IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, et al.,	) Trial Volume 2
Plaintiffs,	)
v.	) C.A. No. 13-527-RGA
NOVEN PHARMACEUTICALS, INC.,	)
Defendant.	)

Tuesday, December 2, 2014
8:30 a.m.
Courtroom 4B

844 King Street
Wilmington, Delaware

BEFORE: THE HONORABLE RICHARD G. ANDREWS
United States District Court Judge

APPEARANCES:

McCARTER & ENGLISH
BY: DANIEL M. SILVER, ESQ.

-and-

FITZPATRICK, CELLA, HARPER & SCINTO
BY: NICHOLAS N. KALLAS, ESQ.
BY: CHARLOTTE JACOBSEN, ESQ.
BY: DOMINICK CONDE, ESQ.
BY: CHRISTOPHER LOH, ESQ.

Counsel for the Plaintiffs

APPEARANCES CONTINUED:

PHILLIPS GOLDMAN & SPENCE
BY: JOHN C. PHILLIPS, JR., ESQ.

-and-

KENYON & KENYON
BY: STEVEN J. LEE, ESQ.
BY: MICHAEL K. LEVY, ESQ.
BY: CHRISTOPHER J. COULSON, ESQ.

Counsel for the Defendants

THE CLERK: All rise. All right.

Good morning, everyone. Please be seated.

Are we ready to begin?

MS. JACOBSEN: There's just an objection to some demonstratives and exhibits.

MR. LEVY: Mike Levy, again for the record on behalf of Noven. We were presented with some exhibits and slides that will be used today in Dr. Klibanov's direct, and we have lodged objections to them on the basis that this will be testimony based on exhibits that does not go to the prior art. These are admittedly facially documents way past 1998, as the Court understands is the priority date in this case. And they cannot and do not go to the state of the mind or what one of ordinary skill in the art would have known.

THE COURT: So you're saying they're not relevant?

MR. LEVY: That's exactly right. Thank you.

THE COURT: Why don't I judge that in context because it's possible that something

that occurred later might shed light on something that occurred earlier; right?

MR. LEVY: I don't believe in this case that would be true.

THE COURT: But it's kind of hard to say in the abstract, isn't it?

MR. LEVY: That's correct. We do have to wait through the testimony. We just think we know how it's going to be used.

THE COURT: Okay. Is there something you want to say about this, Ms. Jacobsen?

MS. JACOBSEN: Just that these go to the ongoing unpredictability of the susceptibility of a drug with a benzylic carbon-hydrogen bond to oxidative degradation. And not only was it unpredictable before the priority date, it remains the case that it's still unpredictable.

And the Federal Circuit has said it's legitimate to rely on post-filing documents to show ongoing unpredictability in the art. And I can give you Your Honor a case in which that occurred.

THE COURT: Okay. Well, why don't you just put that on the record and then proceed.

MS. JACOBSEN: Right.

THE COURT: Are there any other objections, Mr. Levy?

MR. LEVY: No, Your Honor.

THE COURT: All right.

MS. JACOBSEN: So it's In Re: Wright and it's 999 F.2d 1557.

THE COURT: Okay. All right.

MS. JACOBSEN: Thank you.

THE COURT: You may proceed, Ms. Jacobsen.

MS. JACOBSEN: Good morning, Your Honor. Plaintiff's first witness is Dr. Alexander M. Klibanov. As Your Honor knows, Dr. Klibanov is a professor of chemistry and bioengineering at MIT and has over 45 years in experience in chemistry, including medicinal and formulation chemistry.

THE WITNESS: Good morning, Your Honor.

THE COURT: Good morning. Is his

Ph.D. in 1977?

THE WITNESS: 1974, Your Honor. 1977, such a long time ago.

THE CLERK: Please state and spell your full name for the record.

THE WITNESS: Alexander M. Klibanov, K-L-I-B-A-N-O-V.

THE CLERK: Please place your left hand on the Bible and raise your right hand.

Do you solemnly swear that the testimony you are about to give to the Court in the case now pending will be the truth, the whole truth and nothing but the truth so help you God?

THE WITNESS: Yes, I do.

ALEXANDER M. KLIBANOV, Ph.D.,

having first been duly sworn on oath, was examined and testified as follows:

THE CLERK: Thank you. Please be seated.

MS. JACOBSEN: May I approach, Your Honor?

THE COURT: Yeah. Sure.

DIRECT EXAMINATION

BY MS. JACOBSEN:

Q. Good morning, Dr. Klibanov.

A. Good morning.

Q. Can you please state your name for the record?

A. I must apologize to the Court. I recently recovered from a bad cold. I feel fine, but my voice is not what it should be and I apologize.

THE COURT: All right. Thank you.

THE WITNESS: I'll do my best. My name is Alexander M. Klibanov.

BY MS. JACOBSEN:

Q. And Dr. Klibanov, you have a book of documents there. Will you please turn to Tab 1 and you will find PTX 8. Can you identify that document?

A. That is my Curriculum Vitae that I -- that confirms, indeed, my Ph.D. was obtained in 1974.

MS. JACOBSEN: Plaintiffs move into evidence PTX 8.

MR. LEVY: No objection.

THE COURT: Admitted without

objection.

MS. JACOBSEN: Okay. Plaintiffs offer Dr. Klibanov as an expert in chemistry and pharmaceutical formulations, including the use of antioxidants and oxidative degradation.

THE COURT: All right.

MR. LEVY: No objection.

THE COURT: You may proceed.

MS. JACOBSEN: Thank you.

BY MS. JACOBSEN:

Q. Were you asked to consider Noven's allegations that the '031 patent would have been obvious?

A. Yes, I was.

Q. And what were your overall conclusions?

A. My overall conclusion, based on all the information available to me, and as a result of my research that I've conducted, is that both asserted claims of the patent-in-suit are non-obvious.

Q. Were you in court yesterday when Dr. Kydonieus and Dr. Schoneich testified?

A. Yes, I was.

Q. Do you agree with their invalidity opinions?

A. No. I do not agree for at least two reasons.

First, I believe that the first reason I disagree is that, at the time of the invention, the state of the art did not disclose or even suggest that rivastigmine would undergo oxidative degradation in any pharmaceutical formulation let alone specifically transdermal formulation.

The second reason I disagree is that one of skill in the art looking just at the structure of rivastigmine would not have been able to recognize that it would undergo oxidative degradation under pharmaceutically relevant conditions.

Q. Taking those in turn, why do you disagree that the problem of oxidative degradation was known?

A. Well, I have reviewed all the references asserted by Noven's experts. In addition to that, I have conducted my own research of the prior art literature.

And I determined that there was simply no evidence concerning the instability of rivastigmine and no teachings about the need to add an antioxidant to rivastigmine.

Therefore, one of skill in the art in the absence of such evidence simply would not add an antioxidant for the reasons that I will explain in more detail.

Q. So why was the knowledge of the problem of oxidative degradation relevant to your validity analysis?

A. Because as with all other pharmaceutical excipients, Your Honor, if there is no need to add an antioxidant, one would not do so since as you will see very shortly, it is often associated with a substantial downside.

Q. Did you see any data in the prior art relating to rivastigmine instability?

A. No, there was no data in the prior art that related to instability of rivastigmine under pharmaceutically relevant conditions. And in particular, oxidative degradation under pharmaceutically relevant conditions.

Q. And are there other types of

degradation that it's possible for a drug to undergo?

A. Yes. There are many other types of degradation that drugs undergo. They include degradation by acids, by strong bases, by water, by light, by heat, and of course by oxygen.

But the important point is that not all drugs undergo all of these types of degradation. And as a matter of fact, the opposite is true, most of the drugs don't undergo any of these types of degradation. And therefore, in the absence of any teaching or any indication that there was a need to stabilize or to do anything about the instability of a drug, one of skill in the art simply wouldn't attempt to solve an unknown problem.

Q. And how did that apply in this case?

A. Well, it applies in this case because as I indicated and as I will explain in much more detail shortly, there was no evidence and no data that rivastigmine undergoes oxidative degradation under pharmaceutically relevant conditions, in pharmaceutical

formulations.

Q. So turning then to the second reason that you disagreed with Noven's experts, why wouldn't a POSA predict from its chemical structure that rivastigmine would undergo oxidative degradation in a pharmaceutical formulation?

A. Because one of the basic principles in chemistry is that the structure of a molecule as a whole, the entire structure affects the properties of this molecule, including oxidative degradation. And, therefore, one of skill in the art would understand that simply zeroing in on the particular segment of the molecule and ignoring the rest of the molecule is not the way to analyze it.

More importantly, while I disagree with the theoretical arguments made by Dr. Schoneich and Dr. Kydonieus, but rather than engaging in sort of theoretical discussion, I did what chemists and indeed all experimental scientists always do, I said okay, well, you have a theory, let's see whether this theory is

consistent with the available experimental data.

When I have done that, I found that, in fact, the theories with respect to structures advanced by Drs. Schoneich and Kydonieus, simply contradicted by the experimental data available at the time of the invention involving commercial drugs that were on the market that were FDA approved.

THE COURT: Mr. Levy.

MR. LEVY: Noven has an objection. We have never heard an expert opinion from Dr. Klibanov in this case directed to the notion of looking at the whole molecule and the downside or inappropriateness of zeroing on one atom or one of part of the molecule and drawing a conclusion there.

MS. JACOBSEN: Dr. Klibanov has said this in his reports. He criticized Drs. Schoneich and Kydonieus for focusing on just one functional group.

THE COURT: Can you just cite me a paragraph?

MS. JACOBSEN: Sure. 74, 78, 79.

THE COURT: Well, usually one is

better than a slew.

MS. JACOBSEN: Well, 79, and 94 to 97 was also at his deposition discussed at length about the importance of the molecule as a whole.

THE COURT: Right. Well, proceed.

BY MS. JACOBSEN:

Q. So, Dr. Klibanov, how would a person of ordinary skill in the art have determined whether rivastigmine undergoes oxidative degradation in a pharmaceutical formulation?

A. There is only one way to determine that, and this is to conduct experimentation, to simply conduct testing to determine whether or not there is a problem of degradation. And that was important to my opinion because in my view, even if testing were routine, and as in this case as I will explain, I don't think it was, but even if it were, one doesn't know in advance whether this testing revealed any problem, then this problem cannot be obvious.

Q. So I think this, but just so we're clear, would the outcome of those experiments

had been possible to reasonably predict in advance?

A. No, the outcome of this experimentation could not be predicted in advance. It's common sense, Your Honor. If you can predict in advance the results of the experiments, then why do experiments? That's why we chemists do experiments because we don't know what's going to happen.

Q. Let's assume for a moment that a POSA would have known that rivastigmine would theoretically undergo oxidative degradation, with that assumption in mind, would a POSA have been motivated to add an antioxidant to rivastigmine in a pharmaceutical formulation?

A. No. No for a couple of reasons. First of all, because there were other ways to avoid the oxidative degradation. And second of all, because adding antioxidants is associated with potential problems that I will explain in a moment, and one of skill in the art would have known it at the time.

Q. Does the theoretical possibility of oxidation necessarily translate to oxidative

degradation in a pharmaceutical formulation?

A. No. And this, Your Honor, is one of the, I think, critical points of disagreement between the Noven's experts and myself. Under sufficiently hash conditions, any drug, any organic compound will undergo degradation, including oxidative degradation. A classical example of oxidation is burning, and we know from common experience that if a temperature is high enough, you can burn pretty much any organic material.

So in my view, the question is not whether a drug is sort of metaphysically susceptible to oxidative degradation because everything is generally speaking susceptible to oxidative degradation. In my view the question that one of skill in the art would ask is whether a drug undergoes oxidative degradation under pharmaceutically relevant conditions, meaning either during the manufacture or storage or use of the drug. In other words, under pharmaceutically relevant conditions, and that to me is sort of the key difference. That is what I think one of skill in the art would focus

on, rather than a general question of whether a drug can be susceptible to oxidative degradation under any kind of a conditions including very extreme conditions.

Q. Dr. Klibanov, now that we have discussed your overall conclusions, please briefly explain how you made your validity determination?

A. Well, I reviewed the patent-in-suit, of course. I reviewed its prosecution history. I also reviewed all the prior art asserted by Noven's experts. In addition to that, I have conducted my own research of the prior art to be able to look at the prior art as a whole.

And then I put myself in the position of a person of ordinary skill in the art as of the time of the invention, and I assessed the alleged invalidity through the eyes of this individual, and as I said, as a result of this assessment, I saw no evidence that the asserted claims of the patent-in-suit are obvious.

Q. What was the time of the invention

of the '031 patent?

A. The time of the invention as the Court can see, and I don't think it's a controversial issue, it's on the first -- on the cover page of the '031 patent, and as it states there, it's January 12, 1998.

MS. JACOBSEN: And for the record, Dr. Klibanov referred to JTX 1.

Q. Dr. Klibanov, why did you put yourself in the position of a POSA as of January 12, 1998?

A. Well, because it's my understanding that that is the way to assess the obviousness of the patent, or the '031 patent in this case. I mean, obviously today we know much more about the properties of rivastigmine than we knew back then. Today we have the benefit of the teachings of the '031 patent, which of course one of skill in the art wouldn't have had prior to January 12, 1998.

So my understanding is that it is proper to assess the question of obviousness from the standpoint of one of ordinary skill in the art prior to January 12, 1998, and without

the benefit of the teachings of the patent-in-suit.

Q. Dr. Klibanov, what level of skill would a POSA have had in January of 1998?

A. I again presented it on the slide here. And as the Court can see, in my opinion a POSA would have had a Ph.D. in chemistry, pharmacy or a related discipline with at least two years of practical experience; or master's degree in those disciplines with a greater level of experience, four years, approximately, at least; or even bachelor's degree in these areas with at least six years of practical experience.

Q. Does your definition of a POSA differ from Noven's experts'?

A. Yes, it does. And some differences, I don't think are significant, but some others are. And those that are significant I indicated on the slide here.

Now, one of the critical differences is that a POSA whether it is an individual or a group of investigators, either way, in my opinion, a POSA could not reasonably and correctly predict the oxidative instability

of a compound merely based on the structure. That wasn't possible then and, I might add, it's not possible today.

And as a result of that, testing was required to determine the oxidative stability of the compound. And that is sort of the first critical point of disagreement with Noven's experts.

The second one is that, in my judgment, a POSA would have known at the time of the invention and today that drug formulation is complex and inherently unpredictable. And, therefore, a POSA's decisions in formulating a drug would be rational decisions. They would be data driven and they would require testing.

And this testing would be carried out on a case-by-case basis and in response to specific problems that arose. So a person of ordinary skill in the art would conduct the formulation development. And if a problem arises, then this person would tackle this problem.

Q. Now, Drs. Schoneich and Kydonieus said that a POSA would have been able to predict

the physical properties of a compound from the structure. Is oxidative instability a chemical or physical property?

A. Oxidative instability is a chemical property, certainly not a physical property.

Q. What would be an example of a physical property?

A. An Example of a physical property will be melting point, for instance. But an example of a physical instability would be clumping. When you have a free-floating powder, a free-floating powder that, upon standing, upon storage, clumps, forms clumps, that would be physical instability.

Chemical instability is instability associated with the changes in the molecule of the drug.

Q. Would the difference between Noven's experts and your definition of a POSA change your analysis?

A. I mean, they might because I -- I disagree and I believe that the definitions assumed by Noven's experts are incorrect. And,

you know, just the common sense indicates that if you start with a faulty assumption, you very well may arrive at an incorrect conclusion.

Q. And could a POSA predict oxidative instability with a reasonable degree of success?

A. No. No, there was no basis and I heard no evidence to that effect.

Q. Dr. Klibanov, I'd like to turn now to your conclusions on obviousness. And would you briefly explain how you arrived at your conclusions?

A. Well, basically, I asked myself a question, and again, looking at it from the position of a person of ordinary skill in the art.

And the question that I asked was: Was rivastigmine known or suggested to have an oxidative degradation problem? And to address this question, I carefully considered the references, the prior art references asserted by Noven's experts to prove their obviousness theories.

And I, for simplicity, divided all the references that they asserted into three

groups. The first group, as the Court can see on the screen, involve rivastigmine and RA7. Rivastigmine or RA7.

And these references include GB '040, so Great Britain patent application, the U.S. '807 patent and the Elmalem reference. These were the very same references that I already discussed before this Court in the Watson case.

The second group of references encompass structural theories advanced by Noven's experts. And in particular, the benzylic carbon-hydrogen-bond-based theory, which included one particular compound namely nicotine, as the Court heard yesterday. And also the second reference specifically dealing with amines, and that's a Sasaki reference that the Court also heard about yesterday.

And, finally, the third group encompassed what might be called other prior art, and specifically is what defendant's experts testified on yesterday are two references, namely Ebert and the Handbook of Pharmaceutical Excipients.

And I analyzed them one at a time in order to address and answer the question that I mentioned earlier. And my answer to this question was that, no, at the time of the invention, rivastigmine was neither known nor even suggested to have an oxidative degradation problem.

Q. And in addition to considering them one at a time, did you also consider their teaching as a whole?

A. Yes. Having considered them one at a time, I then considered the various combinations of those references that were specifically advanced yesterday by Dr. Kydonieus.

Q. And in addition to the references raised by Noven' experts, did you review any additional literature?

A. Yes. As I mentioned earlier, I conducted my own literature search. And my goal was to assess the prior art as a whole not just a particular segment of the prior art.

Q. And, Dr. Klibanov, does it matter if oxidative degradation occurs in a

pharmaceutical formulation?

A. It does matter. It matters a great deal because if there is any degradation, including oxidative degradation, in a pharmaceutical formulation, then, obviously, the potency of the drug will decrease. If a pharmaceutical formulator tries to compensate for that by adding more drug than is necessary, it increases, obviously, the cost of the drug and may also result in some side effects.

And, finally, in principle, the degradation products of a drug in a formulation may be toxic, although thankfully that is not the case with rivastigmine.

Q. Do all drugs undergo oxidative degradation?

A. Well, again, metaphysically all organic compounds undergo oxidative degradation, but I don't think that's a relevant inquiry. What is relevant, as I mentioned earlier, is whether drugs undergo oxidative degradation in pharmaceutical formulations.

And with that in mind, the answer is no. In fact, most drugs do not undergo

oxidative degradation under pharmaceutically relevant conditions.

Q. And what are pharmaceutically relevant conditions?

A. Conditions that are encountered during drug manufacture, storage or administration.

Q. And can drugs undergo other types of degradation under pharmaceutically relevant conditions?

A. Yes. As I mentioned earlier, there are many others.

Degradation by heat called pyrolysis. Degradation by -- I'm sorry, degradation by light called photochemical degradation. Degradation by water called hydrolysis. Degradation by acids and oxygen, as I already mentioned, and a number of others.

But, again, the critical question is not what can happen in principle, but what actually does happen to a particular drug under pharmaceutically relevant conditions.

Q. So, focusing on oxidative

degradation, is it possible to predict without experimentation whether a drug undergoes oxidative degradation under pharmaceutically relevant conditions?

A. No, it's not. And the literature supports that it wasn't possible to do it.

Not only was it not possible to do it for a person of ordinary skill in the art, but, as I will show shortly, it wasn't even possible to do it for the inventors.

Q. And would a POSA in 1998 have any reason to believe that rivastigmine undergoes oxidative degradation in a pharmaceutical formulation?

A. No. And, in fact, the evidence that I will discuss shortly shows just the opposite. A person of ordinary skill in the art at that time would have had every reason to believe that rivastigmine does not undergo oxidative degradation under pharmaceutically relevant conditions; and therefore, does not require an antioxidant or any other measures to prevent this unknown and possibly nonexistent problem.

Q. Let's take a look at the prior art. Dr. Klibanov, I'd like to start with the three references raised by Dr. Kydonieus that relate to rivastigmine or RA7.

And the first is GB '040. What was your overall conclusion regarding GB '040?

A. Well, my overall conclusion was that GB '040 does not disclose an oxidative degradation problem. GB '040 which, by the way, is the only prior art reference asserted by Noven that specifically deals with rivastigmine none other does.

So GB '040 does disclose rivastigmine. It discloses rivastigmine in a transdermal formulation, but it does not suggest any type of oxidative instability. It certainly doesn't suggest, let alone disclose, the use of an antioxidant.

And as I mentioned earlier, a person of ordinary skill in the art wouldn't have tried to solve an unknown problem. If the problem was not known, as common sense indicates, you wouldn't try to solve it. And also as I will illustrate shortly, a person of

ordinary skill in the art would know that no excipient, in particular antioxidant, should be added to a pharmaceutical formulation unless it was needed.

Q. So would a POSA have had a reason to combine GB '040 with the other prior art?

A. I don't believe so, because it seems to me that since GB '040 does not reveal any kind of -- doesn't even hint at any kind of an oxidative degradation problem, it seems to me that one of skill in the art would have no reason to combine it with any reference to solve the unknown problem.

Q. Before we discuss how you reached your conclusions, was GB '040 or its U.S. counterpart considered by the patent examiner during prosecution of the '031 patent?

A. Yes, the U.S. counterpart of GB '040, the '176 patent, was considered by the PTO during the prosecution of the '031 patent.

Q. And how does GB '040 compare with the '176 patent?

A. With respect to all the information that Dr. Kydonieus relies upon, the

two are identical. So all the information found in GB '040 is also found in the '176 patent.

Q. Did the patent examiner question the validity of the '031 patent over GB '040's counterpart?

A. No, not at all. What is shown on the screen now is an amendment taken from the '031 patent prosecution history, and as the Court can see on the screen now, it says, among other things, "As acknowledged by the fact that the office action contains no rejection over the prior art, the composition and method related to this aspect of applicants' invention are both novel and obvious."

So the '031 patent was never rejected over the '176 patent.

Q. Dr. Klibanov, I think you may have misspoke. I think you said novel and obvious?

A. I'm sorry. Novel and unobvious.

Q. Thank you.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 3 at page 1077 and plaintiffs introduce into evidence JTX 3.

MR. LEVY: No objection.

THE COURT: All right. Admitted without objection.

BY MS. JACOBSEN:

Q. Turning back to GB '040, did you say it discloses rivastigmine?

A. Yes, it does.

Q. What kind of drug is rivastigmine?

A. Rivastigmine is a drug to treat Alzheimer's disease. It does so by inhibiting a particular enzyme that's called cholinesterase or acetylcholinesterase, therefore rivastigmine and other similar drugs of this sort are sometimes called anticholesterase.

Q. What form of administration does GB '040 disclose?

A. GB '040 discloses oral administration in various varieties. It discloses injections, and also discloses transdermal administration as I mentioned a moment ago.

Q. Does GB '040 disclose that rivastigmine undergoes oxidative degradation in a pharmaceutical composition?

A. No, not at all.

Q. Why do you say that?

A. Because GB '040 describes in its various examples and throughout the specification, describes the use of rivastigmine without any visible precautions taken to prevent any kind of degradation, including oxidative degradation.

Q. Does GB '040 include any data regarding stability of rivastigmine?

A. There are no data on any kind of stability of rivastigmine, let alone specifically oxidative instability.

Q. So would GB '040 tell a POSA to add an antioxidant to rivastigmine?

A. No, I think GB '040 would tell the POSA just the opposite, that there was no need to add an antioxidant. And as I mentioned earlier, without the need to add an antioxidant or any other excipient, a person of ordinary skill in the art wouldn't do it.

Q. And Dr. Kydonieus specifically focused on example two of GB '040?

A. Yes.

Q. Are any of those ingredients an

antioxidant?

A. No. None of the excipients that are listed in example two or anywhere else for that matter in the GB '040 patent is an antioxidant.

Q. Does GB '040 indicate that any of those ingredients in example two contained an antioxidant?

A. No, I have seen no good evidence that that is the case.

Q. Now, Dr. Kydonieus cited various documents that he said show Brij 97, which is listed in example two of GB '040, contained an antioxidant. Do you agree?

A. No. Again, there is no clear evidence that that was the case, either at the time of GB '040 itself, which is 1988, or at the time of the patent-in-suit, of the invention of the patent-in-suit, which is 1998, as I mentioned earlier.

Q. Does example two indicate where Brij 97 was obtained from?

A. Yes, it does. The Court can see it's highlighted on the screen. It says

plasticizer, e.g., or for example, Brij 97, then there are three asterisks, and one goes to the footnotes. And it indicates that Brij 97 registered trademark, available from Atlas Chemie in West Germany.

Q. Did Dr. Kydonieus cite any documents relating to a product from Atlas Chemie West Germany?

A. No.

Q. Even if Brij 97 did contain an antioxidant, would a POSA had believed that the antioxidant was present for rivastigmine?

A. No, certainly not. Even if that were the case, and as I said, I do not believe that that's the case, one of skill in the art would understand that if Brij contained an antioxidant, the antioxidant was present to stabilize Brij, which is a polymer that may undergo oxidative degradation.

Q. Does example two require Brij 97?

A. No. Again, as is indicated here in the highlighted portion on the screen, it expressly says plasticizer, e.g., for example, Brij 97. There are many other plasticizers that

were pharmaceutically in wide pharmaceutical use at the time. So Brij 97 would be understood by one of skill in the art would be just one particular example of a plasticizer that could be used.

Q. Was that relevant to your analysis of GB '040?

A. Yes, it was, because even if Brij 97 did contain an antioxidant, the use of Brij 97 is by no means compulsory, and therefore, other plasticizers could have been used as well, and there is certainly no evidence that they would have an antioxidant present.

Q. So would a POSA believe the plasticizers without an antioxidant could also be used?

A. It would have to, because it specifically says e.g., so clearly Brij 97 is just one example and one of skill in the art would understand that other plasticizers could be used as well.

Q. So based on GB '040 as a whole, would a POSA have had a reason to add an antioxidant to a rivastigmine transdermal?

A. No. I analyzed not just example two, but the entire GB '040, and based on everything that this patent says, in my judgment there was no indication at all to lead one of skill in the art to the view that there was either an oxidative degradation problem of rivastigmine, or that an antioxidant was present in the formulation.

THE COURT: I'm sorry, you may have said this or not. The use of the term plasticizer, what does plasticizer mean to a person of ordinary skill in the art?

THE WITNESS: Just something that softens it, so the plasticizers sort of softens it, so it makes it more pliable, more flexible.

THE COURT: Is there anything about a plasticizer that necessarily implies the presence of antioxidant?

THE WITNESS: No. No. People use different -- at the time and now, use different plasticizers, like soapy materials, sort of things like that, so not at all.

THE COURT: All right. Thank you.

BY MS. JACOBSEN:

Q. Would a POSA have nonetheless added an antioxidant to rivastigmine in a transdermal even if he didn't know that one was needed?

A. No, a person wouldn't -- a person of ordinary skill in the art wouldn't do it, because as I alluded to earlier and will illustrate in a moment, there was a substantial downside of doing so. And, in fact, there was specific teachings at the time of the invention not to do that.

