IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, et al.,

Plaintiffs,

v.

NOVEN PHARMACEUTICALS, INC.,

Defendant.

Trial Volume 1

C.A. No. 13-527-RGA

Monday, December 1, 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.

THE COURT: All right. Good morning. Please be seated.

Mr. Lee, I guess you're going first.

MR. LEE: I am, Your Honor.

THE COURT: All right. Yeah.

MR. LEE: May it please the court in the Novartis v. Watson case, Watson attempted to to prove that several claims of the '031 patent, including 7 and 16, that are now at issue, were obvious based on the GB 040 patent, the Elmalem article, the '807 patent and the Handbook of Pharmaceutical Excipients.

Can we put up Slide 2?

The Court found that Watson had not met its burden of proof that those claims were invalid, and explained that, the obvious determination in this case turns on whether a person of ordinary skill in the art in January of 1998, looking at all of the prior art, would have known rivastigmine was susceptible to oxidative degradation. If the answer is yes, the asserted claims of the '023 and '031 patents are invalid because the addition of an antioxidant to a

pharmaceutical composition that oxidatively degrades is one of several known, obvious solutions.

In this case, Noven will prove by clear and convincing evidence that a person of ordinary skill would have known that rivastigmine was susceptible to oxidation, that Claims 7 and 16 of the '031 patent are invalid and will do it based largely on evidence that was not before the Court in those earlier cases.

Noven relies on the same references as before the court in the Watson case, but we do not rely solely on those references. We also rely on these references which were not of record in either the prosecution of the '031 patent or in the previous trials.

Put up Slide 3.

I'll start by talking about the last one on the list, Weinstock 1981, JTX 30, the 1981 article by the same research group that produced the Elmalem article and the '807 patent, professor Marta Weinstock-Rosin's group at the Hebrew University of Jerusalem. One of our two expert witnesses, Dr. Agis Kydonieus, will

explain that the Weinstock 1981 article shows that Elmalem would have been understood by one of ordinary skill in the art as teaching that rivastigmine was susceptible to oxidative degradation. Unlike any of the experts in the Watson case, either for plaintiffs or defendants, Dr. Kydonieus has spent the bulk of his 40-plus-year career formulating and developing transdermal delivery systems.

As the Court will recall, the Elmalem article describes testing a series of drugs, including one called RA7. RA7 is a 50-50 mixture of rivastigmine and its mirror image. Another drug being tested was physostigmine.

Can we put up Slide 5.

Elmalem describes the addition of antioxidants to all drugs in the study, including both RA7 and physostigmine. Elmalem says, "All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite to prevent oxidation."

Novartis argued that one of ordinary skill would understand that the oxidant had been added to the physostigmine solution to protect it

from oxidation, but had been added to the other arms of the study, including RA7, as a control to ensure that the solutions being studied would differ only in the drug that was being studied.

Elmalem was published in 1991. The principal author of the Elmalem article is Dr. Marta Weinstock. There are several other publications and patents describing the work of the Weinstock group.

One of them is the Weinstock 1981 article. That article studies a different set of drugs, not including RA7, but it also compares the different group to physostigmine.

Of critical interest to us is the way the Weinstock group describes their drug preparations.

Let's put up Slide 6.

Here we see Weinstock 1981 on the right. As you can see, the study reports in Weinstock 1981 an antioxidant and ascorbic acid was used only with morphine and physostigmine, not with any of the other drugs that were being tested.

When describing their work in

Weinstock 1981, the Weinstock group said, "Morphine and physostigmine were made up freshly for each experiment in sterile saline which included an equal weight of ascorbic acid to prevent oxidation." The language is almost identical, except that Weinstock only included antioxidant with physostigmine and morphine, and Elmalem included the antioxidant with all drugs, including RA7.

One of ordinary skill in the art, aware that it was not the practice of the Weinstock group to add antioxidants merely as a control, but only added them to those arms of the study in which an antioxidant was required, would have understood from Elmalem that the antioxidant was being added to the RA7 arm of that study to prevent oxidation of RA7. With this understanding, one of ordinary skill in the art would have been aware that rivastigmine was susceptible to oxidative degradation and would have been motivated to add an antioxidant to a rivastigmine pharmaceutical composition.

In addition, we have several new arguments, not predicated on Elmalem or the '807

patent at all, that explain how one of ordinary skill in the art would have expected

That explains how one of ordinary skill in the art would have expected that rivastigmine would be susceptible to oxidative degradation under the appropriate conditions. Some of these arguments will be explained by Dr. Christian Schoneich, a professor of pharmaceutical chemistry and the chair of the department at the University of Kansas. His research has centered on free-radical reactions, including oxidation, and the stabilization of pharmaceutical formulations from oxidation.

