well, did you ask your attorneys if they were aware of any documents that showed that bromfenac does indeed form complexes with BAC?

A. I don't recall doing that. I may have done, I don't recall.

04:59 Q. All right. Did you investigate that issue before you came into court with your opinions today?

A. Well, I looked at all of the information I've been presented with, which is a very large amount, and I haven't seen any -- an example where such a problem is evidenced.

05:00 Q. All right. So let's look at -- I'd like to look at

JTX-26.

A. Okay.

Q. Do you see it says -- this is a Senju document, it says Study Protocol.

05:00 **A. Where am I --**

Q. I'm sorry, let me orient you. That's my fault. I apologize.

The first page says Affidavit of Translation. Do you see that?

05:00 **A. Yes.**

Q. Then if you turn over to the next page, which is 26.2, you see it says Study Protocol, right?

A. Yes.

Q. And this is from the year 2000, right?

05:01 **A. Yes.**

Q. Okay. Now, I'd like you to -- you see the first paragraph says -- let me do this.

The study director is Shirou Sawa. Do you see that?

A. I see that.

05:01 **Can we go back to the date? This -- I don't believe this would have been in the public domain at that time, this looks like it's from an experimental procedure so it would be from a lab notebook.**

Q. I didn't say it was in the public domain.

05:01 **A. Okay.**

Q. I'm asking you -- my question had been did you see any evidence that if the person of ordinary skill in the art in 2003 had done the experiment you said they would perform to test whether there was a complex between bromfenac and BAC, if

05:01 they would have seen such a complex form.

MR. DINER: I'm not sure if there's a question pending or if that was her question, your Honor, but we're going to object to the line of questioning to the extent it goes into whether or not someone skilled in the art would have

05:02 considered a document not in the public domain. And these, of course, are the internal Senju documents we've been talking about for the last couple days and I believe your Honor has ruled that a document of this nature can only be considered as part of this trial in the context of determining what the

05:02 level of skill is. And she's asking him about whether or not this would -- is this evidence of complexation, it has nothing to do with the level of skill, and it's also an internal document that's not in the public domain.

MS. HOLLAND: Your Honor, it does have to do with the

05:02 level of skill. The evidence is that a person of ordinary skill in the art who performed a test in 2003, according to what Dr. Davies said, the question was would that person indeed have found that a complex formed between bromfenac and BAC. I think that's a key issue here because if they had

05:02 found that complex, that's the whole ball of wax, right, then

they would have known to put in the tyloxapol to deal with the physical stability problem.

MR. DINER: And, your Honor --

MS. HOLLAND: So it's relevant to know that in 2003 if the experiment had been done, what the outcome would have been.

MR. DINER: Your Honor --

THE COURT: Had you previously asked the question of whether Dr. Davies is aware of any experimental evidence that displayed such a complex --

MS. HOLLAND: Yes.

THE COURT: Displayed such a complex --

MS. HOLLAND: Yes.

THE COURT: -- or produced such a complex.

MS. HOLLAND: Yes.

THE COURT: And he had said no?

MS. HOLLAND: Right. Now I'm confronting him with the evidence.

THE COURT: So the question is, has he seen this? Is that right?

MS. HOLLAND: The first question is, has he seen this, yes.

THE COURT: And was that answered?

MS. HOLLAND: I don't remember. I believe he had seen it at his deposition, at a minimum.

THE COURT: All right. Well, there's no objection to that -- I mean, there's no problem with asking him whether he has seen this document.

MR. DINER: Agreed, Your Honor, it's just -- I thought she had asked the question of whether or not this is going to be information that would have been considered important to the formulator in terms of whether or not complexation takes place, and the point is, it wouldn't have been because it's not a prior art document and it has nothing to do with the state of the art, as --

THE COURT: I sustain the objection on that ground. If it's not in the public domain, it wouldn't have been available to the formulator who is the POSA here. If it's being asked for a different purpose, I'll permit the question to be reframed --

MS. HOLLAND: Thank you.

THE COURT: -- and then if there's an objection, I'll rule on it.

BY MS. HOLLAND:

Q. As a matter of level of skill in the art as of 2003, if a formulator had tested a bromfenac/BAC solution, would they have found that a precipitate formed?

A. I don't know. I'm sorry, would they have found if a --

Q. That a precipitate formed, a complex formed between the two.

A. I don't know.

Q. All right. Well, let me direct your attention to JTX26.

A. Okay.

Q. And I'd like to direct your attention to -- it's four lines up from the bottom of the objective section.

Do you see that?

A. Okay.

Q. Okay. What it says there is, bromfenac sodium forms insoluble complexes with the addition of quaternary ammonium salts becoming cloudy.

Do you see that?

MR. DINER: Objection, Your Honor. Again, this is getting into this document, as a non-prior art document asking the witness, which he's already said he hasn't seen and doesn't know whether or not the formulator would have expected there to be -- or as this document, would this document establish that there was a complexation, and it's clearly not a prior art document. It's not in the public domain.

It's the inventor's own work and as we discussed many times yesterday, under the statute, an inventor -- the path that the inventor takes his invention cannot negative the invention in the context of obviousness.

MS. HOLLAND: That wasn't my question, Your Honor. I was asking it for the very purpose that we discussed the other day about, you know, what is the level of skill in the art.

Someone confronted with this problem in 2003, what was the level of skill in the art about what they would have done, procedurally, to see whether or not there was a complex.

I find it problematic that they are shielding their experts from testifying about things that are clearly contrary to the opinions they're giving in this case, and I'd like to be able to explore that.

THE COURT: Well, didn't he say that there would have been an experiment done if one were interested in looking at that problem, that they would -- I believe his testimony five minutes ago was --

MS. HOLLAND: Yes.

THE COURT: Yes, that's what a person of ordinary skill in the art would do. They would do an experiment. So this document doesn't add to that, if it just says an experiment was done.

MS. HOLLAND: It says the -- what the outcome of the experiment would have been.

MR. DINER: But, Your Honor, that's the whole point. I mean, it's an internal document, it's the inventor's own work, and she's going to use it, not for skill of the art because now we are beyond skill of the art, she's trying to use it to say that the experiment was done and that this document somehow is going to substantiate that it was -- a complex was formed. But that's -- this document is improper

for that purpose.

He can't -- you can't use it for that because it's not what the skilled formulator would have had in his or her possession before the invention was made. This is something that was in the public domain -- sorry, not in the public domain and was the inventor's own work, and as we've been over and over again, it can't be used to negative a conclusion or -- or to negative the obviousness determination, and it's not about level of skill any longer. It's about what would have done and what would have been seen. So it has nothing to do with level of skill in terms of --

THE COURT: I agree that there's not a level of skill issue here. The witness has not said, it would be impossible to do such an experiment, or no one would have thought to do such an experiment. To the contrary, he said, such an experiment would have been done if someone were concerned about the contraindications that were being, you know, mentioned in the literature.

As to this document though, I still don't know the answer to whether Dr. Davies has reviewed it in connection with formulating his opinion.

BY MS. HOLLAND:

Q. Dr. Davies, have you seen this document before?

MS. HOLLAND: I'm sorry, Your Honor. I banged into this.

THE WITNESS: I don't recall having seen this document.

BY MS. HOLLAND:

Q. Do you recall testifying about it at your deposition?

A. I don't -- I'm looking at this document. I don't know if I've seen this document.

MS. HOLLAND: Your Honor, I can represent to the Court -- I cannot show you the transcript, but I can also represent to the Court that he did review the document and testified about it at his deposition.

THE COURT: Because you showed it to him or because his attorneys had provided it as part of his preparation to testify?

MS. HOLLAND: I believe it was because it was shown to him at the deposition.

MR. DINER: And it's not part of his expert report, Your Honor, as far as I know.

MS. HOLLAND: Your Honor, if I can say one more thing.

THE COURT: Okay.

MS. HOLLAND: Dr. Davies sat -- testified for quite a while this morning about why there would be no complex formed between bromfenac and BAC as a matter of chemistry. That was kind of the substance of what he said this morning. We have a document in front of us that says that that's not right.

Seems to me I should be able to question the witness about it.

THE COURT: As a matter of impeachment?

MS. HOLLAND: Yes.

THE COURT: Because you're taking the adversary's own words?

MS. HOLLAND: Yes.

MR. DINER: But it's not the adversary, Your Honor, and, in fact, what we're talking about here is a document that is not in the public domain. The issue is whether one of skill in the art before January of 2003, looking at what was then available in the prior art, whether it's Desai, whether it's Fu, or whether it's these other patents, would there have been an expectation that those general statements would have been applicable to bromfenac and whether it would have formed a complex.

What happens internally within a company, as they're marching on their way and they're doing their experiments to an invention is completely irrelevant to the inquiry of obviousness. The statute is clear on that, and on top of that, this is not anything that Dr. Davies had in his expert report, he's provided no opinions on it.

THE COURT: Well --

MS. HOLLAND: It's cross-examination.

THE COURT: It's cross-examination and he could be asked whether this changes his opinion. If he were to be

shown an example of an experiment having been done that produced such a precipitate, would that change his opinion that such a precipitate would not -- that there's no evidence for such a precipitate being formed.

I don't think that that's retracing or examining the inventor's steps. It's inquiring into a physical fact. If one does such an experiment, what's the result? I don't see that as probing.

MR. DINER: Well, because the issue --

THE COURT: Just a moment.

MR. DINER: Sorry.

THE COURT: I don't see that as probing the pathway to the -- to the invention. I do see it as -- as an experiment that would -- if it's believed, contradicts his own opinion about a physical fact of whether, when one conducts this mixing under certain conditions, there would or would not be a precipitate.

MR. DINER: Well, can I just make a further statement? The issue again that we're dealing with is obviousness and, of course, that's looked at at a time prior to when the invention was made, based on publicly available information. What she is actually going to, Ms. Holland, is, is it a fact that it's been done.

Well, that's really a question of inherency whether it is or is not. Has nothing to do with obviousness and the law

is quite clear what may be inherent is not relevant to obviousness, because you can't predicate a position of obviousness on what is unknown, based on the prior art, and this is clearly not in the prior art, and there's a number of
05:11 cases on that, like, I can't think of the case off the top of my head, but that much is clear. That -- whether it's a fact or not is irrelevant to the issue of obviousness because obviousness is based on and predicated on what's in the prior art, something there or not there. If it's not known in the
05:12 prior art, then the person skilled in the art would not have it in his or her head in order to make these assessments.

THE COURT: Prior art said that there was a problem --

MR. DINER: Mm-hmm.

05:12 THE COURT: -- with NSAIDs forming complexes with BAC. The witness has said that's too general of a statement, and he's never seen experimental evidence for bromfenac forming complexes with BAC. And he's testified as to why that wouldn't happen. He's being confronted with evidence that it
05:12 does happen. It happens to be in -- in your client's study protocol, but again, if it's a physical fact, why not permit him to be questioned on it, and to see whether it changes an important opinion that he holds in this case, that no such complex is formed.

05:13 MR. LIPSEY: Excuse me, Your Honor. I know it's

irregular. May I be heard just briefly?

THE COURT: Yes.

MR. LIPSEY: You can see in the very first sentence of this document, this problem arose when they went to reduce
05:13 the pH. This is exactly the path of the invention. These are documents reflecting how the invention was made, and to allow the information the inventor discovered and established to then be used directly or indirectly to try to prove the obviousness of the invention is exactly what's prohibited by
05:13 the statute, and that's why we're concerned about this.

THE COURT: Well, then, is your witness willing to retract his testimony that he's never -- he's unaware of any experimental evidence that such a precipitate forms?

MR. LIPSEY: I think his testimony was that there was
05:13 none in the prior art.

THE COURT: Okay. Did the questioning go beyond prior art?

MS. HOLLAND: It did, Your Honor.

THE COURT: That's my recollection, too.

05:14 MR. LIPSEY: I think that's --

THE COURT: So which way do you want to have it? Is he going to, you know, rest upon what he has said or is it going to be modified? If it's not going to be modified, then he can be impeached with experimental evidence that he's been
05:14 -- that he was made aware of for this case.

MR. LIPSEY: But if his testimony was that he had not seen any evidence in the prior art that that happened, that's not impeached with this document, which shows --

THE COURT: I agree.

MR. LIPSEY: Okay.

THE COURT: If his -- if the prior testimony was whether in the prior art he saw experimental evidence of bromfenac complex -- forming complexes with BAC, this document does not impeach that because it's not prior art.

05:14 MR. LIPSEY: I believe that's all he testified to in his --

THE COURT: Well, let's go back, then, and I'll ask that a foundation be laid. It might be that my recollection and Ms. Holland's is not correct.

05:15 MS. HOLLAND: But I think there are -- Your Honor, there are two aspects to the impeachment here. One is the question of, have you seen any evidence that BAC forms the complex. The second matter of impeachment is just the general testimony this morning that it won't happen. I mean, that's
05:15 apart from any specific evidence about whether he's seen any experiments. I mean, he was on the stand for an hour telling us why it wouldn't happen, and now we have a document that says it would. So that's separate -- that's a separate grounds of impeachment.

05:15 MR. DINER: I don't think it has --

THE COURT: Just a moment, please. A foundation has to be laid as to whether when one goes beyond prior art and into the realm of the chemical world, whether he's aware of experimental evidence that such a complex forms.

BY MS. HOLLAND:

Q. Dr. Davies, are you aware of any evidence that bromfenac forms an insoluble complex with BAC?

A. I don't believe I am.

Q. Okay. Well, let's look at JTX26, then.

05:16 MR. LIPSEY: I guess we would just like a standing objection to the line of questioning, Your Honor.

THE COURT: Well, he's indicated that no, he's not aware of such evidence.

MR. LIPSEY: But he's not saying his opinion was that
05:16 it never happened. His opinion -- the opinions he gave were that there was no evidence in the prior art of that complex, and that's all we intend to rely on his testimony for. We are not trying to prove here an absolute negative.

MS. HOLLAND: But that's the testimony that came in.

05:16 MR. LIPSEY: I would --

MS. HOLLAND: Based on your direct examination.

MR. LIPSEY: -- you were asking him about document after document after document, and he said, I don't see evidence there that it happened.

05:17 MS. HOLLAND: Your Honor, my recollection is that we

heard a lot of testimony about hydrogen bonding and why bromfenac, because of its hydrogen bonding won't form this complex while the other stuff in the prior art does.

MR. LIPSEY: I think his testimony was that it might not, that you couldn't tell just because one did, that another didn't. That was the whole point of that testimony. The molecules are different, and just because something happens with one, you cannot, because of the differences, say it necessarily happens with the other, and he said time and again, when faced with documents, that I don't see any evidence there, that it does. That was the extent of his testimony.

THE COURT: Well, perhaps all this could be clarified if there's an agreement by the plaintiffs that Dr. Davies is not testifying that such a reaction, this formation of complex with BAC does not happen or could not happen.

MR. LIPSEY: I think we are prepared to stipulate he's not testifying that it cannot happen. What he's testifying to is that there's no evidence in the prior art that it did happen, and that because of chemical differences, you couldn't predict *a priori* that it would happen from what happened with other molecules. That was the extent of his opinion and the extent of the testimony, as I heard it go in. Am I correct?

MR. HASFORD: Correct.

THE COURT: So you're suggesting at least two things; not testifying that it cannot happen and no evidence in prior art that it did happen.

MR. LIPSEY: Correct.

THE COURT: And anything -- anything that might have suggested that there's no evidence in the world that it happens falls away. Is that correct?

MR. LIPSEY: There's no evidence in the prior art that it happened.

THE COURT: Right. That is his testimony.

MR. LIPSEY: Yes.

THE COURT: But it is not his testimony that -- from what you're saying, that it has never happened in the history of mankind?

MR. LIPSEY: Right. Correct, that it -- that it cannot happen is not the testimony. That it never happened after, you know, in the course of the inventor's discovery, he's not making that testimony.

THE COURT: Well, with that clarification, then, and his opinion being limited to prior art and being limited to what it is that the prior art showed to a person of ordinary skill, then I would sustain the objection.

MS. HOLLAND: Can I ask one more question, Your Honor, and --

THE COURT: I'm almost afraid to hear it but --

(Laughter.)

THE COURT: I have no problem with you asking a question. This is a difficult area for --

MS. HOLLAND: Yes.

THE COURT: -- for all -- all of us, but let me ask you the question first, and I'm asking the defendants collectively, if this witness's expert testimony is confined to those areas of what was shown in the prior art and also a clarification that he's not testifying that it cannot happen, then is that acceptable?

MS. HOLLAND: That's why -- that's why I want to ask one more question, because I think with one more question, that would likely be acceptable. So that the question that I'm proposing is --

THE COURT: Go ahead.

BY MS. HOLLAND:

Q. Is it your opinion that if a person of ordinary skill in the art had performed the experiment in 2003, that they would not have seen complexation between BAC and bromfenac?

A. I -- you have to repeat that question to me.

Q. Is it your opinion that if a person of ordinary skill in the art in 2003 had performed an experiment with bromfenac and BAC to look for complexation, that they would not have seen complexation?

A. I don't know. You have to do the experiment to find out.

MS. HOLLAND: Your Honor, I think it would be in our view, this document goes to that question of what the person of ordinary skill in the art in 2003 would have encountered had they done the experiment, and that's, as you said, I don't know if it's a matter of scientific fact, but it has to do with the motivation of the person of ordinary skill in the art as of 2003, which is a central issue here. If they had done the experiment and they found that there was the complexation, they clearly would have been motivated to do something about it.

THE COURT: I'm going to sustain the objection that counsel is raising to make, because of the witness's testimony in response to your question. He does not have an opinion.

MS. HOLLAND: Okay. I think that's all I have, Your Honor.

THE COURT: Very well. Thank you, Ms. Holland. Redirect?

MR. DINER: No, Your Honor.

THE COURT: Okay. Just one moment. Let me see if I have any clarifying questions.

Oh, before the witness leaves the stand, is there -- are the plaintiffs moving in the documents at this time?

MR. DINER: Oh, I believe, yes. Thank you for reminding us, Your Honor. We talked about that and I think defendants are fine with the documents we seek to move in.

THE COURT: Okay. And that's the list that was previously read?

MR. DINER: Correct.

MS. HOLLAND: Yes, Your Honor.

05:23 THE COURT: Okay. Let me recite into the record what I believe those documents are and you can correct it.

MR. DINER: Sure.

THE COURT: So the following will be received into evidence: PTX-199, PTX-160, PTX-632, JTX001 is already in

05:23 evidence. JTX210, JTX181. Is the next one JTX147? Yes. JTX071.

THE DEPUTY CLERK: JTX147 was already in.

THE COURT: Okay, 147 was already in. JTX071, JTX209, JTX043 and JTX057. Is that correct?

05:24 MR. DINER: Correct.

THE COURT: Okay. So each is in evidence.

THE DEPUTY CLERK: 71 was already in.

THE COURT: Yeah, 71 was already in also. JTX71.

(PLAINTIFF EXHIBITS PTX-199, PTX-160, PTX-632, JTX210, JTX181

05:23 JTX209, JTX043 and JTX057 WERE RECEIVED IN EVIDENCE)

MS. HOLLAND: Your Honor, I believe there are a couple of exhibits used during cross that I'd like to move in. So it's JTX158, JTX207.

THE COURT: Any objection?

05:25 MR. DINER: Just one second, Your Honor. I'm just

looking for 158.

THE COURT: That's the '113 patent of Lucero.

MR. DINER: We're okay with that, Your Honor.

THE COURT: Okay. So these two exhibits will be

05:25 received into evidence. JTX158 and JTX207.

(DEFENDANT EXHIBITS JTX158 and JTX207 WERE RECEIVED IN EVIDENCE)

THE COURT: And I have no further questions and I thank you for your testimony.

05:25 THE WITNESS: Thank you.

THE COURT: You may step down.

MR. DINER: Your Honor, could we just have a few minutes' break to reorganize here?

THE COURT: Sure. Okay. Let's take a ten-minute

05:26 break.

(RECESS TAKEN; 2:42 p.m.)

THE COURT: You can be seated, please.

Mr. Hasford?

MR. HASFORD: Yes, your Honor. Plaintiffs call

05:45 Dr. Robert O. Williams, III.

THE COURT: Okay, Dr. Williams, please come to the witness stand. And, Dr. Williams, I remind you that you are still under oath and so your testimony will be given under oath. Okay?

05:45 THE WITNESS: Yes, sir. Thank you.

MR. HASFORD: And permission, your Honor, to approach and distribute the binders?

THE COURT: Yes. Okay. You may proceed.

MR. HASFORD: Thank you, your Honor.

05:45 (DIRECT EXAMINATION OF ROBERT O. WILLIAMS, III BY MR. HASFORD:)

Q. Good afternoon, Dr. Williams.

A. Good afternoon.

Q. Did you hear Dr. Lawrence testify that the subject matter

05:46 of Claims 6 and 20 of the '431 patent allegedly would have been obvious to a person of ordinary skill in the art over the references she discussed?

A. Yes.

Q. Do you agree with Dr. Lawrence's opinions?

05:46 **A. I do not.**

Q. Let's explore the basis for your disagreement.

First, Noel, would you please put up PDX1-1 on the screen. Oh, I apologize, 2-1.

So, for the record, this is PDX2-1 on the screen. Do

05:47 you see that, Doctor?

A. Yes, I do.

Q. Dr. Williams, you previously testified as to your opinion concerning the level of education and work experience a person of ordinary -- of a person of ordinary skill in the art of the

05:47 '431 patent. Do you remember that?

A. Yes.

Q. Have you heard any testimony from Dr. Lawrence that has changed your opinion in any way with respect to the level of education and work experience of a person of ordinary skill in

05:47 the art of the '431 patent?

A. No, I have not.

Q. Did you hear Dr. Lawrence testify that your proposed definition of a person of ordinary skill in the art, in her words, excludes a pharmaceutical formulator?

05:47 **A. Yes.**

Q. Do you agree with Dr. Lawrence?

A. I do not.

Q. How, if at all, does your proposed definition of a person of ordinary skill in the art of the '431 patent encompass a

05:48 pharmaceutical formulator?

A. So, my definition, I have pharmaceutical chemistry, which encompasses, in my opinion, and what I meant here, was a formulator, in addition to -- I think she excluded preformulation, but that's also included here as part of a

05:48 **person of ordinary skill in the art as a formulation scientist. So that's included in my definition.**

Q. How, if at all, does your use of the phrase "pharmaceutical chemistry" within your proposed definition of a person of ordinary skill in the art encompass a

05:48 pharmaceutical formulator?

A. Well, pharmaceutical chemistry is -- it encompasses or is encompassed by, it's really similar to pharmaceutical sciences. Some places actually grant a degree. My institution grants a degree in pharmaceutical sciences, some pharmaceutical chemistry. But my intent here is it is describing one and the same.

Q. Were you present in the courtroom when the Court asked Dr. Lawrence questions about the definition of a person of ordinary skill in the art?

A. Yeah, I was. Yes.

Q. Is it your opinion that a person of ordinary skill in the art of the '431 patent would need a Ph.D. degree?

A. Not necessarily, no.

Q. Why not?

A. Because, as I've defined it, a Bachelor's Degree with three to five years of work experience in this area, that, to me, that's a senior graduate student, so that's a Bachelor's in Science with -- towards the end of their graduate education, or it's a B.S. level pharmaceutical sciences person that gets hired into a company, undergoes training. I mean, I have hired these people and they can do this type of job. They are persons of ordinary skill in the art.

I've also allowed for a Ph.D. When I state a comparable level of education and training, that could have a Ph.D. with maybe one year experience.

Q. And you have an alternative formulation of your level of ordinary skill in the art. Would you please explain that?

A. Yes. So what I meant here is -- by the alternative definition is the -- as has been discussed over the last couple of days, I mean, to me, one thing is notable, it's this development process is multi-disciplinary. And this hypothetical person of ordinary skill in the art, it's not just one background in solving a problem, as the '431 problem is solved. And so that's why I allow this alternative to also be included, which is a person that is skilled in designing, evaluating and/or administering pharmaceutical formulations.

Q. And what is that obtained by?

A. That, for example, could be a degree in medicine, which would cover the clinical aspects.

Q. Did you hear Dr. Lawrence testify that for a person of ordinary skill in the art as of January 21st, 2003, pharmaceutical formulation development allegedly constituted routine optimization?

A. Yes.

Q. Do you agree with Dr. Lawrence?

A. I don't, no.

Q. Why do you disagree?

A. Because from my experience, it's the antithesis of routine optimization, even for a drug that is known by the person developing it, by the person of ordinary skill in the

art, and -- and over my 30 years of experience, I mean, it's not routine.

When you design a study, even with a known drug, you don't know the outcome, and so you design a study in order to try to figure out what a formulation would be and the factors that impact that formulation such as additives, so it is -- it's not routine optimization at all, in my opinion.

Q. In your opinion, is drug formulation difficult and unpredictable?

A. From my experience, it is, yes.

Q. How, if at all, can a single modification to a pharmaceutical formulation change the properties of a formulation?

A. A single modification, either in the drug substance or one of the additives or a step in the manufacturing process could change the stability, either chemical or physical stability of that formulation, from my experience over the years.

Q. Could that potentially result in substantial changes in the properties of the formulation?

A. It could, yes.

Q. In your opinion, may individual formulation components interact with each other in unpredictable ways?

A. From my experience, they could, yes.

Q. How so?

A. Well, so -- so, components, additives, could interact with the active drug substance or could interact with other additives in the formulation. From my experience, I have an example where -- or more than one example, but one most recently, where it was supposedly the same material as an inactive ingredient, but different vendors where it came from, and in one case, the drug degraded because of something to do -- we hadn't quite figured it out yet, but something to do with the vendor's manufacturing process for that particular additive, whereas the other additive, it's stable. So it can affect.

Q. Is it fair to say that these sorts of interactions may impact efficacy?

A. Well, if it causes drug degradation, then there is less drug, so -- and the end result could be less efficacy.

Q. Is it fair to say that these interactions may impact safety?

A. Well, if it causes a drug degradation and -- or an additive degradation that forms a degradation product in the dosage form, such that that degradation product poses a safety issue, then it could.

Q. Is it fair to say that these interactions may impact stability?

A. Definitely, they could impact stability. And one just has to design studies and figure that out as part of the

formulation.

Q. Is fair to say that these interactions may impact preservative efficacy of a formulation?

A. They could. If the interaction affects the -- the chemical degradation of the preservative or the additive somehow affects the preservative, it could affect the ability of that formulation to pass a preservative efficacy test.

Q. How, if at all, does the selection of inactive ingredients, including the amounts of those inactive ingredients, involve trial and error?

A. Well, from my experience, when designing a formulation, it -- it's -- I mean, we do it by statistical design where we set up a study looking at the variables of additives and processing and the active ingredient, and it -- and it is trial and error. It -- in the end, it really is trial and error.

Q. Is it fair to say that this process may also involve failures and frustration?

A. From my experience, yes.

MS. HOLLAND: Your Honor, I have not objected yet, these are -- all these questions are very leading.

MR. HASFORD: I disagree, your Honor. I think it's just establishing some background here, and it's going to opinions that Dr. Lawrence has offered that this is an oversimplification and we're trying to fairly respond to

those.

THE COURT: Well, be that as it may, refrain from undue leading. All questions are to some extent leading, but they cross the line where they supply the answer to the witness.

BY MR. HASFORD:

Q. As of January 21st, 2003, in your opinion, did the development of ophthalmic formulations in particular constitute routine optimization to a person of ordinary skill in the art?

A. They did not.

Q. Why not?

A. Because ophthalmic solution formulations, they had to be sterile. There was -- in solution form, from my experience, drugs, if they are going to degrade, they tend to degrade at a faster rate. In solution, you have the effective pH. With ophthalmic products, you have the issue of applying this liquid onto the eye, so there is a patient comfort factor. So it makes it, in my opinion, difficult.

Q. Does the residence time for the eyedrop also impact that process or that consideration?

A. That's one of the considerations that a person of ordinary skill in the art, in developing ophthalmic solution formulations, would have to consider, yes.

Q. And earlier you testified about trial and error and

various failures and frustrations. How, if at all, does formulation of ophthalmic solutions involve trial and error, failures and frustration?

A. So, like development of dosage forms, just generally, these liquid solutions -- I mean, again, one has to design the study in a very methodical way, with the additives, with the processing, with the sterilization requirements on how it's going to be sterilized, consider all of that in developing it. So ...

Q. I would now like to discuss the references that Dr. Lawrence has identified. But, first, let's briefly discuss the '431 patent.

You testified previously this week about the claim subject matter of the '431 patent. Do you remember that?

A. Yes.

Q. Have you heard any testimony by Dr. Lawrence that has changed your opinions in any way with respect to the claim subject matter of the '431 patent?

A. I didn't, no.

Q. Did you hear Dr. Lawrence testify about various references in connection with the defendants' obviousness arguments?

A. I did, yes.

Q. In your opinion, do any of these references, each alone or in combination with the teachings of any other references

Dr. Lawrence has identified during her testimony, teach the claim subject matter of the '431 patent?

A. Not in my opinion, no.

Q. Let's now discuss the specific references Dr. Lawrence has identified. Would you please turn to JTX-147 in your binder and identify that document.

A. JTX [sic] is a copy of U.S. Patent 4,910,225. It's the Ogawa '225 patent.

Q. If I refer to JTX-147 as the Ogawa '225 patent or Ogawa, will you understand what I mean?

A. I will.

Q. Do you agree with how Dr. Lawrence has applied the Ogawa '225 patent alone or in combination with any other reference Dr. Lawrence has identified to Claims 6 and 20 of the '431 patent?

A. No, I don't.

Q. Let's explore the basis for your disagreement.

Is the Ogawa '225 patent directed to bromfenac formulations?

A. It is, yes.

Q. Let me direct your attention to Column 3, Lines 7 through 15 of the Ogawa '225 patent.

A. Okay.

Q. Are you there?

A. I'm there, yes.

Q. What does the passage at Column 3, Lines 7 through 15, of the Ogawa '225 patent disclose?

A. So here, Ogawa discloses the fact that "the above compounds," so bromfenac compounds, "may be unstable when stored in an aqueous solution for a long period of time," and recognizes and -- by the stability and says, "and there are some problems in the stability of an aqueous solution containing the compounds. Therefore the inventors extensively investigated the stabilizing method in order to enhance the stability. As a result, unexpectedly, they have succeeded in stabilizing the solution by incorporating a water-soluble polymer and sulfite and adjusting the pH to about 6-9."

Q. What specific water-soluble polymer was used in the formulations of the Ogawa '225 patent?

A. That is polyvinylpyrrolidone or povidone.

Q. What particular sulfite was used in the formulations of the Ogawa '225 patent?

A. That's sodium sulfite.

Q. How, if at all, does the passage at Column 3, Lines 7 through 15, of the Ogawa '225 patent indicate to a person of ordinary skill in the art that Ogawa addressed the issue of bromfenac's stability?

A. So, a person of ordinary skill in the art would understand from this passage that Ogawa solved the bromfenac stability issue by incorporating this water-soluble polymer

and a sulfite and having those two in combination with a pH between about 6 to 9.

Q. Let me now direct your attention to Column 10 and, in particular, Example 6 of the Ogawa '225 patent.

A. Okay.

Q. What is described in the formulation of Example 6 of the Ogawa '225 patent?

A. So, Example 6 describes an ophthalmic solution made according to Ogawa.

Q. Does the formulation of Example 6 of the Ogawa '225 patent include the bromfenac sodium salt?

A. Yes, it does.

Q. Does the formulation of Example 6 of the Ogawa '225 patent contain polyvinylpyrrolidone?

A. Yes, it does.

Q. Does the formulation of Example 6 of the Ogawa '225 patent also contain sodium sulfite?

A. It does, yes.

Q. What, if any, preservative does the formulation of Example 6 of the Ogawa '225 patent include?

A. The preservative is benzalkonium chloride.

Q. Let me now direct your attention toward the bottom of Column 10, in particular, to Lines 50 to 57 in Column 10 of the Ogawa '225 patent.

A. Okay.

Q. What does the passage in Column 10, Lines 50 to 57 of the Ogawa '225 patent disclose?

A. So, in this passage, Ogawa is disclosing the results from including Experimental [sic] 6, and Ogawa states that in "(Table 11) are the residue and appearance of the compositions in Examples 6-8 after 4 weeks at 60° Centigrade."

And then Ogawa states that, "As shown in Table 11, it was found that changes in appearances of the compositions were not observed at all, and the decomposition of the compound was not almost observed, the aqueous compositions being stable, excellent for a long period of time."

Q. I believe in your previous answer you may have said "Experimental 6." Did you mean Example 6 of the Ogawa '225 patent?

A. Yeah, I did not mean experimental Example 6. I meant Example 6. Sorry.

Q. Thank you, Doctor.

Now let's take a look at Table 11 of the Ogawa '225 patent. Let me direct your attention to Column 14, starting at Line 45 where Table 11 begins.

A. Okay.

Q. What is reported in Table 11 of the Ogawa '225 patent with respect to Example 6 of the Ogawa '225 patent?

A. So, reported here in the second column is what Ogawa calls "Appearance." And then the third column is the

"Residue" or it's the amount of bromfenac that's remaining after storage at 60 degrees C. for four weeks.

Q. What amount is reported?

A. 100.9 percent.

Q. In the context of the Ogawa '225 patent, what does the concept of stability entail?

A. In my opinion, one of ordinary skill in the art would understand Ogawa to be talking about chemical stability of bromfenac.

Q. What do you mean by chemical stability?

A. So, chemical, by chemical stability, I mean it's the formation -- so, Ogawa is storing under conditions of 60 degrees C for four weeks, and then is measuring the remaining bromfenac that is being measured chemically. And so if the number decreases, then the bromfenac molecule is not there, it is degrading into some other degradation product that is being formed, which is not bromfenac.

Q. Let's go back to --

THE COURT: Excuse me. May I interrupt and ask a clarifying question?

MR. HASFORD: Certainly.

THE COURT: The residue as reported is 100.9 percent. How is it that residue can be greater than 100 percent? Does that mean that you're getting out more than you put in?

THE WITNESS: I mean, typically, it -- so, there's

variation in the experimental test. They're either using -- they're using, I think, some type of chromatography is what's normally used, and so it could vary according to what they call their standard, gold standard, if you will, or it could be just variation around how it's made or --

THE COURT: Like an experimental artifact?

THE WITNESS: It's not an artifact. It's usually just a variation with the method itself. There's a few percent variation from my experience. You have to prepare standards, and so the standards are made, they're actually weighed out, either by weight or by volume, and so there's -- if you're a little high on the weight, a little bit low on the volume, when you measure the actual percent, you could be off a little bit from 100.

THE COURT: All right. Does it cause you to be suspicious of the result that it ends up being more than 100 percent?

THE WITNESS: It does not, no.

THE COURT: Okay. Very well.

BY MR. HASFORD:

Q. Let's turn back to Example 6 of the Ogawa '225 patent in column 10.

A. **Okay.**

Q. The formulation of Example 6 of the Ogawa '225 patent also contains polysorbate 80. Do you see that?

A. **Yes.**

Q. What role, if any, does the Ogawa '225 patent ascribe to polysorbate 80 in its formulations?

A. **Well, the Ogawa patent doesn't ascribe any particular role to polysorbate 80 in the patent.**

Q. For what reason, if any, would polysorbate 80 have been included in the formulations of the Ogawa '225 patent?

A. **I think a person of ordinary skill in the art seeing this formulation would think one reason could be as a wetting agent. It is an ophthalmic solution drop that's going to be applied onto a hydrophobic surface of the eye. So, it helps wet and spread the liquid over the eye, so that it will keep it in place so the drug can be absorbed.**

Q. Why, if at all, does polysorbate 80 not solubilize bromfenac sodium in the formulations of the Ogawa '225 patent?

A. **Well, it doesn't solubilize polysorbate 80 because bromfenac is, as you've heard over the last couple of days, bromfenac is freely water soluble. So, it's already in solution and polysorbate 80 is not playing a role in its solubilization.**

Q. Have defendants' experts offered any opinion contradicting that bromfenac sodium is freely water soluble?

A. **I have not heard any, no.**

Q. Based on the Ogawa '225 patent, would a person of ordinary skill in the art as of 2003 have expected that

substituting polysorbate 80 with any other nonionic surfactant would improve bromfenac's stability?

A. **I don't think a person of ordinary skill in the art would have an expectation one way or the other what the effect would be.**

Q. Does the Ogawa '225 patent teach the formation of an insoluble complex or precipitate between bromfenac and benzalkonium chloride?

A. **In my opinion, one of skill in the art reading this Ogawa patent would not understand that it's talking about physical stability or -- I mean, I saw no -- nothing that would lead me to think that there's a complex being formed.**

Q. That leads me to my next question. Would a person of ordinary skill in the art understanding the Ogawa '225 -- would a person of ordinary skill in the art -- let me try that again.

Would a person of ordinary skill in the art understand the Ogawa '225 patent to ascribe any physical stability problem for formulations containing bromfenac and benzalkonium chloride?

A. **Not in my opinion, no.**

Q. Looking back at Example 6 of the Ogawa '225 patent in column 10, would a person of ordinary skill in the art have been motivated, as of 2003, to modify the polysorbate 80 component of the formulation of Example 6 of the Ogawa '225

patent to improve bromfenac's chemical stability?

A. **Not in my opinion, they would not have been motivated to do that.**

Q. Why not?

A. **Because Ogawa -- one of skill in the art reading Ogawa would understand that Ogawa has solved the bromfenac chemical stability problem by incorporation of a water soluble polymer and a sulfite and controlling the pH with those two ingredients to between 6, about 6 and 9. And so they understand that Ogawa characterizes that composition as being stable for a long period of time. So, I just -- I don't think one of ordinary skill in the art would understand a motivation would be needed to improve upon the chemical stability of bromfenac.**

Q. Does the Ogawa '225 patent teach tyloxapol?

A. **No, it doesn't.**

Q. Let's now discuss the Sallmann '913 patent. Would you please turn to JTX-071 in your binder and identify that document.

A. **So, JTX-071 is a copy of U.S. patent 5,891,913 to Sallmann.**

Q. If I refer to JTX-71 as Sallmann or the Sallmann '913 patent, will you understand what I mean?

A. **Yes.**

Q. Did you hear Dr. Lawrence testify regarding the Sallmann

'913 patent?
A. **I did, yes.**
Q. Do you agree with how Dr. Lawrence has applied the Sallmann '913 patent alone or in combination with any other
06:11 reference Dr. Lawrence has identified to claims 6 and 20 of the '431 patent?
A. **No, I don't.**
Q. Let's discuss the basis for your opinion. First let me direct your attention to column 1, lines 48 to 54 of the
06:11 Sallmann '913 patent.
A. **Okay.**
Q. What does the passage in column 1, lines 48 to 54 of the Sallmann '913 patent disclose?
A. **So, here Sallmann is disclosing, it states, surprisingly**
06:12 **it was found that the potassium salt -- and then there's a chemical name which is diclofenac potassium -- is especially suitable to treat inflammatory ocular processes in general. It has been demonstrated that, for example, the ocular penetration of diclofenac potassium is much superior in**
06:12 **comparison to the corresponding diclofenac sodium.**
Q. What does the passage in column 1, lines 48 to 54 of the Sallmann '913 patent, indicate to a person of ordinary skill in the art?
A. **So, in my opinion, a person of ordinary skill in the art**
06:12 **reading this would understand that a discovery has been made**

for a different salt, a potassium salt of diclofenac that had superior properties in ocular penetration over that of the sodium salt of diclofenac.
Q. Does the Sallmann '913 patent disclose bromfenac?
06:13 A. **It does not, no.**
Q. Let me now direct your attention to the passage in the Sallmann '913 patent from column 4, line 52, through column 5, Line 2.
A. **Okay.**
06:13 Q. Does the Sallmann '913 patent teach the use of solubilizers in the ophthalmic compositions of diclofenac potassium?
A. **It does, yes.**
Q. Let me direct your attention in particular to column 4,
06:13 lines 65 to 67. What does the passage in column 4, lines 65 to 67 of the Sallmann '913 patent disclose?
A. **So, here Sallmann is talking about solubilizers, and Sallmann says another preferred solubilizer -- sorry, the concentration used depends especially on the concentration of**
06:14 **the active ingredient. The amount added -- so the amount of solubilizer added -- is typically sufficient to solubilize the active ingredient.**
Q. Why is the solubilizer included in the Sallmann '913 patent?
06:14 A. **It's included to help dissolve the diclofenac potassium.**

Q. Why is the solubilizer, sir, needed in the formulations of the Sallmann '913 patent to solubilize diclofenac potassium?
A. **Because diclofenac potassium, depending on pH, will**
06:14 **precipitate out, and so this would keep it solubilized in solution.**
Q. Is tyloxapol disclosed as a solubilizer in the Sallmann '913 patent?
A. **It is, yes.**
06:14 Q. Are the Cremophor surfactants disclosed as solubilizers in the Sallmann '913 patent?
A. **There's two Cremophor examples that are listed as especially preferred solubilizers in Sallmann.**
Q. And I believe you answered my next question. Are the
06:15 Cremophor surfactants as opposed to tyloxapol disclosed as especially preferred in the Sallmann '913 patent?
A. **Yes, that's true.**
Q. Let me direct your attention to column 4, lines 58 through 64 of that previous -- right above where you just
06:15 testified of the Sallmann '913 patent.
A. **Okay.**
Q. Why are the Cremophor surfactants especially preferred, according to the Sallmann '913 patent?
A. **So, Sallmann states here that the Cremophor, he lists two**
06:15 **different types of Cremophor solubilizers, are especially**

preferred because they are particularly good solubilizers that are tolerated extremely well by the eye.
Q. According to the Sallmann '913 patent, is tyloxapol an especially preferred solubilizer?
06:16 A. **No. Sallmann states that tyloxapol is preferred.**
Q. Let me direct your attention now to column 5, lines 55 through 69 of the Sallmann '913 patent.
A. **Okay.**
Q. Does the Sallmann '913 patent separately teach the use of
06:16 stabilizers in its ophthalmic compositions of diclofenac potassium?
A. **It does, yes.**
Q. What stabilizers does the Sallmann '913 patent teach?
A. **So, as stabilizers -- let me find that. Yeah,**
06:16 **stabilizers are listed there at line 56, and Sallmann states stabilizers such as cyclodextrin, thiourea, thiosorbitol, sodium dioctyl sulfosuccinate or monothioglycerol vitamin E and vitamin E derivatives, such as vitamin E Tocopherol Polyethylene Glycol 1000 Succinate, which is also referred to**
06:17 **as TPGS.**
Q. How, if at all, are solubilizers and stabilizers taught as separate excipients in the Sallmann '913 patent?
A. **Well, they are taught as serving different functions. Solubilizers are taught to be present to dissolve the drug,**
06:17 **and the stabilizers are there as serving a function as to**

stabilize against degradation.

Q. Let me direct your attention to column 5, line 39 through 40 of the Sallmann '913 patent. Let me know when you're ready.

06:18 **A. Oh, I'm ready. Sorry.**

Q. Does the Sallmann '913 patent teach the use of preservatives?

A. Yes, it does.

Q. What preservatives does the Sallmann '913 patent teach?

06:18 **A. So, Sallmann lists as preserved preservatives cetrimide, benzalkonium chloride, benzoxonium chloride, and parabens.**

Q. Does the Sallmann '913 patent include any stability data?

A. No.

Q. Let's now turn to the Fu EP 984 reference. I believe

06:18 this one is going to be in the front flap of your binder. It is JTX-209.

A. Okay.

Q. Would you please identify JTX-209.

A. Yes. JTX-209 is -- it's a European patent application

06:19 0 306 984.

Q. If I refer to JTX-209 as Fu or the Fu EP 984 reference, will you understand what I mean?

A. I will.

Q. Did you hear Dr. Lawrence testify regarding the Fu EP 984

06:19 reference?

A. I did, yes.

Q. Do you agree with how Dr. Lawrence has applied the Fu EP 984 reference alone or in combination with any other reference Dr. Lawrence has identified to the asserted claims of the '431

06:19 patent?

A. I don't agree with Dr. Lawrence.

Q. Generally speaking, to what nonsteroidal antiinflammatory drug is the Fu EP 984 reference directed?

A. Fu has data on ketorolac tromethamine.

06:20 Q. Let me direct your attention to page 9 of the Fu EP 984 reference and in particular Example 5.

A. Okay.

Q. What is disclosed in Example 5 of the Fu EP 984 reference?

06:20 **A. So, in Example 5 Fu discloses formulations that are made with either octoxynol 40, Tween 80 or Myrj 52. And then Fu stores these formulations for different periods of time and at different temperatures and then makes an observation as to whether there is the presence of a either physically clear**

06:20 **solution or a precipitant of something.**

Q. Do the formulations of Example 5 of the Fu EP 984 reference contain ketorolac tromethamine?

A. Yes.

Q. In the context of the Fu EP 984 reference, what does the

06:21 concept of stability entail?

A. So, in my opinion to a person of ordinary skill in the art, the Fu reference is concerned with physical stability.

Q. And, in fact, let's take a look at the very first sentence at the top of Example 5 of the Fu EP 984 reference.

06:21 Does the Fu EP 984 reference in Example 5 specifically call out physical stability?

A. Yes, Fu Example 5 states physical stability of the formulations of the present invention is measured, and then Fu goes into detail about how he prepared the formulations.

06:21 Q. Does the physical stability in Fu look to whether the formulation's physical appearance, whether it's clear or turbid, changes over time?

A. That's what it's reporting, yes.

Q. Does the Fu EP 984 reference contain any chemical

06:22 stability data?

A. Not that I saw, no.

Q. What physical stability data, if any, does the Fu EP 984 reference provide for any other NSAID compound besides ketorolac tromethamine?

06:22 **A. There's none. There's only physical stability data with ketorolac tromethamine.**

Q. What physical stability data, if any, does the Fu EP 984 reference provide for any other octoxynol compound besides octoxynol 40?

06:22 **A. It doesn't provide any.**

Q. What, if anything, does the Fu EP 984 reference teach regarding ketorolac's chemical stability?

A. There's -- Fu does not teach the chemical stability of ketorolac.

06:22 Q. Does the Fu EP 984 reference disclose any bromfenac formulation?

A. No, it doesn't.

Q. Does the Fu EP 984 reference disclose any formulation containing tyloxapol?

06:23 **A. No, it does not.**

Q. How does the concept of stability disclosed in the Fu EP 984 reference differ from the concept of stability disclosed in the Ogawa '225 patent?

A. So, the concept of stability in the Fu reference, one of

06:23 **ordinary skill in the art would understand its physical stability by, as I explained, it's looking for presence of clear or turbid formulation, whereas the Ogawa reference, one of ordinary skill in the art would understand that is disclosing chemical stability of bromfenac.**

06:23 Q. Would you please turn in your binder to JTX-157 and identify this document.

A. JTX-157 is a copy of U.S. patent 5,110,493.

Q. Have you considered JTX-157 in connection with your opinions in this case?

06:24 **A. Yes, I have.**

Q. Do you understand that JTX-157 is a U.S. counterpart to the Fu EP 984 reference?
A. That's my understanding, yes.
Q. Did you see anything in JTX-157 that changed any of your opinions regarding the Fu EP 984 reference?
A. I did not, no.
Q. Let's now discuss Dr. Lawrence's obviousness opinions.
MR. HASFORD: I note the time, your Honor. I'm going to be going into a new area here, her overall obviousness opinions. Would your Honor like me to proceed, or is it getting about time to wrap up for the day?
THE COURT: Well, I guess before you get into a new area, then this might be a good time to stop.
MR. HASFORD: Thank you, your Honor.
THE COURT: Okay. Thank you. You can step down, and then we will resume on Monday morning at 9:30.
Just a couple of housekeeping matters. I'm going to enter an order in a couple of minutes pertaining to the discovery appeal, and I'll enter an order that pertains to the three motions in limine, and with regard to all four matters I still have to put a more extended oral opinion on the record, and, unfortunately, time is up for today, but I will attend to that when we resume on Monday.
Are there any questions or any logistics that need to be handled over this recess?

MR. HASFORD: None from plaintiffs, your Honor.
MS. HOLLAND: No, your Honor.
MR. MUKERJEE: No, your Honor.
THE COURT: You're a happy kingdom?
MR. HASFORD: We certainly are, your Honor.
THE COURT: Well, that's great.
MR. DINER: A happy ion.
THE COURT: Good. All right. Then thank you, everybody, and we will resume on Monday.
(Proceedings concluded at 3:42 p.m.)

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-667 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-4149 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

Mitchell H. Cohen United States Courthouse
One John F. Gerry Plaza
Camden, New Jersey 08101
Monday, April 11, 2016

B E F O R E: THE HONORABLE JEROME B. SIMANDLE
CHIEF JUDGE
UNITED STATES DISTRICT JUDGE

Certified as true and correct as required by Title 28, U.S.C., Section 753.
/S/ Lisa Marcus, CCR, CRR, /S/ Karen Friedlander, CCR, CRR, /S/ Carol Farrell, CCR, CRR

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-5144 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-335 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-5144 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-335 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-6893 (JBS/KMW)

-vs-

INNOPHARMA LICENSING, INC., et al.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-3240 (JBS/KMW)

-vs-

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DEPUTY CLERK: All rise.

THE COURT: Be seated, please.

Good morning, everybody. Welcome back.

Are we ready to continue?

00:00 MR. HASFORD: Yes, your Honor, we're ready to resume with Mr. Williams.

Dr. Williams.

THE COURT: Okay. So please resume the witness stand.

00:00 MR. HASFORD: Permission to approach and pass out the binders, your Honor?

THE COURT: Okay.

MR. HASFORD: Thank you.

THE COURT: Good morning, Dr. Williams.

00:00 THE WITNESS: Good morning, your Honor.

MR. HASFORD: And, your Honor, the demonstratives, there's a copy of those in the front flap of that supplemental binder.

THE COURT: Okay.

00:01 MR. HASFORD: May we proceed?

THE COURT: Yes.

HASFORD: Thank you.

(**ROBERT O. WILLIAMS,** HAVING BEEN PREVIOUSLY SWORN AS A WITNESS, TESTIFIED AS FOLLOWS:)

(DIRECT EXAMINATION OF ROBERT O. WILLIAMS BY MR. HASFORD:)

Q. Good morning, Dr. Williams.
A. **Good morning.**
Q. Let's discuss Dr. Lawrence's opinions.
Did you hear Dr. Lawrence opine that the subject matter
00:01 of Claim 6 and 20 of the '431 patent would have been obvious
to a person of ordinary skill in the art over various
references about which Dr. Lawrence testified?
A. **I did, yes.**
Q. Do you agree with Dr. Lawrence?
00:01 A. **I do not.**
Q. Let's start with Claim 6 of the '431 patent.
Did you hear Dr. Lawrence opine that the subject matter
of Claim 6 of the '431 patent would have been obvious to a
person of ordinary skill in the art based on the Ogawa '225
00:02 patent, the Fu EP 984 reference?
A. **I heard that, yes.**
Q. Do you agree with Dr. Lawrence's opinion?
A. **I do not.**
Q. Have you prepared a demonstrative summarizing where you
00:02 disagree with Dr. Lawrence?
A. **I have.**
Q. Let's take a look at PTX-4-1. Would you please explain
the basis for your disagreement with Dr. Lawrence?
A. **Yes. So I've written Claim 6 in its independent form and**
00:02 **compared the limitations of Claim 6 to both the Ogawa**

patent -- the Ogawa patent and the FU application and, as you
can see here, neither Ogawa nor Fu teach tyloxapol as a second
component at a concentration of .2 weight percent.
Q. Just to be clear, have defendants identified any prior
00:02 art whatsoever teaching the 0.02 weight per volume percent
tyloxapol element of Claim 6 of the '431 patent?
A. **I've not seen any, no.**
Q. Let's now turn to Claim 20 of the '431 patent.
Did you hear Dr. Lawrence opine that the subject matter
00:03 of Claim 20 of the '431 patent would have been obvious to a
person of ordinary skill in the art based on the Ogawa '225
patent and the Fu EP 984 reference?
A. **I did, yes.**
Q. Do you agree with Dr. Lawrence's opinion?
00:03 A. **I do not.**
Q. Have you prepared a demonstrative summarizing why you
disagree with Dr. Lawrence?
A. **I have, yes.**
Q. Let's take a look at PDX4-2.
00:03 Would you please explain the basis for your
disagreement with Dr. Lawrence?
A. **Yes. In a similar way I've written Claim 20 in its**
independent form and I've compared Ogawa and Fu to the
limitations of Claim 20 and, as noted here, neither Ogawa nor
00:03 **Fu teach tyloxapol at a concentration of .02 weight percent**

concentration.
Q. Just to be clear, have defendants identified any prior
art whatsoever teaching the 0.2 weight per volume tyloxapol
element of Claim 20 of the '431 patent?
00:04 A. **Not that I've seen. No.**
Q. With respect to Dr. Lawrence's obvious opinions, did you
hear Dr. Lawrence testify that a person of ordinary skill in
the art allegedly would have been motivated to modify the
Ogawa '225 patent in view of the Fu EP 984 reference?
00:04 A. **I did, yes.**
Q. Do you agree with Dr. Lawrence?
A. **I do not.**
Q. Let's discuss Dr. Lawrence's opinions in more detail.
First, let's discuss bromfenac.
00:04 Has Dr. Lawrence identified any reason why a person of
ordinary skill in the art would have been motivated as of 2003
to pursue a bromfenac ophthalmic solution over other
ophthalmic NSAID solutions?
A. **She has not, in my opinion.**
00:04 Q. Would you please turn in the binder to JTX-168 and
identify this document.
A. **So this is -- JTX-168 is a copy of U.S. Patent 5,475,034.**
Q. If I refer to JTX-168 as Yanni or the Yanni '034 patent,
will you understand what I mean?
00:05 A. **Yes.**

Q. Let me direct your attention to Table 1 at Columns 15 and
16 of the Yanni '034 patent.
Did you hear Dr. Lawrence cite the Yanni '034 patent
and testify that a person of ordinary skill in the art
00:05 allegedly would have selected bromfenac over other
nonsteroidal anti-inflammatory drugs, including diclofenac,
because bromfenac is allegedly more effective as an
anti-inflammatory?
A. **I heard that, yes.**
00:05 Q. Do you agree with Dr. Lawrence?
A. **I don't, no.**
Q. Why do you disagree?
A. **I disagree because Dr. Lawrence focused on the in vitro**
column, which is the fourth column, and didn't -- I don't
00:06 **think she considered appropriately the totality of the results**
in Table 1.
Q. How, if at all, does the totality of the results in
Table 1 inform your opinion?
A. **Well, I think a person of ordinary skill in the art**
00:06 **seeing the totality of the data wouldn't draw a preference to**
bromfenac over other compounds that are mentioned. That would
include the ex -- the Column 4 ex vivo, the in vivo and the
in -- both in vivo columns so, again, considering the data in
its totality.
00:06 Q. Let me direct your attention to Column or Compound 8 in

Table 1 of the Yanni '034 patent.

Is it your understanding that Compound 8 in Table 1 of the Yanni '034 patent is nepafenac?

A. Yes.

00:06 **Q.** Is it your understanding that nepafenac is an amide group not a free carboxylic acid group?

A. That's what it shows. If you substitute the Y, the NH_2 for the Y substituent in the structure that's given in Table 1, that is an amide group.

00:07 **Q.** Let me direct your attention to Column 1, Line 60, through Column 2, Line 1, of the Yanni '034 patent.

What does Column 1, Line 60 through Column 2, Line 1, of the Yanni '034 patent disclose?

A. So here Yanni discloses -- he's -- Yanni is stating that although benzoylphenylacetic acids are effective in suppressing ocular inflammation, their full anti-inflammatory potential has not yet been approached due to generally slow rate of penetration through the cornea. Yanni explains that because of this, relatively high concentrations of these drugs are often needed to achieve corneal penetration rates sufficient to provide effective intraocular drug concentrations. Yanni further says, such high drug concentrations are generally not desirable as they may provoke ocular irritation and discomfort.

00:08 **Q.** The portion of the Yanni '034 patent that you just read

references benzoylphenylacetic acid. Is bromfenac a benzoylphenylacetic acid?

A. Bromfenac is an example of a benzoylphenylacetic acid.

Q. How, if at all, does Column 1, Line 60, through Column 2,

00:08 Line 1, of the Yanni '034 patent support your disagreement with Dr. Lawrence?

A. So this passage in Yanni supports my opinion that a person of ordinary skill in the art would not draw a preference to bromfenac over other compounds disclosed in the Yanni reference.

00:09 **Q.** Let me direct your attention to Column 2, Lines 23 through 29, of the Yanni '034 patent.

What does Column 2, Lines 23 through 29, of the Yanni '034 patent disclose?

00:09 **A. So here Yanni states that it's known that 3-benzoylphenylacetic acid derivatives are useful as topically administrable anti-inflammatory compounds for treating ophthalmic inflammation disorders. Yanni describes converting the free acetic acid functional group to ester or amide enhances compound stability by slowing the rate of lactam formation, so it slows the rate of degradation.**

Q. How, if at all, does Column 2, Line 23 through 29, of the Yanni '034 patent support your disagreement with Dr. Lawrence?

A. This passage in Yanni supports my opinion that, again, a person of ordinary skill in the art would not draw a

00:10

preference to bromfenac as I think a person of ordinary skill in the art would be more directed to these derivatives, amide or ester derivatives.

Q. And you mentioned ester or amide derivatives. Is an

00:10 ester or amide derivative of the benzoylphenylacetic acid a different chemical compound from bromfenac?

A. Yes, it is.

Q. Let me direct your attention back to Column 2 and now in particular to Lines 29 through 35 under the summary of the

00:10 invention of the Yanni '034 patent.

What does Column 2, Lines 29 through 34, of the Yanni '034 patent disclose?

A. So here Yanni is stating about the result, and he says, among other factors the present concentration is based on the

00:11 **finding that certain 3-benzoylphenylacetic acid derivatives would show no significant anti-inflammatory activity in vitro are, in fact, as active or even more active than the parent 3-benzoylphenylacetic acids when administered topically to the eye.**

00:11 **Q.** How, if at all, does Column 2, Lines 29 through 35, of the Yanni '034 patent support your disagreement with Dr. Lawrence?

A. So this passage in Yanni supports my opinion because Dr. Lawrence relied on the column of in vitro data in Table 1 and this says clearly that the in vitro data did not show

significant anti-inflammatory activity. But, according then to the ex vivo and in vivo data, Yanni says that these derivatives are as active or even more active when actually administered topically to the eye.

00:12 **Q.** When you refer to the ex vivo and in vivo data, are you referring to those data set forth in Table 1 of the Yanni '034 patent?

A. I am, yes.

Q. Let's switch years a bit. Would you please turn in your

00:12 binder to DTX-110 and identify this document?

A. DTX-110 is a paper on bromfenac sodium that's written by Hara.

Q. If I refer to DTX-110 as Hara or the Hara reference, will you understand what I mean?

00:12 **A. Yes.**

Q. Let me direct your attention to page 2 of the Hara reference, which bears Bates No. PROL 0079164, and in particular the right-hand column.

Did you hear Dr. Lawrence cite the Hara reference and

00:13 testify that a person of ordinary skill in the art would select bromfenac over other nonsteroidal anti-inflammatory drugs, including diclofenac, because bromfenac is allegedly more effective as an anti-inflammatory?

A. I did, yes.

00:13 **Q.** Do you agree with Dr. Lawrence?

A. **I do not.**
Q. Let's discuss the basis for your disagreement. Let me direct your attention to the last paragraph in the right-hand column on the page bearing Bates No. PROL 0079164 and in
00:13 particular to the first sentence of that paragraph.
What does this sentence of the Hara reference disclose?
A. **So here Hara discloses that diclofenac sodium, in parentheses, (Diclod) is an NSAID drug that is indicated for use in treating anterior ocular segment inflammation following**
00:13 **cataract surgery. And Hara states that it, meaning diclofenac sodium, shows particular efficacy in preventing the generation of fibrin, with superior anti-inflammatory efficacy.**
Q. How, if at all, does this portion of the Hara reference support your disagreement with Dr. Lawrence?
00:14 A. **This supports my opinion that a person of ordinary skill in the art would not have a preference to bromfenac based on the Hara reference because Hara states that diclofenac sodium is an approved product and that it's characterized, diclofenac sodium is characterized as having superior anti-inflammatory**
00:14 **efficacy.**
Q. Would you now please turn in your supplemental binder to PTX-294 and identify that document?
A. **PTX-20094 is an excerpt article from the New York Times, it's titled New Painkiller is Withdrawn After 4 Deaths.**
00:15 Q. Is it your understanding that this New York Times

article, PTX-294, involves the drug Duract?
A. **Yes.**
Q. Have you considered PTX-294 in connection with your opinions in this case?
00:15 A. **I have, yes.**
Q. What is Duract?
A. **Duract is the oral form of bromfenac.**
Q. Let me direct your attention to the first page of PTX-294, which is bears Bates No. PROL 0080502. In particular
00:15 let me direct your attention to the first sentence of the second paragraph. What does this portion of PTX-294 disclose?
A. **So here it discusses the fact that the drug Duract, which is a painkiller manufactured by Wyeth-Ayerst, has caused a dozen cases of serious liver failure since it went on the**
00:16 **market last July. It says, four patients died and eight required liver transplants.**
Q. The article refers to last July, what is date of PTX-294?
A. **The date is June 23, 1998.**
Q. How, if at all, does the portion of PTX-294 that you just
00:16 testified about support your opinion regarding bromfenac?
A. **Well, it supports my opinion that a person of ordinary skill in the art would not have a preference for bromfenac.**
Q. In fact, based on PTX-294, is it your opinion that a person of ordinary skill in the art would have tended to shy
00:16 away from bromfenac?

A. **Based on this report and the knowledge of this, yes, they would have.**
Q. Are you aware that Dr. Lawrence has contended that to the extent there was even any need for the claimed bromfenac
00:16 ophthalmic formulations claimed in the asserted claims of the '431 patent that need would have been met by the Ogawa '225 patent and the Hara reference?
A. **I understand that.**
Q. Did Dr. Lawrence identify any reason why a person of
00:17 ordinary skill in the art would focus on developing a bromfenac commercial formulation if the Ogawa '225 patent and the Hara reference already had met any need for a bromfenac ophthalmic formulation?
A. **Not that I heard, no.**
00:17 Q. Let's now discuss benzalkonium chloride.
Do you have any opinion as to whether safety issues existed as of 2003 for benzalkonium chloride in ophthalmic formulations?
A. **I do have one, yes.**
00:17 Q. What is your understanding of the safety issues that existed as of 2003 for benzalkonium chloride in ophthalmic formulations?
A. **As of 2003, a person of ordinary skill in the art, a formulator, would understand that there was reports of ocular**
00:17 **toxicity with benzalkonium chloride use, and so that was a**

known concern as of 2003.
Q. Have you prepared a demonstrative in support of your opinion?
A. **I have.**
00:18 Q. Let me direct your attention to PDX4-3 on the screen, would you please explain the basis for your opinion?
A. **Yes. So the basis of my opinion is that regarding the benzalkonium chloride toxicity, there was the Debbasch paper, PTX-268, where it stated BAC, which is benzalkonium chloride,**
00:18 **causes epithelial toxicity and inflammatory infiltration of ocular surface structures, including growth arrest and cell death.**
The Pisella paper, which is PTX-326, states benzalkonium chloride inhibits proliferation of trabecular
00:18 **cells, and therefore inflammatory reactions may be seen in trabeculum.**
And then the Madhu paper, which is PTX-293, it states, BAK, which is also known as benzalkonium chloride, is known to cause ocular irritation.
00:19 **So those taken together support my opinion that to a person of ordinary skill in the art as of 2003, that there would have been concern using benzalkonium chloride as a preservative in ophthalmic formulation process.**
Q. In your opinion, based on the safety issues, would a
00:19 person of ordinary skill in the art have been motivated as of

2003 to remove benzalkonium chloride from aqueous liquid preparations for ophthalmic use?

A. I think they would have, yes.

Q. How, if at all, does the information on PDX4-3 support your opinion in this regard?

A. So these are examples of literature references that a person of ordinary skill in the art would have known about and therefore in formulating a new ophthalmic formulation they would have been aware of this and they would have been motivated to try alternative preservative systems or preservative free system.

Q. And what alternatives are identified at the bottom of PDX4-3?

A. So at the bottom here as alternatives to benzalkonium chloride the Debbasch article, which is PTX-268, states, it is therefore of striking importance to become aware of the preservative toxicity in order to develop in the near future many more unpreserved drugs, especially for long-term use and/or for patients with pre-existing ocular surface disorders.

And then the Noecker paper, which is PTX-272, states, one such product, a brimonidine compound approved by the FDA in March 2001, has replaced benzalkonium chloride with SOC, SOC is an alternative preservative system, in the current formulation. A 12-month clinical comparison in patients with

glaucoma or ocular hypertension showed that bromindione-SOC was well tolerated and produced a significantly lower incidence of allergic conjunctivitis than brimonidine, as well as equivalent IOP lowering efficacy.

MR. HASFORD: Your Honor, at this point, in the interest of time, I'm happy to, if counsel has no objection, to have Dr. Williams confirm that he obtained the information on PDX4-3 from the four references cited there. However, if there's an objection from counsel, I'm happy to have Dr. Williams identify each of those references individually.

THE COURT: Are you seeking to move them into evidence?

MR. HASFORD: Yes, I am.

THE COURT: Any objection to the four stated references or do you wish to *voir dire*?

MS. HOLLAND: No. I guess Mr. Hasford's point is that he doesn't want to go into each reference individually in the binder but rather just rely on the testimony. I'm fine with that.

MR. HASFORD: Okay.

MS. HOLLAND: No objection.

MR. HASFORD: Thank you.

THE COURT: Okay. Are they then moved into -- or are you going to wait?

MR. HASFORD: I will wait till the end but, yes,

we'll move them into evidence, your Honor.

THE COURT: Okay. Very well.

BY MR. HASFORD:

Q. Now, let's discuss Dr. Lawrence's opinions regarding benzalkonium chloride and NSAIDS in solution.

Did you hear Dr. Lawrence testify that based on the carboxylic acid moiety of some NSAIDS solutions containing benzalkonium chloride and NSAIDS allegedly were known in the prior art to form insoluble complexes or precipitates that result in cloudiness or turbidity?

A. I heard that, yes.

Q. Do you agree with Dr. Lawrence?

A. I don't, no.

Q. Why not?

A. Because as Dr. Davies testified last week, that the -- it's not --

MS. HOLLAND: I have an objection, your Honor. And I'm not 100 percent sure what Dr. Williams is going to say, however, Dr. Williams in his expert report didn't form his own independent opinions on this issue, he relied on the testimony, or I should say on the expert report of Dr. Davies. So I think it would be inappropriate for Dr. Williams to provide opinions that are merely based on reliance on Dr. Davies versus his own personal expertise.

MR. HASFORD: And, your Honor, I believe that

Dr. Williams is entitled to, as a formulator, to rely on the expert testimony of a chemist that there was no evidence in the art as of January 2003 that an insoluble complex or precipitate between bromfenac and BAC formed.

THE COURT: Well, did Dr. Williams disclose that in his expert report?

MR. HASFORD: Yes, he did, your Honor, in his response report, Paragraph --

MS. HOLLAND: The point is Dr. Davies was already on the stand, he gave those opinions. Dr. Williams doesn't have a separate opinion on those issues, that's --

THE COURT: His opinion, as I understand it, he relies on the expertise of the chemist in addressing this issue of NSAIDS and turbidity, is that correct?

THE WITNESS: Yes, sir.

THE COURT: So I think it's a question of weight.

MS. HOLLAND: Okay.

THE COURT: I would assume that a formulator could rely upon a chemist, and does, and here it was disclosed in his expert report. So even though it's not his primary area of expertise, he can derive the chemist's opinion and use it. So I'll permit it.

MS. HOLLAND: Okay. Your Honor.

BY MR. HASFORD:

Q. Do you need the question repeated?

A. If you don't mind. Thank you.
Q. Certainly.
Did you hear Dr. Lawrence testify that based on the carboxylic acid moiety of some NSAIDS solutions containing
00:24 benzalkonium chloride and NSAIDS allegedly were known in the prior art to form insoluble complexes or precipitates that result in cloudiness or turbidity?
A. I understood that, yes.
Q. Do you agree with Dr. Lawrence?
00:25 **A. I don't.**
Q. Why not?
A. Because as I heard Dr. Davies testify to last week, that one of skill in the art can't predict whether a complex is going to form or not, it depends upon the chemical structure
00:25 **of the NSAID, he explained, depends on the formulation, the level of ingredients in the formulation, so there's factors that go into it as I understood Dr. Davies.**
Q. Did you hear Dr. Lawrence testify that the prior art teaches that a person of ordinary skill in the art allegedly
00:25 would have limited the formation of insoluble complexes or precipitates between benzalkonium chloride and an acidic NSAID by the inclusion of certain nonionic surfactant?
A. I heard that, yes.
Q. Do you agree with Dr. Lawrence?
00:25 **A. I do not.**

Q. Why not?
A. Because in my opinion if such a complex did form -- was proven to be formed, the formulation person would seek to avoid that, they would replace the preservative, the
00:26 **benzalkonium chloride, they would possibly formulate a preservative free or potentially switch drugs to where the drug doesn't have the chemical moiety that is causing the complexation.**
Q. Let's explore the basis for your opinion. Would you
00:26 please turn in your supplemental binder to PTX-324 and identify that document.
A. PTX-324 is the label from Drugs at FDA for Acular product.
Q. Let me direct your attention to the line entry for
00:26 original approval or tentative approval. When was Acular PF approved by the FDA?
A. This states Acular Preservative Free or Acular PF was originally approved November 3rd, 1997.
Q. Would you please now turn in the supplemental binder to
00:27 PTX-265 and identify that document.
A. PTX-265 is the label for Acular, so the approved label for Acular.
Q. Is it your understanding that PTX-265 is also a combined package insert for both Acular and Acular PF?
00:27 **A. That's my understanding, yes.**

Q. Is it your understanding that Acular itself was approved in 1992?
A. Yes.
Q. Let me direct your attention to, on the first page
00:27 bearing Bates No. PROL 0332429, to the second paragraph under the chemical structure shown in the description section.
First, what nonionic surfactant is included in the Acular formation?
A. So the nonionic surfactant is in the third line, it's
00:28 **octoxynol 40.**
Q. What preservative is included in the Acular formulation?
A. It states in the second line preservative is benzalkonium chloride.
Q. To what does the PF designation in the name Acular PF
00:28 refer to?
A. PF refers to preservative free.
Q. Let me now direct your attention to the page bearing Bates No. PROL 0332434 in the Acular PF section of the package insert, in particular to the second paragraph under the
00:28 chemical structure shown in the description section.
Is benzalkonium chloride included in the Acular PF formulation?
A. It's not, no.
MR. HASFORD: Noel, would you please now put up
00:29 DDX2-42 on the screen?

BY MR. HASFORD:
Q. Dr. Williams, did you hear Dr. Lawrence testify about the Remington's reference using DDX2-42?
A. I did, yes.
00:29 Q. Let me direct your attention to the third call out with the statement starting, given the alternative, did you hear Dr. Lawrence testifying the Remington's reference allegedly would have taught a person of ordinary skill in the art to use a nonionic surfactant to avoid an alleged complex between an
00:29 NSAID and benzalkonium chloride?
MS. HOLLAND: Your Honor, I have an objection. Dr. Williams doesn't talk about the Remington's reference in his expert report.
MR. HASFORD: So, your Honor, Dr. Williams actually
00:29 was questioned about the Remington reference at two of his depositions, one on February 25th and March 9th, so we believe that that's a proper subject of his testimony here.
He also did submit a supplemental expert report in which he stated he would reserve the right to rely on
00:29 statements that he made during his deposition of questions he was asked, and he was certainly asked about the Remington's reference. So there was, in fact, an exhibit of this portion of the Remington's references was used at one of those depositions.
00:30 Also, your Honor, I'd note that Remington's reference

was relied upon by Dr. Lawrence in her reply expert report for the first time in the context in which Dr. Williams had no opportunity to respond because it was relied on in the reply and then she testified about it in their case in chief in this case.