Q. So could you give us an example of the teachings in the prior art not to add an antioxidant unless needed? .

A. Yes. So what is shown on the screen now, these are a couple of excerpts from a document issued by EMEA, which is a European regulatory agency, which is an equivalent of the United States Food & Drug Administration, the FDA. And they, in 1997 -- obviously, this is prior art, they issued some guidance on the use of antioxidants, published guidance.

And these guidance states, as the Court can see -- and these are just sort of

several probative, I think, excerpts. The first one says, antioxidants should be -- should only be included in a formulation if it has been proved that their use cannot be avoided.

And then it continues, Antioxidants should not be used to disguise poorly formulated products or inadequate packaging.

So one of skill in the art would understand from this guidance that you don't use an antioxidant unless you must. And we certainly wouldn't add it just for the heck of it, so to speak.

Q. And is this guidance applicable to all dosage forms?

A. Yes. This is a general guidance that applies to all dosage forms, including transdermal formulations.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 162, and Pages 1 to 2. And plaintiffs move to introduce into evidence PTX 162.

MR. LEVY: No objection.

THE COURT: Admitted without

objection.

BY MS. JACOBSEN:

Q. Were there any reasons a POSA would not have added an antioxidant to a pharmaceutical formulation?

A. I mean, there are a lot of additional teachings that are consistent with European FDA guidance. And for example, this is another prior art reference.

This is a 1987 U.S. patent, and this is a U.S. patent Number 4,710,376, which has a couple of sort of statements that explain, in perhaps more detail, why you don't want to add an antioxidant unless necessary.

It specifically says, as the Court can see on the screen, in brackets, adding an antioxidant is not an acceptable approach with many known antioxidant agents which tend to be somewhat toxic.

And then it continues, even aside from the problem of toxicity, it is generally undesirable to treat with a drug, treat a patient with a drug composition containing any bio-active component, which is not absolutely

essential.

So one of skill in the art would understand, you know, these teachings to be consistent with the European regulatory agency's guidance and in explaining why you wouldn't add an antioxidant unless you had to.

MS. JACOBSEN: For the record, Dr. Klibanov, referred to PTX 184 at Column 2, Lines 60 to 68, and Column 3, Lines 3 to 7. And plaintiffs move to introduce into evidence PTX 184.

MR. LEVY: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Dr. Klibanov, could an antioxidant increase drug degradation?

A. Yes. There are some instances where that is, indeed, the case.

And one of them will be illustrated on the screen. But, first, as a general proposition, what is shown on the screen now is an excerpt from Remington's Pharmaceutical Sciences, which is probably one

of the most authoritative treatises in pharmaceutical science, and in particular, dealing with many aspects of pharmaceutical formulations.

And a relevant except here states that obvious sources of pharmaceutical instability include the incompatibility of various ingredients with formulations -- within a formulation. And then it states numerous examples are described in other sections of the book -- of this book and the literature is replete with illustrations.

So one of skill in the art would understand that there are issues of pharmaceutical incompatibility, which means that an excipient may be incompatible with the active ingredient or with other excipients. And one has to be mindful of these incompatibilities, and therefore, wouldn't add an excipient unless needed.

Q. And what happens if there is an incompatibility?

A. Well, it could reduce the potency of the drug. It can degrade the drug.

It can cause the formation of toxic products in reacting with other excipients.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 5 at Page 1507 and plaintiffs move to introduce into evidence JTX 5.

MR. LEVY: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Dr. Klibanov, would you give us an example of antioxidant incompatibility?

A. Yes. It is shown on the next slide.

It's an article by Connors and this particular chapter, this particular paper -- it was a book actually -- deals with chemical stability of pharmaceuticals published in 1979.

And it illustrates -- it says sulfites which is a type of antioxidant, can readily form inactive addition compounds, aswith, for example, epinephrine, which is a drug. And then it says, thus, not all antioxidants can be

used with all drugs.

So one of skill in the art would understand from this teaching and similar teachings in the prior art that antioxidants may unpredictably increase drug degradation rather than protect the drug from degradation.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 156 at Page 97. And plaintiffs move to introduce into evidence PTX 156.

MR. LEVY: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. In 1998, were such compatibilities possible to predict without experimentation?

A. It was not possible to predict it without experimentation then, and I might add, it's not possible to predict it without experimentation today.

Q. And does that include antioxidant incompatibilities?

A. It certainly does, yes.

Q. And as of 1998, were there other ways to reduce oxidative degradation without using an antioxidant?

A. Yes, there were. For instance, what is shown on the screen now are alternatives for potentially reducing oxidation or oxidative degradation. So Remington's textbook that I already discussed suggests using nitrogen or carbon -- I'm sorry, nitrogen or carbon dioxide to exclude oxygen, to simply displace it.

Now, the '961 patent, as of 1986, teaches using an occlusive polymer -- occlusive polymer matrix or an occlusive backing layer in a transdermal device. So polymer or a layer that sort of embraces, encloses, if you will, the drug.

Likewise, the '295 patent is -- it's in 1997 using -- teaches using an oxygen scavenger with the sealed pouch containing the transdermal device, which is not within the pharmaceutical formulation. So not only were there -- one of skill in the art would understand that there were alternatives to using antioxidants, indeed, one of skill in the art

would understand that some of these alternatives, like the first one, for instance, preferable to using antioxidants because you don't add anything to the drug formulation.

Q. Could a POSA reasonably have predicted that all of these alternatives would work?

A. No. You don't know what's going to work until you do experiments.

I mean, that is exactly why pharmaceutical formulators conduct testing because the outcome of this experimentation cannot be predicted in advance.

MS. JACOBSEN: And for the record, Dr. Klibanov referred to JTX 5 at Page 1507, JTX 14 at Column 6, Lines 25 to 34 and Column 8, Lines 4 to 8, and JTX 16 at Column 2, Lines 37 to 52.

And plaintiffs move to introduce into evidence JTX 14 and JTX 16.

MR. LEVY: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. So coming back to GB '040, what would a POSA have concluded from GB '040 regarding the stability of rivastigmine?

A. Well, a person of ordinary skill in the art would have concluded that there was no indication in the entirety of GB '040, including example two, that rivastigmine had any kind of an oxidative degradation problem. And no indication that -- and, therefore, a person of ordinary skill in the art would presume that rivastigmine was stable and, therefore, wouldn't try to solve a non-existent problem.

Q. Are you aware of any prior art after the 1988 date of GB '040 that disclosed a rivastigmine transdermal?

A. No. And, in fact, for the convenience of the Court, I'm beginning here to build a timeline, which I will eventually fill up.

And what is shown on this timeline, this is the timeline with respect to the '031 patent. So the Court --obviously, the 1998, as I discussed earlier, is the patent-in-suit, which discloses rivastigmine

plus an antioxidant in a transdermal device.

Now, so GB '040 is here the starting point. It was published in 1988.

It discloses rivastigmine transdermal device, but no antioxidant. And during this interim period of time, during the ten years between 1988 and 1998, there were no publications that I'm aware of or that were asserted by the Noven's experts dealing with rivastigmine on transdermal devices.

Q. Dr. Klibanov, I would like to turn to the '807 patent now.

A. Yes.

Q. And did you consider this patent in your analysis?

A. Yes, I certainly did.

Q. And what was your overall conclusion?

A. Well, my overall conclusion was that there was no good reason for a POSA to combine the '807 with GB '040.

Now, because as I just indicated, GB '040 didn't reveal any oxidative degradation problem, and therefore, there was no reason to

combine it with any reference to solve a nonexistent problem.

Even if one of skill in the art were to combine GB '040 with the '807 patent, I don't think that even though there was no motivation to combine them, but even if one were to combine them, in my judgment that would not make the discovery of the patent -- discoveries of the patent-in-suit obvious because the '807 patent undeniably does not disclose rivastigmine. It does not disclose transdermals on which there seems to be agreement among all the experts in this case.

The '807 patent does not suggest oxidative instability of either rivastigmine or the closest molecules to rivastigmine, which is RA7. And the '807 patent does not suggest that antioxidants are required for any formulation, let alone specifically transdermals, which are not even discussed in the '807 patent.

And, of course, and again, this is something that all the experts seem to be in agreement on, that a POSA would know that degradation is formulation specific, meaning

that even if you had it in one formulation, such as an aqueous solution, for which there is also no evidence in '807, but even if that were the case, it certainly doesn't mean that you will have the same problem in another formulation, such as a transdermal, for instance.

Q. Did the patent examiner consider the '807 patent?

A. Yes, he did.

Q. And did the patent examiner question the validity of the '031 patent over the '807 patent?

A. No, the patent examiner never issued any rejections over the '807 patent.

Q. So you said the '807 patent does not disclose rivastigmine. What compounds does it disclose?

A. It discloses a lot of different compounds, all of which were carbamate compounds, so it discloses a large class of carbamate compounds that have the general structure that is depicted on the slide here now. And the patent refers to them as compounds of general formula one as the Court can see on

this screen.

Q. How large is that class of carbamates?

A. Well, I have conducted a calculation here, so again, as the Court can see, this formula, general formula one, aside from the required elements, such as this benzyl ring, for example, it also has several substituents, like R1, R2, R3, R4, and R5. And each of these substituents right below the formula here is allowed to be various functional groups.

So I have conducted a calculation and conservatively the total number of compounds encompassed by this general formula one, given the teachings as to what these substituents can be, is over eight million different compounds.

And importantly, as the Court can see in the highlighted portion at the bottom of the excerpt here, all of these eight million plus compounds are called compounds of the invention. So compounds of the invention are eight million plus compounds.

MS. JACOBSEN: For the record,

Dr. Klibanov referred to JTX 17 at column four, lines 21 to 73.

BY MS. JACOBSEN:

Q. Does that class of compounds include RA7?

A. Yes, it does, among those eight million plus compounds, there is a compound called RA7.

Q. And is rivastigmine different from RA7?

A. Yes, it is. RA7 is a racemate which consists of two constituent enantiomers, and rivastigmine is one of those enantiomers, namely the S, S enantiomer. It is well-known in chemistry that generally speaking, an individual enantiomer and a racemate which contains it have different properties, so they're different compounds.

Q. Does the '807 patent disclose transdermals?

A. The '807 patent does not disclose transdermals. It talks about as the Court can see, it talks about oral administration and it talks about injections. So these are the only

types of formulations that are taught by the '807 patent.

MS. JACOBSEN: And for the record, Dr. Klibanov referred to JTX 17 and column seven, lines 15 to 19.

BY MS. JACOBSEN:

Q. And there is a reference there to parenteral administration. Would that include transdermals?

A. No, in the context of the '807, and usually it does not include transdermals. And, in fact, as I understand from yesterday's testimony of Noven's expert, in particular Dr. Kydonieus, he agrees that the '807 patent does not disclose transdermal formulations.

Q. Dr. Klibanov, you mentioned that RA7 and rivastigmine are different chemical compounds?

A. Yes.

Q. And would a POSA have expected rivastigmine and RA7 to have the same stability characteristics?

A. Although they are different compounds and generally speaking have different

properties, with respect to stability, and in particular oxidative stability, the properties of a racemate and its constituent enantiomers are typically the same.

Q. Now, was the difference between parenteral and transdermal formulations relevant to your analysis?

A. Yes, it was highly relevant to my analysis, because again, one of the basic principles of pharmaceutical formulations is that the stability of a drug very much depends on the formulation in which it is present and on the conditions. And it's not just antioxidants, at any excipient, it's just sort of common sense.

For example, a well-known excipient is a sweetener. Sweeteners are often added to tablets or elixirs in order to mask a bitter taste. But, of course, nobody would add a sweetener to, for example, an injectable or a transdermal. So it just illustrates that just because you need a particular -- you have a particular type of degradation in one formulation, you will not necessarily have it in

another. And if you add a particular excipient in one type of formulation, it doesn't mean that you will have to add it to another.

Q. Would a POSA have expected the degradation to be different in different dosage forms?

A. Yes. And there are numerous examples of that that I will illustrate in a moment, where there are instances where a particular drug is unstable, for instance, in one formulation, such as a formulation for injection, aqueous solution for injection, but nevertheless stable in a, say, transdermal formulation.

Q. And do transdermal formulations typically include an aqueous solution?

A. Typically they do not. They may, but certainly the vast majority of them do not. And, in fact, as I recall, at the time of the invention, no commercial transdermal formulation included an aqueous solution.

Q. How would a POSA determine whether to add an antioxidant to a particular formulation?

A. Well, the answer is still the same, testing. A person of ordinary skill in the art would conduct experimentation and this experimentation would reveal whether or not an antioxidant is needed or is required.

Q. Did you consider in your analysis whether the '807 patent suggests that rivastigmine undergoes oxidative degradation?

A. Well, first of all, the '807 patent doesn't even involve rivastigmine, it involves RA7. But even with respect to RA7, there was no indication that a rivastigmine -- that RA7, or any other of the eight million plus compounds, requires an antioxidant in any formulation.

Q. And does the '807 patent include any stability data for the compounds disclosed?

A. No, there are no stability data for any of the eight million plus compounds.

Q. And does the '807 patent say anything about the stability of RA7?

A. It does. And what it does say sort of depicts stability in a favorable kind of light. Now, the Court can see on the screen now

a couple of excerpts from the '807 patent, and it specifically says in the preamble of the patent, it says that, "there is a need to provide new carbamate derivatives which show greater chemical stability than physostigmine."

So physostigmine was a prior art compound and what the patent teaches is there was a need to come up with carbamate derivatives that were more stable. And then it specifically says with respect to preferred, preferred from a therapeutic standpoint compounds of the invention of the '807 patent, including RA7, it specifically says, that these preferred compounds including RA7 are all relatively more active in vivo compared to physostigmine, and that this relatively greater in vivo activity may be due to greater chemical stability.

So if anything, one of skill in the art would understand from this language that RA7 and thus rivastigmine is certainly more stable than physostigmine.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 17, column 3, lines 37 to 39, and column 11, lines 21 to 29.

BY MS. JACOBSEN:

Q. Did you consider the disclosure of antioxidants in the '807 patent?

A. Yes, I did.

Q. Did it change your opinion?

A. No. Basically what the patent does, the patent list -- the patent specification list, gives a lengthy list of various inactive ingredients that can be used. The Court can see, there are things like sweetening agents, flavor agents and also antioxidants. So it gives this lengthy list of possible ingredients. But with respect to all of them, the patent specification specifically asserts that they are used as called for by accepted pharmaceutical practice. And the Court will recall that one of the pillars of this practice is that you don't add an excipient unless it's needed.

And then furthermore it continues that these inactive ingredients or excipients can be incorporated as required.

So a person of ordinary skill in the art would understand this teaching saying that if it's required, then you add it. And if

it's not required, then you don't add it.

MS. JACOBSEN: And for the record, Dr. Klibanov referred to JTX 17 Column 7, Lines 15 to 53.

BY MS. JACOBSEN:

Q. Would a POSA have understood that all of those excipients were suitable for all dosage forms?

A. No. A person of ordinary skill in the art would have understood just the opposite.

Again, obviously, it's ridiculous to add a flavoring agent to an injectable formulation. So one of skill in the art would understand that this is just a list of possible inactive ingredients. And you would use those that you need and certainly would not add those that you don't need.

Q. And how would a POSA determine which ones were needed?

A. By testing. A person would proceed with pharmaceutical formulation development.

And if any problems come up, then this person would address these problems using,

for example, adding such inactive ingredients.

Q. Does the '807 patent disclose in what dosage form an antioxidant may be used?

A. Yes. As a possibility, the '807 patent specifically talks about adding antioxidant, but only as required, as I will discuss in a moment, with respect to just one type of dosage form, namely sterile compositions for injection.

And it specifically says that sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection. And then it says, buffers, preservatives, antioxidants, and the like can be incorporated as required.

So specifically, with respect to sterile compositions for injections, because that is the only portion in this column of the patent which is Column 7, this is the first time when antioxidants are mentioned.

So the specification says, yes, in sterile compositions for injection,

antioxidants, in addition to buffers and preservatives, can be incorporated as required, which one of skill in the art would understand to mean that if they are required, you add them, whether it's antioxidants or buffers. And if they're not required, you don't add them.

MS. JACOBSEN: For the record, Dr. Klibanov, he referred to JTX 17 at Column 7, Lines 45 to 53.

BY MS. JACOBSEN:

Q. Is the disclosure of an antioxidant specific to any of the compounds of the '807 patent?

A. No. These are just general statements and, of course, they are not specific to any of the eight million plus of the compounds of the invention of the '807 patent.

Q. And does the disclosure of preferred antioxidants relate to the preferred compounds from a therapeutic standpoint?

A. No. One of skill in the art certainly would not understand it that way.

In fact, would understand -- it

would understand just the opposite because, as I mentioned earlier, these preferred compounds of the '807 patent invention, such as the RA7, have superior stability, for example, greater stability than physostigmine.

Q. And in the sentence starting Preferred antioxidants, there's a reference to the compounds of the present invention. What compounds are encompassed by that?

A. All eight million plus compounds of the present invention.

Q. And would a POSA expect all of the compounds of the invention in the '807 patent to have the same stability?

A. No. A person of ordinary skill in the art would expect just the opposite.

And there's no way that eight million different compounds would have the same stability. So a person of ordinary skill in the art would expect that they will all have different stabilities. And the differences in their stabilities were not predictable. Only testing can show what that difference is, if any.

Q. Does the '807 patent say anything about the amount of antioxidant that can be used?

A. No, no amounts are specified in the '807 patent.

Q. And would a POSA have considered the '807 patent's mention of antioxidants relevant to a transdermal?

A. No, because, as I mentioned earlier, transdermals are not even encompassed by the '807 patent.

The '807 patent does not deal with transdermal formulations. And as I mentioned earlier, even if a drug is unstable in one formulation such as in aqueous solutions for injection, it certainly doesn't mean that it will be also unstable in another formulation. And there are many examples of that.

Q. Well, as of 1998, can you give us an example of a compound that was known to require an antioxidant in aqueous solution, but not in a transdermal formulation?

A. Yes. Physostigmine, for example, the drug that I already mentioned several times,

Your Honor, and will actually discuss in much more detail shortly.

So physostigmine was one of such compounds that required an antioxidant in aqueous solution, but did not require it in a transdermal formulation.

Q. Can you turn to Tab 5 of your witness binder, please?

A. Yes.

Q. And do you recognize this document?

A. Tab 5.

Q. Sorry, Tab 9.

A. Yes, I do. It's a U.S. patent number 5,939,095.

Q. What does this patent relate to?

A. This patent relates to physostigmine and specifically that was a well-known drug to treat Alzheimer's, a natural compound. And specifically this patent includes transdermal devices containing physostigmine.

And as the Court can see here on the screen, so this is an example in this patent. And this example shows that we have

physostigmine.

Laminate here means a transdermal device. So this is a transdermal device containing physostigmine. And then it lists all the components or all the inactive ingredients of this transdermal device. And none of these active ingredients is an antioxidant.

Q. Is there any teaching in the '095 patent that an antioxidant should be added to physostigmine in a transdermal device?

A. No, none.

Q. So what would a POSA have concluded from this patent?

A. Well, it would have confirmed, also, that just because physostigmine, for example, or any other drug requires an antioxidant in an aqueous solution, for example, an aqueous solution for injection, doesn't mean that it will also require it in a transdermal device.

Q. For the record, Dr. Klibanov referred to PTX 190 at Column 4, Lines 32 to 60. And plaintiffs move to introduce into evidence PTX 190.

MR. LEVY: No objection.

THE COURT: All right. Admitted without objection.

BY MS. JACOBSEN:

Q. And, Dr. Klibanov, was the difference between formulations relevant to your analysis of whether Claim 7 of the '031 patent would have been obvious?

A. Yes, it was because Claim 7, as the Court recalls, specifically requires rivastigmine plus an antioxidant in a transdermal device. And, therefore, if any of the -- as I understand it, if any of these elements is missing in the prior art, then the invention is non-obvious.

Q. Dr. Klibanov, is there any other evidence that the '807 patent would not have led a POSA to combine rivastigmine with an antioxidant?

A. Yes, there is. So, for example, the Court can see on the screen now an excerpt from GB '040, which we have considered already and will consider -- will continue considering. And this particular excerpt says, with respect

to RA7, that RA7 is known from the European patent application 193,926.

And that's a patent application that's related to the '807 patent that we're discussing now where -- and it being RA7, is -- it is identified as RA7 HCl. So one of skill in the art would understand from that that the inventor of GB '040 was aware of the '807 patent teachings.

Q. And the European patent that's referenced in GB '040, does that contain the same disclosures as the '807 patent that we've been discussing?

A. Yes, it does.

Q. And does that include a disclosure relating to an antioxidant?

A. Yes, it does.

Q. And for the record, Dr. Klibanov referred to JTX 19 at 2.

And, Dr. Klibanov, can you turn to Tab 10 of your witness binder?

A. Yes.

Q. Do you recognize that document?

A. Yes. That's that European

application, 193,926 that is mentioned on this slide here.

Q. And when was that application published?

A. It was published in 1986.

Q. And how does that compare with the filing date of GB '040?

A. Well, again, this timeline that I started building may be handy because GB '040 was published in 1998, was filed in 1987. So the inventor of GB '040, Dr. Albert Enz was aware of the EP '926 because that was -- you know, that has the priority date of 1986 -- was aware of the teachings of the '807 patent, therefore.

But, nonetheless, Dr. Enz in GB '040 made no efforts and made no statement or indicated no evidence that either there was an instability oxidative degradation problem of rivastigmine or any need to add an antioxidant.

Q. And, Dr. Klibanov, I think you said it was the priority date that was 1986, not the publication date?

A. It was published in 1986. Yes,

sorry.

Q. And just so we're clear, I think you said this, but how was the publication date of EP '926 relevant to your analysis?

A. Well, because it means that this publication date 1986, since it was earlier than when GB '040 was filed, the inventor of GB '040 was aware of the teachings of the '807 patent.

Q. And did that cause the inventor of GB '040 to suggest the addition of an antioxidant?

A. No, it didn't. As I discussed earlier, you know, there was no teachings of an addition of an antioxidant in GB '040.

MS. JACOBSEN: Your Honor, plaintiffs move to introduce into evidence PTX 194.

MR. LEVY: No objection.

THE COURT: All right. Admitted without objection.

BY MS. JACOBSEN:

Q. Dr. Klibanov, I'd like to turn to Elmalem now. And did you consider that reference in your analysis?

A. Yes, of course.

Q. And what was your overall conclusion?

A. Well, my overall conclusion is that a person of ordinary skill in the art would not have combined Elmalem either with GB '040 or with the Handbook of Pharmaceutical Excipients. And the reason that I arrived at that conclusion is that, first of all, as I already mentioned with respect to GB '040, there was no indication that one of skill in the art would find in it that there is any kind of an oxidative degradation problem of rivastigmine.

And, therefore, a person of ordinary skill in the art would have no motivation to combine GB '040 with any reference to solve an unknown problem.

But even if one of skill in the art were to combine, for example, GB ' '040 with Elmalem, that would not teach the invention of the asserted claims of the patent-in-suit because, and I just summarize it here on this slide in a bullet point format, Elmalem does not disclose rivastigmine. Elmalem does not suggest

oxidative instability of even RA7, which is the closest that it comes to rivastigmine. Elmalem does not suggest that antioxidants are required for RA7. Elmalem undeniably does not disclose transdermal formulations, it only discloses aqueous formulation for injection.

And that is important because as I already stated repeatedly, a POSA would know that degradation is formulation specific, and therefore, even if an antioxidant is needed in, for example, aqueous solution for injection, and there is no evidence that that was the case with respect to RA7 in Elmalem, but even if it were the case, it certainly would not indicate to one of ordinary skill in the art that an antioxidant is also needed in a transdermal device, which of course, is required in the asserted claim seven of the '031 patent.

Q. Please can I have the next slide.

So I have put up on the screen the passage that Dr. Kydonieus relied on. And do you agree that an antioxidant was added to all drugs to prevent their degradation?

A. I agree with Dr. Kydonieus that an

antioxidant was added to all drugs. I do not agree that it was added to all drugs to prevent oxidative degradation of all of these drugs. In fact, it demonstrably cannot be the case. So in my opinion, as I will explain and hopefully prove, in my opinion, an antioxidant was added to one drug which required an antioxidant, namely physostigmine. And then it was added to all other drugs as a control.

And in order to -- I think one of skill in the art, in order to understand what is done in Elmalem and why, would have to consider two aspects that are indicated here on this slide. One of skill in the art would have to consider what was known at the time of Elmalem, which is 1991, about phenyl carbamates and their oxidative degradation.

And the second thing that one would have to consider is the purpose of the Elmalem study. And in my judgment, as I will try to explain, if one of skill in the art considers these essential elements in assessing any scientific paper, then one of skill in the art would understand that only physostigmine

required an antioxidant, and all the other drugs with all the other drugs, an antioxidant was used as a control.

Q. Let's discuss those points in turn. And start with what was known about the drugs in Elmalem at that time. When was Elmalem published?

A. Elmalem was published in 1991.

Q. What drugs did Elmalem study?

A. Elmalem studied several drugs. And what Elmalem did is Elmalem compared the physiological effects of these drugs in a head-to-head format. So, in other words, what was done in Elmalem was that morphine was used to induce respiratory depression in rabbits. So morphine was used to depress breathing of rabbits, and then several drugs, RA6, RA7, RA15, physostigmine, and the saline placebo drug. So these five drugs were used to assess their ability to reverse this morphine-induced respiratory depression. So it was a head-to-head study, quantitative study of the effects of these drugs on this physiological condition, morphine-induced respiratory

depression.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 21 at 1059.

BY MS. JACOBSEN:

Q. Dr. Klibanov, did Elmalem study rivastigmine?

A. No. The closest that it came to rivastigmine was RA7, which the Court will recall is a racemate, one of the constituent enantiomers of which is rivastigmine.

Q. You said that Elmalem studied physostigmine. What is physostigmine?

A. Physostigmine is a drug that I already mentioned several times. What is shown on the screen here a chemical structure, this is the chemical structure of physostigmine. I will in time discuss various aspects of this structure.

At this point I would like to invite the attention of the Court to this particular group in physostigmine, which is encircled in the red, which is called the carbamate group. So this group in chemistry is called a carbamate group.

Another important element that we'll look at in a moment is in this particular carbamate group, this nitrogen, which I am pointing at is bonded to a CH3 group, which in chemistry is called the methyl group. So this nitrogen is bonded to the CH3 group, and another bond is to hydrogen.

So since there is one, only one methyl group here present in the case of physostigmine, physostigmine and drugs of this sort are called monomethyl carbamates. So it's a carbamate which has a single methyl group.

Q. How does the structure of physostigmine compare with RA7?

A. So, the chemical structure of RA7 is shown here below that of physostigmine, and the Court can see that RA7 is also a carbamate. Again, the carbamate is encircled in the red. So these are both carbamates.

The Court can also see that this nitrogen here is also bonded to a methyl group just as it is bonded here. However, in contrast to physostigmine, the other bond of nitrogen is not to hydrogen, but to this group which is

H5C2, which is called an ethyl group.