Professor Schoneich will testify that just from looking at the chemical structure of rivastigmine, a structure which was, of course, known in the prior art and disclosed, for example, in GB 040, one of ordinary skill in the art would have expected rivastigmine to be susceptible to oxidation.

Put up Slide 8.

On the left here we have the structure of rivastigmine as it appears in GB 040, and on the right, we have the structure of

rivastigmine, redrawn by Dr. Schoneich to highlight the important structural features.

Dr. Schoneich will testify that rivastigmine contains a conjunction of three structural features on the basis of which one of ordinary skill in the art would have expected rivastigmine to be susceptible to oxidation: The carbon-hydrogen bond, shown here in red, adjacent to an aromatic ring, shown in blue, a tertiary nitrogen, shown in green, and an alkyl group, shown in purple.

As Dr. Schoneich will explain, oxidation starts with the breaking of the red carbon-hydrogen bonds, the red solid-colored wedge there. The propensity for oxidation is a function of how strong that carbon-hydrogen bond is. A strong bond does not easily break.

But the three structural features of rivastigmine, the blue aromatic ring, the green nitrogen and the purple alkyl group, when adjacent to the carbon-hydrogen bond all tend to weaken such bonds. Dr. Schoneich concludes that merely by considering the structure of the rivastigmine molecule, one of ordinary skill in

the art would have a reasonable expectation that rivastigmine would be susceptible to oxidation.

Q. Aware of the susceptibility, one of ordinary skill in the art would have been motivated to combine rivastigmine with an antioxidant with the reasonable expectation that that antioxidant would inhibit oxidative degradation of rivastigmine.

Dr. Schoneich will also explain that those of ordinary skill would have been aware that a drug with those same three structural features, the carbon hydrogen bond adjacent to the aromatic ring, the tertiary nitrogen and alkyl group, was known to be susceptible to oxidative degradation. That drug is nicotine.

Put up slide nine.

On slide nine we can see the central carbon atom with carbon hydrogen bond in red, and the adjacent aromatic ring, blue, tertiary nitrogen atom, green, and alkyl group, purple, which nicotine has in common with rivastigmine.

Nicotine's susceptibility to oxidative degradation was set forth in the 1960s article by Linnell, JTX 032; and in the Ebert

patent application, JTX 28 -- neither of which was of record in the Watson trial -- or before the patent examiner. Ebert describes a transdermal delivery device particularly adaptable to the formulation of nicotine-containing patches. Ebert explains that nicotine is susceptible to oxidation, which can be countered by the addition of antioxidants.

Put up slide ten.

This slide shows part of the disclosure of Ebert, the teaching at the top that nicotine as a problematic tendency to oxidize, the portion in the middle that oxidation can be controlled by an addition of an antioxidant, that a preferred antioxidant is BHT, one of the antioxidants listed in claim 16 of the '031 patent, the range of BHT to use, and other antioxidants which may be used including BHA and tocopherol, also both claimed in claim 16.

Dr. Schoneich will testify that based on the structural relationship between nicotine and rivastigmine, and the known susceptibility of nicotine to oxidative degradation, one of ordinary skill in the art

would have known that rivastigmine would be susceptible to oxidation.

GB 040 discloses all the elements of the claims except for the amount of the antioxidant. Ebert discloses all the elements of the claims, the pharmaceutical composition and the diluent or carrier of claim 1, the substrate of claim 7, and the specific antioxidants of claim 16, including BHT, BHA and alpha-tocopherol, and the effective stabilizing amounts, but for nicotine, rather than rivastigmine. Given Dr. Schoneich's testimony Dr. Kydonieus will testify that one of ordinary skill would have been motivated to add an antioxidant to the transdermal delivery system of GB 040, with a reasonable expectation that it would prevent oxidation of rivastigmine.

Another prior art reference, a Japanese patent application, DTX 12, Sasaki, which was not of record in any prior proceeding, would have suggested to one of ordinary skill in the art that rivastigmine was susceptible to oxidation, and that antioxidants could be used to prevent such oxidation.

Put up slide 13. This is a portion of the Sasaki disclosure.

Dr. Kydonieus will testify that Sasaki teaches that amine compounds are susceptible to oxidation in transdermal delivery systems employing an acrylic adhesive, even when protected by air-tight, oxygen impervious aluminum laminate pouches, but that such transdermal pouches can be protected from oxidation by the addition of an antioxidant, tocopherol, which is one of the listed antioxidants in claim 16 of the '031 patent.