So we respectfully submit that Dr. Williams should have an opportunity to respond to it for all those reasons.

MS. HOLLAND: I have a couple of responses to that, your Honor.

First of all, to the extent it was in a reply report, Dr. Williams was fully able to testify about opinions at his deposition, he just didn't do that. When he was asked about Remington's at his deposition, he said he hadn't looked at it in forming his opinions in this case.

Now, if that's the only testimony that's going to be elicited and it's consistent with his deposition, I'm fine with that. But to the extent there are new opinions now on the stand that could have been offered at the deposition in response to the questions, I have a serious objection.

THE COURT: Well, he's heard the testimony of Dr. Lawrence, is he not permitted to look at the reference that she's used even for the first time and address it?

MS. HOLLAND: I think he's not, your Honor, because Dr. Lawrence had it in her expert report, so to the extent he, Dr. Williams, had any comments to make about it, he had a

forum to do that but he didn't.

THE COURT: Mr. Hasford said that was only in her very final report and that I guess this witness, Dr. Williams, didn't have a written report after that.

MS. HOLLAND: He did, he had his deposition, your Honor, that was really my point. My point is at the deposition he already knew Dr. Lawrence's opinions about this reference and could have, when asked about the reference, given his opinions on those references. Instead he said, you know, I saw Dr. Lawrence talked about it, I didn't look at it before formulating my opinions, and he didn't offer his own opinions. He did have the opportunity to do that after the reply report.

THE COURT: Okay. So Dr. Lawrence's opinion was of record before Dr. Williams was deposed.

MS. HOLLAND: Yes.

THE COURT: And at that time he said he had no opinion as to Remington?

MS. HOLLAND: Yes.

THE COURT: All right. I'll sustain the objection.

BY MR. HASFORD:

Q. Would you please turn to JTX-207 in your binder and identify this document.

A. JTX-207 is a copy of WO 94-15597.

Q. If I refer to JTX-207 as Wong or the Wong reference, will

you understand what I mean?

A. Yes.

Q. Have you considered the Wong reference in connection with your opinions in this case?

A. I have, yes.

Q. Let me direct your attention to Column 6, Line 11, through Column 7, Line 10, of the Wong reference. What does Column 6, Line 11, through Column 7, Line 10, of the Wong reference disclose?

A. Here in Wong it discloses a study comparing lauralkonium chloride to benzalkonium chloride in a formulation that Wong refers to as Oculen formulations, and this contains the active ingredient sodium flurbiprofen, and Wong is describing the fact that lauralkonium chloride doesn't form a cloudy solution when studied under these conditions whereas benzalkonium chloride does form a cloudy solution.

Q. Now, how, if at all, does Column 6, Line 11, through Column 7, Line 10, of the Wong reference support your opinion that the art as of 2003 talked routes for avoiding entirely the alleged complexation or precipitation problem that Dr. Lawrence has raised?

A. So in my opinion a person of ordinary skill in the art considering Wong would understand that under these conditions tested, that there's an alternative to benzalkonium chloride and that is lauralkonium chloride as a preservative, that for

this drug sodium flurbiprofen did not cause a cloudy solution to be formed, so it's an alternative to try.

Q. Please turn back in your binder to JTX-168, which is the Yanni '034 patent, and let me direct your attention to Column 2, Lines 23 through 29. What derivatives of 3-benzoylphenylacetic acids are taught in the '034 patent?

A. Here Yanni states that it's ester and amide derivatives of the 3-benzoylphenylacetic acid.

Q. Would an ester or amide derivative of a benzoylphenylacetic acid compound have a free carboxylic acid group?

A. It would not, no.

Q. Would ester or amide derivative of a benzoylphenylacetic acid compound without a free carboxylic acid group, have any alleged complexation or precipitation problem with benzalkonium chloride that Dr. Lawrence has raised?

A. My understanding from Dr. Davies, it won't if that particular group is involved in the complexation.

Q. How, if at all, does Column 2, Lines 23 through 29, of the Yanni '034 patent support your opinion that the art as of 2003 talked routes for avoiding entirely the formulation of a potential precipitate or insoluble complex?

A. So this teaches an alternative active ingredient that does not have a carboxylic acid group, namely, an amide or ester derivative that -- so one could -- one of skill in the

art will understand possibly using a derivative of these acetic acid compounds.

Q. Based on the references we just discussed, as of 2003, would a person of ordinary skill in the art have been able to avoid entirely any potential precipitate of an insoluble complex between benzalkonium chloride and an NSAID?

A. Well, to a person of ordinary skill in the art, there would have been ways to try to avoid this complexation, as I've discussed.

Q. Now let's discuss Dr. Lawrence's opinions regarding reducing the alleged formation of an insoluble complex between NSAIDs and benzalkonium chloride.

Did you hear Dr. Lawrence cite the Fu EP 984 reference and testify that a person of ordinary skill in the art allegedly would have substituted an ethoxylated octylphenol compound for Polysorbate 80 in the formulation of Example 6 of the Ogawa '225 patent?

A. Yes, I heard that.

Q. Do you agree with Dr. Lawrence?

A. No.

Q. Why not?

A. Because there's no motivation to substitute in a nonionic surfactant into Ogawa Example 6. It's already stable. The problem of bromfenac chemical stability has been solved by the inclusion of polyvinylpyrrolidone and sodium sulfite in

Example 6.

Q. And you mentioned the chemical stability of the Ogawa '225 patent's Example 6. Does the Fu EP 984 reference teach physical stability rather than chemical stability?

A. The Fu reference is focused on physical stability.

Q. Did you hear Dr. Lawrence cite the Fu EP 984 reference and testify that a person of ordinary skill in the art allegedly would have substituted tyloxapol in particular for Polysorbate 80 in the formulation of Example 6 of the Ogawa '225 patent to create a more stable bromfenac formulation without the formation of an insoluble complex?

A. I heard that, yes.

Q. Do you agree with Dr. Lawrence?

A. I do not.

Q. Why not?

A. Because tyloxapol is not taught in the Fu reference. Fu teaches -- actually provides data on Octoxynol 40, which I understand is chemically distinct from tyloxapol.

Q. Did you hear Dr. Lawrence also testify about Octoxynol 9?

A. I did.

Q. Does the Fu EP 984 reference provide any data for Octoxynol 9?

A. It does not, no.

Q. Would you please turn in your binder to JTX-199 and identify this document.

A. JTX-199 is the Schott reference.

Q. If I refer to JTX-199 as the Schott reference, will you understand what I mean?

A. Yes.

Q. Let me direct your attention to Page 501 of the Schott reference, and, in particular, to the "Conclusions" section, and, specifically, to the first paragraph.

A. Okay.

Q. Did you hear Dr. Lawrence point to this portion of the Schott reference and testify that tyloxapol allegedly was considered a preferable surfactant to Octoxynol 9?

A. I did, yes.

Q. Do you agree with Dr. Lawrence?

A. No.

Q. Why not?

A. Because in the context of Schott, Schott is comparing tyloxapol and Octoxynol 9 for, as it states here, stabilizing emulsions, suspensions, ointments and foams, particularly at the critical micelle concentration. And so Schott's context is not providing chemical stability enhancement of the -- an ophthalmic solution. It's about more physical stabilizing these emulsions, suspensions, ointments and foams.

Q. How do the emulsions, suspensions, ointments and foams of the Schott reference differ from solutions such as the claimed aqueous liquid preparations of the '431 patent?

A. So, they're very different.

Emulsions are two liquids, two immiscible liquids, that the -- there is a dispersed phase that has to be stabilized such that the two immiscible phases do not separate on stability.

Suspensions are known by persons of ordinary skill in the art as being -- there is a solid particle that's being carried in a -- a -- an external phase, and so it's not a solution at all.

Ointments are oleaginous, typically don't contain water, and there may be a drug dissolved or suspended in that oleaginous base.

And then foams are -- it's air that's emulsified into some kind of liquid phase to create a foam. So they are very different than an aqueous solution.

Q. Let's now discuss Dr. Lawrence's opinions about nonionic surfactants.

Did you hear Dr. Lawrence testify that a person of ordinary skill in the art, as of 2003, would have looked only to approved surfactants for use in ophthalmic formulations?

A. I heard that, yes.

Q. Do you agree with Dr. Lawrence?

A. I don't.

Q. Why not?

A. Because a person of ordinary skill in the art would

consider what's -- excipients or additives that are in approved products, but they wouldn't limit their choice to that.

From my experience, a skilled person would seek to formulate a stable product, and if there is an ingredient, an additive that is not currently already in an approved product and it works for their product, then there is a way to -- to get that in an approved product with the FDA.

Q. As of 2003, were many classes of surfactants known in the art?

A. Yes.

Q. And as of 2003, were large numbers of surfactants known within each of those classes?

A. There was, yes.

Q. Now let's discuss Dr. Lawrence's opinions regarding the specified amounts of tyloxapol, .02 weight per volume percent, in Claims 6 and 20 of the '431 patent.

Did you hear Dr. Lawrence testify that it would have been obvious to use a concentration of 0.02 weight per volume percent tyloxapol?

A. I did.

Q. Do you agree with Dr. Lawrence?

A. I do not.

Q. Why not?

A. Because there is nothing that I've seen that's been

presented by defendants that has shown .02 percent of tyloxapol that works for chemical stabilization.

Q. Do any of the references cited by Dr. Lawrence teach that tyloxapol could chemically stabilize any NSAID?

A. Not in my opinion, no.

Q. Do any of the references cited by Dr. Lawrence teach 0.02 weight per volume percent tyloxapol as claimed?

A. Not in my opinion, no.

Q. Please turn in your binder to the Sallmann '913 patent which is JTX-71, and let me direct your attention to Column 4, Line 65, through Column 5, Line 2.

What does Column 4, Line 65, through Column 5, Line 2 of the Sallmann '913 patent disclose?

A. So, here Sallmann is -- again, Sallmann is about diclofenac potassium, and so in the context of diclofenac potassium, Sallmann states that the concentration used of these solubilizers, is the context here, "The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient." Sallmann states that, "For example, the concentration of the solubilizer is from 0.1 to 5000 times the concentration of the active ingredient."

Q. How, if at all, does Column 4, Line 65, through Column 5, Line 2, of the Sallmann '913 patent support your disagreement with Dr. Lawrence?

A. So, this passage supports my opinion because this passage in Sallmann is -- is related to solubilization, so use of a solubilizer, and one of the examples is tyloxapol, and it's used to keep the diclofenac potassium dissolved in the -- in the vehicle, in the aqueous solution. It's not in the context of chemical stabilization.

Q. Is the range disclosed in Column 4, Line 67, through Column 5, Line 2, of the Sallmann '913 patent specific to tyloxapol or general instead?

A. That concentration is a general range for all of the listed solubilizers that are disclosed in that particular paragraph.

Q. Let me direct your attention to Example 15 of the Sallmann '913 patent which is in Column 12. What does Example 15 of the Sallmann '913 patent disclose?

A. So, this Example 15 is a diclofenac potassium eyedrop, and it discloses two different formulations of that drug substance, and so it's specific to diclofenac potassium.

Q. Did you hear Dr. Lawrence cite Example 15 of the Sallmann '913 patent and apply Example 15 to her obviousness opinions?

A. Yes, I did.

Q. Do you agree with Dr. Lawrence's reliance on Example 15 of the Sallmann '913 patent in connection with her obviousness opinions?

A. I did, yes.

Q. I'm sorry. Let me ask it again.

Do you agree with Dr. Lawrence's reliance on Example 15 of the Sallmann '913 patent in connection with her obviousness opinions?

A. Sorry. I didn't hear the right question.

Yes, I do not agree, no.

Q. Why do you disagree with Dr. Lawrence?

A. Because in the context of Sallmann, tyloxapol is used in order to solubilize diclofenac potassium, a different drug. It's not used in the context of chemical stabilization.

Q. Please turn back in your binder to the Fu EP 984 reference which is JTX-209, and let me direct your attention to Page 9, and, in particular, Example 5.

Did you hear Dr. Lawrence point to the amount of Octoxynol 40 in Example 5 of the Fu EP 984 reference and testify that it allegedly teaches using tyloxapol at 0.02 weight per volume percent, as claimed in the '431 patent?

A. I heard that, yes.

Q. Do you agree with Dr. Lawrence?

A. I do not.

Q. Why not?

A. Because Octoxynol 40, it's a different entity than tyloxapol. So this teaches Octoxynol 40 at .02 percent, not tyloxapol.

Q. Is it your understanding from Dr. Davies's testimony that

tyloxapol and Octoxynol 40 have different chemical structures and different chemical properties?

MR. HASFORD: Objection, leading.

THE COURT: I'll permit it.

00:47 THE WITNESS: My understanding from Dr. Davies, his testimony, is that Octoxynol 40 and tyloxapol are different chemical structures.

BY MR. HASFORD:

Q. What drug is being tested in Example 5 of the Fu EP 984 reference?

00:47 **A. So, Fu in Example 5 is testing ketorolac tromethamine.**

Q. If the Fu EP 984 reference teaches the use of any surfactant, what surfactant does it teach?

A. Well, there is data actually for the surfactant Octoxynol

00:48 **40.**

Q. And back to your previous answer regarding the drug. Is ketorolac tromethamine a different drug than bromfenac sodium?

A. Yes, it's a different drug.

Q. Please turn to Page 4, Lines 8 to 18, of the Fu EP 984

00:48 reference.

Did you hear Dr. Lawrence cite Page 4, Lines 8 to 18, of the Fu EP 984 reference and testify that it allegedly teaches using tyloxapol at 0.02 weight per volume percent as claimed in the '431 patent?

00:48 **A. I did.**

Q. Do you agree with Dr. Lawrence?

A. No.

Q. Why not?

A. Because this is just a general table that gives wide

00:48 **ranges for active -- active agent, for preservative, for surfactant. It's not specific to any particular substance. It's not specific to tyloxapol and bromfenac.**

Q. Did you hear Dr. Lawrence testify that a person of ordinary skill in the art would have arrived at 0.02 weight

00:49 per volume percent tyloxapol through what she calls routine optimization?

A. I heard that, yes.

Q. Do you agree with Dr. Lawrence?

A. I don't.

00:49 Q. Why not?

A. Because there's nothing in this Fu reference that leads a skilled person to think that tyloxapol is disclosed, for one, or that tyloxapol would act to chemically stabilize because the Fu reference is about physical stabilization. So, a

00:49 **skilled person is not going to have a reasonable expectation that tyloxapol is going to work one way or the other.**

MR. HASFORD: Noel, would you now please put up DDX-2-55 on the screen.

BY MR. HASFORD:

00:49 Q. Dr. Williams, did you hear Dr. Lawrence testify about the

FDA Inactive Ingredient Guide using demonstrative DDX2-55 in connection with your obviousness positions?

A. I did, yes.

Q. Does DDX2-55 depict a portion of the FDA's Inactive

00:50 Ingredient Guide in DTX-196?

A. It does, yes.

Q. Do you agree with Dr. Lawrence's reliance on DTX-196 in connection with her obviousness opinions?

MR. HASFORD: Objection again, your Honor. This is

00:50 another situation where Dr. Lawrence said at his deposition that he hadn't even looked at this when he was forming his opinions in this case.

THE COURT: You mean Dr. Williams said that?

MR. HASFORD: Did I say Dr. Lawrence? Sorry.

00:50 Dr. Williams. Thank you, your Honor.

And this is again, after all the expert reports were in, I asked him whether he even researched what nonionic surfactants were approved as of 2003, and he said no.

MS. HOLLAND: Well, again, your Honor, I think the

00:50 fact that they asked these questions at his deposition and the fact that Dr. Lawrence was relying on this in her reply report for the first time and then testifying about it in open court, I think Dr. Williams is entitled to respond to what he heard here in open court.

00:50 MR. HASFORD: Your Honor, what he heard in open court

is exactly what he had read in her expert report before his deposition. When he was asked about this reference at his deposition, he hadn't looked at it before. He hadn't looked at it in forming his opinions. And if he had an opinion about

00:51 it, he knew what Dr. Lawrence's opinion was at the time of his deposition, and that was the time to offer the opinion, and it's the same exact situation that we brought up earlier.

MS. HOLLAND: Respectfully, your Honor, I mean he was asked certain questions about it. I -- you know, I suspect

00:51 counsel would have objected, had he launched into a narrative about everything he knows about the Inactive Ingredients Guide. He certainly knows about --

THE COURT: But at least he would have been giving notice that he has an opinion on this subject. Coming into

00:51 the trial, the defendants were entitled to believe that he had no opinion on this subject. In other words, when asked about this, he said he didn't know. And so I'll sustain the objection for the same reasons as before.

Let me add, though, that if it's pursued on

00:51 cross-examination, then I might permit it on redirect because on redirect, he's not required to blind himself to everything that he's learned in the trial.

MS. HOLLAND: Thank you, your Honor.

BY MR. HASFORD:

00:52 Q. Let's now turn to secondary considerations of

nonobviousness.

Please turn to JTX-147 in your binder, which is the Ogawa '225 patent. Let me direct your attention to Example 6 of the Ogawa '225 patent which is at Column 10.

00:53 Are you aware that defendants have taken the position that Example 6 of the Ogawa '225 patent is the closest prior art?

A. **Yes, I am.**

Q. Did you hear Dr. Lawrence testify that boric acid, Borax, 00:53 disodium edetate, benzalkonium chloride, polyvinylpyrrolidone, and sodium sulfite in the formulation of Example 6 of the Ogawa '225 patent would not detrimentally affect its basic and novel properties, including stability?

A. **That's what I understood her to say.**

00:53 Q. Let's take a look now at Table 1 of the '431 patent, which is JTX-1 in your binder.

What are the components of Comparison Example 1 in Table 1 of the '431 patent?

A. **The components are the bromfenac sodium, boric acid,**
00:54 **benzalkonium chloride, Polysorbate 80, and purified water.**

Q. How, if at all, do the other formulations in Experimental Example 1 differ from the formulation of Comparison Example 1 of the '431 patent?

A. **The other formulations differ in the type and amount of**
00:54 **surfactant, nonionic surfactant.**

Q. Otherwise, are they the same?

A. **Yes, they are.**

Q. What type of test results are disclosed in Table 1 of the '431 patent?

00:54 A. **The test results that are disclosed are chemical stability results for bromfenac sodium, and it's given by remaining rate as a percent.**

Q. Does Comparison Example 1 in Experimental Example 1 of the '431 patent reflect the closest prior art as defined by 00:54 defendants?

A. **In my opinion, yes.**

Q. Based on the Ogawa '225 patent, would a person of ordinary skill in the art have expected that substituting Polysorbate 80 with any other nonionic surfactant would impact 00:55 Bromfenac's chemical stability?

A. **I don't believe they would have, no.**

Q. Let me direct your attention again to Experimental Example 1 of the '431 patent, and, in particular, to Table 1. To what pH are the formulations of Experimental Example 1 of 00:55 the '431 patent adjusted?

A. **So, the formulas that are made in Table 1 of Experimental Example 1 are prepared at pH 7.**

Q. Please turn back to JTX-147 in your binder, which is the Ogawa '225 patent. Let me direct your attention to Column 8, 00:55 and, in particular, to Experimental Example 4.

What is described in Experimental Example 4 of the Ogawa '225 patent?

A. **So, in Experimental Example 4, Ogawa prepares a bromfenac sodium formulation that contains the ingredients listed here,**
00:56 **Borax, sodium borate, sodium chloride, disodium edetate, benzalkonium chloride, Polysorbate 80, and sterile purified water.**

Q. Let me now direct your attention to Columns 13 and 14, and, in particular, to Table 8, which presents the results of 00:56 Experimental Example 4.

A. **Okay.**

Q. How, if at all, do the results of Table 8 of the Ogawa '225 patent show that bromfenac degrades at a pH lower than 8?

A. **So, Ogawa in Experimental Example 4 studied the solution**
00:56 **as a function of pH, four different pHs, and as shown here in Table 8, it's -- he studied at pH 6, 7, 8, and 9. And after three weeks' storage at 60 degrees Centigrade, the results at pH 8 and 9 were roughly 98 and 99 percent respectively, but at pH 7, after three weeks' storage under those conditions, the**
00:57 **remaining rate or residue percent of bromfenac sodium is only 54.2 percent. So this Ogawa is reporting that at pH 7 under these conditions, bromfenac sodium chemically degrades.**

Q. Please turn back to the '431 patent, and, in particular, to Table 1, Experimental Example 1 in Column 7.

00:57 You testified earlier that the pH of the formulations

that are used in Experimental Example 1 of the '431 patent is pH 7. Do you remember that?

A. **Yes.**

Q. What is the significance, if anything, of the fact that 00:58 the formulations that are used in Experimental Example 1 of the '431 patent were formulated at pH 7?

A. **To a skilled person understanding that bromfenac sodium is not chemically stable, as stable at pH 7, they would understand that to be a condition that may allow**
00:58 **differentiation between formulation experiments to be made at a quicker -- quicker time frame.**

Q. What storage conditions were used in Experimental Example 1 of the '431 patent?

A. **The storage conditions are 60 degrees C., Centigrade, for**
00:58 **four weeks.**

Q. What is the significance, if anything, of the use of storage conditions of 60 degrees Celsius for four weeks in Experimental Example 1 of the '431 patent?

A. **So, that temperature and time would be understood by a**
00:58 **skilled person to be an accelerated stability test, particularly the 60 degrees Centigrade. So, again, it allows a skilled person to make a judgment, and it may be more differentiating in a quicker time frame, to understand the variables that are being studied.**

00:59 Q. How, if at all, does the testing of the formulations of

Experimental Example 1 of the '431 patent at pH 7 and at 60 degrees Celsius for four weeks show the relative stabilization capacity of Polysorbate 80 and tyloxapol?

A. So, in my opinion, a person of ordinary skill in the art, understanding the chemical degradation of bromfenac sodium at pH 7 and 60 degrees C. being accelerated temperature condition, that studying at that pH, pH 7, at 60 degrees C. for four weeks, would all allow the -- a judgment to be made in a quicker time frame, in order to differentiate between variables that are being studied and understand what the effect is on chemical stability of bromfenac sodium.

Q. In your opinion, are the test conditions in Experimental Example 1 of the '431 patent considered stressed conditions?

A. They are. Sometimes that's called accelerated stability conditions.

Q. Do these stress conditions allow a person of ordinary skill in the art to observe the relative stabilization capacity of Polysorbate 80 and tyloxapol in Experimental Example 1 of the '431 patent?

A. They do, yes.

Q. In connection with your opinions in this case, have you considered summary charts of test data related to the '431 patent to which defendants have stipulated?

A. I have, yes.

Q. Please turn to PTX-591 in your binder.

Is PTX-591 a summary chart of test data related to the '431 patent that you considered in connection with your opinions in this case?

A. It is, yes.

Q. Please turn now to PTX-592 in your binder.

Is PTX-592 a summary chart of test data related to the '431 patent that you considered in connection with your opinions in this case?

A. Yes, it is.

Q. Please turn now to PTX-593 in your binder.

Is PTX-593 a summary chart of test data related to the '431 patent that you considered in connection with your opinions in this case?

A. Yes, it is.

Q. Have you prepared a demonstrative that illustrates the unexpected chemical stabilizing effect of tyloxapol in bromfenac formulations of pH 7 using the data from PTX-591?

A. I have, yes.

Q. Let me direct your attention to PDX4-5 on the screen.

Would you please explain what PDX4-5 illustrates?

A. Yes. So what I've taken here is I've summarized the data on formulation.

So there is -- across the top is the formulation code that was noted in the summary tables. A-20, A-21, A-27, A-28, and A-29.

In the second row, if there -- if it corresponds to a formula from Table 1 of Experimental Example 1 of the '431 patent, I've noted that as well.

And so, for example, Comparison Example 1 that's in Table 1 of the '431 patent is also called in the summary tables Formulation Code A-20. And, likewise, Formulation Code A-21 and A-27 are also referred to in Table 1 of the '431 patent, and they're referred to as A-02 and A-03.

And so what's reported here is, first of all, in the second column, is Comparison Example 1, Formulation Code A-20, which contains Polysorbate 80, and then in the next four columns, what's reported is then the same formulation, except tyloxapol as a nonionic surfactant, replaces Polysorbate 80 and then tyloxapol is studied at four levels. And all of those -- all of these formulations are being studied when prepared at pH 7.

Q. How, if at all, do the data in PTX-591 depicted on PDX4-5 demonstrate that the tyloxapol containing formulations of bromfenac are superior in chemical stability as compared to the Polysorbate 80 containing formulations of bromfenac?

A. So, what's shown in the column with the Formulation Code A-20 is a remaining rate or residual bromfenac of -- a percent of 51.27 percent. And then four different levels of tyloxapol are compared.

First of all, there's .15 weight percent of tyloxapol

which is Formulation Code A-21. And when studied, that had a remaining rate of bromfenac sodium of 73.81 percent. So in a comparable level to Formulation Code A-20 that had .17 percent Polysorbate 80, you can see or a skilled person would understand that that change in nonionic surfactant improved the remaining rate of residual bromfenac about 44 percent, which is the difference between 51.27 percent and 73.81 percent.

In the next three columns, the .02 percent tyloxapol, which is Formulation Code A-27, that remaining rate was 89.64 percent.

And when .05 weight percent of tyloxapol is studied in Formulation Code A-28, that remaining rate is 85.96 percent.

And then lastly, the .1 weight percent of tyloxapol as Formulation Code A-29, the remaining rate is 82.01 percent.

And so what a skilled person would understand is that at the lowest amount of tyloxapol that was studied, the 0.02 weight percent, that formulation had the highest amount of residual bromfenac.

Q. How, if at all, are these superior chemical stability results of tyloxapol containing formulations of bromfenac, as shown in PTX-591 and on PDX4-5, unexpected to a person of ordinary skill in the art?

A. Well, there is nothing in the literature that suggested tyloxapol would chemically stabilize a drug like bromfenac.

And this shows that the presence of tyloxapol does, in fact, improve the chemical stability of bromfenac sodium in these aqueous solutions.

Q. How, if at all, does the data in Formulation A-03 for the composition containing 0.02 weight per volume percent tyloxapol inform your opinion in this regard?

A. So in Formulation A-03, which corresponds to Formulation Code A-27 in the summary table, again, a person of ordinary skill in the art would not have expected tyloxapol to chemically stabilize bromfenac sodium, would not have expected it -- it wouldn't have known what level would have worked, if it would have worked, and so at that low level, it seems a surprise to me that -- or it was not known that it would have done that.

Q. Do the results in Experimental Example 1 of the '431 patent show that Formulation A-03 containing 0.02 weight per volume percent tyloxapol was 75 percent more stable under these test conditions than the formulation of Comparison Example 1?

A. It does. That's what I calculated, the difference between the 51.27 percent and the 89.64 percent.

Q. Are you aware that Dr. Lawrence has taken the position that the information provided in the '431 patent specification is allegedly insufficient to make a determination of which formulations show superior stability?

A. I understand that.

Q. Do you agree with Dr. Lawrence's opinion?

A. I don't, no.

Q. Why not?

A. Because in the patent, there is a direct comparison between Polysorbate 80 and tyloxapol, each at .15 percent, and you see a difference of 51.3 percent bromfenac sodium remaining, with the Polysorbate 80 .15 percent, and one observes in Table 1 for Formulation A-02, the remaining rate is 73.8 percent, with .15 percent tyloxapol. So there is an improvement.

Q. Does Table 1 of Experimental Example 1 of the patents-in-suit show test results conducted against Dr. Lawrence's admitted closest prior art?

A. Yes, it does.

Q. Does Table 1 of Experimental Example 1 of the '431 patent show a direct comparison between a formulation containing Polysorbate 80 and a formulation containing tyloxapol?

A. It does, as I've just explained.

Q. Let's now turn -- let's now turn to the prosecution history of the 431 patent. In particular, let me direct your attention to JTX-006A in your supplemental binder.

In PTX-6A, let me direct your attention to the examiner's "Reasons For Allowance" of the '431 patent at the page bearing Bates Number PROL 0000799.

A. Okay.

Q. Specifically, let me direct your attention to the last paragraph, which spills over to the middle of the following page. What does this portion of the prosecution history of the '431 patent disclose?

A. So, in the "Reasons For Allowance" that are stated here, the examiner is stating that "Applicants have found that tyloxapol is not equivalent to Polysorbate 80 when combined with bromfenac." And the inventor states, "The present inventors have discovered that tyloxapol has an unexpected property in stabilizing an aqueous solution of bromfenac in comparison with Polysorbate 80." Then the examiner says, "Please see the description of Experimental Example 1 and Table 1 on Pages 14 through 16 of the specification." The examiner states, "In the Experimental Example, the stability of an aqueous solution of bromfenac was measured by storing the bromfenac solution with Polysorbate 80" and then in parentheses, "(see Comparison Example 1) and, separately, with tyloxapol (see A-02), under conditions of pH 7 at 60 degrees C. for four weeks."

And then the examiner reports the results of 51.3 percent of bromfenac remaining for the Polysorbate 80 solution, and in contrast, 73.8 percent of bromfenac remained in aqueous solution with tyloxapol.

So the examiner states, "Thus the present inventors

have found that tyloxapol has an unexpected stabilizing effect on an aqueous solution of bromfenac in comparison to Polysorbate 80."

Q. What did the examiner say in the next two sentences?

A. So then the examiner states that tyloxapol and Polysorbate 80, that the inventors have found that those two are not equivalent compounds, and the examiner states, "Such unequivalency and such remarkable effects, could not have been obvious to one skilled in the art from the cited references."

Q. And in the following sentence, what did the examiner conclude?

A. So, in conclusion, the examiner states, "For the foregoing reasons, it is respectfully submitted that the teachings of the cited references do not suggest the claimed bromfenac preparation as amended, nor the unexpected properties of the preparation."

Q. How, if at all, does the prosecution history of the '431 patent support your opinion that a person of ordinary skill in the art would not have arrived at 0.02 weight per volume percent tyloxapol through routine optimization?

A. This supports my opinion because it wouldn't have been known in the art, so a skilled person wouldn't have had an expectation one way or the other if tyloxapol would have chemically stabilized bromfenac or not in solution and at what level.

Q. Let's switch gears a bit.

Have you also prepared a demonstrative comparing the chemical stability of tyloxapol-containing formulations of bromfenac at a higher pH of 8.2 based on summary charts of
01:13 test data to which defendants have stipulated?

A. Yes, I have.

Q. Let me direct your attention to PDX4-6 on the screen which cites to PTX-593. Would you please explain what PDX4-6 illustrates?

01:13 **A. So, PTX-593 is a comparative table that I prepared that has two formulations. One is Bronuck®, and it's -- the column heading is "BF" and it says in parentheses, "(Bronuck)," and the second column is labeled "A-01," in parentheses, "PE."**

And these two formulations show that in the Bronuck® formulation, it has the Polysorbate 80, and it has sodium sulfite in it, which, according to Ogawa, solved the problem of chemical stability.

And, as shown in pH 8.2, the residual amount of bromfenac that remains, after storage at 60 degrees C. for
01:14 **four weeks, is 91.45 percent.**

The same formulation then that is prepared with tyloxapol at .02 weight percent, and then not containing Polysorbate 80 or sodium sulfite, the remaining rate is 93.61 percent when that Formulation A-01 was stored at 60 degrees C.
01:14 **for four weeks.**

Q. How, if at all, does the pH test condition of 8.2 in the bromfenac formulations shown on PDX4-6 differ from the pH condition of 7 with respect to bromfenac?

A. So, a person of skill in the art would understand that
01:14 **the rate of chemical degradation at pH 8.2 would be slower, based on what Ogawa found, compared to pH 7. So it would be -- so the conditions here would be such that the -- at least from the pH, the drug would degrade at a slower rate.**

Q. How, if at all, are the results illustrated in PDX4-6
01:15 unexpected to a person of ordinary skill in the art?

A. So, here, at A-01, that contains tyloxapol at .02 percent and no sodium sulfite, the results were -- were -- I think a person of ordinary skill in the art would understand those are good results, and you didn't have to use the sodium sulfite
01:15 **that Ogawa reported as solving the chemical stability problem of bromfenac.**

Q. Do the results set forth in PDX4-6 suggest the ability to remove sodium sulfite from the formulation?

A. They do, yes.

01:15 Q. How, if at all, would it be beneficial to remove an excipient such as sodium sulfite from an ophthalmic formulation?

A. So, generally speaking, a skilled person in formulation, as a formulation scientist, would understand that the least
01:16 **number of excipients is more preferable. So, in other words,**

each excipient has to have a stated function, and if they don't serve a function, then they should not be included. So this would be a way to not have to include an additive.

Q. Let me direct your attention back to the Ogawa '225
01:16 patent, which is JTX-147 in your binder, and, in particular, to Experimental Example 4 in Column 8.

Do you understand that defendants have argued that there is allegedly no unexpected chemical stability effect of tyloxapol because formulations of Experimental Example 4 of
01:16 the Ogawa '225 patent maintained a high level of residual bromfenac without sodium sulfite?

A. I understand that.

Q. Do you agree with defendants?

A. I don't.

01:16 Q. Why not?

A. Because Experimental Example 4 of Ogawa at about Line 19, 20, Ogawa states, in the formula, "the change in residue rate were not almost observed but in three weeks red insoluble matters were observed."

01:17 **And so that's stating that under the conditions that Ogawa was measuring bromfenac chemical stability, over the three weeks at 60 degrees C. at each of those pHs, there was a difference, but in the end, at the three weeks, there was still red insoluble matter found for each of those four**
01:17 **conditions, the four solutions tested.**

Q. Does that reflect chemical degradation?

A. It does, yes.

Q. Have you also prepared a demonstrative showing results from Experimental Example 2 of the '431 patent?

01:17 **A. I have, yes.**

Q. Let me direct your attention to PDX4-7 on the screen, which cites to PTX-592.

Would you please explain what PDX4-7 illustrates?

A. So, yes. So, this is a summary table, and the top row is
01:18 **formulation code, so that is the reference A-0 -- to Formulas A-01, A-02, and A-03. And those correspond to the formulations reported in Table 2 of the '431 patent, and they correspond to Formulas A-04, A-05, and A-06, respectively.**

Q. How, if at all, are the chemical stability results in
01:18 experimental Example 2 of the '431 patent unexpected to a person of ordinary skill in the art?

A. So, these formulations would be unexpected, because they contain three different levels of tyloxapol and no sodium sulfite, and based on the findings of Ogawa that solve the
01:18 **chemical stability problem using sodium sulfite, in part, these results are roughly 92.5 or 92-and-a-half percent, about 91 percent, about 92 percent. So those -- those chemical stability results would be understood by a person of ordinary skill in the art to be good.**

01:19 Q. Were those chemical stability results in the formulations

of experimental Example 2 of the '431 patent obtained without using sodium sulfite in the formulations?

A. Yes, and that's noted here, there's no sodium sulfite used.

01:19 Q. Let's now discuss your opinions regarding unexpected results with respect to experimental Example 3 of the '431 patent.

Have you prepared a demonstrative illustrating preservative efficacy testing data in experimental Example 3 of the '431 patent?

A. I have, yes.

Q. Let me direct your attention to PDX4-8 on the screen.

Would you please explain what PDX4-8 illustrates?

A. Yes, PDX4-8 illustrates the preservative efficacy comparison. So it's tyloxapol versus polysorbate 80. So this is A-04, actually it's just tyloxapol from experimental Example 3. And this shows that A-0 -- formula A-04 that was described in Table 2 of the '431 patent and A-05 that's described in Table 2 of the '431 patent, both with either .02 weight percent or .05 weight percent of tyloxapol, the lowest level of tyloxapol at .02 percent passed the EP Criteria A and, therefore, Criteria B, whereas the slightly higher percent of tyloxapol at .05 weight percent did not pass EP Criteria A, preservative efficacy, but did pass the EP Criteria B.

Q. Do you understand that the European Pharmacopeia Criteria A standard is more demanding than the European Pharmacopeia Criteria B standard?

A. Yes, I understand that.

01:21 Q. Let's switch gears a bit.

Do you recall testifying earlier this week that Prolensa is an embodiment of Claims 6 and 20 of the '431 patent?

A. Yes.

01:21 Q. How, if at all, did the unexpected stabilizing ability of tyloxapol in the aqueous liquid preparations of bromfenac of the '431 patent enable formulating Prolensa at pH 7.8?

A. So, because, according to the patent, because tyloxapol is able to chemically stabilize bromfenac sodium, the pH was able to be lowered from pH 8.3, which is the pH of Prolensa to pH 7.5. So it's a half of pH unit decrease.

Q. And did you mean to say the pH of 8.3 of Bronuck or -- sorry, Bronuck, Xibrom and Bromday?

A. Yes, I misstated that, yeah, Prolensa 7.8, yes.

01:21 Q. How, if at all, did the unexpected stabilizing ability of tyloxapol in the aqueous liquid preparations of bromfenac of the '431 patent enable formulated Prolensa with 0.02 weight per volume percent of tyloxapol?

A. Well, it was found based on the data that the 0.02 weight percent of tyloxapol had the best stability of the

concentrations that were studied, so that's what enabled it.

Q. Do you recall testifying last week that the Prolensa package insert does not identify burning and stinging as adverse reactions associated with Prolensa?

01:22 **A. Yes.**

Q. Before we consider Prolensa further, let's take a look at the FDA-approved Xibrom package insert.

Would you please turn to JTX144 in your binder and identify that document?

01:22 **A. JTX144 is a copy of Xibrom package insert.**

Q. Did you review the FDA-approved Xibrom package insert in connection with your opinions in this case?

A. I did, yes.

Q. Would you please turn to PTX-749 in your supplemental binder and identify that document.

01:23 MS. HOLLAND: Your Honor, we have an objection. This is a new exhibit that was first disclosed last night.

MR. HASFORD: And, Your Honor, this was the exhibit that we brought up last week with Dr Lawrence. She testified that she hadn't seen it before. All we're getting here is to get Dr. Williams to testify that he's reviewed this and finds them to be essentially identical.

It's not an issue that we believe should even be in dispute between the parties. I think Your Honor instructed us to try to get the issue resolved by stipulation. We haven't

been able to do that, so we're just going to have Dr. Williams testify as to his understanding of it.

THE COURT: Okay. Ms. Holland.

MS. HOLLAND: This document is not in Dr. Williams's report. To the extent that Mr. Hasford says it's the same or similar to a document that is in his report, I'm not -- I don't understand why that's not the document that's being used with the witness.

I'm not sure it actually is the same or similar, and it's not -- there's not been a disclosed opinion about it, so to the extent that plaintiffs want to use a Xibrom package insert, we object to using one that wasn't in Dr. Williams's report.

MR. HASFORD: We're merely seeking for Dr. Williams to testify that they appear to be essentially identical, Your Honor.

THE COURT: I'm sorry, what is the "they?" Does he have a different document that he has relied on?

MR. HASFORD: He's got the actual FDA-approved version that he's relied upon in his expert report. This is the version, as you will hear Dr. Williams testify, that was actually included as the insert with the packaging with which Xibrom was sold.

MS. HOLLAND: That's not anywhere in his report or disclosed anywhere and --

THE COURT: Well, is there disagreement about it?
MR. HASFORD: There certainly isn't from plaintiffs, Your Honor.
MS. HOLLAND: The --
01:24 THE COURT: Well, I assume that you wouldn't disagree --
(Laughter.)
MS. HOLLAND: The issue, Your Honor, is, is this the right witness to talk about a package insert, A. B, it's not
01:25 the one in his report. So there's a doctor coming on the stand, I'm understanding, Dr. Trattler, after Dr. Williams, and I don't know if --
MR. HASFORD: Your Honor, Dr. Williams is a licensed pharmacist so he certainly is a correct or a right witness as
01:25 Ms. Holland says, to testify about a package insert, and he provided that background testimony, as Your Honor will recall, as part of his background last week.
MS. HOLLAND: Your Honor, this is not essentially the same as the one in the report. I think that's the -- real
01:25 crux of the objection. So there's a package insert on -- in the expert report. Now this is a different package insert that's not the same as the one in the expert report, so that's the problem here, is that this is a new exhibit disclosed last night that's not the same as something that was already in the
01:25 expert report.

THE COURT: Is what's in the expert report the proposed package insert?
MS. HOLLAND: No, it's the approved package insert.
THE COURT: It's the approved one. And what's this
01:26 one purporting to be? PTX-779?
MR. HASFORD: This one -- this one, Your Honor, is simply the version which we contend and Dr. Williams is prepared to testify is essentially identical. It's the actual version that was placed in the carton, the container, the box
01:26 with the bottle of eye drops.
So it's identical in substance, because the FDA had to approve this as well.
MS. HOLLAND: Perhaps the problem is that -- I'm not sure what the representation is, but perhaps this is something
01:26 intended for a patient, whereas what Dr. Williams talked about in his report was intended for a physician.
So in that respect, there are differences and could be a material difference in the opinion.
MR. HASFORD: I don't believe there will be any
01:26 material difference in the opinion.
MS. HOLLAND: There's more information, for example, that will be available about the Xibrom product in the version that's in the report, and it's important information, we believe, for the case.
01:27 So to the extent that this could be now switching out

to a different Xibrom that doesn't have the information that would be significant for a physician, we have a problem with that.
MR. HASFORD: There's no switching going on here,
01:27 Your Honor, and respectfully, it sounds like Ms. Holland's objection goes to weight, not to admissibility.
MS. HOLLAND: Well, it goes to admissibility because it wasn't on the exhibit list until last night.
THE COURT: All right. I have to sustain the
01:27 objection. If there's not a reason that it was omitted from the exhibit list or, for instance, did it just become apparent during the trial, then it's an unlisted exhibit, and if you have the essential equivalent, then you should use the document previously disclosed that the defendants are familiar
01:27 with. So I will sustain the objection.
BY MR. HASFORD:
Q. Let me direct your attention back to JTX144 and in particular, to Page 3 of the Xibrom package insert, which bears Bates No. PROL 0080488.
01:28 Specifically, let me direct your attention to the second paragraph of the section entitled Adverse Reactions.
Does the adverse reaction section of the FDA-approved Xibrom package insert indicate that eye irritation, including burning and stinging, are associated with Xibrom?
01:28 **A. That's what this approved label states, yes.**

Q. Let me now direct your attention --
MS. HOLLAND: Your Honor, I have an objection to this line of questioning. Dr. Williams is -- was put on the stand as a formulation expert. It appears to me he's now testifying
01:28 about what adverse events are associated with the product. That's not within his area of expertise.
MR. HASFORD: It absolutely is, Your Honor. He's a licensed pharmacist. This is the first time Ms. Holland has raised this objection, and this is fully disclosed in his
01:28 expert report and her -- there's no basis for the objection.
MS. HOLLAND: We raised it last night, Your Honor, in connection with one of the demonstratives that was disclosed to us. The issue is, regardless of whether Dr. Williams is a
01:29 pharmacist or not, I'm not saying he's not a pharmacist, that's not what he was qualified for on the stand. He's a formulator here at trial, and he's not qualified as a formulator to give opinions about medical adverse events that occur with the product.
MR. HASFORD: Your Honor, he's eminently qualified.
01:29 MS. HOLLAND: He has testified at his deposition that he has no -- he does not have a personal opinion on those issues. Dr. Williams said you'd have to ask the doctor about that, about whether they actually occur.
MR. HASFORD: Your Honor, he's eminently qualified to
01:29 testify to what these package inserts show to a skilled

formulator or to a pharmacist.

THE COURT: I'm just looking through my notes to see what exactly he was qualified as an expert in for purposes of this trial. I'm not finding it right off the bat.

01:30 Okay. He's qualified as an expert in the design, evaluation and formulation of drugs, and so the issue is whether -- within his field of expertise, it would include the review of FDA-approved package inserts.

MR. HASFORD: And we --

01:31 THE COURT: Could you lay a foundation, please?

MR. HASFORD: Certainly.

MS. HOLLAND: Your Honor, may I have a brief voir dire after that?

THE COURT: Yes.

01:31 MS. HOLLAND: Thank you.

BY MR. HASFORD:

Q. Doctor, in your general experiences, an expert in the field of the design, evaluation and formulation of drug products, do you review and rely upon FDA-approved package

01:31 inserts?

A. I do, yes.

Q. Do you understand the information contained therein?

A. Generally speaking, yes.

Q. Would that include both safety and efficacy information?

01:31 **A. Yes.**

Q. Would that include information on adverse events?

A. It would, yes. As it relates to formulations.

THE COURT: Okay. You may voir dire on that.

(VOIR DIRE EXAMINATION OF DR. WILLIAMS BY MS. HOLLAND:)

01:31 Q. Dr. Williams, you have no personal opinions as to whether Prolensa is more or less irritating than anything that -- any other prior art bromfenac formulations, correct?

MR. HASFORD: Objection. This doesn't go to voir dire, Your Honor.

01:32 THE COURT: Sustained. It would be as to his qualifications or his use of this sort of material as an expert.

MS. HOLLAND: Your Honor, I think it goes to the issue of whether or not Dr. Williams is qualified to provide

01:32 opinions in this area. The opinions are --

THE COURT: That's -- that's what I meant. Your voir dire is limited in scope. It's limited to his expertise as to one who --

MS. HOLLAND: Okay. Understood, Your Honor.

01:32 THE COURT: -- is a formulator, who says he uses package inserts. That was his testimony a moment ago. And so within that narrow scope, you may cross-examine him.

BY MS. HOLLAND:

Q. Dr. Williams, is it your testimony that you use patent

01:33 package inserts in order to figure out how to formulate a

product?

A. No. As a formulator, I would -- formulators, persons of ordinary skill in the art, look at package inserts when they are looking to formulate a product to see if there's something

01:33 **relevant with regards to -- like burning, stinging of excipients. They do look at that, if there's information in a similar product, they -- they would, yes.**

Q. But in this case, the Prolensa product is not the product that somebody would be looking to formulate?

01:33 MR. HASFORD: Objection, Your Honor. Same issue. It's going beyond the scope of voir dire.

THE COURT: No, I'll permit it. I mean, it goes to the relevance of this field of expertise.

THE WITNESS: So in coming up with Prolensa, one

01:33 would consider literature that's out there including a product label of NSAID products, bromfenac -- other bromfenac products that's out there.

BY MS. HOLLAND:

Q. The person of ordinary skill in the art, however, in

01:33 looking to formulate something, would not be looking at the Prolensa label, correct? That's the product you would be looking to formulate?

A. Well, there would -- well, there would be no Prolensa label if you're looking to formulate Prolensa. But to the

01:34 **extent there's other labels out there for other nonsteroidal**

anti-inflammatory agents, other ophthalmic aqueous solutions that you can -- you can learn what they, from a label, you know the composition of them, maybe not quantitative, but you know the qualitative composition from the label, it's in all

01:34 **the labels, and to the extent that there is a -- like this burning and stinging that could be caused from the formulation, one of skill in the art definitely would look at that.**

MS. HOLLAND: Your Honor, maybe it has to do with the

01:34 scope of the testimony. If Dr. Williams is simply going to be reading off what is on the labels, I think that that's okay. I don't think there's any testimony beyond that in the expert reports, and I don't know if Mr. Hasford is looking to elicit anything beyond that.

01:35 THE COURT: Okay.

MR. HASFORD: The questions that we have, Your Honor, will -- we will have full support for in the expert reports. I can't say that we're going to limit him to simply reading off the labels, but to the extent there's an objection about

01:35 what's in the expert report, we can deal with that --

THE COURT: Well, let's take these one at a time then.

As to the pending objection, I'll overrule Ms. Holland's objection, and I would find that within his

01:35 field of expertise, formulators whom he's defined as the POSAs

for this case would be apt to look at such labels in their design and formulation of drugs. And so I'll permit him to testify about the label that he says a POSA would have looked at.

MS. HOLLAND: Okay. Your Honor. I'll --

THE COURT: And then if there's individual questions that are beyond the scope of his report, then that's a different issue and I would take up any objection that you raise at that time.

MS. HOLLAND: Thank you, Your Honor. It could be beyond the scope of his report or his expertise as it pertains to the labels, but I agree, I'll raise those as they come up.

(CONTINUED DIRECT EXAMINATION OF DR. WILLIAMS BY MR. HASFORD:)

Q. Let me now direct your attention to Page 5 of the Xibrom package insert which bears Bates No. PROL 0080490. And in particular, to the second paragraph under the section entitled Description.

What is the pH of the Xibrom formulation?

A. Here, the pH of the Xibrom formulation, it's stated to be 8.3.

Q. Now, let's take a look at the FDA-approved Bromday package insert.

Would you please turn to PTX-474 in your binder and identify that document.

A. PTX-474 is a copy of the Bromday package insert.

Q. Did you review the FDA-approved Bromday package insert at PTX-474 in connection with your opinions in this case?

A. Yes, I did.

Q. Let me direct your attention to Page 6 of the Bromday package insert which bears Bates No. PROL 0080495, and in particular, to the section entitled Adverse Reactions, followed by Clinical Trial Experience.

Does the adverse reaction section of the FDA-approved Bromday package insert indicate that eye irritation including burning and stinging are associated with Bromday?

A. That's what's stated here for Bromday, including burning and stinging.

Q. Let me now direct your attention to Page 7 of the Bromday package insert which bears Bates No. PROL 0080496, and in particular, to the second paragraph under the section entitled Description.

What is the pH of the Bromday formulation?

A. So the label states the pH of Bromday solution is 8.3.

Q. Have you prepared a demonstrative comparing certain aspects of the formulations of the Xibrom, Bromday and Prolensa products?

A. I have, yes.

Q. Let me direct your attention to PDX 4-9.

What does PDX 4-9 illustrate?

A. So here, I've summarized certain aspects of Xibrom,

Bromday and Prolensa, in particular to the amount of active, which is 0.09 percent bromfenac-free acid equivalent for Xibrom and Bromday, and for Prolensa, it's 0.07 percent equivalent of bromfenac-free acid.

I've also summarized surfactant amount and the surfactant type. So for Xibrom and Bromday, the surfactants polysorbate 80 in both are at 0.15 weight percent, whereas for Prolensa, it contains tyloxapol at 0.02 weight percent.

And lastly, and as I just testified to, the pH of the Xibrom and Bromday ophthalmic solution is 8.3 and Prolensa is 7.8.

Q. From what trial exhibits, if any, have you derived the information summarized on PDX 4-9?

A. I derived this information from JTX144, PTX-474, JTX022.

Q. What is the degree of difference between pH 8.3 and pH 7.8?

A. So that's a half a pH unit. So one whole pH unit is ten times, because it's on a log scale. And so a half a pH unit is roughly a little bit more than three times the acidity.

Q. Are you aware that defendants have taken the position that Prolensa could have a pH as high as 8.1 based on the NDA specification?

A. Yes, I have.

Q. Does the -- does the FDA-approved Prolensa package insert, in fact, specify the pH of Prolensa?

A. It does. It specifies it as pH 7.8.

Q. Are you aware the defendants have taken the position that the disclosure in the Ogawa '225 patent of the pH range of 7.5 to 8.5 allegedly indicates that a commercial formulation of bromfenac containing polysorbate 80 could have been achieved at pH 7.8?

A. Yes.

Q. Do you agree with defendants?

A. I don't.

Q. Why not?

A. Because -- I don't agree with defendants because in the Ogawa patent, all the data that's presented -- that's not true.

So the examples where pH is stated, it's at pH 8. There's one example where pH is not listed. But all the data that -- where it states it, it's a pH 8. And Ogawa teaches that below pH 8 that bromfenac sodium is sensitive to chemical degradation.

Q. And does experimental Example 4 also inform your opinion in that regard?

A. Yes, experimental Example 4, where it says at those four pH values that were studied, after three-week storage at 60 degrees C, there was red insoluble matter, so chemical degradation.

Q. And does the Ogawa '225 patent also teach that bromfenac

degrades precipitously as the pH approaches 7?

A. That's the data, yes, in Table 8 of Ogawa. It says at pH 7, the chemical stability was decreased.

Q. Would you please turn in your binder to JTX18 and identify that document.

A. JTX18 is the Baklayan article.

Q. In what journal is JTX18 published?

A. Clinical Ophthalmology.

Q. Is the Journal of Clinical Ophthalmology a peer-reviewed journal?

A. My understanding is it is, yes.

Q. In your opinion, is JTX18 a reliable authority regarding the studies it describes and the conclusions to be drawn from them?

A. Yes.

Q. Let me direct your attention to the conclusion section right above introduction on the first page of JTX18.

What does the conclusion section of JTX18 disclose?

A. So here, the Baklayan article states: Bromfenac ophthalmic solution 0.07 percent, pH 7.8, readily penetrated ocular tissues with levels similar to those of bromfenac ophthalmic solution 0.09 percent pH 8.3.

Q. Let me now direct your attention to the first paragraph on the second page of JTX18, and in particular, to the sentence beginning with, Prolensa was reformulated.

What does this sentence in JTX18 disclose?

A. So here, Baklayan is disclosing the fact that it states Prolensa was reformulated from bromfenac .09 percent and then mentions Bromday, and he states that was done to achieve similar ocular bioavailability with a lower concentration of active drug, thereby ensuring similar clinical efficacy to Bromday but with reduced exposure of the surgically-compromised ocular surface of the drug.

Q. How, if at all, does this portion of JTX18 support your opinion that tyloxapol's unexpected stabilizing effect led to medical benefits in plaintiff's Prolensa product?

A. So because tyloxapol was able to chemically stabilize bromfenac at pH 7.8, that supports my opinion that it would allow for this unexpected medical benefit.

MS. HOLLAND: Your Honor, I'm going to object and also move to strike the answer. I didn't get a chance to object before Dr. Williams started speaking.

This now goes to medical benefits. That is clearly outside -- we haven't heard any testimony about medical benefits yet. There hasn't been a doctor on the stand. It's clearly outside the scope of Dr. Williams's expertise to comment on medical benefits. That -- I mean, that I can certainly voir dire on. That's from his deposition. He doesn't have opinions on medical benefits.

MR. HASFORD: Well, Your Honor, he has an opinion

here that, as a formulator, the unexpected stabilizing effect of tyloxapol led to these other benefits that are actually real benefits with this product.

THE COURT: Can you rephrase the question?

MR. HASFORD: Sure.

THE COURT: Because if he said he has no opinion on medical benefits, then I would have to sustain the objection.

MR. HASFORD: I can rephrase.

MS. HOLLAND: Your Honor, respectfully, so is the last answer stricken for the moment?

THE COURT: Yes. The last question and answer would be stricken.

MS. HOLLAND: Thank you.

THE COURT: And I agree, you didn't have adequate opportunity to object before the witness -- who I'm not faulting --

THE WITNESS: Sorry.

THE COURT: -- answered.

BY MR. HASFORD:

Q. How, if at all, does this portion of JTX18 support your opinion that tyloxapol's unexpected stabilizing effect led to additional benefits in plaintiff's Prolensa product?

MS. HOLLAND: That's the same objection, Your Honor. The only benefits that are in anybody's expert report are the medical benefits, and this witness isn't competent to testify

about that.

MR. HASFORD: Your Honor, the goal of pharmaceutical formulation is to create additional benefits.

THE COURT: I'll permit it. The objection is overruled.

BY MR. HASFORD:

Q. Do you need me to repeat the question, Doctor?

A. No. So the -- so what was found was tyloxapol was able to chemically stabilize bromfenac sodium, such that the pH could be lowered to pH 7.8, which is closer to the pH of natural tears. And so by that, Baklayan is saying because of that similar ocular bioavailability was able to be obtained.

Q. Have you prepared a demonstrative illustrating these unexpected additional benefits stemming from the use of tyloxapol with bromfenac that we have just discussed?

A. Yes.

Q. Let me direct your attention to PDX10 on the screen.

What does PDX -- what does PDX10 illustrate?

A. So PDX4-10 illustrates -- so starting from the fact that tyloxapol was found to chemically stabilize --

MS. HOLLAND: Your Honor, I'm going to interrupt with an objection. So what you have on the slide here is Dr. Williams apparently saying that the lower pH of Prolensa is responsible for no burning or stinging.

Now, Dr. Williams is not a doctor and -- he has offered

no opinion or no support for the fact that something about the pH was related to burning or stinging.

MR. HASFORD: He certainly has in his expert reports, Your Honor, and what he's doing here is he's tying together his understanding as a formulator of the unexpected benefits of the reduction in surfactant to .02 weight per volume percent to these actual benefits.

THE COURT: Wasn't that part of his testimony the first day in terms of introducing the patent?

MR. HASFORD: Well, his -- he laid some of the background for this in the patent, Your Honor, now he's tying it together with what he just testified about with respect to the Baklayan article and what he just testified about with respect to the package insert and tying this together to his understanding as a formulator.

MS. HOLLAND: I'll just make my objection, then, Your Honor. My objection is this is outside of the scope of Dr. Williams's expertise. He doesn't -- he doesn't know what's responsible for the burning or stinging in the package insert, so that's my objection.

THE COURT: I'm going to sustain the objection. To the extent that he's being asked for medical causation, that does seem to be beyond his -- his opinions and expertise. To the extent that he's being asked with what's been observed or what is associated with, I would permit it.

MR. HASFORD: Okay. Well, I'll rephrase the question then, Your Honor.

THE COURT: Okay.

BY MR. HASFORD:

Q. What is your understanding of what has been observed as you have summarized here in PDX4-10?

A. So what I've summarized here is, starting with the fact that tyloxapol at .02 percent weight -- by weight, is able to chemically stabilize bromfenac sodium in an ophthalmic aqueous solution such that the pH can be lowered to pH 7.8, what I've seen is that -- that now with that product in the Prolensa label, burning, stinging is not recognized.

It wouldn't be recognized by a person of ordinary skill in the art compared to the Xibrom label or the Bromday label, and as a formulator, I recognize in the Baklayan article, that Baklayan is talking about the fact that the pH was able to be lowered such that a similar bioavailability was able to be made such that the drug was able to be lowered in concentration to provide comparable therapeutic benefits. That's what I understand as a formulator.

Q. Let's now discuss copying by others.

In your opinion, has the claimed subject matter of Claims 6 and 20 of the '431 patent been copied by others?

A. **Yes.**

Q. Let me direct your attention to PDX1-51 on the screen.

Is it your understanding that the companies listed on PDX1-51 have copied the subject matter of Claims 6 and 20 of the '431 patent?

MS. HOLLAND: Objection -- I have an objection here, Your Honor. I don't -- again, as a formulator, I don't think the witness is competent to testify about whether or not someone copied. I mean, if he wants to compare labels and say the ingredients are the same, that's one thing, but to go into an extended discussion of why he believes subjectively someone did or didn't, it's just inappropriate for a formulation witness.

MR. HASFORD: He's not going into that, Your Honor, he's simply stating his understanding having read notice letters and having understood what these formulations are, that these are exact copies of Prolensa.

MS. HOLLAND: So, as I said, Your Honor --

THE COURT: Ms. Holland.

MS. HOLLAND: Thank you, Your Honor. My objection, I guess, again, Your Honor, is not to the comparison. It's to an opinion from an expert about whether there was copying. That doesn't seem like something that's the subject of -- should be subject of expert testimony. The documents are in evidence. Plaintiffs can argue whatever they want in their post-trial briefs about them, but it's certainly -- this is not an area of Dr. Williams's expertise as to whether or not

someone copied.

MR. HASFORD: Perhaps I can rephrase the question, Your Honor.

THE COURT: Okay. Please do.

BY MR. HASFORD:

Q. Is it your understanding, Dr. Williams, that Lupin, Metrics, InnoPharma, Apotex, Paddock and Watson all have filed an abbreviated new drug application seeking FDA approval for generic versions of bromfenac ophthalmic solutions 0.07 percent?

A. **Yes.**

Q. Is it your understanding that the ingredients in Lupin's, Metrics's, InnoPharma's, Apotex's, Paddock's and Watson's generic bromfenac ophthalmic solutions .07 percent are the same as the ingredients in Prolensa?

MS. HOLLAND: My objection here, Your Honor, is that most of these companies are not defendants in this case, so I don't see the relevance.

MR. HASFORD: They provided nonconfidential Paragraph IV notice letters, Your Honor, and that's what he's reviewed.

MS. HOLLAND: My objection is different. My objection is as to relevance of what nonparties have done.

MR. HASFORD: The relevance of what nonparties have done, Your Honor, is that they have submitted these ANDAs with

exact copies of Prolensa, and I believe the case is -- well, there's a case in New Jersey that was Rule 36 affirmed at the fed circuit that stated that copying of the claimed formulation is a secondary consideration of nonobviousness.

01:52 MS. HOLLAND: What I said was, you know, regardless of what that case says, and I'm not sure what case counsel is talking about, that can't be the case for nonparties.

MR. HASFORD: It most certainly can, Your Honor.

THE COURT: No, if there is --

01:52 MS. HOLLAND: If the question -- sorry, Your Honor.

THE COURT: Just a moment. My understanding is that if there is copying, even by a nonparty, that that can be evidence of secondary -- secondary considerations, and of course, this is -- just a moment.

01:53 I know you've discussed this in -- in your final pretrial order, I think it was, and --

MS. HOLLAND: If I may, if I may, Your Honor, the issue is that there's nobody here on behalf of those defendants to say yes or no to what happened, so we are kind

01:53 of being -- I guess, what's going to happen is that we're kind of like stuck with whatever nonparties said and they're not here to cross-examine Dr. Williams about their own, you know, filings, so...

THE COURT: Well, if the question is limited to, are

01:53 there other companies that have produced the same formulation,

identified it with their intent to market, then I would permit it. I believe that that is relevant to the concerns of other considerations with regard to the obviousness inquiry.

MR. HASFORD: I'll rephrase the question that way.

01:54 BY MR. HASFORD:

Q. Is it your understanding that six different generic -- at least six different generic drug companies have filed Abbreviated New Drug Applications for proposed generic bromfenac ophthalmic solution products that are exact copies

01:54 of plaintiff's Prolensa product?

A. That's my understanding.

Q. Is it your understanding that Lupin filed its Abbreviated New Drug Application for bromfenac ophthalmic solution 0.07 percent just three months after Prolensa was approved?

01:54 **A. That's my understanding.**

Q. Would you please turn to JTX12 in your binder and identify this document.

A. So JTX12 is an HSBC report that I understand is on Lupin's website.

01:54 Q. Let me direct your attention to the second page bearing Bates No. PROL 0276694 in JTX12, and in particular, to the second paragraph of the section, Lupin recently filed gProlensa in the right-hand column.

Specifically, let me direct your attention to the first

01:55 four lines of that paragraph.

A. So here, Lupin is --

Q. I apologize, Doctor, I haven't asked you a question yet.

A. Oh, I'm sorry.

Q. According to JTX12, were there any generic versions of

01:55 Bromday introduced into the U.S. market?

A. Yes. It states here in the middle of this paragraph, it says the product was approved only last year, April 2013. So it's talking about Prolensa.

Q. And I apologize. I think we need to be in the next

01:55 paragraph, the one that starts with the other known formulation. Just the first four lines of that.

So I'll ask you the question again. According to JTX12, were there any generic versions of Bromday introduced into the U.S. market?

01:56 **A. There was, yes.**

Q. And which were those?

A. There -- it was versions of Bromday.

Q. And were they by Hi-Tech and Mylan?

A. Yes.

01:56 Q. Let's now --

MS. HOLLAND: Your Honor, this is -- I'm going to again move to strike. This isn't in the expert report.

MR. HASFORD: Yes, Your Honor, he relied on this document at Paragraph 389 of his opening expert report for

01:56 Lupin and he had this opinion in there.

MS. HOLLAND: He didn't provide this opinion about the document.

MR. HASFORD: I believe it's in Paragraph 3.

MS. HOLLAND: It was a different opinion that was

01:56 provided about the document. In any event, this is a third-party document. Be that as it may, there was no opinion in the expert report about -- anything about generics related to this document.

MR. HASFORD: I believe --

01:56 THE COURT: I thought this was a Lupin document.

MS. HOLLAND: No. The plaintiffs found it on the Lupin website, apparently, but if you look at the first page, it's a report from HSBC, I believe an analyst's report. So this is not Lupin's opinions, this is what an analyst wrote.

01:57 MR. HASFORD: It's a document that Lupin puts on its own website, Your Honor, and he has opinions about this document. He's expressed those opinions at least in Paragraph 389 of his opening expert report to Lupin, and he's expressed these opinions.

01:57 THE COURT: Well, I don't think that a third-party document placed on a company's website is necessarily a statement of that company.

MR. HASFORD: No, but --

THE COURT: It's just information.

01:57 MR. HASFORD: But, Your Honor, he can rely on this

sort of document in providing his opinion and he can provide the opinions that are -- that are consistent with this document that, in fact, two different generic versions of Bromday have already been introduced into the U.S. market.

01:57 MS. HOLLAND: That opinion is not in the expert report. I'm not even sure if it's relevant to anything that's in Dr. Williams's expert report. Commercial success is out of the case as we know, Your Honor. I'm just not sure what this is about, why is it up here.

01:57 MR. HASFORD: And, Your Honor, I might add --

MS. HOLLAND: What is the relevance to the case whatsoever. I'm just -- I'm at a loss.

THE COURT: Well, let me ask that question, then. Why would the generic, the generic efforts, directed against

01:58 -- against Bromday be relevant here?

MR. HASFORD: Well, as Your Honor --

THE COURT: I thought you were going to be asking about generic efforts that were directed against Prolensa.

MR. HASFORD: And that's correct, we were, but as

01:58 Your Honor will recall, Mr. Mukerjee for InnoPharma argued during opening statement that there was some reason why allegedly the defendants here could not have gone and marketed generic versions of Bromday. Your Honor asked that question.

This establishes that, in fact, two generic companies,

01:58 in fact, one very large one, Mylan, which is aligned with

InnoPharma in this case, in fact, marketed a generic version of Bromday.

MS. HOLLAND: That is not an opinion that was ever offered.

01:59 MR. HOLLAND: It is encompassed within --

THE COURT: Just a moment. We can't have three speaking at once. Mr. Mukerjee.

MR. MUKERJEE: And an opening statement doesn't give a door to Dr. Williams now opining on items that he never

01:59 opined on.

MR. HASFORD: I believe it's within Paragraph 389 of his report.

THE COURT: Wait, let's take a look at that, please.

MR. HASFORD: Yes. So actually, we can -- if we can

01:59 pull up -- Noel, can we pull up Paragraph 389 of Dr. Williams's opening report to Lupin. And it's going to be in the -- the paragraph starts on one page and then spills over onto the next, it will be on the second page.

So, if your Honor will note, he cites, the key phrase

02:00 here is "despite the expected generic competition from Bromday®, PROL 0080436 to 804464," that's the exact document we have been looking at, he has a reference to the generic competition from Bromday® in here.

MS. HOLLAND: Your Honor, this was in the case --

02:00 there was a commercial success allegation in the case that's

no longer in the case, that's what this was directed to. You see clearly -- I believe plaintiffs are trying to backdoor in something when this opinion should not be in the case anymore because of the commercial success dropping out.

02:00 MR. HASFORD: Your Honor, on the previous pages you'll plainly see that this opinion was in the earlier -- two pages before, you'll see this opinion was in connection with a subheading entitled Copying By Others, so this opinion was not in connection with a commercial success opinion, it was

02:00 clearly the subheading there Copying By Others.

MS. HOLLAND: Again, your Honor, if the intent here is for Dr. Williams to give an opinion on copying, I object to that.

MR. HASFORD: And copying --

02:01 MS. HOLLAND: That is not an appropriate subject matter for this expert, although it could be argued, based on the documents, I suppose, in post-trial briefing.

MR. HASFORD: And copying is mentioned in the last paragraph of that document he was just discussing, your Honor,

02:01 which is JTX-12.

THE COURT: Is it being offered as proof of Prolensa's significant and recognized benefits which led Lupin and many other generics to copy plaintiff's Prolensa product?

MR. HASFORD: Despite the expected generic

02:01 competition from Bromday®.

THE COURT: But the evidence is that the generics were directed at Bromday® not at Prolensa.

MR. HASFORD: Well, no, the evidence is that the generics are directed at both, your Honor. They're coming in

02:02 here seeking to market FDA approved copies of Prolensa, yet there were FDA approved copies of Bromday® on the market, including one by Mylan, which is aligned with Innopharma in this case, it goes to the question that you asked Mr. Mukerjee during opening statement.

02:02 MS. HOLLAND: Your Honor, if this testimony comes in, defendants are going to want to put on Dr. Hoffman who was our economics expert who can address this issue. We dropped Dr. Hoffman from the list when we were told that there would be no issues of commercial success or anything related to it

02:02 coming in. Dr. Hoffman actually has it his report. So, you know, if Dr. Williams wants to put in that testimony and your Honor rules that it's admissible, then I'll just request that we be given the permission to put on Dr. Hoffman in response.

MR. HASFORD: And there's no basis for that, your

02:03 Honor. This is not going to an issue of commercial success, this is going to an issue of copying. Mr. Hoffman's only opinions in this case were responsive to a witness we're no longer calling.

MS. HOLLAND: He substantively responds to this

02:03 allegation I'll call it at this point in time, about the, you

know, why -- directly responds to this issue how the suspected generic competition from Bromday® does or doesn't have an effect to secondary considerations. And I'm just asking that if Dr. Williams' opinion comes in, we be permitted to put in an opinion that rebuts that opinion.

MR. MUKERJEE: That's correct, your Honor. Mr. Hoffman goes directly into the whole notion of automatic substitution, which you'll recall from my opening statement, which Mr. Hasford keeps referring to. So if they are allowed to put on this testimony which, frankly, I still don't understand how Dr. Williams is qualified to put in that testimony, then defendants have to then bring Mr. Hoffman to the stand to at least talk about what -- you know, the fact that there is generic Bromday® or could even be gleaned in some instances why that doesn't even matter in light of the way it actually works with respect to automatic substitution and other items.

THE COURT: But did you not argue to me in your opening that it won't be feasible to do a generic of Bromday® because it would never gain market traction, the value and the purpose of ANDA is in being the generic for the new brand, the Prolensa?

MR. MUKERJEE: Right. And I argued that also it undermines the very purpose of the Hatch-Waxman itself. And what Mr. Hoffman goes into in detail in his report, and I

think what I mentioned to your Honor during the opening, is that when plaintiff systematically discontinued the prior formulations like Xibrom® and Bromday® in favor of a new product, in this case let's say Prolensa, four months after Prolensa is introduced they discontinued Bromday®. As a result of that discontinuance, what happened was there was no ability anymore to have automatic substitution. So that generic Bromday® that might be out there in effect really has no real way of getting to the consumer because the way the generic actually goes into the consumer's hand, and the way Hatch-Waxman Act was designed itself, it needs that automatic substitution to be a driving force for getting that generic.

THE COURT: But apparently this witness wants to offer his observation that there's $100 million in product revenues.

MR. MUKERJEE: With respect to Prolensa, $100 million with respect to Prolensa, which, again, goes to what Ms. Holland is saying, that's a backdoor way of getting in commercial success.

MS. HOLLAND: Which has been dropped from the case.

MR. MUKERJEE: Which has been dropped from that case.

MS. HOLLAND: All I'm asking, your Honor, is that we have a chance to put on rebuttal testimony if this comes in. I think the rebuttal testimony would show indeed the generic versions of Bromday® have not been successful in the market

precisely for the reason that they can't -- they're not susceptible to automatic substitution, and that's what Mr. Hoffman would explain as part of his testimony. So to the extent we're getting into this area at all, which I've objected to, but to the extent we are, we just want to put in the rebuttal testimony.