Now, methyl, ethyl and similar groups in chemistry are called alkyl groups. So based on that, RA7 is called by chemists a dialkyl carbamate, meaning that it's a carbamate that has two alkyl constituents at this nitrogen.

So the difference between physostigmine and RA7 and rivastigmine, of course, is in the same camp as RA7, so the difference is that physostigmine is a monomethyl carbamate, whereas RA7 is a dialkyl carbamate. And the significance of this structural difference will become apparent in a moment, Your Honor.

Q. Well, in 1991, what was known about the chemical stability of monomethyl carbamates like physostigmine?

A. It was known as illustrated, for example, by an excerpt of the '807 patent that we just discussed that monomethyl derivatives, monomethyl carbamates tend to be unstable in a solution, an aqueous solution, and they hydrolyze readily at physiological pH. And it

was also specifically known for physostigmine which being a monomethyl carbamate as I just described was known to be chemically unstable and, in fact, require an antioxidant in solution.

MS. JACOBSEN: And for the record, Dr. Klibanov referred to JTX 17 at column 2, lines 45 to 47, and column 1, lines 32 to 34.

BY MS. JACOBSEN:

Q. If a drug hydrolyzes, is that the same as undergoing hydrolysis?

A. Yes, hydrolysis is a reaction, a degradation reaction with water. So when the drug undergoes a degradation reaction with water, chemists say that it hydrolyzes or undergoes hydrolysis.

Q. Would an antioxidant reduce hydrolysis?

A. No, there is no reason for an antioxidant to have an effect on the rate of hydrolysis one way or the other.

Q. Would physostigmine undergo oxidative degradation under pharmaceutical relevant conditions?

A. No, not physostigmine, what was known as I will show shortly, what was known is that a hydrolytic degradant of physostigmine, that is a compound that is formed when physostigmine undergoes hydrolytic degradation, that compound called eseroline as the Court will see shortly, undergoes oxidative degradation.

Q. So why was it necessary to prepare physostigmine with an antioxidant in an aqueous solution?

A. It was necessary to prevent the oxidation of a eseroline, the degradant, the hydrolytic degradant of physostigmine. I think this slide that I prepared hopefully illustrates this point more clearly than I just did.

So this is the information taken from a 1991 Textbook of Organic Chemistry by Wilson.

So what the Court can see in the upper left corner here is the chemical structure of physostigmine. As I already indicated, physostigmine being a monomethyl carbamate undergoes hydrolysis, and hydrolysis, indicated by this blue horizontal arrow, hydrolysis simply

means that there was a cleavage of this particular carbon oxygen bond that I'm pointing at. When this cleavage, hydrolytic cleavage occurs, what is formed is this compound that I referred to earlier, the compound called eseroline. It's a phenol.

Now, eseroline in contrast to physostigmine does undergo oxidative degradation to form this compound. It's a reddish compound called rubreserine, which is unstable and undergoes other degradative processes.

So in a sense this oxidation kind of opens the doors and then subsequent degradation reactions take place.

And this sort of scheme is illustrated by a statement from Wilson which says the addition of sulphite or ascorbic acid, and these as the Court will recall are antioxidants, so the addition of sulphite or ascorbic acid to physostigmine solutions prevents the oxidation of the phenol, eseroline, not physostigmine itself, but the eseroline to rubreserine, as I mentioned, rubreserine undergoes further degradation pathways.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 18 at page 456, and plaintiffs introduce into evidence Exhibit JTX 18.

MR. LEVY: No objection.

BY MS. JACOBSEN:

Q. Why would the POSA want to prevent the oxidative degradation of eseroline?

A. A person of ordinary skill in the art was cautioned by, for example, United States Pharmacopeia, so what is shown on this screen now are two editions of United States Pharmacopeia, 1979 and 1989, so both prior art, and specifically both of them with respect to physostigmine for injection, specifically say do not use the injection if it is more than slightly discolored.

And the Court will recall that rubreserine was colored as are the degradation products of rubreserine. So the United States Pharmacopeia teaches a person of ordinary skill in the art not to use physostigmine if it has discolored.

And the reason for that is not

aesthetic of course, but the reason for that is when rubreserine undergoes further degradation products, you don't know what effect these degradation products may have in an experiment or in the pharmaceutical formulation. And therefore, this is something that is to be avoided.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 215 at page 1079 and PTX 216 at page 624. And plaintiffs move to introduce into evidence PTX 215 and 216.

MR. LEVY: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Now, as of 1991, what was known about the chemical stability of dialkyl carbamates like RA7?

A. In contrast to monomethyl carbamates like physostigmine, dialkyl carbamates were known, known as a result of extensive prior experimentation, they were known to be much more stable, and indeed stable against hydrolysis in pharmaceutical

formulations.

Q. Did you consider any specific examples as part of your analysis?

A. Yes, I certainly did. And as I said, there were a lot of studies, experimental studies on hydrolysis of carbamates, these studies started in the 1930s because they are relevant to some pesticide action.

And so I would like to invite the Court's attention to one particular example which is representative and quite revealing. And this example comes from 1994, a publication entitled Reaction Mechanisms in Environmental Organic Chemistry.

So, I just would like with the Court's permission to walk the Court through this slide.

So what we have at the top here is a particular monomethyl carbamate. So the Court can see that again, the carbamate group is encircled in red, and it has a single methyl group just like physostigmine had. So this compound, therefore, by definition is a monomethyl carbamate.

What is shown at the bottom here is a very similar compound, it's also a carbamate. It also has this methyl group, CH3 group that is bonded to nitrogen, but it has another group that is bonded to the same nitrogen

A. So, therefore, according to the nomenclature that I discussed just a couple of minutes ago, this compound at the bottom is a dialkyl carbamate. So the compound at the top is a monomethyl carbamate. The compound at the bottom is a dialkyl carbamate.

Now, the Court can see that the remainder of the molecule in both of these compounds is the same. So the only difference between them is that one is a monomethyl carbamate. Another one is a dialkyl carbamate.

And what was studied in this, the textbook -- and there were many studies, experimental studies like that -- but this one, I think, is particularly probative. What was studied is the hydrolysis of both of these compounds in water, in aqueous solution under particular conditions.

And what the authors of this study found is that the half life, which is the time of degradation of half of the compounds, so the half life of monomethyl carbamate is 8.5 days. It's slightly more than a week.

Whereas the half life for the dialkyl carbamate under exactly the same experimental conditions was 1,200 years. So a simple conversion from a monomethyl carbamate to the dialkyl carbamate, which is a dimethyl carbamate increased the stability of the compound more than 50,000 fold.

And that example is an illustration of the general notion that dialkyl carbamates were known at the time of the invention to be far more stable against hydrolysis than monomethyl carbamates.

Q. For the record, Dr. Klibanov referred to JTX 26 at Page 133.

MS. JACOBSEN: Plaintiffs move to introduce into evidence JTX 26.

MR. LEVY: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Dr. Klibanov, were the dialkyl carbamates, as a class, considered stable?

A. Yes, they were, because there were numerous studies of the sort that I just mentioned. So, for instance, this is an informative statement from the publication textbook by Wilson 1991 where the authors state, although physostigmine contains a methyl carbamate functional group.

The greater chemical stability toward hydrolysis was obtained with the dimethyl carbamate group in neostigmine. And then so neostigmine is a dialkyl carbamate.

And then with respect to neostigmine, in particular, the Wilson authors particularly state solutions are stable. So these are aqueous solution of neostigmine and may be sterilized by boiling.

So one of skill in the art would understand that not only are they stable, but they're so stable that they can be boiled. So we're talking about a hundred degrees Centigrade without decomposition.

And this is a dialkyl carbamate whereas monomethyl carbamates required protections such as an antioxidant, even in aqueous solution at room temperature.

Q. For the record, Dr. Klibanov referred to JTX 18 at Page 457.

Dr. Klibanov, why was a POSA able to form an expectation about the class of dialkyl carbamate based on chemical structure?

A. As I said earlier, by 1998, there had been a great deal of experimental studies, quantitative studies on hydrolysis of various carbamates. As a result of these studies, mechanism of hydrolysis of monomethyl carbamates and dialkyl carbamates emerged.

And so, again, this is a textbook on reaction mechanisms in environmental organic chemistry which illustrates the point that I will explain in a moment. Now, this textbook says these differences in reactivity between monomethyl and dialkyl carbamates can be explained by comparing their hydrolysis mechanisms.

So what are those hydrolysis mechanisms? I'm not going to go over all of these details, but what I want to point out is that with respect to monomethyl carbamates, the first and critical step of the hydrolysis reaction is the attack on this hydrogen atom by this group HO minus group, which is called a hydroxide group.

So this hydroxide group attacks this hydrogen. This attack is followed by a series of intermolecular rearrangements. And the hydrolysis reaction ensues. And this is a very fast, very fast reaction.

Now, we go to dialkyl carbamates. In dialkyl carbamates, this reaction cannot take place because there is no hydrogen for the hydroxide ion to attack. So we don't have a hydrogen. We have two methyl groups here.

So, therefore, the mechanism of hydrolysis for dialkyl carbamates is different from that for monomethyl carbamates. Here this hydroxide ion instead attacks this carbon. Again, there is a series of subsequent rearrangements, and the hydrolysis ensues.

So the bottom line here is that monomethyl carbamates undergo a very fast hydrolysis because there is this very facile mechanism of their hydrolysis that simply cannot take place, does not exist with dialkyl carbamates.

And that explains mechanicistically why dialkyl carbamates, as was known even then in particular, was known even in 1994, it explains mechanicistically why dialkyl carbamates are much more stable against hydrolysis than monomethyl carbamates.

Q. And for the record, Dr. Klibanov referred to JTX 26 at Pages 133 to 134.

Now, as of 1998, how would a POSA's understanding of hydrolysis have compared with their understanding of oxidation?

A. The hydrolysis reactions, first of all, are to begin with much simpler than oxidation reactions. Oxidation reactions are very complex as was illustrated by Dr. Schoneich's presentation yesterday.

But, in addition to that, the hydrolysis reactions had been very well studied.

As I said, those studies, experimental studies began in the '30s, in the 1930s. That was not the case with respect to the oxidation reactions.

Q. And what would a POSA in 1998 have expected about the stability of RA7 in aqueous solution?

A. Well, based on what I just discussed, one would expect that RA7, which is a dialkyl carbamate will be stable toward hydrolysis in aqueous solution.

Q. Would a POSA have reason to believe that RA7 would undergo the same multi-step degradation as physostigmine?

A. No. In the case of physostigmine, as the Court recalls, the first step, that horizontal blue arrow was hydrolysis.

And what underwent oxidation was the hydrolytic degradation product. Well, since, in the case of rivastigmine or RA7, there is no hydrolysis because it's stable toward hydrolysis, well, then, there will be no subsequent oxidation of the hydrolytic degradants because there are no hydrolytic

degradants.

Q. Now, there are other different structural differences between RA7 and physostigmine. Would they have changed the mechanism by which RA7 or physostigmine underwent degradation?

A. No. Because what is still undeniable is that in the case of a monomethyl carbamate, you have the attack toward hydrogen atom of the hydroxide ion. That's what you have in physostigmine. And that is a very facile hydrolysis mechanism. But in the case of RA7, you cannot have this mechanism; and therefore, it is much more stable toward hydrolysis.

MS. JACOBSEN: Your Honor, I'm about to move on to a different topic. Would that be a convenient time to take the morning break?

THE COURT: Sure. So we'll take a break. I think I have one question.

Early on, there was some prosecution history from 2009; right, on the '031 patent? Or there was prosecution history. What was the date on it?

THE WITNESS: It was 2009.

MS. JACOBSEN: It does say 2009. We can check the date on that, Your Honor.

THE COURT: Because there wasn't any prosecution going on in 2009, was there?

MS. JACOBSEN: I don't recall the issuance date.

MR. KALLAS: May I speak, Your Honor? The patent, the '031 patent, if that's what we're discussing, issued on January 1st, 2002. So that date must be wrong or you're thinking of another date. But --

THE COURT: All right.

MS. JACOBSEN: We'll correct it after.

THE COURT: Okay. I just -- okay. All right. Well, we'll be in recess.

THE CLERK: All rise.

(A brief recess was taken.)

THE CLERK: All rise.

THE COURT: All right. Let's continue.

MS. JACOBSEN: Your Honor, just on

the office action, it was 2000. The slide was incorrect.

THE COURT: Okay. All right.

MS. JACOBSEN: And one other housekeeping matter. I'm told that I didn't say that Dr. Klibanov's CV was PTX 8.

THE COURT: Okay. Well, I found it. But so it's admitted.

You had it admitted, so it's in evidence. So let's go.

MS. JACOBSEN: Okay.

BY MS. JACOBSEN:

Q. Dr. Klibanov, I'd like to continue talking about Elmalem.

A. Yes.

Q. And this time talk about the second thing that you said it was important to consider, which was the purpose of the Elmalem study.

A. Yes.

Q. Would you tell the Court what that purpose was?

A. Well, the purpose was to compare head to head different drugs with each other. I

mean, it's a very common endeavor in medicinal chemistry where you have different drug candidates and you compare them with each other with typically a known drug and also with a control.

And, indeed, as the Court can see on the screen, this is a summary of the Elmalem study. It specifically says that the study compared the effects of three novel anticholinesterase derivatives or agents and specifically it talks about acetylcholinesterase -- my laser pointer died. So if I could just get a new one, that would be great.

And specifically says --

MS. JACOBSEN: May I approach, Your Honor?

THE COURT: Sure.

THE WITNESS: Each drug namely RA6, RA7, RA15, physostigmine or saline. That's the placebo drug, negative control was injected simultaneously with morphine. So it was a classical head-to-head comparison of efficacies of different drugs, which drug is better at the respective concentration.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 21 at Page 1059.

BY MS. JACOBSEN:

Q. How were the drugs in Elmalem prepared?

A. Elmalem provides a description of that and specifically says that all drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite to prevent oxidation.

Q. What is saline?

A. Saline is simply solution of sodium chloride in water. So it's essentially a solution of table salt at a concentration of 4.15 molar in water.

Q. And what is sodium metabisulphite?

A. It's an antioxidant.

Q. And what would a POSA have understood all drugs to refer to in this statement?

A. Well, it's very clear from the description talking about drugs, Elmalem specifically says each drug. And then it says RA6, RA7, RA15, physostigmine or saline was

injected simultaneously with morphine.

So the drugs are physostigmine, which was the drug with which comparisons are made to relatively new, at the time, drugs, RA6, RA7 and RA15 and the placebo drug, namely saline, which was used as a negative control.

Q. And, Dr. Klibanov, I think you said two relatively new drugs.

A. No, three. If I said two, I apologize. Three: RA6, RA7 and RA15.

Q. And for the record, Dr. Klibanov referred to JTX 21 at Pages 1059 and 1060.

Why would a POSA have understood all drugs to include saline solution alone?

A. Well, because -- well, that's what the paper expressly states. And in addition to that, it's common in all drug studies to have a placebo drug with which all the other effects are compared.

Q. Does Elmalem ose the actual amount of antioxidant used?

A. The only thing that Elmalem says in this regard is that all drugs were made up freshly in sterile saline, which included an

equal weight of sodium metabisulphite.

Q. And how would a POSA have understood the equal weight of sodium metabisulphite?

A. A person of ordinary skill in the art would understand it to mean that each drug solution had equal weight or the same quantity of sodium metabisulphite, including the saline placebo solution.

Q. Now, Dr. Kydonieus said that the amount of antioxidant was equal to the amount of drug in each formulation; do you agree?

A. No, I don't agree. And, in fact, in my opinion, this interpretation of the Elmalem study just doesn't make sense from the formulation standpoint because the amount of -- the quantities of the drugs varied from drug to drug, and therefore, according to Dr. Kydonieus, the amount of the antioxidant would also have to vary. But that will eliminate the purpose of using an antioxidant as a control.

What matters is not the ratio of the antioxidant to the drug, which is irrelevant, what matters is the absolute

concentration of the antioxidant, that is what you want to keep constant so you don't have to worry about its effect on the observed physiological differences.

Q. How would a POSA have understood the preparation of the drugs in Elmalem?

A. A person of ordinary skill in the art would understand the preparation of the drug as is shown on this slide. So a person of ordinary skill in the art would understand that the starting point was the saline solution, that is solution of sodium chloride in water. Then to this solution a certain amount of the antioxidant, sodium metabisulphite was added, and then this so-called stock solution was split up into several portions, to one portion physostigmine was added, to another RA6 was added, to yet another RA7 was added, to yet another RA15 was added, and then nothing was added to the placebo drug. And that as I said, is a conventional design of such head-to-head studies.

Q. Why would it have been done that way?

A. It would have been done that way because it keeps the number of variables constant. So in other words, that you have the same concentration of antioxidant in all of these, and therefore, the presence of the antioxidant is not a variable in this experiment.

Q. Is this way of doing it also easier?

A. It is also much easier because you prepare one solution and then you just divide it into several parts. And it is also -- this is also important, it is also much less prone to experimental error. Because if you prepare the solution for physostigmine and separately for RA6 and separately for RA7 and so forth, there is a likelihood that an error in measurements will be made. This way such a likelihood is eliminated.

Q. Earlier you mentioned variables. What do you mean by a variable?

A. Well, chemical and pharmacological studies are usually done in a way that you study the effect of one parameter upon another, for

example, one may want to study the temperature on a reaction rate, so temperature is one variable, reaction rate is another variable.

Common sense indicates when you do this type of study, you want to keep everything else the same. So if you study the effect of temperature on reaction rate, you want to keep the composition of the solution the same so that the compositional solution is not a factor.

So here it's the same sort of thing, Elmalem wanted to study the effect of different drugs in their respective concentrations on a reversal on the morphine-induced respiratory depression. They wanted to keep as many variables as a constant so the variable they were interested in, namely the drug itself, would be really the one that they will be studying. So it makes sense to do it this way.

Q. Did Elmalem control for any other variables?

A. Yes, Elmalem did. It was a well-controlled study. So in addition to having all the drugs formulated with an antioxidant,

although only physostigmine required an antioxidant, in all other cases it was added as a control.

In addition to that, Elmalem also controlled the route of administration. All the drugs were administered the same way, via an injection. In addition, the test subjects were well controlled. There were at least four rabbits per treatment, therefore, by minimizing the likelihood of individual animals affecting the results. All the rabbits were of a similar size, 2.5 to 3 kilograms. Dosages were specifically calculated per kilogram of the body weight. And then blood samples were analyzed before treatment. Changes in body temperature were monitored. And finally differences in respiration rates were also normalized. So it was a well-controlled study.

MS. JACOBSEN: For the record Dr. Klibanov referred to JTX 21 at pages 1059 to 1060.

BY MS. JACOBSEN:

Q. Was the presence of these controls relevant to your analysis?

A. Yes, it was. Because that confirms that what Elmalem tried to do is to keep as many variables constant as possible to make the interpretation of the results on relative importances of different drugs as unambiguous as possible.

Q. Now, Dr. Kydonieus said that a POSA would have believed that an antioxidant was added to all drug formulations because they all needed one to prevent their oxidation. Do you agree?

A. I do not agree. And, of course, it cannot be the case because among -- since it says all drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite. As I showed two slides ago, the antioxidant was also added to the placebo drug, which was the sodium chloride dissolved in water. Well, surely we can all agree that solution of sodium chloride in water does not require an antioxidant.

So the only way to explain why an antioxidant was added to the placebo saline solution was as a control. And this is even in

addition to the fact that as I will explain in a moment, there was evidence that such drugs as RA7, for example, at the time of Elmalem, did not need an antioxidant.

Q. What evidence was there at the time that RA7 would not need an antioxidant in aqueous solution?

A. Well, as I already explained earlier, RA7 is a dialkyl carbamate. This is the structure of RA7 once again, it's a dialkyl carbamate. As I explained just shortly before the break, since it is a dialkyl carbamate in contrast to a monomethyl carbamate as physostigmine, it is stable toward hydrolysis. Therefore, it doesn't produce a hydrolytic degradant and, therefore, there is nothing to stabilize against oxidative degradation. That is how one of skill in the art would view Elmalem in 1998 without the benefit of the teachings of the patent-in-suit.

Q. Would Elmalem have told a POSA that oxidation of RA7 was occurring on aqueous solution?

A. RA7 would do nothing of the sort.

There was no evidence, it was not a stability study, there was no stability data at all on RA7.

Q. Does Elmalem say anything about the stability of RA7?

A. Yes. Elmalem in the introduction made several general statements which, again, depicted the stability of the compounds of the invention -- I'm sorry, of the compounds that were studied including RA7 in a favorable light. For example, it says these agents -- and that includes RA7 plus RA6 and RA15. It says these agents readily penetrate the central nervous system and have a greater chemical stability and longer duration of action than that of physostigmine. So if anything, one of skill in the art would certainly understand that statement to mean that RA7 is more stable than physostigmine and if anything that it is stable in aqueous solution.

Q. Let's assume that you're wrong, Dr. Klibanov, and a POSA would have read Elmalem to suggest that RA7 required an antioxidant in aqueous solution, was there anything in the art

as of 1998 that would have contradicted that reading?

A. Yes, there was. For example, what I show on the screen now are two prior art studies that provide some insights in this regard. The first one is the Enz 1991 study. And the Court will recall that Albert Enz was the inventor of GB '040. In this study it says, "Rivastigmine appears to have greater chemical stability and longer duration of action than does physostigmine."

The second paper I think is particularly instructive, because it is a paper published in 1994, so after the Elmalem study, and it is a paper which has the same lead author, Professor Marta Weinstock, as the Elmalem study, and as the Weinstock 1981 study that I will talk about in a moment. So clearly Professor Weinstock and her co-authors knew everything there was to know about the stability of rivastigmine.

And what they state in 1994, so subsequent to Elmalem, they say, "rivastigmine showed superior chemical stability, oral

bioavailability and a longer duration of action than physostigmine."

So that theme continues including the studies by Professor Weinstock's group.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 174 at page 272, PTX 175 on page 219, and plaintiffs move to introduce into evidence PTX 174 and PTX 175.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Do either of Enz 1991 or Weinstock 1994 discuss adding an antioxidant to rivastigmine?

A. No, neither discusses adding an antioxidant to rivastigmine.

Q. And do either of Enz 1991 or Weinstock 1994 suggest that rivastigmine undergoes oxidative degradation in the formulations they tested?

A. No, they do not.

Q. Dr. Klibanov, in your analysis did you consider the Weinstock 1981 paper that Dr. Kydonieus discussed?

A. Yes, I did.

Q. Does the Weinstock 1981 paper disclose RA7 or rivastigmine?

A. It does not.

Q. And what was your understanding of why Dr. Kydonieus cited the Weinstock 1981 study?

A. Well, my understanding was that Dr. Kydonieus cited this study because in his view, this study ostensibly shows that the Weinstock laboratory studies would add an antioxidant only when it was needed to be added, and would not add it where there was no requirement for it to be added.

Q. And did the Weinstock 1981 paper -- sorry, I'll start that question again.

In your opinion, would the Weinstock 1981 paper have changed the way a POSA read Elmalem?

A. I don't believe so. These were studies published ten years apart, 1981, 1991, of course every study has to be evaluated on its own. There were a number of other experimental differences between Elmalem and Weinstock 1981,

but most important, Your Honor, the purpose of the Weinstock '81 study was very different from the purpose of the Elmalem study.

And, of course, it is the goal of the experiment that dictates what experimental protocol is to be employed. As I will explain in a moment, the goals of the two studies in question, Elmalem on the one hand and Weinstock '81 on the other, were very different.

Q. You may have said this, Dr. Klibanov. Why is a difference in the goals of the studies relevant to your analysis?

A. Because the goals dictate what experimental protocol would be appropriate. The goals determine what you need to do, and how you need to design an experiment so that you can answer the question that the study is aiming to answer.

Q. So what was the goal of the Weinstock 1981 study?

A. Well, the goal of the Weinstock '81 study, it was not a head-to-head comparison of drug study. In fact, there were no head-to-head comparisons at all.

A. The goals, for example, are revealed by a statement from the abstract of this paper, which as the Court can see on this screen, says the results support the hypothesis that the respiratory and cardiovascular depressant effects of morphine, but not the analgesia, result from an inhibition of acetylcholine release from neurons in the central nervous system.

So basically what one of skill in the art would understand from this language and the rest of the Weinstock '81 study was that the purpose of the Weinstock '81 study was as follows: So morphine exerts several effects on respiratory depression, cardiovascular effects, analgesia and a couple of others. And what the Weinstock '81 authors wanted to know is whether these effects are exerted through the central nervous system, which is the brain, and the spinal cord or the peripheral nervous system, which is what permeates the rest of our bodies.

And in order to answer this question, Weinstock '81 used agents such as physostigmine, which were known at the time to

affect the central nervous system, and only the central nervous system, and some other agents that were known to affect the respiratory -- I'm sorry, were known to affect the peripheral nervous system.

So, obviously, for example -- if, for example, physostigmine antagonizes the effect of morphine, then morphine's effect is through the central nervous system. If it doesn't, that means that morphine's effect is through the peripheral nervous system. So that was the goal and the setup of the Weinstock '81 study.

Q. Did Weinstock 1981 explain how physostigmine could be used to test the hypothesis?

A. Yes. It specifically said, for instance, as is shown on the screen, in order to see whether the cardiovascular and respiratory depressant effects of morphine were due to an inhibition of the release of acetylcholine from neurons in the central nervous system, it was decided to administer a centrally acting acetylcholinesterase agent, namely

physostigmine. So it specifically stated what I just alluded to.

Q. And can you explain how physostigmine would have been able to test the hypothesis?

A. Yes. Physostigmine, which was administered prior to morphine, interacts with and blocks acetylcholinesterase in the central nervous system. And, therefore, morphine that is added subsequently to that, if morphine, morphine action is manipulated by the presence of physostigmine, that means that morphine acts on the central nervous system. And if it's not, then it's not.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 30 at Pages 504 and 507.

BY MS. JACOBSEN:

Q. Did Weinstock 1981 study the effects of any compounds other than physostigmine --

A. Yes.

Q. -- to test the hypothesis?

A. Yes, it did. So, for example,

this is a table that I made based on what Weinstock '81 did.

And the Court can see that in this table we have drug tested and then we have the location of action of each particular drug. So, as I mentioned earlier, physostigmine acts on the central nervous system.

In addition to that, physostigmine plus hyoscine, which is scopolamine and atropine methyl nitrate were also used. The first acts on central, the second on peripheral.

And, finally, neostigmine was also used, which affects the peripheral nervous system. So, again, the rationale is the same as I mentioned earlier.

If neostigmine abolishes the effect of morphine, that means for a particular indication like analgesia or respiratory depression, that means that morphine exerts that action through the action on the peripheral nervous system.

Likewise, physostigmine, if physostigmine does that, then morphine does the corresponding effect through the central nervous

system.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 30 at Page 507.