Dr. Kydonieus will testify that rivastigmine is an amine compound within the meaning of Sasaki, and that the transdermal patch of example two of GB 040 is made with an acrylic adhesive. Thus, one of ordinary skill in the art would have been motivated to employ an antioxidant with a rivastigmine transdermal patch. He will testify that the amount of the tocopherol antioxidant which Sasaki recommends, when used in the formulation of example two of GB 040, would fall within the scope of the claimed antioxidant ranges of claim 7.

Novartis has argued that the prior art taught away from the use of antioxidants, generally, in favor of other means of stabilizing pharmaceutical compositions, including transdermal patches. Sasaki is to the contrary. Sasaki teaches that antioxidants prevent degradation when other methods, such as using air-tight, oxygen impervious aluminum foil pouches, don't. Sasaki teaches towards the use of antioxidants. Sasaki is one more piece of evidence that one of ordinary skill in the art would certainly have known of the susceptibility of rivastigmine to oxidative degradation, and considered the use of antioxidants, including tocopherol, in deciding how to prevent that oxidation.

In the Watson trial, Novartis argued that the potential that antioxidants would be incompatible with rivastigmine would have dissuaded one of ordinary skill in the art from using them. Our experts will explain that one of ordinary skill in the art would have not have been dissuaded by the potential incompatibility because the prior art disclosed compositions

containing rivastigmine or related compounds, with antioxidants, with no mention of any incompatibility. Elmalem and the '807 patent taught a composition containing RA7 and sodium metabisulfite, with no mention of incompatibility; Sasaki teaches compositions containing amines of tocopherol, with no mention of incompatibility; and even GB 040 contains no mention of incompatibility of rivastigmine and antioxidants even though, as one of order skill in the art would have known, the GB 040 example two composition contained antioxidants. This is the issue that was brought up during the motions in liminae.

Example two of GB 040 describes a rivastigmine-containing transdermal delivery system containing two polymers and a plasticizer called Brij 97.

Can we put up slide 12. The '480 patent, JTX 9, which was not of record in any prior proceeding, teaches that Brij 97 used in the GB 040 patch, contained two antioxidants, BHA and citric acid.

Regarding the presence of BHA and

citric acid in the example 2 of GB 040, Dr. Klibanov does not dispute the disclosure of the '480 patent, but Novartis argues that there were two Brij 97s, one referred to in the 480 patent, trademarked by ICI, and one referred to in GB 040 which was available from Atlas Chemie, West Germany. There is no reason to believe that there was more than one Brij 97. The statements that Brij 97 was trademarked by ICI and available from Atlas Chemie do not require two different trademarked products, but only one. Novartis presents no evidence to the contrary that there was an another formulation of Brij 97 at that time which did not contain an antioxidant.

Novartis argued in the Watson case and I believe continues to argue in this case that one of ordinary skill in the art would not have been motivated to make a rivastigmine transdermal delivery system starting from GB 040. We will show, again, based on prior art not of record in earlier proceedings, Sramek JTX 11 and the Formulary Article, JTX 25, that at the filing date of the '031 patent, an oral formulation of rivastigmine had already been in large-scale

clinical testing, and that it had been shown to be safe, well-tolerated and effective against Alzheimer's disease, and an improvement over earlier used drugs.

However, that oral rivastigmine formulation had some drawbacks. It had to be dosed two or three times a day, and the competing oral formulations only once, a competitive disadvantage for Novartis, especially for patients who might easily forget to take their medicine.

GB 040 explains that transdermal administration of rivastigmine solves some of the problems of the oral formulations: It could be administered less often, such as once a day; and it could reduce side effects.

However, as Dr. Kydonieus explains, the transdermal formulation of GB 040 was not a finished commercial dosage form, it was a laboratory scale preparation, s starting point for further development, without a release liner or protective packaging, which had not been tested clinically or subject to stability studies. Thus, one of ordinary skill in the art

would be motivated to further develop a transdermal delivery system for rivastigmine.

We have a second defense which was not brought up in the prior litigations, the defense of double patenting. Novartis's patent 5,602,176 is the U.S. equivalent of GB 040, it claims priority from the same German application as GB 040; it identifies the same inventor, Albert Enz, and contains substantially the same disclosure. It is owned by Novartis. It claims rivastigmine, a pharmaceutical composition containing rivastigmine, a method of treating Alzheimer's disease with such a composition, and a systemic, transdermal patch containing rivastigmine and a carrier. Like GB 040, is does not disclose the use of an antioxidant. For the reasons claim 7 and 16 are obvious in view of GB 040 and the other prior art which I referred to, including the structure of rivastigmine, claim 7 and 16 are obvious variants of the claims of the '176 patent, and not patentably distinct.