MR. HASFORD: Your Honor, we disagree with it. The rebuttal testimony from Mr. Hoffman that they've been discussing is not responsive to Dr. Williams' testimony, this goes toward copying, this does not go toward the issues that they've stated.

I'll just note for the record that Mr. Mukerjee's explanation, of course, is not testimony and is not in evidence.

MS. HOLLAND: That's the point.

MR. MUKERJEE: Mr. Hasford can't have it both ways. He can't have it both ways. He can't on the one hand cite to my opening as a basis to try to bring this testimony in for Dr. Williams and then on the other hand say, well, that's not testimony, that's not evidence. I agree that opening statements are not part of evidence *per se*, there's no dispute there.

But to the extent that now plaintiffs are trying to bring in Dr. Williams to testify on generic Bromday®, well, yes, Ms. Holland is exactly right, then we do need to bring in

Mr. Hoffman to at least say, well, generic Bromday® effectively is zero in the marketplace and that's because it's no longer amenable to automatic substitution.

MR. HASFORD: And, your Honor, I note that their experts are saying that Prolensa is no better than Bromday®. All we're using this document to show is generic Bromday® is out there, we're not pointing to the $100 million statement in the document.

MS. HOLLAND: Then what is the relevance?

MR. MUKERJEE: Right.

MR. HASFORD: I have already explained the relevance, your Honor, that the generic Bromday® is out there. It's not that there's -- it's not the allegations that Ms. Holland and that Mr. Mukerjee are trying to make.

MS. HOLLAND: So the fact it's out there has to be -- for that fact to be relevant there has to be some testimony of nexus between that and the sales of the product in market, I guess which is out of the case now. But the fact on its own has no relevance, the only relevance is how it relates to the issue of secondary consideration. And that is exactly what Mr. Hoffman would respond to, why this statement in this document is not relevant to secondary consideration in this case because of the marketplace. And Mr. Hoffman has detailed testimony about that in his expert report. If plaintiffs don't want that testimony, then I guess they shouldn't

withdraw the question.

THE COURT: Well, I'm concerned under Rule 403 that this is going to be undue consumption of time even if in some fashion it might be admissible. Certainly Dr. Williams is not an expert on copying. Nor is he an expert on the markets, as far as I know. And what he's relying on here is some sort of an analyst's report in the trade data about the existence of products that aren't before me in this case, the so-called generic Bronuck®.

And so it's also not clear that this portion of Dr. Williams' original expert report pertains to any issue that remains in the case. It seems that it's directed more toward the commercial success and the projection of success that this analyst is making for a Prolensa product.

MR. HASFORD: Then we're happy to withdraw the document, your Honor.

THE COURT: All right. And if it's questioned on cross, again, it could be the door is open. But I'll sustain the objection for two reasons: That it predominantly relates to issues that are no longer in the case and, second, the underlying source is not terribly probative and, third, it would probably cause the defendants to rightly claim that they should be able to put a witness on the stand to rebut it. So I'll sustain the objection under both the scope of the expert's testimony and also Rule 403.

MS. HOLLAND: Can I ask, your Honor, that any testimony about the document that's come in already be stricken?

THE COURT: Let's see, I don't think we've heard any testimony about this yet, have we?

MS. HOLLAND: I think we have.

MR. HASFORD: I think we just heard, your Honor, that it's an HBSC report that was on Lupin's website, and then we heard about the generic versions of Bromday®, and then there was the objection.

MS. HOLLAND: Those were actually read into the record and testified about so, your Honor, I'd ask that that testimony be stricken, since the document is not going to be admissible.

MR. MUKERJEE: Right.

THE COURT: All right. Consistent with my ruling, I would have to strike the references to JTX-12, that is the document that appeared on the Lupin website, and so that will no longer be under consideration in the case.

Is this a good time for a break?

MR. HASFORD: Certainly, your Honor.

THE COURT: So let's take about a 15-minute break and then we'll resume at 11:55.

(Brief Recess.)

DEPUTY CLERK: All rise.

THE COURT: Be seated, please.

Mr. Hasford, you may proceed.

MR. HASFORD: Thank you, your Honor.

BY MR. HASFORD:

Q. Let's now turn to Dr. Lawrence's opinions regarding obviousness-type double patenting. Would you please turn to JTX-2 in your binder and identify this document?

A. JTX-2 is a copy of U.S. Patent 8,669,290.

Q. And if I refer to JTX-2 as the '290 patent, will you understand what I mean?

A. Yes.

Q. Will you please turn to JTX-3 in your binder and identify this document.

A. JTX-3 is a copy of U.S. 8,754,131.

Q. And I refer to JTX-3 as the '131 patent, will you understand what I mean?

A. I will.

Q. Did you hear Dr. Lawrence testify that the subject matter of Claims 6 and 20 of the '431 patent allegedly would have been rendered obvious by Claim 7 of the '290 patent?

A. I heard that, yes.

Q. Do you agree with Dr. Lawrence's opinion?

A. I don't, no.

Q. Did you hear Dr. Lawrence testify that the subject matter of Claims 6 and 20 of the '431 patent allegedly would have

been represented obvious by Claim 6 of the '131 patent?

A. Yes.

Q. Do you agree with Dr. Lawrence's opinion?

A. I don't.

Q. Let's explore the basis for your disagreement.

Have you prepared a demonstrative comparing Claim 6 of the '431 patent and Claim 7 of the '290 patent?

A. Yes.

Q. Let me direct your attention to PDX4-11 on the screen.

MR. HASFORD: And let's highlight the "consisting essentially of" in Claim 7 of the '290 patent.

BY MR. HASFORD:

Q. Do you see that Claim 7 of the '290 patent recites the transition phrase "consisting essentially of"?

A. I do.

Q. Are you aware that the Court has construed the phrase "consisting essentially of" in the claims of the '290 patent?

A. I'm aware of that, yes.

Q. And what is your understanding of the Court's phrase "consisting essentially of" in the claims of the '290 patent?

A. My understanding is that the phrase "consisting essentially of" means that the listed ingredients, as well as any unlisted ingredients. Unlisted ingredients are extra additives that can be added so long as they do not materially affect the basic and novel property of the claimed

preparation.

Q. So do you see that Claim 7 of the '290 patent recites benzalkonium chloride?

A. **Yes.**

02:31 Q. Is benzalkonium chloride a quaternary ammonium compound?

A. **It is.**

Q. Would a person of ordinary skill in the art understand that Claim 7 of the '290 patent is also open to additional quaternary ammonium compounds other than the benzalkonium

02:31 chloride specified in the claims?

A. **Yes, a person of ordinary skill in the art would understand that because benzalkonium chloride is listed so it must be present and then the use of "consisting essentially of" phrase.**

02:31 Q. Are suitable quaternary ammonium -- strike that and let me try again.

Are suitable quaternary ammonium compounds other than benzalkonium chloride also disclosed in the art?

A. **They are, yes.**

02:31 Q. Would the addition of a second quaternary ammonium compound to the aqueous liquid preparation of Claim 7 of the '290 patent be expected to materially impact the claimed composition's basic and novel properties?

A. **Not in my opinion, no.**

02:32 Q. Please turn back in your binder to JTX-71, which is the

Sallmann '913 patent. Let me direct your attention to Column 5, Lines 30 through 32, of the Sallmann '913 patent. What does Column 5, Lines 30 to 32, of the Sallmann '913 patent disclose?

02:32 A. **So here Sallmann discloses examples of preservatives, and the first class is quaternary ammonium salts. And then examples include cetrimide, benzalkonium chloride, or benzoxonium chloride.**

Q. How, if at all, Column 5, Lines 30 to 32, of the Sallmann

02:32 '913 patent support your opinion that Claim 7 of the '290 patent is also open to additional quaternary ammonium compounds other than the benzalkonium chloride specified in the claims?

A. **It supports my opinion because these are examples that a**

02:33 **person of ordinary skill in the art could consider as additional quaternary ammonium compounds that could be added without affecting the basic and novel properties of the Claim 7.**

Q. Have you prepared a demonstrative comparing Claim 6 of

02:33 the '431 patent and Claim 6 of the '131 patent?

A. **Yes, I have.**

Q. Let me direct your attention to PDX4-13 on the screen. Do you see that Claim 6 of the '131 patent also recites the transition phrase "consisting essentially of"?

02:33 A. **Yes.**

Q. Do you see that Claim 6 of the '131 patent also recites benzalkonium chloride?

A. **Yes.**

Q. Would a person of ordinary skill in the art understand

02:33 that Claim 6 of the '131 patent is also open to additional quaternary ammonium compounds other than the benzalkonium chloride specified in the claim?

A. **They would, for the same reasons I just testified to.**

Q. Let me now direct your attention to the wherein clause at

02:34 the end of Claim 6 of the '431 patent.

MR. HASFORD: And let's actually put back the previous slide PDX11 that compares Claim 6 of the '431 patent to Claim 7 of the '290 patent. Let's highlight the wherein clause. I apologize, highlight the bottom clause, the "where

02:34 a quaternary ammonium compound."

BY MR. HASFORD:

Q. Why, if at all, would a preparation of Claim 7 of the '290 patent or a preparation Claim 6 of the '131 patent that could include an additional quaternary ammonium compound

02:34 besides benzalkonium chloride fall outside the scope of Claim 6 of the '431 patent?

A. **So Claim 6 where it's highlighted, it says, wherein -- and should say when instead of where. When a quaternary ammonium compound is included in said liquid preparation, the**

02:35 **quaternary ammonium compound is benzalkonium chloride. So**

this would be understood by a skilled person to mean that there doesn't necessarily have to be a quaternary ammonium compound, but when there is one, it has to be benzalkonium chloride. That's a different scope of the claim compared to

02:35 **Claim 7 of the '290 patent.**

Q. Have you also prepared demonstrative PDX4-12 comparing Claim 20 of the '431 patent and Claim 7 of the '290 patent?

A. **I have, yes.**

Q. Have you also prepared demonstrative PDX4-14 comparing

02:35 Claim 20 of the '431 patent and Claim 6 of the '131 patent?

A. **Yes, I have.**

Q. Let me direct your attention to the bottom clause in Claim 20 of the '431 patent.

MR. HASFORD: If we could highlight that, please.

BY MR. HASFORD:

Q. Why, if at all, would a preparation of Claim 7 of the '290 patent or a preparation of Claim 6 of the '131 patent that could include an additional quaternary ammonium compound besides benzalkonium chloride fall outside the scope of Claim

02:36 20 of the '431 patent?

A. **So the reason is because a person of ordinary skill in the art understanding Claim 20, so in the list of the aqueous liquid preparation of Claim 20 of the '431 patent, it specifically says benzalkonium chloride. At the end of Claim**

02:36 **20 it says benzalkonium chloride is the only quaternary**

ammonium compound which is included in said liquid preparation, so in my opinion one of skill in the art would understand that the Claim 20 of the '431 patent can only contain the quaternary ammonium compound benzalkonium chloride whereas Claim 6 of the '131 patent could contain other quaternary ammonium compounds besides benzalkonium chloride.

Q. Would that opinion apply also to Claim 7 of the '290 patent?

A. It would, yes.

Q. Did you also hear Dr. Lawrence testify that the claimed amount of tyloxapol of 0.02 weight per volume percent in Claims 6 and 20 of the '431 patent is allegedly obvious in light of Claim 7 of the '290 patent and Claim 6 of the '131 patent?

A. I heard that.

Q. Do you agree with Dr. Lawrence?

A. I do not.

Q. Why not?

A. Because in Claim 20 of the '431 patent, for example, that claim specifically limits tyloxapol to having a concentration of about .02 percent by weight, whereas Claim 6 of the '131 patent has tyloxapol in an amount sufficient to stabilize bromfenac sodium salt. And then it says at the bottom, wherein the concentration of tyloxapol is from about .01 percent by weight to about .05 percent by weight. So in

my opinion, one of ordinary skill in the art would understand the scope of those claims regarding tyloxapol is different.

Q. And would your opinion regarding Claim 20 of the '431 patent with respect to Claim 6 of the '131 patent also be the same if you applied Claim 7 of the '290 patent to Claim 20 of the '431 patent?

A. It would be, yes.

Q. And would your opinions in this regard regarding Claim 20 of the '431 patent also apply to Claim 6 of the '431 patent?

A. Yes.

MR. HASFORD: Nothing further at this time, your Honor. I will move the exhibits into evidence that we used with Dr. Williams.

THE COURT: Okay. Could you read those into the record?

MR. HASFORD: Yes. They'll be PTX-294, PTX-268, PTX-272, PTX-326, PTX-273, PTX-324, PTX-265, PTX-591, PTX-592, PTX-50093, JTX-144, PTX-40074, and JTX-18.

THE COURT: Is there any objection to those?

MS. HOLLAND: Your Honor, we would like to have an opportunity to go through the list and maybe come back after lunch and just confirm whether we have any objections.

THE COURT: Yes, you may.

MS. HOLLAND: Thank you.

THE COURT: Ready for cross-examination?

MS. HOLLAND: Yes, your Honor.

THE COURT: Okay. You may proceed.

(CROSS-EXAMINATION OF ROBERT O. WILLIAMS BY MS. HOLLAND:)

Q. Good afternoon, Dr. Williams.

A. Good afternoon.

Q. Dr. Williams, you provided opinions in your direct examination about ophthalmic drug formulations, correct?

A. Yes.

Q. Okay. And you testified in substance that formulation of ophthalmic drugs is particularly complex, is that right?

A. The ophthalmic solutions, they are, yes.

Q. But you have only been involved in ophthalmic formulation on two occasions in your entire career, isn't that right, Doctor?

A. Two solutions for ophthalmic, that's true.

Q. Okay. And you didn't consult any references on ophthalmic drug delivery in rendering your opinions in this case, correct?

A. Well, I mean, I have -- I teach a subject on ophthalmic solution but I didn't particularly look to -- in preparing for this case look to -- I didn't go search for any, that's true.

Q. Okay. So it's true that you did not consult any references in ophthalmic drug delivery in rendering your opinions in this case?

A. I did not go consult any specifically for this case, no.

Q. Okay. Thank you.

Now, you were asked on direct about some testimony that Dr. Lawrence gave, and I'm going to quote you what the question was. You were asked whether you agree with Dr. Lawrence's testimony that "pharmaceutical formulation development allegedly constituted routine optimization." Do you recall being asked that question?

A. Generally, yes.

Q. Dr. Lawrence never testified that all pharmaceutical formulation development was a matter of routine optimization, did she?

A. I understood her in the context of ophthalmic preparations that are the subject matter here, which was what I was responding to.

Q. But she never give that testimony either, Doctor.

Didn't Dr. Lawrence testify -- well, let me withdraw that.

Wasn't Dr. Lawrence's focus on how a formulator determines concentration of an excipient to use in the formulation, do you recall that that was the context of her testimony on routine optimization?

A. I did, and that's what I disagree with.

Q. Okay. Now, Dr. Lawrence testified that a formulator would prepare a range of concentrations of different excipients in the formulation and test them to determine which

concentration to use. Do you recall that testimony?
A. Generally, yes.
Q. Okay. And you agree that that's a procedure formulators use, right?
02:43 **A. That's one in the steps of what a formulator would do to try to solve whatever problem is faced -- being faced.**
Q. And that procedure or process is generally called optimization, right?
02:43 **A. Well, I disagree it's generally called optimization. I mean, there's a statistical optimization that we use where you look at the variables that are being studied. But, I mean, sometimes it might be called optimization. Routine is definitely not part of the phrase.**
Q. I just want to make sure we're not talking about semantics here.
So would you agree with me that the process Dr. Lawrence described is sometimes called optimization but your quarrel is with the word routine?
A. That's probably right.
02:44 Q. Okay. Now, would you agree that there are some aspects of formulation that are a matter of routine optimization?
A. Some probably would be considered routine, yes.
Q. And there are some aspects of formulation that you'd say are routine experimentation, right?
02:44 **A. Some would be. Towards the end of the development cycle**

they would be.
Q. All right. Now, the two claims that remain in this case require .02 percent tyloxapol, right?
A. They do, yes.
02:44 Q. And you testified that a formulation with .02 percent tyloxapol is stable, right?
A. Well, according to the data in the patent tested under those conditions, a formulation with .2 percent tyloxapol is chemically stable, so, yes.
02:45 Q. It's chemically and physically stable, right?
A. Well, I mean, it would be physically stable because nothing was reported in the patent as to any kind of cloudiness or turbid.
Q. Now, isn't it correct that the formulations with the
02:45 ingredients in Claim 6 and 20 would still be stable even if a higher amount of tyloxapol were used?
A. They might be chemically stable. They might be.
Q. All right. Well, let's be sure. Let's look at the '431 patent.
02:45 **A. Okay.**
Q. We put up JTX-1. Let's go to Column 5, Lines 41 to 47. And do you see, Doctor, that that portion of the patent talks about tyloxapol content of the inventions claimed in the patent?
02:46 **A. Yes.**

Q. Okay. And what the text of the '431 patent says is that the formulations can contain, for example, the minimum content of about .01 percent, .02 percent, or .03 percent tyloxapol and the maximum content about .05, .1 percent, .3 percent, or
02:46 .5 percent tyloxapol. Do you see that?
A. Yes.
Q. And the '431 patent is disclosing that that concentration would fall within the claimed inventions in this case, right?
MR. HASFORD: Objection, mischaracterizes the
02:46 document, your Honor. Claims 6 and 20 plainly specify .02 weight by volume percent tyloxapol.
THE COURT: For Claims 6 and 20.
MS. HOLLAND: I'll ask a broader question, your Honor.
02:46 MR. HASFORD: Well, the way she phrased it mischaracterizes the document, your Honor.
THE COURT: Please reframe the question.
MS. HOLLAND: I'll reframe it, your Honor.
BY MS. HOLLAND:
02:47 Q. Doctor, does the specification indicate in the disclosure of the invention that a range of tyloxapol from about .01 percent through to about .5 percent would be sufficient to be within the disclosure of the '431 patent?
A. So, I mean, generally speaking that's what this patch
02:47 **says in the '431 patent.**

Q. So at least the specification doesn't indicate that you must have .02 percent to have a stable formulation, right?
A. I mean, this part of the specification states that at a minimum about .01 percent and then up to about .5 percent by
02:48 **weight.**
Q. Then if you go to Table 2 in Column 8, there are three different tyloxapol concentrations listed for formulations A-04, A-05 and A-06. Do you see that?
A. I do, yes.
02:48 Q. And those are .02 grams and .05 grams, and .03 grams. Do you see that?
A. As the amount, and so it's to .02, .05, and .03 percent by weight.
Q. And Table 2 indicates that all three of those
02:48 concentrations of tyloxapol led to stable formulations, correct?
A. That's true, yes.
Q. Now, another part of what a skilled person does in formulation development is look at the compatibility amongst
02:49 different components of the formulation, right?
A. That's true.
Q. Okay. And that's a standard part of the formulation process?
A. That's probably more part of the pre-formulation process.
02:49 **But on continuum, the excipient compatibility between**

themselves or between the particular excipient and the active drug, those are done, yes.

Q. As a standard matter in every formulation, right?

A. I mean, from my experience, they are done when one is coming up with a formulation for a particular drug substance.

Q. Okay. So if a skilled person were going to formulate bromfenac sodium, for example, together with BAC, they would look to see whether there was an interaction between the two just as a matter of standard formulation development, is that right?

A. I think when a skilled person is studying formulations containing bromfenac sodium, they're going to look at each of the excipients and in combination together to see if there's any type of chemical or physical interaction generally from my experience.

Q. Now, you've given the opinion in this case that the goal behind -- well, let me withdraw that.

Is it your opinion that the goal behind any substitution or modification of Ogawa Example 6 would have been to improve upon the formulation's stability?

A. Say that again, please?

Q. Yeah, sure.

Is it your opinion that the goal behind any substitution or modification of Ogawa Example 6 would have been to improve upon the formulation's stability?

A. I think that's right, yes. To turn it around the other way, which I think is what I said, there's no motivation that I see because Ogawa Example 6 is stable in Ogawa, so I think that's how I had answered the question.

MS. HOLLAND: Well, let me see if I can -- do we have back Dr. Williams' expert reports for him? Thank you.

BY MS. HOLLAND:

Q. First I'll just see if I can refresh your recollection.

MS. HOLLAND: Counsel, it's in Paragraph 86 of his responsive report.

MR. HASFORD: Actually, do you have an extra copy?

THE WITNESS: Thank you.

Paragraph 86?

MS. HOLLAND: Yes.

BY MS. HOLLAND:

Q. I'm referring to Paragraph 86.

MS. HOLLAND: And can we highlight the sentence that begins "the goal behind," it's like four lines up from the bottom.

THE WITNESS: Yes, I see it.

BY MS. HOLLAND:

Q. Okay. Does that refresh your recollection that you offered an opinion that the goal behind any substitution or modification of Ogawa Example 6 would have been to improve the formulation's stability?

MR. HASFORD: Just for completeness, your Honor, can we have the next sentence of that paragraph read in, please?

THE COURT: Yes, it may.

BY MS. HOLLAND:

Q. The next sentence reads, a person of ordinary skill in the art would not have pursued excipients that would not be accepted to have any effect on or would lessen the stability benchmark set for Ogawa Example 6.

MR. HASFORD: I apologize, your Honor. We might have to have the previous sentence to place it in proper context.

MS. HOLLAND: Your Honor, would you like me to do that?

THE COURT: Well, the witness can read the whole paragraph to himself.

MS. HOLLAND: Thank you.

THE WITNESS: Okay. I've read it.

BY MS. HOLLAND:

Q. Now, you testified previously that there are two types of stability, chemical and physical, right?

A. That's true.

Q. And so potentially the goal behind any substitution or modification of Ogawa Example 6 could be to improve either chemical or physical stability, right, those are both possibilities?

A. I mean, Ogawa doesn't talk about physical stability, but

if assuming you had a reason to modify it, which I'm not saying you do, but if you did, if you were making a substitution, you would consider stability as a whole, which would mean chemical and physical.

Q. And just to be clear, in your opinion a change in appearance of a formulation is a problem of physical stability, correct?

A. If it's related to -- yeah, I think generally that's right.

Q. All right. Let's go to the Ogawa '225 patent, JTX-147. And I'm going to refer you back to something you talked about in your direct testimony, it's Table 8 in Columns 13 and 14. So let's go back there.

Do you recall talking about this in your direct testimony?

A. I do, yes.

Q. And you talked about it, I believe, in the context of unexpected results, is that right?

A. I believe so.

Q. Okay. Now, if you look at Table 8, you focused on the column that says residue percent and you said that that reflected chemical stability, right?

A. That's true, yes.

Q. Now, if you look just one column over to the left, you'll see a column for appearance. Do you see that?

A. **Yes.**
Q. And appearance, as we just heard, speaks to physical stability, right?
A. **Well, Ogawa says there's red insoluble matter, which is -- I think to me and to a person of ordinary skill in the art that's chemical stability, so --**
Q. Well, there's nothing in the appearance column that would take you away from the general view that you've expressed that appearance relates to physical stability, right?
A. **Well, but if you go back to experimental Example 4, which is the basis for Table 8, Ogawa is talking about the change in residue was almost non-observed but in three weeks red insoluble matters were observed, so that red insoluble matter that's -- the degradation product apparently is not soluble so it's precipitated out.**
Q. And so you're saying that appearance there does not refer to physical stability, is that your opinion?
A. **Well, it starts as a chemical because he's explaining it's a red insoluble, insoluble means whatever that degradation product is, it's coming out of solution and so that is -- that then becomes a physical because it's -- there's something that's not dissolved.**
Q. So now you agree with me that the appearance column there refers to physical stability, right?
A. **Well, it says -- yeah. I just think in the context of**

Ogawa appearance is talking about the red insoluble matter, so it's the degradation product that's coming out of solution.
Q. All right. But let's see. Go back to Experimental Example 4. It says, in -- do you see there are two paragraphs under the actual example, and it says, "of the above four," do you see that?
A. **Yes.**
Q. And then it says, in the formula, "the change in residue rate were not almost observed but in three weeks red insoluble matters were observed," right?
A. **That's what it says, yes.**
Q. Okay. But if you look at -- and that's just -- one more time, I'm sorry -- that's going back and it's -- it refers to pH of 8, right? It says of the above four, the formula with the pH of 8 is most stable?
A. **Yeah, the first sentence of that paragraph in column 8 says, the formula at the pH of 8 is most stable.**
Q. Okay. So let's go back to Table 8 then. If you look at a pH -- for pH of 8, there is no change in appearance, right?
A. **Well, I mean, there's -- there's a negative dash symbol that, according to Ogawa in Table 8, change in appearance was not observed, but in the paragraph, Ogawa states that no change -- sorry -- it says in the formula, "the change in residue rate were not almost observed but in three weeks red insoluble matters were observed."**

Q. Yeah, exactly my point. So there is a seeming inconsistency there, correct?
A. **Well, okay. I mean it says in the spec that -- with regards to Experimental Example 4, it describes at three weeks there is red insoluble matter, so degradation of bromfenac, but it apparently wasn't enough to attain a positive sign on the appearance column is the way I've reconciled it.**
Q. But isn't there another explanation for this, Dr. Williams?
A. **Okay. What --**
Q. Isn't another possible explanation that the appearance column here, what they're looking at, is cloudiness or turbidity as in -- as you've previously testified, would be indicative of lack of physical stability.
A. **Yeah, I mean, in the context of Ogawa, I don't think that's a possibility. I think Ogawa is talking about insoluble degradation product because it calls it this red insoluble matter." It doesn't talk about physical stability.**
Q. And that's even though there is an inconsistency between the language in the Experimental Example 4 and Table 8, the way you've interpreted it?
A. **I'm -- I didn't say there was an inconsistency. It's just that's the way that it's presented, it's worded in Experimental Example 4. It describes the red insoluble matter after three weeks, and then that's how it's reported in Table**

8.
Q. All right. Now, you testified that sodium sulfite and povidone were used in the Ogawa '225 formulations to improve chemical stability, right?
A. **That's true, yes.**
Q. Okay. And then -- and you said that the problem of chemical stability was solved by the use of sodium sulfite and povidone, right?
A. **Within the pH range that Ogawa specifies.**
Q. Okay. But, as we've already discussed in your testimony, if there were a problem with bromfenac forming a precipitate with BAC, that would be a problem of physical stability, not chemical stability, right?
A. **Say that again, please.**
Q. Yeah.
If there were a problem with bromfenac forming a precipitate with BAC in a solution, that would be a problem of physical stability, right, not chemical stability?
A. **If that occurred, that would be a physical stability.**
Q. And sodium sulfite and povidone wouldn't address that physical stability issue, right?
A. **From my experience, that's probably true.**
I'm not sure about PVP. PVP may have some effect or not. I think the sodium sulfite is there as an antioxidant for degradation. I'd have to think about the PVP.

Q. Okay. And you -- I apologize.
And in your testimony, you said that the Fu 984 reference was focused on physical stability, right?
A. True, yes.
03:02 Q. So is it fair to say that a person of ordinary skill in the art concerned about the physical stability of a formulation would look at the Fu reference?
A. They might, if -- if they could learn about Octoxynol 40 and its effect on the physical stability, yes.
03:03 Q. Now, I want to talk about a different ingredient used in Example 6 of Ogawa '225 patent, and that's Polysorbate 80.
Now, one of the known functions of Polysorbate 80 is as a physical stabilizer, right?
A. That's true, yes.
03:03 Q. Okay. And another term for physical stabilizer is solubilizer?
A. No, I disagree with you.
Q. Does a physical stabilizer -- is it used to solubilize things in solution?
03:03 **A. Well, I'm missing something in your question. Sorry.**
Q. Okay. A physical stabilizer like Polysorbate 80 is used in connection with things that are not soluble in water, right?
A. That's true. That's like a suspension, an emulsion,
03:03 **that's true. So it's a physical stabilization of the**

suspension or the emulsion, as example.
Q. Or an aqueous dispersion?
A. Aqueous dispersion as in suspension? That would be a suspension.
03:04 Q. All right. Now, you, yourself, have used Polysorbate 80 as a physical stabilizer, right?
A. I have, yes.
Q. But you testified that Polysorbate 80 was not used as a physical stabilizer in Example 6 of Ogawa, right?
03:04 **A. Wait. But there's nothing to physically stabilize in Example 6 because it's a -- it's a solution.**
Q. Well, let me ask you again.
You testified that Polysorbate 80 was not used as a physical stabilizer in Example 6 of Ogawa, right?
03:04 **A. I don't recall exactly, but I would have, yes.**
Q. Okay. And you said this was because bromfenac sodium is freely water soluble, right?
A. You're asking about physical stabilization?
Q. Yes.
03:05 **A. I talked about Polysorbate 80 in the context as a solubilizer.**
Bromfenac is freely water soluble, so there's no need for a solubilizer. And there's nothing dissolved in it, so there is also no need -- sorry. There is nothing suspended in
03:05 **it, so there is also no need as a physical stabilizer.**

Q. Let's explore that.
So, you agree with me that your reasoning for why Polysorbate 80 is not used as a physical stabilizer in Ogawa is that bromfenac sodium is already freely water soluble so
03:05 you don't need a solubilizer; is that right?
A. I'm sorry. I'm hearing solubilizer and stabilizer, and they're different to me, and I want to make sure I get your question.
Q. Right. So -- all right. Let me try it this way then.
03:05 You said that bromfenac sodium is freely water soluble, right?
A. It is, yes.
Q. And you gave that as a reason for knowing that Polysorbate 80 was not in Example 6 of Ogawa to address
03:06 solubility issues, right?
A. That's true, yes.
Q. Correct. But just to be clear here, if a complex forms between bromfenac and BAC, its solubility would be different from the solubility of bromfenac sodium, right?
03:06 **A. I actually don't -- I don't know. It may. It depends on the characteristics of the complex that's formed.**
Q. Okay. But your opinion that bromfenac sodium is freely water soluble would not necessarily be relevant to a complex that forms between bromfenac and BAC, right?
03:06 **A. That's true. It wouldn't.**

Q. Okay. So, is it at least a possibility that Polysorbate 80 is used in the '225 formulation to solubilize bromfenac-BAC complexes?
A. I don't know. I mean, there is nothing in the '225 Ogawa
03:07 **patent that would lead one of skill in the art to believe that there is a complex formed and that's its function. It doesn't ascribe any particular function to Polysorbate 80 in the Ogawa patent.**
Q. But you know, don't you, Dr. Williams, why Polysorbate 80
03:07 was used in Ogawa?
A. Well, I've testified one use could be as a wetting agent because it's an ophthalmic solution.
Q. Well, didn't you review documents in the course of forming your opinions in this case that told you exactly why
03:07 Polysorbate 80 was used in Ogawa?
MR. HASFORD: I'll object to the extent she's looking to go into plaintiff's internal documents. I think we have had -- we have already been down this road, your Honor.
MS. HOLLAND: Your Honor, there was extensive
03:07 testimony about unexpected results, A, which is not limited to any piece of prior art.
In addition, the -- Ogawa is actually prior art, so nothing in the internal documents could go to the invention in this case. It could only go into explaining the prior art.
03:08 So, for two reasons, I think that the objections that

have previously been raised are not relevant. And I think as a matter of impeachment of this witness, I should be permitted to ask these questions. These are documents that he actually gave opinions on in his report. They're in his direct binder, and I can show you that.

03:08

MR. HASFORD: Your Honor --

MS. HOLLAND: I would like to know if he -- when he gave his opinions to the Court, why didn't he tell the Court about what's in the documents in his direct binder that answer this question definitively.

03:08

MR. HASFORD: Your Honor, we presented no evidence through Dr. Williams of any of those documents that were in his direct binder that she's referring to, and we've already explained to your Honor that by statute, obviousness is assessed from a hypothetical person of ordinary skill in the art, not the inventor. Patentability shall not be negative by the manner in which the invention was made.

To the extent she's trying to go back and reargue the issue that your Honor has already decided, we believe that's improper.

03:09

The Federal Circuit has made clear, time and again, that the path that an inventor leads -- the path that leads an inventor to the invention was expressly made irrelevant to patentability by statute. It's the *Life Tech* Case, 224 F.3d 1320.

03:09

There was no door opened on direct, there was no testimony that would warrant anything to -- for your Honor to reconsider that earlier ruling or for Ms. Holland to go into this with Dr. Williams now on cross.

03:09

MS. HOLLAND: Your Honor, it's a completely -- if I may, it's a completely different situation. We heard extensive testimony this time about unexpected results based on plaintiffs' internal testing and documents.

MR. HASFORD: No, Your Honor. We heard unexpected results based on the patent, and we heard unexpected results based on certain data that were stipulated to by defendants, but there were no -- there was no testimony provided about plaintiff's internal documents. We never showed Dr. Williams an internal document on direct exam, we never offered one into evidence, and we didn't provide any -- have Dr. Williams provide any testimony on that.

03:09

03:09

MS. HOLLAND: Dr. Williams has provided testimony on the stand inconsistent with documents that are in his direct binder, that plaintiffs chose not to show him today but there surely are opinions on them in his expert report, and he was surely ready to testify about them. They are in his direct binder.

03:10

THE COURT: Well, has he offered opinions in his deposition that are inconsistent with what he's saying today?

MR. HASFORD: No.

03:10

MS. HOLLAND: In his deposition, your Honor?

THE COURT: Right.

MS. HOLLAND: I don't understand the question. I apologize.

THE COURT: You said that he was -- that in his expert report, that he made reliance upon the internal documents. Was he questioned about those during his deposition and was his testimony inconsistent with what he's offering today?

03:10

03:10

MS. HOLLAND: His testimony -- his testimony today is that Polysorbate 80 was not used as a physical stabilizer in Example 6 of Ogawa, and I have documents to show otherwise, that I'd like to impeach the witness with. I feel like it's a straightforward married.

MR. HASFORD: To the extent these are the inventor's own documents, your Honor, again, this does not go toward any issue of obviousness. It does not go to the motivation that has to be found in the prior art, and we've heard testimony on that and there is case law to that effect, your Honor. If she's trying to use this for that purpose, that's completely improper.

03:11

03:11

MS. HOLLAND: It goes to unexpected results and what exactly was meant by stability when Dr. -- when Dr. Williams was looking through all these documents and giving testimony about stability. Was it actually physical stability or was it

03:11

chemical stability?

MR. HASFORD: Your Honor --

MS. HOLLAND: I should be entitled to probe that.

He offered testimony about internal documents. He said they showed stability. If I -- and he said that showed chemical stability. If there are other internal documents that show that that is not the case, I don't see why Dr. Williams can't be impeached on them.

03:11

MR. HASFORD: Your Honor, these documents are not in the public domain and they do not go at all to how a person of ordinary skill in the art would have understood the disclosure of the Ogawa '225 patent as of 2003. That's the issue for obviousness.

03:11

MS. HOLLAND: I'm talking about unexpected results, counsel. And as you know, Dr. Williams testified on direct with internal data to support his unexpected results opinion.

03:12

MR. HASFORD: Your Honor, while --

THE COURT: Was that the same internal data though that's disclosed in the patent?

MS. HOLLAND: No. No. It's internal data that was from the IPR declaration of Dr. Sawa, who is not here today to talk about his internal results.

03:12

MR. HASFORD: Your Honor, there were -- there were two or three additional pieces of data that defendants stipulated to in those documents, and they were not -- you

03:12

know, those -- so the evidence of unexpected results may, in fact, come from something that is not in the prior art. However, the evidence of actual obviousness, the evidence of whether there would have been a motivation to make this
03:12 claimed invention, needs to be based on what was known in the prior art, and the attempt in which Ms. Holland is trying to use this is not to go toward unexpected results but is to try to go toward a prima facie case of obviousness, and that's impermissible, your Honor.

03:13 MS. HOLLAND: I just said it wasn't, your Honor.

And I can -- I mean Dr. Williams put up, actually from Mr. Sawa's IPR declaration, little -- I don't remember the PTX numbers, but they were charts from the declaration with Mr. Sawa's summarized internal data. Mr. Williams took
03:13 that internal data, he put it into these demonstratives. He talked about residual bromfenac and that that means chemical stability, based on the internal documents. We have documents that show that that's not the case, and that these opinions that were given about chemical stability are just simply
03:13 incorrect, based on the internal data.

THE COURT: And which demonstrative are you holding up?

MS. HOLLAND: Right now I'm looking at PDX4-5.

And, in particular, your Honor, in Paragraph 371 of
03:14 Dr. Williams' opening expert report, he says that the data and

results that he's presenting come from the specification of the patents-in-suit and Ogawa and laboratory notebooks of Mr. Shirou Sawa. That's what I want to ask about.

MR. HASFORD: Your Honor, they're trying to use
03:14 this --

MS. HOLLAND: Laboratory notebooks that were used in the direct to support unexpected results.

MR. HASFORD: Your Honor, they're trying to back door this as a way of using it to show how a person of ordinary
03:14 skill in the art would have understood Ogawa, and that's the impropriety here. It's not proper in an obviousness case, and your Honor has already ruled to that effect.

THE COURT: Well, when I ruled, I didn't know that he was relying upon that data, the internal data of Sawa from the
03:14 IPR, and that forms the basis or seems to form a basis of his opinion.

I think the witness needs to be asked whether he is relying upon that data as a basis of his opinion. If he says he's not, he can be impeached with his prior testimony. If he
03:15 says he is, then I'll permit the questioning on the merits.

MR. LIPSEY: Excuse me, your Honor, and I know it's irregular, but if I may just briefly.

There is a fine but important point of patent law here, and that is, everybody has said and the cases hold that
03:15 the evidence of the properties of the invention and its

comparative properties and its benefits and advantages, that evidence does not have to be in the prior art. And that's basically the *Sanofi-Aventis* case that I think everybody has been talking about. Patentability may consider all of the
03:15 characteristics possessed by the claimed invention whenever those characteristics become manifest.

And so it's quite common, as we have here, to use comparative data that was generated which itself is a prior art, and indeed often may be generated years after the patent
03:15 issues, to demonstrate what the properties of the invention are, which go to the secondary considerations.

Reaching into things that the inventor may have known that are not in the prior art to try to prove how a person of ordinary skill in the art would have read that prior art,
03:16 that's an absolutely impermissible use.

THE COURT: Well, if your own witness made that use of it, though, then he can be cross-examined on it. So I'm permitting the threshold question to be asked of whether he relied upon such data. If he did, then of course he can be
03:16 cross-examined on it because he's relying on it in his opinions about prior art.

MR. LIPSEY: Agreed, as to the data and experiments.

But the question that counsel wants to ask is what did the internal documents show about what the thought process
03:16 was about why Polysorbate 80 was in the original formulation.

That's not part of the prior art, your Honor.

THE COURT: Well, let's all listen carefully to the question, if and when it's asked. I don't believe that that is the pending question. In other words, the "why" question
03:17 isn't being asked.

I think that the question, as I understand it, is going to concern itself with whether he was aware of experimental results that contradict his -- his opinion about something that couldn't happen.

03:17 MS. HOLLAND: Well, let's put PTX-591 up, if you don't mind, Mr. Chase. Thank you.

BY MS. HOLLAND:

Q. This is a document you relied on in your direct examination, correct?

03:17 **A. Yes.**

Q. And is your understanding that this document is from the IPR declaration of Mr. Sawa?

A. You know, I actually don't recall. I was thinking it was part of the prosecution history and the declaration, but I
03:17 **don't. Sitting here right now, I don't recall.**

Q. Okay. Well, is part of the data here from, as you said in your expert report, laboratory notebooks of Mr. Shirou Sawa?

A. I don't think this is taken from the laboratory notebook.

03:18 Q. Does the data in this table come from, among other

sources, laboratory notebooks of Mr. Shirou Sawa?
A. It may. Actually sitting here, I don't remember if it does.
Q. Okay. Well, let me see if I can refresh your recollection.
Do we have the opening expert report? Do you have that?
A. I do, yes.
MS. HOLLAND: Okay. Your Honor, do you have it as well?
THE COURT: I don't have it in front of me. But --
MS. HOLLAND: Shall we just put it up on the screen?
THE COURT: Yes, that would be fine.
Do you recall whether that was passed up the other day?
MS. HOLLAND: Can you say that one more time, your Honor?
THE COURT: Okay. Here it is. Thank you.
MR. HASFORD: Can we get a copy?
MS. HOLLAND: Let's put it up on the screen. In the meantime, it's Paragraph 371.
I'd like to look at the first sentence.
MR. HASFORD: We need a copy first actually.
MS. HOLLAND: I'm just putting it up on the screen.
MR. HASFORD: Thanks.

MS. HOLLAND: So then, your Honor -- is everybody ready now? Do you have it?
MR. HASFORD: Yes.
MS. HOLLAND: Okay. Now I lost my ...
BY MS. HOLLAND:
Q. So you see the first sentence in Paragraph 371 says the data and results for the following table came from the specification of the patents-in-suit, Ogawa, and laboratory notebooks of Mr. Shirou Sawa. Do you see that?
A. Yes.
Q. Was that a true statement in your expert report?
A. It -- yes.
Q. Okay. Now, if we can go back to PTX-591.
A. Okay.
Q. That is the same table that appears in Paragraph 371, except you have an additional column from Ogawa, right?
A. That's -- that's true, yes.
Q. Okay. So, now, have we established that what you showed the Court here, PTX-591, was actually partially from Ogawa -- from Sawa laboratory notebooks?
A. Yes.
MS. HOLLAND: So, may I question, your Honor?
THE COURT: Well, it doesn't open all the notebooks to scrutiny. It opens this particular data to scrutiny. And so the answer is yes, you may question about the information

that he's relying on.
MS. HOLLAND: I actually have one more question and I think this will do it.
BY MS. HOLLAND:
Q. You gave testimony in connection with your unexpected results testimony that the tyloxapol in -- let me withdraw that.
You gave testimony that the tyloxapol in the formulations you discussed was there for purposes of chemical stability, right?
A. In the context of the '431 patent, that's true, yes.
Q. Well, now we are talking about unexpected results so I'm asking you in every context.
Is it your testimony that the unexpected stability that you are talking about for tyloxapol is chemical stability?
A. Yes.
Q. Okay. All right. So let's go to JTX-25.
MR. HASFORD: And --
MS. HOLLAND: I'm sorry, your Honor. I'm -- I actually want to go to DTX- -- PTX-125A.
MR. HASFORD: Your Honor, I think we are going to have to object to this. Your Honor --
MS. HOLLAND: This is in evidence already.
MR. HASFORD: This looks like part of the New Drug Application, and I think your Honor's ruling was that he could

be questioned about the data in these tables and not into any further underlying materials.
MS. HOLLAND: I just asked a different question, Your Honor. I asked whether the testimony about tyloxapol being -- having unexpected stability, in the context of unexpected results, where you can go outside of the scope of the prior art, was that about it having unexpected chemical stability. And the witness said yes. Now I'm going to cross-examine him on that point.
MR. HASFORD: I don't think she said anything about the prior art in her question, your Honor.
MS. HOLLAND: You're right, I didn't. I didn't. I'm not asking about the prior art. PTX- -- oh, I'm sorry, your Honor. Did you rule?
THE COURT: Well, no, I didn't.
What's the pending question? Could it be read back, please.
(The court reporter read back the following:
"QUESTION: You gave testimony in connection with your unexpected results testimony that the tyloxapol in -- let me withdraw that.
You gave testimony that the tyloxapol in the formulations you discussed was there for purposes of chemical stability, right?
"ANSWER: In the context of the '431 patent, that's

true, yes.

"QUESTION: Well, now we are talking about unexpected results so I'm asking you in every context.

"Is it your testimony that the unexpected stability that you are talking about for tyloxapol is chemical stability?

"ANSWER: Yes."

THE COURT: Okay, I'll permit it.

BY MS. HOLLAND:

03:25 **Q.** All right. Let's look at PTX-125A.

MS. HOLLAND: And this is actually already in evidence, your Honor.

BY MS. HOLLAND:

Q. Can we -- can we go to the first page again, please.

03:25 **A. Do you know, do I have this in my notebook?**

Q. You should have it in your cross binder.

A. Cross binder?

Q. Do you have a cross binder?

THE COURT: I don't think that's been handed up.

03:25 MS. HOLLAND: Well, all right. That's going to delay things for a moment. I apologize. But we're getting the cross binders.

THE COURT: It wasn't a trick question asking what's in a binder he hasn't received yet?

03:26 (Laughter.)

THE COURT: Thank you.

Let me know when your questioning comes to a good time for a lunch break. It's about five of one.

MS. HOLLAND: Sure. I can do it after this document, your Honor.

03:26

THE WITNESS: Oh, you know what? There's notes in here.

MR. LIPSEY: Just answer the questions written in the margin.

03:26 THE WITNESS: I know I don't want that.

(Laughter.)

BY MS. HOLLAND:

Q. How are we doing now, Dr. Williams?

A. Okay. So it's DT --

03:26 **Q.** Clean --

A. Yes, it's clean.

Q. -- copy? Okay.

A. Okay. 125.

Q. PTX-125A.

03:26 **A. Okay, I'm there. Thank you.**

Q. Okay. So this is -- do you see this is a section of the New Drug Application that plaintiffs submitted to the FDA for Prolensa®, correct?

A. I see that, yes.

03:26 **Q.** Okay. Now, in this New Drug Application for Prolensa®,

there is a pharmaceutical development section. Do you see that?

A. Yes.

MR. HASFORD: And, your Honor, I think this is an

03:27 appropriate time to object because if there is a pharmaceutical development section, this is going to pharmaceutical development of the invention. This is exactly what we've been concerned about, that they're trying to use this non-prior-art document, this New Drug Application that

03:27 was submitted to the FDA long after the priority date of the patents-in-suit, as evidence toward their obviousness case. That's impermissible, your Honor.

MS. HOLLAND: Your Honor, may I ask my question? It will be evident that that's not where I'm going.

03:27 THE COURT: All right. You may ask the question and then I'll hear any objection to it.

BY MS. HOLLAND:

Q. All right. Well, my first question was just do you see that there is a -- this is a pharmaceutical development

03:27 section?

A. I do.

Q. Okay. Now, turn to the next page. Well, actually, turn to Page 7 of 16.

A. Okay.

03:28 **Q.** Now, three paragraphs up from the bottom there, I'd like

to -- can you put that up on the screen, please?

So, what plaintiffs told the FDA in trying to get approval for Prolensa® was that tyloxapol acts as a solubilizing agent to prevent interaction between

03:28 benzalkonium --

MR. HASFORD: And I'll object at this point, your Honor. I object, move to strike it from the record. I have to object. I apologize, Your Honor.

This is going to the exact issue that we're concerned

03:28 about, and your Honor said that the "why" couldn't be admitted here and shouldn't be.

He didn't testify -- he testified that tyloxapol was added as a chemical stabilizer. This goes to, you know --

MS. HOLLAND: This goes to why that's not true.

03:28 MR. HASFORD: No, that's -- your Honor, it's -- the basis for their obviousness case has to be what the prior art taught as of 2003. This document is not in the prior art and the path that led the inventor to the invention is irrelevant by statute. This is on a New Drug Application that was filed

03:29 long after the patents-in-suit were filed.

MS. HOLLAND: Your Honor, could we go back to the question that I asked which led to this impeachment? Because the question was, when you looked at stability for unexpected results and you saw that -- what you said was improved

03:29 stability for tyloxapol, was it your understanding or did you

believe that tyloxapol was using -- being used to chemically stabilize the Prolensa® or the formulations of the claims in suit? That's a question that goes to unexpected results, to the basis of his opinions about unexpected results. What is this increased stability?

MR. HASFORD: Your Honor --

MS. HOLLAND: Dr. Williams says it's chemical stability. Plaintiffs tell the FDA it's physical stability to prevent interaction between BAC and bromfenac.

THE COURT: The paragraph you're asking about is not about the prior art, is it?

MS. HOLLAND: I'm not asking about the prior art, again, your Honor. I'm asking about unexpected results.

Dr. Williams testified that the Prolensa® formulation was unexpectedly superior in terms of stability to the prior bromfenac formulation. Necessarily, Dr. Williams has to -- well, let me not -- not saying necessarily.

Dr. Williams said that the unexpected stability of tyloxapol in the formulation is with respect to chemical stability. That's just a fact he said for purposes of his unexpected results opinion.

What I'm now going into questioning Dr. Williams about, is the -- is that actually accurate? If there is increased stability here for purposes of unexpected results, which has nothing to do with the prior art, is that really

chemical stability or is it physical stability? It goes to the very heart of his unexpected results opinion.

THE COURT: And, of course, you can ask that question of him. The objection, though, is as to your use of this particular document.

MS. HOLLAND: Well, this particular document -- Dr. Williams says it's chemical stability. I should be able to show him a document that says that no, actually, it's physical stability and ask him if it changes his opinion. This is a document -- a document that plaintiffs submitted to the FDA.

MR. HASFORD: Your Honor --

MS. HOLLAND: They told the FDA, this is the -- we're brought into court and we have an expert on the stand who tells us there is all these unexpected properties based on chemical stability. Meanwhile, plaintiffs go to the FDA and say that the reason for the tyloxapol has nothing to do with chemical stability. It has to do with interaction between BAC and bromfenac.

MR. HASFORD: Your Honor, the unexpected results about which Dr. Williams testified were unexpected results as to chemical stability. They are trying to use this document for purpose of showing what would have been known in the prior art, and that's not -- I mean, so what is expected or unexpected is based on the prior art. It's not based on this

internal document. It's not based on this document that was submitted to the FDA long after the earliest priority date of the patents-in-suit.

MS. HOLLAND: There's a pattern in this case, Your Honor, and I've said this before, of having internal documents, even sworn documents to the FDA, completely inconsistent with expert testimony we hear on the stand. Then there's an objection, I can't ask the witness about it. So basically the witness is permitted to put in testimony that everybody knows is not true because everybody else here except you has the documents.

THE COURT: Well, is the ANDA considered -- or I'm sorry, the NDA considered an internal document after the FDA has given approval?

MS. HOLLAND: Some parts of it become public after that.

MR. HASFORD: The -- and not before 2003, Your Honor. And this document is marked confidential. It was produced internally from plaintiff's files.

MS. HOLLAND: Again, Your Honor, I'm not asking this for a matter of prior art. Whether or not the unexpected results are truly unexpected is going to depend, at least in part, about what's -- what is the stability that is allegedly unexpected. Is it physical stability or chemical stability?

Because Dr. Williams testified this morning that the

reason tyloxapol -- the reason why it's unexpected is because tyloxapol was not used as a chemical stabilizer in the prior art previously, so now that it's chemically stabilizing, wow, what an invention. In fact, it's not used for that purpose in the formulation. It's used for the exact purpose it was used in the prior art. Dr. Williams used it for that purpose based on his testimony today as a physical stabilizer to solubilize things. It's not unexpected.

THE COURT: Okay. I'm going to permit the testimony for that limited purpose, of being that the plaintiff's own statement to the FDA, as to the purpose for which the substance tyloxapol was -- was being used.

MR. HASFORD: If I may, Your Honor. So the --

THE COURT: I've ruled. And the parties are free to brief this when -- when all the evidence is in, as your objection is preserved as to whether it can be used for even this limited purpose. But basically, the thrust of my ruling is that this is a statement, not in an internal document, not in a laboratory report, but in a statement to the FDA about the purpose of a particular constituent, additive, tyloxapol.

And the witness, it's fair to question him, because his direct testimony touched upon this very subject, and it's fair to ask him whether this changes his -- his views, since this is a statement that was from the plaintiff and dignified by being part of the NDA process. So I'll permit it.

BY MS. HOLLAND:

Q. Dr. Williams, do you see that in the NDA for Prolensa, plaintiffs explain what the function of tyloxapol is in Prolensa? Do you see that?

A. **I do, yes.**

Q. What plaintiffs say here is that tyloxapol acts as a solubilizing agent to prevent interaction between benzalkonium chloride and bromfenac sodium. Do you see that?

A. **I do.**

Q. Now, based on this statement to the FDA, do you now agree that the purpose of tyloxapol and any stability that it gave to the formulation was as a result of preventing interaction between benzalkonium chloride and bromfenac sodium?

A. **I don't. I've seen -- I was aware of this statement. I've seen no data supporting it, that I'm aware of, that actually shows where they prevented a complex. I've seen data where the addition of tyloxapol prevents or really improves the chemical degradation of bromfenac. So I still stand by my opinion.**

Q. And you think the statement to the FDA that was made was -- by plaintiffs in the NDA was just wrong?

MR. HASFORD: Objection, Your Honor. Mischaracterizes the witness's testimony. Argumentative.

THE COURT: No. He may explain.

THE WITNESS: I'm just saying, I have not seen data

that proved what they're saying there. I'm not taking a stand one way or the other whether they're right or wrong. I don't know that. But I've not seen data that supported that fact. I've seen data on the use of tyloxapol to chemically stabilize bromfenac.

MS. HOLLAND: Your Honor, the witness, I believe, has now opened the door to me showing him data that he's seen about tyloxapol acting as a stabilizer to prevent interaction of BAC. It's -- he said he hasn't seen the data. He's seen the data. I'd like to be able to question him about that.

MR. HASFORD: Your Honor, I disagree. He was responding in the context of this statement that Your Honor allowed him to go into, that Your Honor allowed Ms. Holland to go into, and that hasn't opened any door at all.

MS. HOLLAND: The witness testified he has not seen data showing that tyloxapol is used as a solubilizer in Prolensa and in the patented formulations to prevent interaction of BAC and bromfenac. That was the testimony just now, and I would like to impeach the witness on that point.

MR. HASFORD: Your Honor --

THE COURT: By impeachment, you mean something that goes to his credibility?

MS. HOLLAND: Yes, showing -- yes.

MR. HASFORD: Well, Your Honor --

THE COURT: And not for the substance of the internal

result?

MS. HOLLAND: For this -- right now, the question is on impeachment, yes.

MR. HASFORD: If it's a prior statement of Dr. Williams that she's asking about, we have no problem with that. If it's an internal document that she's trying to get in and show some result that allegedly goes toward her obviousness case, we would strongly object to that, Your Honor.

MS. HOLLAND: Well, can I try -- can I ask some questions and then we will see if it actually is impeachment, as I think it is, or whether it goes to some other nefarious purpose, as Mr. Hasford thinks? If --

THE COURT: All right, you can ask a different question.

MS. HOLLAND: Why don't you go to JTX-25 and -- just go to what -- your direct binder your counsel put together, okay?

MR. HASFORD: And we're going to object to this, Your Honor. This is an internal document. It's an internal laboratory or research report document, and this is exactly the problem.

THE COURT: What's the document?

MS. HOLLAND: JTX25.

MR. HASFORD: And this -- this document is not in

evidence.

MS. HOLLAND: This directly impeaches the testimony that was just given.

MR. HASFORD: Again, Your Honor --

THE COURT: Well, was there an objection to JTX25?

MS. HOLLAND: It's in his direct binder. There couldn't have been an objection.

MR. HASFORD: We objected to it when they tried to use it previously. We objected to these documents --

THE COURT: But pretrial, in the final pretrial order, it's something that was in your direct binder, I assume that there was no objection to JTX25 expressed in the pretrial order?

MR. HASFORD: No, sorry. It's not something we used directly with Dr. Williams. There would have been a relevance objection to how they tried to use it. I mean, they're --

THE COURT: I understand that.

MR. HASFORD: Right.

THE COURT: My question is whether there was an objection to JTX25 that you staked out in the pretrial order.

MR. HASFORD: I need to --

MS. HOLLAND: Dr. Williams relied on this document heavily in his expert report, so I highly doubt there's an objection.

THE COURT: Well, that doesn't mean that they're

bound to it. They could withdraw that aspect of his proposed testimony.

MS. HOLLAND: It's still for impeachment, Your Honor. I'm not sure -- respectfully, I'm not sure whether or not there was an objection to the document would even matter as a matter of impeachment.

THE COURT: Well, it would matter as to your argument if they've waived any objection that they're now raising because it was in their direct binder. The question is whether they preserved an objection in the final pretrial order. Does somebody have that document?

MR. HASFORD: Your Honor, does it make sense to take a lunch break at this point --

MS. HOLLAND: No.

MR. HASFORD: -- so we can try to -- we can try to look this up?

MS. HOLLAND: Your Honor, I would prefer to continue. I just want to finish this document.

THE COURT: We had a supplemental.

MS. HOLLAND: I think there was an objection as to the translation, which was resolved, because we were using plaintiff's translation.

MR. HASFORD: No, no, we preserved a relevance objection here, Your Honor. We have with the code R in here.

MS. HOLLAND: Let's see.

MR. HASFORD: The objection codes are MIS, R, OSE, and TRAN. And the R, as Your Honor will note on Page 30, is for lacks relevance.

THE COURT: Okay. All right. So that objection was preserved.

MR. HASFORD: Thank you, Your Honor.

MS. HOLLAND: As I said, Your Honor, this goes to -- Dr. Williams clearly read this document, and so that's what I'm asking him about. I'm asking him about it in purposes of impeachment, him having said he's not seen any data that tyloxapol was used to prevent interactions between BAC and bromfenac.

MR. HASFORD: It's not a proper source of impeachment, Your Honor, and it's not relevant in any event. She's trying to get this in for purposes of her obviousness case.

THE COURT: I'll permit the question, whether he's seen this data.

BY MS. HOLLAND:

Q. Dr. Williams, have you seen JTX25 before?

A. **Yes.**

Q. Okay. You've read this document, right?

A. **I have, yeah.**

Q. Okay. Now, let me draw your attention to Page 4 of this document.

A. **Okay.**

Q. Table 4 refers to a Table 1 below, right?

A. **It does.**

Q. Okay. And what table -- what the -- what it says -- well, let me direct -- make sure everybody is looking at the same place. In the results and discussion section, in the middle of the page, there's something that says surfactant test.

THE COURT: Excuse me. I think I've lost you.

MS. HOLLAND: Sorry, Your Honor.

THE COURT: Are we on Page 4 of 125? Of JTX25?

MS. HOLLAND: We are.

THE COURT: Just a second.

THE WITNESS: JTX025.

MS. HOLLAND: I'm sorry?

THE COURT: Just a moment. Okay. I'm there.

BY MS. HOLLAND:

Q. Okay. So under surfactant test, Dr. Williams, do you see it says: Table 1 shows the concentration of each nonionic surfactant needed to prevent the precipitation of bromfenac sodium in benzalkonium chloride?

Do you see that?

MR. HASFORD: And I'll object and move to strike, Your Honor. This goes to the exact purpose that Your Honor already ruled on that it was prohibited for.

MS. HOLLAND: This is impeachment. It directly contradicts testimony Dr. Williams gave, where he said he never saw any data showing that tyloxapol was used to prevent the precipitation of bromfenac sodium and benzalkonium chloride.

THE COURT: I'll permit it for the limited purposes of impeachment. I'm not permitting it for any other purpose at this time.

THE WITNESS: I'm sorry, what's your question?

BY MS. HOLLAND:

Q. I'm not sure there is one.

A. **Okay.**

Q. So let me start again, then. You see that the first sentence says: Table 1 shows the concentration of each nonionic surfactant needed to prevent the precipitation of bromfenac sodium in benzalkonium chloride.

Do you see that?

A. **Yes.**

Q. And the next sentence says that polysorbate 80, tyloxapol, and another surfactant prevented the precipitation at about .03 percent, .01 percent and .02 percent respectively. Do you see that?

A. **Yes.**

Q. Okay. So, Dr. Williams, there is data that you've seen in JTX25 that shows the ability of tyloxapol to prevent

precipitation of bromfenac sodium in benzalkonium chloride. Do you see that?

A. I see that, but these are for the polysorbate 80 and tyloxapol solutions. This is not in the presence of the other ingredients. That's why, in the precipitation, I'm not sure how relevant it is, so --

Q. So you knew about this testimony when you said no earlier?

A. Yeah, I was talking in the context of the ophthalmic formulation. Was there -- was there information that I had seen, where a precipitation had been shown to form where there's all these other ions present, and I was aware of this document, and that's -- this is -- this is not a formulation study. This is a solution of surfactants, where -- where bromfenac and benzalkonium chloride are being manipulated.

Q. So is it now your testimony that unless we look at the actual formulations that are used in the prior art and in Prolensa and compare them, that your testimony on other formulations earlier this morning was irrelevant?

A. Well, the --

MR. HASFORD: I'll object, Your Honor. It characterizes the witness's testimony.

THE COURT: I'll sustain it.

BY MS. HOLLAND:

Q. Earlier today, Doctor, you put some demonstratives up on

the board, and you showed the Court formulations that did not contain PVP and sodium sulfite, right?

A. That's true.

Q. And you made -- you gave opinions about those formulations, even though both Ogawa Example 6 and Prolensa contained PVP and sodium sulfite, right?

A. That's true, yes.

Q. Okay. And you said you were able to do that even though it wasn't the exact solutions that -- of Prolensa and Ogawa Example 6, right?

A. But they had the borax, the boric acid. They had the ingredients in there that made it a proper comparison.

Q. They didn't have all of the same ingredients, did they?

A. They had the ions that were in there. So they had -- well, and that question, I was answering with regards to proper comparison to the closest prior art.

Q. Right. And the point is that this morning you said you didn't need to look at the full formulations in either -- in order to be able to make those comparisons, right?

A. One of -- I mean, you heard Dr. Davies testify last week, what's present in the solution is going to -- could affect the -- whether a precipitant is formed in their level, and that's consistent with experimentally my experience, and so that's -- I mean, that's what I think.

MS. HOLLAND: All right. I think we can take a lunch

break now, Your Honor.

THE COURT: All right. Let's take an hour for lunch and we will return at 2:15.

(LUNCHEON RECESS TAKEN; 1:18 p.m.)

THE DEPUTY CLERK: All rise.

(OPEN COURT; 2:21 p.m.)

THE COURT: Be seated, please. Good afternoon. Yes, Mr. Mukerjee.

MR. MUKERJEE: Before we continue with the cross of Dr. Williams, may I just address a trial logistics issue?

THE COURT: Sure.

MR. MUKERJEE: Your Honor, one of the witnesses that defendants intend on calling is Dr. Mark Prausnitz. Dr. Prausnitz is someone that we'll be proffering as an expert in the area of ophthalmic drug delivery.

Now, originally -- and his opinions actually go to -- respond to or in rebuttal to Dr. Williams and Dr. Trattler's testimony on secondary considerations, particularly on expected results.

Now, originally, we were hoping that Dr. Prausnitz would be testifying today, and certainly, that's what we disclosed to plaintiffs. It does appear, though, now, given the time of the day and where we are, that that's likely not to happen today. Now, Dr. Prausnitz is not available, unfortunately, due to another commitment tomorrow. He is

willing to come back for his testimony on Wednesday.

Now, I know, technically, we don't have Wednesday as a trial day yet, Your Honor. I don't know if I'm recalling incorrectly, but I thought that your calendar may be open on Wednesday, if we needed to extend to that day.

THE COURT: Yeah, I've kept it open for that purpose, if we need to extend it. This may be a reason to do that.

MR. MUKERJEE: Okay.

THE COURT: Is there any objection to Dr. Prausnitz coming in on Wednesday?

MR. LIPSEY: No objection, Your Honor.

THE COURT: Okay.

MR. MUKERJEE: Thank you, Your Honor, I appreciate it.

THE COURT: You're welcome.

MS. HOLLAND: May I proceed?

THE COURT: Yes, you may.

BY MS. HOLLAND:

Q. Dr. -- Dr. Williams, good afternoon.

A. Good afternoon.

Q. For your unexpected results opinions, you compared Prolensa to Xibrom and Bromday, correct?

A. Yes.

Q. Okay. Now -- and you actually showed the Court a section of the Xibrom NDA to support your opinion, correct, the

prescribing information?
A. **A part of it, yes.**
Q. Now, neither of those products are in the prior art, right? I should say none of those products, Prolensa, Xibrom and Bromday, none of them are in the prior art, right?
A. **That's my understanding.**
Q. Okay. But you still use the information about those products to support your unexpected results position, correct?
A. **Well, with the Xibrom and Bromday, that's because they're embodiments of the Ogawa patent, which is prior art. That's my understanding.**
Q. But you looked, for example, at the pH of those products, which is not a pH exactly found in Ogawa, right?
A. **So in Xibrom and Bromday, it's 8.3, and examples in the Ogawa patent, I believe the ones that are stated, there are actually generating data of pH 8.**
THE COURT: Excuse me. Can you pull the mic a little closer.
THE WITNESS: Oh, I'm sorry, excuse me.
THE COURT: I can hear fine, but the folks in the back might not.
BY MS. HOLLAND:
Q. Now, the difference between Prolensa on the one hand and Xibrom and Bromday on the other hand, in terms of the ingredient list, is that Prolensa has tyloxapol, and Xibrom

and Bromday have polysorbate 80, correct?
A. **That's true, yes.**
Q. All right. And you compared the stability of those products, Prolensa versus Xibrom and Bromday, correct?
A. **The stability? Well, I looked to the product label to get the pH of what it stated was the actual product, and then I looked at stability that's in the Ogawa patent.**
Q. And as well as in Dr. Sawa's -- or Mr. Sawa's laboratory notebook, correct?
A. **For Bronuck, that's right.**
Q. Okay. Now, we looked at the NDA for Prolensa before lunch. Do you recall that?
A. **A portion of it, yes.**
Q. Okay. And we looked at the purpose of tyloxapol in the Prolensa formulation. Do you recall that?
A. **Well, yeah, the part I looked at is what the -- the NDA stated was the reason for tyloxapol in the formulation.**
Q. Okay. Now, in formulating your unexpected results opinions, did you assume that polysorbate 80 had a different function for -- in Xibrom and Bromday than tyloxapol has in Prolensa?
A. **Well, in Ogawa, there's no role ascribed to polysorbate 80, so in -- and what I said is, in the '431 patent, that the role of tyloxapol, in my opinion, for chemical stabilization of bromfenac sodium.**

Q. So now I'm talking about your unexpected results opinions, okay, where you went outside of the patents, right? You actually looked at product labeling, correct?
A. **For pH and -- yes.**
Q. Okay. And from the pH you -- you derived some opinions about stability, correct?
A. **Well, I noted what the stability was of Xibrom and Bromday.**
Q. Okay. And that -- but that was based on pH data that was not in the prior art, right?
A. **Not in the prior art?**
Q. Yes.
A. **Well, in the Ogawa patent, the examples were noted pH was at pH 8, and Ogawa also in the pH stability study that was done, a pH above 8, it was more stable, and so, I mean, it seemed although pH 8.3 and specifically noted in Ogawa '225 --**
Q. Can we put up the last demonstrative that was used this morning in the direct of Dr. Williams, please? Oh, I'm sorry, it's a couple -- before we get to the double patenting, there was one that had the pictures of the products on it. Thanks.
Okay. So let me -- maybe I didn't focus you enough. This is what I was talking about. Okay? So you put up a demonstrative where you compared the actual product pHs, right? You had the pH of Prolensa of 7.8.
A. **That's correct.**

Q. True?
A. **Yes.**
Q. And you had the pH of the actual product, Xibrom and Bromday, 8.3, right?
A. **From their label, yes.**
Q. Yes. And none of that is in the prior art, right?
A. **I don't think so, no.**
Q. Okay. Now -- and as we said, the one difference between -- in the ingredient list between the Xibrom and Bromday, on the one hand and Prolensa on the other, is the substitution of tyloxapol for polysorbate 80, right?
A. **That's one difference, yes.**
Q. Okay. And you said that that led to an unexpected result, correct?
A. **That's true, yes.**
Q. And that was because you believe that the function of polysorbate 80 and Xibrom and Bromday was different than the function of tyloxapol in Prolensa, right?
A. **I don't think I said that about the function of polysorbate 80 in Xibrom and Bromday.**
Q. Well, did you say that tyloxapol is performing a function in Prolensa that polysorbate 80 is not performing in Xibrom and Bromday, is that right?
A. **I don't -- I actually don't recall saying it like that.**
Q. Do you agree with that statement?

A. Well, I mean, there's no role ascribed in the Ogawa patent which embodies -- which Xibrom and Bromday are an embodiment of. There's no role --

Q. I'm not talking about the -- oh, I'm sorry, I apologize.

04:59 MR. HASFORD: Your Honor.

THE WITNESS: There's no role ascribed to polysorbate 80 in there, and so that Ogawa patent solves the chemical stability problem a different way with the water soluble polymer and the sulfite.

BY MS. HOLLAND:

Q. All right. Let me try this again. I'm not -- I want you to think broader than the Ogawa patent, okay? Because when you testified about unexpected results, you went a lot broader than the Ogawa patent. You looked at actual products on the

04:59 market. So my questions are not about the Ogawa patent but about the actual products on the market, okay?

Is it your opinion that the function of polysorbate 80 in Xibrom and Bromday, the actual products on the market, is different than the function of tyloxapol in Prolensa?

05:00 **A. I don't know what the function of polysorbate 80 is in the Bromday and Xibrom. I know from Ogawa it doesn't stabilize bromfenac sodium, but I don't -- I mean, maybe it's a wetting agent. I'm not really sure what the function is.**

Q. Well, you knew about --

05:00 **A. It doesn't seem like it's the same function as tyloxapol**

in Prolensa.

Q. When you were gathering up all your data about Xibrom and Bromday, did you try to figure out what the role of polysorbate 80 was in those products? You figured out what

05:00 the pH was, right?

A. The pH is stated in the label.

Q. Yeah. Did you try to figure out what the function of polysorbate 80 was?

A. Well, like I just said, I'm not sure why it's in there.

05:00 **It's -- I mean, in the patent, it -- polysorbate 80 does not stabilize bromfenac sodium. There's data on that.**

Q. Okay. Now --

A. The role that it's playing, I'm not sure.

Q. I'm asking a different question, though. Did you try to

05:01 investigate what the role was in the actual products? Did you try to investigate the role of polysorbate 80 in Xibrom and Bromday?

A. In Xibrom and -- well, not apart from my analysis of the Ogawa patent.

05:01 Q. Okay. Can we see DTX-479A. It should be in your binder. Well, actually, let's go to 478 first. It's in your binder.

Do you see this is a section from the Xibrom NDA? So this are statements that plaintiffs made to the FDA about the Xibrom product.

05:02 **A. Okay. Let me make sure. So this is DTX-479A?**

Q. 478A first, please.

MR. HASFORD: And I'll just object and note for the record, Your Honor, this Xibrom NDA, much like the Prolensa NDA or the Bromday NDA is not prior art, it's not publicly

05:02 available. To the extent counsel is attempting to use this in connection with an obviousness case, it's not proper.

MS. HOLLAND: I'm using it for unexpected results, as I think -- thought the lead-up to that made clear, Your Honor.

MR. HASFORD: And it's certainly not based on what's

05:02 known in the prior art. Because that wouldn't have been known in the prior art if it was part of the confidential Xibrom NDA that was submitted to the FDA, Your Honor.

MS. HOLLAND: I just -- Your Honor, we heard a lot of testimony this morning about the actual Prolensa, Xibrom,

05:02 Bromday products that Dr. Williams just said were not prior art. Notwithstanding that, he gave testimony about them and their properties in connection with his unexpected results opinion.

THE COURT: Isn't that correct?

05:02 MR. HASFORD: What he gave testimony based on publicly-available documents that are out there in the art, and this was not a publicly-available document. This was a submission to the FDA that was confidential and so it's not something that's properly part of an obviousness case.

05:03 MS. HOLLAND: That --

THE COURT: Well, he can be asked his understanding of the qualities of the other products, because that's within the scope of his direct. If he didn't rely upon this NDA that was submitted with regard to -- is it Xi --

05:03 MS. HOLLAND: Xibrom, Your Honor.

THE COURT: Okay. Then he can't be asked about that.

MS. HOLLAND: He can?

THE COURT: He cannot because it would not be in the prior art.

05:03 MS. HOLLAND: Your Honor, nothing that was said by Dr. Williams about those products was in the prior art. I think there was a little confusion based about what Mr. Hasford said.