BY MS. JACOBSEN:

Q. Did Weinstock 1981 draw any conclusions based on the compounds it studied?

A. Yes. Weinstock '81, for example, concluded that physostigmine can overcome the respiratory depressant action of morphine, which indicates that physostigmine and morphine, with respect to respiratory depression, act on the same part of the central nervous system, namely the central nervous system.

And Weinstock '81 continues morphine depresses respiration by reducing the release of acetylcholine in the CNS. CNS, central nervous system.

So, in fact, Weinstock used the experimental design that I explained, and indeed, made appropriate conclusions based on the observations made.

Q. And how would a POSA characterize this type of conclusion?

A. Well, this type of a conclusion is what we call sort of a qualitative conclusion. Or another way of saying it is it's a yes-or-no-type of a conclusion. Does it act on the central nervous system or does it act on the peripheral nervous system?

So it's not a quantitative study, just simply what does it act on? Does it exert the effect on central or through peripheral nervous system? So that's a qualitative type of a study where it's a yes or no that's in question.

As compared to Elmalem, where it was very different, where the purpose was to quantitatively compare the effects of different drugs in their respective concentrations, head-to-head comparison of different drugs.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 30, Pages 507 to 508.

BY MS. JACOBSEN:

Q. Dr. Klibanov, was Weinstock 1981 a controlled head-to-head study?

A. It was a controlled study. It was a well-controlled study, but it certainly was

not a head-to-head study. There was no need for that because there was no comparison on different drugs with each other.

The goal was to determine what part of the nervous system morphine acts upon.

Q. And is that different from Elmalem?

A. It's very different from Elmalem because there, there was no question of that sort. The question was which drug is better in the particular concentration.

And it was a quantitative head-to-head comparison of the efficacy of different drugs.

Q. And were there any other differences between the protocols used in Elmalem and Weinstock 1981?

A. Yes. There were a number of other differences.

For example, even the antioxidant was different in Weinstock '81. It was ascorbic acid, as the Court heard yesterday.

In Elmalem, it was sodium metabisulphite. So there were a number of other

differences.

The two studies have to stand on their own. They shouldn't be kind of lumped together into one study because the goals were entirely different.

Q. So would Weinstock 1981 have changed the way a POSA would have read Elmalem?

A. I don't believe so.

Q. Well, let's assume, nevertheless, that a POSA read Elmalem to suggest that rivastigmine required an antioxidant in aqueous solution.

Would that reading have suggested to a POSA that rivastigmine required an antioxidant in a transdermal?

A. No. Even with this assumption, the answer is no, because I think that all the experts in this case agree that oxidative degradation is formulation specific.

And, therefore, just because you have -- even if you do have oxidative degradation in aqueous solution for injection, it certainly doesn't mean that you will have it in transdermal formulation. And, in fact, the

physostigmine example, Your Honor, that I discussed before the break with physostigmine required an antioxidant in aqueous solution, but did not require it in a transdermal formulation confirms that notion in my opinion.

Q. So would a POSA in 1998 have been motivated to combine Elmalem with GB '040?

A. No. I don't think that there would be a motivation to combine GB '040 with Elmalem simply because there was no problem that one of skill in the art would understand in GB '040 that needed a solution. But even if one were to combine them, then they -- obviously, the invention of the, for example, Claim 7 of the patent-in-suit still wouldn't be obvious because it specifically requires transdermal formulation, whereas undeniably Elmalem does not deal with transdermal formulations.

Q. Thank you, Dr. Klibanov.

I'd like to turn now to Noven's structural theories. And, first, do you agree with Drs. Kydonieus and Schoneich that a POSA would have expected rivastigmine to undergo

oxidative degradation based on its structure?

A. No, I do not. And the reasons why I don't are sort of briefly outlined here, and then I will go in a bit more detail.

A POSA would have known that the oxidation reaction is complex. A POSA -- and this is a very important point -- would know that the whole molecule influences stability, including oxidative stability of a particular compound.

A POSA could not reasonably predict instability based on the structure. And another piece of evidence is that the inventors themselves, who certainly knew more than anybody else about rivastigmine, did not predict and did not expect instability of rivastigmine. And they certainly knew the structure of rivastigmine.

Q. Is your opinion that oxidation is complex supported by the prior art?

A. Yes, it is. There is ample evidence of that.

For example, here on this slide now, I show excerpts from two prior art publications. The first one is 1986, Chemical

Stability of Pharmaceuticals, which says our overall mechanistic understanding of oxidative and photochemical reactions is poor.

And the second reference, it's 1996, Modern Pharmaceutics, says the mechanisms of oxidation reactions are usually complex. So one of skill in the art would have known that, and would have known on the basis of these and other references that oxidation reactions were not well understood. And I might add are not well understood even today.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 22 at Page 82 and PTX 153 and Page 183. And plaintiffs move to introduce into evidence JTX 22 and PTX 153.

MR. LEVY: No objection.

THE COURT: All right. Admitted without objection.

BY MS. JACOBSEN:

Q. Now, as of 1998, were any groups of atoms known to potentially undergo oxidative degradation in pharmaceutical formulations?

A. Yes, with potentially being the key term.

In other words, the mere presence of certain functional groups wasn't determinative, you know, in predicting whether there would be oxidation. But there was some groups that would potentially be conducive to oxidation, although, of course, the final determination still has to be done experimentally.

And this follows, for instance, from a table that is on the screen now that is taken from the 1996 publication in the textbook Modern Pharmaceutics.

And basically what it does, it lists several functional groups, that is several chemical groups that, when present in pharmaceutical molecules, potentially can oxidize.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 153 at page 183, table 2.

BY MS. JACOBSEN:

Q. Now, are any of the functional groups that Drs. Kydonieus or Schoneich relied on mentioned here?

A. No. What they identified is not depicted in this table.

Q. And that includes benzylic carbon hydrogen bonds and amines, they're not present there?

A. That's correct.

Q. Does rivastigmine have any of the functional groups in table two of Modern Pharmaceutics?

A. No, it does not.

Q. Now, you may have said this, Dr. Klibanov, but just so we're clear, if a compound contained one of the functional groups in this slide, would a POSA have concluded that that compound would undergo oxidative degradation in a pharmaceutical formulation?

A. No, a POSA would simply conclude from that there is a potential for such a degradation to take place, which may or may not take place depending on the rest of the molecule and experimental conditions, but the ultimate determination can only be done by testing.

Q. And whether or not one of those compounds undergoes or whether or not a compound

with one of those groups would undergo oxidative degradation depends on the conditions?

A. It would depend on the conditions and it would depend on the rest of the molecule, absolutely.

Q. And Dr. Klibanov, would you give us an example of how the molecule as a whole can influence stability?

A. Yes. We can go, for example, to the molecule that I have discussed in detail and the Court will recall that this was the structure of the physostigmine molecule.

Maybe just to orient the Court a little bit, what we have in the center of this structure is this hexagon with alternating double bonds, that's a benzyl ring. What we have to the left is the carbamate that we will discuss in much detail. What we have to the right from the benzyl group are these two chemical groups that are called tertiary amines. So we have the central element in the molecule, the benzyl ring, then on the one hand of that benzyl ring we have a carbamate and on the other hand, on the opposite end we have tertiary

amines.

And with that information in mind, it's instructive to see what this patent that is shown on this slide, this is U.S. Patent Number 5,338,548, which was a 1994 patent specifically says physostigmine freebase, that's the compound whose structure is shown on the screen here, is a particularly labile compound because its two basic tertiary amine groups facilitate hydrolysis of its carbamate group.

So what one of skill in the art would understand from that is that these two groups, tertiary amines, even though they're located on the opposite side of the physostigmine molecule, nonetheless affect the hydrolysis of this carbamate, which confirms the basic notion that I mentioned previously which is one of the pillars of chemistry, that the structure of the molecule as a whole, not just the particular presence of a particular group, that affects the stability of the molecule, including its oxidative degradation stability or instability.

MS. JACOBSEN: For the record,

Dr. Klibanov referred to JTX 33 at column 3, lines 51 to 56.

THE WITNESS: And just to add to that, of course in this case what the '548 patent talks about is stability or instability towards hydrolysis, specifically. But the same basic notion applies to other modes of degradation of drugs, including oxidative degradation.

Q. Thank you, Dr. Klibanov.

MS. JACOBSEN: I'm not sure if I moved to introduce JTX 33 or not.

MR. LEVY: I don't think you did, but no objection.

THE COURT: It's admitted without objection.

MS. JACOBSEN: Thank you. And Dr. Klibanov referred to column 3, lines 51 to 61.

BY MS. JACOBSEN:

Q. Dr. Klibanov, did you consider the inventor's development work in determining whether it was known that rivastigmine undergoes oxidative degradation?

A. Yes, I did.

Q. And why did you do that?

A. Well, because my understanding of Noven's arguments is even a person of ordinary skill in the art would be able to predict or to recognize just based on the structure of rivastigmine that it would undergo oxidative degradation. So I thought it would be instructive to test that hypothesis by looking at what the inventors did. The inventors, who as the Court will see in a moment, are at least as qualified as a person of ordinary skill in art, but in contrast to a person of ordinary skill in the art knew a great detail about rivastigmine whether they expected any oxidative degradation.

Q. What did you discover?

A. I discovered that, in fact, the evidence in the case that I will show in a moment indicates that they did not expect any oxidative degradation, that it came as sort of a surprise to them, an unpleasant surprise, I presume.

Q. How was that relevant to your analysis?

A. Well, I think that it follows that if even they despite their experience with physostigmine did not expect that oxidative degradation of rivastigmine, then surely the oxidative degradation of rivastigmine could not have been obvious to a person of ordinary skill in the art.

Q. Dr. Klibanov, I think you misspoke. You said their experience with physostigmine?

A. I'm sorry, with rivastigmine. I apologize.

Q. Before we discuss the inventors' development work, what level of technical training did they have?

A. They were all Ph.D.'s. and this is actually, it follows from the testimony of one of the inventors, Dr. Harry Tiemessen, his trial testimony in this courtroom in Novartis against Watson. He was specifically asked what his education and training was, and he said I did Ph.D. focusing on the development of topical formulations for drug delivery. And then when asked what his responsibilities were, he said,

while there, according to the transdermal rivastigmine project, I was formulation expert for the rivastigmine transdermal drug delivery project.

And then when subsequently asked about the educational level of other inventors, he said, they were all Ph.D.'s in their areas. And in addition, he said they had quite some development experience.

So all the inventors were Ph.D.'s which is at least as high if not higher than the level of ordinary skill in the art defined either by the defendants' expert or myself. But they certainly knew much more about rivastigmine than a person of ordinary skill in the art could have known. And even they did not expect oxidative degradation of rivastigmine.

Q. Well, how did the inventors formulate rivastigmine when they began their transdermal delivery work?

A. Well, we -- there are some materials that I reviewed in this regard, and in particular there is this table that is shown, it's table 2-2 that is shown on this slide. So

over a couple of years, they prepared several different formulations, transdermal formulations containing rivastigmine.

Indicatively, none of these formulations contained an antioxidant. So they obviously knew the structure of rivastigmine, they had been involved in development of oral rivastigmine drug, and yet, they did not expect any oxidative degradation problem. And for that reason, they didn't include an antioxidant in any of their initial formulations.

Q. Did the formulations without an antioxidant contain rivastigmine base or rivastigmine salt?

A. Both. Both base and -- both base and salt.

Q. How was the absence of an antioxidant in these formulations relevant to your analysis?

A. Well, in my view it indicates that the inventors didn't see any need to add an antioxidant and, therefore, didn't expect any oxidative degradation of rivastigmine.

MS. JACOBSEN: And for the record,

Dr. Klibanov referred to PTX 242 at page 244, and Plaintiffs move to introduce into evidence PTX 242.

MR. LEVY: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Is the absence of an antioxidant in these formulations consistent with your opinion of whether a POSA would add an antioxidant to a formulation?

A. Yes, it basically showed that a person of ordinary skill in the art at the time had no reason to add an antioxidant because the oxidative degradation problem of rivastigmine was not known, not only to this person, but even to the inventors.

Q. And what was the inventors' expectation with respect to the stability of rivastigmine?

A. Actually as the next couple of slides show, their expectations were pretty favorable. For example, this table that is shown on the screen now, it shows sort of their

expectations with respect to technical hurdles, and they expected that combined issues of stability and quality of base, base as a reference to rivastigmine freebase, was only 15 percent.

And when asked, Dr. Tiemessen's at trial testimony in this courtroom in the Watson trial, can you characterize the team's expectation, this is a development team for rivastigmine, a transdermal formulation, regarding encountering the stability issue, he said in fact we didn't expect stability issues. And then adds, and at that point in time, we also had quite experience with the chemical stability of the first generation, which is the first lead formulation,so they didn't expect any stability issues and attached a very low probability to combine the possibilities of all stability and quality of base issues.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 246 at page 70 and Plaintiffs move to introduce into evidence PTX 246.

MR. LEVY: No objection.

THE COURT: Admitted without

objection.

BY MS. JACOBSEN:

Q. And what does stability refer to in the technical hurdles?

A. Again, Dr. Tiemessen at the trial here was asked that question, he was asked, so, you see the word stability, that is this word stability that's highlighted, that's referred to in this document. Is that a reference to oxidative degradation? And he said no. This is referencing to stability in general. He says then, the chemical stability in general, and also the physical stability in general. So this 15 percent wasn't even his -- their expectation of encountering oxidative instability, that was their expectation of encountering any type of instability, whether it's chemical or physical combined.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 246 at page 70.

BY MS. JACOBSEN:

Q. So how did the inventors discover that rivastigmine undergoes oxidative degradation?

A. Well, they proceeded with their formulation development, and as they state in their development report, what they found they say in preliminary stability tests after three months storage of the patches, and these are transdermal patches containing rivastigmine, the occurrence of two unknown degradation products of ENA713, ENA713 is their abbreviation for rivastigmine, was observed.

So they unexpectedly discovered these two unknown peaks that corresponded to unknown degradation products. And then as they -- the inventors explain in the specification of the '031 patent, the patent-in-suit, it has now been found after exhaustive testing that rivastigmine is susceptible to degradation, particularly in the presence of oxygen.

So one of skill in the art would understand from all that information that they didn't expect to see any degradation, in particular oxidative degradation, but they nonetheless encountered it, and they determined that it was oxidative degradation and then they

discovered how to prevent it from happening.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 242, the page 24, and JTX 1, column 1, lines 22 to 24.

BY MS. JACOBSEN:

Q. And did the inventors discover a solution to this problem?

A. Yes, they discovered that the problem could be solved by adding antioxidants as is taught by the '031 patent claims.

Q. Dr. Klibanov, let's turn to Dr. Schoneich's theory about benzylic carbon hydrogen bonds. Did you consider that theory in your analysis?

A. Yes, I did.

Q. What was your overall conclusion?

A. Well, my overall conclusion was that I do not agree with that theory. And among the reasons why I don't agree are that as I mentioned earlier, a POSA would know that the whole molecule influences stability, including oxidative instability.

Many commercial or patented drugs with benzylic carbon hydrogen bonds were, in

fact, not reported to undergo oxidation. And finally, in my opinion that I will explain shortly, nicotine is not structurally similar to rivastigmine.

So maybe to put it sort of differently and simply, I have some major theoretical disagreements with Professor Schoneich's theory, but rather than engaging in theoretical discussion, I thought it would be more useful to the Court if I were to do what chemists and indeed all experimental scientists always do when they have a theory, they simply say okay, I have a theory, I'm going to test this theory. I'm going to test it experimentally.

What I have done here, I tested Professor Schoneich's theory using commercially available at the time of the invention FDA approved drugs and also a number of other drugs that were patented.

And in regard to the structural theory predictions, they all had benzylic carbon hydrogen bonds which the theory, Dr. Schoneich's theory predicts that that should

make them unstable, but the reality is as the Court will see in a moment, that in fact there was no evidence that they were unstable toward oxidative degradation.

So I mean, to put it simply, I mean, I always thought that the proof of the pudding is in the eating, so if there is no degradation, that means that the theory is untenable.

Q. Dr. Klibanov, you said many commercial patented drugs with benzylic carbon hydrogen bond were not reported to undergo oxidation?

A. Yes.

Q. Can you give some examples?

A. Sure. I prepared several, several tables listing them. So the first table lists drugs with a benzylic carbon hydrogen bond and adjacent nitrogen, so these are the requirements of Professor Schoneich's structural theory, that were not reported to undergo oxidation, even though they have all of the elements required by that theory.

And these drugs include

Ampicillin, Hydroxyzine, Meclizine, Mirtazapine, and Benzquinamide. And for comparison, the structure of rivastigmine is shown in the lower right corner. And for convenience of the Court in the case of each of these molecules, I encircled in red that benzylic carbon hydrogen bond adjacent to a nitrogen atom that is supposed to make this molecule unstable.

So the Court can see that Ampicillin has it; Hydroxyzine has it; Meclizine has two of them; Mirtazapine has it; and Benzquinamide has it, as does rivastigmine of course. And yet none of these molecules was reported, and these were all FDA approved drugs. None of them was reported to undergo oxidative degradation problems.

Q. And were any of them reported to contain an antioxidant in their commercial formulations?

A. No, none of them was reported to contain an antioxidant in their commercial formulations.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 157 at 1878, 1992,

2007, 2015, 2035, 2044, and 2872. And Plaintiffs move to introduce into evidence PTX 157.

MR. LEVY: No objection. But I believe you cited 2044 instead of 2042.

THE COURT: I'm sorry. What is PTX 157?

MS. JACOBSEN: These are excerpts from the Physician's Desk Reference.

THE COURT: All right. Okay. It's admitted without objection.

BY MS. JACOBSEN:

Q. Dr. Klibanov, can the absence of an antioxidant in these formulations be attributed to the dosage form that they're in?

A. No, because they were both liquid and solid dosage forms. And besides, all dosage forms are known to undergo oxidative degradation. It's just a question of rates.

Q. Are you aware of any other examples of compounds with a benzylic carbon-hydrogen bond that were not reported to undergo oxidative degradation in a

pharmaceutical formulation as of 1998?

A. Yes, I am. And they are shown on the next slide.

So these are examples of either commercial or patented drugs that had a benzylic carbon-hydrogen bond. And these compounds that are shown here include dexsecoverine, scopolamine, fetanyl, benztropine, and secoverine. And, again, rivastigmine structure is shown in the lower right corner here.

In the case of each of these drugs, the benzylic carbon is encircled in red. So all of them, just like rivastigmine, have it, and yet none of these either commercial or patented drugs was reported to undergo oxidative degradation or was reported to contain an antioxidant.

MS. JACOBSEN: And for the record, Dr. Klibanov referred to PTX 157 and Pages 890 and 1336. PTX 185, Column 5, Line 55 to Column 7, Line 10, and PTX 186 at Column 6, Line 15 to Column 8, Line 32.

And plaintiffs move to introduce into evidence PTX 185 and PTX 186.

MR. LEVY: No objection.

THE COURT: All right. Admitted without objection.

BY MS. JACOBSEN:

Q. So, Dr. Klibanov, what would a POSA in 1998 have concluded from these examples?

A. Well, a person of ordinary skill in the art would have concluded that the mere presence of a benzylic carbon-hydrogen bond with or without nitrogen adjacent to it by itself cannot possibly predict whether or not a drug will undergo oxidative degradation under pharmaceutically relevant conditions, and therefore, whether or not this drug would require an antioxidant.

So, in my opinion, these and other examples that I will show refute the theory that suggests otherwise.

Q. Are there other drugs with a benzylic carbon-hydrogen bond that have been approved since 1998 in pharmaceutical formulations without a reported antioxidant?

A. Yes. After the date of the invention, after 1998, there were several other

drugs, namely Selegiline that was mentioned yesterday in Dr. Kydonieus' testimony and buprenorphine that also have this benzylic carbon-hydrogen bond that also were not reported to contain an antioxidant.

MR. LEVY: Objection, Your Honor.

THE COURT: Is this your earlier objection?

MR. LEVY: Yes.

THE COURT: And I'm going to overrule it.

MR. LEVY: Thank you, Your Honor.

BY MS. JACOBSEN:

Q. I'm sorry, Dr. Klibanov. Can you just explain what these examples show?

A. Yeah. These are later examples.

And in the case of both of these drugs, again, the carbon, benzylic carbon is encircled here. Rivastigmine is given for comparison.

And as I said, these were the two FDA-approved drugs and neither of them -- both of them have benzylic carbon-hydrogen bonds, but neither of them was reported to contain an

antioxidant.

Q. One of those, the examples you gave is Selegiline, that includes a benzylic carbon-hydrogen bond?

A. Yes, it does.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 188 at Page 903 and PTX 189, at 2684.

And plaintiffs move to introduce into evidence PTX 188 and PTX 189.

THE COURT: And they're admitted. You got the objection made earlier.

BY MS. JACOBSEN:

Q. Dr. Klibanov, are you aware of any drugs containing a benzylic carbon-hydrogen bond that were reported to be stable?

A. Yes. There were drugs such as, for instance, dextromethorphan that I'm showing on this slide and a couple of other subsequent slides that also has this benzylic carbon that is supposed to do it with respect to the oxidative instability.

But, in fact, it was reported to be stable in the prior art literature. For

instance, what is shown on this slide are the data from Boccardi 1994 reference.

And here, Boccardi states that dextromethorphan hydrobromide is a very stable drug substance. So this is the structure of dextromethorphan, and what is encircled in red, Your Honor, is the benzylic carbon bonded to hydrogen.

And, nonetheless, dextromethorphan was very stable. And Boccardi continues, in the case of dextromethorphan, the low reactivity in the free radical test reflects the good stability of the substance.

Q. And what is the free radical test that's referred to in Boccardi?

A. That is what Dr. Schoneich talked about yesterday. So you expose a drug to conditions that generate these free radicals that cause oxidative degradation.

So here, dextromethorphan was exposed to such conditions, but nonetheless, as Boccardi states, shows good stability.

MS. JACOBSEN: And for the record, Dr. Klibanov referred to JTX 24 at Page 433.

And plaintiffs move to introduce into evidence JTX 24.

MR. LEVY: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Dr. Klibanov, did any other scientific literature confirm that dextromethorphan is stable?

A. Yes. This is a -- what is shown on the screen now are data from a paper by Magid, M-A-G-I-D -- I'm not sure I pronounced it correctly -- but in 1963. And this paper specifically says dextromethorphan hydrobromide has excellent stability and is unaffected by mild oxidizing or reducing agents.

Importantly, the Magid paper specifically characterizes the stability of dextromethorphan both in crystal in a solid state and in aqueous solution. In both cases, under air.

And in both cases, both in the solid state and in aqueous solution, the stability was found to be good. So, as is stated

here, under both sets of conditions, dextromethorphan, even though it has a benzylic carbon-hydrogen bond was stable.

Furthermore, with respect to tablets and capsules, Magid specifically concluded that dextromethorphan in them was "Stable under all normal conditions of storage".

That's a direct quote.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 180 and Pages 621 and 622. And plaintiffs move to introduce into evidence PTX 180.

MR. LEVY: In objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Was dextromethorphan reported to require an antioxidant in pharmaceutical formulations?

A. No. Dextromethorphan was used in many commercial, obviously FDA-approved pharmaceutical formulations in the United States.

And what I list on the next slide

are data from Physician's Desk Reference 1997. And what the Court can see here is 17 -- is different commercial formulations containing dextromethorphan.

Okay. I'm not going to read the names, but they're all familiar. Many of these names are familiar to us.

Tylenol Cold and Cough, that's what I was taking when I was sick. But basically what's important here is that none of these 17 commercial formulations that existed prior to 1998 was reported to contain an antioxidant.

MS. JACOBSEN: And for the record, Dr. Klibanov referred to PTX 157, again the Physician's Desk Reference.

BY MS. JACOBSEN:

Q. So what conclusion would a POSA have drawn regarding the stability of dextromethorphan from the prior art?

A. Well, in my opinion, a person of ordinary skill in the art would have no choice, but to conclude that the theory, based on the benzylic carbon-hydrogen bond that predicts that

if this particular structural element is present in the molecule, means that the compounds will undergo oxidative degradation in any formulation, that this theory is incorrect because it is directly contradicted by numerous experimental data.

Q. Would a POSA have concluded that dextromethorphan is stable under pharmaceutically relevant conditions?

A. That's the conclusion that the one of skill in the art would have to arrive at in the absence of any indication of instability. One of skill in the art would assume that the drug is stable.

Q. So moving on to the one drug that Dr. Schoneich relied on, nicotine, did you consider nicotine in your analysis?

A. I did.

Q. Would a POSA consider it structurally similar to rivastigmine?

A. I do not believe so. I mean, they certainly don't look similar, but the person of ordinary skill, they are, indeed, the chemists, would not just rely on superficial impressions.

There is a systematic way to compare the structures of chemical compounds that chemists routinely use in their work. And this systematic way is to say, okay, I have, let's say, two different compounds. They all have functional groups.

Let's systematically analyze whether each particular functional group is present in one molecule and present in another. And it is this type of analysis that I carried out in the slide that's on the screen now.

So we have functional group here. This is the chemical structure for rivastigmine. This is a chemical structure of nicotine.

So with respect to functional groups, I started with the carbamate moiety that we talked so much - that I talked about so much about. And the Court can see that the carbamate moiety really is present in rivastigmine. It is not present in nicotine.

The next structural element was the benzene ring that I also talked about. It's this hexagon that is encircled in red. The Court can see that the benzene ring is present

in rivastigmine. It is undeniably not present in nicotine.

The next functional group is tertiary amine group. Okay. Here again, it's encircled in rivastigmine.

It's encircled in red in nicotine. So it's present in both of them; however, the type of tertiary amine present is different.

In nicotine, the amine is a part of a ring. In rivastigmine, it is not.

The next functional group is pyrrolidine ring. It is this ring that is encircled in the red in nicotine.

So, obviously, it's present in nicotine. It is not present in rivastigmine.

The next functional group is pyridine ring. Again, it's a group that is encircled in red in nicotine. Obviously, present in nicotine. It is not present in rivastigmine.

And, finally, we come to the benzylic carbon-hydrogen bond. Benzylic carbon-hydrogen bond is present in rivastigmine.

It is this bond right here. And

it is not present in nicotine because nicotine doesn't have benzylic carbon-hydrogen bond.

The reason that benzylic carbon-hydrogen bond is called benzylic is because it stems from benzene or, as I mentioned earlier, there is no benzene in nicotine.

There is another aromatic ring, namely pyridine that is present there.

Q. And how does the pyridine ring compare with the benzene ring?

A. It is structurally different, a different chemical moiety. So what one would conclude based on these -- on this comparison is that the structures of rivastigmine and nicotine are very different.

And since, as I mentioned earlier, one of skill in the art would know that the stability of a chemical molecule is determined by the entirety of its structure. If the structures are very different, then the stabilities have to be different. And, therefore, one of skill in the art would not mechanically extrapolate from whatever is known about nicotine to rivastigmine.