In conclusion, Noven will submit clear and convincing evidence, not previously considered, which shows that one of ordinary

skill in the art, looking at all the prior art would have known that rivastigmine was susceptible to oxidative degradation, that the use of antioxidants to prevent such degradation was one of several known obvious solutions and that therefore claims 7 and 16 of the '031 patent are obvious and, therefore, invalid.

Thank you, Your Honor.

THE COURT: Thank you, Mr. Lee. Ms. Jacobsen.

MS. JACOBSEN: Good morning, Your Honor.

MS. JACOBSEN: For the record, Charlotte Jacobsen on behalf of the plaintiffs.

As Your Honor just heard, Noven alleges that Claim 7 and 16 of the '031 patents are invalid as obvious or for obviousness-type double patenting.

But no matter the legal theory, the question for Your Honor is the same. And that is: As of 1998, would a person of ordinary skill in the art have been motivated to combine rivastigmine with an antioxidant in a transdermal patch? The answer to that question is no.

As the evidence will show, the problem of oxidative degradation of rivastigmine in a pharmaceutical composition was not known or suggested by the prior art. And because the problem was not known, a person of ordinary skill would not have been motivated to try to solve an unknown problem. After all, as the saying goes if it ain't broke, don't fix it.

Now, plaintiffs admit that rivastigmine was known. Rivastigmine in a transdermal patch was known. And antioxidants were known. But identifying the individual elements of the patent claims in the prior art is not sufficient to establish obviousness.

Instead, the Supreme Court in KSR instructed District Court judges to make explicit in their obviousness analysis the motivation that would have caused a person of ordinary skill in the art to select and combine the elements in the prior art in the way in which the patent claims did.

And that means that Noven has to establish the motivation that would have caused a person of ordinary skill in the art to select

rivastigmine and an antioxidant and combine them in a transdermal patch. Your Honor, Noven must do so by clear and convincing evidence, and Noven cannot meet that heavy burden.

Noven's obviousness case can be broken down into three parts. First, Noven alleges that it would have been obvious to add an antioxidant to rivastigmine in a transdermal patch based on three references that relate to rivastigmine or the racemate RA7. And those references are GB 040, the '807 patent and Elmalem. And those are the same three references that were in the Watson case and they're the same three references over which Your Honor found Claim 7 and 16 non-obvious. And as before, the evidence will show that none of these references taught or suggested that rivastigmine undergoes oxidative degradation in a pharmaceutical composition, including a transdermal device.

Now, Noven tries to create the impression that the case is different from Watson's. But the fact of the matter is that Noven has not identified a single prior art reference that specifically addresses

rivastigmine or RA7 that was not before the Court in the Watson case.

So, second, Noven alleges that a person of ordinary skill in the art would have recognized just by looking at the structure that rivastigmine had the potential to undergo oxidative degradation; and therefore, a person of ordinary skill would have added an antioxidant to rivastigmine in a transdermal patch. But as Your Honor will hear, Noven's structural theories are unproven and they are contradicted by pharmaceutical realities.

Pharmaceutical formulators simply do not add antioxidants unless they are actually needed. And, in fact, the literature and the regulatory guidelines instruct formulators not to do so.

Third, Noven alleges that it would have been obvious to add an antioxidant to rivastigmine in a transdermal patch based on general references relating to antioxidants or antioxidants in transdermal patches with other drugs. But these general references say nothing about rivastigmine or its instability, and that

means that these general references cannot provide the motivation that is missing from the rest of Noven's prior art.

Your Honor, I'll briefly address each part in turn starting with the rivastigmine and RA7 references. The first is GB 040, which was published in 1988. That is ten years before the priority date of the '031 patent.

Importantly, the U.S. equivalent of GB 040, the '176 patent was before the examiner during prosecution of the '031 patent.

The '176 patent contains all the same disclosures that Noven relies on in GB '040, and yet the examiner issued the '031 patent over the '176 patent without issuing a rejection. Your Honor, as in the Watson case, there is no dispute here that GB '040 is silent with respect to rivastigmine's instability and that's significant for two reasons.

One, it's significant because there are many different types of degradation. Degradation can be caused by light, by heat, by water, by acid, by oxidizing agents, to name just a few. And not every drug undergoes every type

of degradation in every formulation.