The information about Xibrom and Bromday and Prolensa,

05:03 that we just saw in the slide ahead up there, none of that is in the prior art, and Dr. Williams just agreed to that. Dr. Williams testified about a lot of stuff that wasn't in the prior art this morning to support unexpected results.

THE COURT: But you can't use the NDA that was

05:04 submitted to direct his attention to something that he overlooked or whatever. You can impeach him or you can cross-examine him --

MS. HOLLAND: Yes, Your Honor.

THE COURT: -- based upon what he -- what he actually

05:04 knows, what he testified to.

MS. HOLLAND: All right.
BY MS. HOLLAND:
Q. Dr. Williams, I want to focus your attention to the second full paragraph -- well, first of all, let's look at the
05:04 top of the page. It says 2.3.P.1, description and composition of the drug product. Do you see that?
A. **I do.**
Q. And it says bromfenac ophthalmic solution. Do you see that?
05:04 A. **Yes.**
Q. And then the second paragraph in that section says: The drug product solution contains bromfenac sodium as the active ingredient.
Do you see that?
05:04 A. **Yes.**
Q. And then it goes through a list of other -- the other ingredients in Xibrom, and it says that polysorbate 80, as a solubilizer.
Do you see that?
05:05 A. **Yes.**
Q. Okay. And do you understand that to mean that it -- polysorbate 80 is used in Xibrom to solubilize something that's insoluble in the formulation?
MR. HASFORD: I'll object, Your Honor. This is the
05:05 issue. To the extent she is trying to use this non-prior art

document in connection with an obviousness case, it's improper; and if it's secondary consideration, secondary considerations are based on what would be expected or unexpected based on the prior art. And this document is not
05:05 prior art.
MS. HOLLAND: Your Honor, there seems to be a double standard here. We heard a lot of testimony this morning on unexpected results, all kinds of stuff that's not in the prior art that's in internal documents, documents that are generated
05:05 years after the prior art date of 2003, and it's just as relevant as any other piece of non-prior art that Your Honor has heard about this morning, to hear what the actual function of these excipients are in Xibrom.
The unexpected results opinion is based on Dr. Williams
05:06 saying that the stability, that tyloxapol does something different in the formulation than polysorbate 80 did. Again, Your Honor, there's --
THE COURT: So are you asking whether he agrees with this statement, that polysorbate 80 is a solubilizer?
05:06 MS. HOLLAND: I can ask that statement, Your Honor.
THE COURT: I'll permit that.
BY MS. HOLLAND:
Q. Do you agree with what plaintiffs told the FDA here, that polysorbate 80 is a solubilizer?
05:06 A. **I don't, no.**

Q. Okay. Well, let's turn to DTX-479, then. All right.
And I'd like you to turn to Page -- it has 110 on the bottom. It also has 18443?
MR. HASFORD: If I may, Your Honor, going back to one
05:07 of the previous questions, I'd just like to lodge an objection. Ms. Holland said what the plaintiffs told the FDA. This was ISTA Pharmaceuticals. This was a different corporation, you know. It was not plaintiffs in the sense of Senju and B and L telling this to the FDA. So I'd like to
05:07 just lodge that objection for the record, just to keep that clear.
MS. HOLLAND: B and L acquired ISTA, Your Honor.
THE COURT: Right, I understand that. But technically, it wasn't -- it wasn't the plaintiffs making the
05:07 statement when it was given.
MS. HOLLAND: Well, it was ISTA, which is now part of plaintiffs.
THE COURT: Right.
MS. HOLLAND: So you could look at it either way, I
05:07 guess.
BY MS. HOLLAND:
Q. In any event, if the -- the NDA holder is telling the FDA that polysorbate 80 is being used as a solubilizer in Xibrom, right?
05:07 A. **That's the statement that's made there, yes.**

Q. Okay. Now, I'd like you to turn, as I said, in your -- the next exhibit in your binder, 479A.
A. **Okay.**
Q. Look at the top of the page. Again, the NDA holder here
05:08 is again telling the FDA that benzalkonium chloride was used as a preservative in Xibrom. Do you see that?
A. **No. Where are you?**
Q. The top of the page, it's the second page of Exhibit 479A?
05:08 A. **Yes, I'm there, thanks.**
Q. Okay. So let me just repeat. Do you see it says benzalkonium chloride was used as a preservative. Do you see that?
A. **Yes.**
05:08 Q. Then it says: Polysorbate 80 was added as a stabilizer to prevent interaction with bromfenac sodium.
Do you see that?
A. **Yes.**
Q. Do you agree that that was the reason polysorbate 80 was
05:08 added?
A. **Well, that's what they state, but again, I've not seen any evidence that actually shows that, in fact, occurred.**
Q. Let me try one more time, then. Why don't you go to Page 112 in this exhibit.
05:09 A. **Okay.**

Q. And this says summary from Senju. Do you see that?
A. **Yes.**
Q. All right. And again, this is part of the NDA. You understand that, right?
05:09 A. **Yes.**
Q. So you look at the fourth paragraph down on Page 184447. It says: As the preservative, benzalkonium chloride was used because parabens are unstable within the pH range of the product.
05:09 Do you see that?
A. **Yes.**
Q. And then it says: To prevent the action of -- and then we have the code name for bromfenac -- with benzalkonium chloride, polysorbate 80 was added as a solubilizer.
05:09 Do you see that?
A. **Yes.**
Q. Do you disagree with that statement, as well?
A. **I mean, they've made that statement. Again, I've seen -- I've not seen evidence where that's, in fact, supported by data.**
05:09 Q. Well, do you think it was just conjecture on their part?
A. **I haven't -- I don't know what it is. I read this statement, but again, I haven't seen any evidence to support it.**
05:10 Q. All right. I want to -- I want to look at one of the

prior art documents you looked at this morning, JTX168. All right. And JTX168 is the '034 patent, right?
A. **Yes.**
Q. Now, I'd like you to tell the Court when -- when did this
05:11 patent become -- when did this patent issue?
A. **It says date of patent, December 12, 1995.**
Q. Okay. And as of that time, bromfenac had not yet become a marketed NSAID, correct, for ophthalmic use?
A. **You know, I don't remember when Bronuck was marketed. I**
05:11 **can't quite remember that sitting here.**
Q. Okay. Assuming Bronuck was marketed in 2000, you agree that as of 1995, bromfenac was not yet known as a marketed NSAID, correct?
A. **If that's true, yes.**
05:11 Q. All right. Now, let's -- so let's talk about what happened in the interim between 1995 and 2003. As of 2003, Bronuck was already on the market in Japan, right?
A. **That's my understanding.**
Q. Okay. So as of that time, bromfenac had gone through a
05:11 battery of clinical trials, right?
A. **I would assume so, yes.**
Q. Bromfenac had been shown to be a safe and effective ophthalmic NSAID as of that time, correct?
A. **I would assume that's true in Japan.**
05:12 Q. Okay. But none of that was known yet in 1995 when you --

well, you pointed out some of the statements were made in the '034 patent, right?
A. **That if -- that's true.**
Q. Okay. All right. Now, can we go back to the '034
05:12 patent, please. And I'd like to go to column 2, line 23, in the summary of the invention, and I think that that's something that you looked at in your direct testimony. And I think you pointed to the second line in the summary of the invention, and you pointed out the three benzoylphenylacetic
05:13 acid derivatives, right?
A. **Well, I read from that, yes.**
Q. All right. And I think you said that someone of ordinary skill in the art would have perhaps pursued those in place of bromfenac. Is that what you said this morning?
05:13 A. **Well, I mean, it -- based on Yanni, this patent, the -- Yanni presents evidence that bromfenac wouldn't necessarily be the preferred out of Table 1, based on what's shown about the NSAID, about the derivatives of these compounds.**
Q. And again, that was as of 1995, correct?
05:13 A. **That's true.**
Q. All right. So let's fast forward to 2003. None of those three benzoylphenylacetic acid derivatives in Yanni was a marketed NSAID at that point in time, right?
A. **I -- sitting here right now, I don't know that.**
05:14 Q. So at least as of 2003, bromfenac had a big lead on these

other compounds, right? It was actually a marketed drug?
A. **Yeah. I just -- I don't know. I mean, the one on there, compound 8, nepafenac, I don't know when it was -- I don't recall when it was marketed.**
05:14 Q. Now, are you aware that there are different FDA requirements to pursue a new -- a different formulation of an already-marketed drug versus trying to get a completely new drug on the market?
MR. HASFORD: Objection, Your Honor. It calls for a
05:14 legal conclusion as to FDA law.
THE COURT: Just a second.
Well, I think his direct actually touched on this, but I'll -- I'll permit him to answer this question about whether he's aware of the different FDA requirements.
05:14 THE WITNESS: I mean, I've been involved with new drugs and developing them for market, just in a limited sense from the -- it's called the CMC section viewpoint. So to that extent, I understand there's requirements.
BY MS. HOLLAND:
05:15 Q. Okay. Now, to market a completely new drug in 2003 would have required a full battery of clinical trials, right?
A. **A new -- a new chemical entity?**
Q. Yes.
A. **There would have -- well, ultimately, my understanding is**
05:15 **there would need to be a new drug application ultimately filed**

covering whatever indication for that -- that new chemical entity.

Q. Right. And there would need to be Phase 1, 2 and 3 trials as well?

05:15 **A. I -- this is probably out of my area. I mean, generally, I understand that's what's required.**

Q. And is it -- are you aware, based on your time in industry working on these things, that to get a new drug approved takes years and years?

05:15 **A. I think it varies depending on what the drug is and the delivery system, but that's all I could say basically about the time.**

Q. And you don't know the cost to develop a new drug, do you?

05:16 **A. No.**

Q. All right. All right. Now, I want to -- I want to turn to your testimony about the use of BAC as of 2003. Do you agree that as of 2003 ophthalmic solutions that were packaged in multi-dose containers had to contain a preservative?

05:16 **A. Yes.**

Q. Okay. And that's true today as well, right?

A. That's my understanding, yes.

Q. All right. And preservative-free formulations are limited only to ones that are single-dose unit, correct?

05:17 **A. That's true.**

Q. And Prolensa is a multi-dose unit, right?

A. It is.

Q. So a preservative would be required in Prolensa, right?

A. Yes.

05:17 Q. All right. You mentioned a product called Acular PF in your direct testimony. Do you recall that?

A. Yes, I do.

Q. And you said that was a preservative-free formulation, right?

05:17 **A. Yes.**

Q. And now, that was a preservative-free formulation because it was a single-dose formulation, right?

A. It is, yes.

Q. The Acular that's not single dose contains BAC, right?

05:17 **A. That's correct.**

Q. Do you know what the relative cost to a patient is of a multi-dose versus a single-dose ophthalmic product?

A. I don't.

Q. All right. You agree that BAC was used as a preservative

05:18 in ophthalmic compositions in 2003, right?

A. It was, yes.

Q. And it's still used in ophthalmic compositions today, right?

A. It is.

05:18 Q. And, in fact, BAC was the most common preservative used

in 2003, right?

A. I've read that, yes.

Q. Now, you had a slide up with quotes that you excerpted from several articles that you said talked about the BAC

05:18 toxicity. Do you recall that?

A. I do.

Q. All right. Let's look at slide -- I think it's PDX4-3, but I'm not exactly sure at this point. Yes, it's PDX4-3.

Now, you told the Court that those slides -- I'm sorry,

05:18 you told the Court that those articles talk about BAC toxicity, right?

A. They do, yes.

Q. Okay. And did you actually read all those articles?

A. I did, yeah.

05:19 Q. Okay. So you know, then, that all those references, at least the ones that talk about testing in humans, they all discuss toxicity associated with long-term use, right?

A. That's true.

Q. That's not on your slide, though.

05:19 **A. Well, I mean, it's part of the reference that I've got it from.**

Q. Okay. And so you didn't -- you didn't want the Court to understand from that slide that any of the toxicity issues were associated with short-term use, did you?

05:19 MR. HASFORD: Objection, argumentative.

THE COURT: Sustained.

BY MS. HOLLAND:

Q. All right. Let's look at that Debbasch article, PTX-268 at Page 106. Let's go to Page 106, thanks, and let's look at the first sentence there.

It says: Long-term use of anti-glaucoma drugs has been associated with toxic, as well as inflammatory changes of the ocular service -- surface.

Right?

05:20 **A. That's what it says.**

Q. Right. And glaucoma drugs or anti-glaucoma drugs are intended to be taken over many years, correct?

A. That's my understanding, yes.

Q. All right. Prolensa is not a drug like that, right?

05:20 **A. Prolensa is not an anti-glaucoma drug.**

Q. And Prolensa is also not meant to be taken every day for years and years, right?

A. Yeah, I think it's 14 days, but Dr. Trattler can answer that kind of question.

05:20 Q. Okay. But your understanding is that it's a 14-day dose after surgery, right?

A. That's my understanding.

Q. Right. Let's go to Page 107 in this Debbasch reference and -- yeah, thank you.

05:20 I want to focus your attention on the paragraph that

begins: To understand the role of preservatives.
Do you see that?
A. Yes.
Q. Okay. And that says: To understand the relative role of
05:21 preservatives such as benzalkonium chloride in the toxicity of
long-term use of anti-glaucomatous drugs, we performed a
series of in vivo and in vivo -- in vitro experiments.
Do you see that?
A. Yes.
05:21 Q. Okay. And there's nothing in this article that talks
about toxicity related to 14-day use, right?
A. There's not for 14 days, no.
Q. All right. So I don't want to go through -- I can go
through all of these, but do you agree with me that none of
05:21 these articles address short-term toxicity in the range of 14
days, that you would have, for example, with a drug like --
well, let me withdraw that.
None of these references that you have on your slide
addressed short-term use of ophthalmic compositions containing
05:22 BAC; is that right?
A. Well, they -- they address BAC used as a preservative in -- in this particular study, like it was over a long-term use is what the focus was.
Q. All right. Well, are you willing to agree with me that
05:22 the focus of all the studies were long-term use, or should we

go through them one by one?
A. No. They were.
Q. Okay. Now, you also -- you also mentioned in your direct
testimony PTX-294, which was a 1998 reference -- well, I
05:22 shouldn't -- I'm not even going to call it a reference. It
was a 1998 article from *The New York Times*, correct?
A. Yes.
Q. And it talked about -- what you said was it talked about
an oral bromfenac product, right?
05:23 **A. It does, yes.**
Q. And that product was withdrawn from the market in 1998,
right?
A. That's my understanding.
Q. Okay. Just to be clear, there has never been any safety
05:23 concerns associated with -- using bromfenac as an ophthalmic
product, correct?
A. From a liver toxicity standpoint, like Duract?
Q. Yes.
A. I don't know. You would have to ask Dr. Trattler.
05:23 Q. All right.
A. I'm not aware of that.
Q. When you -- when you were putting your testimony together
here with this *New York Times* article that talked about
toxicity of oral bromfenac, did you do any research to see if
05:23 there was any -- ever any toxicity associated with ophthalmic

bromfenac?
A. I didn't. This is -- I mean, there's a passage in Hara also that talks about the oral bromfenac, and my point was, is if there's sufficient absorption, you know, that, you know,
05:23 **that might be considered relevant to one of skill in the art.**
Q. As of 2003 -- well, let me withdraw that. Is it your
opinion that as of 2003 there were formulators who were
concerned about liver toxicity in administering or developing
ophthalmic bromfenac compositions?
05:24 **A. Well, as of 2003, a skilled person would have known that oral bromfenac, taken as this was taken, did cause liver toxicity and --**
Q. Would they know also that ophthalmic --
MR. HASFORD: Your Honor, I think he had some
05:24 additional testimony.
THE COURT: Okay, you may continue.
BY MS. HOLLAND:
Q. Go ahead. I'm sorry, I didn't mean to interrupt you.
A. Thank you, thanks.
05:24 **So they would have known that. So working with bromfenac, I mean, by other routes of administration, you're concerned possibly if it -- depending on how much is absorbed.**
Q. Well, by 2003, the person of ordinary skill in the art
knew that bromfenac had passed enough safety and efficacy
05:25 clinical trials to be a marketed product, right, as an

ophthalmic?
A. In Japan, yes, that's true, yeah.
Q. Okay. So you pointed to an article in 1998 about oral
bromfenac, but as of 2003, there was no safety -- there were
05:25 no safety concerns about ophthalmic use of bromfenac, correct?
A. I'm not aware of it.
Q. Now, is it your testimony, Dr. Williams, that as of 2003,
a person of ordinary skill in the art would not have included
BAC in a formulation?
05:26 **A. No, I mean, not exactly. My testimony is if there was a known interaction problem, that a person of ordinary skill in the art would avoid the problem and either -- what I said is either use another preservative or a preservative free or possibly switch the active ingredient.**
05:26 Q. Well, let me ask you about from the toxicity perspective
that you had that slide with the different references that
were intended to show some toxicity of BAC.
Is it your testimony that any of -- that there was a
toxicity issue that would have precluded someone of ordinary
05:27 skill in the art from wanting to work with a BAC formulation?
A. No, my testimony is one of skill in the art would have been aware of studies that talked about the -- when benzalkonium chloride is applied to the ocular surface. And so from a formulation standpoint, knowing that, then, in my
05:27 **opinion, a formulator would maybe include other types of**

preservatives in their studies. But I think once -- that they would do the study to confirm if or if not benzalkonium chloride caused toxicity or not to the surface.

Q. All right. Well, you used benzalkonium chloride in products in 2003, right?

A. That's true, yes.

Q. All right. And is it also correct that you worked on some formulations for NSAIDS in 2003?

A. Yes.

Q. All right. And you have a patent on those NSAIDS formulations, right?

A. I have a -- I think the patent is more process related, that NSAIDS are examples of drugs that we studied that work under that platform.

Q. And in your patent you gave examples of suitable NSAIDS that could be used in your invention, right?

A. I would have to look at it, I may have.

MS. HOLLAND: Your Honor, this is not on the exhibit list, but I'm using it for impeachment or to refresh his recollection, he just asked to see it.

THE COURT: Is it his own patent?

MS. HOLLAND: Yes.

THE COURT: Any objection?

Mr. HASFORD: So our issue, if it's just for impeachment purposes, your Honor, it's not being moved into

evidence, that's fine.

THE COURT: Okay. Very well.

BY MS. HOLLAND:

Q. All right. So let me --

A. I didn't get a copy, sorry.

MS. HOLLAND: Oh. We have another copy.

THE COURT: Do you want to borrow mine?

MS. HOLLAND: We'll get you another one. Sorry about that.

THE WITNESS: Thank you.

BY MS. HOLLAND:

Q. So let's look at what you've just been handed. This is U.S. Patent 6,509,028, correct?

A. Yes, it is.

Q. And you're the first named inventor on this patent?

A. Yes.

Q. And the date of the patent is January 21, 2003, right?

A. Yes.

Q. And just to orient you, I'm going to ask you to look at Column 10, Line 26.

A. Okay.

Q. Do you see you have a list there of suitable nonsteroidal anti-inflammatory agents to be used in your invention?

A. Yes.

Q. Okay. And you have a pretty long list there, right?

A. There is a long list.

Q. And you include bromfenac on that list?

A. It may be.

Q. If you look at one, two, three, four, five, six, seven -- eight lines down.

A. Yes, it's there.

Q. And you include at the end of that same line diclofenac, right?

A. Yes.

Q. A couple of lines down, 15 lines down, I believe, at Line 40 in Column 10 you include ketorolac, right?

A. That's true, yes.

Q. And Line 43 you include flurbiprofen, right?

A. Yes.

Q. And in your invention any of those NSAIDS could be used interchangeably, right?

A. So remember this is for nasal and buccal delivery, not for ophthalmic use.

Q. For nasal or --

A. But, yes, that is what our intention was, is that these drugs would be applicable to our platform.

Q. All right. So at least for your nasal or buccal delivery platform those drugs, bromfenac, diclofenac, ketorolac, and flurbiprofen, any of those could be used in that same platform, correct?

A. That's what we thought.

Q. And you also used benzalkonium chloride in this patent as a preservative, right?

A. It may have been because it's a preservative used in nasal products.

Q. All right. Just to confirm, I'll direct your attention to Column 7, Line 60.

A. Okay.

Q. And you'll see there that the first preservative listed is benzalkonium chloride, correct?

A. Yes, it is.

Q. All right. Now, it's true, isn't it, that in this patent there's no discussion of the different chemical structures of the different NSAIDS that you say can be used in the invention, right?

A. We just presented the drugs.

Q. No discussion of the different hydrogen bonding capacity of those drugs in this patent?

A. No.

Q. You gave some testimony in your direct about the IIG, correct, the Inactive Ingredient Guide?

A. Well, I was going to testify about it but I was thinking it all got struck, so I actually don't recall.

Q. That was Remington that got struck.

A. Well, I did talk about IIG then.

Q. That was spoken about as well.
So I think -- let me ask you this first. You know that the IIG is a list of excipients contained in approved products, right?
05:33 **A. Yes.**
Q. And you've used the IIG in your own work, right?
A. I do use it, yes.
Q. And you use it as a starting point in selecting excipients, right?
05:33 **A. Well, that and other references, but I do use it, yes.**
Q. And you are aware, aren't you, that if you want to use an excipient that's not listed in the IIG, you need to conduct additional safety studies, right?
A. Yes, and that's what I testified to earlier.
05:34 Q. And it was your experience in industry that you always used excipients listed in the IIG, right?
A. That's true. You have to have -- from my experience, you had to have a reason to, you know, to use an excipient that is not in an approved product for that route of administration,
05:34 **it's possible but that was the easier path if it worked.**
Q. Now, you talked in direct testimony about the use of tyloxapol in prior art formulations and you mentioned that they were suspension based formulations. Do you recall that?
A. Yes.
05:34 Q. All right. The IIG actually showed five ophthalmic

solutions that use tyloxapol, right?
A. It did, yes.
Q. I'm sorry?
A. It did, yes.
05:35 MS. HOLLAND: Let's put up PDX-4-5. It might not be the right number anymore. Yes. Thank you.
BY MS. HOLLAND:
Q. All right. So you testified about this on direct examination, right?
05:35 **A. I did.**
Q. And this was meant to show comparative stability, right?
A. Yeah, it's comparing formulations containing either polysorbate 80 or different concentrations of tyloxapol, the chemical stability of bromfenac.
05:35 Q. And comparison Example 1 is what you chose to use for the stability of polysorbate 80, right?
A. Well, that's the formulation showing the stability of bromfenac containing polysorbate 80.
Q. That formulation is nowhere in the prior art, right?
05:36 **A. I think that formulation is similar to Experimental Example 4 in Ogawa.**
Q. It's not the same as Experimental Example 4, is it?
A. It's slightly different in the ingredients.
MS. HOLLAND: Now, I put a demonstrative together,
05:36 DDX-61, could we put that up?

BY MS. HOLLAND:
Q. And it should be in your binder, DDX-4 in your binder.
So what -- you can check this out. But what I've done is taken the five formulations that you had in your
05:36 demonstrative and I added Ogawa '225 Example 6. Do you see that?
A. Yes.
Q. And Ogawa '225 Example 6, in addition to the ingredients in comparison Example 1, also contains polyvinylpyrrolidone
05:37 and sodium edetate and sodium sulfite, right?
A. It does, yes.
Q. Now, when Ogawa '225 Example 6 was tested at a pH of 8, it had a stability of 100.9 percent, right?
A. Yes.
05:37 Q. And when comparison Example 1 was tested, it had a stability of 51.27 percent, right?
A. Under the conditions of pH 7, that's what -- that's the results, yes.
Q. But that formulation did not have polyvinylpyrrolidone or
05:38 sodium sulfite, right?
A. Comparison Example 1 does not have polyvinylpyrrolidone nor sodium sulfite.
Q. And you had testified in your direct testimony that those two ingredients, polyvinylpyrrolidone and sodium sulfite, were
05:38 used for stability purposes, right?

A. According to Ogawa, that's how Ogawa solved the chemical stability problem of bromfenac sodium.
Q. You would expect a formulation that didn't have those two ingredients to be less stable than one that did, right?
05:38 **A. Well, according to Ogawa, that's true.**
Q. Okay. Now, there was no example in Ogawa where the formulation of Example 6 was tested at a pH of 7, right?
A. There's not, no.
Q. And if Ogawa Example 6 was tested at a pH of 7, you would
05:39 expect the stability to be higher than the 51.27 percent for comparison Example 1, right?
A. I mean, that's what Ogawa states, but he doesn't have any data so I actually don't know what it would be.
Q. But you testified, didn't you, that your opinion would be
05:39 that the stability would be somewhere in between 51.27 and 100.9, right?
A. That's probably right, yeah.
Q. And it could be somewhere in the ballpark of the tyloxapol compositions that are on this page, right?
05:39 **A. It could be, yeah.**
Q. Before lunch today, we were talking about the stability data that you had included in your direct testimony that was based on internal laboratory notebooks of Mr. Sawa. Do you recall that?
05:40 **A. Yes.**

Q. This isn't your binder but I'm going to hand up what we've marked as JTX-33A.

MR. HASFORD: Your Honor, we are going to have to object to it. This appears to be Mr. Sawa's laboratory notebook. To the extent counsel, again, is attempting to use the internal documents to show obviousness, that's improper. We object.

MS. HOLLAND: Your Honor, earlier this morning I believe you had made the ruling that I could question the witness based on the underlying data that appeared in the tables that he used in his direct testimony, that's what I'm doing for unexpected results.

THE COURT: If it's limited to the underlying data he actually used in the table he presented there, I'll overrule the objection. I'll permit it.

BY MS. HOLLAND:

Q. All right. If you look at the last page, which is JTX-33.204 -- well, you see a table there, right?

A. On JTX-33.204?

Q. 204.

A. I do, yes.

Q. And at the top of the page you see it says P2000B177. Do you see that, top right-hand portion of the page?

A. Yes, I do.

Q. You understand that that was the study protocol that was

being used to generate this data?

A. I'm -- actually sitting here right now, I'm not sure what that number refers to.

Q. Did you review this entire document before giving your testimony this morning about the stability data?

A. No, I think I have reviewed it in the past, but it's been a while.

MR. HASFORD: I'll also note for the record, your Honor, it appears that this is a Japanese language document, so to the extent there are questions on that and counsel has a translation, that might be relevant.

MS. HOLLAND: I apologize. It's actually earlier in the document. This is a document that was produced by plaintiffs to us.

BY MS. HOLLAND:

Q. So now if you turn to Page 33.30, I think you'll see it in English. And I apologize for that.

A. Okay.

Q. And you see this is test code P2000B177, right?

A. That's what it says, yes.

Q. And the tester is Shirou Sawa, right?

A. Yes.

Q. Now, if you look at the left-hand column, there's two formulations that are labeled A-28 and A-29. Do you see that?

A. Yes.

Q. And you see that they were tested at 60 degrees C. for four weeks. Do you see that?

A. So A-27 and A-28?

Q. No, A-28 and A-29.

A. I see that.

Q. Those were two samples you had on the stability demonstrative this morning, right?

A. That's true, yes.

Q. And if you look at A-28 and A-29, it says 85.96 for A-28 as the remaining percent, and 82.01 for A-29 as remaining percent. Do you see that?

A. Yes.

Q. And that's the data you had up this morning, is that correct?

A. That's true.

Q. Do you know the data you used this morning came from this test P2000B177?

A. It appears to be, yes.

Q. Okay. Now, in relying on this data did you review the protocol for how the data was generated?

A. I don't recall seeing -- I may have, I just don't remember, sitting here right now.

Q. Well, let's look at the beginning of the document. Page 2, do you see it says "test protocol?"

A. Yes.

Q. And it says for test code P2000B177. Do you see that?

A. I do.

Q. And that's the same test code we saw on the table of data that you had used in compiling your stability testing results, correct?

A. Yes.

Q. Okay. Does this refresh your recollection that you reviewed the test protocol?

A. No, not really.

Q. Okay. So you don't know one way or the other that before you presented the data, whether you reviewed the protocol for how it was generated?

A. I reviewed a lot of documents, and just sitting here right now this doesn't look familiar.

Q. Well, did you look at the purpose of the data, the stabilized data that was being presented in this document before presenting it in the Court today?

A. Did I look at -- I'm sorry?

Q. The purpose of this test protocol.

MR. HASFORD: I'll just note an objection for the record, your Honor, to the extent this is again being attempted to be used for purposes of obviousness.

THE COURT: It will be based on his next answer, so your objection is premature.

THE WITNESS: I'm sorry, could you please repeat the

question?
BY MS. HOLLAND:
Q. Does this refresh your recollection that you reviewed the test protocol on this document prior to giving your opinions about the stability data that was generated pursuant to the test protocol?
A. I would have seen it. It's been a while, I would have to reread it again.
Q. At the time that you were reviewing the stability data in this document, you were aware then that the stability testing was being done because bromfenac sodium --
MR. HASFORD: Objection, your Honor. Move to strike. This is exactly the purpose they're trying to get it in for and it's improper. They're trying to get in obviousness. We objected on this basis. Your Honor allowed them to use this for the sole purpose of showing him the data, and whatever other statements they're trying to use this for is improper.
MS. HOLLAND: Your Honor, I don't know how it could possibly be improper to ask about the protocol of a test that the expert used in his direct testimony.
THE COURT: You can ask about the protocol but not the purpose. Your question goes to the purpose.
MS. HOLLAND: It goes to protocol and it goes to what the stability testing data means.
THE COURT: The protocol in a scientific sense is

what did the scientist do that led to the results that this witness relied on, the purpose isn't part of that, the scientific setup. And so if you want to ask how were the tests conducted, what were the conditions, then I'll permit it because it reflects on the data.
But my ruling -- my permitting you to use this at all is a very, very narrow one, it has to be exploring the data that A-28 and A-29 experiments that the witness actually relied on as part of his direct testimony.
MS. HOLLAND: So, your Honor, in exploring the data the question is whether the data reflects physical or chemical stability data. We heard testimony about the data this morning with respect to the unexpected results opinions. It makes a difference as to whether or not the data was generated to show chemical stability or physical stability, that makes a difference in terms of the unexpected results.
THE COURT: You can ask what the data showed. But, again, the purpose, what they expected is intruding into the area of the inventor's mind of why the inventor was doing what he was doing.
MS. HOLLAND: Well, I'm sorry, your Honor, can I just try one more time?
THE COURT: I've ruled. Let's move on.
BY MS. HOLLAND:
Q. Would you turn to JTX-71? This is the '931 Sallmann

patent you testified about this morning, right?
A. Yes.
Q. And you talked about the disclosure in this reference of tyloxapol as a solubilizer, right?
A. Yes.
Q. So let's look at that bottom of Column 4, Line 64. It says, "another preferred solubilizer is tyloxapol," right? Do you see that?
A. Yes.
Q. And then it says, "the concentration used depends especially on the concentration of the active ingredient." Do you see that?
A. Yes.
Q. Then it says, "the amount added is typically sufficient to solubilize the active ingredient." Do you see that?
A. I do.
Q. And there's no more information there provided to a person of ordinary skill in the art, right?
A. No more information about what?
Q. About the concentration of tyloxapol to be used in the formulation.
A. I think the next line --
MR. HASFORD: I object, your Honor, to the extent it mischaracterizes the document. I don't believe it discloses an amount of tyloxapol there.

THE COURT: The witness can answer if he understands the question.
THE WITNESS: I think I do. The next sentence gives direction on -- well, the solubilizer's concentration relative to the active -- to the diclofenac potassium, which is what Sallmann is about.
BY MS. HOLLAND:
Q. So it says that the -- for example, the concentration of solubilizer is from .1 to 5000 times the concentration of the active, right?
A. Yes.
Q. Okay. And, at least according to this patent, the person of ordinary skill in the art is supposed to determine the concentration to use themselves based on the concentration of the active, right?
A. Well, the -- well, this is talking about the diclofenac potassium because that's what Sallmann is talking about, and this is telling a skilled person that the amount of the solubilizer is going to depend on how much of the active is present. So the more active, then the more solubilizer one needs to dissolve that amount of active ingredient.
Q. And the skilled person would have performed some experiments to determine that amount, correct?
A. Presumably they would have to. You know, given this guidance they would have to figure that out what an

appropriate amount is under the conditions of what's in the -- other ingredients in the formulation, pH, parameters such as those in order to come up with the amount of solubilizer.

MS. HOLLAND: Your Honor, would it appropriate to take the afternoon break now?

THE COURT: Okay. Sure.

MS. HOLLAND: Thank you.

THE COURT: Let's about a ten-minute break and we'll resume about 3:35.

(Brief Recess.)

DEPUTY CLERK: All rise.

THE COURT: Be seated, please.

You may proceed.

MS. HOLLAND: Thank you, your Honor.

BY MS. HOLLAND:

Q. Dr. Williams, you testified on your direct examination about some of Dr. Davies' opinions as to chemistry issues in this case, correct?

A. **I mentioned my reliance on some of his opinions, yes.**

Q. And you relied on his opinions as of the time you submitted your expert reports in this case as well, right?

A. **True, yes.**

Q. At the time you submitted your expert reports, you had never met Dr. Davies, right?

A. **That's true.**

Q. You've never spoken to him, correct?

A. **That's true.**

Q. And to the extent that Dr. Davies and Dr. Heathcock have opposing views on the chemistry issues, you can't offer any opinion on which of the two is correct, right?

A. **That's true.**

Q. I just want to turn briefly of your opinions on pH in connection with unexpected results.

You testified that Prolensa has a pH of 7.8 and Bronuck®, Xibrom®, and Bromday® have a pH of 8.3, right?

A. **Yes.**

Q. Now, the Ogawa Example 6 has a pH of 8, right?

A. **Yes.**

Q. And do you agree that the preferred pH range in the Ogawa patent is 7.5 to 8.5?

A. **That's what Ogawa states, yes.**

Q. To be clear, Claim 6 and 20, the two asserted claims here don't have any specific limitation as to pH, right?

A. **They have the limitation suitable for ophthalmic administration but there's no specific pH value or range.**

Q. And you agree that pH 8.3 would be suitable for ophthalmic administration, right?

A. **Yes.**

Q. Now, you testified that the pH difference between the prior formulation, which is the Xibrom®, Bromday® formulation,

and the Prolensa is .5 units on the pH scale, right?

A. **Yes.**

Q. Okay. Now, you've said that the pH of Prolensa is 7.8. Are you aware that there's actually a range of pH at which Prolensa can be released?

A. **Can be released?**

Q. Well, let me do this in the context of the document. Let's look at PTX-125C, and this is the section of the Prolensa ANDA. Do you see that?

A. **I do.**

Q. And this section is entitled specifications. Do you see that?

A. **Yes.**

Q. It says it contains the release and shelf specifications for Prolensa, right?

A. **Yes.**

Q. And if you look down at the pH specification --

MS. HOLLAND: Can you highlight that? Thank you.

BY MS. HOLLAND:

Q. It says release 7.6 to 8.0. And then shelf 7.4 to 8.1. Do you see that?

A. **I do.**

Q. And you've had experience with specifications before in your time in industry, right?

A. **Yes.**

Q. So you know that a release specification means that if a batch of Prolensa has a pH anywhere between 7.6 and 8.0, it can be released to the market, right?

A. **That's true. Yes, that's my understanding.**

Q. And similarly, a shelf specification means that the pH of Prolensa can go up between -- anywhere between 7.4 and 8.1 during its shelf life and that would still be within FDA approved product, correct?

A. **That's my understanding, yes.**

MS. HOLLAND: That's all I have, your Honor.

THE COURT: Okay. Thank you.

Redirect?

MR. HASFORD: We have some redirect, your Honor.

(REDIRECT EXAMINATION OF ROBERT O. WILLIAMS, III BY MR. HASFORD:)

BY MR. HASFORD:

Q. Let's pull up PDX4-5, please.

Did you hear -- or Dr. Williams, do you recall Ms. Holland asking you various questions about the closest prior art in connection with PDX4-5?

A. **Yes.**

Q. Did you hear Dr. Lawrence testify that boric acid, Borax, disodium edetate, benzalkonium chloride, polyvinylpyrrolidone, and sodium sulfite in the formulation of Example 6 of the Ogawa '225 patent would not detrimentally affect its basic and

novel properties, including stability?
A. Yes, I heard her say that.
Q. And PDX4-5 includes the three formulations that were tested in Experimental Example 1 of the '431 patent. Do you see that?
A. Yes.
Q. What are the components of Comparison Example 1 in Table 1 in Experimental Example 1 of the '431 patent?
A. So that's the bromfenac sodium, boric acid, Borax -- I'm sorry, there is no Borax -- benzalkonium chloride, Polysorbate 80, and then water.
Q. How, if at all, do the other formulations in Experimental Example 1 differ from the formulation of Comparison Example 1 of the '431 patent?
A. They differ in the surfactant that's added, being tyloxapol, and then there is different levels of tyloxapol being studied.
Q. Does Table 1 of the '431 patent disclose chemical stability test results?
A. Yes.
Q. Does Comparison Example 1 in Experimental Example 1 of the '431 patent reflect the closest prior art as defined by defendants?
A. In my opinion, yes.
Q. Do you recall that Ms. Holland asked you various

questions on cross exam about the FDA's Inactive Ingredients Guide?
A. Yes.
Q. Let's put DDX2-55 up on the screen.
Does DDX2-55 depict a portion of the FDA's Inactive Ingredient Guide in DTX-196?
A. It does, yes.
Q. Let me direct your attention to the top line for tyloxapol-containing ophthalmic solutions. As of the date of DTX-196, how many ophthalmic solutions containing tyloxapol had been approved by the FDA?
A. It lists five here.
Q. As of the date of DTX-196, were any of the five FDA-approved tyloxapol-containing ophthalmic solutions NSAID products?
A. No.
Q. Did you hear Dr. Lawrence testify that, in her opinion, a person of ordinary skill in the art would only have looked as of 2003 to those excipients listed in DTX-196 when formulating an ophthalmic NSAID solution?
A. I heard that, yes.
Q. Do you agree with Dr. Lawrence's opinion?
A. No.
Q. Why not?
A. Because, as I testified earlier to, that is one source,

but a skilled person, if an excipient that's not in the IIG list works in the formulation and nothing else does, then there is a path in order -- a path to get that particular additive in an approved product. I mean, in essence, somebody's got to be the first.
MR. HASFORD: Noel, can you please put DDX-1-18 up on the screen.
BY MR. HASFORD:
Q. Do you see that DDX1-18 also reflects portions of DTX-196 which the defendants have introduced into evidence as the FDA's Inactive Ingredients Guide?
A. Yes.
Q. As of 2003, how many ophthalmic solutions containing Octoxynol 40 had been approved by the FDA?
A. There's one listed there.
Q. Do you recall testifying earlier that Acular included Octoxynol 40 and was approved in 1992?
A. It did, and yes, I remember testifying.
Q. As of 2003, what was the one ophthalmic solution containing Octoxynol 40 that had been approved by the FDA?
A. That's Acular.
Q. Did the developers of Acular use a nonionic surfactant, namely Octoxynol 40, that had not previously been listed in the FDA Inactive Ingredient Guide?
A. They did, yes.

Q. How, if at all, does this relate to your opinion that a person of ordinary skill in the art as of 2003 would not have limited the choice of surfactants for an NSAID ophthalmic solution to only those listed in the FDA Inactive Ingredient Guide?
A. Well, it's an -- it's an example of -- of product that's developed with an excipient that wasn't previously listed in the IIG, and that they apparently undertook studies to get it approved and now it's listed.
Q. Do you remember Ms. Holland asking you questions on cross-examination about one of your patents?
A. Yes.
Q. Does that patent deal with nasal and buccal formulations?
A. Yes, it does.
Q. Do nasal and buccal formulations differ from ophthalmic solutions such as the aqueous liquid preparations of the '431 patent?
A. It's a different route of administration, yes.
Q. Do you remember Ms. Holland asking you questions on cross-examination about whether the pH of Xibrom® and Bromday® is in the prior art?
A. Yes.
Q. Is it your understanding that the pH of Bronuck® is 8 to 8.6 and that was disclosed in the prior art? And, if necessary, we can go to the new drugs in Japan reference to

refresh your recollection.

A. **Okay.**

Q. Okay. Let's pull up the new drugs in Japan reference. Let's turn to the next page. Following page.

06:19 Okay. So, take a look, if you would, at the page bearing Bates Number -- I'm sorry, Noel, go up.

Let's take a look at JTX-210, at the package bearing Bates Number PROL 0364732. Let me direct your attention to the right-hand column and, in particular, the table that says 06:20 "Composition/Properties." Do you see that?

A. **Yes.**

Q. Does JTX-210 disclose the pH of Bronuck® as 8 to 8.6?

A. **It does, yes.**

Q. Is it your understanding that the defendants have taken 06:20 the position in this case that Bronuck®, Xibrom®, and Bromday® all have the same composition?

A. **That's my understanding.**

Q. Do you remember Ms. Holland asking you various questions on cross-examination about the unexpected results disclosed in 06:20 the '431 patent?

A. **I do.**

Q. Let's take a look, if we would, at the '431 patent, and, in particular, Experimental Example 1. It's going to be JTX-1.

06:20 Do you have an understanding as to whether the '431

patent discloses chemical stability results for formulations of bromfenac containing tyloxapol?

A. **It does -- it does.**

Q. Where, if at all, does the '431 patent disclose chemical 06:21 stability results for formulations of bromfenac containing tyloxapol?

A. **So, there is a row that's titled "Remaining Rate," as -- and a percent, so that's the chemical stability of bromfenac sodium that is remaining in solution, integrated as a function 06:21 of the testing conditions.**

Q. Are those results disclosed in, among other places, Table 1 in Experimental Example 1 of the '431 patent?

A. **They are, yes.**

Q. During prosecution of the '431 patent, did the patent 06:21 examiner credit the unexpected chemical stability results of Experimental Example 1 in allowing '431 patent to issue?

MS. HOLLAND: Your Honor, all these questions have been leading.

MR. HASFORD: I'm happy to rephrase that one, your 06:21 Honor.

THE COURT: Okay. Please do.

BY MR. HASFORD:

Q. What, if anything, did the patent examiner say about the results in Experimental Example 1 of the '431 patent during 06:22 prosecution?

A. **As I testified to earlier, the patent examiner credited in the notice of allowance the stability results presented in Table 1 --**

Q. Did --

06:22 A. **-- of Experimental Example 1.**

Q. I apologize.

Did the patent examiner credit them as unexpected?

A. **Yes, that's the word he used.**

Q. Regardless of whatever else tyloxapol may do in the 06:22 Prolensa® formulation, do you have an opinion as to whether or not tyloxapol chemically stabilizes bromfenac?

A. **I do.**

Q. What is your opinion?

A. **My opinion is, based on the data I've seen, that -- is 06:22 that tyloxapol does chemically stabilize bromfenac sodium in solution.**

Q. In your opinion, was that expected or unexpected?

A. **In my opinion, it was unexpected. I've not seen anything in the literature that would have suggested tyloxapol would 06:22 have chemically stabilized bromfenac sodium.**

MR. HASFORD: Nothing further at this time, your Honor.

MS. HOLLAND: Your Honor, can I follow up with just a couple of questions on one topic?

06:23 THE COURT: Okay. Couple means two.

MS. HOLLAND: Now I have to select carefully.

(RECROSS EXAMINATION OF ROBERT O. WILLIAMS, III BY MS. HOLLAND:)

Q. Dr. Williams, I want to talk very briefly about your 06:23 testimony that you gave on the notice of allowance. You just testified about that on redirect, correct?

A. **Yes.**

Q. Isn't it correct that the examiner who -- who you said issued the notice of allowance didn't have all the prior art 06:23 that's been discussed in this case?

A. **I -- I'm not sure. I haven't considered that question.**

Q. So you don't know whether or not the Court has more prior art at its disposal than the examiner did during prosecution?

A. **I just haven't compared what's -- what the prior art is 06:23 now compared to what the examiner had. I mean, I think on the face -- let's see -- that's JTX-2?**

Q. So you have --

MR. HASFORD: I believe he's asking for JTX-1 --

THE WITNESS: I'm sorry, the '431 patent. JTX-1? 06:24 Thank you.

So the examiner had -- I'm sorry?

BY MS. HOLLAND:

Q. You don't see the Schott reference there, for example, right?

06:24 MR. HASFORD: Hold on. I think we're trying to get

the '431 patent, the face, put up, your Honor.
THE COURT: Okay.
MS. HOLLAND: I'm sorry. It's my examination. Can I put up the exhibits I want to put up? Thank you.
06:24 THE COURT: All right. Let's proceed.
BY MS. HOLLAND:
Q. Dr. Williams, do you recall the question?
A. I don't. I'm sorry.
Q. All right. I apologize.
06:25 All right. Before offering your opinion today about the notice of allowance, you did not check to see whether or not the examiner had all the prior art before him that we have before us at the trial of this case, correct?
A. I mean, I was aware that the examiner had the Ogawa '225 patent, the Yanni '034 patent, the Desai '929 patent, so, I mean, the examiner had some of the prior art that I've been speaking of.
Q. Okay. Some but not all, correct?
A. I -- I hesitate to say that because I hadn't actually done the comparison.
Q. Okay, that's fine.
But you are aware that the examiner didn't have the benefit of any expert testimony on the issues before issuing the notice of allowance, right?
06:25 **A. I -- I actually -- I don't know what -- if -- I'm not**

sure the answer to that question.
Q. Okay. Nothing further. Thank you.
MR. HASFORD: Nothing further from us, your Honor.
THE COURT: Okay. I have no questions.
06:26 THE WITNESS: Thank you, sir.
THE COURT: So you may step down.
THE WITNESS: Thank you.
MR. HASFORD: I think we still have a bit of a housekeeping matter, your Honor, in terms of getting the
06:26 exhibits moved into evidence.
THE COURT: Yes.
MR. HASFORD: I think we read the list that we had already, and counsel was going to consider whether they had any objections to those.
06:26 MS. HOLLAND: We don't have any objections to those, but I would also like to move in some of the exhibits that were used during cross-examination.
THE COURT: Okay. Just a moment. Let me return then to the plaintiff's list and I'll read those into the record.
06:26 Okay. The following exhibits are received into evidence: PTX-294, PTX-268, PTX-272, PTX-326, PTX-273, also PTX-324, PTX-265, PTX-591, PTX-592, PTX-593, JTX-144, also PTX-474, also JTX-18. They are all received into evidence.
(EXHIBITS PTX-294, PTX-268, PTX-272, PTX-326, PTX-273,
06:26 PTX-324, PTX-265, PTX-591, PTX-592, PTX-593, JTX-144, PTX-474,

AND JTX-18 WERE RECEIVED IN EVIDENCE.)
MR. HASFORD: Thank you, your Honor.
THE COURT: Okay, Ms. Holland?
MS. HOLLAND: Yes, your Honor. It's JTX-25,
06:27 DTX-479A, DTX-478.
THE COURT: Those were only for impeachment, weren't they?
MR. HASFORD: Yes.
THE COURT: So they wouldn't come into evidence.
06:27 MS. HOLLAND: I apologize, your Honor. Why don't I -- is it okay if I discuss this and then come back to you rather than taking the time now? Because I agree there were some used for impeachment.
THE COURT: All right.
06:28 MS. HOLLAND: Thank you. We will do it at the end of the day.
MR. HASFORD: We are happy to confer with them, your Honor, and see if we can come to an agreement.
THE COURT: All right. Okay. Are we ready for
06:28 another witness?
MR. HASFORD: We are, your Honor.
THE COURT: Now, there are some documents up here that you may wish to retrieve.
MS. LEBEIS: Good afternoon, your Honor. Jessica
06:29 Lebeis of Finnegan, Henderson for plaintiffs.

THE COURT: Okay, Ms. Lebeis, you may proceed, and please call your next witness.
MS. LEBEIS: Plaintiffs would now like to call Dr. Trattler.
06:29 THE COURT: Dr. Trattler, please come to the witness stand.
MS. LEBEIS: Your Honor, may we please pass out binders?
THE COURT: Yes.
06:29 MS. LEBEIS: Thank you.
THE DEPUTY CLERK: Sir, place your left hand on the Bible right there and raise your right hand.
(**WILLIAM B. TRATTLER**, HAVING BEEN DULY SWORN/AFFIRMED, TESTIFIED AS FOLLOWS:)
06:30 THE WITNESS: Yes, I do.
THE DEPUTY CLERK: Can you please state your name, sir, and I need you to spell your first and last name, please.
THE WITNESS: Sure. It's William, spelled W-I-L-L-I-A-M, last name is Trattler, T-R-A-T-T-L-E-R.
06:30 THE DEPUTY CLERK: Thank you, sir. Please speak into the microphone when you get in the seat, please.
THE COURT: Okay, Ms. Lebeis, you may proceed.
(DIRECT EXAMINATION OF WILLIAM B. TRATTLER BY MS. LEBEIS:)
Q. Good afternoon, Dr. Trattler.
06:30 **A. Good afternoon.**

Q. Would you please state your address for the record.
A. **Sure. My address is Center for Excellence in Eye Care, 8940 North Kendall Drive, Number 400E, Miami, Florida, 33176.**
Q. Where are you presently employed?
06:30 A. **I am employed at the Center for Excellence in Eye Care.**
Q. What is your current position at the Center for Excellence in Eye Care?
A. **I'm an ophthalmologist.**
Q. Do you specialize in any area of ophthalmology?
06:31 A. **Yes. I specialize in cornea, cataract, and refractive surgery.**
Q. What is refractive surgery?
A. **Refractive surgery are procedures to help eliminate people's need for glasses, whether it's glasses for distance**
06:31 **or glasses for reading.**
Q. How long have you been an ophthalmologist at the Center for Excellence in Eye Care?
A. **Nineteen years.**
Q. Would you please describe your responsibilities as an
06:31 ophthalmologist at the Center for Excellence in Eye Care?
A. **Yes. During the week I see patients who come in for consultations for typical eye problems, and they can include consultations for corneal problems, they may come in for cataract consultations, or for refractive surgery which is**
06:31 **like LASIK surgery, which you may have heard of, and then I**

also perform those procedures, I perform corneal procedures, lots of cataract surgery, as well, laser vision correction such as LASIK.
Q. How much cataract surgery do you perform?
06:32 A. **I perform approximately 60 cataract surgeries per month, so a little bit over 700 per year.**
Q. What, if any, experience have you had with drugs used to treat pain and inflammation after cataract surgery?
A. **Well, when we perform cataract surgery, you're basically**
06:32 **performing surgery, and all patients experience inflammation after cataract surgery, so all cataract surgery procedures are -- all patients who have cataract surgery are treated with anti-inflammatory medications to control and reduce the inflammation after surgery.**
06:32 Q. Would you please turn to PTX-164 in your binder and identify that document.
A. **Yes. This is my curriculum vitae.**
Q. Does your curriculum vitae accurately reflect your educational and work experience?
06:32 A. **Yes, it does.**
Q. Would you please briefly describe your educational background following your graduation from high school?
A. **Of course. I went to Dartmouth College in New Hampshire for my undergraduate degree and graduated with honors.**
06:33 **I then went to Miami, I went to the University of Miami**

School of Medicine, where I graduated from medical school.
I then spent one year doing my internship at Mount Sinai Hospital in Miami Beach.
I then came here -- came to Philadelphia, to University
06:33 **of Pennsylvania, Scheie Eye Institute, where I completed my ophthalmology residency.**
I then spent an extra year of training called a Cornea Fellowship which I completed in Dallas, Texas, at the University of Texas, Southwestern Medical Center.
06:33 Q. What did you do after completing your Cornea Fellowship?
A. **After my training, I returned to Miami, and I joined the practice at Center for Excellence in Eye Care.**
I was also hired to be -- to work at the Veterans Hospital in Miami where I trained the Bascom Palmer
06:33 **Ophthalmology residents how to do cataract surgery and perform exams.**
Q. What, if any, academic appointments have you held?
A. **Well, since I -- when I arrived into Miami, I started teaching at Bascom Palmer and supervising residents, so I was**
06:34 **given a volunteer assistant professor of ophthalmology appointment from Bascom Palmer Eye Institute, and then we also teach the -- I also teach at Florida International University College of Medicine, so I'm on the volunteer faculty for that medical school as well.**
06:34 Q. What, if any, teaching have you done?

A. **Well, I love teaching. I started off teaching during my residency. The medical students would rotate through ophthalmology and I'd always volunteer to be one of the instructors, and I did win two teaching awards while I was a**
06:34 **resident. And then since then, I always love teaching, both supervising young doctors in training, also participating in giving lectures and writing articles and things like that, but just trying to help educate my colleagues.**
Q. You mentioned that you won a teaching award. What, if
06:34 any, other honors or awards have you received in connection with your work?
A. **Right. Well, the C.V. is pretty much up to date, but there was one recent award. I was given an award by the American Academy of Ophthalmology, there is a part of it**
06:35 **called the International Society of Refractive Surgery, and I was given one of the big awards for the year called the Casebeer Award for my work in refractive surgery.**
I have received the Senior Achievement Award from the American Academy of Ophthalmology; a number of other awards.
06:35 One that may be of interest, since we're talking about cataract surgery, is in 2006, I was given the Top 50 Cataract and Refractive Surgery Opinion Leaders, as voted on by the readers of *Cataract & Refractive Surgery Today*, and a number of other awards. I have been very fortunate.
06:35 Q. Have you published any research articles?

A. **Yes, I have.**
Q. Are your published research articles listed in your curriculum vitae?
A. **Yes, they are.**
06:35 Q. Generally speaking, what types of research articles are reflected in your list of publications in your curriculum vitae?
A. **There are articles in and around the areas of cataract surgery, refractive surgery, and dry eye, as well as corneal surgery.**
06:36 Q. Have you conducted any clinical trials?
A. **Yes, many.**
Q. In how many clinical trials have you been involved?
A. **I think it's been in the approximate range between 80 and a hundred clinical trials during my career.**
06:36 Q. Generally speaking, in what types of clinical trials have you been involved?
A. **I have been involved in a whole -- a wide variety of clinical trials. I have been involved in pharmaceutical trials for drugs to be used in and around cataract surgery, so both NSAID studies and steroid studies in and around cataract surgery. I have been involved in other medication studies such -- for approvals for dry eye products. I have been involved in -- in interocular lens technologies, both in patients that wanted to get rid of their need for glasses for**

myopia, as well as for patients that are undergoing cataract surgery.
Q. Are the clinical trials in which you've been involved listed on your curriculum vitae?
06:37 A. **Yes, they are.**
Q. Have you conducted any clinical trials involving bromfenac-containing products?
A. **Yes, I have.**
Q. Which bromfenac-containing products?
06:37 A. **So, I was involved in the -- in the clinical trial for Xibrom®, for the FDA approval for that, as well as involved in one of the studies for -- that eventually led to the approval of Bromday®.**
Q. Have you conducted any clinical trials involving any
06:37 other NSAID-containing products?
A. **Yes. I was also an investigator for ketorolac 0.45 percent, which eventually got FDA approved and is known as Acuvail®.**
Q. Do you regularly attend and present at scientific
06:37 meetings?
A. **Yes, I do.**
Q. Approximately how many such scientific meetings have you attended?
A. **Well, I typically speak at about 15 conferences or -- conferences a year, in the 15 range.**

Q. Have you previously been recognized by other courts as an expert in the field of ophthalmology, including cataract, corneal and refractive surgery?
A. **Yes, I have.**
06:38 MS. LEBEIS: Your Honor, plaintiffs offer Dr. Trattler as an expert in the field of ophthalmology, including cataract, corneal and refractive surgery, and the drugs used in connection with cataract surgery.
THE COURT: Any objection?
06:38 MS. HOLLAND: No, your Honor.
THE COURT: All right. The Court will recognize Dr. Trattler as an expert in those fields.
MS. LEBEIS: Thank you, your Honor.
BY MS. LEBEIS:
06:38 Q. Let's now discuss your opinions in this case.
A. **Yes.**
Q. Let's first discuss cataracts and cataract surgery. First of all, what are cataracts?
A. **So, cataracts are a natural aging of the lens inside your eye, and cataracts can occur in young patients, in infants, but typically they occur in patients aged 50 or older, and it's just a natural aging change leading to blurring of vision over time.**
Q. Have you prepared a demonstrative to assist the Court with your testimony?

A. **Yes, I have.**
MS. HOLLAND: Is this moved in or --
MS. LEBEIS: No.
BY MS. LEBEIS:
06:38 Q. What is illustrated in the demonstrative marked as PDX5-1?
A. **All right. This is an example of a patient with a cataracts. You can see the eyelids above and below, to give you an orientation. The brown part of the eye is the iris and**
06:39 **in the white central area is the lens of this patient that's turned white, and that is a very advanced cataract.**
Q. What, if anything, are the symptoms of cataracts?
A. **So, cataracts, as they develop, you slowly lose your ability to see crisply and you get blurred vision, and it**
06:39 **starts to impact your ability first to -- often to drive, so people can have difficulty seeing road signs. They can experience glare when driving at nighttime. Patients can report difficulty reading, working on the computer, and other visual tasks.**
06:39 Q. How common is the development of cataracts?
A. **So cataracts are universal. All patients, if you live long enough, will develop cataracts, and I guess probably by the age 80 or so, pretty much everyone has some degree of cataract formation in their eye.**
06:40 Q. What, if anything, occurs if cataracts are left

untreated?
A. Well, cataracts are progressive and over time, they lead to worse vision over time. So, you know, patients can decide at what point they want to have surgery, but eventually, it leads to loss of vision and blindness.
Q. Why do cataracts form?
A. It's unknown why cataracts form. It's just a natural aging change of the eye.
Q. How, if at all, are cataracts treated?
A. The only treatment for cataracts is surgery. And so at some point during the development -- during a patient's experience with a cataract, they'll opt to have cataract surgery to basically, essentially, remove the cataract and to have a new artificial lens placed inside their eye.
Q. How is cataract surgery performed today?
A. Well, minor cataract surgery today is performed basically by using an ultrasound device to basically vibrate and break up the cataracts, and then following that, we place a new lens in the eye. We also can use laser to pretreat the cataract to soften the cataract, making it a little bit easier to remove. I think -- I like to think of cataract as kind of like a peanut M&M, to try to make it simple. So the outer layer of the cataract is called the capsule, similar to candy coating of a peanut M&M. There is a -- the chocolate area is kind of the cortex area that was removed near the end of the surgery.

And the central part is the -- there is this dense central part which we call a nucleus, which is kind of similar to the peanut in a peanut M&M, but when we do cataract surgery, we will work first on removing the nuclear part, and then work on the cortex part, but leave the capsule in place because that's where the new intraocular lens will rest after surgery.
Q. To assist the Court with your testimony, have you prepared a demonstrative video showing how you perform cataract surgery using phacoemulsification?
A. Yes.
MS. HOLLAND: Your Honor, we have an objection to this video. A, we don't see the relevance of it to this case in terms of the drugs that are used to treat postsurgery, and it is a graphic video, so I think that the prejudice outweighs the relevance in this case.
THE COURT: Well, what would be the relevance? I didn't know that the drug was associated with anything that happened before the end of surgery.
MS. LEBEIS: Your Honor, the video is relevant because Prolensa®, as you know, is indicated for the treatment of pain and inflammation following cataract surgery. It's instilled before cataract surgery and then immediately thereafter. But the video is relevant because it shows the environment in which the drug will be instilled following surgery, and it's just a visual aid to -- to illustrate how

the surgery is performed and then the -- how the eye is affected by the surgery, which is where Prolensa® will be instilled.
THE COURT: Well, I'm interested in the latter part, but the earlier part, I would just permit the witness to quickly describe it. I am not unfamiliar with eye surgery. I have not had it, but it's a subject that comes up in litigation from time to time.
MS. LEBEIS: Well, I would add, your Honor, that the video -- it's a short video. And I would -- it's not -- I wouldn't describe it necessarily as graphic. It just shows actually how it occurs. It shows how, as Dr. Trattler just described, the capsule is removed from the eye and the cataract is removed from the eye. As you know, Prolensa® is used to treat inflammation.
THE COURT: Well, how short is it?
MS. LEBEIS: It's just over two minutes, between two and three minutes.
THE COURT: Okay, I will permit it. I didn't realize it was that short.
MS. LEBEIS: Yes. Thank you, your Honor.
Noel, will you please pull up the video.
THE WITNESS: Okay. You can see --
BY MS. LEBEIS:
Q. Dr. Trattler, would you just please explain what's being

shown? And let Noel know when you're ready to start the video.
A. So this is a patient of mine that had the laser treatment of their cataracts. You see that's what the grid pattern in the nucleus has already been created and is actually one of the incisions, the main incision which is going to be right here, has already been created with a laser, so you would just open it up without using a -- a blade. But we will make a tiny incision to help with the surgery so you can go ahead and start the video.
And the first step is we're going to place an anesthetic inside the eye so that during the surgery it's comfortable. And then we're going to place a gel to kind of keep the eye formed. You see, this is the anesthetic going in and on the surface of the eye. And that's the gel that's placed. And we're going to open up the incision. Right here, you can see that it's just opened. And we're not going to -- we're not going to use a suture at the end of this surgery. No sutures are needed. I will explain how that works. But we basically take off the very outer layer of the candy coating we talked about, the capsule. We then inject a little fluid just around the nuclear -- or part of the lens, to free it up. And so now this lens is -- or the central dense part has been freed up. It makes it much easier to remove. And it's -- it's a device called ultrasound, called phaco, where we're --

this little device is vibrating back and forth, and that's where there is inflammation that occurs with this procedure is because, as you can see, we're basically breaking up this lens into tiny, tiny little pieces and it's vacuumed into the little central port.

We can see that most of the nucleus is being removed at this point, and this is the very last piece of the nucleus being removed.

You can see at this point we're left with just some wisps left, and that's called the cortex, and we're going to use this little device here just vacuuming out the wisps of cortical material that's left.

Any cortical material that is not removed will lead to further inflammation, so it would be best to remove all the material from the eye, of the cortex and the nucleus during the procedure, although sometimes small tiny fragments, sometimes tiny amounts of the nuclear material or cortical material can be left behind. But most of it's removed with vacuum.

So now we're injecting the -- the gel back into the eye, and we're placing the plastic lens inside the eye. And so this is the lens, and it's going to be just positioned in the capsule, and we're going to remove the gel from the eye. And at the very end, you will see we're going to basically fill up the eye with fluid, but we do not use a suture during

this procedure at all, and the incisions are all kept watertight by the internal pressure. They can be opened by just pressing on the edge or the lip of the incisions that are created, so that's why it's very important and we advise our patients not to rub their eyes during the postoperative period. But you can see no stitches are needed, and this is the end of the case, with the eye firm and the incisions are therefore closed.

Q. Thank you, Dr. Trattler.

You just mentioned that you do not --

THE COURT: Excuse me. May I ask a clarifying question? And, again, if there is any objection, then object.

Was this in realtime? Is this how quickly the procedure goes?

THE WITNESS: No. We -- I cut out a few little parts, like where I transition with the instruments or in showing the nuclear removal. The typical case is about eight minutes. This is about I believe two minutes and 30 seconds or so.

THE COURT: Okay. Thank you.

BY MS. LEBEIS:

Q. Dr. Trattler, you mentioned that you do not use sutures or stitches. How, if at all, does the incision heal?

A. Right. So the incision will heal over the first four -- four to -- four or five days. The next day it's still very

easy, if the pressure is elevated, we can actually press on the lip of one of the incisions and release some fluid if needed. So, typically, over the first few days, the incision slowly heals. But it is an open incision, which is why we instruct our patients to sleep with a shield at nighttime so they don't rub their eyes during nighttime, and also advise them to not rub their eyes because they can lead to, you know, opening of that wound which could lead to infection or other complications.

Q. How, if at all, does the cataract surgery which we just saw result in pain and inflammation in patients who undergo it?

A. Right. So, as you can see from the -- from how the surgery is performed, we make incisions in the eye, and we're using ultrasonic energy within the eye, and that leads to inflammation being generated.

Q. How, if at all, are pain and inflammation after cataract surgery treated?

A. Right. So the -- so what we typically use is we use eyedrops actually prior to surgery to pretreat the eye, and we use anti-inflammatory eyedrops, and then we continue the same anti-inflammatory drops during the postoperative period to suppress the inflammation and to treat the inflammation, and also to try to knock out the pain that's a result of the inflammation from surgery.

Q. What types of anti-inflammatory drugs are used?

A. There is two classes of agents that we use: We use both topical steroids and topical nonsteroidal drops.

Q. What types of drugs do you use?

A. So I use both, the combination, both of steroids and nonsteroidal drops.

Q. Why do you use both steroids and nonsteroidal drops?

A. Both steroids and nonsteroidals suppress inflammation, but they work on different parts of the inflammatory pathway and so they work synergistically. They help reduce inflammation, reduce pain, and lead to faster visual recovery by working -- by having both work together.

Q. And when you say nonsteroidal drops, do you mean NSAIDs?

A. Yes, nonsteroidal drops are -- are NSAIDs.

Q. Is Prolensa® indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery?

A. Yes.

Q. Have you prescribed Prolensa®?

A. Yes, I have.

Q. What, if anything, are the consequences of not treating pain after cataract surgery?

A. Well, the procedure itself will result in inflammation and therefore pain after surgery. And so if patients experience pain afterwards, they may rub their eyes, if their

eyes painful. It leads to very poor postoperative experience. Patients have very high expectations that when they have surgery, they will have a comfortable experience and end up with good vision, so experiencing significant pain afterwards is a real problem.

Q. And what, if anything, are the consequences of not treating inflammation after cataract surgery?

A. Inflammation is caused by the surgical procedure. So what happens is we use the topical medications to reduce the inflammation; if not, the eye will remain red, it will remain sensitive to light, there will be blurred vision, as well if it's not treated, it can lead to chronic problems such as cystoid macular edema or CME.

Q. What is cystoid macular edema?

A. So cystoid macular edema is a condition of the retina. Even though we are doing surgery in the front part of the eye, the inflammatory, you know, mediators can get back to the retina and cause swelling of the retina, right in the -- where we see, and that can lead to blurred vision that can, in some cases, be permanent.

Q. Is cystoid macular edema also abbreviated as CME?

A. Yes, it is.

Q. How, if at all, can cystoid macular edema lead to vision loss?

A. Cystoid macular edema is a swelling of the retina, the

central retina, and we call that area the macula, and that's -- when we're looking at the world, we're seeing through that region, and so if there is a swelling occurs, it causes blurring of vision, the photoreceptors can't function normally, and patients have loss of vision, and they can end up either legally blind or not legal to drive. And, again, some patients can get recovery but there are some patients that will have permanent vision loss from CME.

Q. How, if at all, does failing to treat postoperative inflammation increase the risk for development of CME or cystoid macular edema?

A. It's the inflammatory mediators associated with performing cataract surgery that result in the development of CME. So not being aggressive at and not treating inflammation completely leads to increased risk of developing CME postoperatively.

Q. What patients are at risk of developing CME?

A. So, all patients undergoing contract surgery are at risk for developing CME. There are some patients that are at higher risk, but every single patient that has surgery are at risk for developing CME.

Q. I would now like to turn to discuss the treatment of pain and inflammation after cataract surgery using bromfenac-containing ophthalmic NSAID therapies.

A. Perfect.

Q. Before Prolensa®, were other bromfenac-containing ophthalmic NSAID therapies available to treat postoperative inflammation and ocular pain in patients who have undergone cataract surgery?

A. Yes.

Q. Have you prepared a demonstrative to assist the Court with your testimony?

A. Yes, I have.

Q. Would you please explain what is illustrated in the demonstrative marked as PDX5-2?

A. So, this is basically a summary of four -- four bromfenac-containing nonsteroidal drops used with cataract surgery.

The top one is Bronuck®, which is available in Japan. Then we have Xibrom® and Bromday®, which are -- are available in the U.S. or were available in the U.S. And then, lastly, Prolensa®, which is also available in the U.S.

Q. What, if anything, is your understanding regarding the formulation components of Bronuck®, Xibrom®, and Bromday®?

A. It's my understanding that the components are the same in all three products.

Q. How, if at all, are Bronuck®, Xibrom®, and Bromday® limited by their side effects?

A. So, as you can see from this chart, all three products, Bronuck®, Xibrom®, and Bromday®, have the postoperative side

effect of causing stinging and burning and having a burning sensation. You can see that's present in the product labels of all three products.

Q. Is Prolensa® associated with the side effects of burning and stinging?

A. Right. Prolensa®, per the FDA label, is not associated with either burning or stinging.

Q. Let's discuss the basis for your opinion.

Would you please turn to PTX-277 in your binder and identify that document?

A. Yes. So this is the -- the package insert for Bronuck® Ophthalmic Solution, and it's translated from its Japanese version.

Q. Did you review PTX-277 in connection with your opinions in this case?

A. Yes, I did.

Q. Let me direct your attention to the page of PTX-277 bearing Bates Number PROL 0333505, and, in particular, to the top of the right-hand column.

A. Okay.

Q. How, if at all, does this portion of the Bronuck® package insert relate to your opinion that Bronuck® is limited by the adverse events of burning and stinging?

A. You can -- this is the adverse events listed in the product -- in the package insert, and it lists both burning

sensation and stinging as adverse events that occur with the use of this product.

Q. Would you now please turn to JTX-144 in your binder and identify that document?

06:55 **A. This is the package insert for Xibrom®.**

Q. Is it the FDA-approved package insert for Xibrom®?

A. Yes, this is the FDA-approved package insert for Xibrom®.

Q. Have you reviewed the FDA-approved Xibrom® package insert in connection with your opinions in this case?

06:55 **A. Yes, I have.**

Q. Have you ever treated patients with Xibrom®?

A. Yes, I have.

Q. Let me direct your attention to Page 3 of the Xibrom® package insert which bears Bates Number PROL 0080488, and, in

06:56 particular, to the second paragraph of the section entitled "Adverse Reactions."

How, if at all, does this portion of the Xibrom® package insert relate to your opinion that Xibrom® is limited by the adverse events of burning and stinging?

06:56 **A. This is the adverse reactions section of the FDA-approved package insert, and you can see that burning and stinging occurred, was reported in -- burning and stinging was reported in 2 to 7 percent of patients.**

Q. In that same portion of the Xibrom® package insert, is

06:56 eye pain listed as a separate adverse event from eye

irritation, including burning and stinging?

A. Yes, it's listed as a separate adverse event.

Q. To an ophthalmologist, why is eye pain a separate adverse event from eye irritation, including burning and stinging?

06:56 **A. That's a great -- it's important to distinguish those two sensations.**

So, pain is if you get poked in the eye or get injured in the eye, and you could see in surgery, we're making incisions and that causes pain.

06:57 **When we think of burning and stinging, we think of like if you ever have a lemon and that juice hits you in the eye, that's going to cause a burning sensation.**

It's distinct, and patients can definitely tell the difference between a burning and stinging sensation versus the

06:57 **sensation of pain, which is why they're listed as separate adverse events on the package insert.**

Q. In your experience treating patients, including in clinical trials for ophthalmic formulations, can patients determine the difference between the adverse event of eye pain

06:57 and the adverse events of burning and stinging?

A. Without question, yes.

Q. How do patients convey the difference between the adverse event of eye pain and the adverse events of burning and stinging?

06:57 MS. HOLLAND: I have an objection here as outside the

scope of the report, or maybe Ms. Lebeis can direct me to where in the report it is.

MS. LEBEIS: Well, certainly.

First of all, Dr. Trattler's testified -- or in his

06:57 expert Report at Paragraphs 29, 31 and 33, he separately listed eye pain from burning and stinging as adverse events listed on these labels. But he was also asked about the difference between eye pain and burning and stinging at his deposition, and I know that your Honor asked a question during

06:58 defendants' opening about -- of defendants' counsel regarding eye pain versus burning and stinging. And so Dr. Trattler is simply explaining eye pain and burning and stinging which were both identified in his expert reports as adverse events for Xibrom® and Bromday®.

06:58 THE COURT: All right. So they're separately listed and he wishes to -- or you wish to have him explain the difference?