Q. And as of 1998, was nicotine known to undergo oxidative degradation?

A. Yes, under some pharmaceutically relevant conditions, nicotine was known to undergo oxidative degradation.

Q. Would that have caused a POSA to expect rivastigmine to potentially undergo oxidative degradation in a pharmaceutical formulation?

A. No. I mean, as I just indicated, there are two different molecules. And whatever may hold for nicotine certainly doesn't have to hold for rivastigmine or any other chemical molecule.

Q. Well, let's assume that a POSA would have expected rivastigmine to potentially undergo oxidative degradation based on nicotine. Would that have led a POSA to add an antioxidant to rivastigmine?

A. No. Because, in fact, an antioxidant wasn't even added to nicotine transdermal devices.

At the time of the invention in 1998, there were three commercial transdermal

formulations containing nicotine: Habitrol, Prostep, and Nicotrol. So they were all transdermal devices containing nicotine.

Furthermore, containing nicotine in the free base form. And yet, none of them, even though nicotine was known to undergo oxidative degradation in some other formulations, none of these commercial transdermal formulations included was reported to include an antioxidant.

So. Even with respect to nicotine itself, that wasn't the case, let alone rivastigmine.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 157 and that's the Physician's Desk Reference at Pages 884, 1439, and 1568.

BY MS. JACOBSEN:

Q. So, Dr. Klibanov, what conclusion would a POSA draw from these nicotine transdermal formulations?

A. Well, it basically would confirm a person of ordinary skill in the art's opinion that the stability of a drug, including

stability toward oxidative degradation, is formulation specific; and therefore, even though nicotine undergoes oxidative degradation in some, for example, aqueous formulations, it, nevertheless, doesn't require an antioxidant in a transdermal formulation as is evidenced by these -- all of these transdermal nicotine-containing formulations at the time of the invention.

Q. Well, let's assume that a POSA would recognize that degradation at the benzylic carbon hydrogen bond in rivastigmine was theoretically possible. Would that change your opinion regarding whether a POSA would add an antioxidant to rivastigmine in a pharmaceutical composition?

A. No, it still would not. And the reason for that is -- and just because something is theoretically possible, as I alluded previously, doesn't mean that it actually happens. And certainly doesn't mean that it happens to any measurable extent.

And in this regard, the book by Connors that I previously referred to, 1986, I

think provides some constructive information, and specifically this chapter that's shown on the screen specifically says kinetically. And kinetics is the area of chemistry that studies how chemical reactions occur as a function of time.

So it says kinetically, however, there is sufficient energy barrier to many such reactions, that not all molecules are, and this is -- this is a reference to oxidation reactions, that not all molecules are subject to measurable rates of spontaneous oxidation or autoxidation.

So even though theoretically a molecule may undergo oxidative degradation, but as a matter of reality, due to this high kinetic barrier, it may not do so at a measurable rate.

And whether it undergoes this degradation and whether the rate is measurable can only be established by experimentation.

Q. For the record, Doctor Klibanov referred to JTX 22 at Page 82.

Would a POSA have been able to predict the outcome of that experimentation in

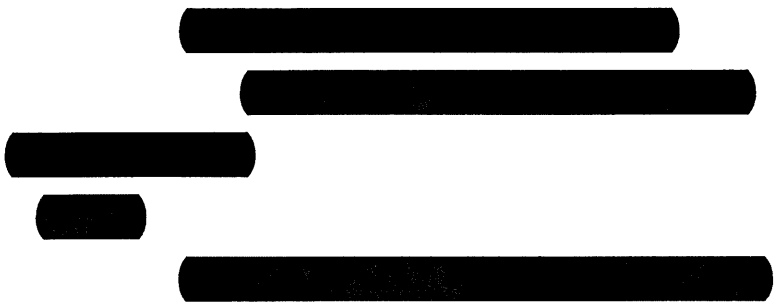
advance?

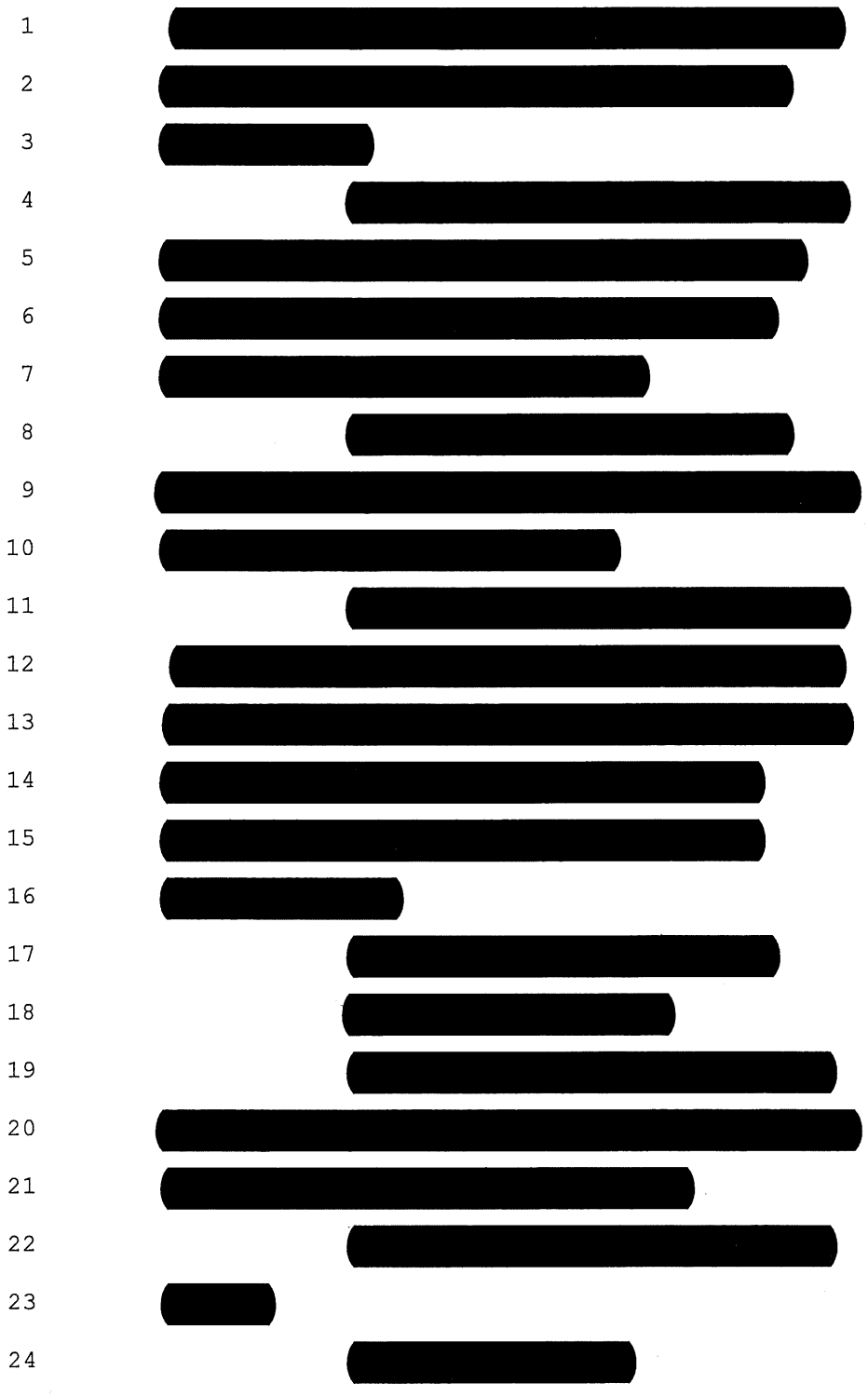
A. No. If a person could predict the outcome of these experimentations in advance, then there would be no need to do this experimentation.

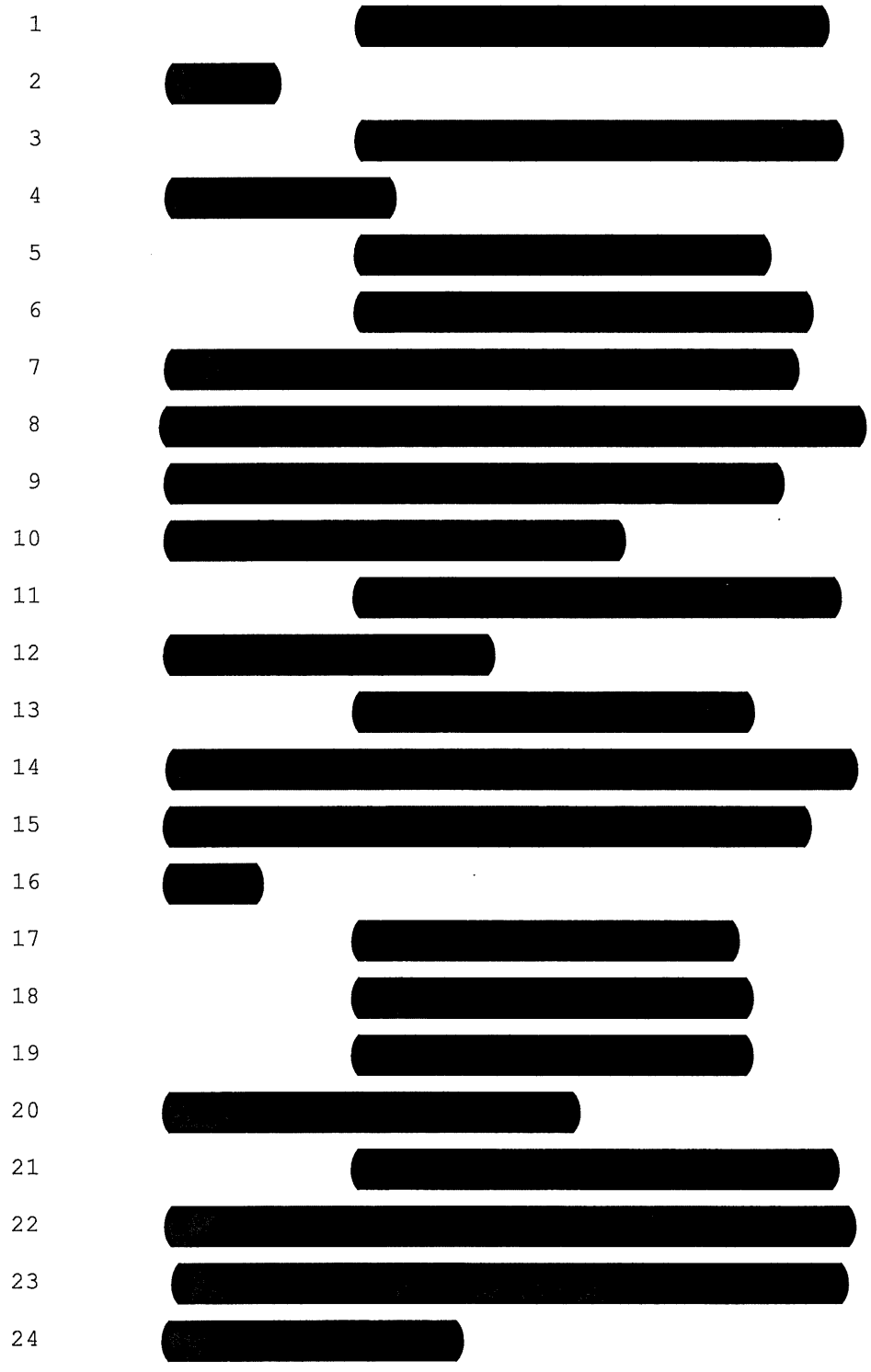
So the outcome of the experimentation was not predictable, which is why experimentation was required.

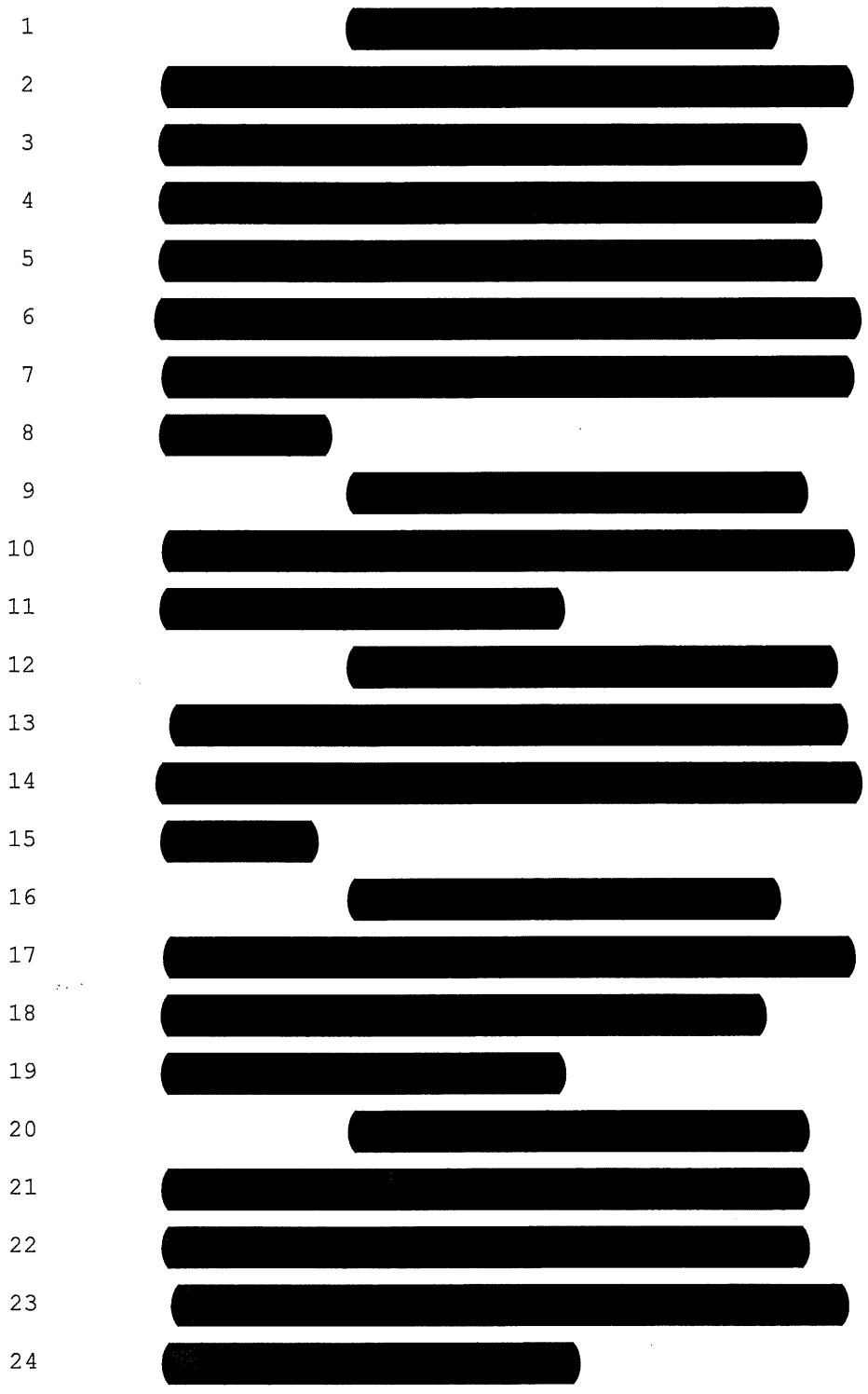
Q. And was that relevant to your analysis of whether or not the '031 patent was non-obvious?

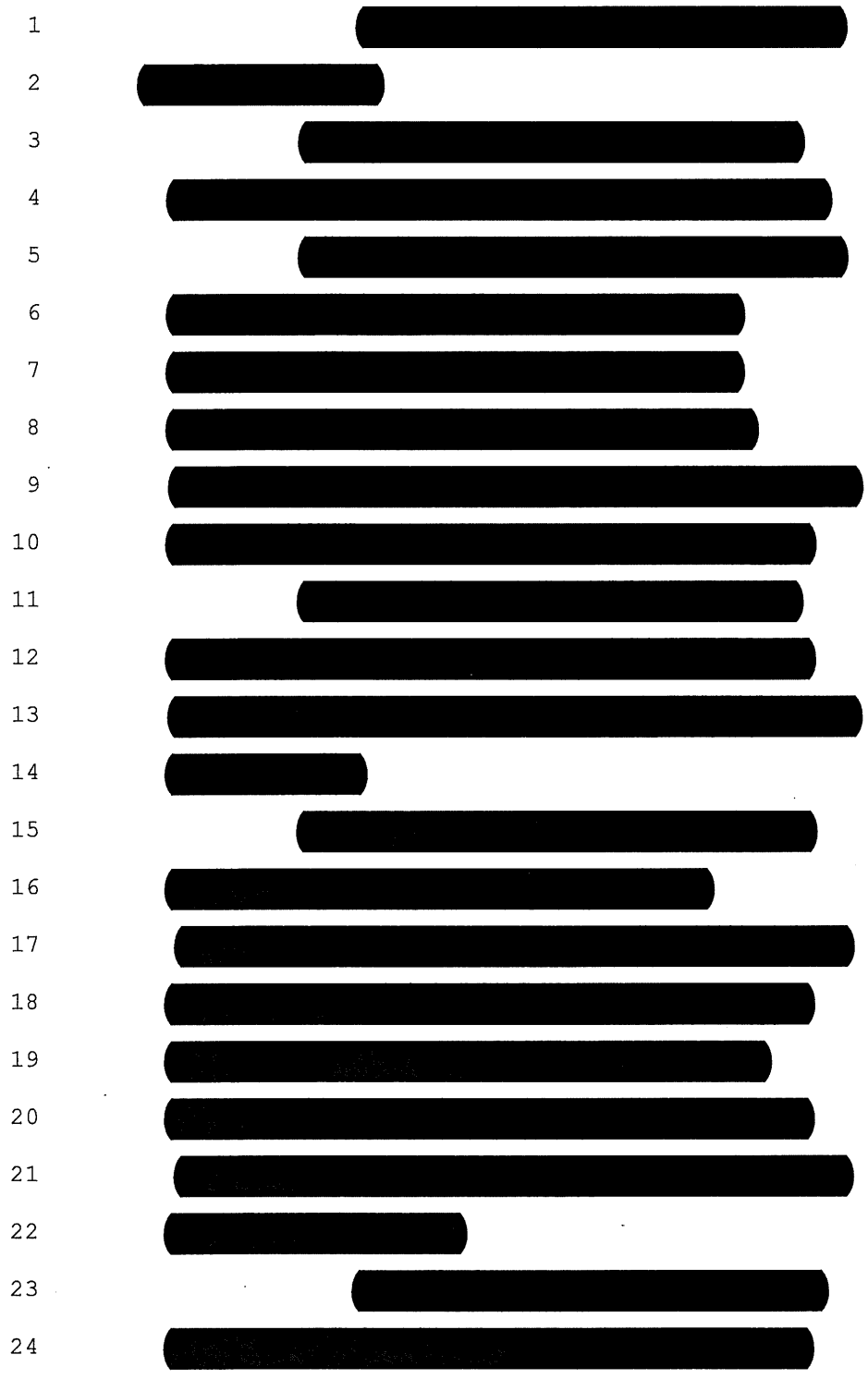
A. Yes, because, in my opinion, if -- as I said earlier, even if the experimentation is routine, and I do not believe that it is routine here, but even if it were, if one of skill in the art cannot -- doesn't know whether a problem would be revealed as a result of this experimentation, well, then this problem can't possibly be obvious to one of skill in the art.

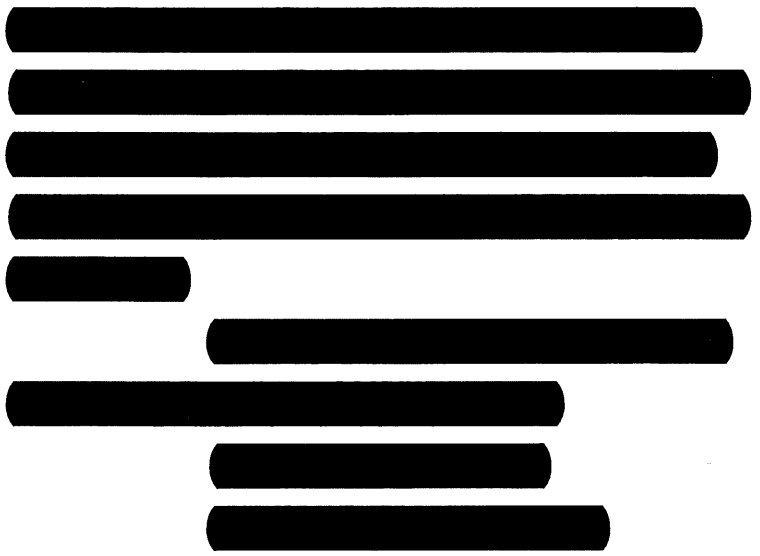












BY MS. JACOBSEN:

Q. Just so we're clear, would the tertiary amine of rivastigmine have led a person of ordinary skill in the art in 1998 to believe that it would undergo oxidative degradation in a pharmaceutical formulation?

A. No. Because as I said, there were a lot of tertiary amines that where pharmaceutical compounds, drugs, that did not undergo oxidative degradation under pharmaceutically relevant conditions.

Q. Let's assume that a POSA would have believed that rivastigmine base would undergo oxidative degradation because of its amine, would a POSA believe that that potential

instability could have been solved by converting it to a salt form?

A. No, because in some cases, if there is a freebase, where we just have a nitrogen atom as in the case of rivastigmine and it can also form a salt. In some cases, salts are more stable toward oxidative degradation than freebases, in some other cases, they're less stable. It could go either way, again, depending on the structure of the entire molecule, including the nature of the salt.

Q. Let's turn to Dr. Kydonieus' theory based on amines. Did you consider the Sasaki reference in your analysis?

A. I did.

Q. What did you conclude?

A. I concluded that the Sasaki reference did not, would not inform the person of ordinary skill in the art that rivastigmine or RA7 would undergo oxidative degradation. Again, the preface is that the POSA would know that the whole molecule influences stability.

Now, a POSA would not draw conclusions about all amines, and there are many

thousands based on just two amines as Sasaki studied in just one transdermal as Sasaki studied. And, in fact, there was much evidence to the contrary where commercial or patented transdermals containing an amine were, in fact, not reported to contain an antioxidant.

So in my opinion, a person of skill in the art looking at the prior art as a whole would not make such conclusions based on Sasaki as Dr. Kydonieus advanced yesterday.

Q. Is Sasaki a peer reviewed reference?

A. No, it is a non-reviewed. It is a non-reviewed Japanese application, unexamined I believe is the proper term, Japanese patent application.

Q. Does Sasaki disclose rivastigmine?

A. It does not.

Q. What does Sasaki relate to?

A. Sasaki basically relates to transdermal formulations containing some compounds with phenolic hydroxyl groups as the Court can see here or with amine groups. And this phenolic and amine containing compounds

were placed in an adhesive, acrylic adhesive and were found that three compounds, there were only three compounds that were examined in Sasaki and only two of them were amines. So it was found that these three Sasaki compounds undergo degradation in acrylic adhesive substances and therefore an antioxidant was added to prevent it.

Q. There is a reference in Sasaki to phenolic hydroxyl group-containing compounds. Does rivastigmine contain a phenolic hydroxyl group?

A. No, it does not.

MS. JACOBSEN: For the record, Dr. Klibanov referred to DTX 12 at page 186.

BY MS. JACOBSEN:

Q. What were the amine containing compounds that Sasaki tested in an acrylic adhesive?

A. So Sasaki tested only three compounds, and the names and the structures of these compounds are shown on this screen now. The first compound is a phenolic compound, it doesn't have an amine moiety. The second and

the third compounds were amines. And they were tested, these two amines and one phenol were tested in one particular transdermal formulation, a prototypical transdermal formulation containing an acrylic adhesive.

Q. And what did Sasaki detect in that one formulation?

A. Sasaki detected that all of them underwent what Sasaki calls breakdown, degradation, and in order to prevent it from happening, Sasaki added an antioxidant to them.

Q. Would a POSA have concluded from these two amines that Sasaki tested that all amines undergo oxidative degradation in an acrylic adhesive?

A. No, certainly not. I mean, it's just sort of common sense that you wouldn't extrapolate from just two amines to many thousands of known amines. And likewise, you would not extrapolate from one transdermal formulation to all possible transdermal formulations.

And in addition to that, there were examples to the contrary, which I am going

to discuss in a moment. So I think that looking at all of this evidence as a whole, in my opinion one of skill in the art would not make such an extrapolation.

MS. JACOBSEN: For the record, Dr. Klibanov referred to DTX 12, page 188.

BY MS. JACOBSEN:

Q. What was the evidence to the contrary that you referred to, Dr. Klibanov?

A. For example, this slide that the Court can see on the screen now depicts six different amine drugs, or drugs that just like Sasaki's drugs and just like rivastigmine, contain amine moieties. They were used in transdermals, and they were either commercially available as of 1998, or patented.

So these six compounds include Dexsecoverine, Scopolamine, Fentanyl, Benztropine, Secoverine, and physostigmine.

Now, in the case of each of these compounds, the Court is pointed to the amine circled in the red, this is an amine, this is an amine, this is an amine, this is an amine, and these are two amines in

physostigmine as I discussed earlier.

So as I said, these were amine drugs in transdermals that were either FDA approved or were patented, and in no case was an antioxidant reported to be present in these formulations.

Q. What would a POSA have concluded from these examples?

A. This would have confirmed the POSA's opinion that the stability toward oxidative degradation as well as other properties is dependent on the structure of the molecule as a whole. And the only way to find out whether, in fact, the molecule undergoes oxidative degradation is to conduct direct experimentation or conduct testing.

Q. Do these compounds contain tertiary amines like rivastigmine?

A. All of these compounds do. I might add that of the Sasaki amines, only one is a tertiary amine which is a type of an amine that we have in rivastigmine. The other is a primary amine, a different type of an amine. All six of these compounds have tertiary amines

just like rivastigmine.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 157 at pages 890 and 1336, PTX 185, column 5, lines 55 to column 7, line 10, PTX 186 at column 6, line 15 to column 8, line 32, and JTX 33 at column 8, lines 50 to 65.

Q. And Dr. Klibanov, are there any examples of compounds with an amine group that were not reported to contain an antioxidant in a pharmaceutical formulation that was developed after 1998?

A. Yes. After '98, so that obviously these are not prior art references, there were three other amine containing drugs in transdermals where antioxidants were not reported to be present.

And they include oxybutynin, selegiline, and buprenorphine. All of them have these tertiary amines just like -- so we have it here, it's encircled in red, and here it's encircled in the red, and the Court can see that rivastigmine has the same type of an amine where three alkyl groups are attached to this nitrogen

atom. So none of these were prior art compounds even though they were all amines in transdermal, none of them was reported to have an antioxidant.

THE COURT: I will note Mr. Levy's objection to this as being I guess irrelevant because it post dates the invention, but I will overrule the objection.

MR. LEVY: That's correct, Your Honor. Thank you.