MS. LEBEIS: Yes, Your Honor.

THE COURT: Okay. I will permit it.

BY MS. LEBEIS:

Q. Would you like me to repeat the question?

A. Yes, please.

Q. How do patients convey the difference between the adverse event of eye pain and the adverse event of burning and

06:58 stinging?

A. They convey by just, you know, explaining it to me, you know, when I talk to them. So patients who have undergone surgery and those that have eye pain will explain that their eye, you know, feels painful, there is pain in their eye.

06:58 **Again, they've had surgery, so that can be expected.**

The burning and stinging is typically, you know, related to the use of eye drops. So the eye drops can cause the burning and stinging. We have a lot of, you know, experience with various eye drop formulations causing burning

06:59 **and stinging, because typically patients will complain that they're -- they're experiencing a burning sensation with the use of an eye drop.**

Q. How, if at all, does the adverse event section of the Xibrom package insert comport with what you've observed in

06:59 your practice?

A. With Xibrom, it's been very -- I agree with, you know, the adverse events. The adverse events listed in FDA package insert are what we expect as clinicians and all of the -- the adverse events listed here, I've seen in patients following

06:59 **cataract surgery.**

Q. Let me now direct your attention to Page 5 of the Xibrom package insert, which bears Bates No. PROL 0080490 and in particular, to the third paragraph under the section entitled Description.

07:00 What is the pH of Xibrom?

A. **This is the FDA-approved package insert, and it reports that the pH of Xibrom is 8.3.**
Q. Could you now please turn to PTX-474 in your binder and identify that document?
07:00 A. **Yes. This is the FDA-approved package insert for Bromday.**
Q. Have you reviewed the FDA-approved package insert for Bromday in connection with your opinions in this case?
A. **Yes, I have.**
07:00 Q. Have you ever treated patients with Bromday?
A. **Most definitely.**
Q. Let me direct your attention to Page 6 of the Bromday package insert, which bears Bates No. PROL 0080495 and in particular, to the section entitled Adverse Reactions.
07:00 How, if at all, does this portion of the Bromday package insert relate to your opinion that Bromday is limited by the adverse events of burning and stinging?
A. **You can see here in this FDA-approved package insert that burning and stinging are listed as an adverse event in two to**
07:01 **seven percent of patients.**
Q. How, if at all, does the adverse event section of the Bromday FDA-approved package insert comport with what you have observed in your practice?
A. **All right. I have a lot of experience using Bromday in**
07:01 **my patients following cataract surgery and I did have patients**

who report that they experience burning with the product and we did have to switch some patients. I either stopped -- switched NSAIDs because of the experience patients were having.
07:01 Q. In the Bromday package insert, is eye pain also listed as a separate adverse event from eye irritation, including burning and stinging?
A. **Yes.**
Q. Let me direct your attention to Page 7 of the Bromday
07:01 package insert, which bears Bates No. PROL 0080496, and in particular, to the second paragraph under the section entitled Description.
What is the pH of Bromday?
A. **The pH of Bromday, according to the FDA-approved package**
07:02 **insert, is 8.3.**
MS. LEBEIS: Your Honor, I'm moving on to another document now and noting the time. Would it might be a good time to stop for the day?
THE COURT: All right, unless you wanted to go a
07:02 little bit more. But if this is a good time, then let's stop here.
MS. HOLLAND: All I would suggest, Your Honor, is that we -- I feel like we are a bit behind with witnesses in terms of timing, so, I guess, if it's -- if the Court is okay
07:02 with sitting a little longer today, it might make sense in

terms of just the overall schedule.
THE COURT: Well, why don't we go ten more minutes and try to make up some time.
MS. LEBEIS: Certainly, sure.
BY MS. LEBEIS:
Q. Dr. Trattler, would you please turn in your binder to JTX-023 and identify that document.
A. **Yes, this is the FDA-approved package insert for Prolensa.**
07:03 Q. Have you reviewed the FDA-approved package insert for Prolensa in connection with your opinions in this case?
A. **Yes, I have.**
Q. You said earlier that you've treated patients with Prolensa, correct?
07:03 A. **Yes, I have, I definitely have treated patients with Prolensa.**
Q. Let me direct your attention to the first page of the Prolensa package insert which bears Bates No. PROL 0080219 and in particular, to the section in the left column entitled
07:03 Indications and Usage.
According to the FDA-approved Prolensa package insert, what is the FDA-approved indication for Prolensa?
A. **So, Prolensa is a nonsteroidal anti-inflammatory drug indicated for the treatment of postoperative inflammation and**
07:03 **reduction of ocular pain in patients who have undergone**

cataract surgery.
Q. Let me direct your attention on the same page of the Prolensa package insert to the section entitled Dosage and Administration.
07:04 According to the Prolensa package insert, what is the FDA-approved dosage and administration for Prolensa?
A. **This says instill one drop into the affected eye once daily beginning one day prior to surgery, continued on the day of surgery and through the first 14 days postsurgery.**
07:04 Q. Let me now direct your attention to Page 3 of the Prolensa package insert, which bears Bates No. PROL 0080221, and in particular, to the section entitled Adverse Reactions.
How, if at all, does the adverse event section of the Prolensa package insert relate to your opinion that Prolensa
07:04 is not associated with the adverse events of burning and stinging?
A. **Yes. So this is the FDA-approved package insert for Prolensa and it lists in here the adverse reactions that occurred during the clinical trials, and you could see that it**
07:05 **does not list either burning or stinging as an adverse event in this package insert.**
Q. How, if at all, does the adverse event section of the Prolensa package insert comport with what you have observed in your practice?
07:05 A. **It is exactly what I've seen. It's a very comfortable**

drop. Patients are able to use it before and after cataract surgery as prescribed, and they do very, very well with it and I've had no patients report burning or stinging and I've never had to stop a patient from continuing on with the drop.

07:05 Q. Let me now direct your attention to Page 4 of the Prolensa package insert, which bears Bates No. PROL 0080222 and in particular, to the second paragraph on the page.

What is the pH of Prolensa?

A. According to the FDA-approved package insert, the pH of Prolensa is 7.8.

07:06 Q. How, if at all, does Prolensa's pH of 7.8 as compared to Xibrom and Bromday's pH of 8.3 contribute to the fact that Prolensa does not cause burning and stinging?

A. Probably the best -- when I think of the drops that we use for patients, you know, having a pH of the drop that's closer to our own -- patient's own natural pH seems to be more comfortable in general for patients, although that's not always the case.

Q. What is a patient's own natural pH?

07:06 A. The -- the average pH for a patient, patient tear is at 7.4.

Q. Prior to Prolensa, was a bromfenac-containing NSAID therapy available to treat inflammation and pain after cataract surgery without causing burning and stinging?

07:06 A. No.

Q. How, if at all, is the absence of burning and stinging from Prolensa as reflected in the package insert, a benefit to patients?

A. These are very critical benefit to patients. Patients have undergone cataract surgery and we want to have a good postoperative course and one of the keys is, we don't want our patients rubbing their eyes and that can happen if a patient is experiencing burning or stinging from a drop, and as well, we want them to be compliant with their medications because we know that inflammation needs to be knocked out by the -- by the anti-inflammatory drops.

If not, a patient will get -- will have worse vision just from blurred vision, from the inflammation not going away, and as well, they increase their risk for developing CME, which is a major risk with cataract surgery. So, you know, having a drop that's comfortable is very important for patients undergoing cataract surgery.

Q. How, if at all, does discontinuation of treatment with an NSAID after cataract surgery because of adverse events like burning and stinging impact patient outcomes?

A. It can be very challenging for patients, very difficult for patients because they would have prolonged inflammation and inflammation leads to -- you can get corneal swelling, you get reduced vision and again, you can have an increased risk for developing cystoid macular edema postoperatively.

Q. How, if at all, does burning and stinging impact patient compliance?

A. Well, patients, you know, have to use eye drops both before or after surgery. So if the drops burn and sting upon placement, patients may decide not to take the drop, and that can lead to, again, inability of the medication -- postoperative drops to knock out the inflammation. So poor compliance or noncompliance can lead to worse visual outcomes and increase risks for complication.

Q. Let's explore the basis for your opinion.

Would you please turn in your binder to JTX143 and identify that document.

A. This is a article written by Dr. Rajesh Rajpal and it's entitled: Bromfenac Ophthalmic Solution for the Treatment of Postoperative Ocular Pain and Inflammation, Safety, Efficacy and Patient Adherence.

Q. Have you reviewed JTX143 in connection with your opinions in this case?

A. Yes, I have.

Q. Do you regard this article as a reliable authority on the studies to which it refers and the conclusions to be drawn from them?

A. Yes.

Q. Let me direct your attention to Page 928 of JTX143, and in particular, to the right column and to the paragraph under

the heading Bromfenac Compliance and Adherence.

What do the first two sentences of this paragraph disclose?

A. So, the article states that cataract surgery is typically performed in an older population already known for poor medication compliance in other ophthalmic disorders. Commonly prescribed postsurgical ophthalmic medications with varying dosing schedules can be particularly troublesome for these patients to manage, especially if accompanied by stinging and/or burning upon installation.

Q. How, if at all, does this portion of JTX143 relate to your opinions regarding burning and stinging?

A. Well, this is very accurate. Patients who undergo cataract surgery will be placed on a few drops both before and after cataract surgery, including antibiotics and anti-inflammation drops with different dosing regimens and, you know, compliance can be an issue. These are older patients and we want them to use the drops, and if a drop is burning or stinging, they may be less likely to use that drop and that's been shown to be -- be a risk factor for noncompliance.

Q. What, if any, ophthalmic NSAID do you routinely prescribe to treat pain and inflammation following cataract surgery?

A. Currently, a typical nonsteroidal drop that we will use for our -- for my patients is Prolensa.

MS. LEBEIS: Your Honor, I think we've gone another ten minutes.

THE COURT: This is a good time to stop then.

Let's resume tomorrow morning at 9:30 a.m.

07:11 Is there any housekeeping that we need to attend to at this time?

MS. HOLLAND: No, Your Honor.

MS. LEBEIS: No, Your Honor.

THE COURT: Doctor, you may step down. I want to

07:11 take a peak at where we are on time, so that if we need to use Wednesday, which we already do for one witness, we can kind of map out how to use the next two days. Okay. You can be seated and we will take a moment to do this.

THE DEPUTY CLERK: 10.30 for the plaintiff and 7.50

07:12 for the defense.

MR. LIPSEY: I'm sorry, could you repeat that please.

THE DEPUTY CLERK: 10 hours and 30 minutes for the plaintiffs and 7 hours and 50 minutes for the defense.

THE COURT: Okay. And between Tuesday and Wednesday,

07:12 we have -- I'll say approximately 11 hours, figure five-and-a-half each day.

Now, you don't have to use all your time.

(Laughter.)

THE COURT: But what would your time budget be going

07:12 forward, or do you want to think about that overnight?

MS. HOLLAND: Your Honor, from defendant's perspective, we're happy to keep within the 13 hours that we had been originally allotted, and...

THE COURT: Okay.

07:13 MS. LEBEIS: Your Honor, if you wouldn't mind, we would like to think about it overnight and get back to Your Honor tomorrow regarding the rest of the time allotted.

THE COURT: Okay. Let's do that. Now, I'm not inviting, you know, that we fill Wednesday. We do have the

07:13 one witness. What was the doctor's name?

MR. MUKERJEE: Dr. Prausnitz, Your Honor.

THE COURT: How long will his testimony be Wednesday, do you know?

MR. MUKERJEE: I anticipate his direct will probably

07:13 be within the range of about one hour or two, max, maybe one hour, 15 minutes.

THE COURT: Okay. Well, maybe we're more or less on schedule except for that. That would be great. Okay.

Then if there's nothing else, let's adjourn for

07:14 tonight. Good night.

RESPONSE: Thank you, Your Honor.

(4:45 p.m.)

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V

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-667 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-4149 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

Mitchell H. Cohen United States Courthouse
One John F. Gerry Plaza
Camden, New Jersey 08101
Tuesday, April 12, 2016

B E F O R E: THE HONORABLE JEROME B. SIMANDLE
CHIEF JUDGE
UNITED STATES DISTRICT JUDGE

Certified as true and correct as required by Title 28, U.S.C., Section 753.
/S/ Lisa Marcus, CCR, CRR, /S/ Karen Friedlander, CCR, CRR,
/S/ Carol Farrell, CCR, CRR

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-5144 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-335 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-5144 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-335 (JBS/KMW)

-vs-

LUPIN LTD., LUPIN PHARMACEUTICALS, INC.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 14-6893 (JBS/KMW)

-vs-

INNOPHARMA LICENSING, INC., et al.,

Defendants.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., BAUSCH AND LOMB PHARMA HOLDINGS CORP.,

Plaintiff, CIVIL ACTION NUMBER: 15-3240 (JBS/KMW)

-vs-

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INDEX

EXHIBITS

THE DEPUTY CLERK: All rise.

(OPEN COURT, April 12, 2016, 9:33 a.m.)

THE COURT: Good morning, be seated, please.

RESPONSE: Good morning.

00:00 THE COURT: And are we ready to resume? Okay.

(**DR. TRATTLER,** HAVING BEEN PREVIOUSLY SWORN AS A WITNESS, TESTIFIED AS FOLLOWS:)

(DIRECT EXAMINATION OF DR. TRATTLER BY MS. LEBEIS)

Q. Good morning, Dr. Trattler.

00:00 **A. Good morning.**

Q. Prior to January 21st, 2003, were ophthalmic NSAID therapies available to treat pain and inflammation after cataract surgery?

A. Yes, they were.

00:00 Q. What, if any, diclofenac product was available to treat pain and inflammation after cataract surgery prior to January 21st, 2013?

A. Voltaren.

Q. Have you prescribed Voltaren?

00:00 **A. I have, yes.**

Q. What, if any, ketorolac product was available to treat pain and inflammation after cataract surgery prior to January 21st, 2003?

A. Acular, 0.5 percent.

00:01 Q. Have you prescribed Acular?

A. **Yes, I have.**
Q. Are diclofenac and ketorolac NSAIDs?
A. **They both are, yes.**
Q. How, if at all, are Acular and Voltaren limited by their side effects?
A. **So the challenge of those medications is they are -- they work as nonsteroidals, but they had a lot of side effects, and the main side effect they had was burning and stinging. With Acular, you know, in the 40 percent range of patients, which made it very difficult for some patients to use the product, even though it was -- it could help them, it was difficult for them to use it. And Voltaren also, about 15 percent of patients had burning and stinging with instillation. So again, there are some limitations for the patients.**
Q. Let's discuss the basis for your opinion. Would you please turn to JTX135 in your binder and identify that document?
A. **Yes. This is the FDA-approved package insert for Voltaren.**
Q. Did you review the FDA-approved package insert for Voltaren in connection with your opinions in this case?
A. **Yes, I did.**
Q. Let me direct your attention to Page 6 of the Voltaren package insert. And in particular, to the section entitled, Adverse Reaction, in the paragraph labeled Ocular.

How, if at all, does this portion of the Voltaren package insert relate to your opinion?
A. **We can see at the very beginning, it says: Transient burning and stinging were reported in approximately 15 percent of the patients across studies with the use of Voltaren ophthalmic.**
Q. How, if at all, does the adverse event section of the Voltaren package insert comport with what you have observed in your practice?
A. **Very similar. Again, Voltaren at the time was a very -- a nice, you know, an effective product at the time, but, you know, patients would experience burning that could impact their compliance and their ability to use their product.**
Q. Would you please turn to JTX051 in your binder and identify that document?
A. **051. Okay. Just make sure I get to the right one.**
Yes, so this is from the FDA's website. Basically, it's just information from the website about Voltaren.
Q. Did you review JTX051 in connection with your opinions in this case?
A. **Yes, I did.**
Q. When was Voltaren approved?
A. **It says the approval date was March 28th, 1991.**
Q. Could you now please turn to PTX-265 in your binder and identify that document?

A. **Yes. This is the FDA-approved package insert for Acular, 0 -- which is 0.5 percent.**
Q. Did you review the Acular package insert in connection with your opinions in this case?
A. **Yes, I did.**
Q. Let me direct your attention to Page 7 of the Acular package insert, and in particular, to the first paragraph of the section entitled, Adverse Reactions. How, if at all, does this portion of the Acular package insert relate to your opinion?
A. **We can see here it says: The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by up to 40 percent of patients participating in clinical trials.**
Q. How, if at all, does the adverse event section of the Acular package insert comport with what you have observed in your practice?
A. **We saw this -- you know, again, we really like ketorolac as a product, but, you know, the challenge was for patients, they would get this burning and stinging upon instillation, which really impacted their ability to use the product.**
Q. Could you now please turn to JTX052 in your binder and identify that document?
A. **Yes, this is a document from the FDA's website and it's**

on Acular.
Q. Did you review JTX052 in connection with your opinions in this case?
A. **Yes, I did.**
Q. When was Acular approved by the FDA?
A. **On November 9th, 1992.**
Q. I would now like to discuss in more detail Prolensa as compared to the other bromfenac-containing products, Xibrom and Bromday. Is it your understanding that Xibrom and Bromday contain a different surfactant than Prolensa?
A. **Yes.**
Q. What surfactant does Prolensa contain?
A. **Tyloxapol.**
Q. And what surfactant do Xibrom and Bromday contain?
A. **Polysorbate 80.**
Q. Let's discuss the pH of these products. Were you in the courtroom yesterday when Dr. Williams testified that the formulation of Prolensa with tyloxapol is allowed for Prolensa to be formulated at pH 7.8, as compared to the pH of 8.3 for Xibrom and Bromday containing polysorbate 80?
A. **Yes.**
Q. How, if at all, is the lower pH of Prolensa a benefit to patients?
A. **Well, having more physiologic pH has the potential benefit of being more comfortable for patients.**

Q. Have you had an opportunity to consider the opinions being offered by defendant's expert, Dr. Cykiert, in this case?

A. Yes, I have.

Q. Are you aware that Dr. Cykiert has taken the position that the lower pH of Prolensa has no impact on clinical safety or efficacy or patient comfort and confers no clinical benefits over Xibrom and Bromday?

A. Yes, I'm aware of his opinions.

Q. Do you agree with Dr. Cykiert?

A. I disagree.

Q. Why do you disagree with Dr. Cykiert?

A. I disagree because, you know, when we use Prolensa, patients -- you know, patients who use it feel that it is a very comfortable drop, that it works well, and they don't experience the burning and stinging that they can experience with the previous generation with Xibrom or Bromday. So there's quite a difference.

Q. How, if at all, is the pH of Prolensa closer to the pH of natural tears?

A. So the typical pH for natural tears is 7.4 and Prolensa is 7.8. So it's much closer to the physiologic pH of tears.

Q. Have you also had an opportunity to consider the opinions being offered by defendant's expert, Dr. Prausnitz, in this case?

A. Yes, I have.

Q. Does Dr. Prausnitz share Dr. Cykiert's opinion, that lower pH has no impact on clinical safety and efficacy?

A. He does not.

Q. What is your understanding of Dr. Prausnitz's view of pH on clinical safety and efficacy?

A. It's my understanding that Dr. Prausnitz agrees that having a more physiologic pH can be, can be beneficial to comfort, and to overall efficacy of a product.

Q. How, if at all, does Dr. Prausnitz's opinion relate to your opinion regarding the clinical benefits of Prolensa's pH?

A. They are similar.

Q. Let's now discuss the amount of active ingredient. Were you in the courtroom yesterday when Dr. Williams testified that the formulation of Prolensa with tyloxapol has allowed for lowering Prolensa's bromfenac concentration to .07 percent compared to .09 percent bromfenac in Xibrom and Bromday?

A. Yes.

Q. How, if at all, is lowering the concentration of bromfenac a benefit to patients?

A. Well, it helps because the active ingredients can have toxicity, and having a lower concentration of the active ingredients while still maintaining similar efficacy is beneficial.

Q. Let's explore the basis for your opinion. Would you

please turn to JTX018 in your binder and identify that document?

A. Yes. This is an article by George Baklayan, is entitled, "The Ocular Distribution of C 14 Labeled Bromfenac Ophthalmic Solution 0.07 Percent in a Rabbit Model."

Q. Have you reviewed JTX018 in connection with your opinions in this case?

A. Yes, I have.

Q. Do you regard this article as a reliable authority on the studies to which it refers and the conclusions to be drawn from them?

A. Yes.

Q. Let me direct your attention to Page 1718 in JTX018, which bears Bates number PROL 0080506.

A. Okay. Yes.

Q. And in particular to the left-hand column at -- around Line 16, to the sentence beginning with Prolensa. What does this passage in JTX018 disclose?

A. It says: Prolensa was reformulated from bromfenac 0.09 percent, in parenthesis, Bromday, Bausch & Lomb, close parentheses, to achieve similar occular bioavailability with a lower concentration of active drug, thereby ensuring similar clinical efficacy to Bromday but with reduced exposure of the surgically-compromised ocular surface to the drug.

Q. Let me also direct your attention to Page 1722 in JTX018,

which bears Bates number PROL 0080510. And in particular, to the right-hand column, about three lines down, to the sentence beginning with, Even, what does this sentence in JTX018 disclose?

A. It says: Even at a lower concentration, the bromfenac 0.07 percent pH 7.8 solution exhibited similar, in the case of scleral tissue, increased penetration of ocular tissues studied, when compared with bromfenac 0.09 percent pH 8.3 solution.

Q. Would you also read the sentence just below that to the record?

A. This is likely due to the difference in pH between the solutions; lowering the -- lowering the pH increases the unionized fraction of drugs, which can lead to enhanced corneal permeability.

Q. How, if at all, do these passages in JTX018 relate to your opinions regarding Prolensa?

A. All right. The key is that despite Prolensa having a lower concentration of active ingredient, it has similar penetration into the eye. So it has a clinical efficacy for patients undergoing cataract surgery.

Q. Are you aware that Dr. Prausnitz has taken the position that lowering the pH from 8.3 to 7.8 could cause increased ocular penetration?

A. Yes.

Q. How, if at all, is Dr. Prausnitz's opinion consistent with your opinion?
A. His opinion is consistent with my opinion and is supported by this article and study.
Q. Let's now discuss the adverse event profiles. Are you aware that Dr. Cykiert has taken the position that Prolensa is clinically indistinguishable in its safety profile from Xibrom and Bromday?
A. Yes, I'm aware of his opinion.
Q. Do you agree with Dr. Cykiert?
A. I do not.
Q. Why do you disagree?
A. I disagree because, you know, I've had the opportunity to use both Xibrom and Bromday, and it works well, but patients can experience burning and stinging, which can impact their compliance. Having used Prolensa, patients find it very comfortable. I have not had a single patient, you know, complain to me that they've experienced burning or stinging, and none have had to stop the use of the medication, you know, in and around cataract surgery.
Q. Does Prolensa differ in its safety profile from Xibrom and Bromday based on their package inserts?
A. Yes.
Q. Are you aware that Dr. Cykiert has taken the position that burning and stinging caused by a drug product do not

impact the prescribing habits of ophthalmologists?
A. I'm aware of his opinion, yes.
Q. Do you agree with Dr. Cykiert?
A. I completely disagree with his opinion.
Q. And why do you disagree?
A. Because, you know, every single patient that comes to us for cataract surgery is expecting to get -- not only see well but have a good postoperative experience. And if they experience burning and stinging from the use of a medication, it makes their experience worse. It can lead to noncompliance and just a less happy patient.
So, you know, we have a lot of responsibility for every single patient that comes to us for surgery, and so it's really important that if we have an opportunity to use a product that doesn't cause burning and stinging, that's efficacious, it's very beneficial to patients.
Q. Are you also aware that Dr. Cykiert has taken the position that because certain patients will always experience burning and stinging, ophthalmologists do not consider whether formulation causes burning and stinging when prescribing ophthalmic NSAIDs?
A. I'm aware of his opinion, yes.
Q. Do you agree with Dr. Cykiert?
A. I disagree.
Q. Why do you disagree?

A. I disagree. He's talking about a rare patient that's not the typical patient that we'll see in our practice. I'm sure there are patients out there like that, but even knowing that, since -- first of all, since all patients undergoing cataract surgery, we want them to use the medication and have a comfortable experience, we want to use a product that is comfortable for patients. And if there was that theoretical rare patient having a product that was less likely to cause burning or stinging would be beneficial versus one that wouldn't be more likely to cause burning or stinging.
Q. How, if at all, do ophthalmologists consider burning and stinging caused by a drug product when making prescribing decisions?
A. We consider it because it's part of the patient experience. With cataract surgery, they are coming to us and they expect to have, you know, a positive experience. They want to see better, but they also -- to see better, it requires their use of a medication -- medications postoperatively, and having drugs that are comfortable is just critical to a positive experience, as well as getting good postoperative outcomes.
Q. Are you aware that defendants are taking the position that because there are no head-to-head clinical trial data comparing Prolensa to Xibrom or Bromday, no comparison can be drawn across these products regarding burning and stinging?

A. Yes, I'm aware.
Q. Do you agree with defendants that no comparison can be drawn between Prolensa and Xibrom or Bromday?
A. I disagree.
Q. Why do you disagree?
A. I disagree for a few reasons. No. 1, the FDA, you know, evaluates clinical trial results, and then develops a package, you know, an FDA-approved package insert for us to -- for us as clinicians to evaluate, to understand what potential adverse events a product may cause patients, so we can advise them.
And, you know, when you compare the different NSAID formulations, you know, it's pretty obvious that there are differences both in the package insert but also clinically and how we take care of patients. So postoperatively, patients that there -- you know, we can see the difference postoperatively as well, you know, in how patients, you know, feel about the different medications.
Q. If you would please turn back in your binder now to JTX023, which is the FDA-approved package insert for Prolensa. Let me draw your attention to Page 6, which bears Bates number PROL 0080221, and in particular, to the first paragraph under Adverse Reactions. What does this portion of the Prolensa package insert disclose?
A. This -- this is in the package insert, FDA-approved

package insert, and it says: Clinical trial experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Q. How, if at all, does this portion of the Prolensa package insert relate to your opinions regarding adverse event profiles?

A. I agree with the FDA's statement here. There certainly can be -- you know, each study is performed under different -- slightly different conditions and so there can be differences. But overall, the FDA package inserts, you know, gives us the information on what to expect, but also, you know, from clinical experience, I'm able to also determine how the package insert compares from one product to another.

Q. And in light of this statement, how, if at all, do physicians compare the adverse event profiles of different drug products, such as Prolensa on the one hand and Xibrom or Bromday on the other hand?

A. They compare in two ways. One, they'll look at the FDA package insert upon approval or if they're going to prescribe the medication, and they can see what adverse events are reported. And then if they choose to use the product, they have the clinical experience with the product and they talk to

patients and can find out how well it works and what the adverse events are.

Q. Now let's discuss why Prolensa is prescribed. Are you aware that Dr. Cykiert has taken the position that persistent clinically-verified cystoid macular edema is the only clinically-verified reason to prescribe ophthalmic NSAIDs like Prolensa?

A. Yes, I'm aware of his opinion.

Q. Do you agree with Dr. Cykiert?

A. I disagree.

Q. Why do you disagree?

A. Well, I disagree for the fact that Prolensa is FDA approved for cataract surgery for -- for reduction in inflammation and also reduction in pain with cataract surgery. So it's -- there's no -- it's not indicated and not approved for treatment of CME. It can work. My experience is that it does work for that, but it's not approved for that, and so we use it during -- in and around cataract surgery for what it is FDA approved for, which is pain and inflammation.

Q. How, if at all, does the treatment of inflammation after cataract surgery with an NSAID like Prolensa prevent the development of CME?

A. All right. As you may recall from the surgical video I showed yesterday, we're doing surgery, we're, you know, making incisions in the eye, there is ultrasound energy that is used

to break up the cataract, so inflammation is released. And it's really important to use anti-inflammatory medications to suppress the inflammation to help patients experience good vision postoperatively but also prevent the development of cystoid macular edema, you know, postoperatively.

Q. Let's explore the basis for your opinion. Would you please turn to PTX-270 in your binder and identify that document?

A. Yes. This is an article by Dr. Allan Flach, and is entitled, The Incidence, Pathogenesis and Treatment of Cystoid Macular Edema Following Cataract Surgery.

Q. Have you reviewed PTX-270 in connection with your opinions in this case?

A. Yes, I have.

Q. Let me direct your attention to Page 568 of PTX-270, and in particular, to the second paragraph, under the heading, Pathogenesis. What does the first sentence of this paragraph disclose?

A. Okay. It says that: Most investigators agree that inflammation is the major -- major etiologic factor in the development of CME following cataract surgery.

Q. Going down a little bit in the paragraph, what does the fourth sentence of this paragraph in PTX-270, starting with Clinical descriptions disclose?

A. It says: Clinical descriptions of patients with CME

following cataract surgery suggest that inflammation is an important factor.

Q. How, if at all, does this passage in PTX-270 relate to your opinion that effective treatment of inflammation following cataract surgery can avoid complications such as CME?

A. Right. This article supports the finding that inflammation is the -- leads to the development of cystoid macular edema, if not treated, so being proactive in treating it -- treating inflammation in and around the time of cataract surgery will lower the incidence or risk for a patient developing CME.

Q. Would you please turn to JTX146 in your binder and identify that document?

A. Yes. This is an article, a peer-reviewed article by Dr. Steven Silverstein, and the article is entitled, The Efficacy of Bromfenac Ophthalmic Solution 0.07 Percent Dosed Once Daily in Achieving Zero-to-Trace Anterior Chamber Cell Severity Following Cataract Surgery.

Q. Have you reviewed JTX146 in connection with your opinions in this case?

A. Yes, I have.

Q. Do you regard this article as a reliable authority on the study to which it refers and the conclusions to be drawn from them?

A. **Yes.**
Q. Let me direct your attention to Page 966 of JTX146, and in particular, to the first paragraph in the left-hand column. What does the last sentence of this paragraph disclose?
00:21 A. **The article says: The management of postoperative inflammation is essential, both to ensure rapid recovery following surgery, as well as to prevent or decrease the potential for long-term complications, such as cystoid macular edema.**
00:22 Q. How, if at all, does this passage relate to your opinion that effective treatment of inflammation can avoid complications such as CME?
A. **It is exactly how I feel when I treat my patients. Every patient who is coming in for cataract surgery has an**
00:22 **expectation that they're going to see better after surgery and won't experience a complication. So there's always risk with surgery, so effectively suppressing inflammation in and around the time of cataract surgery with anti-inflammatory medications is critical to a good postoperative experience and**
00:22 **visual result, as well as preventing or reducing the risk for developing CME.**
Q. Can you now please turn to PTX-281 in your binder and identify that document?
A. **Yes. This is an article by Stephen Kim entitled, Topical**
00:23 **Nonsteroidal Anti-Inflammatory Drugs and Cataract Surgery.**

Q. Have you reviewed PTX-281 in connection with your opinions in this case?
A. **Yes, I have.**
Q. Are you aware that Dr. Cykiert has cited PTX-281 and
00:23 taken the position that no evidence supports the practice of administering ophthalmic NSAIDs prophylactically to prevent CME?
A. **I'm aware of his opinion, yes.**
Q. Do you agree with Dr. Cykiert's characterization of
00:23 PTX-281?
A. **I disagree.**
Q. Let's explore the basis for your disagreement. Let me direct your attention to Page 2167 of PTX-281. And in particular, to the left-hand column in the second paragraph
00:23 and the sentence starting, Although long-term.
What does this sentence of PTX-281 disclose?
A. **Okay. So this says: Although long-term visual acuity greater than three months after cataract surgery is an important clinical measure of a therapeutic intervention, this**
00:23 **assessment was not designed to comment on the rationale and potential value of NSAID therapy in preventing CME soon after surgery and the patient's satisfaction and quality of life improvement associated with more rapid visual rehabilitation.**
Q. Does this portion of PTX-281 reflect long-term or
00:24 short-term outcomes after cataract surgery?

A. **All right. So the -- this article was focused on the long-term outcomes, three months or greater, not short-term.**
Q. How, if at all, are short-term outcomes important after cataract surgery?
00:24 A. **They are critical. We are performing surgery on patients. They have expectation that they're getting improvement in their vision, and their vision will typically start to improve after vision -- after surgery. But if two weeks after surgery they've had improvement and all of a**
00:24 **sudden their vision starts to worsen, it really impacts their happiness and their ability to function.**
MS. HOLLAND: Your Honor, I have an objection to that last question and answer, is outside of the scope of the expert reports.
00:25 THE COURT: Okay. Was -- did the expert comment on the Kim article and his expert report?
MS. LEBEIS: Yes, he did, and I can direct you to the paragraphs.
MS. HOLLAND: I'm not -- I don't have a problem with
00:25 the Kim article and the rest of the testimony he's given on it. It's only his explanation about the difference between short-term and long-term benefits. That's a new opinion.
MS. LEBEIS: I believe that the expert quoted this exact portion of the Kim article in his expert reports.
00:25 MS. HOLLAND: Would you mind just giving me a cite so

maybe I can withdraw the objection.
MS. LEBEIS: Sure. Yes. It will be in the Trattler reply report at paragraph 12 and paragraph 22.
MS. HOLLAND: It's not there exactly, but I'll let it
00:26 go, Your Honor, I'll withdraw the objection.
THE COURT: Okay. Very well, the objection is withdrawn.
MS. LEBEIS: Thank you.
BY MS. LEBEIS:
00:26 Q. Let me now direct your attention to Page 2159 of PTX-281, and in particular, to the first sentence in the section entitled, Results. What does this sentence of PTX-281 disclose?
A. **It states: Nonsteroidal anti-inflammatory drug therapy**
00:26 **was effective in reducing CME detected by angiography or optical coherence tomography, in parentheses OCT, close parentheses, and may increase the speed of visual recovery after surgery when compared directly with placebo or topical corticosteroid formulations with limited intraocular**
00:27 **penetration.**
Q. And what does this portion of PTX-281 reflect?
A. **Well, this reflects our experience, that nonsteroidals are effective in reducing CME postoperatively, which is exactly what this says.**
00:27 Q. And how, if at all, is restoration of vision soon after

surgery an important benefit to patients?
A. I mean, it's critical. They're coming to us because they can't see. They're having difficult with their activities of daily living of seeing and functioning, and if -- and the surgery should provide them excellent postoperative vision, so if they develop a serious complication like CME that reduces their vision, it really is very impactful in a negative way to the patient overall.
Q. Are you aware that defendants have taken the position that CME is a less serious complication that usually resolves without the need for treatment in most patients?
A. I'm aware of that opinion.
Q. Do you agree with defendants?
A. I completely disagree with that opinion.
Q. Okay. And why do you disagree?
A. I disagree because in -- in the occasional situation when a patient does experience or develop CME, we don't just watch them and hope they get better. We actually immediately initiate therapy with various anti-inflammatory medications, because studies have shown that anti-inflammatory therapies do help improve vision in patients with CME. So we immediately initiate treatment in patients that have vision loss from CME. We don't just hope it may get better.
Q. Let me direct your attention back to PTX-281, to Page 2159. And in particular, to the second sentence under the

heading, Background, in the right-hand column. What does this sentence in PTX-281 disclose?
A. It states: Development of CME after cataract surgery is the most common cause of visual impairment.
Q. And how, if at all, does this passage in PTX-281 support your opinion that CME is a serious complication?
A. Right. Again, we're performing cataract surgery and we want patients to have an excellent postoperative visual result, and the most common postoperative complication that impacts vision, as stated here, is CME. And it is preventible or -- and the risk can be reduced with treatment.
Q. I'd now like to discuss the medical community's acclaim for Prolensa.
What, if anything, have leaders in the field of cataract surgery publicly stated about Prolensa compared to existing therapies?
A. I mean, I think that in general the experience has been very positive with the introduction of Prolensa® for patient care after cataract surgery, it's been a very positive experience for the product.
Q. Let's discuss the basis for your opinion.
Have you prepared demonstratives to assist the Court with your testimony?
A. Yes, I have.
Q. Let's pull up PDX5-3 on the screen.

What does PDX5-3 illustrate?
A. This is from Dr. Thomas Walters' article on Bromfenac Ophthalmic Solution 0.07 percent Dosed Once Daily for Cataract Surgery.
Q. What does Dr. Walters conclude?
A. The advance formulation of bromfenac with a lower concentration of active ingredient has a similar efficacy profile as higher concentrations of bromfenac previously approved by the FDA in the United States and safety profile with consistently lower incidence rates than those seen in the placebo group.
Q. If you could please turn to JTX142 in your binder.
Is JTX142 the document cited on PDX5-3 we just discussed?
A. Yes, it is.
Q. Have you reviewed JTX142 in connection with your opinions in this case?
A. Yes, I have.
Q. Do you regard this article as a reliable authority on the studies to which it refers and the conclusions to be drawn from them?
A. Yes.
Q. Okay. Let's now pull up PDX5-4 on the screen.
What does PDX5-4 illustrate?
A. This is the article by Dr. Steven Silverstein entitled

The Efficacy of Bromfenac Ophthalmic Solution 0.07 percent dosed once daily in achieving zero to trace anterior chamber cell severity following cataract surgery.
Q. What does Dr. Silverstein conclude regarding Prolensa®?
A. The data show that once-daily dosing -- sorry. I just did conclusion.
The bromfenac ophthalmic solution 0.07 percent dosed once-daily was clinically effective in achieving zero-to-trace anterior chamber cell severity after cataract surgery and was superior to placebo in all anterior chamber cell severity and inflammation outcome measures.
Q. At the bottom of the slide how did Dr. Silverstein describe Prolensa®?
A. He described as: The data show that once-daily dosing with Prolensa® provides powerful and rapid control of inflammation and pain following cataract surgery, confirming the potency of this NSAID and benefits of the new formulations, said Steven M. Silverstein, M.D., FACS, founder of Silverstein Eye Centers in Kansas City, Missouri. Prolensa® reduces the amount of medication placed on the healing eye while maintaining a high degree of efficacy and ocular comfort.
Q. Please turn back to JTX146 in your binder.
Is JTX146 the first document cited on PDX5-4 we just discussed?

A. Yes, it is.
Q. If you could please now turn to JTX145 in your binder.
Is JTX145 the second document cited on PDX5-4 we just discussed?
00:33 **A. Yes.**
Q. Have you reviewed JTX145 in connection with your opinions in this case?
A. Yes, I have.
Q. Now, let's pull up PDX5-5 on the screen.
00:33 What does PDX5-5 illustrate?
A. This is an article by Rajesh Rajpal entitled Bromfenac Ophthalmic Solution for the Treatment of Post-Operative Ocular Pain and Inflammation: Safety, Efficacy, and Patient Adherence.
00:33 Q. What did Dr. Rajpal conclude regarding Prolensa®?
A. He wrote: The lower concentration of bromfenac, 0.07 percent, combined with once-daily dosing may help further improve patient adherence and compliance.
Q. If you could please turn back to JTX143 in your binder.
00:34 Is JTX143 the document cited on PDX5-5 we just discussed?
A. Yes.
Q. Are you aware that Dr. Cykiert has taken the position that the articles you just discussed in support of the medical
00:34 community's opinion regarding Prolensa® are entitled to little

weight because of the author's consulting or editorial arrangements with Bausch & Lomb?
A. I understand his opinion.
Q. Do you agree with Dr. Cykiert?
00:34 **A. I disagree.**
Q. Why do you disagree?
A. Well, these articles are providing data from FDA conducted clinical trials, they're double-mass placebo controlled clinical trials and they provide the results from
00:34 **these clinical trials, and the information provided in these articles are very reliable.**
Q. In your experience in the clinical trials in which you have been involved, how, if at all, does company sponsorship of independent clinical trials influence the results reported
00:35 in peer reviewed journal articles such as the ones we have discussed?
A. They do not have -- clinical trials are expensive to run and the support helps the clinical trials run. But the studies, if they're mass and double-blind, we have no idea
00:35 **what the results will be. And once we get the results, we'll then provide the results.**
Q. Just to sum up, Dr. Trattler, is it your opinion that Prolensa provides meaningful benefits to the patients that you treat?
00:36 **A. No question, yes.**

Q. Why is that?
A. My patients who are coming to see me for cataract surgery have very high expectations, it's a real surgery with real risks, and so having a product like Prolensa® that can help
00:36 **suppress inflammation and reduce pain after surgery is very beneficial to my patients, providing a better outcome, visual outcome and reducing the chance -- reducing the amount of inflammation.**
MS. LEBIS: I have no further questions, your Honor.
00:36 THE COURT: Okay. Thank you very much.
MS. LEBIS: I'd like to move into evidence a list of exhibits. I can list them off right now.
THE COURT: Okay. Could you state the exhibit numbers?
00:36 MS. LEBIS: Sure. PTX-164, PTX-277, JTX144, PTX-PTX-40074, JTX023, JTX143, JTX135, JTX051, PTX-265, JTX052, JTX018, PTX-270, JTX146, PTX-281, JTX142, and JTX145.
THE COURT: Ms. Holland, do you need some time to review those?
00:37 MS. HOLLAND: I do, your Honor. And, in any event, I believe we're going to have to talk about the exhibits that I moved into evidence or we have to talk about the exhibits I would like to move into evidence based on the cross-examination of Dr. Williams yesterday, so maybe we can
00:37 handle all the exhibit issues at once.

THE COURT: Okay. We'll reserve on the admissibility of the list that's just been read.
Do you want to take up the Dr. Williams cross exhibits at this time?
00:38 MS. HOLLAND: No, I don't want to keep Dr. Trattler on the stand for that, so we can do it afterwards.
THE COURT: It won't take that long.
MS. HOLLAND: It might, your Honor. Unfortunately, it might be a bit of argument about it.
00:38 THE COURT: Okay. We'll do that when there's no witness on the stand.
MS. HOLLAND: Okay.
(CROSS-EXAMINATION OF WILLIAM B. TRATTLER BY MS. HOLLAND:)
Q. Good morning, Dr. Trattler.
00:38 **A. Good morning.**
Q. In your direct examination you discussed incidence rates for burning and stinging for Bronuck®, Xibrom®, Bromday® and Prolensa®, correct?
A. Yes.
00:38 Q. All right. And you just agreed in your direct examination that there never have been any head-to-head clinical trials comparing Prolensa® with Bronuck®, Xibrom®, or Bromday®, correct?
A. Yes.
00:38 Q. So there is no data directly comparing the incidence of

burning and stinging among those products, right?
A. Well, there's no head-to-head clinical trials, but we have our information from using the medications on patients so we have our personal clinical experience using those products.
00:39 **And we also have the information from the product, FDA product label on the differences between the two.**
Q. All right. But there is no clinical data you can point to that shows a direct head-to-head comparison that Prolensa® has less burning and stinging than Bronuck®, Xibrom®, or
00:39 Bromday®, right?
A. We don't have any clinical studies, but we have our experience, which is there is a difference and it matches --
Q. You haven't --
A. -- the FDA --
00:39 Q. Okay. Go ahead. I'm sorry. I don't want to interrupt.
MS. LEBIS: Let him finish the answer.
THE WITNESS: It matches what we see on the FDA product -- FDA approved product package insert.
BY MS. HOLLAND:
00:39 Q. Well, let's -- I'd actually like to talk about those product inserts.
In your direct examination you presented information from the inserts for Bronuck®, which is a Japanese product, obviously, and Xibrom®, Bromday®, and Prolensa®, right?
00:40 **A. Yes.**

Q. I'd like to drill down a little bit more on those numbers that you put on the screen. Let's start with Bronuck® and let's go to PTX-277.
This is the exhibit you used as the package insert for
00:40 Bronuck®, correct?
A. Yes.
Q. Okay. And you pointed to the box in the upper right-hand corner of the page that says "ocular" and then -- yeah. No, upper right-hand corner that says "ocular" and then there's a
00:40 box that says .01 percent less than 5 percent. That's what you pointed to in your direct examination, right?
A. Yes.
Q. All right. So I'd like to look at the beginning of the Adverse Events section, the section right before that box that
00:41 you pointed to. And it gives a little more granular information on the adverse events, right?
A. Yes.
Q. All right. So let's look at the particular adverse events you've been talking about, which is burning and
00:41 stinging. Okay?
A. Yes.
Q. So in the Bronuck® package insert it says that there were three cases of stinging reported and that would be a rate of .71 percent, right?
00:41 **A. Yes.**

Q. And there was one case of burning reported and that is an incidence rate of .24 percent, right?
A. Yes.
Q. All right. Let's move on to Xibrom® then. Let's go to
00:41 JTX144.
This is the Xibrom® prescribing information that you talked about in your direct testimony, right?
A. Yes.
Q. And let's go to Section 6.1 on Page 3 of 7, and it's PROL
00:42 0080488.
And you pointed to the adverse reaction section on that page, right?
A. Yes.
Q. And you pointed out that there was a list of various
00:42 adverse events, including what's denoted here as eye irritation (including burning/stinging), right?
A. Yes.
Q. And then you said that there was an adverse reaction rate of 2 to 7 percent, right?
00:42 **A. That's correct.**
Q. All right. Now, you cannot tell from this package insert what the specific incidence rate was for burning and stinging, right?
A. That is between 2 and 7 percent.
00:42 Q. That's all you can tell from the package insert, right?

A. Yes.
Q. All right. Now, the adverse event information in the package insert was taken from clinical trials of Xibrom®, right?
00:43 **A. Yes.**
Q. And those trials were reported in a paper with the lead author Donnenfeld, right?
A. I believe so, yes.
Q. All right. So let's look at that paper. I think I'm
00:43 going to need to hand it out, we tried not to use cross-binders just to save some trees.
THE COURT: And some hydrocarbons to the extent binders are made of plastic.
So you've handed DTX-210.
00:43 MS. HOLLAND: Yes, your Honor.
BY MS. HOLLAND:
Q. So let's look at DTX-210 now.
Is this the Donnenfeld paper that reports on the Phase III clinical trials of Xibrom®?
00:44 **A. Yes.**
Q. Let's start out by looking at the Results section on the first page. It's in the abstract. Do you see that?
A. Yes.
Q. And I would like to point your attention to two lines up
00:44 from the bottom with the sentence beginning eye irration. Do

you see that?
A. **Yes.**
Q. It says, eye irritation was reported in a lower percentage of subjects for bromfenac versus placebo, as were
00:44 burning and stinging. And then it gives the incidence rate of burning and stinging as 1.4 percent. Do you see that?
A. **Yes.**
Q. Okay. Then I would like to -- now I'd like to turn your attention to Page 1650 in the reference. I'm sorry, I gave
00:45 you the wrong page number. It's Page 1659, I'm sorry, under the paragraph that says "Safety." Do you see that paragraph?
A. **Yes.**
Q. Okay. And it says Ocular Adverse Events. Do you see that?
00:45 A. **Yes.**
Q. About five lines down there's a -- it says eye irritation. Do you see that?
A. **Yes.**
Q. It says 2.5 percent. Do you see that?
00:45 A. **I do, yes.**
Q. All right. I'd like you to go a little further down in that paragraph, there's a sentence four lines up from the bottom that says, it's starts with the word "furthermore" and it says, furthermore, if the burning and stinging were
00:45 separated, the proportion of the bromfenac group was

1.4 percent. Do you see that?
A. **Yes, I do.**
Q. So apparently based on the Donnenfeld results, the only reason burning and stinging were included in this Xibrom®
00:46 label is because they were included within a broader category of eye irritation, right?
A. **Well, they're included, but there're also patients that experienced burning and stinging from clinical trials and they do experience it -- they can experience it potentially**
00:46 **clinically.**
Q. But it didn't meet that 2 percent threshold that we saw on the label, right?
A. **Correct, it reports here that for this particular study it was 1.4 percent.**
00:46 Q. Right. I'd like to now move on to Bromday®. Can we turn to PTX-474. And PTX-474 was the package insert that you used for your testimony about Bromday®, right?
A. **Yes.**
Q. Let's go to Page 3 of 5, it has the Bates number PROL
00:47 0080495. And under the Adverse Reaction section, we see something very similar to the Xibrom® label, right?
A. **Yes.**
Q. It has burning and stinging included within the larger category of eye irritation, right?
00:47 A. **Yes.**

Q. And it says in general that the adverse events were reported in 2-7 percent of patients, right?
A. **Correct.**
Q. From the label itself or the package insert itself, you
00:47 can't tell what percentage of patients experienced burning and stinging, right?
A. **From this label between 2 and 7 -- in the range of 2 to 7 percent was reported on the package insert.**
Q. And again, the data that's -- let me withdraw that.
00:48 I should say the statement that is here in the Adverse Reaction section is, again, taken from clinical trial data, right?
A. **Yes.**
Q. And the results of the Phase III clinical trials for
00:48 Bromday® were reported in a paper by Henderson, right?
A. **I'd like to see that.**
Q. Sure.
A. **Yeah.**
Q. DTX-215. I'm going to hand that one out as well.
00:48 Do you have that in front of you now, Doctor?
A. **Yes, I do.**
Q. Have you had a chance to look at it?
A. **Yes.**
Q. And is that indeed the results of the clinical trial for
00:49 Bromday®?

A. **Yes.**
Q. Okay. Let's go to Page 215.7. I apologize for that, I'm sorry, I just wanted to make sure I pointed you to the right place in the handout.
00:50 This document talks about the various adverse events that occurred in this trial for Bromday®, correct?
A. **It includes that, yes.**
Q. And if you look at Page 215.6, right above Figure 4, four lines above that you'll see a statement that begins "In the
00:50 clinical trials." Do you see that? It says, in the clinical trials of Bronuck®, .09 percent dose twice-daily, it give you the most frequent AE's there, right?
A. **Yes.**
Q. And then the next page says -- before I ask you that, so
00:51 that's the -- those are the adverse events that were reported for Xibrom®, which is what we just looked at in the Donnenfeld paper, right, .09 percent dose twice-daily?
A. **Yes.**
Q. So what it's saying here is that it's reporting what the
00:51 adverse events were in the clinical trial for Xibrom®. And again, we see what we saw earlier, eye irritation, which includes burning and stinging. Do you see that?
A. **Yes.**
Q. Then the next sentence says, the AE's reported with
00:51 Bronuck® .09 percent dose once-daily in these four clinical

trials were comparable. Do you see that?
A. Yes.
Q. Okay. So that means the adverse events for Bromday® were comparable to Xibrom®, right?
00:52 **A. Yes.**
Q. As we saw for Xibrom®, the percentage of burning and stinging was 1.4 percent, right?
A. Yes.
Q. And again, burning and stinging was a subset eye
00:52 irritation on the package insert, right?
A. Correct. Well, it was listed as -- you know, in parentheses on the package insert.
Q. All right. Now, let's talk about Prolensa®. And I'd like to go to JTX23.
00:52 This is the Prolensa® prescribing information you talked about in your direct examination, right?
A. Yes.
Q. Let's go to the Adverse Reaction Section 6.1 on JTX23.3. And I'm going to -- I'd like to look at the second paragraph
00:52 where it says "the most commonly reported adverse events." Do you see that?
A. Yes.
Q. This is a section of the package insert you pointed to on your direct, right?
00:53 **A. Correct.**

Q. And I believe you based your opinion that Prolensa® has no burning or stinging associated with it from the fact that burning and stinging is not listed in this section, right?
A. Correct.
00:53 Q. And, as you can see, however, this section includes only those adverse events that occurred in 3 percent or more of patients, right?
A. Yes. This was asked of me at my deposition.
Q. Is the answer yes?
00:53 **A. Yes.**
Q. Okay. And, as we saw from Bronuck® and Xibrom®, burning and stinging occurred for those products at a rate well below 3 percent, right?
A. For those products, yes.
00:53 Q. Okay. So Bronuck® was less than 1 percent and Xibrom® was 1.94 percent, right?
A. Xibrom® was 1.4 percent.
Q. So you can't actually tell from the Prolensa® prescribing information whether burning and stinging were reported for
00:54 that product at a similar rate for what was reported for Bronuck® and Xibrom®, right?
A. Yes. This question was asked of me at my deposition --
Q. I just wanted to know the answer. Is that correct?
A. I would like to complete my answer.
00:54 **So the answer was this one question was asked of me at**

my deposition. So following my deposition I actually looked at the clinical trial data to determine the exact incidence of burning and stinging.
MS. HOLLAND: I'm going to move to strike that
00:54 testimony, your Honor. My -- whatever -- if it's appropriate on redirect, and I'm not sure it is, to bring in a new opinion. I just asked simply whether you can tell from the label, the only testimony that went in on direct was what was in the label. And I'd like to know, based on the label, you
00:54 can make those comparisons.
THE COURT: All right. That's the pending question. So please answer that question.
THE WITNESS: Could you just repeat the question one more time, please, so I can make sure I answer properly?
THE COURT: Would you like it read back?
MS. HOLLAND: Pardon?
THE COURT: Would you like it read back?
MS. HOLLAND: Yeah, maybe that's the best thing.
(Designated question is read back.)
00:55 THE WITNESS: Well, the FDA included burning and stinging on the label in Xibrom® and Bromday® and they chose not to include it in this FDA package insert, so the assumption is that it's insignificant to the FDA, which is why they did not include it.
BY MS. HOLLAND:

Q. That wasn't my question, so let me try again.
A. All right.
Q. I'd like to know, looking at the Prolensa® label can you tell for sure whether or not the rate of burning and stinging
00:55 in the Prolensa® clinical trial was any different from the 1.4 percent or the less than 1.4 percent we saw with Xibrom® and Bronuck®?
A. Well, the FDA product insert says the risks of burning and stinging was between 2 to 7 percent in Xibrom® and
00:56 **Bromday® and Xibrom® -- in Bromday® package insert. So my assumption would be based on the package insert, that it was 2 percent or higher. So you're asking a question about the percents in the FDA package insert is between 2 and 7 percent that it looked at -- that it mentioned in the package insert.**
00:56 Q. Well, the package insert for Prolensa® doesn't have 2 to 7 percent, does it, it has 3 to 8 percent, correct?
A. That's correct, yes.
Q. So I'll ask my question again.
Can you tell just by comparison of the package inserts
00:56 whether or not there's any difference in rate of burning and stinging among the products?
A. The package insert, you know, reports on the FDA clinical trial data, so -- and the FDA makes a determination what to list, so clearly it did not list burning and stinging as an
00:57 **adverse event.**

Q. I don't believe that answer was responsive. Let me try one more time.

I'm asking you whether you can tell from the label, if you compared the labels of Bronuck® -- I'm sorry, let's stick with the U.S. products. The labels of Xibrom® and Bromday® versus the label of Prolensa®, can you know for sure that Xibrom® and Bromday® had any greater level of burning and stinging reported than was reported in the Prolensa® label?

A. The FDA label did not mention burning and stinging, so it must be less than 3 percent.

Q. And you can't tell me whether or not from the Xibrom® and Bromday® label the levels were less than 3 percent, can you?

A. Well, we know it was less than 3 percent because -- true, it could have been higher, it's between 2 and 7 percent, the label.

Q. So between 2 and 3 -- for example -- let me try to do this one a different way.

The Prolensa® label has reports on 3 to 8 percent -- withdrawn.

The Prolensa® label reports on adverse events in 3 to 8 percent of patients, right?

A. Correct.

Q. And the Prolensa® -- I'm sorry.

And the Xibrom® and Bromday® labels report on 2 to 7 percent, right?

A. That's correct, yes.

Q. So, for example, there could be burning and stinging with Prolensa® in somewhere between 2 to 3 percent of patients, right, and it wouldn't have appeared in the adverse reaction section of the Prolensa® label?

A. It's theoretically possible.

Q. Thank you.

And you agree, don't you, that there can be adverse reactions when using Prolensa® that aren't among those listed in Section 6.1 of the Prolensa® label, right?

A. Yes.

Q. All right. Now, I want to discuss the Silverstein article, JTX146, you talked about that in your direct examination.

A. Can you just give me the number again so I can find it?

Q. Sure. JTX146.

This is an article you discussed in your direct examination, right?

A. Yes.

Q. And did you say this was a result of an FDA clinical trial?

A. I said that this was basically the two Phase III double-mass placebo controlled multicenter clinical trials.

Q. That's not what this paper is. Isn't it a post-hoc analysis of the data from those trials? I'll direct you to

the section of the study protocol section on Page 957.

A. I'm sorry, what page?

Q. 957 of the article and it's PROL 0333516.

A. Okay.

Q. Do you see it says, these post-hoc analyses were based on Phase III clinical trials. Do you see that?

A. Yes.

Q. So what that means is that the clinical trials were not designed to look for this particular end point, right?

A. Which particular end point are you referring to?

Q. The one that's described in the Silverstein paper. If you look at the Purpose on the first -- in the abstract on the first page.

A. So you're asking me whether -- so the two clinical trials, multicenter clinical trial were performed, the data was -- the studies were completed, the data was analyzed. And you're saying that -- and basically this is looking at the data and presenting data from those clinical trials.

Q. Do you know what a post-hoc analysis is as differentiated from a forwardly designed clinical trial?

A. Of course.

Q. Okay. So what is that difference?

A. So prior to initiating a clinical trial, the study investigators will develop a clinical protocol with expected outcome measures to analyze. Then the study's completed. So

that would be the prospective study. But once you have the data, you can then conduct additional analysis of data to come up with other findings that are present.

Q. All right. So I guess my question, again, and I'll ask it now with that explanation is, the study that was done and reported in this paper was not part of the original forwardly designed clinical trial for Prolensa®, correct?

A. Well, the study was -- this is an FDA -- FDA clinical trial and it was completed. And then this is a paper looking at data from the clinical trial.

Q. All right. Let me try to ask my question again because I think I had a very particular question, which was, do you agree with me that this is a post-hoc analysis and wasn't part of the original prospectively designed clinical trial?

A. Let me look at it. Yes, this is a study looking at additional, for example, additional end points is what you're asking. So after the study was completed, the investigators can look at data from the study and write -- an article written about the data from the study.

Q. So you're agreeing it's a post-hoc analysis, right?

A. Yes.

Q. Okay. And if you turn to Page 971, the first full paragraph on the left-hand side, it says, the clinical results are similar to other trials evaluating higher concentrations of bromfenac. Do you see that?

A. Yes.

Q. And you agree with that statement as a general statement about the clinical trial results presented here?

A. Well, obviously, there's a lot to all the different clinical trials and so -- well, there's -- the results for inflammation for efficacy were similar, there's obviously some differences in adverse events. So this is just a general statement so it's not quite accurate, but it's in general -- provides a general summary but there's definitely differences in the clinical trial results.

Q. Now, I'd like to look at the disclosure section on the bottom of Page 971. I think in your direct testimony you were talking about trials that were sponsored by drug companies, right?

A. Yes.

Q. Okay. Now, this wasn't just sponsored by Bausch & Lomb, right? If you look at the disclosure section on the bottom of Page 971, it says that the sponsor -- that's Bausch & Lomb, right?

A. Yes.

Q. Participated in the design of the study data collection, data management, data analyses, data interpretation, and preparation, review, and approval of the manuscript, right?

A. Yes.

Q. Now, let me move on to your testimony about burning and

stinging experienced with other NSAIDS.

You testified that other NSAIDS, non-bromfenac NSAIDS caused burning and stinging, right?

A. Yes.

Q. The two examples you gave was Acular® and Voltaren?

A. Yes.

Q. And you said Acular® had a 40 percent rate and that Voltaren had a 15 percent rate, right?

A. Yes.

Q. All right. Now, neither of those products have bromfenac as the active, right?

A. That's correct.

Q. All right. And as we've seen, the rates of burning and stinging with the bromfenac products were much lower than this 40 percent or 15 percent, right?

A. Right.

Q. So with Xibrom® we saw 1.4 percent and with Bronuck® way less an 1 percent, right?

A. That's correct. And the key there is that we have a lot of experience with non-steroidals that cause burning and stinging and it really impacted our patient care and surgical outcome so we're very attuned, you know, to burning and stinging with nonsteroidals.

Q. So you don't have that issue of 40 percent and 15 percent, you didn't have it with Xibrom® or Bromday®,

correct?

A. Correct.

Q. Let me turn now to the Flach paper, PTX-270, that you cited in your direct.

A. Yes.

Q. You cited this paper when you were talking about CME's, right?

A. Correct.

Q. But I'd like to look at a different part of the paper. Can we go to Page 591?

There's a Section B on Page 591 and it says "comparison of ketorolac and diclofenac, right, in reducing post-operative inflammation after cataract extraction and intraocular lens implanting. Do you see that?

A. Yes.

Q. And you've seen this before, right?

A. I have, yes.

Q. And so this is a study comparing ketorolac and diclofenac, right, so that's comparing Acular® and Voltaren, right?

A. Yes.

Q. Let's go to Page 594. 594 in the first full paragraph says Results. Do you see that?

A. Yes.

Q. All right. And you see it was a trial of 120 patients.

Do you see that?

A. Yes.

Q. And then if you look two paragraphs down, it says, no adverse reactions were reported or observed during the study. Do you see that?

A. Yes.

Q. All right. Now, I'd like you to turn to another study that's reported in this paper. Let's go to Page 602.

And if you look at the Purpose, and you'll see the goal of the study is to evaluate the effect of ketorolac in patients with acute clinical CME. Do you see that?

A. Yes.

Q. All right. And ketorolac was one of the drugs you talked about earlier as having a high rate of burning and stinging, right?

A. Correct.

Q. So if you look under materials and methods on Page 602, you'll see it was 350 patients, correct?

A. Correct.

Q. And then I'd like to look over to Page 603, there's a section that says Results, right? It's in the middle of the page. Do you see the Results section?

A. Yes.

Q. And you'll see the Results section goes on for a couple of pages, and the part I want to ask you about is at the top

of Page 605. And the first full sentence at the top of 605, again talking about ketorolac, is both treatment regimes were well-tolerated by the patients. There were no complaints about burning and stinging following eyedrop instillation. Do you see that?

A. **I see that.**

Q. Let me ask you about another article you talked about, that was the Baklayan reference, JTX18, and this paper does not report on a clinical trial, right?

A. **Let me just find the page -- the section, please.**

Q. Sure. Go ahead.

A. **Sorry, what was the number?**

Q. 18.

A. **Okay. I got it.**

Q. So this Baklayan paper is not a clinical trial, right?

A. **Well, it's a study on -- it's a rabbit model study.**

Q. So that's not a clinical trial, right?

A. **It's not on humans, it's on animals.**

Q. If you look at this paper, there's two authors, right?

A. **Yes.**

Q. And these are both Bausch & Lomb employees, right?

A. **I don't know that.**

Q. It says right underneath Bausch & Lomb, Irvine, California. Do you see that?

A. **It sounds like it could be, yes.**

Q. Let me help you out then. Why don't we go to the disclosure section on Page 1723 of the article with the Bates No. PROL 0080511.

A. **Right.**

Q. Okay. So in the disclosure section it says George Baklayan, an employee of Bausch & Lomb, and Mauricio Munoz was an employee at the time the manuscript was developed, right?

A. **Yes, I agree.**

Q. This was not one of those independent studies you talked about in your testimony, right?

A. **This is a study looking, right, looking at an animal model, looking at data from two different formulations.**

Q. And this was just kind of top to bottom on internal Bausch & Lomb papers, right?

A. **It appears that way, yes.**

Q. You testified that lower concentration of drug in Prolensa® places less drug in contact with the eyes, correct?

A. **Yes.**

Q. And you said that that's good because the active can have toxicity, right?

A. **Yes.**

Q. Okay. But there is no evidence that bromfenac has any toxicity related to it that would cause a difference between putting .09 percent versus .07 percent in the eye, right?

A. **We know that bromfenac can cause toxicity to the ocular surface, especially in patients who have undergone cataract surgery, so there is a risk with toxicity.**

Q. But there is no difference in adverse events related to that between the .09 percent formulation and the .07 percent formulation, right?

A. **There can be differences in adverse events and, you know, we don't know, is it the concentration or the pH, but there definitely can be a difference in the adverse events.**

Q. But you don't know if there is a difference in the adverse events, right? You say there potentially could be.

A. **I have seen, for example, I had a patient that was on Prolensa® that I prescribed and got switched to the .09 percent, and that patient experienced toxicity from the .09 percent. It was the generic, but had toxicity with poor vision and stinging of the cornea. So .09 percent can cause toxicity which I haven't -- to a different degree than .07 percent, in my experience.**

Q. You have one anecdotal experience with that happening, correct?

A. **I have a patient that, you know -- just -- it was just -- I have had other patients as well, but this is a patient that was quite, you know, impactful to me because they had gone through the first surgery, was seeing very well, they were set up for their second surgery, and they got switched to the generic without my authorization, and ended up with, on the**

generic .09 percent, and experienced toxicity of the cornea and blurred vision in both eyes from the .09 percent.

I have had other patients that I found surprisingly had been switched, without my authorization, that had been switched and have also had toxicity, so it's not an isolated incident.

Q. And your policy is not to prescribe generics for that reason?

A. **No, I prescribe generics all the time for various situations. I use -- generics can be quite effective. But there are differences in certain generic classes, and bromfenac 0.09 percent generic has toxicity that I've seen and many of my colleagues have reported in seeing. So it's different from the brand name.**

Q. Well, let me ask you this: There are no studies that show that a lower concentration of bromfenac in contact with the eye is associated with fewer adverse events, right?

A. **Well, there is less burning and stinging in the study comparing Xibrom® and Bromday® versus Prolensa®, so yes, there is an FDA clinical trial showing there is less adverse events, of certain types, with one versus the other.**

Q. And do you attribute that to the lower concentration of Bromfenac? I thought you had attributed that to the pH earlier.

A. **It's probably the -- it's a combination. It's the agent.**

I am not a formulator or a chemist so I can't tell you why, but we definitely see a difference.

Q. Okay. Now, I want to -- I want to get to your testimony about CME. Okay?

You testified that Prolensa® is not indicated for the treatment or prevention of CME, right?

A. Correct.

Q. All right. Now, so I want to try to understand your argument about the connection between Prolensa® and CME, so I think you testified that a certain percentage of patients are going to experience burning and stinging when they take a -- the prior Xibrom® or Bromday® formulation, correct?

A. Yes.

Q. And, as we saw, let's take Xibrom® for an example, that was 1.4 percent burning and stinging, right?

A. Correct.

Q. All right. So what you're saying is that some fraction of that 1.4 percent are going to stop taking their medication because of the burning and stinging, right?

A. Correct.

Q. And then some fraction of that fraction of 1.4 percent may develop CME, right?

A. Right. Since I do lots of surgery and, typically, many cataract surgeons do 500 to a thousand cataract surgeries a year, those percentage fractions are real patients and they

really add up. So when a patient comes to us and they have expectations, and they develop CME and loss of vision, it's a horrible situation. You feel horrible as a surgeon. So it is -- the fraction that you're calling is a real person, not a fraction.

Q. Well, it's a fraction of the percentage, right? I'm not downplaying anybody's problems after surgery.

I'm just saying the way you got to your opinion was by saying a fraction of the patients who stopped taking their medication because of burning and stinging will, in your opinion, develop CME, right?

A. Right, that's one of the side effects of not taking the prescribed NSAID would be -- it helps with inflammation overall, and also one of the risks is CME.

Q. Okay. And then so we started out with 1.4 percent. We have a fraction of those who may stop taking their medication. We have a fraction of that fraction who may develop CME. And then, of the people who develop CME, there is an even smaller fraction where it doesn't resolve on its own, right?

A. I disagree with the way you're characterizing things because -- a number of things.

First of all, per Dr. Cykiert's, you know, report, he reports that 10 to 15 percent of patients experience CME after cataract surgery and, depending on how you classify it, it can be 18 to 20 percent or, you know, if you look at the Kim

article, depending on the study, a good percentage of the patients can experience CME after cataract surgery, so it's not a super low percent.

But, more importantly, these are real patients, and when those patients, you know, are doing well at one week and all of a sudden at two and three weeks come back and they can't see and they can't drive and they can't function, those are real things that, as a clinician, as a surgeon, you do not want to see happen in your patients.

Q. All right. Let's turn to the Kim article because you've just mentioned it in your answer and I was going to get there anyway.

A. Of course.

Q. Okay? This is PTX-281. Let's turn to Page 2160 of that article. And I would like to look at the last sentence on the left-hand column. Okay? Are you there?

A. Yep. Yes.

Q. And what Kim says, and this is the article you just quoted, it says, "because many cases of CME are mild and resolve spontaneously, it remains unknown whether prophylactic NSAID treatment improves long-term visual outcomes," right?

A. Well, he says that here, but then he also writes in the very beginning that CME is the most common cause of visual loss after cataract surgery. So it's interesting, he's saying two things here at once. If you go to the other section which

I quoted previously, development of CME after cataract surgery is the most common cause of visual impairment.

Q. But we don't know how common that is, right, because many cases of CME are mild and resolve spontaneously, right?

A. It's a good percentage that, you know, they put them in the papers.

But, again, by resolve spontaneously, they're talking about six months or a year that some can resolve spontaneously.

I know that if I diagnose CME and any of my colleagues diagnose CME, we're going to treat that patient. We're not going to let it spontaneously -- hope it improves. And then even with treatment, some patients will not get improvement in vision.

Q. I understand that's your opinion, Doctor. But I'm just asking you if you agree with the statements in the Kim paper. You cited the Kim paper.

A. Of course. And there are some definite flaws in this paper which is without question.

Q. Okay. I want to -- let's move on to the Walters paper, JTX142. And this is a Phase 3 clinical trial for approval of Prolensa®, right?

A. Yes.

Q. All right. And this clinical trial compared Prolensa® to placebo, right?

A. **Yes.**
Q. It didn't compare it to any of the other bromfenac formulations, right?
A. **Correct.**
01:20 Q. And I would like to again turn to the end of the paper, it's on Page 33 of the paper, and it's PROL 0333862.
And you see that the Walters/Goldberg piece and Gow are referred to as consultants to Bausch & Lomb; do you see that?
A. **Okay, yes.**
01:21 Q. Okay. And it says, again, that it was sponsored by Bausch & Lomb and that Bausch & Lomb participated in the design of the study, data analyses, interpretation, and supervised the preparation of the manuscript and approved the final version, right?
01:21 A. **Well, if you could see just below that, if you could just highlight below that, please? This is critical --**
Q. I'm sorry. You can -- why don't you give your answer?
A. **Well, I think it's the whole thing. You're asking about a statement that's being made, but you're cutting a paragraph off with a critical issue, which is that the authors had full access to all study data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in the interpretation of the study findings and in the drafting --**
THE COURT: Please slow down.

THE WITNESS: Oh, so sorry.
All authors participated in the interpretation of the study findings and in the drafting of critical revision of the manuscript or both.
01:22 So these -- this is -- while it's sponsored by Bausch & Lomb, because it's clear the authors here take full responsibility for the -- all of the information contained in this article, all the data, all of their thoughts, and all their comments.
01:22 BY MS. HOLLAND:
Q. Okay. I just wanted to make clear that when you were testifying in your direct testimony that Bausch & Lomb just sponsored these studies, it went a little further than that. I mean, they actually approved the manuscripts, right?
01:22 A. **They review the manuscripts and they would approve it as well.**
Q. All right. So let me point you to another place in the Walters paper then that I wanted to talk about. It's on Page 30. It's PROL 0333859.
01:22 A. **Okay.**
Q. And the "Discussion" section, the right-hand side, in the right column, I should say, the second paragraph starts with "The results with bromfenac." Do you see that?
A. **Yes.**
01:23 Q. And in the middle of that paragraph, several lines down,

there is a sentence that says, "Although all of the bromfenac once-daily trials used a similar study design, direct comparisons between the studies cannot be made." Do you see that?
01:23 A. **If you highlight it just because --**
Q. Oh, yeah, of course. I'm sorry.
A. **Perfect. I found it, yes.**
Q. Do you see that?
A. **Correct.**
01:23 Q. And that's referring to direct comparisons between the studies for Bromday® and Prolensa®, right?
A. **Yes.**
Q. And if you turn -- if you go to the next page, 31, with Bates Number PROL 0333860, in the left-hand column, first full
01:24 paragraph that begins with the sentence, "There are limitations," do you see that? And we will highlight that.
A. **Perfect.**
Q. And I would like to go to the second sentence in that paragraph actually that begins with "The current trials."
01:24 A. **Yes.**
Q. It says, "The current trials," meaning the Prolensa® trials, "included a smaller sample size than in other clinical trials evaluating higher concentrations of bromfenac, making direct comparisons difficult." Do you see that?
01:24 A. **Yes.**

Q. And if you look at the bottom of that column, it talks about the safety profile of Prolensa®. Do you see that? The last line on the left-hand column on Page 31. There is a sentence that says, "This advanced formulation of bromfenac"
01:25 and then it says it "has a similar efficacy profile as higher concentrations of bromfenac," and then when it compares safety profiles, it compares it to placebo, right?
A. **Can you just get the next sentence or --**
Q. Sure. It's also in your book.
01:25 A. **That is correct. That's how -- that's how that particular sentence reads.**
Q. So the safety there was compared not to another bromfenac formulation but to placebo.
A. **That's just -- I mean, obviously, we have the data of**
01:25 **the -- of the active ingredients, but this is just this particular sentence is referring to the placebo.**
Q. All right. So let's look at the Rajpal reference, 143. And I want to look at the safety profile on Page 927. It's on the right-hand side of the page. And what Rajpal says is
01:26 that, "The safety of the bromfenac molecule has remained consistent throughout the various formulations," right?
A. **Yes.**
Q. "And adverse events have been minimal in most studies," right?
01:26 A. **Yes.**

Q. Let's go back to the Baklayan paper for a minute, JTX18.
We looked at this a few minutes ago, but I want to talk about a different part of the paper now.
I want to go to 18.2, and I want to look at the
01:27 left-hand column, the last paragraph. This is a sentence -- five lines up that begins, "The presence of a bromine." Do you see that?
A. Yes.
Q. It says, "The presence of a bromine in the 4-prime
01:27 position, as in bromfenac, was found to improve in vitro and in vivo potency, absorption across the cornea, and penetration into ocular tissues." Do you see that?
A. Yes.
Q. And is that something you agree with?
01:27 **A. Well, they're comparing -- this is a study -- this is comparing to other nonsteroidals that bromfenac -- you know, has a very good overall potency and absorption, but, obviously, things can impact those things, but it's comparing it to -- I believe here it's comparing it to other**
01:28 **nonsteroidals.**
Q. And but you agree, as compared to other nonsteroidals, bromfenac had improved in vitro and in vivo potency, absorption across the cornea, and penetration into ocular tissues?
01:28 **A. Right. That's why the concentration is so much lower of**

bromfenac versus -- like ketorolac is 0.5 percent, versus, you know, the much lower percentage in -- of bromfenac of Prolensa® -- of, for example, Bromday® and Xibrom®. And Prolensa® is just, you know, orders lower in concentration
01:28 **because of the way the molecule works.**
Q. All right. And then you see the sources for that statement are -- it says 13 to 15. Those are the end notes, right?
A. Okay.
01:28 **Q.** So let's look at the end notes there, and I want to focus on End Note 14.
Do you see the support for that statement is the Yanni U.S. Patent 475,034?
A. Okay.
Q. Do you agree with that?
A. I do not know anything about this patent.
Q. Do you agree that that's the reference that's being used to support the proposition about the superiority of bromfenac?
A. 13 to 15? I don't know the accuracy of that, but it's
01:29 **obviously in the article, but I don't know the accuracy. And I'm not familiar at all with this patent.**
Q. All right.
MS. HOLLAND: I have nothing further, your Honor.
THE COURT: Okay. Thank you. Is there a redirect?
01:29 MS. LEBEIS: Your Honor, we'd need the time to take

the morning break.
THE COURT: Okay. Let's take a 15-minute break and we will resume at 11:15.
(A recess was taken at 11:03 a.m.)
01:48 THE DEPUTY CLERK: All rise.
THE COURT: Okay. Be seated, please. You may resume with redirect.
MS. LEBEIS: Your Honor, I have no redirect.
(EXAMINATION OF WILLIAM B. TRATTLER BY THE COURT:)
01:49 THE COURT: Okay. Just a couple of questions.
Doctor, in evaluating scientific articles, are those that are authored by the employees of a company entitled generally to less weight or stricter scrutiny than those that are independently done by, say, university scientists?
01:49 THE WITNESS: Absolutely. So, in the review process, if there is someone who works for a company, then it's much more difficult to get that peer reviewed and published because everyone is more suspicious that there is going to be bias involved. So it's a more difficult process and more scrutiny
01:49 to look at it because they know it's someone who has a vested interest in that -- whatever is being written for, about.
THE COURT: Do you serve on editorial boards yourself?
THE WITNESS: Absolutely, yes.
01:50 THE COURT: And is that the standard you apply when

you receive the submission of a corporate-sponsored article?
THE WITNESS: Absolutely. So, you know, they have to disclose all those pieces of information, so we have the article and we're carefully evaluating the article to look
01:50 for, you know -- to understand, you know, what's being written about and if there is any biasness because, you know, if one of the authors or the authors are employees of a company.
THE COURT: What does it mean, as indicated in at least two of these articles, that Bausch & Lomb approved the
01:50 manuscript? Does that mean that a company can disapprove and either censor or cut off the publication?
THE WITNESS: Not that I'm aware of. I think, to me, what that means is that the articles went through the peer-reviewed process, and that they're acknowledging that
01:51 they have reviewed it on their own and they agree with -- or approve -- or agree with what's being written, as well. I don't think it's that they have -- with what's being written, they don't have the ability to censor in any way what's being written. It just -- I think that was a statement stating that
01:51 they reviewed what was written and what's being published and agreed with it from a company -- or -- from a company standpoint.
THE COURT: Well, I don't think it used the word "agreed." I think it said "approved."
01:51 THE WITNESS: Right. So that they approved it,

that -- their company approved the -- or agreed -- for me, the word "approved" means agreed with what was written.

Again, as you saw from the articles, these authors had access to the data and wrote these articles and reviewed it and it's their words and information that was used. And I think that's just a statement that Bausch & Lomb provided financial support and they also, you know -- that at the end of the day, they also approved what was being written.

THE COURT: All right. I had a question about placebos that are used in the study.

THE WITNESS: Yes.

THE COURT: I think all the studies used placebos as a comparator.

THE WITNESS: Yes.

THE COURT: Is there a standard for what the placebo is comprised of in an ocular solution?

THE WITNESS: Yes. It is the vehicle or everything in the study product except for the active agents. It's the typical vehicle that's used.

THE COURT: Would it be important to know what the pH of the placebo is when you're comparing results between the formulation and the placebo?

THE WITNESS: Well, I think that -- in answering the question, we're looking at clinical data. We're looking at the clinical results of the clinical trial, including all the

adverse events, and there can be reasons that the placebo can have a different adverse -- adverse event profile than the active ingredient. And pH could be a factor. It could also be the lack of the inactive -- lack of the active ingredients.

THE COURT: In several of the studies, the adverse effects of burning and stinging were pretty much the same for the bromfenac solution as for the placebo. Did you notice that?

THE WITNESS: Yes. Sometimes the -- well, the placebo can be higher sometimes -- I can go back and look at the particular studies. They were all in close range but sometimes, from what I recall from the Silverstein and from the Walters papers, is that the adverse events in general were higher in the placebo group versus the active ingredient -- active group.

THE COURT: There was one, which was the Donnenfeld article, and that was looking at Xibrom®, where the placebo was 1.75 percent burning and stinging and the solution being studied was only 1.4 percent.

THE WITNESS: Yes.

THE COURT: Would you say that, in theory, that's about as low as a result -- you know, the best result that you could ever expect, if it's even better than placebo?

THE WITNESS: Right, so nonsteroidals are -- well, yes, we would like to have the active agent be the same as the

vehicle, unless the active agent also had pain-suppressing properties, and these are nonsteroidal so they also have pain-suppressing, you know, properties, so maybe that can help too. But in the same ballpark is a good range, as you're pointing out.

THE COURT: All right. I don't think I have any other questions. Thanks.

Are there any follow-ups, first by the plaintiff?

MS. LEBEIS: Yes, Your Honor, just one follow-up question.

(REDIRECT EXAMINATION OF WILLIAM B. TRATTLER BY MS. LEBEIS:)

Q. Dr. Trattler, once the peer-review process is completed, is there any reason to doubt the accuracy of an article?

A. Well, I think the peer-review process is an important part of the process, but even after it's published, there is -- there are situations, you know, papers where other people may disagree with the result, so it's -- so, for example, the Kim article or things like that, they are not always -- they are put into peer review but they are subject to further evaluation further down the road. But the peer-review process is very helpful because only certain articles will actually be allowed to make it through to that -- to that state.

MS. LEBEIS: Thank you. That's all from plaintiffs.

THE COURT: Any follow-up by the defendants?

MS. HOLLAND: No, Your Honor.

THE COURT: Okay. Then thank you very much, Doctor.

THE WITNESS: Thank you very much as well.

THE COURT: You may step down.

(The witness left the stand.)

MS. LEBEIS: Your Honor, that's our last live witness for plaintiffs.

THE COURT: All right. And so, other than deposition excerpts, does the plaintiff rest?

MS. LEBEIS: Other than keeping it open for the designated deposition excerpts and also the associated exhibits, yes.

THE COURT: Okay. Is this a good time to return to the exhibits?

MS. HOLLAND: Your Honor, I was going to suggest that perhaps we do it at the end of the day because some of the witnesses I believe have timing issues, so maybe they should get on and off the stand as quickly as we can.

THE COURT: Okay. Is that acceptable?

MS. LEBEIS: Yes, that's fine, your Honor.

THE COURT: Okay. Thank you.

MS. LEBEIS: Thank you.

All right. You may proceed.

MR. MARGOLIS: Thank you, your Honor. Defendants call Dr. Clayton Heathcock.

THE COURT: Okay, Dr. Heathcock, please come to the witness stand.

MR. MARGOLIS: Your Honor, may I have permission to approach and pass out binders?

01:57 THE COURT: Yes, of course.

THE DEPUTY CLERK: Sir, can you please place your left hand on the Bible and raise your right hand.

(**CLAYTON H. HEATHCOCK**, HAVING BEEN DULY SWORN/AFFIRMED, TESTIFIED AS FOLLOWS:)

01:57 THE WITNESS: I do.

THE DEPUTY CLERK: Can you please state your name, sir, and I need you to spell your first and last name, please.

THE WITNESS: Clayton Heathcock, C-L-A-Y-T-O-N, H-E-A-T-H-C-O-C-K.

01:57 THE DEPUTY CLERK: P-H? Sorry.

THE WITNESS: H-E-A-T-H-C-O-C-K.

THE DEPUTY CLERK: Thank you, sir. You can be seated and please speak into the microphone.

(DIRECT EXAMINATION OF CLAYTON H. HEATHCOCK BY MR. MARGOLIS:)

01:58 Q. Good morning, Dr. Heathcock.

A. **Good morning.**

Q. Where do you live?

A. **I live in Martinez, California.**

Q. And are you employed?

01:58 A. **I'm retired.**

Q. And prior to retiring, what did you do?

A. **Well, I was a professor at the University of California. I retired several times actually. I retired as professor in 2004, when my pension reached its maximum entitlement.**

01:58 **I was a dean at the time, and there was not another person in line to take over, so I continued to be employed as a dean for another year. In 2005, I retired as dean.**

And at that point I was recalled by the university to be chief scientist for an interdisciplinary research institute

01:59 **that had just been created, and I occupied that position for three more years, and I finally went off the payroll in 2008.**

And now I'm Emeritus Professor, and I still occupy -- have an office, and which I don't go to very often, but I operate a seminar, a regular seminar --

01:59 THE COURT: Can you please pull the mic toward you.

THE WITNESS: Okay. What did you not hear?

A regular seminar that I created about ten years ago, and I still do that on a volunteer basis.

BY MR. MARGOLIS:

01:59 Q. And so now you're an Emeritus Professor at the University of California at Berkeley; is that correct?

A. **Yes.**

Q. And in what fields do you specialize?

A. **I'm a chemist. My specialty within the field of**

01:59 **chemistry is organic chemistry.**

Q. Okay. And during your professional career, what were your responsibilities as a professor?

A. **Well, I taught classes. At a place like Berkeley, we**

02:00 **have two kinds of teaching responsibility. One is classroom teaching in which we have a class of students that we meet with several times a week, and I did different kinds of courses during my 40 years as a professor. Usually, it would be undergraduate, introductory organic chemistry class. Sometimes it was advanced laboratory practice in organic**

02:00 **chemistry for undergraduates. Other times it would be advanced chemistry course for graduate students.**

But the main teaching responsibility was a one-on-one mentor/apprentice relationship with students who were working, doing research and working towards a doctorate. I would have

02:00 **at any given time between 10 and maybe as many as 16 or 18 students who worked full-time on research projects that I designed and met with them on a regular basis to evaluate and suggest new lines of research and so forth. These students would occupy laboratories and offices near my office, and we**

02:01 **met on a regular basis over a period of about four years until they received their Ph.D.**

I also had regular teaching responsibilities for postdocs; these were student who already had a doctorate and had come to Berkeley to get further research experience.

02:01 **And so by far, the bulk of my teaching was this**

personal mentor/apprentice relationship with these graduate students and postdocs.

Q. And over the course of your career as a professor, approximately how many doctoral students did you train?

02:01 A. **About 80 doctoral students, and I had about 50 postdoctoral students over my career.**

Q. And during your active research career, what subjects did you focus on?

A. **My -- the main focus of my interest was synthetic organic**

02:02 **chemistry. Synthesis is making complicated compounds from simple things that you can buy. It's the main tool, the first tool in drug discovery, and almost all of my doctoral students eventually left to take jobs in drug companies or biotech companies as medicinal chemists or process chemists.**

02:02 **I also studied a range of other kinds of -- or had projects that ranged from other -- in other areas of organic chemistry. Medicinal chemistry is a subfield of organic chemistry. And most of my research, as a matter of fact, was funded by the National Institutes of Health, and it was**

02:02 **research directed at synthesis of complex compounds that were already known to have some interesting biological activity and could possibly have been developed into drugs.**

I also had a good deal of research on creation of new synthetic methods, particularly for the control of the

02:03 **three-dimensional shape of molecules that were being made.**

Q. And, in addition to your positions as a professor, department chairman, and dean, have you held any other positions at the University of California at Berkeley?

A. Yes. Well, as I mentioned, after my second retirement, I was recalled as chief scientist for the -- for QB3-Berkeley, it has an interdisciplinary organization. It's part of the California Institute for Quantitative Biosciences. We call it QB3. The "QB" stands for Quantitative Biosciences. "3" stands for the fact that three of the campuses of the University of California are involved: Berkeley, San Francisco, and Santa Cruz.

And the purpose of QB3, when it was first established, was to bring together in a way that could result in collaborative research the quantitative scientists, mostly from Berkeley and Santa Cruz -- physicists, engineers and chemists, with the biologists and clinical practitioners at San Francisco and Berkeley to solve problems of human health that were more amenable to group efforts than to individual efforts.

Q. And what specifically were your responsibilities as chief scientist at QB3?

A. Well, I was brought on board as an experienced administrator to help get it up and running. I set up all of the core facilities at the Berkeley -- in the Berkeley branch, which was a new building, which was built about the time I

took the job. And the core facilities are analytical laboratories, mass spectrometry, nuclear magnetic resonance, and things that the scientists used for analysis in their research.

I also established this seminar, which is a regular meeting of all of the -- of professors who are affiliated with QB3, where we meet together and people share the recent results from their laboratory. And these regular meetings have resulted in a number of productive collaborations between, for example, engineers and clinicians from -- from San Francisco even.

Q. Are you still involved with QB3?

A. Yes, I still operate the seminars on a volunteer basis.

Q. Would you please turn to DTX-440 in your binder and identify that exhibit?

A. Okay, that's my curriculum vitae.

Q. Okay. And did you prepare your curriculum vitae?

A. Yes, I did.

Q. And does it accurately reflect your education and experience?

A. Yes, it does.

Q. Would you briefly describe your educational background?

A. Yes.

I grew up in San Antonio, Texas, where I had my secondary education.

I attended college in a small college in West Texas, Abilene Christian College, received a Bachelor of Science Degree there in Chemistry in 1958.

I worked for a couple of years in industry, and then entered graduate training at the University of Colorado in Boulder, received a Doctorate in Organic Chemistry from the University of Colorado in 1963.

And then I had one more year of study at Columbia University as a postdoctoral associate, 1963 to 1964.

Q. Okay. And what did you do after completing your postdoctoral studies?

A. I -- while I was at Columbia, I received and accepted an offer as assistant professor in the Chemistry Department at the University of California at Berkeley, and I started my work there in 1964, in the fall.

Q. And over the course of your career, have you followed the literature related to medicinal compounds and their structural properties?

A. Yes, I have.

Q. And approximately what percentage of your research has related to medicinal compounds?

A. Well, a lot of it, in the sense that my interest is in developing the methods and concepts for synthesizing complicated compounds. Mostly, my targets were natural products that had been discovered to have interesting,

promising biological activity, and the bulk of my work, maybe two-thirds to three-fourths was funded by research grants from the National Institutes of Health, the Cancer Institute, the Allergies and Infectious Diseases Institute, or the Institute For General Medical Studies. So, in that -- because of that connection, I had to keep up with the, you know, potential drugs, what were needed, what was interesting, and so forth.

Q. Okay. Have you had any experience consulting in the pharmaceutical industry over the course of your career?

A. Yes. I have had three long-term consultancies. One that lasted for ten years with Merck in the '60s and '70s. I was for 11 years a member of the Abbott Laboratory Scientific Advisory Committee in the '80s, and then for -- I think nine years recently, I was a member of the Scientific Advisory Board for Flexicon Incorporated, a small drug discovery company in California.

Q. And can you briefly describe the nature of your consulting work?

A. As a consultant, I would go to the laboratory; for example, when I was a consultant at Merck, I would go to Rahway or West Point two or three times a year, spend one or two days on each visit, having meetings with the various medicinal chemists, and they would then share with me what they had accomplished since the last time we met. I would provide advice on often it was synthetic problems they were

having. Sometimes I would provide suggestions on new compounds they might make, based on structure activity relationships that they described to me.

The consultancy with Abbott was a little different. I was a member of a committee that consisted of eight senior scientists. I was the chemist. The others were MDs and various specialties. And we would meet for three days twice a year to hear reports from the group leaders about the projects that had been -- that they were working on at Abbott, and then we would have a follow-up meeting with the management, CEO and president, for example, to give kind of a report card and make suggestions on new things they could be doing.

Q. And as a consultant, were you involved in the development of pharmaceutical formulations?

A. No. Formulations would be something that would come rather late in the drug discovery process. My involvement would be in the drug discovery area. The finding of new activities and selectivities, helping to solve pharmacokinetic problems, bioavailability, things of that sort. The formulation would be something that would be well downstream from where I was involved.

Q. Have you given any talks in the pharmaceutical industry?

A. Yes. It's common for companies to invite professors like me because they want to know what we're doing before it gets to the -- to the journals, and they also want to develop

relationship to hire our students. And so I gave dozens of talks at all of the major pharmaceutical companies in the United States and many overseas.

Q. During the course of your career, have you been involved in any professional organizations?

A. I was a member -- I've been member of the American Chemical Society for over 50 years. I got my 50-year pin a few years ago. I was elected in 2009 to the initial class of American Chemical Society Fellows. I served as the -- on the executive committee of the organic chemistry division and chair of that organization, and I've been a long-term member of the national academy -- of the American Association for Arts and -- for the Advancement of Science, and I shared the chemistry division of that organization for one year.

I also served for four years as a member of the National Institute's of Health medicinal chemistry study section and was chair of that organization as well.

Q. Have you published in the field of chemistry?

A. About 275 peer-reviewed and book chapters, a couple of patents.

Q. Do any of those papers relate to organic chemistry?

A. Yeah, they're basically all related to organic chemistry, and mostly to synthesis, some to stereochemical control. There's a few even theoretical papers that have to do with computational things, and a few papers -- some of the papers

were published in medicinal subjects.

Q. So do any of those papers relate to medicinal chemistry?

A. Well, yes, as I say, the bulk of the work was funded by the National Institutes of Health, and so possible medicinal uses would be mentioned in a large number of my articles. Two, I think, were published in the *Journal of Medicinal Chemistry*. A number of others were published in the Journal of Organic and the American Chemical Society journal, but included biological data.

Q. Have you authored any textbooks?

A. I'm coauthor of a textbook named, *The Introduction to Organic Chemistry*. It was published first in the mid-1970s. It was in print for about 30 years. It was translated into a number of different foreign languages as well.

Q. Have you had a role on any journals during the course of your career?

A. I served as a member of the advisory boards for a number of journals, and I was editor-in-chief for the *Journal of Organic Chemistry* for 11 years.

Q. Have you won any awards in connection with your work?

A. Yes, and they are listed on the front page of my curriculum vitae down here at the bottom.

Q. Can you identify a few of your more significant awards?

A. Well, yes. Probably the one that means a lot to me was my first major American Chemical Society award. That was the

award for creative work in organic synthesis. I'm fond of the Prelog medal, which was an award from the --

THE COURT: It's spelled P-R-E-L-O-G.

MR. MARGOLIS: Thank you, Your Honor.

THE WITNESS: Thank you, Your Honor.

It was awarded by the Swiss Federal Institute of Technology. And of course, I guess my highest honor was to be elected to the National Academy of Sciences.

MR. MARGOLIS: Defendants offer Dr. Heathcock as an expert in chemistry.

THE COURT: Any objection?

MR. DINER: No, Your Honor.

THE COURT: All right. The Court will permit the witness to offer opinions in the field of chemistry.

MR. MARGOLIS: Thank you, Your Honor.

BY MR. MARGOLIS:

Q. Dr. Heathcock, are you aware that Dr. Davies testified in this case last week?

A. Yes. Yes, I am.

Q. And have you had the opportunity to review the transcript of Dr. Davies's testimony?

A. Yes, I have.

Q. And do you understand that Dr. Davies testified that the person of ordinary skill in the art would not have expected bromfenac to form an insoluble complex with benzalkonium

chloride?
A. **Yes.**
Q. And do you agree with Dr. Davies that the person of ordinary skill in the art would not have expected bromfenac to
02:15 form an insoluble complex with benzalkonium chloride?
A. **No, I don't agree with that opinion.**
Q. Why not?
A. **Well, it -- it seems to me that by 2003, there was a widely-held belief in the community that formulations that**
02:15 **contained a particular preservative, benzalkonium chloride, and also an NSAID that has a carboxylic acid group were subject to forming these insoluble complexes that resulted in cloudy or turbid mixtures.**
And because bromfenac is a -- is another NSAID that has
02:16 **also a carboxylic acid group, I believe that a person of ordinary skill would have a reasonable expectation that that problem might extend to bromfenac as well and that it would also form soluble -- it would be likely to form soluble -- insoluble complexes that would result in turbid solutions.**
02:16 Q. Have you prepared a slide showing what a carboxylic acid group is?
A. **Yes.**
Q. Can we pull up DDX5-2, please. Thank you.
Can you explain what a carboxylic acid group is?
02:16 A. **This drawing is just a generic representation of an**

organic chemical structure in which a part of it in green is a particular arrangement of atoms. There's a carbon that's doubly bonded to an oxygen and singly bonded to an oxygen that also has a hydrogen attached to it. That grouping is called a
02:17 **carboxyl group. And that kind of compound, and I have the Ar which is a generic part of the structure that stands for aromatic because these NSAIDs that we will be talking about have aromatic -- different aromatic groups attached at that position.**
They all have this kind of structure and that is called
02:17 **in organic chemistry a functional group. A functional group is a particular group of atoms that can occur in a lot of different molecules with other structural features, but that functional group is what determines the reaction personality**
02:17 **of compounds that have it. And so that's a carboxyl group.**
Q. And have you prepared a slide showing the types of reactions that carboxylic acid groups undergo?
A. **We're showing one reaction that they undergo and that's on this slide.**
02:17 MR. DINER: Your Honor, at this point we would like to lodge an objection. We spoke with defendants last night. We have an objection as to this slide, that it's beyond the scope of his expert report.
This depiction of this scheme here appears nowhere in
02:18 his report. He has other schemes of reactions that are in

there. This one is nowhere in there, and as a general matter, this kind of information is not in there, and so essentially, he would be offering new opinions.
What he has in there -- well, it's actually going to be
02:18 on the next slide. But what he has in there is the potential reaction that could take place between a carboxylic acid group and benzalkonium chloride, but this general schematic here where they are illustrating at a more -- at a different level is not actually depicted in his -- in any of the schemes of
02:18 his expert report, or has not provided any opinions on that scheme in his expert report.
MR. MARGOLIS: Your Honor, this is basic fundamental underlying chemistry that's referred to throughout Dr. Heathcock's report. For example, footnote 7 in paragraph 54,
02:19 he describes in the last sentence, a pH greater than 7, more than 99.9 percent of the bromfenac and these other NSAIDs is present in solutions in anionic form. This is explaining visually to aid in his explanation to the Court how that ionization occurs.
02:19 THE COURT: I'll permit it as a visual aid. It seems to be within the scope of his testimony that's already been put into the report, but on a more basic level. And that's a function of a visual aid. It's not evidence, but if it helps him to explain, I'll permit it.
02:19 MR. MARGOLIS: Thank you, Your Honor.

BY MR. MARGOLIS:
Q. So just to go back, Dr. Heathcock, would you please explain the types of reactions that carboxylic acid groups can undergo?
02:19 A. **Well, yes. Functional groups have typically associated with them systematic reaction -- a characteristic reaction profile. The simplest reaction of a carboxylic acid is to simply lose the hydrogen from the OH. Now, it's shown here with the hydrogen and the oxygen connected together by a line.**
02:20 **That line is a bond, and all of the lines in these drawings that we use represent bonds, and when there's a single line, that means there's two electrons in that bond.**
And carboxylic acid has this property that the hydrogen
is not -- is easily lost, and when it's lost it can be
02:20 **transferred to another oxygen, for example, to a water molecule, that would be the solvent, and that leaves behind a carboxylate ion, the anion. The carboxylate ion is what's left behind when the hydrogen plus goes away. Because the electrons that were holding the hydrogen to the oxygen both**
02:21 **stay with the oxygen, it has a negative charge.**
When a species has a charge in chemistry, it's called an ion. If it has a negative charge like this, it's called an anion, and this anion comes from a carboxylic acid, so it's call a carboxylate ion.
02:21 **So this top reaction just illustrates that carboxylic**

acid spontaneously lose a hydrogen ion to give a carboxylate ion. And at physiologic pH, the pH of, you know, of 7 or around 7, the vast majority of this carb -- of any carboxylic acid would be present as the carboxylate ion.

02:21 Q. And you've identified H_2O on your slide. Does that indicate that this is a type of reaction that takes place in water?

A. Yes. This would be -- this would be a reaction that -- in water. And this reaction, I'm showing, is actually a

02:22 transfer of the H-plus from the carboxylic acid to one of the water oxygens.

Q. And once the carboxylate ion or the anion is formed, what types of reactions can that anion undergo in water?

A. Well -- sorry. If there are, in the solution, other

02:22 ions, for example, a sodium ion, which is now a positively charged ion, so it's called a cation. If there are cations in solution, then it's possible for the anion and the cation to form a kind of a loose association that is sometimes referred to as an ion pair.

02:22 That ion pair is not bonded to -- the sodium and the oxygen in the ion pair are not bonded like the hydrogen and the oxygen are in the carboxylic acid itself. They're attracted to each other by an electrostatic attraction. Electrostatic means they just -- that a positive and a

02:23 negative kind of have an attraction for each other, kind of

like a boy and a girl. You know, they just kind of hang around each other, but they're not really permanently bonded.

It could also be thought of as like two magnets, the positive end of one magnet and the negative end of the other

02:23 magnet, kind of are attracted to each other, but they're not firmly bonded by any material.

So that's an ion pair, and ion pairs are -- are, you know, they are very dynamic. They are separating and forming and separating and forming quite rapidly.

02:23 Q. And is the formation of an ion pair a reaction that any NSAID having a carboxylic acid group will undergo?

A. Well, any ion that -- any carboxylate ion that's in solution with cations will form ion pairs to some degree. Including NSAID carboxylate ions.

02:24 Q. And have you prepared a slide that shows what happens when an NSAID having a carboxylic acid group pairs with a positive ion?

A. Yes, that's just a more -- excuse me -- specific version of what was on this slide. At the top I'm showing again the

02:24 sodium cation and the carboxylate ion coming closer together so that they form an ion pair.

Something like this, when sodium is involved, is generally going to be quite water soluble because the -- the charges are accessible to the water molecules that are forming

02:24 the bulk of the solvent. They can easily get around there,

and so this is a relatively happy situation, solvent -- a soluble ion pair.

Some ions are -- some cations, like this one that's shown on the bottom of the slide, have a positive charge like

02:25 the sodium ion, but also there's a large organic part attached to that positive charge, and the organic part of any molecule is less happy being in water solution. It's what we call hydrophobic. These large hydrocarbon parts don't like water very much.

02:25 And so when this cation comes close to the carboxylate ion to form an ion pair, that is now quite a different kind of ion pair than the sodium carboxylate ion pair because the cation part has this large hydrocarbon surface. And so this would generally not be as soluble in water because of the fact

02:25 that the hydrocarbon part is not really liking to be in water.

And that's why some of these benzalkonium carboxylates that were -- that were forming insoluble salts do separate from solution.

Q. And is the large cation that you've depicted on the

02:26 slide, is that a benzalkonium cation?

A. Yeah, that's one of the benzalkonium cations.

Q. And you used the term "hydrophobic" to refer to the benzalkonium cation. What does hydrophobic mean?

A. Hydrophobic means hates water, really. Hydro is water,

02:26 phobia is hates. So something that's hydrophobic does not

like to be in water.

Q. And the bottom right structure that you've depicted as an insoluble ion pair, is that what you also refer to as an insoluble complex?

02:26 A. Yeah. That would be a complex. The complex is a -- sort of a general term that refers to an association of two things, two or more things.

Q. And what do you mean in this case when you're using the term "insoluble complex"?

02:27 A. Well, solubility is a gradual term. Anything can be soluble. You know, things can be soluble at one concentration but not soluble in another.

So if you have water like this bottle of water and I add a little bit of something and shake it up, let's say I add

02:27 a little bit of sugar and shake it up, it will go clear. That's because all the sugar is soluble. If I keep adding sugar, more and more and more, at some point it's not all going to go into solution, and so at that point you can say is it insoluble? Well, it's soluble at some concentrations and

02:27 not soluble at other concentrations, not completely soluble at other concentrations.

So because of that sort of gradation, my definition for the purpose of this testimony is that when you talk about -- when I talk about an insoluble ion pair, I'm talking about at

02:28 the concentrations that are relevant for these ophthalmic

formulations.

Q. And when an insoluble complex forms in such a formulation in solution, what happens to that solution visually?

A. Well, if you -- if you add something to this bottle of water that isn't sufficiently soluble, then it will look cloudy. You can have little particles floating around. They can be very tiny particles, it can be turbid. The particles could be big enough that if you let the bottle sit, they actually will settle out to the bottom of the bottle. So that when something is insoluble, you will get this behavior that it's turbid, cloudy, or you see actual precipitate falling to the bottom.

Q. Are there any prior art references that indicate that an insoluble complex would be expected to form between bromfenac and benzalkonium chloride?

A. Yes, there are quite a lot of literature in 2003 that indicated that -- that benzalkonium chloride was a bad actor in that respect, that it was forming insoluble complexes and that bromfenac could be expected to be the same way.

Q. And have you prepared a slide identifying some of these references?

A. Yes. On this slide I've listed four patents and applications. One at the top is international patent application WO 9,415,597. That's JTX207, and I'll refer to that as WO '597 application.

The second one is a U.S. patent, 5,558,876. That's JTX201. I'll refer to that as the '876 patent, and then another U.S. patent, 5504113, that's JTX158, and I'll call that the '113 patent. And then finally, a European patent application, 0 306 984, that's JTX209, and I'll refer to that as the EP '984 application.

Q. And this was Slide DDX5-5, correct?

A. Yeah.

Q. Let's take those one at a time. If you could please turn to JTX207 in your binder and identify that document. 207.

A. Okay. That's the -- that's the '597 application, the international application, published in 1994.

Q. And generally speaking, what's the subject matter to which WO '597 is directed?

A. This deals with ophthalmic formulations that contain acidic NSAID.

Q. Okay. And what, if anything, does WO '597 teach about complexation?

A. If you look on Page 2 of this, at the top. Yeah, if you look at the -- in the first paragraph on Page 2 of this patent, you see that it is taught here that benzalkonium chloride, which is a quaternary compound, has been widely used in ophthalmic solutions, but it is considered to be incompatible with anionic drugs because it forms insoluble compounds that cause the solutions to turn cloudy.

Q. And what is an anionic drug?

A. Well, an anionic drug would be a drug that exists in an anionic form. For example, the -- the carboxylate ions that I showed in the general slide a couple of minutes ago would be anionic, and the NSAIDs that contained carboxylic acid groups would exist at physiological pH in those anionic forms, and those would be examples of anionic drugs.

Q. Okay. And does WO '597 explain why anionic drugs form insoluble complexes with benzalkonium chloride?

A. Yes. If you look at the next paragraph, the next two paragraphs on this same page, at first, it says what I showed you on that slide that was disputed, that at negative -- at physiological pH, the acidic drug exists as an anion, that it carries a negative charge, and that all acidic drugs will carry a negative charge at a pH above their PKA. So that means that at physiologic pHs they will be 99 point something percent negative or in an anionic form.

And then it goes on to explain in the next paragraph that because benzalkonium chloride is a positively charged species, ion pairs can be formed with these negatively-charged drug compounds, and this leads to an insoluble ion pair that causes the drug to precipitate from solution.

Q. And just to be clear, is bromfenac an anionic drug?

A. Yeah -- well, bromfenac would be anionic at physiological pH. Bromfenac is an NSAID that has a carboxylic acid group,

and it would be almost completely ionized at pH 7.

Q. And at the pHs of ophthalmic formulations relevant to this case, would bromfenac be an anionic drug?

A. Yes. I think I was hearing pHs of 7 and-a-half or so in testimony earlier today, so it would be, you know, 99.9 percent ionized under those conditions.

Q. And is bromfenac also considered an acidic drug?

A. Yes.

Q. So would WO '597 suggest anything to the person of ordinary skill in the art about bromfenac?

A. Well, because this is -- this is a general teaching, and bromfenac is a compound that has this -- this property, this structure, it's -- it's a carboxylic acid, and I think this would give a person of ordinary skill good reason to believe that bromfenac will form an insoluble salt that will cause cloudiness when used with benzalkonium chloride.

Q. And does the next slide, I believe it's DDX5-6, does that explain how bromfenac could interact with benzalkonium chloride to form an insoluble complex?

A. Yeah. This is essentially a more explicit description of what I had in the general sense a few slides back. Here is bromfenac in the upper left of this slide, and you can see now that it's aryl is given in detail. It's a relatively complex group of atoms.

The first part of it is an aromatic ring. But here is

the acetic acid side chain, that's the carboxyl group, and it's shown here losing an associating or ionizing -- losing a hydrogen to give the bromfenac anion on the upper right, and then I've just simply shown that bromfenac anion forming an ion pair with this benzalkonium cation, and this is the same kind of ion pair I showed in a more general sense previously.

And I think a person of ordinary skill would have a reasonable expectation that this ion pair is going to behave like the other BAC cation, NSAID ion pairs, and be insoluble at the relevant ophthalmic formulation concentration.

Q. And again, does the H_2O you've indicated on the slide suggest that this is happening in an aqueous solution?

A. Yes.

Q. Could you now turn to JTX158 in your binder and identify that document?

A. Okay. This is the '113 patent and it was published in 1996, and it also is a patent that deals with ophthalmic formulations that contain acidic -- carboxylic acid containing NSAID.

Q. And what does the '113 patent teach about complexation?

A. If you go to column 1, and it's in about -- okay. It's right down here at about the middle of the page, it teaches that it is well-known that benzalkonium chloride is considered to be incompatible with anionic drugs because it forms insoluble complexes that cause the solutions to be cloudy, and

it mentions that these insoluble complexes precipitate from solution. I think that's part of a -- the same thing, the same thing, that benzalkonium chloride and a negatively charged or an anionic drug, you -- it's well-known that you get cloudiness resulting from precipitate.

Q. And so would a person of ordinary skill in the art have understood the teaching of the '113 patent to be applicable to bromfenac?

A. Yes. Again, I think that because bromfenac is an acidic drug and it's in this same general family of NSAIDs that have a carboxylic acid functional group, a person of ordinary skill would have a reasonable expectation that it would behave the same way and result -- and be at least partially insoluble at the important -- at the important concentration.

Q. Okay. Could you next turn to JTX201 in your binder, please, and identify this document?

A. Okay. This is the '876 patent. It was published in 1996, and as you can see, its title also deals with ophthalmic formulations that contain acidic drugs.

Q. And what does the '876 patent, if anything, teach about complexation?

A. Okay. Go to column 1 again, and it's right there in the first paragraph, and it teaches that acidic drugs that have carboxyl groups tend to form insoluble complexes with quaternary ammonium preservatives like benzalkonium chloride.

Q. And is bromfenac an acidic drug with a carboxyl group?

A. Yes.

Q. And so would a person of ordinary skill in the art have understood the teaching of the '876 patent to be applicable to bromfenac?

A. Yes, I think that, generally, you would read this and understand that this is -- this is giving you, certainly, reasonable expectation that bromfenac is going to form an insoluble complex with BAC.

Q. Okay. Would you please turn to JTX209 in your binder and identify this document?

A. This is the European '984 application, and it was published, I think, in 1989, right about here, and it also is a patent application that deals with ophthalmic formulations that contain acidic NSAIDs.

Q. And what, if anything, does EP '984 teach about complexation?

A. On Page 2 of this, down toward the bottom here, it is taught that anti-inflammatory or NSAIDs that contain a carboxylic acid group -- can you make that just a little bit larger? I'm having trouble reading it just from here. I can read it from here, but then I've got to face away.

The -- they -- that anti-inflammatory -- or NSAIDs that contain a carboxylic acid group are considered to have proven to be incompatible with quaternary ammonium compounds like

BAC, and this incompatibility results from the fact that the carboxylic acid group forms a complex with the quaternary ammonium compound and -- although they don't say the words "precipitate" in this passage, it renders a preservative less available, and I think a person of skill would understand they're talking about the same kind of turbidity or partial insolubility that we've been -- that we've seen in the other patents.

Q. To be clear, BAC, B-A-C, refers to benzalkonium chloride; is that right?

A. Yes, that's one of the acronyms for benzalkonium chloride.

Q. And benzalkonium chloride is a quaternary ammonium compound; is that right?

A. Yes.

Q. Okay. And is bromfenac an NSAID with a carboxylic acid group?

A. Yes.

Q. So would a person of ordinary skill in the art have understood the teaching of EP '984 to be applicable to bromfenac?

A. Yes. As far as this general teaching goes, it tells a person of skill that you have a reasonable expectation that bromfenac is also going to form -- form complexes and be subject to this incompatibility that they're talking about.

Q. So from all these references that we've looked at, what would the person of ordinary skill in the art have understood?

A. Well, there was a consistent pattern that's clearly the people who are writing these patents are all teaching, that there is a problem that benzalkonium chloride is not compatible with these acidic drugs because it forms complexes which are insoluble, at least insoluble enough to make the solutions be cloudy and turbid.

And since bromfenac is -- although -- also a member of this class of NSAIDs that contain a carboxylic acid group, I think that the overall teaching is clearly that there is a reasonable expectation that there's going to be problems with bromfenac and benzalkonium chloride and that you are likely to see -- you know, you'd expect that you're going to be seeing the same kind of partial insolubility with that as well.

Q. And were there any specific NSAIDs that had been shown in the prior art to form insoluble complexes with benzalkonium chloride?

A. Yes, there were three, and they're listed on the next slide.

Q. The next slide, DDX5-7?

A. Yes.

Q. And could you identify those three NSAIDs that you were discussing?

A. The first is a compound called flurbiprofen, and it's the

subject of WO '597 international patent application. The second is a compound called ketorolac, and it's discussed in the European patent application, the '984 -- EP '984, and then the other is diclofenac, and it's discussed in the '560 patent.

Q. Okay. Let's start with flurbiprofen. Could you turn to JTX207 in your binder, which is WO '597?

A. Okay.

Q. And when you get there, could you let me know how WO '597 shows that flurbiprofen formed an insoluble complex with benzalkonium chloride?

A. Yeah, if you go over to pages 8 and 9, there's a table that -- that goes over those two tables -- those two pages, Table 1, and that table lists two formulations called examples A and B. And these, if you follow down all the ingredients in those two formulations, they are identical, except at Example A formulation has benzalkonium chloride and Example B formulation has another compound, and it does not have any benzalkonium chloride.

Then if you look at the bottom of the table, there's a passage that explains that Example A results in a cloudy solution with precipitate, and that clearly is because of some interaction between flurbiprofen and the benzalkonium chloride, because that's the only difference between Example A and Example B.

Q. So would the person of ordinary skill in the art understand from this, that flurbiprofen and benzalkonium chloride had formed an insoluble complex?

A. Yes.

Q. Okay. Could you turn to JTX209 in your binder, the EP '984, and does EP '984 show that ketorolac formed an insoluble complex with benzalkonium chloride?

A. Yes. If you go over to Page 209.9, there's a table, Example 5, in this patent -- in this table, is a part of Example 5. This table reports several -- there's actually six different formulations with three different surfactants.

The -- each of the surfactants has two concentrations of surfactant. One of the surfactants that's used is Tween 80, that's another name for polysorbate 80. And you see that in that -- in both of the formulations that contain that surfactant there was turbidity. The one on the left --

MR. DINER: Excuse me, Your Honor, I'm sorry to interject. I would like to lodge an objection at this point in time. When he -- Dr. Heathcock spoke about or talked about the Fu reference in his report, he talked about it in the context of the general statement that he referred to at Page 2 of the Fu reference. But I don't believe that in the context of his report, he got into the specific details concerning Example 5. And so I think this is outside the scope of his report. If counsel could suggest a passage elsewhere in his

report.

MR. MARGOLIS: Yes. Your Honor, if you look at paragraph 50, last sentence, the Fu reference EP '984 discloses formation of a precipitate under certain conditions and formulations containing ketorolac and BAC, citing EP '984 at Page 9, lines 11 to 39, which is exactly what's up on the screen right now.

MR. DINER: Withdrawn, Your Honor.

THE COURT: All right. I'll permit it.

Would you like the question repeated?

THE WITNESS: I think I know where we were. I was just pointing out that this table shows that in this -- in this formulations in the middle, there was turbidity, and if you go down below the table, the -- the inventors state that the presence of turbidity suggested the inability to solubilize -- the inability of this surfactant, to solubilize a precipitate formation between the ketorolac and benzalkonium chloride.

Q. And so, would this suggest to the person of ordinary skill in the art that an insoluble complex had formed between ketorolac and benzalkonium chloride?

A. Yes, that's clearly what the inventors were telling and teaching in this patent.

Q. Now, are you aware that Dr. Davies testified that the use of the word "suggested" in that last sentence that you

discussed implies that the authors did not know what the precipitate actually was?

A. Yeah, I -- I read that.

Q. And do you agree with his understanding?

02:48 **A. Well, no. I think, if you look at the whole context of this example. I mean, can we pull back and look at the language in the -- you know, this is an -- this is an experiment that was set up. Clearly, these -- what they say about the design of the experiment was, three surfactants were evaluated for their ability to dissolve the ketorolac benzalkonium chloride complex and maintain a physically clear solution.**

So although they don't show any experimental data to the -- they clearly knew there was a complex between those two things, and that's why they did this experiment, to find some surfactant that would dissolve that -- that precipitate.

Q. Okay. Could you turn to JTX057 in your binder, please. And identify that document?

02:49 **A. Okay. That's a patent -- that's a U.S. patent, 5,597,560. It's a patent that was published in 1997.**

Q. And what is the subject matter to which the '560 patent is generally directed?

A. Generally, this is another patent dealing with ophthalmic formulations and -- formulations that do contain an acidic NSAID.

Q. Okay. And is the '560 patent directed to solving any particular problem?

A. Yes, the particular problem that this patent was directed at was that the formulation being developed here in addition 02:49 **-- excuse me, in addition to containing the NSAID also contains an antibiotic.**

The antibiotic was a compound name tobramycin, and what the researchers were finding was that diclofenac and the tobramycin interacted with each other to form an insoluble 02:50 **complex, and they were looking for -- they were looking for a formulation that would dissolve that complex, that diclofenac tobramycin complex.**

Q. And does the '560 patent also suggest that diclofenac formed an insoluble complex with benzalkonium chloride?

02:50 **A. Yes. If you look on a -- yeah, there we go. It's at the bottom of -- I can't read the page number from here. It's at the bottom of Page 10. There is -- this paragraph describes that they had developed a formulation that included a relatively large concentration of surfactant and other** 02:51 **conditions that permitted -- that solved the problem. It dissolved the tobramycin diclofenac complex, but they go on to say that these same condition also inhibit the unacceptable interaction between diclofenac and the quaternary ammonium compound.**

02:51 **And so that would be understood by a person of ordinary**

skill to be referring to the same kind of undesirable insoluble complexes that were -- that were being taught by all of these patents.

Q. Do you understand that Dr. Davies testified that the 02:51 person of ordinary skill in the art would not have expected bromfenac to form an insoluble complex with benzalkonium chloride because it differs in some respects from these other NSAIDs?

A. Yes.

02:52 Q. And do you agree with Dr. Davies's opinions that bromfenac differs in some respects from flurbiprofen, diclofenac and ketorolac?

A. Certainly it differs. It has different functional groups, and if it didn't have, it would be the same compound.

02:52 Q. Now, do you agree with Dr. Davies's opinion that the person of ordinary skill in the art would not have expected bromfenac to form an insoluble complex with benzalkonium chloride because it differs in some respects from other NSAIDs?

02:52 **A. No, I don't agree with that. I don't think the differences are sufficient to give a person of ordinary skill confidence that that systematic problem would be obliterated.**

Q. Are there any differences among flurbiprofen, diclofenac and ketorolac?

02:52 **A. Yes, they -- they differ from each other, as well as each**

of them differing from bromfenac.

Q. Could we pull up the next slide, please. DDX5-8.

Does that -- can you explain using DDX5-8, what the differences are between flurbiprofen, diclofenac and 02:53 ketorolac?

A. Yes, on this slide, I just joined -- I've just gathered together those three carboxylic acid NSAIDs, and you can see that each of them differs from each of the other ones in significant ways. For example, flurbiprofen has two aromatic 02:53 **rings with a fluorene attached to one. Diclofenac has two aromatic rings, but they're attached by an amino group.**

Flurbiprofen doesn't even have an amino group. Diclofenac has a couple of fluorenes where -- instead of the one fluorene.

02:53 **So there are a lot of differences between flurbiprofen and diclofenac, also between diclofenac and ketorolac. So...**

Q. So why is it that despite all of these differences between flurbiprofen, diclofenac and ketorolac, all three compounds formed insoluble complexes with benzalkonium 02:54 chloride?

A. Well, I think it's because they all are carboxylic acids that are ionized in the carboxylate form at the pH 7. And although there are differences in the hydrophobic parts of these molecules, those differences aren't enough to overwhelm 02:54 **the fact that these are basically carboxylic acids, and they**

all have this common property of being able to associate with a cation and form -- and when the cation is a big greasy one like the benzalkonium chloride, to form an insoluble complex.

Q. And have you prepared a slide showing how bromfenac differs from flurbiprofen, diclofenac and ketorolac? I'm sorry. Have you prepared a slide showing how bromfenac differs from flurbiprofen, diclofenac and ketorolac?

A. Yes.

Q. And so could you explain how these compounds different?

02:55 A. Well, there's bromfenac, and you can see that it does differ from each of these other three compounds, but really not more than they differ from each other. It certainly has -- it has an amino group, diclofenac has an amino group. It has two benzene rings that are joined by a carbonyl. Ketorolac has that. So it has some common features with each of these and it also differs. But it has over -- one overwhelmingly important common feature and that is the carboxylic acid group.

Q. So in view of the structural differences between bromfenac, diclofenac, ketorolac and flurbiprofen, would the person of ordinary skill in the art have expected that an insoluble complex would form between bromfenac and benzalkonium chloride, as it did with diclofenac, ketorolac and flurbiprofen?

02:55 A. Yes. I think you would certainly have a reasonable

expectation that you would have an insolubility problem at the relevant ophthalmic concentrations.

Q. Now, do you understand that Dr. Davies testified that because of these differences in structure, bromfenac would be

02:56 expected to be more soluble than these other NSAIDs?

A. Well, it is more soluble than these other three compounds, and I understand that. But that insolubility -- that additional solubility is going to be moderated a lot when it's paired with this very hydrophobic benzalkonium chloride

02:56 cation.

Q. So have you prepared a slide to explain that a little bit more?

A. Yeah. Next slide.

Q. Okay. Let's pull up 5 -- DDX5-11, please. And could you

02:56 explain why it's your opinion that the difference in solubility between bromfenac and the other NSAIDs would not cause the person of ordinary skill in the art to doubt that bromfenac would form an insoluble complex with benzalkonium chloride?

02:56 A. Sure. What I've done here is just shown each of the three NSAIDs that were -- that were implicated with these insoluble complexes, flurbiprofen on the upper left, diclofenac on the upper right, and ketorolac on the lower left. I showed them in -- associated with the benzalkonium

02:57 cation in an ion pair relationship.

And the reason that these compounds -- that these complexes are all partly insoluble at the important concentration is certainly that this big hydrophobic cation is overwhelming -- each of these, each of these NSAIDs by itself

02:57 would be soluble under these conditions, but when associated with this big hydrophobic cation, the complex is at least partially not soluble, and so you get a precipitate in that cloudiness.

And here's bromfenac and it forms the same kind of

02:57 thing. And when you look at bromfenac in association with this cation, the whole complex is dominated by this big hydrophobic cation. And so even though bromfenac itself might be quite water soluble, when it's ion paired with this big greasy cation, I think a person of ordinary skill would

02:58 understand that there's a high probability that it's going to be insoluble, just like the others.

Q. Do you understand that Dr. Davies also testified about the structural differences between tyloxapol and polysorbate 80?

02:58 A. Yes.

Q. And is the interchangeability of surfactant something that is typically encountered by an organic chemist?

A. Well, no, it's not something that I think we would normally do in our research. It's something -- it's a

02:58 formulation matter and formulation is not something that an

organic chemist of my type would be normally concerned with.

Q. Do you have a general understanding of what a surfactant is?

A. Oh, yes, certainly.

02:59 Q. Do you have prepared a slide identifying the general properties of a surfactant?

A. Yes, it's shown here. This is a charming little drawing that shows a molecule that has a split personality. Surfactants or organic compounds that have a part that wants

02:59 to be dissolved in water, that's called the hydrophilic part, hydrophilic means loves water, and that's often sometimes called the head group of the surfactant. And then it has another part which is hydrophobic and doesn't like to be in water, and that's sometimes called the tail group. So a

02:59 surfactant is a kind of a bipolar molecule, one end of the molecule wants to be dissolved in water and the other end doesn't want to be anywhere near water. And so it's sometimes called amphiphilic, it has both hydrophilic and hydrophobic properties.

02:59 Q. And have you prepared a slide illustrating what happens when a surfactant is placed in water?

A. Yes. If you look at this slide, you see what happens. When you start dissolving or adding the amphiphilic surfactant molecule to water, because the hydrophobic tails don't want to

03:00 be anywhere near water, they will tend to stick together and

form a kind of a loose association so that they can benefit from being around more hydrophobic things than being away from the water.

And when you get enough of the surfactant around enough 03:00 **of the molecules around, you can form these actual closed units that are called vesicles or micelles. And what a micelle is, it's like a spherical structure, compartment where all of the hydrophobic parts of the molecules get together in the middle and that leaves the hydrophilic head groups on the** 03:01 **outside of the ball. When the micelle -- when there are enough molecules, the micelle will form a completely spherical or somewhat spherical structure with all of the hydrophobic parts on the inside and the hydrophilic head groups on the outside. And so you can think of this like maybe a basketball** 03:01 **filled with oil in the middle, and the outside is really water soluble.**

And the way a micelle works to dissolve things, is if you have in solution also something like that's oily, like say butter or machine oil or, you know, one of these hydrophobic 03:02 **ion pairs that we've been talking about, that can get in the middle of the ball where it's oily and the hydrophobic interior of the ball can act as a good solvent and then it can solubilize that material.**

So it would be like if you got butter on your dinner napkin and you wash it with water, you don't get the butter 03:02

out. But if you add some soap to the water you wash the dinner napkin with, the soap forms these micelles and the butter molecules are happy to go in there in the oily part of the interior of the micelle and then washes away and your 03:02 **dinner napkin is clean.**

The next slide shows kind of an interesting little picture that my students took once of our group. And they wanted to lie down on -- they wanted to have a group picture that wasn't standing in front of a library door and they 03:03 **organized this thing where they all lie down on the air intake valve with their feet pointed in and they wanted me to stand in the middle. One of my students, after I gave the intro course one day and the lecture that talked about micelles, came back to my office and said Professor Heathcock, you have** 03:03 **a picture of a micelle on your wall and a blob of fat right in the middle.**

So that's a cross-section of the micelle.

THE COURT: Excuse me, is that a good place to stop for lunch?

03:03 MS. HOLLAND: Your Honor, we have a timing issue with Dr. Heathcock, Dr. Heathcock has a flight that he's trying to catch. So I know it's not the Court's usual practice, but would it be okay to take a later lunch today so we can get Dr. Heathcock off the stand before lunch?

03:03 THE COURT: Well, Tuesday is the only day when the

judges in this building meet in the building for a quick lunch. I can shorten my time at that lunch if that helps. Do you want to go about ten more minutes now and then we'll resume like 1:30? I mean, I can't solve the time problem 03:04 overall because I don't know how long cross-examination is going to take.

MR. MARGOLIS: If it helps at all, I probably have, like, five minutes or so left.

THE COURT: Well, let's complete the direct then and 03:04 then we'll take a shorter lunch break.

MR. MARGOLIS: Thank you.

THE COURT: I assume there's a decent amount of cross?

MR. DINER: Yes, your Honor.

03:04 THE COURT: Okay.

BY MR. MARGOLIS:

Q. Given that understanding of how micelles work, is there anything about the structural differences between tyloxapol and polysorbate 80 that would have suggested to the person of 03:04 ordinary skill in the art that they could not be used interchangeably?

A. Actually, there was a reason to think that they could be and that tyloxapol might be even better than polysorbate, and that was in the European application, the '984.

03:05 MR. DINER: Your Honor, at this point I'd like to

lodge an objection. Dr. Heathcock is starting to make opinions and give testimony outside the scope of his expert report. He's testified in his expert report that they're simply the substitutable, now he's starting to tell you that 03:05 they're somehow better, and that wasn't in his expert report.

THE COURT: Well, you can impeach him with that on cross if he's made an inconsistent statement today. I'll permit it. Well, I assume that there's something in his report that would contradict what he's being asked here.

03:05 MR. DINER: Well, it's just outside the scope of his report. The scope of his report, the thrust of his report is that they're interchangeable, they're substitutable, now he's starting to argue that one is better than the other and that's not in his report.

03:05 MR. MARGOLIS: Your Honor, if I may.

THE COURT: Mr. Margolis.

MR. MARGOLIS: Paragraph 70, last sentence, indeed, the prior art EP '984 patent suggested that surfactants in the ethoxylated octylphenol class of which tyloxapol is a member 03:06 are preferable to polysorbate 80 in solubilizing NSAID BAC complexes.

THE COURT: I'll permit it, it's within the scope.

MR. MARGOLIS: Thank you, your Honor.

BY MR. MARGOLIS:

03:06 Q. Dr. Heathcock, could you explain why it is that the

person of ordinary skill in the art would have believed that tyloxapol would have been better able to solubilize an NSAID BAC complex than polysorbate 80?

A. Yeah, you just read it. It's in the EP -- it's in the EP '984.

MR. MARGOLIS: Could we pull that up, please?

THE WITNESS: And it's on Page 5. Let's see what number --

BY MR. MARGOLIS:

Q. JTX209.

A. That's right. I've got it here. I can see it on the screen.

In this patent it teaches that nonionic surfactants that are useful in these formulations were preferably these ethoxylated octylphenol compounds of which tyloxapol would fall in that family.

Q. Can you remind the Court what the purpose of the invention of EP '984 was?

A. This was where they were using different surfactants to solubilize an insoluble complex that formed between benzalkonium chloride and ketorolac, the examples that we went through a few moments ago.

Q. So does this suggest to the person of ordinary skill in the art that ethoxylated octylphenol compounds would be better able to solubilize an NSAID BAC complex than polysorbate 80?

A. That is what it says, yes.

Q. And is tyloxapol an ethoxylated octylphenol compound?

A. Yes, it is.

Q. And do you have a slide where you can explain why tyloxapol is considered an ethoxylated octylphenol compound?

A. Yes. Here's the -- here's tyloxapol. And the octyl group is this group at the bottom of the six membered ring, it's got eight carbon, hence the octyl part. The six membered ring with an oxygen attached to it is the phenol part, and this phenol is functionalized by a long chain attached to the oxygen and extending out, and that's the polyethoxyl part.

So this is a polyethoxylated octylphenol and seven of them are already joined together by CH_2 bridges. It's kind of like -- so this molecule ends up being sort of like a picket fence with seven staves or seven children holding hands in a line. And the reason I think that this would be viewed as a particularly attractive member of this ethoxylated octylphenol family is that because seven of these are covariantly bonded together, they're already -- they have a head start on forming a micelle.

Q. Do you understand that in the example of EP '984 oxtoxynol 40 and not tyloxapol was used?

A. Yes.

Q. And is there anything about the structural differences between octoxynol 40 and tyloxapol that would cause the person

of ordinary skill in the art to expect tyloxapol to be less effective as a solubilizer of an NSAID BAC complex?

A. Less soluble, no.

Q. And is there anything about the structural differences between octoxynol 40 and tyloxapol that would cause the person of ordinary skill in the art to expect tyloxapol to be more effective as a solubilizer of an NSAID BAC complex?

MR. DINER: Your Honor, I would like to again lodge an objection here. This is clearly outside the scope of what he was talking about before. In his expert report, as we established, it was with regard to polysorbate 80 -- polysorbate 80. Now he's starting to make an offer of testimony that's not in his expert report about why tyloxapol would be better than octoxynol 40, and that's not in his expert report.

MR. MARGOLIS: Your Honor, he testified about this at his deposition on Page 121, Line 17, through 122, Line 14, he talk about how you would expect tyloxapol to be an exceptionally good octylphenol because of the picket fence structure he's been talking about.

MR. DINER: Your Honor, there is nothing about picket fence or anything of that stuff in his expert report. And there's been a bright line ruling in these proceedings so far is that your Honor has basically taken the position if it's not in the expert report, their witness is not allowed to

testify about it. And whether it's in his deposition or not, the fact is that we were working off of what is in fact in the pretrial order is what is in his expert report. And we haven't been given fair notice to be able to depose or cross-examine him on those issues. We feel --

THE COURT: Well, did you question him, or a member of your team, about this subject in his dep? If you brought out the question, then his opinions wouldn't be a surprise. If the other side brought it out, then it could be.

MR. HASFORD: I apologize, your Honor, I realize this isn't quite standard, but I can address that because I took his deposition.

THE COURT: Yes.

MR. HASFORD: Mr. Margolis pointed to Page 117, the question there was:

QUESTION: Why are the CMC, which is Critical Micelle Concentration, a unique characteristic of each surfactant?

And he launched into a page and a half answer, but there wasn't anything about tyloxapol being superior in there.

MR. MARGOLIS: Mr. Hasford, I'm sorry, it was Page 121, Line 17. I apologize if I misspoke.

MR. HASFORD: The question on Page 121, Line 17:

QUESTION: What does it mean that tyloxapol is a nonionic surfactant?

There was no question about whether tyloxapol would be

better or worse or anything like that. The only question was:

QUESTION: What does it mean that tyloxapol is an nonionic surfactant?

The door was not opened to any of this, your Honor.

03:12 MR. MARGOLIS: Your Honor, Dr. Heathcock proceeded to give all the information he's about to testify about. Then was asked:

QUESTION: When you testified that tyloxapol is a different kind of surfactant, different from what?

03:12 He continued to explain. They had ample opportunity to investigate his opinion further.

MR. HASFORD: We disagree, your Honor. He's mischaracterizing the deposition testimony. There was no question that that brought out any differences or would have

03:12 asked him to explain his opinion as to whether tyloxapol was superior in any way.

THE COURT: All right. I'm going to sustain the objection. It doesn't appear that it's in his report or in his deposition in questioning by the plaintiffs themselves.

03:12 MR. MARGOLIS: Thank you, your Honor.

BY MR. MARGOLIS:

Q. Dr. Heathcock, would the person of ordinary skill in the art have expected tyloxapol to stabilize bromfenac against complexation with benzalkonium chloride?

03:13 **A. Yes.**

MR. MARGOLIS: I have no further questions. If I could just move some exhibits into evidence, please?

THE COURT: Okay.

MR. MARGOLIS: JTX057, JTX158, JTX201, JTX207,

03:13 JTX209, and DTX-440.

MR. DINER: What was the last number?

MR. MARGOLIS: DTX-440.

THE COURT: His CV.

MR. DINER: Your Honor, I don't suspect we'll have a

03:13 problem, but I would like to at least consider these and we'll pick that up at the end of the day when we're preparing the evidence about each of the supplemental documents.

THE COURT: All right. Well, if there's a foundational problem, it's always better, of course, to clear

03:14 it up while the witness is still on the stand. But we can look at this after lunch if there is any issue.

So we'll resume cross-examination, let's say, in 45 minutes.

MR. MARGOLIS: Thank you, your Honor.

03:14 THE COURT: So at 1:30 we'll resume.

(Luncheon Recess)

(Open Court)

DEPUTY CLERK: All rise.

THE COURT: Be seated, please.

04:04 Okay. Mr. Diner, you may proceed.

MR. DINER: Thank you, your Honor.

(CROSS-EXAMINATION OF MR. HEATHCOCK BY MR. DINER:)

Q. Good afternoon, Dr. Heathcock.

A. Good afternoon.

04:04 Q. Dr. Heathcock, even though different NSAIDS have the carboxylic acid functional group, different NSAIDS nevertheless possess different physical/chemical properties, correct?

A. Yes, that's correct.

04:04 Q. And different NSAIDS have different physical/chemical properties because they have different chemical structures, correct?

A. They have different structures. Their physical structure will tend to be more different than their chemical properties.

04:04 Q. And different NSAIDS in terms of having different properties could have different solubilities, correct?

A. Yes.

Q. The solubility of an NSAID is going to be related to its structure, correct?

04:05 **A. Yes, it will be.**

Q. And so different NSAIDS having different solubilities have that different solubility because of their -- logically because of their different structures, right?

A. Yes.

04:05 MR. DINER: Okay. Now, Noel, can you bring up

DDX5-10?

BY MR. DINER:

Q. And I believe you should have this in your binder or you can look at the screen.

04:05 **A. Yes.**

Q. Now, you testified on direct examination about bromfenac, flurbiprofen, diclofenac, and ketorolac. Do you recall that?

A. Yes.

Q. And each of bromfenac, diclofenac, flurbiprofen, and

04:05 ketorolac have different chemical structures, correct?

A. Yes, they're all -- they have different structures or they would be the same.

Q. I'm sorry?

A. They have different structures or else they would be the

04:05 **same.**

Q. Right.

And those different structures will lead to different solubilities in aqueous systems, correct?

A. They all have different degrees of solubility.

04:06 Q. Now, we talked about, or you testified on direct examination about nonionic surfactants. Do you recall that?

A. Yes.

Q. And similarly, nonionic surfactants are going to have different chemical and physical properties because they have

04:06 different structures as well, correct?

A. **Yes.**
Q. And, generally speaking, the chemical and physical properties of organic compounds are going to be related to their exact structure, is that right?
04:06 A. **Yes, that's right.**
Q. Okay.
A. **We can't group them in families, of course, but they'll be in a family, but even within a family there will be differences.**
04:07 Q. Okay. Now, you testified on direct examination that there would be a reasonable expectation of success that an NSAID would complex with benzalkonium chloride and form a precipitate. Do you recall that?
A. **I don't think I said success. But I think I said there**
04:07 **would be a reasonable expectation that it would complex and that such a complex would be sufficient and soluble as to form one of these insolubility issues.**
Q. So you don't believe there would be a reasonable expectation of an NSAID successfully complexing with
04:07 benzalkonium chloride and forming an insoluble salt?
A. **Well, I don't think that's a success. I mean, I think that's a failure. If it forms the insoluble salts, that's the only thing. I think just to be perfectly clear, I think because of what was taught in the literature quite widely, a**
04:08 **person reading that literature would have a reasonable**

expectation that benzalkonium chloride would be likely to form an insoluble complex with any acidic NSAID drug, that wouldn't be a success, I think that would be a failure.
Q. Okay. So is it your opinion that all acidic NSAIDS are
04:08 going to form complexation with benzalkonium chloride, is that right?
A. **No, my opinion is that in light of the literature that was available, a person of ordinary skill would have a reasonable expectation that any of them would be likely to do**
04:08 **that.**
Q. And so the flip side of that is that they, of course, may not form a complex, that is, the NSAID with benzalkonium chloride?
A. **I didn't say it would be certain. I think it would be,**
04:08 **you know, a reasonable expectation that something's going to happen does not mean you're certain that that's going to happen.**
Q. And it's also reasonably likely that it wouldn't occur, right, that there would be no complex formed as between the
04:09 NSAID and benzalkonium chloride, is that right?
A. **I wouldn't say -- I wouldn't agree with that. I would say if you have a reasonable expectation that it's going to happen, you don't have a reasonable expectation that it's not going to happen.**
04:09 Q. Dr. Heathcock, have you ever conducted any research on

any product containing benzalkonium chloride?
A. **No, I have not.**
Q. And have you ever formulated a product -- a formulation containing benzalkonium chloride?
04:09 A. **No, I have not.**
Q. Have you written any papers dealing with benzalkonium chloride?
A. **No.**
Q. And you've never measured, have you, the solubility of
04:09 bromfenac, correct?
A. **No, I looked it up, but I haven't measured it.**
Q. Okay. And you never measured the solubility of any complex or salt of bromfenac and benzalkonium chloride, correct?
04:10 A. **No.**
Q. And you didn't conduct any of your own testing in conjunction with your opinions in this case, is that correct?
A. **No.**
Q. Now, the formulation of an NSAID without any
04:10 preservative, would that avoid what you have called that complexation of benzalkonium chloride and the NSAID?
A. **Well, if you didn't have the benzalkonium chloride, yes, you would not be -- it would not be possible that you would have the complex with it.**
04:10 Q. Okay. And how about a formulation of an NSAID with

something like lauralkonium chloride instead of benzalkonium chloride, would that avoid any alleged precipitation between an NSAID and lauralkonium chloride?
A. **I only can answer that in light of one case that I've**
04:11 **seen listed where that was done and where it was reported that there was not turbidity. So I don't know that I could generalize that, there was this one example certainly.**
Q. But at least based on that one example, it's your opinion that the use of lauralkonium chloride would avoid the problem
04:11 of complexation, is that correct?
A. **In that case it certainly did.**
Q. Okay. Thank you.
Now, Dr. Heathcock, are you familiar with the nonionic surfactants, nonoxynol, polaxamer 1888, polyoxyethylene, polyoxypropylene 1800, polyoxy135caster oil, or polyoxyl 40 monostearate?
A. **Are those all different compounds or is that all one long name?**
Q. No, those are all nonionic surfactants.
04:12 A. **I'm not familiar with those.**
Q. I'd like to try to refresh your recollection on that.
MR. DINER: With the Court's permission, I'd like to hand out up.
THE COURT: I think the problem then is in the
04:12 question. I had the impression you were reading one long

name, you didn't pause between those substances.

MR. DINER: Let me try it again then.

BY MR. DINER:

Q. So, Dr. Heathcock, so you don't know whether the use of other FDA approved surfactants such as nonoxynol or polaxamer 1888 or polyoxyethylene or polyoxypropylene 1800 or polyoxy135caster oil, or polyoxyl 40 monostearate in an aqueous liquid preparation of an NSAID with BAC would avoid complex, correct?

A. I don't know because I'm not sure -- I recognized one of those names when you read them slowly. And I don't think I know about its use for this particular issue.

Q. Okay. So you haven't formed your opinion whether any of those nonionic surfactants that I just mentioned would avoid the alleged complex of an NSAID and benzalkonium chloride, correct?

A. No, I haven't formed an opinion on that.

Q. Okay. And in your opinion or your inquiry in forming your opinions was focused just on tyloxapol and whether it would avoid a complex with, as between bromfenac and benzalkonium chloride, correct?

A. I'm sorry, would you restate the question?

Q. Your inquiry for purposes of your opinions was focused on tyloxapol and whether it would avoid the alleged complex of bromfenac and benzalkonium chloride, is that right?

A. That was what I was asked to give an opinion about.

Q. Would you please turn in your binder to JTX209. Do you recall testifying about JTX209 on direct examination, Dr. Heathcock?

A. Yes.

Q. And this is the Fu EP '984 reference, correct?

A. Yes.

Q. The Fu reference does not teach the use of bromfenac, correct?

A. No, bromfenac is not explicitly mentioned in this reference.

Q. And the Fu reference does not teach specifically the use of tyloxapol, correct?

A. It does not name tyloxapol. It names a generic class of surfactant to which tyloxapol belongs. Just as it names generically bromfenac as a member of the NSAID family but it does not name it explicitly.

Q. But the Fu reference doesn't teach the use of tyloxapol or mention it explicitly anywhere, is that correct?

A. Does not give its name explicitly.

Q. Okay. And similarly with regard to bromfenac, the Fu reference does not teach or otherwise specifically name the use of bromfenac, correct?

A. It teaches the use of carboxylic acid NSAIDS generally and it does not name bromfenac explicitly. Same for

tyloxapol, it teaches the use of ethoxylated octylphenols of which tyloxapol is one but it does not mention it as an explicit example.

Q. So just to be clear, it's -- tyloxapol is not mentioned in the Fu reference, correct?

A. Not explicitly.

Q. Okay. And the same with bromfenac, it is not mentioned specifically in the Fu reference, correct?

A. Yes, that's what I said.

Q. Now, I believe you testified, as Fu discloses, this broad class of ethoxylated octylphenols and that that would include tyloxapol, that's your testimony, correct?

A. Yes.

Q. By the time -- are you aware that the Fu patent eventually -- the Fu reference eventually issued into a European patent?

A. I haven't seen that.

Q. Okay.

A. So I wasn't aware of it. I assumed it probably did.

Q. And you also were aware by the time it was examined and issued, it was limited exclusively to octoxynol 40, is that right?

A. I'm sorry.

Q. By the time -- you were not also aware that by the time the Fu patent issued in Europe, it was limited exclusively and

directly to octoxynol 40?

A. You mean the claims?

Q. Yes.

A. I haven't seen that patent so I'm not aware what went on in the claims. So you're saying that the claims were narrowed to name only octoxynol 40?

Q. Actually it's the claims and the specification that were so narrow. Were you aware of that?

A. Well, I haven't seen the patent, so I wasn't aware of these things you're asking me about.

Q. I would like to refresh your recollection.

MR. DINER: May I approach?

MR. MARGOLIS: Your Honor, he just testified he's never seen this exhibit. How can he refresh his recollection with something he's never seen?