BY MS. JACOBSEN:

Q. And one of these compounds is selegiline; is that right?

A. Yes.

Q. Is selegiline a tertiary amine?

A. Yes, it is.

Q. And is selegiline also a compound with a benzylic carbon hydrogen bond?

A. Yes, it is. This carbon here is a benzylic carbon and there is a hydrogen attached to it.

MS. JACOBSEN: For the record, Dr. Klibanov referred to PTX 187 at 59, PTX 188 at 903, and PTX 189 at 2864. Plaintiffs move to

introduce into evidence PTX 187.

MR. LEVY: No objection.

THE COURT: All right. Admitted without objection.

MR. LEVY: I'm sorry, subject to the prior objections.

THE COURT: Good point. Thank you.

BY MS. JACOBSEN:

Q. Dr. Klibanov, was there any suggestion in the prior art that rivastigmine was unstable in an acrylic adhesive?

A. No. In fact, there was suggestions to the contrary, because if we go back to GB '040, which we discussed in the beginning of my direct testimony, and that example two that I also talked about, it specifically says that with respect to composition of this transdermal it specifically says -- so it's compound A which is -- the compound A which is rivastigmine, it also says that among other components, other ingredients, inactive ingredients is acrylate polymer. So example two of GB '040 is an example of an amine

drug compound in a transdermal formulation containing acrylate polymers.

Q. Is the amine-containing compound in example two rivastigmine?

A. Yes, it is, it could be rivastigmine.

Q. Is there any suggestion that that would have given rise to a stability problem?

A. No. As I mentioned earlier, GB '040 gives no indication, in fact gives opposite indications, but gives no indication to one of ordinary skill in the art that rivastigmine needed an antioxidant or that rivastigmine undergoes oxidative degradation.

MS. JACOBSEN: So for the record, Dr. Klibanov referred to JTX 19 at page 19.

BY MS. JACOBSEN:

Q. So would a POSA in 1998 have been motivated to combine Sasaki with GB '040?

A. No, I see no such motivation, because GB '040 didn't identify any oxidative degradation problem and, therefore, a person of ordinary skill in the art wouldn't look for a reference to combine GB '040 with Sasaki to

solve an unknown problem. But even aside from this lack of motivation, even if one of skill in the art were to combine GB '040 with Sasaki, in my opinion, this combination doesn't make the invention of the patent-in-suit obvious because Sasaki doesn't deal with rivastigmine, doesn't deal even with RA7, it deals with just two particular amine compounds in one particular transdermal formulation, and therefore, I don't see how it can possibly make the invention of the patent-in-suit obvious.

Q. Dr. Kydoniues also discussed the Ebert reference?

A. Yes.

Q. Did you consider that reference in your analysis?

A. Yes, of course.

Q. What was your overall conclusion?

A. Well, again, my overall conclusion is that a POSA would not have combined Ebert with GB '040, and briefly, the reasons for that are outlined on this slide that's on the screen now.

First of all, Ebert does not

disclose rivastigmine or even RA7. Ebert solves problems that are not related to rivastigmine, meaning it solves problems that do not exist with rivastigmine.

And also, Ebert discloses, and that's important, nonconventional manufacturing of a transdermal device, whereas GB '040 expressly prefers conventional manufacturing for rivastigmine, and reiterates that.

Q. So what problem does Ebert address in the prior art?

A. It follows from what is shown on the screen now, so there were several problems that Ebert addressed that were present with nicotine. So as the citation from Ebert says, an object of the present invention, that's Ebert's invention, is to provide a method of fabricating transdermal devices with volatile or heat-sensitive drugs, and as a result of their volatility and sensitivity to heat, such components cannot be subjected to drying or heating.

And there is no evidence that rivastigmine is either volatile or heat

sensitive. And, in fact, there is evidence that transdermal devices containing rivastigmine can be subjected to drying and heating because they are both in the Novartis manufacturing process and in the Noven manufacturing process.

Q. Does Ebert identify any particular drugs that are heat sensitive or volatile?

A. Yes. There are a number of drugs that are mentioned, but all of the experimentation is done with just one particular drug, namely nicotine.

Q. And does Ebert suggest that rivastigmine would be heat sensitive or volatile?

A. No. As I said, it doesn't mention rivastigmine at all.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 28 at page 5, line 16 to 21.

BY MS. JACOBSEN:

Q. And did Ebert address any other problems?

A. Yes. Ebert addressed some other manufacturing problems, but again, problems that

were specific for nicotine. So as the Court can see on the screen now, these are two other excerpts from Ebert, the first one says with above about 50 percent nicotine by weight, the polymer fails to solidify. This is the polymer that is used to make the transdermal device.

And then it continues, common materials used to make transdermal devices, such as backing layers, adhesives and release liners, are dissolved or degraded by nicotine.

So Ebert specifically identifies a couple of other problems with nicotine in transdermal devices in terms of manufacturing issues, one is prevention of the polymer from solidification, and another one is degradation by nicotine or dissolution. And again, there is no evidence presented that rivastigmine will have any of these problems. So these were all the problems that were specific for nicotine.

Q. And you mentioned the polymer that's used to make the transdermal device. Is that a reference to the adhesive?

A. Yes.

MS. JACOBSEN: Just for the

record, Dr. Klibanov referred to JTX 28 at page 3, lines 17 to 25, and page 4, lines 1 to 4.

BY MS. JACOBSEN:

Q. Now, how did Ebert address these problems with nicotine?

A. Well, basically what Ebert did, Ebert prepared -- he employed a very unusual manufacturing process. So what Ebert did, he first extruded the polymer, which didn't contain a drug, and then -- this polymer was dissolved in the solvent and the solvent was evaporated in an oven. And then subsequent to that, Ebert extruded a mixture of nicotine with a polymer, with another polymer, in this particular case, and in this particular case as the Court can see it was hydroxy propyl cellulose, and this mixture which was very thick, it required stirring for as I recall twenty-four hours. And since nicotine as I mentioned earlier, Your Honor, under some conditions undergoes oxidative degradation, to prevent this degradation of nicotine while stirring, Ebert added the antioxidant BHT due to the fact that nicotine was stirred over an extended period of time.

So the rationale for this unusual manufacturing process is that unlike rivastigmine that can and is heated during the manufacturing, nicotine cannot be because it is heat sensitive and therefore it had to undergo this laborious procedure and requiring lengthy stirring and to prevent its oxidation during this lengthy stirring the antioxidant was added.

Q. And the mixture of hydroxy propyl cellulose and nicotine, is that the active gel that's discussed?

A. Yes, that's what Ebert calls the active gel, yes.

Q. And is this how transdermal devices are conventionally made?

A. No, that's not how they are conventionally made. They are conventionally made using a matrix method where you basically mix the adhesive with the drug and then subject it to drying. Ebert couldn't use it with nicotine because nicotine is heat sensitive and, therefore, doesn't tolerate drying.

Q. And is the mixing for the extended period of time, say twenty-four hours, a

conventional manufacturing step?

A. No, it's obviously, you know, wasteful, takes a long period of time, there are all kinds of issues, that is not how it's usually done. Ebert was forced to employ this method because of the specific features of nicotine as a drug.

MS. JACOBSEN: For the record Dr. Klibanov referred to JTX 28 at page 1, lines 13 to 20, and page 19, lines 34 to page 20, line 3.

BY MS. JACOBSEN:

Q. You mentioned that Ebert disclosed the use of an antioxidant. Why was that antioxidant added in Ebert?

A. Ebert explains that, and specifically says another trait of nicotine that can be problematic is its tendency to oxidize readily in the presence of light and air. So that's the problem that nicotine was known to have.

And then Ebert says during fabrication of nicotine patches, oxidation is controlled by addition of an antioxidant to the

active gel. So the purpose of the antioxidant was to prevent this oxidation during the lengthy stirring that Ebert had to employ.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 28 at page 19, lines 17 to 19, and lines 23 to 24.

BY MS. JACOBSEN:

Q. If a POSA didn't prepare the active gel as in Ebert, would a POSA have been motivated by Ebert to add an antioxidant?

A. No, then there would be no reason to do that.

Q. And if a POSA didn't already know the drug would potentially undergo oxidative degradation, would Ebert have told the POSA that an antioxidant was required?

A. No. Again, the answer is no.

Q. Does Ebert suggest that any drug other than nicotine is sensitive to oxidative degradation?

A. No the focus is on nicotine with nicotine's specific problems and issues, as I just explained.

Q. Would a POSA have been motivated

to use the teaching in Ebert with rivastigmine?

A. I mean, I see no such motivation. Again, GB '040 didn't report any oxidative degradation problem of rivastigmine, hence there was no motivation to combine rivastigmine -- to combine GB '040 with any other reference to solve this unknown problem, but in any event, even if one of skill in the art were to combine GB '040 with Ebert, given that Ebert doesn't deal with rivastigmine, it employs a nonconventional manufacturing process as opposed to conventional processes in the case of GB '040, certainly this combination wouldn't make the invention of the patent-in-suit obvious in my opinion.

Q. Is there any evidence that rivastigmine suffered from any of the problems with nicotine that were addressed by Ebert?

A. No. In fact, if rivastigmine was known to -- not to have these problems, for example, as I mentioned previously, Your Honor, nicotine was known to be volatile, so to have very high vapor pressures, so that would be very susceptible to evaporation. In contrast -- this

is nicotine. In contrast to that, rivastigmine was not known to be volatile. Also, nicotine has a very low viscosity. It's only a few fold more viscous than water, whereas rivastigmine has a very high viscosity, much, much higher than water.

So that once again confirms that what you -- you have to consider the molecule as a whole to understand or predict its physical properties, and chemical properties because here we have some similarity as was explained yesterday between rivastigmine structure and nicotine structure, although I think it's very modest as I explain in my testimony, and yet their properties are very different, and therefore, in my opinion, one would not extrapolate mechanically what's known for nicotine to rivastigmine. There was just no good reason for doing that.

Q. And just for the record, what does GB '040 say about the methods that can be used to manufacture rivastigmine formulations?

A. Well, as the Court can see on the screen, there are several excerpts from the GB

'040, and basically it says that rivastigmine transdermal system may be manufactured in conventional manner, active agents may be administered in any conventional liquid or solid transdermal pharmaceutical composition. And then finally that the rivastigmine transdermal formulation is prepared using a conventional apparatus.

So the key word here is conventional, whereas Ebert is anything but. So whereas Ebert due to the specific properties of nicotine was forced to employ nonconventional manufacturing, rivastigmine in fact not only allowed, but indeed with rivastigmine conventional manufacturing were employed.

Q. Were those conventional apparatus included an oven and did the process include heating?

A. Yes.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 19, at 10, 16 and 19.

BY MS. JACOBSEN:

Q. Dr. Klibanov, does GB '040 make

any reference to Ebert?

A. No, it does not.

Q. Does GB '040 refer to any other references concerning manufacturing of transdermal devices?

A. It does. GB '040 specifically refers to the European Patent Application Number 155,229 with respect to how the transdermal formulation may be prepared.

MS. JACOBSEN: For the record, Dr. Klibanov referred to JTX 19 at 16, and JTX 29, which is the '229 patent, plaintiffs move to introduce into evidence JTX 29.

MR. LEVY: No objection. I'm sorry, 29.

MS. JACOBSEN: 29 is the EP '229.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Dr. Klibanov, does EP '229 disclose the use of an antioxidant in a transdermal?

A. No, it does not.

Q. What's your overall conclusion with respect to Ebert?

A. Well, my overall conclusion as I mentioned earlier would be that first of all, a person of ordinary skill in the art would not be motivated to combine GB '040 with Ebert. If anything, one of skill in the art would be motivated to combine GB '040 with European Patent Application '229 which expressly cites, which discloses conventional as opposed to unconventional as in Ebert manufacture of a transdermal device.

Q. Dr. Klibanov, I would like to turn to the Handbook of Pharmaceutical Excipients next.

MS. JACOBSEN: Before I do that, Your Honor, may I approach? We just had some replacement slides because Dr. Klibanov's testimony was shortened and they didn't find their way into the binder.

THE COURT: Sure.

BY MS. JACOBSEN:

Q. So, Dr. Klibanov, would the Handbook of Pharmaceutical Excipients have told the POSA that rivastigmine undergoes oxidative degradation and requires an antioxidant?

A. It certainly does not. I mean, the Handbook of Pharmaceutical Excipients doesn't mention rivastigmine, doesn't talk about drugs. It's simply a handbook that list pharmaceutical excipients that have previously been used in pharmaceutical products. It in no way specifically relates to rivastigmine.

Q. And would the Handbook of Pharmaceutical Excipients have told a POSA that rivastigmine could be combined with an antioxidant?

A. Again, it's in no way related specifically to rivastigmine. It does list a number of antioxidants, but it certainly doesn't talk about rivastigmine, doesn't talk about other drugs, so it would be -- there would be no motivation for one of skill in the art to combine a rivastigmine reference with the Handbook of Pharmaceutical Excipients.

Q. And would the '807 patent have told the POSA that rivastigmine can be combined with or is compatible with antioxidants?

A. The '807 patent would not suggest anything of the sort.

Q. And why not?

A. Well, because, as I said, the '807 patent doesn't even deal with transdermal formulations. And, in any event, it only talked about antioxidants in the context of injectables. And even then, only as required.

Q. Did the '807 patent specifically combine RA7 with an antioxidant?

A. It certainly did not.

Q. What about Elmalem, would that have told a POSA that rivastigmine was compatible with antioxidants?

A. No. Again, there are no evidence, no tests of compatibility, no information with respect to that at all.

Q. And is the time over which the Elmalem formulations existed relevant to whether or not it discloses compatibility?

A. Yes, in some way, because it specifically says that the formulations of Elmalem, when prepared freshly, which, I mean, I guess one of skill in the art would understand means that they were used either right away or shortly thereafter.

So there was certainly no prolonged storage, otherwise, they wouldn't say freshly prepared.

Q. Finally, would GB '040 have shown a POSA that rivastigmine is compatible with antioxidants?

A. Again, there was no information with respect to that at all. So no compatibility information. No compatibility conclusion, in my judgment, can be drawn whatsoever.

Q. And I'd just like to briefly discuss the documents that Dr. Kydonieus cited relating to Brij 97.

A. Okay.

Q. Where was the Brij 97 that was used in GB '040 obtained from?

A. Well, again, as I already discussed earlier today, and the Court can see, that it's highlighted on the screen, it was expressly obtained from Atlas Chemie and the company which at that time was called West Germany which, of course, is Germany now. And from Atlas Chemie in West Germany.

Q. And did Dr. Kydonieus cite any documents relating to Brij 97 from Atlas Chemie?

A. No.

Q. And where were the documents that he cited from obtained from?

A. Well, he specifically cited -- Dr. Kydonieus specifically cited two references. So, one of them, as the Court can see on the screen, JTX 9. That particular Brij 97 was obtained from ICI Americas, Incorporated.

And that was as of 1991. So what we know from that is that in 1991, Brij 97 obtained from ICI Americas contained 0.01 percent antioxidant, namely BHA.

I might also add that after 1991, they stopped adding antioxidants. So there was certainly no antioxidant in Brij 97 as of 1998, which is the priority date of the patent-in-suit.

The second thing that is there is that the reference DTX 89, which they indicated that as of 1972, a Brij 97 from Atlas Point. So, again, a different company, according to the tentative specifications, contained an

antioxidant solution.

So, as I understand it, and I think that's the way one of skill in the art would look at it, would know that in 1991, but not thereafter, Brij 97 from ICI Americas contained an antioxidant, this particular antioxidant.

We know that tentatively Brij 97 from Atlas Chemie in 1972 also contains some antioxidant solution without explaining what the antioxidant was or what the concentration was.

And, in my judgment, therefore, these data provide no evidence that, as of 1988, Brij 97 from Atlas Chemie in West Germany contain an antioxidant, let alone in 1998.

Q. Thank you, Dr. Klibanov.

Turning, finally, to Dr. Kydonieus' argument that the '031 patent is -- Dr. Klibanov, I'm told you said Atlas -- you made reference to Brij 1997 obtained from Atlas Point in West Germany.

A. Oh, I'm sorry. So Atlas Point is a company where it doesn't say where it was located, so I don't know.

And I was talking about Brij 97, of course. Okay.

And so the conclusion that one of skill in the art would have made, and I hope that I made, but maybe I didn't, was that one of skill in the art from these data could not, in my opinion, legitimately conclude that, as of 1998, Brij 97 obtained -- from Atlas Chemie in West Germany contained an antioxidant.

And, likewise, the same applies, as I said -- what I just said about 1998 equally applies to 1988. So, at none of those dates, that is, whether we're talking about the publication date of GB '040 or the priority date of the patent-in-suit, was there any evidence that an antioxidant was present in Brij 97.

Q. Thank you.

And did you see any documents that originated from Atlas Chemie in West Germany?

A. I did not.

Q. So turning to Dr. Kydonieus' argument that the '031 patent is invalid over the '176 patent for double patenting.

A. Yes.

Q. Did you consider that argument?

A. Yes, I did.

Q. Did the patent examiner consider the '176 patent?

A. Yes. As I mentioned in the beginning of my testimony before the break, that the patent examiner did not reject the patent-in-suit over the '176 patent.

Q. What does the '176 patent claim?

A. The '176 patent claims, as is shown on the screen now -- it provides the (S)-{N-ethyl-3-{(1-dimethylamino)ethyl-N-methyl-phenyl-carbamate}enantiomer. That is what we now call rivastigmine.

And Claim 7 claims a method of systematically administering rivastigmine which comprises administering the active agent transdermally through the skin.

Q. And do any of the claims of the '176 patent disclose an antioxidant?

A. No.

Q. Would the prior art have suggested to a POSA to add an antioxidant to the claims of the '176 patent?

A. No. As I just explained, with respect to obviousness, the same applies here.

There was no motivation to this effect. In fact, if anything, there was an opposite motivation.

Q. So all of your opinions with respect to obviousness apply here?

A. In my opinion, they do everything I just said with respect to obviousness, and my judgment fully applies to the double patenting argument.

MS. JACOBSEN: Thank you, Dr. Klibanov. I have no further questions at this time, but I do have one housekeeping matter. I may not have moved PTX 242 and 246 into evidence.

MR. LEVY: No objection.

THE COURT: All right. Okay. They're admitted without objection.

MS. JACOBSEN: Thank you, Your Honor.

THE COURT: Mr. Levy, can I see you and Ms. Jacobsen over here for a second?

(A conference was held at side-bar

off the transcript record:)

THE COURT: So we'll break for lunch. And as I've said, or as I just told the attorneys, I have something at one o'clock and I'm not sure how long it's going to take.

So let's plan to reconvene at 1:45, but I may be late. All right?

We'll stand in recess.

THE CLERK: All rise.

(A brief recess was taken.)

THE CLERK: All rise.

THE COURT: All right. Please be seated. Are we ready to proceed?

MR. LEE: Your Honor, before we begin our cross-examination, we have a request to make.

THE COURT: Okay.

MR. LEE: We have reviewed the information that Novartis has provided us as to the support for the testimony of Dr. Klibanov as to the mechanism of the oxidation, and whether we now know today that there is -- oxidation does not occur at the benzylic compound. This is a very important point and it is not

addressed in either his deposition or in the paragraphs that they've cited to us.

There is the paragraph that they've cited to us in the opening report that refers to an Exhibit 15, but not to the page that Dr. Klibanov is relying on. There is a paragraph in his reply report.

THE COURT: Well, wait. Just so I understand that.

MR. LEE: Yeah.

THE COURT: His opening report says something and it cites an Exhibit 15 and --

MR. LEE: Cites to Page 2401.

THE COURT: Yeah.

MR. LEE: But that is not the page that, I believe, Dr. Klibanov is relying on in his testimony.

THE COURT: What page do you believe he's relying on?

MR. LEE: Page 2403. His opening report, of course, is on infringement, not on invalidity. And he, of course, doesn't address this issue.

And his reply report is also on

infringement and doesn't address the issues of validity.

Frankly, I've looked at the deposition transcript that we've been pointed to and I don't see this issue there at all. And we have not been pointed to a particular line number in the three-page sequence that they say supports this point.

I believe that we have been sandbagged about this point, Your Honor, because it was not in his expert report. We could not reasonably expect he would testify about it and we had no reason to put it on in our direct case.

Dr. Schoneich is here. He is ready to testify about this issue, and we would ask permission for a very short rebuttal, a matter of a few minutes on this one point.

THE COURT: Well, does he address it in his reports?

MR. LEE: Yes, he does. Well, let me say this: He addresses -- he has in his expert report in the appendix a list of the oxidation products, the final products of

oxidation. One of them is the product that is shown on Page 2403.

Dr. Schoneich's opinion is consistent with the Novartis page and I expect that Dr. Schoneich will testify to that. He will also testify that on the page that Dr. Klibanov is relying on, or I believe he is relying on, it does not show the initial point of oxidation which, as Dr. Schoneich testified on direct, is a radical.

There are no radicals shown on Page 2403. That's not the purpose of Page 2403. Page 2403 shows degradation products, not radicals.

THE COURT: All right. Anything else you want to say?

MR. LEE: No, Your Honor.

THE COURT: All right. Ms. Jacobsen.

MS. JACOBSEN: Your Honor, in Dr. Klibanov's opening report, he sets out the oxidative degradation products that are now known to be generated through the degradation of rivastigmine and he pointed to the document in

which rivastigmine -- sorry, Novartis identified the degradation pathway. And in his --

THE COURT: And is this Exhibit 15?

MS. JACOBSEN: It is, yes, Your Honor. And that includes the degradation pathway.

And in his reply report, he specifically points to that page where the 2403 which shows the degradation pathway, that shows that it proceeds through the formation of the N oxide, which is the product of oxidation of the amine and then forms to the styrene and the ketone degradants, which is what Novartis measures in its products and what Noven measures in its products to check whether oxidative degradation is occurring.

And that's what Dr. Klibanov relied on in his opening report and also in his reply report on infringement.

THE COURT: So in the opening report, did he cite to Page 2401?

MS. JACOBSEN: He did, yes.

THE COURT: All right. But in his

reply report, he cites to Page 2403?

MS. JACOBSEN: He did, yes. And then at his deposition, he was asked in the context of validity of the stability of amines. And what Dr. Klibanov said is there are some that are stable and some that undergo oxidative degradation.

And he said before 1998, a person of ordinary skill in the art would have believed that rivastigmine was stable, even though it has an amine. And now we know that's not the case. And that it's an amine compound that degrades oxidatively.

THE COURT: So it sounds to me from what you just said about his deposition that, at least the way you just said it, maybe this is -- maybe you're not being entirely precise, I don't know. It sounded like it wasn't exactly a direct head on addressing the issue in the deposition.

MS. JACOBSEN: It was addressing whether or not you could predict from the structure whether or not rivastigmine was stable and where the degradation occurred, the fact

that it's an amine that undergoes degradation for that reason.

THE COURT: All right. Is there a page or two that I can look at?

MR. LEE: I'm sorry, Your Honor?

THE COURT: I was just going to say, you know, maybe it's time for me to look at the page or two and see if I can figure it out.

MS. JACOBSEN: It's over a couple of questions. Do you have a copy of it?

Okay.

MR. LEE: We can put it up on the screen, Your Honor.

THE COURT: All right. Put it up on the screen.

So, but just while you're doing that, Mr. Lee, so what you want is to be able to recall Dr. Schoneich and ask him some questions about the same topic; is that right?

MR. LEE: Same topic.

THE COURT: And Ms. Jacobsen, what's your point on that?

MS. JACOBSEN: Well, if it's in his report, he could have reasonably anticipated

that this was coming. He's responded on how he believes that it undergoes oxidative degradation.

And, in fact, during direct, he was asked: Are there other sites on rivastigmine that a person of ordinary skill in the art would expect to be susceptible to oxidative degradation? And he says, yes, there are.

And if you go to the next slide, and he discusses the tertiary amine. So, Your Honor, to the extent that he wanted to discuss it on his direct, he's already had the opportunity to do so.

MR. LEE: I think maybe, Your Honor --

THE COURT: Yes.

MR. LEE: I think we're confusing two amines. Part of the discussion is whether the amine group would influence the susceptibility of a carbon-hydrogen bond to oxidize. What Dr. Klibanov was talking about was whether the oxidation takes place on the amine.

The testimony in his deposition, I think, is Page 153 to 155 was about the first issue about whether amine compounds, not the amine itself, are susceptible to oxidation. So the portion of his deposition doesn't go to this same issue of the mechanism.

As far as whether we had a reasonable basis to believe this, there is no statement in his report that he believes that Dr. Schoneich was wrong in saying that oxidation takes place at the hydrolytic carbon. And that's why we had no reason to address that issue, whether it takes place at some other position because there was no counter testimony.

And, now they've put in this testimony and we will need to recount it and we need Dr. Schoneich to do it.

THE COURT: And what's the relevance of which one it takes place out of?

MR. LEE: Well, so our case relies on the fact that the structure of rivastigmine is very special. It has a carbon-hydrogen bond, which is surrounded by three groups, each of which renders that carbon hydrogen bond weak and

susceptible to oxidation.

If, in fact, oxidation takes place at a different position, then our whole argument about why one of ordinary skill in the art would have relied on this basic structure rivastigmine to show that it was susceptible to oxidation, that falls apart.

THE COURT: And so what is it that Dr. Schoneich is going to testify to again?

MR. LEE: What Dr. Schoneich is going to testify to, Your Honor is that the evidence to which Dr. Klibanov replied is completely consistent with his opinion that the initial oxidation takes place at the carbon-hydrogen bond and that the evidence that Dr. Klibanov is relying on, if I am correct that this is what he's relying on, that it does not disclose at all the initial point of oxidation, which is, as Dr. Schoneich testified on direct, was the formation of a radical.

There are no radicals in the flow chart that Dr. Klibanov, I believe, is relying on.

THE COURT: All right. Yes, Ms.

Jacobsen.

MS. JACOBSEN: Your Honor, you know, we believe the testimony is fairly supported by his reports, but if Your Honor is minded to allow a reply, then we'll withdraw the question and answer. And we don't see that there's any need for recalling a witness here.

THE COURT: What do you think about that?

MR. LEE: That's fine, Your Honor.

THE COURT: All right.

Okay. All right.

So maybe just put on the record so that it will be easy for me to figure out later on what question and answer do we think is withdrawn? It was your question, Ms. Jacobsen, so why don't you tell us.

MR. KALLAS: It may be difficult for us to do that without the transcript.

THE COURT: Well, do your best. You know, you don't have to do it literally, just basically the topic of whether the tertiary amine has something to do with the actual oxidation process in rivastigmine is withdrawn.

MS. JACOBSEN: Yeah. The question is whether it, in fact, undergoes oxidative degradation at the tertiary amine, and Dr. Klibanov's testimony that that's now known to be the site of oxidation.

THE COURT: All right. Well, that testimony of Dr. Klibanov will be struck by agreement of the parties.

So go ahead with cross-examination.

MR. LEVY: May it please the Court, Your Honor, Mike Levy on behalf of Noven.