THE COURT: Well, you can reframe the question. It wouldn't be refreshing recollecting, but you're drawing other authority to his attention.

MR. DINER: Yes.

BY MR. DINER:

Q. So, Dr. Heathcock, I would like to draw to your attention to the issued patent that came out of the IP '984 application.

THE COURT: Is there any objection?

MS. HOLLAND: We don't know what it is.

MR. DINER: It's going to be PTX-778.

MR. MARGOLIS: That's not even on the exhibit list, your Honor. There's nothing inconsistent in what he's testifying versus what is in his report. The claims of the patent are not even an issue in this case. It's a patent that he hasn't testified about the claims. And he's talking about issue claims that came from the prosecution down the line way later than anything he's looked at.

MR. DINER: Your Honor, he's testified that this broad group of ethoxylated octylphenols encompassed tyloxapol. What the issued version of the European patent application to Fu will establish is that the European authorities looked at it, examined it and actually limited it to just octoxynol 40 not just in the terms of the claims but the specification, which is an indication of what the European authorities thought of what this actually disclosed and support it for and to those skilled in the art about what this invention was about.

MR. MARGOLIS: Your Honor, what did or did not happen in the prosecution of the European patent is not impeachment of the witness' testimony about the subject matter of the disclosure in the underlying specification. There could be any number of reasons why claims could have been narrowed, could have been on the side of the applicant, could have been on the side of the examiner, and you can't draw any inference just from looking at the claims.

MR. DINER: Well, it will be for impeachment purposes, your Honor, and in fact as a document that is in the public domain and therefore prior art, it speaks to what a person of ordinary skill in the art would have understood based on what was broadly disclosed from Fu in his original application than towards what was ultimately issued in terms of the patent, including the narrowing of its specification.

MR. MARGOLIS: So then they're offering--

THE COURT: Well, it's an unlisted document, so the question is is it being used only for impeachment purposes?

MR. DINER: Yes, your Honor.

THE COURT: I don't know that he's given inconsistent testimony about how the patent was issued. If he had testified as to how the Fu patent ended up being issued and this contradicted it, I would permit it. But I don't think that he's gone that far in his opinion, he only talked about the application IP '984. So I don't believe it's for impeachment purposes and I would sustain the objection.

MR. MARGOLIS: Thank you, your Honor.

BY MR. DINER:

Q. Dr. Heathcock, could you please turn to in your binder JTX201.

A. Okay.

Q. And with regard to JTX201, which is the Desai '876 patent, you testified on direct that this patent provides or

supports your opinion that the skilled person would understand that NSAIDS would tend to form complexation with benzalkonium chloride, correct?

A. Yes, I did.

Q. Now, you don't know if the formulations in the '876 patent have any stability problems, is that correct?

A. I don't know about the formulations in this patent, I was quoting the background teaching in the disclosure in which the inventors called the problem to the attention of the reader.

Q. And so in looking at the '876 patent, you did not inform your opinions as to whether there were any formulations in there that had a complexation issue or problem, correct?

A. No, I did not see that this particular -- the formulations that they reported here had complexation problems.

Q. Okay. And you don't know if the '876 patent teaches a solution therefore to the complexation problem, correct?

A. They -- you know they don't -- their formulations don't have this turbidity issue, and I think that's the reason they felt he deserved a patent because they had found a way to avoid what they described as a common problem, that's the formation of the insoluble benzalkonium NSAID complex.

Q. And their solution to a problem that was not substantiated, is that an approach that was different from the approach that was taken in the '431 patent?

A. I'm sorry, I didn't understand that question.

Q. Well, the approach that was taken in the Desai '876 patent, is that a different approach than was taken in the '431 patent?

A. Yes.

Q. Okay. And, just to be clear, the '876 patent does not teach the use of tyloxapol, is that correct?

A. That's correct, tyloxapol is not in this formulation.

Q. Now, let's go to in your binder JTX207.

A. Okay.

Q. And JTX207 is the WO '597 patent that you testified about on direct, correct?

A. Yes.

Q. Now, I'll refer to it as WO '597 patent.

The WO '597 does not teach the use of bromfenac, correct?

A. That's correct, bromfenac is not explicitly mentioned in this patent.

Q. Okay. And I believe that you indicated a publication date for the WO '597 on direct. Do you recall that?

A. Yeah, I think the publication is July 1994.

Q. And by July 1994 it was known that bromfenac could be used in aqueous ophthalmic formulations, correct?

A. I'm just not quite sure when bromfenac was first introduced into these formulations, but I believe it was

before that time, yes.

Q. And despite the fact that bromfenac and bromfenac formulations were known, it's not mentioned anywhere in the WO '597 patent as being an NSAID that has any kind of

04:26 complexation problem, is that correct?

A. No, it's not explicitly -- it's not explicitly stated. I mean, this is like the other -- the other one, a generic statement that this was a common problem. And benzalkonium chloride was considered incompatible because it formed these

04:26 **complexes generally, it didn't say it formed -- it didn't say in the disclosure which compounds it had formed these complexes with.**

Q. And the particular NSAID that is the focus of the WO '597 patent is flurbiprofen, correct?

04:27 **A. Yes.**

Q. And WO '597 does not teach the use of tyloxapol, correct?

A. That's right, they use other surfactants.

Q. And I believe we established earlier that the WO patent teaches one skilled in the art to replace benzalkonium

04:27 chloride with lauralkonium chloride as a way of addressing the complexation issue, is that correct?

A. Yes, that was their invention, they found that they did not get the turbid mixtures if they used lauralkonium chloride instead of benzalkonium chloride.

04:27 Q. And the approach that was taken in WO '597 is different

from the approach in the '431 patent, is that correct?

A. Yes.

Q. Now, can you please turn to JTX158 in your binder. Are you there?

04:28 **A. Yes.**

Q. JTX158 is what you referred to on direct examination as the '113 patent, is that correct?

A. Yes, it is.

Q. And I believe when referring to the '113 patent, you

04:28 referred to a passage at Column 1, I believe it's Lines 31 through 36. Does that look about right?

A. Yes.

Q. Okay.

A. This was a similar generic statement that benzalkonium

04:29 **chloride is forming these -- forming these insoluble complexation with anion drugs.**

Q. Actually, if you don't mind, if you would also at the same time refer to the WO patent, which is WO '597, which is JTX207. And picking up on your last statement where you said

04:29 it's a similar generic statement, in fact the same generic statement, as you put it, appears at Page 2 of the WO '597. Do you see that?

A. Let's see. Sorry, you want me -- you want me -- let me take the page out so I can compare it.

04:29 **So you're saying you want me to compare something from**

the '113 patent with something that's in this other patent?

Q. Right. WO '597, Page 2, top of the page, and the '113 patent, Column 1, Line 31.

A. Okay. Yeah, they're pretty much the same. That's pretty

04:30 **much the same thing.**

Q. And it's pretty much the same thing because both patents were owned by the same company?

A. I was just going to say that, they're both Allergan patents, so it's probably not a surprise that they used the

04:30 **same language.**

Q. They just perpetuated a template that they had, is that correct?

A. I don't know.

MR. MARGOLIS: Objection.

04:30 THE WITNESS: I just know they're both Allergan patents, I agree with that, and they both use that same paragraph.

THE COURT: I'll permit the answer.

BY MR. DINER:

04:30 Q. Now, let's take a further look at the '113 patent, Dr. Heathcock. The '113 patent does not teach the use of bromfenac, is that right?

A. That's right.

Q. And the '113 patent does not teach the use of tyloxapol,

04:31 is that correct?

A. Yes, that's also correct.

Q. And the '113 patent was issued in April 1996, is that correct, from the first page of that patent?

A. Yes, it is.

04:31 Q. Okay. And by that date, at least April 1996 or even its filing date of March 1994, aqueous solutions of bromfenac containing benzalkonium chloride were known, correct?

A. Well, yes, but I think they were known in terms of these

04:32 **other products that, yeah, we heard testimony about earlier today.**

Q. Now, I'd like to refer you -- actually, one further question on that. So would you agree, Dr. Heathcock, that the approach taken in the '113 patent is different from the approach taken in the '431 patent?

04:32 **A. The approach -- well, they're different patents so its got to have different content. Yeah. The approach I assume you mean -- what do you mean by the approach?**

Q. Well, the '113 patent, if you take a look at it, they are using an amino acid as part of their invention, correct?

04:32 **A. Yes. They use arginine as one of their components. Right.**

Q. And so the approach of the '113 patent took was different from the approach taken in the '131 patent-in-suit, is that right?

04:33 **A. Yes, because they include arginine in their composition,**

in their formulation, and I don't think -- that's not a part of the '431, the patent-in-suit.

Q. Okay. I'd like to refer your attention now to JTX057. I don't know how you referred to it before, as the Bergamini patent or '560 patent?

A. **I call it the '560. I have an easier time remembering numbers than names, especially when they're names like Bergamini.**

Q. Fair enough. We'll refer to it as the '560 patent.

Now, the '560 patent does not teach the use of bromfenac, correct?

A. **That's correct.**

Q. And the '560 patent does not use tyloxapol in any of the formulations in the '560 patent, correct?

A. **That's also correct.**

Q. I would like to refer or direct your attention to Column 8 of the '560 patent that you referred to during your direct examination.

A. **Okay.**

Q. And, particularly, at the bottom of that column.

And I would like you to please read into the record above the sentence that you referred to, the first sentence of that paragraph that begins with, "as a result."

A. **Yeah, okay. I think I summarized that but didn't read it.**

"As a result of these experiments, we discovered the preferred conditions (pH between 8 and 9; high concentration of solubility agent) necessary to obtain a pharmaceutically acceptable solution of diclofenac and tobramycin, thus overcoming the precipitation problems of the Fu, et al. formulations."

Q. And now, would you read the second sentence into the record for context?

A. **"The discovered conditions also permit including in the formulation quaternary ammonium compounds as preservatives, since these same conditions also inhibit the unacceptable interaction between diclofenac and the quaternary ammonium compounds."**

Q. So would you agree with me that the sentence that you just read into the record about discovered conditions is referring to the first sentence where it says, "we discovered the preferred conditions"?

A. **Yes.**

Q. And those preferred conditions are a pH between 8 and 9 and a high concentration of the surface -- or the solubility agent, correct?

A. **Yes.**

Q. Dr. Heathcock, over the past four years, you've testified at deposition and trial in 12 separate cases besides this case, correct?

A. **Sounds about right.**

Q. And in all of those cases in which you've testified at deposition and in trial, you've testified on behalf of a generic pharmaceutical company, correct?

A. **Yes, that's correct.**

Q. Dr. Heathcock, you are not an expert in pharmaceutical formulation, correct?

A. **That's right, I'm not a formulation scientist.**

Q. And, in fact, you've never practiced pharmacy, either, correct?

A. **That's right.**

Q. And you're not an expert in ophthalmology or any field of medicine, correct?

A. **That's correct.**

Q. You never formulated any marketed drug product, correct?

A. **That's correct.**

Q. And you've never authored any papers dealing with the formulation of an aqueous liquid preparation, correct?

A. **Yes, that's correct.**

Q. You have never authored or edited any book chapters dealing with the formulation of aqueous liquid preparations, correct?

A. **That's right.**

Q. And you're not an expert in the stability testing of aqueous liquid preparations, correct?

A. **That's right.**

Q. You never published any paper involving NSAIDs, correct?

A. **That's correct.**

Q. And you never conducted any research on any product containing an NSAID, correct?

A. **That's also correct.**

Q. And you have never formulated a product containing an NSAID, correct?

A. **Yes, that's correct.**

Q. You have never conducted any research on any drug product containing any nonionic surfactant, correct?

A. **No, I have not used -- I have not used surfactants in my research, ionic or nonionic.**

Q. And you've never formulated any product containing a nonionic surfactant, correct?

A. **That's correct.**

Q. You have no understanding as to how -- how complex the types of formulation problems encountered in the patents-in-suit are, correct?

A. **I'm sorry. Could you --**

Q. No problem.

You have no understanding as to how complex the types of formulation problems encountered in the art of the '431 patent is, correct?

A. **I'm not sure I understand. You say I have no**

understanding about it. Of how complex they are?
Q. Yeah.
A. You mean -- do you mean I don't really know how complicated this is or -- I don't quite know if I'm understanding.
Q. Let me try again.
You have no understanding about how complex the technology is that is part of the art of the '431 patent; is that correct?
A. Well, I don't hold myself out to be an expert in formulation science, and so if that's what you're asking, I don't know what -- you know, the fine points of what ingredients are compatible with each other and what -- you know, why they add these different things. So if that's what you mean by the complexity, yes, I don't have an understanding of that.
Q. You also don't know how a person of ordinary skill in the art would go about formulating new aqueous liquid preparations of NSAIDs, correct?
A. Again, that's -- that's not my area of expertise.
Q. Okay. And you don't know how a person of ordinary skill in the art would go about characterizing the physical and chemical properties of aqueous liquid preparations of NSAIDs, correct?
A. Well, no, I do know more about that. I mean, I know

about how to analyze things, and so I can certainly -- I know how to measure properties but ...
Q. Well, I would like to go to your deposition transcript at Page 109, please. We will just put it up. Noel, can you put up Page 109, Lines 12 to 20.
So the question that was asked at your deposition, Dr. Heathcock, was: "How would a person of ordinary skill in the art go about characterizing the physical and chemical properties of aqueous liquid preparations of NSAIDs?"
There was an objection, and then you responded: It's something that I studied so -- "It's not something that I studied so I don't have -- I don't really know."
A. Can I see what came after that? I'm not sure. Is that the end of my answer?
Q. Yes.
A. Okay. Well, you know, as I say, I don't know exactly what you would do but I -- if you say that you want me to determine the viscosity of something, I know how to do that, but I don't know what things to do.
Q. And you don't know what things to do in terms of formulating NSAIDs into pharmaceutical formulations, correct?
A. A person who -- who specializes in developing formulations would know what kind of tests they need to do. I wouldn't know that. If they asked me to determine the viscosity or the density or the -- you know, or the opacity, I

know how to do those things, but I'd have to be told which thing, which measurements to make.
MR. DINER: Your Honor, I have no further questions.
THE COURT: Is there any redirect?
MR. MARGOLIS: No, your Honor.
THE COURT: Okay. I don't have any questions, either, so you may step down. Thank you.
(The witness left the stand.)
MR. MALIK: Good afternoon, Your Honor.
THE COURT: Good afternoon.
MR. MALIK: Jitendra Malik, counsel for InnoPharma.
MR. HASFORD: And I apologize, Your Honor. I don't mean to cut off my opponent here, Dr. Malik, but one of the court reporters asked us for a list of the chemical names that were read into the record and we have that to provide to the court reporting staff, your Honor.
THE COURT: Okay. Let's take a moment.
(Discussion held off the record.)
MR. MALIK: Okay. Your Honor, may I proceed?
THE COURT: Yes.
MR. MALIK: Defendants call Dr. Robert Cykiert.
THE COURT: Okay, Dr. Cykiert, please come to the witness stand.
THE DEPUTY CLERK: Sir, can you please place your left hand on the Bible and raise your right hand.

(ROBERT CYKIERT, HAVING BEEN DULY SWORN/AFFIRMED, TESTIFIED AS FOLLOWS:)
THE WITNESS: Yes, I do.
THE DEPUTY CLERK: Can you please state your name, sir, and spell your first and last name.
THE WITNESS: Sure. It's Robert Cykiert, R-O-B-E-R-T, and last name is C-Y-K-I-E-R-T.
THE DEPUTY CLERK: Thank you, sir. Can you please speak into the microphone.
MR. MALIK: Your Honor, may my -- can my colleague pass the binder?
THE COURT: Yes.
MR. MALIK: May he approach?
THE COURT: Thank you.
(DIRECT EXAMINATION OF ROBERT CYKIERT BY MR. MALIK:)
Q. Good afternoon, Dr. Cykiert.
A. Good afternoon.
Q. Would you please state your full name and address for the record.
A. Sure. It's Robert Cykiert, and it's 345 East 37th Street, New York, New York, 10016.
Q. Can you briefly describe for the Court your educational background after high school?
A. Sure. I went to Brooklyn College, which is part of the City University of New York, from 1969 to 1973, and I

graduated with a B.S. Degree in Chemistry.

Following that, I went to New York Medical College, which is in Westchester, New York, from 1973 to 1976 and graduated with an M.D. Degree.

04:46 After that, I did a year of internship in Internal Medicine at Lenox Hill Hospital in New York City, from 1976 to 1977.

Following that, I did a three-year residency in ophthalmology at the Albert Einstein College of Medicine in 04:47 Bronx, New York, from 1977 to 1980. And in my last year, I was picked as the chief resident.

Q. Did you have any further post-medical-school training?

A. Yes. After completing my three-year ophthalmology residency, I did a fellowship in Cornea and External Disease 04:47 at the Wills Eye Hospital, which is nearby in Philadelphia.

Q. And after your medical training was complete, what did you do?

A. After that, I went back to New York City and went into private practice and additionally joined the faculty of the 04:47 NYU Medical Center in Manhattan.

Q. Are you currently employed?

A. Yes, I am. I'm self-employed currently in my medical practice.

Q. Do you have a private practice?

04:48 A. Yes, I do.

Q. And where do you currently practice?

A. At the address I gave, 345 East 37th Street in New York City.

Q. Are you an attending surgeon anywhere?

04:48 A. Yes. I'm an attending physician and surgeon at NYU Medical Center, also at the New York Eye and Ear Infirmary, which is part of the Mount Sinai Medical Center in Manhattan, and also the Manhattan Eye, Ear and Throat Hospital.

Q. How long have you had attending privileges?

04:48 A. Since 1981, when I finished my fellowship, so it's about 35 years now.

Q. You also mentioned that you have a position at the New York Medical University Center; is that correct?

A. Yeah. NYU Medical Center, right.

04:48 Q. What is your current title at NYU Medical Center?

A. I'm a Clinical Associate Professor of Ophthalmology there.

Q. And how long have you been with NYU Medical Center?

A. Since 1981.

04:49 Q. Can you describe for me what you do at NYU Medical Center?

A. Sure. I do several things there.

One is I do surgery on my patients there.

I also teach ophthalmology residents who are in 04:49 training, and I teach them about the medical and surgical

aspects of ophthalmology.

And I also teach medical students who rotate through the various affiliated hospitals of NYU School of Medicine and Medical Center.

04:49 Q. Do you serve on any committees at NYU?

A. Yes, I do.

Q. Which ones?

A. Well, currently, I have been on the Credentials Committee. In the past, I've been on the Pharmacy and 04:49 Therapeutics Committee of the NYU Medical Center.

Q. When were you on the Pharmacy and Therapeutics Committee?

A. From 1983 to 1991.

Q. Okay. Let's focus first on the Pharmacy and Therapeutics Committee at the NYU Medical Center. What is that?

04:50 A. It's a committee composed of physicians in all the specialties in medicine, and we meet regularly to review in great detail any medications that might be admitted to the formulary at the hospital.

For example, if there's a new drug approved by the FDA, 04:50 before the hospital admits it into the hospital formulary, before doctors can use it, prescribe it, the Pharmacy and Therapeutics Committee evaluates the drug.

We also from time to time will reevaluate other drugs that have been approved in the past but possibly new adverse 04:50 side effects may be known or there might be some issues with

the drug, or perhaps newer drugs or medications have come in, and so we might decide to remove some medications from the hospital formulary from time to time.

Q. What was your specific role on that committee?

04:51 A. My specific role was to evaluate any medication that's brought forward to the committee for approval for the hospital formulary, and also for any medication that might be taken off. That includes both ophthalmic drugs as well as other systemic medications.

04:51 Q. Now, you also mentioned the Credentials Committee that you serve on. What is the Credentials Committee?

A. The Credentials Committee at NYU Medical Center basically decides whether to allow physicians on staff. Somebody may be applying to join the staff at NYU Hospital because they want 04:51 to admit their patients there or they want to do surgery there. This committee, which is comprised of every specialty in medicine and surgery, goes through the doctors' credentials in great detail to make sure they have the correct qualifications and meet all the regulatory requirements to 04:51 join the staff.

Also, on a regular basis, approximately every two years, we go through the credentials of every doctor to make sure they are fulfilling all their requirements for remaining on staff.

04:52 Q. And what is your role on that committee?

A. **My role is to evaluate every physician who has applied to join the staff and also who has applied every couple of years to be recredentialed.**

Q. Okay. Now, you also mentioned that you still maintain a private practice. How long have you had that practice?

A. **Since 1981, so 35 years, approximately.**

Q. And approximately how many patients do you see each week?

A. **It varies from about 120 to 150 patients per week.**

Q. And do you still perform eye surgeries?

A. **Yes, I do, regularly.**

Q. What kind of eye surgeries do you perform?

A. **I perform a variety of surgeries, things like cataract surgery, refractive surgery, laser vision correction, corneal transplant surgery, LASIK, PRK, and other types of surgeries.**

Q. Let's focus a little bit on cataract surgery. How many cataract surgeries do you perform each week?

A. **Currently, approximately five to six per week, on the average.**

Q. And over the course of your career, how many cataract surgeries have you performed?

A. **I've performed thousands of cataract surgeries over the past 35 years.**

Q. Dr. Cykiert, I believe you have a binder in front of you. Would you mind turning to DTX-446?

A. **Okay, I have it.**

Q. Dr. Cykiert, could you identify DTX-446?

A. **Sure. That's my curriculum vitae, C.V., or resume.**

Q. Does DTX-446 accurately reflect your education and experience?

A. **Yes, it does.**

Q. Now, Dr. Cykiert, I would like to ask you a few questions about your involvement in matters outside your professional practice.

Over the course of your career, have you followed the literature related to post-cataract, cataract surgery treatments?

A. **Sure, I follow the literature very carefully all the time. I read several journals every month. I have to stay on top of the latest developments in eye surgery and cataract surgery and ophthalmology, especially because I teach residents and medical students, so I have to be updated on the latest news and the latest research and the latest articles that come out.**

Q. Let me ask you, have you participated in any clinical trials?

A. **I personally have not participated in any clinical trials, but I have a good knowledge of how clinical trials work. I frequently have to review the results of clinical trials with regard to medications that I may be using or that I come across, and I frequently go to the clinicaltrials.gov**

website to look up information about various drugs that have been approved or are in the process of undergoing clinical trials.

Q. Are you active in any professional organizations?

A. **Yes. I've been active in many. Currently the most important one is the American Academy of Ophthalmology.**

Q. What is the American Academy of Ophthalmology?

A. **It's the largest organization or association of ophthalmologists worldwide. They're -- about 90 percent of all USA ophthalmologists are members, and thousands of other doctors in other countries belong to the American Academy of Ophthalmology.**

Q. Do you recall how long you have been a member of that academy?

A. **Since 1981, when I first finished my fellowship and started practice.**

Q. Have you published any papers in the field of ophthalmology?

A. **Yes, I have.**

Q. How many?

A. **Approximately 37.**

Q. And have you presented any lectures or presentations in the field of ophthalmology?

A. **Yes, I have.**

Q. How many?

A. **I've given about 150 lectures to other ophthalmologists, doctors and residents, and also I've been interviewed on TV a couple of dozen times on various eye, vision, and ophthalmology-related topics.**

Q. Have you won any awards or received any recognition in connection with your work in ophthalmology?

A. **Yes, I have. For four years in a row consecutively, I've been nominated and voted for as one of the best ophthalmologists in New York, as per New York Magazine, and this is a peer-review nomination and voting by other ophthalmologists, as well as other doctors of various specialties.**

MR. MALIK: Your Honor, at this time defendants offer Dr. Cykiert as a medical expert in the field of ophthalmology and ophthalmic surgery, including cataract surgery and postoperative treatment regimens.

MR. LIPSEY: No objection.

THE COURT: All right. Then the Court will recognize Dr. Cykiert as an expert in those fields.

MR. MALIK: Thank you, your Honor.

BY MR. MALIK:

Q. Dr. Cykiert, why have you been called today to testify?

A. **I have been called today to basically discuss Dr. Trattler's opinions that he's given earlier today and yesterday.**

Q. So you were present when Dr. Trattler was on the stand yesterday and this morning?
A. **Yes, I was.**
Q. Okay. And did you form any opinions of your own
04:58 regarding his testimony?
A. **Yes, I did.**
Q. Okay. Before we get into the substance of your opinions, why don't we focus a little bit on the background, the relevant background.
04:58 Let's talk briefly about cataract surgery. What is a cataract?
A. **A cataract is a clouding of the natural lens of the eye. Each one of us has a lens that sits behind our pupil. That lens focuses the light that comes into the eye and gives us a**
04:58 **clear image and allows us to see properly. A cataract is when this lens becomes cloudy, usually due to an aging process. If the lens is cloudy, then it can no longer focus images properly, and our vision gets blurry and distorted and hazy.**
Q. Dr. Cykiert, how are cataracts treated?
04:58 A. **When the cataract gets to a point where it significantly interferes with the patient's life or activities or functioning or work, we do surgery to remove the cataract.**
Q. What is the name of the surgery?
A. **The most common surgery that is used is**
04:59 **phacoemulsification.**

Q. Can you briefly describe for the Court what the process of phacoemulsification involves?
A. **Sure. Basically, I make a small incision into the eye, usually it's about 2.4 millimeters, which is approximately a**
04:59 **tenth of an inch. I then insert a probe into the eye called a phacoemulsification probe. What that does is by high frequency vibration, it turns the solid cataract into a liquid, and then I aspirate or vacuum out this liquid from the eye. In the process, I leave behind what's called the capsule**
04:59 **of the cataract. I then put a small plastic lens in the eye called an intraocular lens, and I insert that into the capsule, so that now the eye has a new lens that can focus light clearly and sharply.**
Q. In your experience, how long does it take a patient to
05:00 recover from cataract surgery?
A. **The recovery these days is very quick. Almost all of my patients are able to go back to their normal activities the day after surgery.**
Q. Do any of your patients experience pain or inflammation?
05:00 A. **Most patients who have cataract surgery have some mild inflammation, but with current techniques, the inflammation is usually mild.**
With regard to pain, only a small, very small minority of patients experience pain with the current modern techniques
05:00 **which you saw a video of yesterday.**

Q. How do doctors treat pain and inflammation after cataract surgery?
A. **The universal way that I do and all other ophthalmologists is by treating the patient with**
05:00 **corticosteroid eyedrops after the cataract surgery.**
Q. What are corticosteroids?
A. **Corticosteroids are a class of steroid medications which basically, through several pathways, prevent and get rid of inflammation inside the eye and also eliminate pain inside the**
05:01 **eye.**
Q. Are you familiar with nonsteroidal anti-inflammatory drugs?
A. **Yes, I am.**
Q. What are they?
05:01 A. **Nonsteroidal antiinflammatories, or NSAIDs for short, are a different type of anti-inflammatory eyedrop that also has some effects on inflammation and pain after cataract surgery.**
Q. Does Prolensa® contain a NSAID drug?
A. **Yes, Prolensa® is one of the NSAID drops.**
05:01 Q. And have you prescribed Prolensa®?
A. **Yes, I have.**
Q. From your experience, what do you understand to be the side effects of Prolensa®?
A. **Well, Prolensa® has a number of side effects. They can**
05:02 **be things like photophobia or light sensitivity; there's**

burning, there's stinging; there's sometimes pain and inflammation in the front of the eye; there's also foreign body sensation as well.
Q. Can you turn in your binder to JTX023?
05:02 A. **Okay, I have it.**
Q. What is JTX023?
A. **This is the package insert which is the official FDA package insert for Prolensa®.**
Q. Let me direct your attention to Paragraph 6.1 of JTX023.
05:03 Now, you mentioned earlier that, from your experience, you see burning and stinging with your patients who are using Prolensa®. Do you recall that testimony?
A. **Yes, I said that.**
Q. Let me ask you this: Do you see burning and stinging
05:03 listed as a side effect on the label for Prolensa®?
A. **No, I don't see it there.**
Q. Then let me ask you: What basis do you have for indicating that burning and stinging are side effects for Prolensa®?
05:03 A. **The basis is that my patients, after I prescribe Prolensa®, come back to me postoperatively, they speak with me, they tell me they're taking it and they have symptoms of burning and stinging and sometimes other side effects, so I hear it directly from my patients.**
05:03 Q. Now, in connection with your patients, how do they

typically explain the burning and stinging manifests itself?

A. Typically, they tell me it's kind of mild and persists for only a few seconds, in other words, it's transient, it's usually not significant. But patients don't know whether 05:04 **burning or stinging is significant or not, so they just mention it to me and say, "Is that okay?" And I tell them, "Sure, that's expected, don't worry about it, and it only lasts for a brief few seconds and it's very mild."**

By the way, that's very different than the example you 05:04 **heard yesterday from Dr. Trattler who said that it's like getting lemon juice in your eye. Now, for those of you who have experienced lemon juice in your eye, which I'm sure some of you have, you know that that's severe burning and stinging. That will stop you in your tracks. You won't be able to** 05:04 **continue what you're doing. It may take you three, four, five minutes to recover from that. That is radically different than the burning and stinging that you get from Prolensa® which is transient, lasts only for a few seconds. So the lemon juice example is, I think, a highly exaggerated burning** 05:05 **and stinging.**

Q. In your experience, is burning and stinging common to all ophthalmic NSAIDs?

A. Yes. It's common to all of them, and, in fact, it's common to most ophthalmic eyedrops, even non-NSAIDs.

05:05 Q. Switching gears a little bit, Dr. Cykiert, did you hear

Dr. Trattler testify regarding the role of pH in the side effect profile for Prolensa®?

A. Yes, I did, I heard that.

Q. Do you agree with Dr. Trattler's opinions that 05:05 Prolensa®'s lower pH improves its side effect profile?

A. I disagree with that.

Q. Why do you disagree with Dr. Trattler's opinion?

A. Well, for several reasons. There's no clinical evidence whatsoever that reducing the pH is of any benefit or value. My patients who take Prolensa®, with the different pH, still 05:06 **have burning and stinging.**

Now, yes, you might expect possibly, gee, if I lower the pH, it might be better, but clinically speaking, from a clinical perspective, there is no benefit whatsoever that's 05:06 **been demonstrated.**

Q. Dr. Cykiert, do you also recall Dr. Trattler testifying regarding CME or cystoid macular edema?

A. Yes, I do.

Q. Okay. And I'm just going to call it CME for short. Is 05:06 that fair?

A. That's a good abbreviation, right.

Q. All right. What's CME?

A. CME or cystoid macular edema is a swelling or fluid buildup in the center of the retina called the macula, which 05:06 **occurs after cataract surgery. But it's very important to**

know the facts and to differentiate that there are two different types of CME. There is something called clinical CME, which is significant, occurs in approximately 2 to 5 percent of patients who have cataract surgery; and then 05:07 **there's something called clinically insignificant or subclinical CME, which occurs in a greater percentage, maybe 15 percent or possibly more in some studies, but this is a very minimal swelling and a very minimal buildup of fluid in the retina such that the patient has no symptoms from this.** 05:07 **The patient would not complain about blurry vision, and also, myself, the ophthalmologist or other doctors, will not actually see it during their examination using standard examination techniques. So subclinical CME is not clinically significant.**

05:07 Q. Dr. Cykiert, would you please turn in your binder to PTX-281. Let me know when you are there.

A. Yes, I have that.

Q. Is PTX-281 the document that Dr. Trattler discussed this morning?

05:08 **A. Yes, it is.**

Q. Let me direct your attention to PTX-281, first page, under "Conclusions." And can you please read for the Court the first sentence right after "Conclusions"?

A. Sure. It's "Cystoid macular edema after cataract surgery 05:08 **has a tendency to resolve spontaneously."**

Q. What does that sentence mean to you?

A. That means that in most cases, the vast majority of cases, CME resolves on its own, without any problems or clinical difficulties.

05:08 Q. Now, when discussing this article this morning, PTX-281, did you also hear Dr. Trattler make a distinction between short-term and long-term recovery for CME using NSAIDs?

A. Yes, I did, I heard that.

Q. Okay. Let me direct your attention again to the first 05:09 page of PTX-281, under "Results," the first complete sentence. Can you read that sentence into the record?

A. Sure.

"Nonsteroidal anti-inflammatory drug therapy was effective in reducing CME detected by angiography or optical 05:09 **coherence tomography, OCT, and may increase the speed of visual recovery after surgery when compared directly with placebo or topical corticosteroid formulations with limited intraocular penetration."**

Q. Let me ask you: Do you agree with Dr. Trattler's 05:10 characterization of this article with respect to the purported short-term benefits for using NSAIDs for treating CMEs?

A. I disagree with Dr. Trattler.

Q. In your opinion, what does this article conclude about any short-term benefits of using NSAIDs for treating CME?

05:10 **A. So, if you're talking about short-term, yeah, maybe**

NSAIDs have some value, if you're comparing them to placebo. They may have some value if you're comparing them to a weak steroid. They may have some value if you're talking about subclinical CME, which I discussed before. But we don't treat with weak steroids after cataract surgery. We treat with potent steroid eyedrops. We never prescribe placebo for patients. So we also, as I mentioned, don't treat subclinical CME. So, therefore, this short-term benefit of NSAIDs is clinically totally insignificant and irrelevant.

Q. I have no further questions at this time. Thank you.

A. **Thank you.**

THE COURT: Okay. Thank you. Cross-examination?

MR. LIPSEY: May it please the Court, Charlie Lipsey for plaintiffs.

We have a binder, if we may hand it up.

THE COURT: Very well.

(CROSS EXAMINATION OF ROBERT CYKIERT BY MR. LIPSEY:)

Q. Are we all set? Okay.

Good afternoon, Dr. Cykiert.

A. **Good afternoon.**

Q. I would like to start by exploring a little bit your sense of minimal, as you described it, in terms of the effect of some of these effects.

And to lay a little foundation, could you turn, please, in your binder to JTX51.

A. **That's JTX051?**

Q. Yes.

A. **Okay. I have it.**

Q. Okay. And that's the sheet from drugs@FDA that indicates the date of approval of Voltaren, diclofenac sodium, correct?

MR. MALIK: Objection, Your Honor, outside the scope.

MR. LIPSEY: This is foundation to get to the question I need to ask.

THE COURT: Okay, I'll permit it as foundation.

BY MR. LIPSEY:

Q. Okay. And that product was approved in March of 1991 by Novartis, correct?

A. **It says 1991. And where does it say Novartis?**

Q. Right above 1991.

A. **Right.**

Q. Okay. Now, it's your view that a very small percentage of patients report mild stinging and/or burning when using diclofenac drops, correct?

A. **Right.**

Q. And you would recognize Novartis as a reliable authority on ophthalmic NSAIDs, correct?

A. **They're a manufacturer of the product. Whether they're reliable authority, it depends how you define reliable authority.**

Q. Well, reliable authority about the nature and properties

of their own products, correct?

A. **Again, they make the product. I think other people can review the products, and there are different types of authorities. There may be differences of opinion between what Novartis says about their drugs and what other parties say about their drugs. So it's -- it's a difficult answer because it's -- the question is not precise.**

Q. Do you think that the information put out by Novartis about its own products is unreliable?

A. **I didn't say that, but I don't see anywhere on this sheet where --**

MR. MALIK: Objection.

THE COURT: Just a moment, please.

MR. MALIK: Your Honor, again, objection. Outside the scope. We are well past foundation at this point.

THE COURT: I'm going to sustain the objection. I don't believe that he relied upon anything about Voltaren.

MR. LIPSEY: He has testified that the burning that is seen is mild, and I'm about to show that at least Novartis doesn't -- and minimal, and involves only a few people, that Novartis doesn't feel the same way. It's an impeachment point, your Honor.

MR. MALIK: Your Honor he, testified about his experience with his patients. He didn't make any representations about what Novartis did on the FDA or its

label. Again, we think it's outside the scope.

THE COURT: Is this document in evidence, JTX51?

MR. LIPSEY: I believe it was offered in evidence this morning, with Dr. Trattler.

THE COURT: If it's in evidence, then I'll permit questioning from it.

MR. MUKERJEE: Your Honor, I do not believe it's been entered into evidence.

THE COURT: All right. It's in the list to be considered from this morning.

THE DEPUTY CLERK: Yes.

THE COURT: Is there any objection to this document being received into evidence?

MR. LIPSEY: No.

MR. MALIK: No, your Honor.

THE COURT: All right. Then I'll permit limited questioning from the document.

MR. LIPSEY: Well, let me move on to the next exhibit.

THE COURT: No, you can't do this to me.

MR. LIPSEY: Okay.

(Laughter.)

THE COURT: No, go ahead.

MR. LIPSEY: In order to vindicate the effort, your Honor, I'll try one more time.

THE COURT: No, I'm sorry.

MR. LIPSEY: No, no, no, I understand.

BY MR. LIPSEY:

Q. Could you take a look at JTX135, please.

05:17 **A. Okay, I have that.**

Q. Okay. And that's -- you recognize that as the Voltaren package insert, correct?

A. It appears to be, that's correct.

Q. Okay. And if you'll turn to the fourth page of the

05:17 exhibit, under the heading "Adverse Reactions Ocular," we see there that Novartis reports that transient burning and stinging were reported in approximately 15 percent of patients across studies with the use of Voltaren Ophthalmic. Do you see that?

05:17 **A. Right. I see that. And you'll notice the first word in that sentence is "transient," and you'll recall that I defined "transient" previously as momentary, lasting a few seconds, and being clinically insignificant.**

Q. Okay. And that 15 percent there that Novartis

05:17 recognizes, that's what you called a very small percentage, correct?

A. That 15 percent speaks for itself. You can say that's either small or large. It's 15 percent.

The main point is, is that it's transient, it's mild,

05:18 **it's clinically insignificant. Patients are not bothered by**

it. They may mention it to me, "Doc, by the way, this drop burns and stings a little. Is that okay?" And I'll say, "Yeah, don't worry about it, that's pretty common, some people have that." It's transient, it's mild, it's clinically

05:18 **insignificant.**

Q. I'm happy to work with you, if there are things you want to say that explain your answer, that's fine. If you could try to answer my question first, I'll try to be fair and let you then explain. Okay?

05:18 **A. Okay.**

Q. You said that a very small percentage of patients report mild stinging with diclofenac, correct?

A. I said that, right.

Q. Okay.

05:18 MR. MALIK: Your Honor, objection, outside the scope again. He never provided any testimony about diclofenac.

MR. LIPSEY: He testified about all NSAIDs. He said that they -- that the effects are mild and minor and nobody cares about them, in sum or substance, is what the testimony

05:19 was. And I'm simply trying to show that there is some contrary authority out there on this point.

THE COURT: I'll permit it. It's impeachment evidence.

BY MR. LIPSEY:

05:19 Q. Okay. And by pouring a foundation, if you could take a

look at JTX52, which was also offered into evidence earlier today. That's the drugs@FDA information about the approval of Acular, right?

A. Yes.

05:19 Q. Okay. And it indicates that Acular contains ketorolac, was approved in November of 1992, and is marketed by Allergan, correct?

A. Right.

Q. Okay. Now, you have said that people on Acular reported

05:20 some mild stinging and/or burning on administration, correct?

A. Where do you see that?

Q. Why don't we take a look at your expert report, Page 11, Paragraph 36.

MR. MALIK: Your Honor, again, objection, outside the

05:20 scope.

MR. LIPSEY: It's exactly the same point, your Honor.

THE COURT: He may be questioned on the prior statements. I'll permit it.

BY MR. LIPSEY:

05:20 Q. Now, four lines down, it says, "Also, similarly to Voltaren, patients using Acular -- and the preservative-free formulation Acular PF first marketed in 1997 -- reported some mild stinging and/or burning upon administration." That's what you said there.

05:21 **A. That's correct. Because if you look at the Acular**

package insert, you'll also have that word "transient" which means mild and clinically insignificant.

And, by the way, you misquoted me a few minutes ago saying that nobody cares about this stuff. I never said that.

05:21 **That was an exaggeration of what I said. I just want to clarify that.**

Q. Okay. That's important. Thank you.

A. Okay.

Q. Can you take a look at plaintiff's trial Exhibit 265?

05:21 **A. Okay, I have that.**

Q. Okay. This is the package insert for Acular, right?

A. Yes, it is.

Q. Okay. And, again, do you recognize Allergan as a reliable authority about the properties and benefits and

05:22 advantages of its own drugs?

A. We talked about that earlier, and I'm not prepared to say whether Allergan is a reliable authority or not. It depends on your definition. We can debate the definition endlessly.

Q. Let's use your definition. Using your definition, do you

05:22 regard Allergan as a reliable authority about the properties of its own drug products?

A. I don't believe I've come up with a definition yet.

Q. Of "reliable"?

A. Yeah. I don't have a definition for that. That's not

05:22 **what I was asked to do. I'd have to think about what that**

means and define it before I could answer your question.

THE COURT: Excuse me. May I suggest rephrasing the question? Do ophthalmologists rely upon a publication of this type?

05:22 MR. LIPSEY: Sure. Thank you, your Honor.

BY MR. LIPSEY:

Q. Do ophthalmologists rely upon the information provided by Allergan about the properties of its own drug products in making decisions in the course of their work?

05:23 **A. Yes, definitely.**

Q. Okay. And -- okay. Thank you.

Now, if we go to the fourth page of the exhibit, under the heading "Adverse Reactions," it states there, "The most frequent adverse events reported with the use of ketorolac

05:23 tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by up to 40 percent of patients participating in clinical trials."

Do you see where I read?

A. Yes, I see that.

05:23 Q. Okay. And that's what you had described as some mild stinging, correct?

A. Yes. Again, the word "transient" is used there, as I mentioned earlier, and that is -- means mild and clinically insignificant.

05:24 Q. Okay. And just, again, by way of foundation, back on the

first page of PTX-265, the package insert, Acular had a .01 -- I'm sorry -- .5 percent ketorolac and .01 percent benzalkonium chloride, right?

A. Yes, I see that.

05:24 Q. Okay. Now, you would agree that eliminating or reducing ocular irritation from Acular has the potential for improving tolerability compliance and effectiveness of treatment, correct?

MR. MALIK: Your Honor, objection, outside the scope.

05:24 MR. LIPSEY: It's the very essence of the invention here, your Honor.

MR. MALIK: Your Honor, Acular is not at issue in connection with the patents-in-suit.

THE COURT: Is the question directed at Acular?

05:25 MR. LIPSEY: It is directed at Acular.

MR. MALIK: He offered no testimony regarding preservatives. Dr. Cykiert offered no testimony on benzalkonium chloride when he was on the stand.

MR. LIPSEY: The witness, as I understand his

05:25 testimony, has suggested that the elimination or reduction of ocular irritation doesn't have the potential of improving tolerability, compliance or effectiveness, and I want to explore that.

THE COURT: Did the witness offer an opinion on

05:25 tolerability and effectiveness of the patent?

MR. MALIK: On the patent? No, Your Honor.

MR. LIPSEY: I believe the testimony was or the point of the testimony was that there's no particular advantage to Prolensa® because of the reduced burning and stinging, and I

05:26 would like to challenge that.

THE COURT: Right. I mean, I think all the questions were asked in terms of burning and stinging rather than effectiveness or compliance.

MR. LIPSEY: Well, I believe --

05:26 THE COURT: But I'll permit the pending question.

MR. LIPSEY: Thank you.

BY MR. LIPSEY:

Q. You would agree that eliminating or reducing ocular irritation from Acular has the potential for improving

05:26 tolerability, compliance, and effectiveness of treatment, correct?

A. The keyword there is "potential." It might have the potential, but it's not necessarily so. There are numerous other factors involved, so that might be one of them,

05:26 **possibly. Potential.**

Q. I would like to show you a document that's been marked for identification as plaintiff's trial Exhibit 789.

MR. LIPSEY: May I approach, your Honor?

THE COURT: Yes.

05:27 THE WITNESS: Thank you.

BY MR. LIPSEY:

Q. This is U.S. Patent 8,008,338, assigned to Allergan.

MR. MALIK: Your Honor, we are going to object. This is not on the exhibit list, nor is this for impeachment.

05:27 Dr. Cykiert is not an inventor on the patent.

MR. LIPSEY: And at least -- it is exactly impeachment, your Honor. And if you'll allow me to proceed, I think you'll see why.

THE COURT: All right. You would have to lay a

05:28 foundation as to whether statements in such a document are -- are deemed reliable. No, strike that.

I'll permit it, and if there's a follow-up question that provokes an objection, then you should object.

MR. MALIK: Thank you, your Honor.

05:28 BY MR. LIPSEY:

Q. Okay. If you will turn with me to Column 1, starting at about Line 37, near the end of that paragraph, the first sentence is just to get our bearings.

A. Excuse me. Are we -- what page are we on?

05:28 Q. It's the page that's got the column Numbers 1 and 2.

THE COURT: It's the seventh page of the document.

THE WITNESS: Seventh? Thank you.

Okay. So I'm on the seventh page. And the columns are 3 and 4?

BY MR. LIPSEY:

Q. 1 and 2.
A. **Oh, let me go back a page. Sorry. Okay, I have that. Thanks.**
Q. Okay. And to get oriented here, starting at about Line 37, Allergan says, "The most common adverse event associated with the use of the 0.5 percent ketorolac formulation is ocular irritation, primarily burning and stinging on instillation." Do you see where I've read?
A. **I see that highlighted there.**
Q. Okay. And then Allergan states, "Eliminating or reducing ocular irritation has the potential for improving tolerability, compliance, and effectiveness of treatment." That was Allergan's view of that issue, correct?
MR. MALIK: Your Honor, again, I object. This is entirely outside the scope. This is not impeachment.
MR. LIPSEY: Your Honor --
THE COURT: What is this? Is this a fact or an opinion that's stated in this column?
MR. LIPSEY: This is Allergan commenting on the very deficiency in their own product which our product was intended to solve in relation to our earlier products, and commenting that, in fact, being able to eliminate the burning does, in fact, have the potential of improving more than simply being happy; it has the potential to improve tolerability, compliance and effectiveness of treatment.

MR. MUKERJEE: Your Honor, forgive me for jumping in, and I know it's unorthodox, but plaintiffs have done this too.
We do object to this. This document is not into evidence. It was not ever cited by Dr. Cykiert. It was not ever cited by Dr. Trattler. It was sprung right now. And it's clearly improper impeachment. There is nothing in here that contradicts what Dr. Cykiert said on the stand.
Dr. Cykiert's testimony was his experience with his patients, just as Dr. Trattler testified about what his experience allegedly was with his patients.
What Allergan thinks, what these FDA documents that they're trying to put -- has no bearing and in no way impeaches what Dr. Cykiert said.
If Mr. Lipsey has a document to show that one of Dr. Cykiert's patients came in and said, "I never complained about burning and stinging, I never thought that was an issue," fine, that might be proper impeachment.
But this document that is not in evidence does nothing. It's a patent. It's a patent that -- and Allergan is putting whatever data or whatever suggestions they have in here. It in no way impacts what Dr. Cykiert said.
And so I do object to this and this line of questioning. We have given him a pretty wide leash here, and yet I still don't see how any of it undermines what Dr. Cykiert said.

THE COURT: Well, it's a document that's not in evidence. It's not been previously identified. It can be used if it's impeachment.
MR. MUKERJEE: For impeachment. I'm sorry, your Honor.
THE COURT: And I don't see that this particular couple of sentences is directly impeaching to something that the doctor testified to. Certainly, it's not his statements or that of the party that retained him, and, secondly, I think it's opinions that are just set forth in the patent to give a framework.
MR. LIPSEY: With respect, Your Honor, it's opinions from who ought to know, if anybody should, who is the originator.
THE COURT: But they're not here to be cross-examined and he's not testifying as to prior art. He's a clinician. He doesn't seem to be familiar with patents, so I don't think it's a proper zone to draw impeachment material from.
MR. MUKERJEE: Thank you.
MR. MALIK: Thank you, Your Honor.
THE COURT: And let me know whenever it's time for a break or if you're going to --
MR. LIPSEY: No, that's fine. It would give me a moment. My examination just got shorter, as you can imagine and it would be a good time.

THE COURT: This would be a good time?
MR. LIPSEY: Yes.
THE COURT: All right. Then let's take about a ten-minute break. We will resume at 3:15.
(RECESS TAKEN; 3:07 p.m.)
THE DEPUTY CLERK: All rise.
(OPEN COURT; 3:21 p.m.)
THE COURT: Be seated, please.
Okay. Mr. Lipsey, you may resume.
MR. LIPSEY: Thank you.
BY MR. LIPSEY:
Q. Welcome back.
A. **Thank you.**
Q. You would agree that some patients have a very low tolerance for putting any products in their eyes and will note a burning and stinging sensation no matter what you prescribe for them, correct?
A. **Right. There are some patients that have that, right.**
Q. Okay. And -- and there are some patients for whom the stinging and burning is a genuine response to the drug product, correct?
A. **Right. There's all different types of patients with different reactions.**
Q. And it's difficult or impossible to predict which patients may experience these symptoms in advance, correct?

A. Right, in advance, you can't tell.
Q. Now, you gave some testimony about your experience with Prolensa, but the fact of the matter is that you prefer to prescribe generic .09 percent bromfenac solution over Prolensa, correct?
MR. MALIK: Your Honor, objection. Outside the scope. We never talked about his preferences.
MR. LIPSEY: Goes to his --
THE COURT: I'll permit it. He testified as to what he prescribes.
THE WITNESS: I used to prescribe Prolensa a lot, but due to patient complaints about the cost of it, it's extremely expensive. I've switched to other products, such as Ilevro, which is made by another company, and so I have used other products because of complaints.
BY MR. LIPSEY:
Q. To the extent you seek to prescribe the once-daily bromfenac-containing ophthalmic solution, you generally prefer to prescribe generic bromfenac .09 percent solution, correct?
A. That's again because of an expense issue. If a patient calls me from the pharmacy and tells me, this is incredible, it's like a car payment, and it's a little bottle, then I will find alternatives. And so Ilevro is a good alternative, and I will also prescribe Acular four times a day. I will also prescribe Voltaren four times a day, because there is a

significant, very significant cost saving for the patient.
Q. Perhaps let's take a look at your expert report, Page 16, Paragraph 48.
And in the second sentence there, you wrote: To the extent I seek to prescribe a once-daily bromfenac-containing ophthalmic solution, I generally prefer to prescribe generic bromfenac 0.09 percent solution over Prolensa because, as mentioned above, Prolensa is considerably more expensive for the patient. That's what you wrote there.
A. Can I see the rest of that?
Q. Help yourself.
THE COURT: Do you want a copy of your report?
THE WITNESS: That would be helpful. Thank you, Your Honor.
MR. LIPSEY: It's in the notebook.
THE WITNESS: What tab is it?
BY MR. LIPSEY:
Q. Should be the first or second tab right in the front.
Before we get there, and I'll give you a chance to explain, but will you acknowledge that that's what you wrote in your expert report?
A. I wrote that, but there are other things there, so I need some time to look at that as well, because that may be taken out of context.
So I'm sorry, which tab is that, so I can find it

quickly and not waste time?
THE COURT: The very first tab.
MR. LIPSEY: The very first tab. PTX-743.
THE WITNESS: First one? And that's Page 16?
MR. LIPSEY: Yes.
THE WITNESS: Okay.
MR. LIPSEY: Thank you.
THE WITNESS: You're welcome.
BY MR. LIPSEY:
Q. And again, to get our bearings, if you turn, please, to DTX-159 in your notebook, that is the package insert for a generic bromfenac .09 percent solution of the sort that you prefer to prescribe, correct?
A. I'm sorry, what was that number of the tab again? I'm sorry.
Q. DTX-159.
THE COURT: Second from the back.
THE WITNESS: Thank you. Okay. I have that, thanks.
BY MR. LIPSEY:
Q. And that is a copy of the packaging and package insert for a bromfenac 0.09 percent ophthalmic generic solution specifically from Apotex Corp., correct?
A. I haven't seen this before, but it looks like that's what it is, just from a quick glance at it.
Q. Well, the fact of the matter is, that it's cited on

Page 1 of the materials considered at the back of your expert report, correct?
A. I'm not sure. I'll take your word for that.
Q. Okay. So you acknowledge this is a -- this DTX-159 is a copy of the packaging and package insert for a generic .09 percent bromfenac ophthalmic solution from Apotex, correct?
A. It appears to be that way.
Q. Okay. Thank you.
Now, the fact of the matter is that you prescribed Prolensa only on rare occasions, correct?
A. I used to prescribe it a lot more, as I mentioned to you, but because of significant and frequent patient complaints about cost, I have to find other alternatives, such as Ilevro, such as Acular, such as Voltaren and also generic bromfenac.
Q. Okay. So it is true that you prescribed Prolensa on rare occasions, correct?
A. That's not exactly true. I didn't state it that way. That's not what I said. I said I used to prescribe it a lot, now I've reduced the amount of prescriptions that I'm using for Prolensa because of cost. That's not the same as what you said to summarize what I said.
Q. Would you turn to Page 24 of your expert report, specifically Paragraph 62.
A. I have that, thanks.
Q. And the last sentence there of that Paragraph 62, you

stated: Additionally, on the rare occasions I do prescribe Prolensa, I do so because it contains bromfenac sodium and not because of any other characteristics of the formulation and because my patients cannot find an available source for generic bromfenac .09 percent solution.

That's what you said there, correct?

A. That's what it says.

Q. Now, in connection with the preparation of your report in this case, and at the time of your expert -- your report, you did not conduct any testing comparing bromfenac-containing compositions, correct?

A. I did not.

Q. Okay. Now, you have suggested that there's no relation between pH and eye comfort.

Did I understand that correctly?

A. That's not exactly what I said.

Q. What did you say?

A. I said it earlier, I said you might expect that if the pH is reduced, that there might be more comfort. But, in fact, there is no clinical evidence or support or benefit or advantage to reducing the pH and, in fact, the proof is that my patients who use Prolensa still have burning and stinging, so that proves it.

Q. You would agree that it is known in the scientific literature that stinging and burning of the eye is affected by

pH and a more physiological pH causes less ocular discomfort, correct?

A. If taken in a vacuum, where all other ingredients of the product are exactly identical, then perhaps that would be the case, or one might expect that. But since there are other parameters, such as drug concentration, surfactants, other variables, other additives, other excipients, you can't state that the way you said it.

Q. Do you know Dr. Mark Prausnitz?

A. What do you mean by do I know him?

Q. Do you know who he is?

A. I know who he is.

Q. He's one of the experts testifying for the defendants in this case, correct?

A. Right.

Q. And you have a copy of his report at PTX-710 in your notebook. Could you turn to that, please?

A. Sure.

Q. And specifically to Page 16 when you get there.

MR. MALIK: Your Honor, objection, outside the scope. Dr. Prausnitz never came up, we never discussed his report. This is clearly outside the scope of any opinion. The only opinion he gave with respect to pH is his experience from a clinician's point of view.

THE COURT: Well, he can be shown a statement and

asked if he agrees or disagrees with it.

THE WITNESS: What was that PTX number again? I'm sorry.

BY MR. LIPSEY:

Q. 710.

A. Oh, okay. I have it, thank you.

Q. Page 16.

A. Okay. I'm there, thanks.

Q. Paragraph 41. First sentence. Dr. Prausnitz states: Even if there were a reduction in pH, it is known in the scientific literature that stinging and burning of the eye is affected by pH and a more physiological pH causes less ocular discomfort.

Do you see where I've read?

A. Yes, I see that.

Q. Do you agree or disagree with defendant's expert, Dr. Prausnitz?

A. Well, again, it depends what scientific literature you're referring to. I haven't reviewed all the scientific literature that's referenced in that sentence, so I can't give you a really good answer for that.

And again, as I explained earlier, if you look at it in a vacuum with all other additives, excipients, ingredients, concentrations, et cetera, if they're all identical, absolutely identical, then perhaps maybe that might be

correct.

But if there are other changes in the formulations or solutions, then you can't categorically state that. But again, I can't answer this accurately because I haven't looked at the scientific literature that it refers to.

So I can read you the sentence, but that's as far as I'll go.

Q. Well, maybe there's something we can agree on, and that is, I gather from your answer that it's your view that there are a lot of different factors, possibly including pH, possibly including the ingredients, possibly including the amount of active, the nature of the active that can affect ocular comfort. Would you agree?

A. Yes, that, I would agree with.

Q. Okay. Now, would you turn, please, to PTX-281, which was the Kim article.

And just to be clear about what this is, this article is based not on a clinical trial, but on a literature review; is that right?

A. It's a very extensive literature review done very carefully by a panel of experts at the American Academy of Ophthalmology.

Q. Okay. And they did run into some limitations, in terms of their ability to draw conclusion from that literature, correct?

A. What specifically are you referring to?

Q. Well, I'm referring specifically to the -- Page 2167, the last sentence before the heading Future Research. The authors acknowledge that lack of a validated and universally used
06:03 definition of CME limits accurate estimation of its incidents and assessment of treatment benefit with cross-trial comparisons.

Do you see where I've read?

A. Yes, I see that.

06:03 Q. So that was an acknowledged limitation that they ran into in trying to sort this all out, right?

A. That's a small limitation. I previously defined for you the difference between clinically significant CME and insignificant CME, which is known as subclinical CME.

06:03 Q. Now, I think you said quite vigorously that saying that this feeling of burning, as if acid had been in your eye was an exaggeration, or lemon juice which is acetic acid burning in your eye was a gross exaggeration of the burning and stinging sensation; is that right?

06:04 **A. Yes, I didn't mention the word "acid," I said specifically lemon juice, but I was referring to what Dr. Trattler said, that it's like getting lemon juice in your eye, and I did say that is a huge exaggeration.**

Q. And the reason lemon juice hurts, it's because it's a
06:04 dilute solution of acetic acid, correct?

A. I'm not a lemon juice expert, but I have gotten lemon juice in my eye and I can tell you that it stings like hell for several minutes, and usually I have to wash my eye out with water and so on.

06:04 Q. And you don't remember that it's acetic acid, that doesn't ring a bell?

A. Again, it may contain acetic acid, but it contains many other ingredients and I don't want to state the wrong ingredient. If you have a reference for lemon juice, I'll be
06:05 **happy to look at it.**

Q. But the fact of the matter is that patients using Bromday, which is the .09 percent ophthalmic bromfenac solution have, in fact, characterized the sensation as the burning feels like acid being put in my eyes, it goes on for
06:05 several minutes after instilling the drops. I have two weeks ahead of me for the use and do not know how I'll get through it. There have been comments like that, correct?

A. Where are you reading from?

MR. MALIK: Objection. It's outside the scope.

06:05 Yeah, and also what is he citing, exactly?

THE COURT: All right.

MR. LIPSEY: Right now, I'm just asking the question.

THE COURT: Whether he agrees that a patient could have that sort of report?

06:05 MR. LIPSEY: Yes.

THE COURT: I'll permit that.

THE WITNESS: I'm sorry, could you ask that again?

BY MR. LIPSEY:

Q. Yes. You could have a report from a patient using
06:06 Bromday, the .09 percent bromfenac solution that the burning feels like acid being put in my eyes, then goes on for several minutes, right?

THE WITNESS: Excuse me, Your Honor, I think I'm entitled to know where he's reading from. I don't know where
06:06 that comes from. I don't know who said that or why they said it. I don't know.

BY MR. LIPSEY:

Q. I'm asking your --

A. I don't know anything about it.

06:06 Q. Let me -- backing up from the details, is that the kind of comment that you could get from somebody who had been using the .09 percent bromfenac in your experience?

A. I don't recall such a comment.

Q. Okay. Do you recall that in your expert report, you made
06:06 reference to WebMD?

A. Yes, there is mention of WebMD in my expert report, right.

Q. Would you turn in your book to PTX -- what's been marked for identification as PTX-791.

06:07 **A. Okay. I have that.**

Q. And you recognize that as a screen shot from WebMD?

MR. MALIK: Objection. Outside scope. And also it's not an exhibit.

MR. LIPSEY: It's impeachment, Your Honor.

06:07 MR. MALIK: Your Honor, he's on WebMD. I mean, are we -- every web page on WebMD at least mentioned that material?

MR. LIPSEY: The witness cited WebMD in his expert report, Your Honor.

06:08 MR. MALIK: Your Honor, the WebMD citing in his expert report was to Prolensa, not Bromday.

MR. LIPSEY: What's sauce for the goose is sauce for the gander, Your Honor.

MR. MALIK: Your Honor, that doesn't mean that
06:08 everything on WebMD --

THE COURT: I agree. Is this some anecdote that's reported to WebMD?

MR. LIPSEY: Absolutely, Your Honor.

THE COURT: All right. I'll sustain the objection.

06:08 This could come from anywhere.

MR. LIPSEY: We have nothing further. Thank you very much.

THE WITNESS: Thank you.

THE COURT: All right. Thank you. Any redirect?

06:08 MR. MALIK: No, Your Honor.

THE COURT: Okay. I have a couple of follow-up questions and again, if there's any objection, don't hesitate to raise the objection. And if there is an objection, sir, then don't answer until I have a chance to sort it out, okay?

06:09 You mentioned that in your practice, that you prescribe a number of -- of the types of drugs that contain bromfenac; is that right?

THE WITNESS: Yes.

THE COURT: And you said that recently, or at some

06:09 point in time, you've tapered off in prescribing Prolensa and you attributed that to costs --

THE WITNESS: Yes.

THE COURT: -- is that right?

And you also remarked that your patients have seldom --

06:09 well, how often have your patients reported what you would characterize as a serious problem with burning or stinging following cataract surgery?

THE WITNESS: You mean burning and stinging from the medication?

06:09 THE COURT: That you would attribute to the medication.

THE WITNESS: It's a small percentage. I would say it's in the range of one or two percent.

THE COURT: And is that consistent, as far as you

06:10 know, with the different clinical studies that have been done

that are reporting between one and two percent?

THE WITNESS: Yes, it's very consistent for Prolensa and the other bromfenac NSAIDs.

THE COURT: And so in the bromfenac NSAIDs, are you

06:10 relying on your memory or have you kept some sort of a log or record about postoperative reactions or complaints?

THE WITNESS: I don't keep a log like that because it's -- it's a small percentage and it's not a significant complaint as I mentioned. It's transient or mild, so I

06:10 usually wouldn't log something like that, because it's not clinically significant.

THE COURT: Would you, in hindsight, be able to detect a small improvement, for instance, from three percent complaints to one percent complaints?

06:11 THE WITNESS: I don't think so. I think difference between one and three percent, without actually logging it, as you mentioned, I think would -- would not be perceptible.

It's a very, very low number.

THE COURT: All right. I don't have any other

06:11 questions. Anything else?

MR. LIPSEY: Nothing further.

MR. MALIK: Your Honor, we would just like to move one exhibit into evidence. It's DTX-446, which is the CV of Dr. Cykiert.

06:11 THE COURT: DTX-446. Any objection to the CV coming

into evidence?

MR. LIPSEY: No, but I would like to move in DTX-159, which was the generic bromfenac package insert and packaging.

THE COURT: Any objection to DTX-159?

06:11 MR. MALIK: No, Your Honor.

MR. LIPSEY: And I also used four documents that had previously been offered into evidence this morning, which -- lest they get lost, I would --

THE COURT: Well, we will return to those in a

06:12 moment, okay? Okay.

So DTX-446 is received into evidence and DTX-159 is received into evidence at this time.

(EXHIBITS DTX-446 and DTX-159 WERE RECEIVED IN EVIDENCE)

THE COURT: Are there any further questions for this

06:12 witness?

MR. MALIK: Not from defendants, Your Honor.

MR. LIPSEY: Did you get their exhibit number correct, the information I got was that it might be wrong.

THE COURT: I said DTX-446?

06:12 MR. MUKERJEE: That's correct, that's correct, Your Honor.

MR. MALIK: Yes, yes.

MR. LIPSEY: I'm sorry, we thought it was a JTX, Your Honor.

06:12 THE COURT: All right, then, thank you, sir. You may

step down.

THE WITNESS: Thank you.

THE COURT: Is there any other witness?

MS. RAPALINO: Your Honor, Emily Rapalino again on

06:13 behalf of the Lupin defendants. We're heading into the home stretch both for today and as it turns out, for the trial. Due to the way that the evidence has come in thus far and some scheduling issues, defendants do not plan to call Dr. Prausnitz tomorrow as we had originally thought, and so

06:13 our next and last rebuttal witness will be Dr. Jayne Lawrence.

THE COURT: All right. So the defendants, then, will not be calling Dr. Prausnitz, and your last witness is Dr. Lawrence.

MS. RAPALINO: That's correct. And I have one

06:13 request, if I could make that request. Professor Lawrence has a flight to catch tonight. I expect that her direct testimony won't run longer than about 20 to 30 minutes, and so if the Court has the time to sit a little bit later if necessary today, just to complete her testimony, that would be much

06:14 appreciated on the part of Professor Lawrence who would very much like to get her flight back to London.

THE COURT: Well, I can do that if you keep it down to about 20 minutes and that will give -- you know, between 20 and 40 minutes, I would say, for cross-examination. Not knowing, you know, what you're going to cover, it's hard to

predict. But I'd have to curtail you before I curtail the other side, since it's your witness that has the problem.

MS. RAPALINO: Understood, Your Honor. That's fine.

THE COURT: Okay. All right. So are you calling Dr. Lawrence at this time?

MS. RAPALINO: Yes. Defendants call Professor Jayne Lawrence.

THE COURT: So please come to the witness stand and I'll remind you that you remain under oath.

THE WITNESS: Yes.

MS. RAPALINO: Your Honor, may we approach with some small binders?

THE COURT: More?

MS. RAPALINO: These are very short, I promise.

THE COURT: Okay.

THE WITNESS: Thank you. Thank you.

MS. RAPALINO: May I proceed, Your Honor?

THE COURT: Yes.

(DIRECT EXAMINATION OF DR. JAYNE WILLIAMS BY MS. RAPALINO:)

Q. Welcome back, Professor Lawrence.

A. Thank you.

Q. Were you here in the courtroom for the testimony of Dr. Davies and Dr. Williams last week and earlier this week?

A. Yes, I was.

Q. Have you been asked to render opinions in response to

their testimony?

A. Yes, I have.

Q. Were you in the courtroom when Dr. Davies testified about a number of references, prior art references that say that it was well-known that NSAIDs and benzalkonium chloride form complexes in solution at the relevant pH here?

A. Yes, I was.

MR. HASFORD: And if I may, Your Honor, I think I need to lodge an objection at this point to the extent -- so as Your Honor ruled earlier this -- this week or last week, I believe it was, if the point of this recall of Dr. Lawrence is simply to say what she previously said in their case in chief, more loudly, we would object to that. I think that the proper scope, if anything, of Dr. Lawrence's testimony here would be a response to secondary considerations of nonobviousness at this point.

MS. RAPALINO: Your Honor, all of Professor Lawrence's testimony will be responsive to the testimony of either Dr. Davies or Dr. Williams, and as far as we're concerned, her rebuttal testimony isn't limited to issues of secondary considerations, but is -- we are also permitted to have Professor Lawrence rebut testimony that those experts offered in response to our prima facie case of obviousness.

THE COURT: As long as you're not repeating Dr. Lawrence's prior testimony, I'll permit it.

MS. RAPALINO: Understood.

BY MS. RAPALINO:

Q. Now, Professor Lawrence, did you hear Dr. Davies testify that a person of ordinary skill in the art would not have believed the statements in Remington's and the multiple other references because there was no experimental data or evidence in those documents?

A. Yes, I did.

Q. As a pharmaceutical formulator, do you agree that a person of ordinary skill in the art would disregard those statements regarding complexation when formulating a bromfenac product?

A. No, I do not, because there was so much in the prior art and in the reference literature, a pharmaceutical formulator would have done -- would have used that regarded this complexation as a matter of fact. A person of ordinary skill in the art would have been aware that this complexation between benzalkonium chloride and bromfenac was likely to occur.

Q. Did you also hear Dr. Davies testify that the structural differences between bromfenac and other acidic NSAIDs would lead a person of ordinary skill in the art to conclude that complexation was unlikely to occur with bromfenac?

A. Yes, I did.

Q. Now, based on your own experience as a pharmaceutical

formulator working with NSAIDs, do you agree with that testimony?

MR. HASFORD: And I'll object, Your Honor, to the extent this goes to chemical issues about structural differences. We have already established that Dr. Lawrence is not an expert in chemistry.

MS. RAPALINO: I would disagree. I believe the Court actually qualified Professor Lawrence as an expert in the chemistry as it relates to pharmaceutical formulation.

MR. HASFORD: No, Your Honor. In fact, the Court specifically only qualified her as to formulation issues and we were clear on that.

THE COURT: I think Ms. Rapalino is correct that there is a later point in the examination when her credentials in chemistry came at issue, and I even permitted voir dire on it and I ruled that she may give opinions regarding chemistry, so I enlarged the scope of her recognized expertise for the trial. So you may answer.

MS. RAPALINO: Thank you.

BY MS. RAPALINO:

Q. Professor Lawrence, do you need me to repeat the question?

A. Yes, please.

Q. Okay. So you remember that Dr. Davies testified that the structural differences between bromfenac and other acidic

NSAIDs would lead a person of ordinary skill in the art to conclude that complexation was unlikely to occur with bromfenac?

A. **Yes. I've been in pharmaceutical formulation for over 25 years and a lot of that time, I've been looking at complexation and that's often complex, as being complexation of nonsteroidal anti-inflammatories, and the pharmaceutical formulator would treat a class of molecules or a group of molecules that are in the same class, such as a nonsteroidal anti-inflammatories, as one group of materials when looking at -- at formulating them in the first instance.**

Q. Now, does the '431 patent-in-suit say anything about the problem the inventors were trying to solve with their alleged invention here?

A. **Yes, it does.**

Q. Could you turn in your binder to JTX1, the '431 patent, and directing your attention to JTX1.3, Column 1, starting at Line 62 through Column 2, Line 11, that goes to the end of the background art section.

Can you explain what the patent-in-suit and what the inventor has said here about the problem they were trying to solve?

A. **The inventors obviously realized there was a problem between benzalkonium chloride and acidic drugs such as the nonsteroidal anti-inflammatories and the result of which was a**

problem with preservative efficacy, and they assumed that somebody of ordinary skill would look to overcoming those problems.

Q. Did you hear Dr. Davies testify that a person of --

MR. HASFORD: Actually, I'll object, Your Honor, and move to strike the last testimony. Apparently, it's not in her reply report and that's what the scope of this testimony should be directed to at this stage.

THE COURT: No, it's rebuttal. She's not cabined by her reply report. If other testimony came in during the plaintiff's case that calls for rebuttal within her area of expertise that she hasn't testified on before, I'll permit it.

MS. RAPALINO: Thank you, Your Honor.

BY MS. RAPALINO:

Q. Did you hear Dr. Davies testify that a person of ordinary skill in the art would have tested a bromfenac-backed formulation to see whether it formed a complex?

A. **Yes, I did.**

Q. And had a person of ordinary skill in the art performed such a test, what would he or she have found?

A. **They would have found that the complex was formed between benzalkonium chloride --**

MR. HASFORD: Objection, Your Honor. This is nowhere in any of her expert reports and I move to strike.

THE COURT: I'll sustain the objection.

MS. RAPALINO: Okay.

BY MS. RAPALINO:

Q. Let's turn now to the Ogawa '225 patent, JTX147.

A. **Yes.**

Q. Do you recall Dr. Davies offered testimony about this patent?

A. **Yes, I do.**

Q. Specifically, if we look at Column 10, Lines 49 through 57, which appears just under Example 8.

A. **Yes, I'm there.**

Q. Do you recall Dr. Davies testified that the statement in the '225 patent that the formulation of Example 6 was stable, excellent for a long time, would have taught the person of ordinary skill in the art that for a long period of time, the stability was excellent and that bromfenac and benzalkonium chloride do not form an insoluble salt?

A. **Yes, I do.**

Q. Now, let's look at Example 6 again, further up in that same Column 10.

Can you remind us what the ingredients were of Example 6?

A. **Certainly. In addition to bromfenac benzalkonium chloride and polysorbate 80, the formulation contained boric acid, borax, disodium edetate, polyvinyl pyrrolidone, sodium sulfite and obviously water.**

Q. What would the person of person of ordinary skill in the art understand the function of polysorbate 80 to be in that formulation?

A. **A person of ordinary skill in the art would assume the function of polysorbate 80 in that formation was a solubilizer.**

Q. And what is polysorbate 80 known to be in the prior art literature?

A. **It's a surfactant, a commonly-used surfactant that's known to be a very effective solubilizer amongst other things.**

Q. Now, did you hear Dr. Williams testify regarding his view on the nomenclature relating to the terms "stabilizer" and "solubilizer" as they apply to polysorbate 80?

A. **Yes, I do.**

Q. Can you just explain how you would apply those terms to polysorbate 80 in the context of this case?

A. **It's my understanding that the person of ordinary skill in the art would assume that polysorbate 80 was present to disrupt the complex formed between benzalkonium chloride and bromfenac and in that way --**

MR. HASFORD: Object. Objection, Your Honor. This again is not in her expert reports. She's trying to testify to information outside the scope of her expert reports and we move to strike.

MS. RAPALINO: Again, this testimony is squarely

within -- it sort of goes to the heart of her testimony and her -- and the heart of her expert reports in this case about the function of surfactants in these solutions to solubilize the complex --

MR. HASFORD: It's not in her expert reports, Your Honor.

THE COURT: Well, do you have a reference, Ms. Rapalino?

MS. RAPALINO: Yes. If you give me one moment, I'll get you a reference.

So as just one example, Your Honor, at Paragraph 57 of Professor Lawrence's reply report, and I'm looking at Footnote 8, Professor Lawrence states: I agree that these surfactants, speaking of tyloxapol and polysorbate 80, do not perform alike and that is why, for example, tyloxapol interrupts the complexes between bromfenac and BAC more effectively than polysorbate 80.

THE COURT: All right. Well, if you reframe the question along those lines, I'll permit it.

BY MS. RAPALINO:

Q. Can you explain how, if at all, polysorbate 80 is functioning in the formulation of Example 6 in this case?

A. Yeah. Polysorbate 80 is a very well-known nonionic surfactant, and it's my opinion that polysorbate 80 is acting as a solubilizer in this formulation and acting to disrupt the

complex formed between benzalkonium chloride and bromfenac. And so it's acting as a solubilizer, but in disrupting the complex. It's also acting as a physical stabilizer in the formulation.

Q. Could any of the other ingredients in the formulation of Example 6 have been performing that function?

A. Absolutely not. For example, boric acid and borax are buffers, disodium edetate is there to chelate any divalent cations and polyvinyl pyrrolidone and sodium sulfite are obviously there to stabilize the bromfenac.

Q. Would a person of ordinary skill in the art have been aware of the functions of each of those excipients?

A. Yes, they are very well-established.

Q. What was the pH of the formulation of Example 6 of the '225 patent?

A. That was pH 8.

Q. Under what conditions was the formulation of Example 6 placed to test its stability?

A. A very limited single condition of four weeks at 60 degrees C.

Q. You previously testified that a person of ordinary skill in the art would have been motivated to replace polysorbate 80 with tyloxapol. Given the, quote, excellent stability recorded for Example 6, under those conditions, why would a person of ordinary skill in the art have been motivated to

modify that formulation?

A. Firstly, the excellent stability refers to only one experimental condition, obviously, 60 degrees for four weeks. As a formulator, you would need to know stability, the stability of the formulation at other temperatures, and by using the Fu EP '984 reference, someone ordinarily skilled in the art would get the stability information they needed to look at enhancing, improving the performance of the formulation.

Q. So given what you've just said about the Fu reference, does the Fu reference teach the person of skill in the art that their stability results would have been any different under different temperature conditions?

A. Yes, it tells a person of ordinary skill in the art that a low polysorbate 80 was sufficient to stabilize formulations at the higher temperature of 60 degrees for four weeks. It was not suitable for stabilizing the formulation at 40 degrees C. room temperature for four weeks.

Q. Can you turn in your binder to JTX209, which is the Fu '984, EP '984 reference.

Can you show us where in the EP '984 reference it discussed those different conditions?

A. Yes, certainly. That would be JTX209.9, and that would be Table 5, that would be the table that's included in Example 5.

Q. And can you just remind us what does the table in Example 5 say about what would happen to an NSAID benzalkonium chloride polysorbate 80 formulation under other conditions?

A. Yes, certainly. In this case polysorbate 80 is called a tween 80. And when an NSAID, in this case ketorolac, is mixed with benzalkonium chloride in the present salt tween 80, the solutions were clear -- I'm sorry, the solutions were clear after one month storage at 60 degrees C., which agrees with the data in the '225 patent, but with turbid or very turbid, in other words, cloudy when stored at 40 degrees C., at room temperature for one month.

Q. What does the cloudiness or turbidity of the solutions that were stored at the temperatures other than 60 degrees suggest?

A. It suggests that the surfactant tween 80 was insufficient to disrupt the complexes formed between benzalkonium chloride and ketorolac.

Q. Given the teachings of EP '984, would a person of ordinary skill in the art simply rely on the stability data at 60 degrees in the Ogawa '225 patent alone and conclude that there was no problem of complexation between bromfenac and benzalkonium chloride in a formulation with polysorbate 80?

A. No, they would not. They would use the '225 patent in combination with EP '984 and realize that there were problems with using polysorbate 80 at lower temperatures.

Q. Could altering other conditions besides temperature affect the physical stability of the formulation?

A. Yes, they could. For example, pH is one of those. If you look at the pH of Example 6 in the '225 patent, that has a pH of 8, and a formulator may be motivated to try and formulate a product at a lower temperature that is closer to that of the pH of the tears of the eye and may have problems in achieving that formulation.

Q. I think you may have misspoken. Did you mean a lower pH not temperature?

A. Sorry, yes. A lower pH.

Q. Thank you.

Now, were you here for Dr. Williams' testimony about the allegedly unexpected stabilizing effect of tyloxapol as compared to polysorbate 80?

A. Yes, I was.

Q. And did Dr. Williams summarize a comparison that he made of tyloxapol formulations and of polysorbate 80 formulations in a demonstrative?

A. Yes, he did.

MS. RAPALINO: Can we pull up PDX4-5?

BY MS. RAPALINO:

Q. Now, did you hear Dr. Williams testify with respect to PDX4-5 that the stability of the claim tyloxapol formulations represented on his demonstrative by formulation codes A-21,

A-27, A-28, and A-29 were unexpectedly better than the stability of comparison Example 1 in the '431 patent?

A. Yes, I did.

Q. As an initial matter, is comparison Example 1 in the '431 patent prior art?

A. No, it's not.

Q. What is the closer prior art to the claimed formulations?

A. The closer prior art is Example 6 in the '225 patent.

Q. So let's go back for a moment to Example 6 of the '225 patent at JTX147. And if I could direct your attention to Table 11 at Column 14 of JTX147.

MS. RAPALINO: Could we pull up Column 14? Okay.

BY MS. RAPALINO:

Q. What was the reported stability for bromfenac sodium -- the bromfenac sodium formulation of Example 6?

A. That was it was clear in appearance and had residue of 100.9 percent, which is a bromfenac content.

MS. RAPALINO: Now, if we could pull up DDX4-2.

BY MS. RAPALINO:

Q. If we compare the stability of the actual closer prior art formulation of Example 6 of the '225 patent to the tyloxapol containing formulations, how does that stability compare -- how does that stability compare?

A. The stability of Example 6 is obviously better than that of the ones that contain tyloxapol, it's better by about 10

percent.

Q. Now, I note that the pH of Example 6 of the '225 patent is 8 and the pH of the other formulations that -- the tyloxapol formulations that Dr. Williams spoke about was 7.

Did you hear Dr. Williams testify that the stability of the Ogawa '225 patent, Example 6 formulation, if formulated at pH 7, would have a stability that would be right in the range of the stability reported for the tyloxapol containing formulations?

A. Yes, I did.

Q. Does that seem reasonable to you as well?

A. It doesn't seem unreasonable.

Q. And so what does that comparison tell you about whether the claimed formulations with tyloxapol demonstrate unexpectedly superior stability over the closer prior art?

A. Okay. The formulations obviously don't demonstrate superior stability over the prior art.

Q. Now, turning to a slightly different topic, were you also here when Dr. Williams testified that an unexpected benefit of the claimed tyloxapol formulations was that they allowed for a stable formulation even without requiring sodium sulfite?

A. Yes, I did.

Q. And do you recall that he used DDX4-6 to show that comparison?

A. Yes, I do.

Q. Now, as an initial matter, does asserted Claim 20 of the '431 patent require sodium sulfite?

A. Yes, it does.

Q. Does Claim 6 of the '431 patent permit sodium sulfite?

A. Yes, it does.

Q. Does the Prolensa product contain sodium sulfite?

A. Yes, it does.

Q. Now, did you hear Dr. Williams point to Experimental Example 4 of the Ogawa '225 patent as showing that -- in his view showing that a polysorbate 80 containing preparation would not have been stable without sodium sulfite?

A. Yes, I do.

Q. Okay. So let's turn to back to the '225 patent at JTX147.

A. I'm there.

Q. And let me direct your attention to Column 8.

A. Yes.

Q. At around Lines 3 through 14. You see Experimental Example 4?

A. Yes, I do.

Q. What stabilizer is used in Experimental Example 4?

A. Polysorbate 80.

Q. Is sodium sulfite included in that preparation?

A. No, it's not.

Q. And now if I could direct your attention just below

Experimental Example 4 in Column 8 of the '225 patent, the paragraph just below that, where are the stability data for the formulation of Experimental Example 4 reported?

A. They're shown in Table 8.

MS. RAPALINO: So if we could look at Table 8 now, which is at Column 14, and this is Lines 23 to 32. Thank you.

BY MS. RAPALINO:

Q. What is the stability reported for this polysorbate 80 containing formulation without sodium sulfite at pH 8?

A. After three weeks storage at 60 degrees, the formulation was both clear in appearance and had 8 -- sorry, had 98 percent of residue or bromfenac sodium remaining.

Q. Have you prepared a demonstrative showing these data in comparison to the data Dr. Williams presented?

A. Yes, I have.

MS. RAPALINO: Can we pull up DDX6-3?

BY MS. RAPALINO:

Q. Based on your review of these data, is the formulation of Experimental Example 4 of Ogawa stable?

A. Yes, it is.

Q. Now, do you remember that Dr. Williams pointed to the text in JTX147, the Ogawa patent, under Experimental Example 4 that said that red insoluble matters formed after three weeks?

A. Yes, I do.

Q. And do you recall Dr. Williams testified that in his view

that allegedly showed that the formulation was not stable?

A. Yes.

Q. Do you agree that means the formulation was not stable?

A. No, I don't. The formulation remained clear and it had over 98 percent of the drug remaining. So, as far as any red insoluble matter was indeed formed, if it was, that must have only been a small amount of the composition because --

Q. What's the maximum amount of bromfenac sodium that could have degraded to form red insoluble complexes based on the stability reported in the table?

A. The maximum amount of bromfenac sodium that could have formed the red precipitants is 2 percent.

Q. Now, taken together then, what does -- what do these data say about whether there is anything unexpected about tyloxapol allowing for a stable formulation without sodium sulfite?

A. There's nothing unexpected about tyloxapol forming a stable solution in the absence of sodium sulfite.

Q. Did you hear Dr. Williams testify that another allegedly unexpected benefit of the claimed formulations is that they have improved preservative efficacy?

A. Yes, I did.

Q. And do you recall he testified specifically that inclusion of tyloxapol allowed for the claimed formulations to pass the European pharmacopeia criteria?

A. Yes, I do.

Q. Do you agree that that was unexpected?

A. No, I don't.

Q. Can you explain why that was not unexpected?

A. Yes, certainly. That's because if you overcome the problem of complexation between benzalkonium chloride and bromfenac sodium, there'll be more benzalkonium chloride left in solution to exert its effect and that's obviously why it passed the test.

Q. Did you also hear testimony from Dr. Williams about replacing benzalkonium chloride with other preservatives or even removing benzalkonium chloride from ophthalmic solutions entirely to avoid the problem of complexation?

A. Yes, I did.

Q. And one example of that was replacing benzalkonium chloride with lauralkonium chloride, is that right?

A. Yes, that was one example.

Q. In your opinion would a person of ordinary skill in the art have taken the approach of replacing benzalkonium chloride with another preservative like lauralkonium chloride to solve the problem of complexation?

A. No, I don't believe they would, that's because a person of ordinary skill in the art would read all the body of literature, including the information in Remington's, which says that it is preferable to reformulate rather than replace benzalkonium chloride if there is a problem of complexation

with the benzalkonium chloride.

MS. RAPALINO: Okay. Thank you, Professor Lawrence. I pass the witness.

THE COURT: All right. Cross-examination?

MR. HASFORD: Yes, your Honor.

(CROSS-EXAMINATION OF JAYNE LAWRENCE BY MR. HASFORD:)

Q. Good afternoon, Dr. Lawrence.

A. Good afternoon.

Q. You testified on direct exam about the Ogawa '225 patent.

A. Yes, I did.

Q. To be clear, you have neither stated nor suggested that the Ogawa '225 patent teaches the formulation of a complex between bromfenac and benzalkonium chloride, correct?

A. I take the section on -- if I can just turn to it if you allow me. Sorry. Beg your pardon. I got confused. Sorry. Repeat the question again.

Q. Would you like me to repeat the question?

A. Yes, repeat the question. Sorry.

Q. To be clear, you have neither stated nor suggested that the Ogawa '225 patent teaches the formulation of a complex between bromfenac and benzalkonium chloride, correct?

A. That is correct, because I had the surfactant in to overcome it.

Q. Let's take a look, if you would, at your deposition transcript. It's going to be the February 29th deposition

transcript.
A. Okay.
Q. And let's pull up Page 186 --
A. Could I have a copy?
06:45 Q. -- line 22.
Oh, certainly.
MS. RAPALINO: Your Honor, while we're getting her a copy of her transcript, I'm not entirely certain what Mr. Hasford will point to, but I will note that Professor Lawrence
06:45 answered the last question in the affirmative so I'm not sure what he means to impeach her with here.
MR. HASFORD: I believe she qualified her answer, your Honor. And I'll point out that when she was asked this exact same question in her deposition, she answer it was an
06:45 unqualified correct and yes.
MS. RAPALINO: And I'll just note that she didn't qualify as much as explain why it was the case. We do see that as proper impeachment but I don't think there's any harm letting that come into the record.
06:45 THE COURT: Nor do I. I'll permit it.
But before we proceed, I lost my LiveNote. Can we catch it up?
We're there. Thank you very much.
MR. HASFORD: May I approach, your Honor?
06:46 THE COURT: Yes.

THE WITNESS: Thank you very much.
MR. HASFORD: You're welcome.
THE WITNESS: Sorry, can I ask what page that's at --
BY MR. HASFORD:
06:46 Q. Certainly. It's --
A. -- it's not clear.
Q. Let me direct your attention to Page 186, Line 22, and the testimony goes to Page 187, Line 5.
Are you there, doctor?
06:47 **A. Yes, I am.**
Q. I asked you:
QUESTION: To be clear, you have neither stated nor suggested that the Ogawa '225 patent teaches the formulation of a complex between bromfenac and benzalkonium chloride, correct?
And you answered:
ANSWER: Correct, that's what I say. And yes.
That was your testimony, wasn't it, doctor.
A. I see that, yes.
06:47 Q. You may put that aside.
Now, you testified an direct exam about the concepts of solubility and stability. Do you remember that?
A. Yes, I did.
Q. With respect to aqueous liquid preparations, the concepts
06:47 of stability and solubility are not synonymous at all,

correct?
A. I've said that, yes.
Q. You testified on direct exam about the Remington's reference. Do you remember that?
06:48 **A. Yes, I do.**
Q. The portion of the Remington reference about which you testified on direct exam does not teach the use of bromfenac, correct?
A. That is correct, yes.
06:48 Q. The portion of the Remington reference which you testified on direct exam does not teach the use of any NSAID, correct?
A. Without reading it, I believe it doesn't.
Q. The portion of the Remington reference about which you
06:48 testified an direct exam does not provide any chemical stability data, correct?
A. No, I believe it doesn't.
Q. You testified an direct exam about various chemistry issues. Do you remember that?
06:48 **A. Yes, I do.**
Q. You have never been qualified by any court or by the U.S. Patent and Trademark Office as an expert in chemistry, correct?
A. No, I have not.
06:49 Q. You're not a expert in medicinal chemistry, correct?

A. No, I'm not.
Q. You're not an expert in organic chemistry, correct?
A. No, I'm not.
Q. You are not a member of the American Chemical Society,
06:49 correct?
A. No, I'm not.
Q. You have never punished anything in the Journal of the American Chemical Society, correct?
A. Not in JACS, no.
06:49 Q. You testified an direct exam about the Experimental Examples of '431 patent. Do you remember that?
A. Yes, I do.
Q. Let me direct your attention to Experimental Example 1 and Experimental Example 2 of the '431 patent.
06:49 MR. HASFORD: Noel, maybe you can pull that up on the screen.
BY MR. HASFORD:
Q. Feel free to go to it in your binder, doctor.
Experimental Example 1 and Experimental Example 2 of
06:50 the '431 patent deal with chemical stability, correct?
A. Can I just check that Tables 1 and 2 -- but you're talking -- so you're talking about -- okay. Fine. I'm with you now. So you're talking about tables?
Q. I'm talking about Experimental Example 1 and Experimental
06:50 Example 2.

A. Which are in the tables, is that correct? Just let me -- I want to check.
Q. They include those tables, that's correct.
A. Thank you.
06:50 Q. I'll ask the question again just to be clear.
Experimental Example 1 and Experimental Example 2 of the '431 patent deal with chemical stability, correct?
A. They certainly show the rate remaining of bromfenac. But I also assume that if there had been major stability, they
06:51 **would have also stated that.**
Q. Let me direct your attention to your deposition transcript of September 4, 2015.
A. Can I have a copy, please?
Q. Oh, yes.
06:51 **A. Thank you.**
Q. You said --
A. It's okay, I'm happy to see it on the screen.
Q. You're fine with seeing it on the screen?
A. I don't want to cause any trouble.
06:51 Q. That's fine. Take a look then, let's go to Page 117, Line 10, through 118, Line 3. And I asked you:
QUESTION: Do Experimental Example 1 and Experimental Example 2 of the patents-in-suit deal with physical or chemical stability?
06:52 You answered:

ANSWER: Sorry, this Experimental -- this is on Page 7, Column 7?
I said:
QUESTION: Correct, Column 7 and 8.
06:52 You answered:
ANSWER: Okay. That deals with chemical stability but only as far as it does also indicate there's some physical component to it because it's correcting for moisture vaporization from the container.
And I asked:
QUESTION: Aside from the correction for moisture vaporization from the container, do Experimental Example 1 and Experimental Example 2 in the patents-in-suit deal with chemical stability?
06:52 And you answered:
ANSWER: I guess so. Yes.
That was your testimony, wasn't it, doctor.
A. Yes, it is, and I don't think it's inconsistent with what I just said.
06:52 MR. HASFORD: Let's pull up DDX6-2.
BY MR. HASFORD:
Q. You testified on direct exam about comparative stability data. Do you remember that?
A. Yes.
06:53 Q. You have never published a paper that mentions

comparative stability, correct?
A. I don't think I've ever used the phrase comparative stability, no.
Q. You testified on direct exam about the stability of the
06:53 claimed formulations of the '431 patent. Do you remember that?
A. Yes, I do.
Q. Yet you do not understand how the aqueous liquid preparations disclose and claimed in the '431 patent regulate
06:53 the dose of drug to the patient, correct?
A. I didn't understand the phrase "regulate the dose," no.
MR. HASFORD: Please turn to -- let's bring up DDX2-57.
BY MR. HASFORD:
06:53 Q. DDX2-57 shows Claim 20 of the '431 patent rewritten in independent form. Do you see that?
A. Yes, I do.
Q. The formulation of Claim 20 of the '431 patent specifies seven different excipients, correct?
06:54 **A. Yes, it does.**
Q. A formulator, in fact, would want to use the minimum number of excipients possible, correct?
A. That's consistent with the inflammation.
Q. Let's turn back to the '431 patent. Actually, let me
06:54 return to your previous answer.

A formulator, in fact, would want to use the minimum number of excipients possible consistent with achieving a formulation, correct?
A. Achieving the required properties of formulation.
06:54 MR. HASFORD: Let's go to your deposition transcript of February 16th. Let's bring it up at Page 324, Lines 13 through 19. I asked you:
QUESTION: A formulator, in fact, would want try to use the minimum amount of excipients possible, correct?
06:55 And there was and objection.
And you said:
ANSWER: The minimum number of excipients that's consistent with achieving a formulation, yes.
That was your testimony, wasn't it, doctor?
06:55 **A. Yes. I think that's consistent with what I just said.**
Q. Okay. Let's turn back to the '431 patent. Let me direct your attention to Experimental Examples 1 and 2 again. Experimental Examples 1 and 2 of the '431 patent entitled Stability Test of Sodium 2-amino-3-4-bromobenzolphenylacetate
06:55 disclose specific conditions under which stability may be measured, correct?
A. They define the stability condition, yes.
Q. Experimental Example 1 tested four formulations with identical compositions expect for variations in the type and
06:56 amount of surfactant, correct?

A. Could you repeat the question, please?
Q. Certainly.
Experimental Example 1 of the '431 patent tested four formulations with identical compositions except for variations
06:56 in the type and amount of surfactant, correct?
A. I probably -- I wouldn't myself use the term "identical concentrations."
Q. Let's take a look at your deposition transcript then.
A. Okay.
06:56 Q. Let's go to the February -- or, sorry, the September 4, 2015, deposition transcript at Page 227, Lines 9 through 19. I asked you:
QUESTION: Take a look now at Paragraph 63 of your declaration on Page 18. You state, Experimental Example 1
06:56 tested four formulations with identical compositions except for variations in the type and amount of surfactant. Comparison Example 1 used 0.15 grams of polysorbate 80, Sample A-02 used 0.15 grams of polyoctoxyl 40 stearate, Sample A-0 -- I believe that's meant to be A-01.
06:57 A-02 used 0.15 grams of tyloxapol, and Sample 3 used 0.02 grams of tyloxapol.
And I asked you:
QUESTION: Is that a true statement?
And you answered:
ANSWER: Yes.

That was your testimony, it wasn't, doctor?
MS. RAPALINO: Objection, your Honor. It's improper impeachment. What the witness testified to is that she wouldn't say identical concentrations, and this goes to a
06:57 different point.
MR. HASFORD: She said that at her deposition, your Honor.
MS. RAPALINO: And just now at trial she said I wouldn't say identical concentrations, which is exactly what
06:57 she said at her deposition.
MR. HASFORD: But What she said was: Experimental Example 1 tested four formulations with identical compositions except for variations in the type and amount of surfactant, that was the question I asked her.
06:58 THE COURT: I think that's exactly what she testified to on direct. I don't see this as impeaching.
MR. HASFORD: May I ask her the question then?
THE COURT: Which question?
MR. HASFORD: May I ask her did Experimental Example
06:58 1 test four formulations with identical compositions except for variations in the type and amount of surfactant?
THE WITNESS: I don't know what I'm supposed to answer here. I can explain there's a limitation with your question.
BY MR. HASFORD:

Q. I'm simply asking you did Experimental Example 1 test four formulations with identical compositions expect for variations in the type and amount of surfactant?
A. That's not how I would put it. But if you want me to
06:58 **answer yes because I answered yes before, I see that statement.**
Q. Comparison Example 1 used 0.15 grams of polysorbate 80, Example A-02 used 0.15 grams of tyloxapol, and Sample A-03 used 0.02 grams of tyloxapol, correct?
06:59 **A. That is a correct statement, yes.**
Q. Let me direct your attention to the discussion after Experimental Example 1.
A. Okay.
Q. The discussion after Experimental Example 1 states that
06:59 the bromfenac in each eyedrop was stable in the order of tyloxapol-containing preparation greater than polyoxyl 40, stearate-containing preparation --
A. Sorry. Can you just -- I just need -- exactly where are you, please?
07:00 Q. Oh, yes. I'm in the last sentence of that first paragraph in the discussion.
A. Okay.
Q. Do you see it there?
A. Yes, I do. Thank you.
07:00 Q. Okay. I'll ask it again.

The discussion after Experimental Example 1 states that the bromfenac in each eyedrop was stable in the order of tyloxapol-containing preparation greater than polyoxyl 40 stearate-containing preparation, greater than Polysorbate
07:00 80-containing preparation." Correct?
A. That's what it says, yes.
Q. You would agree that when the '431 patent compared the stability of bromfenac at pH 7.0, tyloxapol stabilized the aqueous liquid preparation better than Polysorbate 80,
07:00 correct?
A. The same concentration of the surfactant, that is a correct statement, yes.
Q. Experimental Example 1 also states that the composition containing 0.02 percent by weight tyloxapol is more stable
07:01 than a concentration containing 0.15 percent weight per volume tyloxapol, correct?
A. Certainly, in terms of percent remaining, that's a correct statement, yes.
Q. Specifically, Experimental Example 1 compares the
07:01 stability of two different aqueous liquid preparations with identical compositions, A-02 and A-03, where only the amount of surfactant was varied, correct?
A. Yes, that is correct.
Q. You would agree that a person of ordinary skill in the
07:01 art could conduct an experiment comparing the stability of two

different aqueous liquid preparations with identical compositions where only the amount of surfactant was varied, correct?

A. Yes, that's correct.

07:01 MR. HASFORD: May I have a moment, your Honor?

THE COURT: Yes.

BY MR. HASFORD:

Q. The '431 patent discloses stable preparations of bromfenac and tyloxapol, even without sodium sulfite, correct?

07:02 **A. Wait a minute.**

Yes, that's correct. That's -- could I just qualify? That's correct in the terms of the definition of stability, yes.

Q. You testified on direct exam about the closest prior art. Do you remember that?

07:02 **A. Yes, I do.**

Q. You do not know whether Experimental Example 1 of the '431 patent tests against the closest prior art for comparison purposes, correct?

07:03 **A. Perhaps you could explain to me what you mean, "test against."**

Q. What is your understanding of testing against?

A. I don't have an understanding. That's why I've asked.

Q. Okay. Well, let me direct you to your deposition because

07:03 I asked you this question and you understood it there, so I'll

refresh your recollection.

Let's go to the September 4th deposition, at Page 228, Lines 8 through 14.

And I asked you:

07:03 "QUESTION: Do you know whether Experimental Example 1 tests against the closest prior art for comparison purposes?"

And there were some objections, and you said: "I don't have that information to hand to make that comparison." That was your testimony, wasn't it, Doctor?

07:03 MS. RAPALINO: I'm just going to object, your Honor. We did preserve an objection that the question was vague, and I believe that the witness just testified that she felt the question was vague as well.

MR. HASFORD: If she felt the question was vague,

07:04 your Honor, she could have asked me to repeat it or rephrase it at her deposition.

THE COURT: Well, there was an objection, and I agree that the question was vague.

And, in any event, the response given at the dep is

07:04 not impeaching today.

MR. HASFORD: Well, if I may, Your Honor, I mean she has testified extensively today about what she believes that the closest prior art was for comparison purposes. And at the deposition, she said she did not have that information at hand

07:04 to make that comparison, so I believe her testimony at the

deposition does undercut the testimony she gave here to your Honor today.

MS. RAPALINO: And, just to put context to this, this was at her deposition in the context of claim construction,

07:04 before she had written any of her expert reports in this case and before she had fully formed all of those opinions. And what she said here is that the information -- she didn't have the information at hand, which I don't think is inconsistent with her knowing that information sitting here today.

07:04 MR. HASFORD: Well, she also testified, your Honor, at that deposition that she had made certain -- or she had formed certain opinions prior to that time. She also expressed essentially the statement substantive opinions in a declaration on April 21st, 2015, before the U.S. Patent and

07:05 Trademark Office in the parallel IPR proceedings, and I can point to deposition testimony that substantiates that in her February 16th transcript.

MS. RAPALINO: And, again, your Honor, I would just say that her testimony at her deposition was not inconsistent.

07:05 Her testimony was she didn't have the information at hand to make that comparison, suggesting that she didn't have the information in front of her at her deposition, not that she was unaware of that or wouldn't be able to make that comparison if presented with the right materials.

07:05 MR. HASFORD: Well, your Honor, I asked whether she

knew, and I asked her at the beginning of the deposition that if she didn't understand a question, to please ask me to rephrase the question and I would do so.

THE COURT: Okay, time is running short.

07:05 I will permit the witness to explain her deposition answer, if you care to do so. Do you see it on the screen?

THE WITNESS: Yes, I do.

I believe, without reading the context of the discussion, I didn't have the understanding to be able to make

07:06 any comparison because I didn't understand the question.

BY MR. HASFORD:

Q. When I asked you do you know whether Experimental Example 1 tests against the closest prior art for comparison purposes, you answered, I don't have that information at hand to make

07:06 that comparison, correct?

A. Yes, I did, and I don't think that's inconsistent.

Q. Okay. You can put that aside.

MR. HASFORD: And I have no further questions at this time, your Honor.

07:06 THE COURT: All right. Any redirect?

MS. RAPALINO: No redirect, your Honor.

THE COURT: Okay. I have no questions. Professor Lawrence, thank you again.

THE WITNESS: Thank you.

07:06 THE COURT: You can step down.

(The witness left the stand.)

MS. RAPALINO: Your Honor, with that, we conclude our presentation from our live witnesses, and I believe the only issue that remains to be addressed is the exhibits that need 07:06 to be moved into evidence and the arguments with respect to those exhibits.

THE COURT: Okay. So there was a long list of exhibits at the close of the Trattler direct today, beginning with PTX-164. Is that the list that we're talking about?

07:07 MS. HOLLAND: That's one of them, your Honor. We can start there.

THE COURT: Okay. And are there objections to any on that list?

MS. HOLLAND: No, your Honor.

07:07 THE COURT: All right. Then shall I read the exhibits that are now received into evidence?

PTX-164, PTX-277, JTX144, PTX-474, JTX023, JTX143, JTX135, JTX051, PTX-265, JTX052, JTX018, PTX-270, JTX146, PTX-281, JTX142, and JTX145, all are received into evidence.

07:08 (EXHIBITS PTX-164, PTX-277, JTX144, PTX-474, JTX023, JTX143, JTX135, JTX051, PTX-265, JTX052, JTX018, PTX-270, JTX146, PTX-281, JTX142, and JTX145 WERE RECEIVED IN EVIDENCE.)

MS. HOLLAND: Your Honor, may I continue with two exhibits that were used during the Trattler cross-examination?

07:08 I would like to move those into evidence. DTX-210, which was

the Donnenfeld article, and DTX-216, which was the Henderson article.

THE COURT: Any objection?

MR. HASFORD: No objection, Your Honor.

07:09 THE COURT: Okay. Each of these are received into evidence. DTX-210 and DTX-216.

(DEFENDANT EXHIBITS DTX-210 and DTX-216 WERE RECEIVED IN EVIDENCE.)

MS. HOLLAND: So, your Honor, I think that leaves us

07:09 with exhibits that were introduced during the cross-examination of Dr. Williams, and there are four of those, and I understand there are objections to them, so I will give you the list, your Honor. Maybe we can go through them one by one?

07:09 THE COURT: Okay. Just a moment.

Okay. Ms. Holland?

MS. HOLLAND: Your Honor, I'm not -- I'm not sure if you want to do this before or after, but there are also some exhibits from Dr. Heathcock's direct, and I don't know if

07:10 those are objected to or not. Most of them are already in evidence. It's JTX57, JTX158, JTX201, JTX207, JTX209, and DTX-440.

THE COURT: That was the end of Dr. Heathcock?

MS. HOLLAND: That was during the direct of

07:11 Dr. Heathcock, yes.

THE COURT: Any objection?

MR. HASFORD: We have no objection to those, Your Honor.

THE COURT: Okay. Each of the following are received

07:11 into evidence: JTX57, JTX158, JTX201, JTX207, JTX209, and DTX-240.

MS. HOLLAND: 440.

THE COURT: 440, pardon me. DTX-440.

(EXHIBITS JTX57, JTX158, JTX201, JTX207, JTX209, and DTX-440

07:11 WERE RECEIVED IN EVIDENCE.)

MS. HOLLAND: Shall we move on then to Dr. Williams' cross?

THE COURT: Yes.

MS. HOLLAND: Okay. So, first, I will give you the

07:11 list and then we can -- I can discuss them.

So, the first one is PTX-125C, the next one is JTX33A, DTX-478, and DTX-479A.

THE COURT: Okay. And are there objections?

MR. HASFORD: Yes, there are objections to these,

07:12 your Honor. I can summarize the substance of our objections.

THE COURT: Just a moment. Will these be in the Williams' cross binder?

MS. HOLLAND: All except 33A, which is one I handed up separately. Would you like a copy of that one, your Honor?

07:12 THE COURT: Well, I will ask my law clerk to retrieve

Dr. Williams' cross binder, please.

MS. HOLLAND: Your Honor, I don't know if you have a copy of the trial transcript from yesterday. That may be helpful in trying to figure this out. If you don't mind, I

07:13 can hand one up.

THE COURT: Okay.

MS. HOLLAND: This is yesterday's transcript.

THE COURT: All right. Why would each be admissible?

MS. HOLLAND: So, your Honor, 125C is a document from

07:14 the NDA for Prolensa®, and you may recall it contained the release and shelf-life pH specifications for the product. I used this in Dr. Williams' cross-examination without objection. And it's proper substantive evidence as to the actual pH of the Prolensa® product, which is something that

07:14 Dr. Williams talked about in his direct examination. It went in without objection. It's clearly a party admission. It's in their NDA. So I just don't see any basis for objection.

MR. HASFORD: Shall we address these one by one, your Honor?

07:15 THE COURT: Yes, please.

MR. HASFORD: Because that's inaccurate. We made the objection, we preserved the objection. Counsel has attempted during Dr. Williams' cross exam to use all four of these documents for impeachment purposes only.

07:15 I can start with PTX-125C. This is a portion of the

Prolensa® NDA. She attempted to use it for impeachment on the pH level. Your Honor actually precluded them, based on my objection, from asking about the inventor's purpose set forth in these documents. And --

07:15 MS. HOLLAND: Your Honor, I don't want to --

MR. HASFORD: Your Honor, may I finish?

MS. HOLLAND: Can I point you to the transcript? It just might facilitate the discussion.

MR. HASFORD: And I'm happy to -- I was just going to point out the transcript.

MS. HOLLAND: Go ahead. I'm sorry then. I apologize.

MR. HASFORD: Counsel represented that these were for impeachment purposes.

07:15 So, among other places, Page 844 and Page 847, she stated that I think --

THE COURT: Just a moment.

MR. HASFORD: -- as a matter of impeachment of this witness, I should be permitted to ask these questions --

07:15 THE COURT: Just a moment.

MR. HASFORD: I apologize.

MS. HOLLAND: Your Honor, the actual part where PTX-125C is discussed is on Page 918, beginning on Line 7. That's where the -- that's where I started talking about this

07:16 exhibit.

MR. HASFORD: Well, your Honor --

MS. HOLLAND: And it goes through till 919, Line 9.

MR. HASFORD: This preliminary discussion on 844 and 847 applies to all these exhibits actually, and I will point

07:16 your Honor to 847 in particular.

So Page 847, Line 6: If there are other internal documents that show this is not the case, I don't see why Dr. Williams can't be impeached with them. And she repeated that mantra throughout the next several pages of the

07:16 deposition transcript.

I pointed your Honor to Page 844 where she stated: And I think as a matter of impeachment of this witness, I should be permitted to ask these questions.

Page 859: Your Honor, can we go back to the question

07:16 that I asked which led to this -- she stated impeachment?

Page 865: That was the testimony just now, and I would like to impeach the witness on that point.

Page 866: She stated, for this right now, the question is on impeachment? Yes. Then she stated again, can

07:17 I ask some questions and then we'll see if it actually is impeachment?

867: Ms. Holland states, this directly impeaches the testimony that was just given.

Page 868: It's still for impeachment, your Honor.

07:17 869: I'm asking about it for purposes of

impeachment.

871: This is impeachment.

And then, as your Honor will recall, we -- at the end, your Honor asked, those were -- and this is Page 930 --

07:17 those were only for impeachment, weren't they? I answered yes, and the Court acknowledged, so they wouldn't come into evidence. And that's our objection here.

MS. HOLLAND: Your Honor, I think the problem is that when you look at the testimony, it's not about the exhibit

07:17 we're talking about. That's the problem.

There were some exhibits that were only used for impeachment, and I didn't put those on the list of four that I gave you.

If you look specifically at Page 918, it's a

07:18 completely different exhibit we're talking about. It wasn't used for impeachment because it wasn't inconsistent with Dr. Williams' testimony. He agreed with what was in PTX-125C that those were the specifications for the pH for Prolensa®. There is no objection there.

07:18 I'm not -- apparently, Mr. Hasford saying that if he objected once on the basis of one document being used for impeachment, it applies to the entire testimony thereafter. Clearly, that's not the case.

THE COURT: Well, is it necessary to have this

07:18 document in evidence? You have the testimony that says what

the -- what the pH is in this formulation.

MS. HOLLAND: Your Honor, for purposes of appeal, we should be able to have our documents in evidence. There is -- there is no reason not to put this into evidence. So --

07:19 THE COURT: Well, to avoid a fight that is probably one that's going to require me to read about a hundred pages of transcript and relive the glories of yesterday.

MS. HOLLAND: I apologize for that, your Honor.

I thought this was very straightforward. If you look

07:19 at PTX --

THE COURT: But didn't the witness give you the answer that you were looking for? So why do you need the document?

MS. HOLLAND: Your Honor, I don't -- I don't want you

07:19 to have to read a hundred pages. My only point is that to make an evidentiary record, the best record that I can make for my client is to have the document into evidence. I understand what you are saying, your Honor.

There is nothing in this, for example, that says

07:19 exactly what the page is from the transcript. It says PTX-125C.

Your Honor, if the other side is willing to stipulate that those are the release specifications and shelf-life pH specifications for their Prolensa® product, I agree with you,

07:19 I don't -- this is not a stipulation. If there is a

stipulation like that, I agree with you, your Honor --

THE COURT: Well, would that solve the problem? Is there any reason not to stipulate that that's -- those are the release stipulations?

07:20 MR. HASFORD: I think we can stipulate that those are the release specifications set forth in the NDA, your Honor. And Dr. Williams' testimony about that is what his testimony is. On only the page PROL 0003890.

THE COURT: Do you want to look at that page of the

07:20 document and see if that's the one that is -- that you were asking about?

MS. HOLLAND: Yes, Your Honor. And, again, I apologize. I just want to make sure for appeal purposes that I have it.

07:20 THE COURT: Oh, no. And you should make the record that you feel is appropriate.

MS. HOLLAND: And with A stipulation, I believe that's fine. It's just his testimony is not -- it doesn't mean I can't argue against that later. That's why I wanted

07:20 the stipulation.

All right. So I guess the stipulation would be that PTX-125C, which is PROL 0003890, contains the specification for plaintiff's Prolensa® product and that the pH specification is for release 7.6 to 8.0, and for shelf, 7.4 to

07:21 8.1.

THE COURT: All right. And does the plaintiff so stipulate?

MR. HASFORD: We stipulate that that's exactly what the document says, your Honor, yes.

07:21 THE COURT: All right. Then that stipulation is received as evidence and need not be proven further. And so that resolves 125C.

MS. HOLLAND: It does, your Honor.

THE COURT: All right. JTX33A I think was next?

07:22 MS. HOLLAND: Yes, your Honor. And just to remind the Court, this was -- Dr. Williams had some testimony about stability data that, if you recall, came from internal documents of Mr. Sawa. There was a ruling that I could use the document insofar as it was -- pertained to the underlying

07:22 data that was used in the demonstrative exhibit, and that's what JTX33A is and what it would come in for.

THE COURT: Is there any objection to JTX33A?

MR. HASFORD: Well, yes, there's an objection to the document going into evidence, Your Honor, because she used it

07:22 only for purposes of attempted impeachment with respect to the data that she just discussed. If she's looking for a stipulation as to whether one particular page depicts certain data about what she questioned Dr. Williams, we would be amenable to considering that. But it's the placing of the

07:22 entire document into evidence is what we're objecting to.

MS. HOLLAND: This was part of a document that there was a stipulation in this case that this document contained the underlying data for Dr. Williams's exhibits. I can hand up the stipulation, I hope, if we have it.

07:23 MR. HASFORD: No. I apologize, Your Honor. It was the summary of this document that was a stipulation. The document itself was not part of the stipulation. It was the summary of the underlying data.

MS. HOLLAND: The stipulation said that this, what

07:23 I'm seeking to put into evidence, was the underlying data for the stability chart that Dr. Williams put into evidence.

MR. HASFORD: Yeah. I can read the stipulation, Your Honor: The parties agree that documents with Bates Nos. PROL 0359933 to PROL 0359941 are admissible summaries under

07:23 Federal Rule of Evidence 1006. Neither plaintiffs nor defendants will object to the admission into evidence of any document within this Bates range other than on grounds of relevance or inaccurate translation. That's Docket Item 155 in the 14 CV 667 Docket, that was the extent of the

07:24 stipulation. That stipulation did not state that JTX33A --

MS. HOLLAND: Can I have that, please?

MR. HASFORD: Certainly, certainly.

MS. HOLLAND: Thanks.

Oh, here, yeah, Mr. Hasford didn't exactly read in the

07:24 whole stipulation. Do we have another copy of this?

MR. HASFORD: What part were you looking at because I read in the entire relevant paragraph.

MS. HOLLAND: Well, I guess we probably have an issue about relevance but...

07:24 MR. HASFORD: Okay. Which paragraph do you believe I left out?

MS. HOLLAND: Yeah, I think the issue is that in Paragraph 3, plaintiffs stipulated that the documents that make up 33A are the underlying documents for Dr. Williams'

07:25 charts.

MR. HASFORD: No.

MS. HOLLAND: So I seek to put them in on that basis.

MR. HASFORD: No, Your Honor. Those -- the documents in Paragraph 3 have entirely different Bates numbers from the

07:25 JTX33 document that Ms. Holland is attempting to get into evidence.

MS. HOLLAND: Yes. Plaintiffs produced them twice under different Bates numbers.

MR. HASFORD: I don't believe that they are the same

07:25 documents, Your Honor.

Would Your Honor like a copy of the stipulation?

THE COURT: Yes.

MS. HOLLAND: There's a stipulation not to object to admission.

07:25 MR. HASFORD: That's -- no, Your Honor, the -- the

stipulation, as far as the summary is in Paragraph 4.

MS. HOLLAND: Yeah.

MR. HASFORD: And then there's a stipulation about various other documents in Paragraph 3, but that's not JTX33.

07:26 MS. HOLLAND: Yes, they are, and maybe we don't need to do this today, but I can show you it's the same documents.

MR. HASFORD: Your Honor, I'd like to resolve this today because I don't want this to turn into a round of briefing before Your Honor to burden the Court.

07:26 MS. HOLLAND: This is your --

THE COURT: Let's take a moment and see if the same document was produced twice. I think that's the dispute.

MR. HASFORD: And, Your Honor, we -- I would also note in here that we've preserved a relevance objection and

07:26 the relevance objection is actually what we've made here and I can explain that to Your Honor. As Your Honor will recall, you precluded them --

THE COURT: Just a moment.

MR. HASFORD: I apologize.

07:26 MS. HOLLAND: It may take us a few moments to put this together, Your Honor.

THE COURT: Okay. I agree that we should work it out now.

MS. HOLLAND: Yeah, please. Your Honor, maybe we can

07:27 go on to the next ones then while we're having people look at

those Bates numbers.

MR. HASFORD: Maybe if you'll give us a second, Your Honor.

Do you just want to do another stipulation like we did

07:27 on the last one, you take the portion that you used with Dr. Williams and stipulate that that portion is what it purports to be?

MS. HOLLAND: Well, I think we have a bigger problem here, because we have a stipulation where you said you weren't

07:27 going to object to those documents going into evidence if we agree to your summaries, and now you're objecting.

MR. HASFORD: We maintained a relevance objection there in the stipulation.

MS. HOLLAND: Okay. Well, let's -- I think, Your

07:27 Honor, maybe it's better to move on then, too.

THE COURT: All right. Then we will set that aside for a moment. The next one is DTX-478.

MR. HASFORD: And, Your Honor, I might be able to short-circuit this, because DTX-478 and 479A, I think we can

07:27 lump them both together.

First off, these were not identified in the final pretrial order so they are improper for that reason, No. 1 -- but at least for moving into evidence. But No. 2, as Your Honor will recall, these were internal documents from Xibrom

07:28 NDA, the only purpose Your Honor allowed Ms. Holland to use

these documents for, was for attempted impeachment, not to show any purpose of any experiments or anything like that.

And so, that's why we object to -- to placing the entire document into evidence. And again, it goes to Your

07:28 Honor's ruling that Page 930 of the transcript yesterday, where Your Honor asked: Those were only for impeachment, weren't they?

We confirmed that they were, and Your Honor stated that they wouldn't come into evidence because they were just for

07:28 impeachment.

MS. HOLLAND: Your Honor, again, we have an issue of different places in the transcript talking about different documents.

Let me just -- let me get the first issue off the table

07:28 about the pretrial order. The final pretrial order that was -- the amended one that was delivered to Your Honor did have these exhibits. Plaintiffs produced their FDA 30(b)(6) witness after the initial pretrial order was filed with Judge Williams, and we had permission to supplement the trial list

07:29 with documents that were connected with the 30(b)(6).

These particular ones were not marked at the deposition but they were FDA documents that were relevant to FDA issues raised that were part of this 30(b)(6) deposition.

Plaintiffs withheld -- well, I don't want to get into

07:29 why it happened, but the 30(b)(6) on FDA issues didn't happen

until after the pretrial order was entered, and we had explicit permission to amend our exhibit list to include documents connected with the issues in the 30(b)(6) depositions.

07:29 MR. HASFORD: If they felt those documents were so important, Your Honor, why didn't they use them at that 30(b)(6) deposition? That's problem No. 1. But the bigger problem, of course, is the fact that they were used at trial only for impeachment purposes, and they shouldn't go into --

07:29 be entered into evidence on those grounds.

MS. HOLLAND: Your Honor, so I think what happened at trial is that there was a distinction made between internal documents like Mr. Sawa's notebooks, et cetera, and between plaintiff's NDA documents. And on Page 863 of the transcript,

07:30 we got into this issue about NDA documents, and basically, Your Honor, you said you were going to permit the testimony for that limited purpose of being plaintiff's own statement to the FDA and then later on, you explained the ruling on Page 863, Line 17: The thrust of my ruling is that this is a

07:30 statement, not in an internal document, not in a laboratory report, but in a statement to the FDA about the purpose of a particular constituent, in that case it was tyloxapol. And the witness, it's fair to question him because his direct testimony touched upon this very subject, et cetera.

07:30 And then -- so that ruling, my understanding was that

for that purpose, the NDA was coming in as substantive evidence on that point and not as impeachment. Other documents I agree with Your Honor were different, and you put them in the category of an internal document and a laboratory report where I could only do impeachment. The FDA admissions contained in plaintiff's NDA, I believe, were ruled on as substantive evidence.

MR. HASFORD: It's not prior art. We also, as Your Honor will recall, we raised the issue and this was ISTA who filed the NDA. It was not plaintiffs. Your Honor then later clarified on Page 913 of the transcript when Ms. Holland was asking to use these documents to -- as to what they expected and intruded into the inventor's area or the area of the inventor's state of mind, Your Honor said, you could ask what the data showed, but again, the purpose, what they expected is intruding into the area of the inventor's mind of why the inventor was doing what he was doing, and the Court instructed Ms. Holland that the Court had already ruled to move on.

Again, as we go back in the transcript to Pages 844, 847, for example, Ms. Holland makes clear that the point of using all of these documents was for alleged impeachment, and it was not for the substance of the documents and that's how Your Honor ruled on our objection.

MS. HOLLAND: Your Honor, Page 913 testimony that you were just pointed to had to do with the internal documents and

as I said, there was a distinction both in my questioning and in the admissibility of the documents between FDA admissions and NDA documents and the internal lab notebooks, and I believe that that ruling is clearly stated on Page 863 when the Court made that distinction between internal laboratory documents and FDA documents.

MR. HASFORD: And Your Honor, these are non-prior art documents. These are documents that were transmitted under confidentiality to the FDA. Ms. Holland was only attempting to use them for impeachment and she made that clear on the record time and time again, and I've already read that -- those portions of the record.

MS. HOLLAND: I never made that statement about FDA documents. We had a whole discussion on this. Your Honor made a ruling yesterday.

THE COURT: Well, my ruling on Page 863 permitted you to use the documents to question the witness, and I permitted you to use the document to see if it changed the witness's mind or changed the witness's view, as to that particular subject. And I did so because it wasn't just some idle statement from the literature, but rather a statement by the plaintiff's predecessor to the FDA.

But I didn't admit the document into evidence. I permitted questioning that's based on the document as is done all the time with regard to impeachment materials. So in

permitting the questioning, it doesn't lay the foundation for the admission of the -- of the document itself. If this actually might be an area where the parties, if the defendant feels strongly about its admissibility, you may want to address this in your post-trial submissions 30 days from now about why this confidential submission to the FDA may be admitted into evidence.

MS. HOLLAND: Just so I understand --

THE COURT: Into evidence.

MS. HOLLAND: I'm sorry, Your Honor. Just so I understand, is the objection relevance? Because clearly, it's a party admission that can come in.

THE COURT: Yeah, the relevance objection, I would overrule at this point in time.

MS. HOLLAND: So what is the objection, then? I just don't understand. What is the federal rule of evidence by which it can't come in?

MR. HASFORD: The objection, Your Honor, it's not prior art and they're attempting to use other portions of the document improperly. The document was only being used -- Your Honor allowed it to only be used for the limited purpose of certain portions of the document. They actually attempted to go to portions of these documents and try to reach into the inventor's state of mind.

So it was irrelevant for that purpose but it's also --

it's not a proper document to be admitted into evidence, because it was only being used for the limited purpose of impeachment, and that's exactly how Your Honor ruled on Page 930 of the transcript.

THE COURT: And that was -- that was intentional.

MS. HOLLAND: It was a lot -- I'm sorry.

THE COURT: It was propounded as impeachment, I permitted it as impeachment, and that nose inside the tent doesn't permit the whole camel to come in. If there's things in the record that are derived from the document, then so be it. They are in the record and they can be used and the witness has testified to them. That doesn't make the entire document admissible. There's other areas of the document where I sustained objections.

MS. HOLLAND: Not on that particular document.

THE COURT: Not on that particular one?

MS. HOLLAND: No.

THE COURT: Okay.

MS. HOLLAND: Well, Your Honor, I would -- maybe I can suggest that we have the same sort of stipulation we had for 125C, where the pieces that were -- actually came into the record, we can stipulate that those were in the Xibrom NDA. Would that be okay?

MR. HASFORD: I think we would have to look at exactly what came into the record and how it did, Your Honor.

I apologize, but I don't think we can agree to that at this point because I'm not sure what Ms. Holland tried to read into the record and what was objected to without scouring the whole transcript, unfortunately.

07:36 MS. HOLLAND: And just to make clear again, Your Honor, I recognize these are not prior art, but a lot of what Dr. Williams talked about in his direct was not prior art because you don't have to be within the scope of the prior art for any secondary considerations, and we -- it seemed like

07:36 Dr. Williams was pulling stuff from all over the place for his secondary considerations, labels that came later on products that weren't even around as of 2003. So to be clear, there is no prior art problem when you come to secondary considerations.

07:37 MR. HASFORD: And our --

THE COURT: And if Dr. Williams had testified that he relied upon this document as a basis for his testimony and was -- and testified as to its contents in his direct, then that would strengthen your hand as to its admissibility, but he

07:37 didn't do that.

MS. HOLLAND: But he based his opinions on his testimony that the stability data was -- and I think we went through this yesterday, that the stability data that he put up on the screen was chemical stability data, and that -- that's

07:37 not a matter of prior art or not, it's factual. Was the data

he was relying on, was that really chemical stability data or was it something else?

And that goes to secondary considerations and it really -- I don't think does it matter whether he used it or not.

07:37 Maybe he purposely didn't use it because he didn't like what was in there. But the point is, to get to the bottom of the fact of when he put the stability up there -- data up there, was that chemical stability or physical stability?

The way to get to the bottom of that issue is to look

07:38 at the actual fact of whether it was physical or chemical stability. Again, it's not a matter of prior art. It goes to whether there's an unexpected result here, which could turn on what the purpose of the use of the tyloxapol and polysorbate 80 was in the formulations, not as a matter of prior art or

07:38 obviousness, but as a factual matter, why were they in these compositions.

MR. LIPSEY: Your Honor --

MS. HOLLAND: So I believe that's an appropriate basis to put these into evidence.

07:38 MR. LIPSEY: Your Honor, if I may. This is the fifth time we've had this discussion. The data that was put up for unexpected results, the number was the percent drug remaining, which is a chemical stability number.

MS. HOLLAND: We don't agree.

07:38 MR. LIPSEY: Counsel has wanted to get before Your

Honor information suggesting that it also played a role in physical stability, and she certainly, you know, played that out in front of Your Honor many, many times here. But the

07:39 fact of the matter is, why the inventor put it in what other things it may do or may not do is within the forbidden realm. She cannot take that and say, see, it's obvious that it affects physical stability because they mentioned in their non-prior art documents, physical stability. The unexpected result was chemical stability.

07:39 MS. HOLLAND: With all due respect, Your Honor, Mr. Lipsey's saying that the unexpected result is chemical stability doesn't make it a fact. The fact is, there's a dispute about it, whether it was chemical or physical stability.

07:39 THE COURT: All right. I understand and that's why I overruled the relevance objection. But the greater objection here is that this takes us into the inventor's mind about the purpose or the why of why the inventor was doing what they were doing.

07:39 MS. HOLLAND: This is not -- this is about the prior art. It's not about the invention. This is about Xibrom.

MR. LIPSEY: It's the inventor's own work, the inventor's non-public own work, and that whole spectrum of stuff is not available for purposes of attacking the validity

07:40 of the patent. She's allowed to use what's in the public

domain.

MS. HOLLAND: I'm not sure if Mr. Lipsey is suggesting that Mr. Sawa was also the inventor of the '225 patent, because that's prior art. The Xibrom NDA has nothing

07:40 to do with the invention here. It's in the -- it's about the prior art.

MR. LIPSEY: It's only in the prior art --

THE COURT: Just a moment.

MS. HOLLAND: So that particular objection of

07:40 Mr. Lipsey that he's been raising that we can't get into the inventor's own mind is completely irrelevant here because this doesn't have to do with the invention. This particular document has to do with Xibrom which is a prior art compound that -- I don't know or think the inventors in this case had

07:40 anything to do with. So that needs to be taken off the table for this particular document.

MR. LIPSEY: It is not prior art under any section of the statute. It's not a patent, printed publication, public use, offer for sale, sale in the United States.

07:41 MS. HOLLAND: And I never said it was.

MR. LIPSEY: It's not prior art under any section of the statute and Ms. Holland knows that full well.

MS. HOLLAND: Neither was the internal documents on stability that Mr. -- Dr. Williams put up on the screen. That

07:41 wasn't prior art either. The reason he could do it was

because it went to secondary considerations, Your Honor.

MR. LIPSEY: It was --

MS. HOLLAND: And, Your Honor, respectfully, if everything is off the table that's not prior art, that's fine, I guess we will take back all of Dr. Williams' testimony about stability data that wasn't in the prior art.

But to the extent he put in something that's not in the prior art that goes to a fundamental issue in the case, I have a document, an NDA, doesn't have anything to do with the inventor's mindset in this case. It's Xibrom. It's not the inventors. It's not these inventors at all.

MR. LIPSEY: The point, there's a line in the patent law, the comparative evidence of the properties of the invention is relevant and admissible, no matter when it shows up. That's a very different question from what can be used to allege the obviousness of the invention, and there, it must be in the prior art.

She is complaining because the statute imposes upon her the obligation to come forward with evidence of the prior art to invalidate the patent, and the statute allows, and the case law on it allows us to come forward with comparative evidence of the properties of the invention, whenever it comes to pass.

MS. HOLLAND: And the comparative -- I'm sorry.

MR. LIPSEY: And that's just the law.

MS. HOLLAND: And the comparative properties of the

prior art. That's the whole point. We have to be able to compare the invention to the prior art outside the scope of the prior art. We're bringing in now -- and I'm not sure if Mr. Lipsey is doing this on purpose or not, but it's kind of like we're two ships passing in the night.

I keep saying it's about secondary considerations and Mr. Lipsey keeps telling you why it can't come in as prior art. Those are -- I agree it's not prior art. I'm not suggesting it should come in as prior art. I'm suggesting it should come in to the live issue of the case of secondary considerations and whether the comparisons of stability that were made in this case by Dr. Williams were properly made, whether they were actually chemical stability data or whether they were physical stability data.

There's no suggestion that there -- I mean, maybe there is a suggestion that there was some false information, but -- in the Xibrom NDA, but I'm not aware that that's what plaintiffs are arguing.

THE COURT: All right. So the purpose that you're seeking to admit to -- 478 and 479A into evidence is that it's a secondary consideration and whether the comparisons of stability of the plaintiff's witness, Dr. Williams, were properly made?

MS. HOLLAND: Yes.

THE COURT: And didn't your examination already with

the witness explore exactly those points without having to introduce the document into evidence?

MS. HOLLAND: No, Your Honor, because the key point here is what was -- the stability data that had to do with Ogawa Example 6 that had polysorbate 80 in it, was that or was that not stability data that had to do with physical stability and disruption of the interaction between BAC and bromfenac. That, we believe, was the purpose of that stability study that was done, and that's the comparison that should be made, not chemical stability like Dr. Williams was saying.

And we have a document in the NDA that goes to the very heart of that issue. Without that document -- that document is the evidence of exactly what that formulation was and exactly why polysorbate 80 was in there and exactly what the stability data means when you look at formulations containing the polysorbate 80.

THE COURT: So --

MS. HOLLAND: That's why I need the document or I need a stipulation about what's inside the document, either one.

MR. LIPSEY: The words "purpose" and "why" were the important words in that sentence. And that is what cannot come in. The fact she wants to say that number is a physical stability number, it -- physical stability is whether it gets cloudy, Your Honor. We talked about that. Was it clear or

was it turbid? Chemical stability was how much of it is left, and that's all those numbers were.

MS. HOLLAND: Well, that is a dispute. That's a very hotly disputed issue. And again, Mr. Lipsey's saying that that's all those numbers were doesn't make it -- that's not evidence and it doesn't make it an undisputed fact in the case.

THE COURT: What you're seeking to establish, then, is, what are the characteristics of Xibrom as reflected in the Xibrom NDA?

MS. HOLLAND: Yes.

THE COURT: All right. Can there be a stipulation as to what those characteristics are?

MS. HOLLAND: I'm happy to take a stipulation if we can get one.

THE COURT: Without reference to the NDA.

MR. LIPSEY: I am always happy to talk about stipulations. That's not clear to me what it would be. As much as Mr. Hasford wants to straighten this out, if this is a way to do it, that's something I think we're going to have to chat about to see what it is you propose.

MS. HOLLAND: I'm happy to come back for a conference tomorrow morning, Your Honor, to tie up these loose knots of the evidence, if you think that would be helpful.

MR. LIPSEY: I'm not sure we need to do that.

MR. HASFORD: I don't think --

MS. HOLLAND: Well, then I think we need a written -- I don't want to leave Camden without having gotten this taken care of and I know Your Honor has time tomorrow morning

07:46 potentially if you want to --

THE COURT: Of course I do. I set all day tomorrow aside.

Well, I think there's two realistic options rather than bringing everyone back tomorrow. This is the only dangling

07:47 participle that I'm aware of at the moment, that either the parties reach a stipulation within the next day or two, or the parties will be granted leave to brief this issue of admissibility of DTX-478 and DTX-479A, and there, what I'm interested in, is something that I haven't had the opportunity

07:47 to look up myself which is how the admissibility of NDA documents are treated generally in patent litigation of this type, and whether it matters that it's not the NDA on the invention but of a prior composition, and, therefore, entitled to less protection or secrecy.

07:47 MR. LIPSEY: I think that's a perfectly acceptable resolution from our standpoint, and probably the only realistic one.

THE COURT: All right. And so what I'm asking you to do is to see whether in the next 24 hours, you can agree to a

07:48 stipulation as to -- maybe a compromised version of the data

that the defendant is seeking to receive into evidence.

If there's not a suitable stipulation forthcoming, then you'll have the opportunity to brief this as part of your -- maybe you want to brief it sooner than 30 days from now

07:48 because when you are formulating your proposed findings of fact and conclusions of law, you will want to know whether these documents are in. They sound like, you know, respectable, important documents to know whether they are in or out. I'm willing to rule on them sooner if you can brief

07:48 it sooner.

MS. HOLLAND: Yeah, we would be willing to brief that sooner, Your Honor. That's a good solution, I believe. So if we can't reach agreement, can we brief just that one evidentiary issue within a week?

07:49 THE COURT: Yeah. And you have the burden seeking admissibility and so the defendant's brief would be due seven days from now.

MS. HOLLAND: Okay.

MR. LIPSEY: Your Honor, if I may, and I know Your

07:49 Honor and I had a chat about this a long time ago, but we have been struggling with this parallel patent office proceeding that has been going on in the hearing and it is next Tuesday, and I guess we would like a little bit of leeway to deal with that just so that we can get that out of the way.

07:49 THE COURT: Well, you have a very supple team on your

side. This is one limited issue.

MR. MURKERJEE: Your Honor, may I?

THE COURT: And also the defendant would have to go first next week.

07:49 MR. LIPSEY: Fair enough.

THE COURT: And then the plaintiff, your brief would be due, let's say seven days after that.

MR. LIPSEY: Okay. We can do that. I jumped the gun on that. I'm sorry.

07:49 MR. MUKERJEE: And Your Honor, if I may just clarify, plaintiff's law firm, Mr. Lipsey's law firm is not handling that proceeding. It's the law firm of Crowell & Moring that's representing.

MR. HASFORD: We are certainly handling it on behalf

07:50 of Senju, Your Honor. He said plaintiff's law firm. No, Crowell & Moring is not representing Senju in that proceeding. We are.

MR. MUKERJEE: That is correct, Your Honor. I misspoke. I apologize.

07:50 MR. LIPSEY: We --

THE COURT: Well, look, if the briefing schedule is impossible, then I'm not going to require it. If you're able to do it and if you still have this dispute -- this is only if you have the dispute. I guess it's an incentive to work a

07:50 little harder on a stipulation when you have time. On your

feet, I understand that it's hard, I'm not being critical of either side.

And so see what you can do. But that's how we will leave it, and if there's a stipulation, then I would simply

07:50 ask Ms. Holland to reduce it to writing and send it my way and it will be included as if it's part of the evidence in the case.

MS. HOLLAND: Thank you, Your Honor.

THE COURT: Okay.

07:50 MS. HOLLAND: Then the last thing was that 33A that we needed to match up the Bates numbers, but I suggest we also wrap that up in the next day or so, together with the other issues, and hopefully that we can come to resolution on that one.

07:51 MR. LIPSEY: As a very last final matter on behalf of the plaintiffs, we would like to thank the Court and the Court's staff and particularly, the long-suffering court reporters for their many courtesies that have been extended to us over the last week or so, and thank you very much.

07:51 THE COURT: Well, that's very kind of you to say.

And so for 33A, we will wrap it up in the next day for briefing, same thing, is that the understanding?

MR. HASFORD: That's our understanding, Your Honor. 33A, you want to wrap that into the briefing as well?

07:51 MS. HOLLAND: Well, I don't know if we need the

briefing. If we need it.

MR. HASFORD: Oh, if we need it, sure.

THE COURT: So we will use the same procedure for 33A.

07:51 And do you have your respective excerpts from the depositions?

MR. HASFORD: Deposition designations, Your Honor?

THE COURT: Yes, designations.

MS. HOLLAND: I think there's an issue. We still

07:52 have an issue with respect to some of plaintiff's designations. I believe they've designated testimony from Dr. Lawrence's deposition, and Dr. Lawrence was a live witness and I don't think that that's appropriate.

MR. HASFORD: We can probably take care of any of

07:52 those issues with a meet and confer, Your Honor.

THE COURT: All right. I would, off the top of my head, agree that a live witness can't be supplemented by her deposition excerpts. You can offer a party's own deposition against them, whether they were here live or not, but not an

07:52 expert.

MR. HASFORD: We're happy to address that with defendants, Your Honor.

THE COURT: Okay.

MS. HOLLAND: All right. So given Your Honor's

07:53 statement just now, I assume that Mr. Hasford is going to

withdraw the Lawrence deposition designations?

MR. HASFORD: I believe we are, Your Honor, but if you'll -- I just need to confer with my team and make sure that there wasn't some other reason why that may have been

07:53 included. I just don't have it in front of me and I will do that in short order, Your Honor.

THE COURT: Okay.

MS. HOLLAND: Of course, Your Honor, it goes without saying that defendants also appreciate the Court's time and

07:53 the court reporters and courtroom staff and clerk and everybody who's helped us out on the last few days as well. Thank you.

THE COURT: You're welcome.

Okay. And so subject to the deposition excerpts and

07:53 subject to a determination of the admissibility of DTX-478, 479A and 33A, the parties have rested, and I'll take the matter under advisement.

You have your briefing schedule for the next 30 days and the simultaneous submissions, and so we will keep to that

07:54 schedule unless I hear differently from you after you confer about them.

MS. HOLLAND: Your Honor, just to -- I just want to make clear -- be clear on the briefing schedule. So in 30 days, there is simultaneous briefing and are there responsive

07:54 briefs after that, or is there one round?

THE COURT: Yes, there's an order that --

MS. HOLLAND: Okay.

THE COURT: -- spells it out.

MS. HOLLAND: That's fine, Your Honor, I just wanted

07:54 to make sure we were still sticking with that.

THE COURT: No, we are, unless the parties agree that there's a different scheme. It's a trial logistics order that was filed on March 23rd.

MR. HASFORD: From plaintiff's side, Your Honor, I

07:55 don't believe we have any requests at this point to -- for that to be modified.

THE COURT: Okay. So it simply says in Paragraph 3: Simultaneous submissions of proposed findings of fact and conclusions of law shall be due no later than 30 days from the

07:55 last day of trial.

So we are talking about May the 12th.

And responses are due from both sides no later than 14 days thereafter, and it indicates that no surreplies shall be permitted, because all good things must come to an end.

07:55 (Laughter.)

THE COURT: And then it says: Post-trial briefs shall not exceed 40 pages and shall also be filed not later than 30 days from the last day of trial and no responses shall be permitted. You can respond orally when we have the

07:55 arguments.

The next paragraph says: Closing arguments will be heard approximately 14 days after final submissions at a date to be set by the Court.

And so that would be roughly 60 days from today. I

07:56 don't have that for you right now, to -- well, what do we have around June 11th?

THE DEPUTY CLERK: June 11th is a Saturday.

THE COURT: Perfect.

(Discussion off the record.)

07:58 THE COURT: Okay. I'd like to set the date for argument so that you can place it on your schedule, and I'll move my schedule around a little to accommodate it. Friday, June 24th would be the date at 10:00 a.m.

Does that work as far as you know?

07:58 MS. HOLLAND: Your Honor, may I consult with my client for a moment -- he's in the gallery -- about this?

THE COURT: Yes.

MS. HOLLAND: Thank you.

(Off the record.)

08:00 MS. HOLLAND: Your Honor, the reason I wanted to consult with my client is because he has the issue of the 30-month stay worked into this, and June 24th, I believe, is after the expiration of the 30-month stay, which is June 19th. So I don't know what the Court's schedule is, but to the

08:00 extent we can --

THE COURT: Well, if you want to keep this briefing schedule and argument schedule so that all this could be handled in the way that it is, could you confer with your clients and see if they could agree not to launch for 30 days after oral argument is heard?

MS. HOLLAND: That would be June --

THE COURT: That would push it to July 19th -- I'm sorry, to July 24th.

MS. HOLLAND: I'll confer, Your Honor.

(Off the record.)

MS. HOLLAND: Your Honor, we don't have -- the personnel in the courtroom don't have the authority to do that but I'm told that in the next day or so, we can get back to the Court on that.

THE COURT: All right. That's fair. And so what I'm asking is whether the defendants, both defendants, would voluntarily agree to not launch until at least July the 24th, and if the answer is yes, you can agree, then it solves the timing problem.

If not, then I'll simply advance the briefing dates and the argument dates in a way that works for the June 19th, 30-month stay date. Is that fair?

MS. HOLLAND: Yes, Your Honor.

MR. HASFORD: I think that's fine with plaintiffs, Your Honor. I think I would note that the 30-month stay date

is different for Lupin and for InnoPharma, so it may only be an issue as to Lupin.

THE COURT: That's right. InnoPharma doesn't have a 30-month problem yet?

MR. MUKERJEE: We do, Your Honor, but our 30-month stay date is considerably after the expiry of Lupin's 30-day stay date.

MR. HASFORD: It's March 2017, Your Honor.

MR. MUKERJEE: Thank you, Mr. Hasford.

THE COURT: I would say March 2017 is not imminent.

(Laughter.)

THE COURT: And so again, in lieu of everyone coming back tomorrow, I will just say within the next 24 hours, if you can do so, well, please let me know whether this is an acceptable arrangement, and if so, June 24th would be our argument date. And if so, I would be committed to getting the opinion out before July 24th.

MS. HOLLAND: Thank you, Your Honor. Just a couple very small housekeeping questions that we have for the Court. In terms of the admitted exhibits, do you want those paper copies in binders? Would you like it on a CD or DVD? We can do both, whatever is most helpful.

THE COURT: If you can do both, then that is most helpful. It makes it portable but it's -- also, I'm still a paper guy at heart.

MS. HOLLAND: Me, too.

MR. HASFORD: We can do that as well, Your Honor.

THE COURT: And so for the admitted exhibits, what I'm asking is that I receive an ordered pair of copies of the exhibits, you know, seriatim, plaintiff's exhibits and defense exhibits. And who would do the joint exhibits, the party that offered it? Or how do you want to do that?

MS. HOLLAND: We can do it that way.

MR. HASFORD: That's fine.

MS. HOLLAND: We can figure that out.

MR. HASFORD: That's fine.

MS. HOLLAND: That's pretty minuscule for us, I believe.

And the last question was in terms of the briefing. Would the Court like them hyperlinked; briefs with the cases and exhibits?

(Laughter.)

THE COURT: Okay. I'm getting some coded signals. The answer is yes.

MS. HOLLAND: Okay. Thank you.

THE COURT: Okay. Is there anything else this afternoon while we're all together?

MR. HASFORD: Nothing from plaintiffs, Your Honor.

MR. MUKERJEE: Nothing, your Honor.

THE COURT: Okay. If you run into any roadblock,

then ask for a conference call and we will take a call and the call can be on the record. I think it is highly unlikely that you will have to be reassembled here before the date in June when we have arguments.

So that concludes, then, our trial. I'd like to compliment both the plaintiffs and the defendants. The case has been extremely well-prepared. It's clear that you put an awful lot of thought into your positions and into your advocacy. It makes my job a pleasure, although the issues may be difficult, but they were not complicated by -- by anything less than the best professionalism, and that's what I hope for in every case. And so, you know, I extend thanks to the litigants and to your clients for the efforts that you have put in so far. And so with that, let's adjourn.

RESPONSE: Thank you very much, Your Honor.

(5:39 p.m.)

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