CROSS-EXAMINATION.

BY MR. LEVY:

Q. Good afternoon, Dr. Klibanov.

A. Good afternoon, Mr. Levy.

Q. Pleasure to meet you.

May I please have PDX 11? Dr. Klibanov, earlier today you testified about an Exhibit PTX 162, which was some guidelines from an organization called EMEA.

Do you recall that?

A. Yes.

Q. Now, this Exhibit PTX 162, which

supports this slide, that's just a set of guidelines; isn't that right?

A. It's a set of guidelines by the European equivalent of the FDA for pharmaceutical formulators. Yes.

Q. Do these guidelines have any authority in the United States?

A. I don't think so, but I don't know.

Q. Were you confining your person of ordinary skill in the art to just the European jurisdiction?

A. I mean, I'm just relying on all the documents that were public documents that one of skill in the art would have access to, and this was one of these documents.

Q. There is no rule or provision in this document proscribing the use of antioxidants; isn't that right?

A. As I just said, these are guidelines that one of skill in the art would read in the context of the entire prior art.

Q. And there is no rule or provision in that document, those guidelines, that

proscribes the use of antioxidants in pharmaceutical formulations; isn't that right?

A. If you don't consider these excerpts rules or guidelines, then that's what's more pertinent to that issue.

Q. Now, these guidelines aren't limited to transdermals; correct?

A. That's correct.

Q. In fact, they also address perhaps eyedrops that are given to infants; isn't that right?

A. They address a number of formulations as I said in my direct testimony.

Q. So there could be incompatibility or toxicity issues related to formulations that have nothing to do with transdermals such as infant eyedrops; right?

A. Well, these are general statements, they're not limited to any particular formulation, so I don't agree with you.

Q. When you cut out that excerpt that

antioxidants should only be included in a formulation if it has been proved that their use cannot be avoided, are you saying that is what people always do in the field of pharmacy formulation?

A. This is sort of the general sort of state of mind at the time and even now of one of skill in the art in this area.

Q. I believe that document had a publication date on its face of 1997. Was that the same guidance that ordinarily skilled artisans followed prior to 1997?

A. I mean, I don't know. These seem to be sort of general principles that are consistent with what I explained in my testimony as how formulations scientists work.

Q. So for all you know it wasn't until 1997 that this type of advice was given by a regulatory authority?

A. That's not true.

Q. So it was possible that was true before 1997; is that right?

A. It is definitely true that that was the case before 1997 because I was working

in the field long before 1997, and I knew and regular practitioners knew that you don't add an excipient such as an antioxidant unless needed.

Q. Now, the Exelon patch marketed by Novartis has an antioxidant; isn't that right?

A. Yes.

Q. Was Novartis aware of these guidance points when they developed the Exelon patch?

A. I cannot speak for Novartis. Again, one of skill in the art of this is a mythical person who is expected to be familiar with all the literature that was available. People who work with Novartis are real people, so I don't know what they were aware of, what they were not aware of.

Q. But you spoke very eloquently this morning about the development of the Exelon patch; right?

A. I just relied on the evidence that was before, that's in this case. I'm glad that you found it eloquent, but I just relied on the

documents that I showed on the slides.

Q. Did Novartis to your knowledge try any other solutions before it decided on an antioxidant consistent with that guidance?

A. I don't recall.

Q. People don't always follow such guidelines, do they?

A. People don't always follow guidelines, that's true. Such guidelines and any other guidelines, yes.

MR. LEVY: May I have PTX 13, please.

BY MR. LEVY:

Q. In this slide, Doctor, you pointed out by excerpts that excipient incompatibility may cause degradation. Is that right?

A. Yes.

Q. Did you intend for your testimony to explain that persons of ordinary skill in the art would have been reluctant to even consider antioxidants?

A. No, I don't think there is any harm considering, but in doing so a person of ordinary skill in the art would be aware that

there are downsides of doing that.

Q. You didn't testify this morning that the person of ordinary skill in the art could not run routine stability testing to identify an appropriate compatible antioxidant; correct?

A. There was no law against trying routine tests. I was talking about whether one of skill in the art would add excipients that are not necessary to a pharmaceutical formulation.

Q. So this would not discourage an ordinary skilled artisan from running a routine test with a desired antioxidant if one was so desired; right?

A. It may.

Q. Is it your testimony, sir, that persons of ordinary skill in the art will not even attempt to test for an appropriate antioxidant?

A. No, that is not my testimony.

Q. May I have PTX 61, please.

This morning, Doctor, you testified about the inventors having a

particular level of skill that matched the person of ordinary skill that you have talked about; correct?

A. Not quite correct, no.

Q. Is there any evidence on this slide, Dr. Klibanov, that the inventors knew about the Ebert reference, the Elmalem reference, the Sasaki reference and the Handbook of Pharmaceuticals?

A. There is no evidence on this slide one way or another.

Q. In fact, you have cited no evidence that any of the inventors alone or collectively had knowledge of all of the relevant prior art; correct?

A. I cited no such evidence. And it wasn't probative with respect to the opinions that I was asked to opine on. These were the inventors. I was asked to opine on one of ordinary skill in the art and what this person would do.

Q. And you through that slide allowed the inventors to meet that qualification; isn't that right?

A. That's not right.

Q. With this slide, you were saying that the inventors had the level of ordinary skill in the art that you applied to your validity analysis; isn't that right?

A. No, that's not correct.

Q. You offered no testimony in your direct that any of the inventors was actually an organic chemist; isn't that correct?

A. I did not offer any testimony with respect to that.

Q. May I have PDX 12, please.

Dr. Klibanov, you also had a slide talking about the use of antioxidants in which you cited the Evans '376 patent; isn't that right?

A. Yes.

Q. Now, are you saying that the person of ordinary skill in the art would have regarded most antioxidants as toxic, therefore to be avoided?

A. I made no such statement.

Q. Then could you please -- strike that.

And you cited the Handbook of Pharmaceutical -- I'm sorry, strike that.

Can we bring up JTX 008, page 12. The entry for tocopherol. Do you see that, Dr. Klibanov?

A. I do.

Q. This is an antioxidant; right?

A. Yes.

Q. In fact, this is one of the antioxidants of claim 16; right?

A. Yes.

Q. Could we please go to the regulatory status on the next page in the left column, entry 16.

Alpha-tocopherol is identified as being GRAS listed; is that right?

A. Yes.

Q. And that means generally regarded as safe; isn't that correct?

A. That's correct.

Q. In fact, this is accepted in Europe as a food additive; right?

A. That's what it says.

Q. Can I also go up a paragraph

above, the paragraph beginning the use of tocopherol. The third from the bottom. I'm highlighting a sentence from that entry.

It says the use of tocopherols in pharmaceuticals and food products is unlikely to pose any hazard to human health since the daily intake from such uses is small compared to the intake of naturally occurring tocopherols in the diet. Do you see that?

A. I do.

Q. Is there anything in that entry that I have shown you about tocopherol that would discourage a generally skilled artisan from using it in a pharmaceutical formulation?

A. With respect to tocopherol, which is one of many FDA approved antioxidants, with respect to tocopherols, the statement speaks for itself.

Q. There is no toxicity issues that would discourage the use of tocopherols by an ordinarily skilled artisan; is that right?

A. You know, in the passages that you

specifically asked me to look at.

Q. And you didn't testify this morning contradictory to that; correct?

A. I wasn't talking specifically about tocopherol. I was talking about antioxidants in general.

Q. Can we please go to page 15. This is the entry for ascorbic acid?

A. Yes.

Q. Do you see that on the screen doctor?

A. I do.

Q. And ascorbic acid is also one of the claim 16 recited antioxidants; isn't that correct?

A. That's correct.

Q. And I'm referring to claim 16 in the '031 patent. We're in agreement there?

A. Yes.

Q. Can we go to the regulatory status, please, on page 17.

And here this is also identified as GRAS listed; is that right?

A. Yes, this is the second

antioxidant that's identified as such, yes.

Q. And, in fact, this is also accepted as a food additive in Europe; isn't that right?

A. That's what it says.

Q. And there is nothing there teaching the ordinarily skilled artisan to avoid that particular antioxidant based on toxicity issues; is that right?

A. That's right, ascorbic acid is vitamin C. In fact, we take it when we get sick or are sick, so I don't think there is any problem with vitamin C. I certainly wasn't talking about that.

Q. Can we please bring up PDX 14.

This is another slide I believe you discussed this morning entitled Antioxidants May Unpredictably Increase Degradation. Do you recall that?

A. I do.

Q. You didn't refer to any reference in your direct testimony confirming an instance where formulators could not formulate a drug with an antioxidant; correct?

A. I'm sorry, could you repeat -- are you asking me about sulfites or are you asking me a more general question.

Q. I'm asking a question based on this reference, this slide, and your citation to Connors. You didn't refer to any reference in your direct testimony confirming any instance where formulators could not formulate a drug with an antioxidant; correct?

A. I mean, I was just mentioning this as an example. There are many references like that. The Sasaki reference specifically says that you should not use BHT, which is also mentioned in claim 16 of the '031 patent, because it says that it is believed to cause cancer, so BHT, which is also a claimed antioxidant, is just one of those. So yes, there are some good ones and there are some not so good ones.

Q. You didn't cite any reference confirming there is a drug that couldn't be matched to a compatible antioxidant; correct?

A. I mean, I can only say that I specifically presented this reference, the

Connors reference, and I stand by that reference.

Q. Can we bring up claim 7 of the '031 patent, please. Claim 7 depends from claim 1. I'm sure you know those requirements from memory. This claim 7 is not limited to any particular antioxidant; correct?

A. That's correct.

Q. Can we look at claim 16, please.

And here in claim 16, none of these antioxidants are of the sulfite variety that was warned against in your citation to Connors in your testimony this morning; correct?

A. That's correct, but that is butylhydroxytoluene, and Sasaki says it shouldn't be used because it causes cancer.

Q. Persons of ordinary skill in the art don't need all antioxidants to work with all drugs; correct?

A. A person of ordinary skill in the art may not need any antioxidants to work with any drugs if drugs do not undergo oxidative degradation.

Q. If they do select an antioxidant

to address that issue, they just need one to work properly; right?

A. Could be one, could be combination, but there are other considerations that go into creating pharmaceutical formulations.

Q. Can we please go back to PDX 14. And despite this warning about sulphites, we know that sodium metabisulfate was compatible with RA7 in the Elmalem reference; right?

A. We do not know that, first of all it's not sodium metabisulfate, it's sodium metabisulfite.

Q. Thank you for correcting me.

A. Second of all, we don't know that, we only know that sodium metabisulphite was added. What the consequence of that was, we don't know.

Q. Can we have PDX 49, please.

Now, you testified that because RA7 is a dialkyl carbamate, a person of ordinary skill would have had an expectation of stability in water; correct?

A. A greater stability in the case of

monomethyl carbamate, yes.

Q. In making this, and in sharing that opinion with the Court today, you focused us on the left side of the molecule; correct?

A. I focused on the entire molecule, but since the carbamate moiety is located in the left-hand side molecule, that is what I circled, but I presented the structure of the entire molecule.

Q. And you're saying here, aren't you, that the property of water stability is affected by the left side of the molecule and the right side you did not testify about any contribution it makes to that; correct?

A. No, that's not correct.

Q. I don't recall hearing any testimony that the right side of the molecule contributes to water stability; is that right?

A. Well, I'm sorry that you don't recall it, but if you go to the slide where I specifically talked about the effect of the amine moieties of physostigmine on the carbamate moiety, that is exactly what the point of that slide was.

Q. I understand. This isn't physostigmine, is it?

A. This is not, this is RA7.

Q. And those amino moieties that you pointed to this in the physostigmine slide aren't present here, are they?

A. They're not present here. One of the other amines is present. The point of what I demonstrated was to show that it is the entire molecule that determines the stability of the compound.

Q. Dr. Klibanov, in so testifying about the impact of the alkyl groups on stability in water, aren't you confirming that a person of ordinary skill in the art can look at the structure of a chemical compound and make a reasoned prediction about a physical property, yes or no?

A. No.

Q. That was not the substance of your testimony regarding the -- regarding the title, the title of your slide, because RA7 is a dialkyl carbamate, a POSA would expect it to be stable in water. Did I say that correctly?

A. You read the title correctly, yes.

Q. Your testimony about that expectation was based on looking at the structure and making a reasoned judgment about what was known about those functional groups of that particular structure as disclosed in the prior art; correct?

A. That's not correct.

Q. So is it your testimony that a person of ordinary skill in the art would not harbor the expectation of water stability by looking at the structure of the molecule?

A. It is my testimony that one of skill in the art relying on the vast amount of experimental studies that were carried out with monomethyl and dialkyl carbamates would know from those experimental studies that in general, dialkyl carbamates are much more stable against hydrolysis than monomethyl.

Q. I think we agree with each other that when you take that information that would have been available to the person of ordinary skill in the art as you just articulated, you look at a structure and make an informed

prediction about behavior; correct?

A. That's not correct.

Q. May I have PTX 59, please.

You testified this morning, Dr. Klibanov, about a table containing functional groups subject to autooxidation; is that correct?

A. You misstate what the table shows, but I did testify about this table and I did show this slide.

Q. I misstated the purpose of the table when I said it contains functional groups subject to autooxidation?

A. First of all, it doesn't talk about autooxidation at all. Second of all, it talks about potentially oxidized, and as I specifically emphasized during my testimony, the word potentially is a key word here.

Q. And this is from the Modern Pharmaceutics text; correct?

A. Yes.

Q. PTX 153?

A. Yes.

Q. That's an authoritative text in

pharmaceutics; correct?

A. Yes.

Q. Perhaps you and I aren't meeting eye to eye on what this table is because I think your slide elected to show some of the table. Can we show some of the complete table, please.

On the left is your slide, on the right is the table that's actually taken from there. And I think you cut off the title. It says, "Table 2, Some Functional Groups Subject to Autooxidation." Do you see that?

A. Yes.

Q. And I think you testified that look, here is a list of functional groups that are known to be susceptible to oxidation; is that right?

A. These are some functional groups that are susceptible to oxidation, that is correct.

Q. And I think your slide -- strike that.

That's not an exhaustive list; isn't that right?

A. It's not an exhaustive list, which

is what the word some signifies. This is a table that with respect to the data and the statements is taken verbatim from Modern Pharmaceutics. And I specifically said that these are some functional groups that have been known to potentially oxidize in pharmaceutical compounds.

Q. You're not saying, are you, Doctor, that a person of ordinary skill undertaking the task of inspecting a chemical structure for susceptibility to oxidative degradation would consult this table only to the exclusion of any other information, are you?

A. No, I think that one of skill in the art would examine the prior art as a whole as I have been emphasizing during my direct testimony.

Q. Doesn't the very existence of a table like this in an authoritative text in the field confirm that the person of ordinary skill in the art could make reasonable predictive judgements about a molecule's susceptibility to oxidation based on chemical structure?

A. Certainly not.

Q. This table is giving guidance to the ordinarily skilled artisan in the text Modern Pharmaceutics to help spot and I'll quote, some functional groups subject to autooxidation; is that correct?

A. The groups that can potentially undergo oxidative degradation, that's correct.

Q. And we agree it's not an exhaustive list; right?

A. We do agree it's not an exhaustive list and I never claimed it to be one.

Q. And that table does not say potentially; correct?

A. That table does not say that, but if you read the text that precedes this table, that in the context of the entire chapter, this is what one of skill in the art would understand.

Q. Dr. Klibanov, wouldn't a person of ordinary skill in the art in 1998 undertaking to formulate a drug look at the structure of the molecule and make educated assessments about the molecules potential for degradation?

A. As I already explained in my

direct testimony, any organic molecule has a potential for degradation under sufficiently harsh condition. Any organic molecule will oxidize, such as in burning, for example.

That, by itself, has no bearing on what will happen in the pharmaceutical formulation or under pharmaceutically relevant conditions.

Q. That really wasn't my question. Let me rephrase or ask it again.

A. Please.

Q. Wouldn't a person of ordinary skill in the art in 1998, undertaking to formulate a drug, look at the structure of the molecule and make educated assessments about the molecule's potential for degradation?

A. No.

Q. Wasn't a person of ordinary skill in the art in 1998 instructed to look at a molecule's features in order to anticipate potential modes of degradation?

A. Person was instructed to look at the molecule as a whole without ignoring any parts of that molecule. The molecule as a

whole.

Q. Let's turn to Page 181 of this exhibit that supported that slide.

A. Yes.

Q. Sorry Page 181, first full paragraph, third sentence.

MS. JACOBSEN: What's the exhibit number? We haven't gotten cross books.

MR. LEVY: It was the -- I think it was Modern Pharmaceutics. I'm sorry.

MS. JACOBSEN: Do you have it? 153.

Exhibit PTX 153.

BY MR. LEVY:

Q. Can I please have the third sentence highlighted beginning, Yet through the application? Dr. Klibanov, I've highlighted a sentence from this text, this authoritative text that you cited --

A. Yes.

Q. -- to the Court. And I want to find out if you agree with this.

It says, "Yet through the application of functional group chemistry, it is

possible to anticipate the potential modes of degradation that drug molecules will likely undergo. Do you agree with it?

A. I do. And in particular, I want to again emphasize the word potential, which is found in this sentence. With the word potential there, I do agree with this sentence.

Yes, sir.

Q. Can we please have PDX 105 up, please?

I just want to clarify the record. Dr. Klibanov, I don't think you and I will have a dispute here at all.

Your slide says GB '040 references EP '229, not Ebert; is that right?

A. Yes.

Q. Were you trying to show through your testimony that the inventors chose not to refer to Ebert?

A. The inventor of GB '040 did not refer to Ebert. Yes.

Q. Okay. It was your testimony, wasn't it -- I'm sorry.

Was it the intent of your

testimony to communicate to the Court that the inventor made a conscious decision not to refer to Ebert?

A. I have never spoken with the inventor. Actually, in this case, it's singular. One inventor, Albert Enz.

I have never spoken with him, have never met the man. I don't know what his intention was.

I can only look at this prior art reference as one of skill in the art would, and the fact of the matter is that this reference GB '040 references the European application, the '229 application and does not reference Ebert.

Q. In fact, it couldn't reference Ebert; right? Wasn't Ebert published in 1995?

A. That's right. It doesn't -- it doesn't refer to either Ebert or another publication that deals with unconventional, unusual methods of manufacturing of transdermal devices, but it clearly does not cite Ebert.

Q. And it couldn't, right, because GB '040 published in 1988; correct?

A. That's right. It could not cite Ebert, but it certainly could cite another Ebert-like reference. But it didn't do that, either.

Q. Well, in any event, Doctor, you and I can certainly agree that by 1998, the person of ordinary skill in the art would have had the benefit of both references; correct, Ebert and GB '040?

A. That's right. That's correct.

Q. Can we please bring up PDX 85?

Thank you. You had a slide today that talked about Sasaki. Does that slide -- do you recall this slide that I've brought up on the screen?

A. Yes, I do.

Q. And it's titled Sasaki Broadly States Amines Undergo Oxidation in Acrylic Adhesives; is that right?

A. Well, you said adhesives. It actually says adhesive --

Q. I appreciate again the correction.

A. -- singular. No problem.

Q. The call out from Sasaki that you

discuss with the Court talked about acrylic adhesive substances; correct?

A. Again, it's not plural, it's singular.

Q. Are acrylic adhesives made by a free radical reaction, Doctor?

A. They may be, but don't have to be.

Q. Can we please bring up PTX 183?

Dr. Klibanov, you testified this morning that I believe you relied on this exhibit, which is testimony taken in this courtroom in 2013, the testimony of Dr. Harry Tiemessen; is that correct?

A. That's right.

Q. And PTX 138 is a collection of excerpts from the testimony of Dr. Tiemessen; is that right?

A. Yes.

Q. And it's not the whole testimony of Dr. Tiemessen; is that correct?

A. That's right.

Q. In fact, it contains almost none of the cross-examination that Dr. Tiemessen received on this day when he was sitting in the

same chair that you are; is that right?

A. I didn't cite it because I only cited what was relevant to my testimony this morning.

Q. Were you here on that day in 2013 and hear Dr. Tiemessen's testimony?

A. No, I was not.

Q. Well, do you recall, Doctor, reading whether or not Dr. Tiemessen was asked about how Novartis started with a salt form of rivastigmine and not the free base?

A. What I recall is that they started -- well, first of all, it's not clear what they started with.

Second of all, what they started with, what they at some point used was a salt. But they also used an ion exchanger there that would, as they stated in those documents that I recall, convert that salt into a free base.

Q. I want to show you just a couple excerpts that you may not have reviewed. Perhaps you did and you can confirm for me otherwise.

A. Sure.

Q. Can we please see Page 794, beginning at Line 14 and going through 795, 10. I want to know if you considered the following question and answer testimony in your analysis when you testified this morning based on the Tiemessen testimony.

The question was: "And so base drugs can exist either as the free base or in the acid addition salt form?

"Answer: That's correct."

A. I'm sorry. Where are you reading?

Q. I'm reading from the top.

A. Oh, okay.

Q. This is still Dr. Harry Tiemessen, the guy you cited to.

"Question: And so base drugs can exist either as the free base or in the acid addition salt form?

"Answer: That's correct.

"Question: And you were using the acid addition salt form during that first several years of your development program?

"Answer: Mm-hmm. That's correct.

Question: And you were aware at

the time that, in general, the flux of a basic drug through skin is much better with the base form of the drug than with the salt form of the drug; correct?

"Answer: That's correct.

Question: And you were trying a rather unique approach of freeing that base using this Eudragit polymer; correct?

"Answer: That's correct.

Question: But in the final analysis, that just didn't work out?

"Answer: That didn't work out because we always had to add so much of the Eudragit that we could not increase the drug load as we would like to."

Do you see that?

A. I do see that.

Q. Did you consider that testimony this morning before you answered -- you discussed the inventorship story today?

A. I don't specifically recall this particular testimony. But during my deposition, I had a very substantive discussion about this very issue with your former partner, Ms.

Hardman. And she showed me a number of development documents which revealed expressly that, in fact, when they used salts of rivastigmine, due to the fact that they used Eudragit, which is an ion exchanger, the salt was converted into free base.

And whether or not that ultimately resulted in a workable pharmaceutical formulation, in my judgment, is not relevant to this particular fact.

Q. Can we go to Page 796, please, beginning at Line 6?

A. By the way, could I see just the pages, so I can read them, so I can actually see the context of what you're reading?

Q. I'm just asking: You presented certain excerpts this morning. I just want to show you a couple at -- one more excerpt and then I'll move on.

A. Okay.

Q. And there is -- can you see it on your screen?

A. Yes.

Q. -- 796 to Line 6 through 797, Line

8. This, again, is the testimony in Court of Dr. Harry Tiemessen. Another excerpt that I want to find out if you considered it.

"Question: And the formula that you developed after you got those unfavorable results with the tartrate form of rivastigmine, that formulation contained the rivastigmine free base, the Duro-tak 280-2516 adhesive and Blastoid B; is that correct?

"Answer: That's correct.

"Question: And that's essentially the same formula that you used, then, throughout the development of the project?

"Answer: That's correct. It was the second lead formulation, and that was then developed further.

"Question: So, Doctor, in the book I gave you, could you turn to Exhibit DTX 129? Withdrawn."

The question then became: "I think you've already talked about some of this, and we might be able to short circuit this.

So if I understand, with the second formulation, you discovered there was a

stability problem in June of 1995?

"Answer: Yes, that's correct.

"Question: And in July of 1995 is when you wrote your memo including as a possible solution the addition of an antioxidant?

"Answer: Mm-hmm that's correct."

Did you consider that testimony?

A. I read the entire testimony of Dr. Tiemessen and I certainly considered it in the context of the entirety of the information available to me, including the Novartis development documents, including those that I discussed with your former partner, Ms. Hardman during my deposition. Yes, sir.

Q. Can we please bring up Slide DDX 222 from yesterday?

Now, Doctor, you gave testimony this morning that rivastigmine is not structurally similar to nicotine; is that correct?

A. I explained and substantiated that they are not structurally similar molecules. Correct.

Q. Okay. And I thought -- if you and

I go through it, I think you and I will probably be able to agree on some things that are similar. So let's see if we can do that.

Using the slide from yesterday, were you here in the courtroom for this presentation?

A. I certainly was.

Q. And I'm using the slide I used because it has the colors, and it makes it easy for you and I to communicate better. Is that okay?

Have I presented the structures accurately?

A. The colors don't bother me. Sure.

Q. You will agree that rivastigmine and nicotine both have a tertiary carbon that is identified as the red carbon; correct?

A. They both have a tertiary carbon, as I said in my direct testimony. But in one case, it's part of a ring and another case it is not.

Q. But in both cases, it's a tertiary carbon; right?

A. It's not a tertiary carbon you're

talking about.

Q. In both molecules?

A. Yeah.

Q. It's simply a tertiary carbon?

A. You're talking about the carbon that's right next to the arm?

Q. Yes, it's the red C.

A. Yes.

Q. And in rivastigmine, that is a tertiary carbon; is that right?

A. That is correct.

Q. And nicotine, that's a tertiary carbon; is that correct?

A. That is correct as well.

Q. Now, in both compounds, that red C, the tertiary carbon is bonded to another carbon atom shown in purple; is that right?

A. Well, that is what makes it a tertiary carbon. Otherwise, it wouldn't be a tertiary carbon.

Q. So we agree; is that right?

A. I'm not sure I understand the question.

Q. The question is: The red carbon,

the tertiary carbon --

A. Yes.

Q. -- in both cases is bonded to another carbon atom that is shown in purple?

A. That's correct.

Q. And that tertiary carbon in both cases is bonded to a tertiary amine shown in green; isn't that correct?

A. Yes. As I said, one of these amines is a part of a ring. Another one is not.

But in both cases, it's bound -- it's bonded to a nitrogen atom thereby making the resulting structure a tertiary amine.

Q. And you'll agree with me, won't you, that the tertiary carbon in both cases is also bonded to an aromatic ring system; is that right?

A. To a different or aromatic ring structure, yes.

Q. But they're both aromatic rings in rivastigmine and nicotine; correct?

A. Yes. They're both aromatic rings, just as I said in my direct testimony.

Q. Now, will you also agree with me

that the pyridine ring, it undergoes --

A. I'm sorry. Which ring?

Q. The pyridine in nicotine. I'm sorry, pyridine. I apologize for my pronunciation.

A. No problem.

Q. It's the nitrogen-containing aromatic ring in this picture for the record.

A. Pyridine ring, yes.

Q. Will you agree with me that the pyridine ring in nicotine can undergo resonance stabilization?

A. It depends on the conditions in which it is placed. If it is placed in an aqueous solution and it is in a protonated state, then resonance stabilization will be almost non-existent.

Q. Will you agree with me that a person of ordinary skill in the art would conclude that information about nicotine is relevant to the development of a transdermal product?

A. Which transdermal product?

Q. Rivastigmine.

A. I don't see any particular relevance of that. I mean, certainly one of skill in the art wouldn't disregard anything. But I don't see any particular relevance, no.

Q. Going back to the question I asked about resonance stabilization, absent the condition that you mentioned, will the pyridine ring undergo resonance stabilization?

A. Yes. If it's not in an acidic aqueous solution, it will undergo resonance stabilization.

Q. Can we please bring up PDX 71?

You testified earlier this morning about the compound dextromethorphan. Do you recall that?

A. Yes.

Q. And you testified about the alleged stability regarding dextromethorphan; is that right?

A. No, I testified about stability, not alleged stability.

Q. And you discussed with the Court a Boccardi article as I recall; is that right?

A. That's right.

Q. Let's look at what you have highlighted here in this article. Can we please bring up Exhibit JTX 04?

Actually before we do that -- I'm sorry, but before we do that, you've highlighted two sentences here in your slide that you've discussed with the Court. One, that dextromethorphan hydrobromide is very stable.

Do you see that?

A. Yes.

Q. And a second sentence in the case of dextromethorphan, the low reactivity in the free radical test reflects good stability of the substance; correct?

A. Yes. You didn't read the first sentence in its entirety, but that's correct.

Q. And I think you took these sentences from the same paragraph. I want to go look at the actual exhibit where we got that paragraph.

A. May I also see it, please?

Q. I'm sorry?

A. May I also see this?

Q. Sure.

A. Just hard copy of this.

Q. Well, I'll bring it up on the screen for you right now.

A. Could I see a hard copy, please.

MS. JACOBSEN: Dr. Klibanov, you have it in your binder. It's at Tab 30.

THE WITNESS: Which one?

MS. JACOBSEN: Tab 30.

THE WITNESS: Thank you.

BY MR. LEVY:

Q. Can we bring up the paragraph on Page 433, the second from the bottom?

A. Just a second. Just a second.

Let me orient myself. What page is that?

Q. We are on Page 433.

A. Okay.

Q. I've blown up the paragraph, and I'd like to highlight the third sentence beginning, The same impurity was found.

A. Yes.

Q. And you, in your slide, highlighted the first sentence and the last sentence; isn't that correct?

A. Yes.

Q. You didn't highlight the middle sentence that I just highlighted here in the courtroom. I'm going to read it.

It says, The same impurity was found in trace amounts during preformulation of an antitussive syrup combining 8. And 8 is a compound that we know from reading the article is one of the degradants of dextromethorphan; correct?

A. Well, first of all, you are mistaken. Dextromethorphan hydrobromide, as is evident from the very first sentence, in this paragraph. So when you called it a degradant. That's just wrong.

Q. Okay.

A. Second of all -- may I finish?

Q. Yes.

A. Okay. Second of all, yes, it is true that I did not highlight this because this is, obviously, a reference to the previous sentence, the second sentence, which talks about photochemical meaning, oxidation meaning oxidation by light, which is not relevant to the

issue at hand.

Q. Okay. The second sentence says that the impurity, which from the previous sentence we learned is a degradant. The ten-keto dextromethorphan compound was found in trace amounts during preformulation in an antitussive syrup. You see that?

A. I do see that.

Q. Now, you didn't mean to suggest that the person of ordinary skill in the art would understand that dextromethorphan does not undergo oxidative degradation under pharmaceutical relevant conditions; correct?

A. No, that's exactly what I meant to indicate because the key element of the phrase that you read was found in trace amounts. You always have trace amounts of things.

As Dr. Kydonieus pointed out yesterday, the important thing is whether you have a significant concentration of the degradant. This specifically talks about trace amounts.

Q. And that's trace amounts of the oxidative degradant were found in a syrup under

pharmaceutically relevant conditions; correct?

A. Photochemical oxidation degradation product, correct. So a light-induced oxidation degradation product.

Q. Can we please go to PDX 87? Dr. Klibanov, you testified earlier about some amine-containing compounds or amine-containing drugs in transdermals; correct?

A. Yes.

Q. And I believe you spoke from this slide PDX 87 this morning and you spoke about the compound dexsecoverine. And, again, please permit my mispronunciation of these pharmaceuticals.

A. Well, I'm certainly no expert. It's dexsecoverine.

Q. Thank you. Scopolamine?

A. Yes.

Q. Fetanyl?

A. Yes.

Q. Benztropine?

A. Yes.

Q. Secoverine?

A. Secoverine.

Q. Yes. And physostigmine?

A. No, physostigmine. It's the same compound that I talked about quite a bit this morning.

Q. Thank you.

Now, you asserted that all of these are amine-containing drugs in a transdermal without listed antioxidants that were commercially available or disclosed in patents; correct?

A. That's correct.

Q. And just so we have a clean record here, you did not testify on direct that any of the transdermal products that are highlighted on this slide contain any of the active compounds on this -- I'm sorry. Let me strike that question.

You did not testify on direct that any of the transdermal products containing any of the active compounds on this page are formulated with an acrylic adhesive; correct?

A. No. I did not testify to that effect. Some of them may have been, some of them may not have been.

Q. In fact, you're not aware of any evidence that the active compounds on the screen that we just read into the record are formulated in transdermal products with an acrylic adhesive; right?

A. Yes. I don't recall at the moment.

Q. And just so we're also clear, none of the six compounds whose names we just read into the record contain the same structural feature of rivastigmine that includes a tertiary benzylic carbon-hydrogen bond immediately adjacent to a tertiary amine; correct?

A. These ones do not, that's correct. They have benzylic -- they have benzylic carbon-hydrogen bonds, but the amine is not immediately adjacent.

Q. Right. So they don't share that same important feature as rivastigmine; correct?

A. They do not have that feature. As I said, the amine is not immediately adjacent.

It's one carbon atom away.

Q. Doctor, you've testified that

approved transdermal systems prior to 1998 contained no listed antioxidants; correct?

A. Not quite.

Q. Well, did you testify that approved transdermal systems prior the 1998 contained no listed antioxidants in their PDR entries?

A. That's right.

Q. Okay. And I think the implication of that testimony was that the person of ordinary skill in the art would deduce that the API, the drug in that particular product is not susceptible to degradation if it's not accompanied by a listed antioxidant; is that correct?

A. That was not the implication. The implication was that none of these compounds, although those compounds contained all the structural elements mentioned by Dr. Schoneich, none of them was listed to contain an antioxidant. That was the statement, and that was the implication.

Q. And the implication is that if it's not accompanied by an antioxidant, there

must not be an oxidation issue present; is that right?

A. No, that's not right.

Q. That's right, because you didn't investigate each of those drugs; correct?

A. I'm sorry.

Q. You didn't do any testing on any of those products; right?

A. I have done no testing, but I specifically indicated in my testimony this morning that there are many different ways, and I illustrated that, to prevent oxidative degradation and some of them actually are preferable to using antioxidants, so I don't know how one could possibly draw the implication that you drew.

Q. Dr. Klibanov, you didn't confine your person of ordinary skill in the art to just examining approved pharmaceutical products, did you?

A. No. And, in fact, I, for example, as I do on the very slide that's on the screen now, it specifically says were commercially available or patented.

Q. Will you agree with me that a commercial product that does not list an antioxidant among its ingredients does not necessarily tell you that the API, the active drug is not subject to oxidative degradation?

A. Yes, I agree with that.

Q. Can we please go to PDX 27. You testified this morning that physostigmine -- did I mispronounce that again?

A. Yes.

Q. Can you correct me? What is it again?

A. I'm not an expert, but it's physostigmine. That's the way everybody...

Q. I mean, I just want to make sure we're talking about the same compound.

You testified that physostigmine did not require an antioxidant in a transdermal device; correct?

A. No. What I testified on is that in this example, for instance, there is a transdermal device containing physostigmine, and there was no antioxidant there.

Q. And the implication of that

testimony is that physostigmine did not require an antioxidant; isn't that correct?

A. Well, it certainly didn't require it in this particular formulation.

Q. Now, you know that physostigmine was known to be susceptible to oxidative degradation; correct?

A. No, as a matter of fact, I know just the opposite. As I said in my direct testimony, what is susceptible to oxidative degradation is the degradant of physostigmine. Physostigmine in contrast to that under pharmaceutical conditions is not undergoing oxidative degradation.

Q. Thank you for that clarification.

Can we go to PDX 68. You also testified today that you looked at a number of commercial products containing the benzylic carbon hydrogen bond; correct?

A. Yes, and specifically adjacent to nitrogen atom.

Q. And your authority for that testimony was the PDR; isn't that correct?

A. That's where this information came

from, yes.

Q. So all you did, and correct me if I'm wrong, I want to find out what you did, I believe all you did was look at the entry for each drug and the PDR and look to see if there was a listed ingredient that was an antioxidant; is that correct?

A. I reviewed each monograph, and I presented the structural formulas for the monographs where no presence of an antioxidant was reported, even though all of these drugs had the benzylic carbon hydrogen bond and an adjacent nitrogen atom.

Q. Let's look at Ampicillin. Can we blow that up, please. Ampicillin does not have a tertiary amine bonded to the benzylic carbon; is that correct?

A. That's right. It's a primary amine.

Q. And this particular drug, Ampicillin, is formulated as a dry powder; isn't that correct?

A. It can be formulated in a number of different ways.

Q. It's also formulated as a capsule; isn't that right?

A. It could be.

Q. Well, when you looked at the PDR for Ampicillin drugs, did you look at the drug Tunicine and Omnipen?

A. I don't recall.

Q. Why don't we go please to PDX 157, and if we could bring up page 2035.

MS. JACOBSEN: It's tab 25.

THE WITNESS: Okay. What page?

Q. Let me move on, Doctor.

A. Pardon me?

Q. Let me move on.

The drug Hydroxyzine is -- the drug Hydroxyzine, this is formulated as a hydrochloride salt; isn't that correct?

A. I don't recall right now. I will be happy to look up. Just a second.

Q. Let's look at page 1992.

A. Just a second.

Q. For the drug Atarax, A-T-A-R-A-X.

A. Sir, please bear with me. Okay?

Q. Yes, sir.

A. You said 992.

Q. 1,992.

A. Okay. Sorry.

Q. This is all the support that was on the slide. I'm finding the pages from your slide.

A. It's okay. Just a second. Okay.

Q. And the entry for Atarax says it's formulated as Hydroxyzine hydrochloride; correct?

A. Yes.

Q. And on page 2042, we see the drug Vistaril -- actually, page 2042, Vistaril. And in the upper left-hand corner at the entry for Vistaril, we see that it is formulated as the Hydroxyzine pamoate salt; correct?

A. Yes.

Q. And if we can go on to the drug Meclizine -- let's go to page 1992 for the drug Antivert in the middle. And this is formulated as Meclizine hydrochloride; isn't that correct?

A. That's correct.

Q. And it's in tablet form; right?

A. That's correct.

Q. And let's go to the drug mirtazapine at page 1878. And this is the drug Remeron in the lower right-hand corner. And those are mirtazapine tablets; correct, it's formulated as a tablet?

A. That's right.

Q. If you look under the drug there is a paragraph beginning mirtazapine is a white to creamy white crystallin powder. And that list some ingredients that are in the tablet; is that right? And the last ingredient after lactose is quote, "and other inactive ingredients." Do you see that?

A. Yes.

Q. Did you -- I'm sorry, I don't believe you testified this morning that any of those inactive ingredients are an antioxidant; correct?

A. I did not testify, no. And one of skill in the art looking at this language in fact would have no reason to believe that they are antioxidants. I mean, they wouldn't know, and, therefore, would presume that that wasn't

the case. And this compound by the way was a freebase.

Q. Why would an ordinarily skilled artisan simply look at that language and stop right there and not investigate whether or not there was an antioxidant in the formulation?

A. Well, I mean, there is nothing in this description that would suggest to one of skill in the art or to me that there is an antioxidant, that there is an antioxidant. I mean, they mention several ingredients that presumably were more important than others and then they say other inactive ingredients. I don't know what they are. And one of skill in the art wouldn't know what they are, but certainly there is no reason for one of skill in the art in my opinion to presume that they were antioxidants.

Q. So one of skill in the art would not do any further investigation to find out the extent of any reported oxidation or what those inactive ingredients might be?

A. I don't know what further investigation you're referring to. This is the

Physicians Desk Reference, this is the product insert, so that's the description of the product. So I don't know what further investigation you're referring to.

Q. When you were talking about the Elmalem article today, do you recall that?

A. Yes, of course.

Q. You had about twenty to twenty-five slides explaining why one of skill in the art would see language about physostigmine receiving an antioxidant and that ordinarily skilled artisan doing further work, researching, looking at reaction kinetics of physostigmine and dialkyl carbamate and reaction products of physostigmine and hydrolysis, all in support of understanding a one-sentence discussion of how an antioxidant was delivered to all the drugs, do you remember that?

A. I disagree with your characterization.

Q. Now, your person of ordinary skill in the art reading Elmalem, did a lot of work, did a lot of stuff, did a lot of research to arrive at the conclusion about how he or she

would understand Elmalem; correct?

A. As I explained during my direct testimony, one of skill in the art, and I specifically showed it in the slide, one of skill in the art as with any paper would endeavor to understand what the state of the art was at that time. And furthermore, would endeavor to understand what the goals of this study were. And those slides that I showed aimed to illustrate answers to these two questions, and that's what I did.

Q. And here in the PDR, your ordinarily skilled artisan just looks at a bunch of ingredients and just makes a decision; isn't that right?

A. One of skill in the art doesn't make a decision, one of skill in the art simply looks at the description of the product, does not see an antioxidant listed there, and therefore, presumes that an antioxidant is not there. I'm not saying that it's not there, I don't know, but one of skill in the art not seeing it there would have no reason to believe that it is there in my opinion.

Q. The drug benzquinamide is next. If we could go back to PDX 68. Thank you very much. Let's go to page 2008 of the PDR that you still have open I believe in front of you. And --

A. I'm just looking at the screen.

Q. Okay. I will take you there. I believe it's on page 2007, there is the drug Emete-Con. And this drug is formulated as the hydrochloride salt; is that correct?

A. That's right.

Q. And it's formulated as a dry dosage form; isn't that right?

A. Yeah, it's formulated for intramuscular and intravenous use.

Q. Can we please bring up slide PDX '81. You also testified this morning that no commercial nicotine transdermal device was reported to contain an antioxidant; is that correct?

A. Not quite.

Q. What did I get wrong there?

A. No commercial device -- no transdermal device commercially available as of

1998, none of the three was reported to contain an antioxidant, that was my testimony.

Q. Okay. Thank you.

It's true, isn't it, Doctor, that the transdermal product Habitrol that you mentioned utilizes an airtight pouch to prevent oxidation of nicotine; isn't that right?

A. That's my recollection, yes. But of course that wouldn't preclude -- as in Sasaki, it won't preclude oxidation by the oxidants present in the adhesive.

Q. Can we please bring up slide PDX 88. Dr. Klibanov, you testified about the compounds on this screen and I'll mention them for the record. Oxybutynin, buprenorphine, and selegiline; is that right?

A. That's fine.

Q. We're on the same page?

A. Yes.

Q. Your basis for discussing transdermals containing these compounds is information contained in the Physicians Desk Reference dated 2004 or later; is that right?

A. That's correct.

Q. You're not asserting that any of the information you testified about, oxybutynin, buprenorphine and selegiline would have been known to the person of ordinary skill in the art into 1998; correct?

A. No, I'm not asserting that.

Q. Just so the record is clear, none of the three compounds I just read contain the same structural feature rivastigmine of a tertiary benzylic carbon immediately adjacent a tertiary amine; correct?

A. No, they're all tertiary amines, but they were brought up in the context of Sasaki, not in the context of the benzylic carbon hydrogen bond theory. And Sasaki didn't have all those benzylic carbon elements either.

Q. Can we bring up the compound oxybutynin; please? Oxybutynin doesn't even have a benzylic hydrogen; isn't that right?

A. That's correct.

Q. And certainly the tertiary amine that you circled in red is not bonded adjacent to a benzylic carbon; isn't that right?

A. That's right. As I explained,

this was in reference to Sasaki and none of the Sasaki amines also had a benzylic carbon adjacent to an amine.

Q. I'm just asking a yes or no question.

Can we bring up selegiline, please. And here the amine that you have circled in red is not adjacent to a benzylic carbon; isn't that right?

A. That's right.

Q. And, in fact, the carbon that is the benzylic carbon is only a secondary carbon and not a tertiary carbon; is that right?

A. That's right.

Q. If we can go through the compound of buprenorphine. The compound buprenorphine only has a secondary carbon as the benzylic carbon; isn't that right?

I'll withdraw the question.

The amine that you have circled in red is not adjacent to any of the benzylic carbons in that compound; is that right?

A. That is correct. Not immediately adjacent. It has one carbon between there.

Q. I guess it wouldn't be a rivastigmine discussion if we didn't address Elmalem just for a moment. Can we please bring up JTX 021, page 1060, lower left paragraph.

A. Excuse me?

MS. JACOBSEN: It's tab 11.

THE WITNESS: Pardon me?

MS. JACOBSEN: 11.

THE WITNESS: 11.

MS. JACOBSEN: Yes.

BY MR. LEVY:

Q. And I would like to highlight the sentence beginning, "all drugs were made up freshly".

A. Yes.

Q. And I'll read that sentence, the sentence I'm bringing to your attention. "All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite to prevent oxidation."

Do you see that?

A. Again. The key of this is not the pronunciation, but what you pronounce is a different compound. You said metabisulfate.

That's a different compound from the compound that's listed there. I don't want to be picky, but I think the record should be clear.

Q. I appreciate. We both want a clear record.

Does that language convey to a person of ordinary skill in the art that all drugs studied in Elmalem were prepared from the same antioxidant containing sterile saline solution?

A. This sentence taken in isolation and then turning a blind eye to the rest of the paper would not be indicative in this respect one way or another. But when read in the context of the entire paper, that is what it would do.

Q. I think it's your position that this language would permit a person of ordinary skill in the art to understand that all of the injection formulations tested were prepared from the same stock solution with each formulation containing an equal weight of sodium metabisulphite; correct?

A. Yes.

Q. And I think it's your position that using the same stock sodium metabisulphite containing saline solution for all injections removes one variable that could potentially effect the outcome of the experiment?

A. Not the outcome of the experiment, but the interpretation of the results of the experiment.

Q. And I believe it's your position that this is consistent with a head-to-head study; right?

A. That is correct.

Q. Now, can we please bring up the Weinstock 1981 article next to it, if that's possible, split screen.

JTX 030. And I would like to bring up page 1981, two paragraphs above the word results.

A. Just a second, let me find it here.

MS. JACOBSEN: It's tab 16.

THE WITNESS: 16, thank you.

A. So where are you reading?

Q. I'm in two paragraphs above the

word "results".

A. Okay. Three paragraphs, actually, it seems.

Q. And the sentence begins -- I apologize, Doctor.

After Garden City, New York.

I'm going to read this sentence that it took me a while to get to. "Morphine and physostigmine were made up freshly for each experiment in sterile saline which included an equal weight of ascorbic acid to prevent oxidation."

Do you see that sentence?

A. I do.

Q. Dr. Klibanov, is it your position that that sentence conveys to the person of ordinary skill in the art that physostigmine and morphine were prepared from the same antioxidant containing sterile saline solution?

A. No, one would have to again, read the paper in its entirety and assess exactly what I explained in my direct testimony.

Q. But you'll agree with me that just as in Elmalem, the words stock saline solution

do not appear here; correct?

A. Just a second. I'm sorry, could you repeat the question, please?

Q. Yes. In Elmalem, the word stock saline solution do not appear here; correct?

A. No, they do not appear. That is something that will be understood in the context of the paper as a whole.

Q. Is it your testimony in Weinstock they're also using a stock saline solution albeit just for two drugs?

A. That is not -- I don't believe that that's the case in the case of Weinstock '81 because there was no particular reason there to do it this way.

Q. Now, isn't it essentially the same language that is used in both papers describing the preparation of the solutions?

A. Well, obviously it's not the same language. For starters, the antioxidant is entirely different. The antioxidant in Elmalem is sodium metabisulphite. In Weinstock '81, it's ascorbic acid. The language is also different because in Weinstock '81, it says

morphine and physostigmine were made up freshly for each experiment, whereas in the case of Elmalem, it doesn't say that. It doesn't say in each experiment.

But most importantly, the rest of the papers in Elmalem and Weinstock '81 were different. And one would read this particular sentence in each one of them in the context of the entire paper.

Q. Wouldn't it have been just -- wouldn't the easiest solution -- I'm sorry, wouldn't it have been easy just to employ a stock solution in the 1981 study if it didn't matter whether an antioxidant was used?

A. No. Because it was a study which aimed to obtain qualitative conclusions where the morphine was exerting its effect via the central nervous system or the peripheral nervous system and it didn't make any difference.

MR. LEVY: I have no further questions at this time.

THE COURT: All right. Thank you, Mr. Levy.

Any redirect?

MS. JACOBSEN: No, Your Honor, no redirect.

THE COURT: All right. Thank you Ms. Jacobsen.

Doctor, you may step down.

THE WITNESS: Thank you, Your Honor. Once again, I apologize for my voice.

THE COURT: So do the plaintiffs have anything more?

MS. JACOBSEN: No, Your Honor.

THE COURT: All right. So you rest?

MS. JACOBSEN: We rest.

THE COURT: All right. And I take it we're done with the defendants here, you have nothing more?

MR. LEVY: Nothing more, Your Honor.

THE COURT: All right. Okay. So the evidentiary record is closed.

So we have an argument tomorrow at two o'clock; right? So I have two things going which has nothing to do with the argument, it just has to do with my remembering things for

the short term.

The interim part review proceeding that's going on, is that between Noven and Novartis.

MS. JACOBSEN: Yes, Your Honor.

THE COURT: And it says neither party is bringing it up. Maybe I should just leave well enough alone and not ask any questions, but I thought that actually -- and I know you all told me the other day when the decision is required, or when the hearing is supposed to be, something that is not too far off in the future, but my recollection is that the IPR proceeding, I guess if it's determined before this, has some, not preclusive, but doesn't it have some effect on this proceeding?

MR. KALLAS: I don't believe it does. It would have to go up on appeal. The patent office doesn't invalidate the claims, doesn't give a certificate for invalidating the claims, it would have to go up on appeal, and only then would it come back down to the patent office to invalidate the claims.

And as far as the timing is

concerned, I think the proceeding, the oral argument which they call a trial was in June of next year, and they're mandated to give a decision by I believe October 14th. I think your decision will come out before October 14th.

THE COURT: I certainly hope so.

MR. KALLAS: Yes.

THE COURT: But the --

MR. KALLAS: There is a preclusive effect to the extent that if Noven loses on particular arguments, they're precluded from bringing those same arguments in this Court. But again, because of the nature of this, I think your decision will come out after there.

Now whether we can move to preclude them from those arguments afterward, it's a good -- I don't know that there has been a case on that, but we're going to look into that immediately after we leave this courtroom, Your Honor.

THE COURT: You're an optimist.

All right. So in any event, for present purposes, I should basically put that out of my mind; right?

MR. KALLAS: I think so.

THE COURT: All right. So to the more mundane that's actually related to this, I was hoping that between now and tomorrow you all, perhaps not the ones who are actually going to give the argument, but could talk about sort of the posttrial briefing schedule.

I would like to suggest something, but I'm willing to listen to something else. What I was going to suggest was that we do this in two parts, and what I was going to suggest was that we have some factual briefing where basically Noven would go first, could have up to thirty pages to write down facts one at a time, you know, number them, each one limited to a sentence with some citation or whatever it is that supports it in the record.

Then after you're done with your thirty pages, Novartis could add up to an additional thirty pages, and basically every fact that you say, you know, if they disagree with it, besides disagreeing with it, they have to say, you know, if what you're saying is wrong, they have to say what the right version

is, they can't just say disagree.

And then maybe you could have some number of pages, I was thinking fifteen, so that where basically again, you follow this same pattern, you're not adding new facts but now that they have said what their facts are, you can just pick which ones to disagree with, you know, you don't even have to actually use all your pages. But something along those lines to get the factual record argued.

And hopefully the end product that I would get out of that would be one document that would then be linked to whatever piece of the factual record you were actually citing in support.

And then when all that was done, which I thought maybe it would be done before Christmas, after January 1st, then you could basically brief it and I would think that twenty, twenty and ten, normal kind of briefing schedule would be sufficient to basically write legal briefs where you basically got the facts, you already, you know, sort of put down that you know what both sides are saying the facts are.

In any event, I suggest this because -- and I've tried doing this in a different case, nonpatent case, but I didn't put a sufficient page limit on the facts, so I got way too many facts. So one thing I'm trying to do is figure out a page limit that would actually only force you to give me the relevant facts or at least what you thought was relevant.

I don't know whether any of you have any experience with doing something like this, but I was thinking that might be more beneficial to me than having you write a brief, and a brief and a brief.

But I'm -- but part of the reason I just wanted to suggest that if you all -- and Mr. Kallas, you don't really need to -- I was thinking maybe it would be better for you all to talk to each other and then tomorrow we could discuss it again once we're finished with the argument.

MR. KALLAS: I just have one concern I would like to address. To me it seems very easy to write out the facts, Noven writes out the facts it wants, but for us on this side

to explain why those facts are wrong may take us more if they give us thirty pages, we're only limited to thirty pages, and having to explain why they're wrong and include the facts we want in it. So I think it would be a little unfair to limit us to the same thing depending on what their facts are.

THE COURT: Well, you know, that's the kind of thing you can discuss with each other. I can't remember actually the last time I did it, I think because I give unlimited pages, bad move, that you know, I didn't have to deal with that issue. But that's something you can talk with each other and maybe you'll decide --

MR. KALLAS: I think we have all had experience with this type of briefing, maybe in the summary judgment context where one side puts in their facts, undisputed facts and the other side has to agree or disagree which is a little different than that, but similar.

THE COURT: So in any event, why don't you talk to each other, see if you can't come up with some suggestion. If you come up

with something like this, that would be great. If you, you know, both think that it's not a good idea, you come up with something else, I mean, if you can agree to something, even though I always agree to cut down on the number of pages, you know, I'll probably go along with whatever you agree, and you know, to be reasonable about the holidays, in terms of the demand of each other.

So, in any event, if you could discuss that some time between now and tomorrow and see what you come up, that would be good.

Is there anything else to talk about before I see you tomorrow? Okay. Thank you very much and I'll look forward to seeing you tomorrow.

(Court recessed at 3:24 p.m.)

State of Delaware)
)
New Castle County)

CERTIFICATE OF REPORTER

I, Heather M. Triozzi, Certified Professional Reporter and Notary Public in the State of Delaware, do hereby certify that the foregoing record, Pages 305 to 275 inclusive, are a true and accurate record of the above-captioned proceedings on the 2nd day of December, 2014, in Wilmington.

IN WITNESS WHEREOF this 2nd day of December, 2014, at Wilmington.

Heather M. Triozzi, CSR, RPR
Cert. No: 184-PS
Exp: Permanent

DATED: December 2, 2014