In fact, most drugs are stable and they don't undergo degradation in pharmaceutical formulations. So a person of ordinary skill in the art would not have taken measures to reduce a degradation that he or she had no reason to believe was actually occurring.

Two, the silence is significant because antioxidants can be incompatible with the drugs and cause an unexpected increase in degradation. So a person of ordinary skill in the art would not have been motivated to add an antioxidant unless one was actually needed.

And so it follows from GB '040's silence with respect to rivastigmine's instability that the motivation to add an antioxidant to rivastigmine in a transdermal patch must come from some other source.

That brings me to the '807 patent which is another reference that was before the examiner during prosecution and the examiner did not issue a rejection in light of. This reference does not disclose transdermal patches and it does not disclose any stability data for

any compound, including RA7.

The '807 patent does mention antioxidants, but it is only among a laundry list of excipients. It's only for sterile use during injection, and even then only as required. And importantly there is nothing in the '807 patent that would have taught a person of ordinary skill in the art that RA7 required an antioxidant.

To the contrary, to the extent the '807 patent mentions stability, it portrays RA7 in a positive light. And as a result, the '807 patent cannot provide the motivation to add an antioxidant to rivastigmine and the transdermal patch formulations of GB '040.

Turning then to the Elmalem article, there is no dispute that that reference does not disclose transdermals and it does not disclose any stability data for any compound including RA7.

Like Watson before it, Noven alleges that Elmalem added an antioxidant to RA7 in an aqueous solution for injection to prevent its oxidation. But as before, Dr. Klibanov will walk the Court carefully through this article and he will explain two important things. First,

Dr. Klibanov will explain the broader context of this paper. And specifically, he will explain what was known in the art at that time about the compounds tested in Elmalem. Those compounds including physostigmine, which was known to be unstable in an aqueous solution and require an antioxidant. But there was no suggestion in the prior art that the same was true for RA7. In fact, to the extent that Elmalem mentions stability, like the '807 patent, Elmalem portrays RA7 in a positive light stating that it has greater chemical stability than physostigmine.

Second, Dr. Klibanov will explain the purpose of the Elmalem study. Your Honor, Elmalem was not a stability study, but rather its purpose was to compare the relative biological effects of three new compounds, one of which was RA7 to the well-known compound physostigmine and a saline placebo.

When read in context, it becomes clear that a person of ordinary skill in the art would not have understood Elmalem to teach that RA7 undergoes oxidative degradation, but rather that the antioxidant was added to RA7 as a

control, meaning that it was added to minimize the differences between the formulations tested in Elmalem so that any differences in the biological effects that were observed could be attributed to the drugs themselves.

Noven, however, points to another paper published by one of the authors of the Elmalem study called Weinstock 1981. Weinstock 1981 did not report any stability testing on rivastigmine. In fact, Weinstock 1981 did not report any study result on rivastigmine or RA7 because those compounds didn't even exist in 1981.

Nevertheless, Noven argues that the Weinstock paper that was published ten years before Elmalem would have changed the way a person of ordinary skill in the art interpreted Elmalem.

But, Your Honor, Weinstock 1981 would not have changed anything because it addressed a completely different question from Elmalem and it used Physostigmine for a completely different purpose.

Unlike Elmalem, the purpose of the

study in Weinstock 1981 was not to compare the relative biological effects of Physostigmine with new compounds. Instead, the purpose was to study whether the side effects of morphine are caused by morphine acting on the central nervous system, that is the brain and the spinal column, or alternatively whether the side effects of morphine are caused by the action on the peripheral nervous system. That's the nerves that run all over our body.

To do that, Weinstock 1981 used Physostigmine simply because it was known to act on the central nervous system and not as a comparator to new drugs as was the case in Elmalem.

A person of ordinary skill in the art would not assume the two studies with two different purposes and that used Physostigmine for two different reasons should have the exact same protocol as Noven's expert will ask Your Honor to assume. Instead, a person of ordinary skill in the art would have understood that different studies carried out for different purposes require different experimental

protocols.

But even assuming for a minute that Elmalem would have suggested that RA7 had the potential to undergo oxidative degradation in an aqueous solution for injection, whether RA7 or rivastigmine undergoes oxidative degradation is undeniably formulation specific. And that means a person of ordinary skill in the art would not have believed that what happened in the aqueous solutions for injection in Elmalem would happen in the transdermal patches in GB '040.

Indeed, Physostigmine was known to require an antioxidant in the aqueous solutions for injection in Elmalem, but Physostigmine did not require an antioxidant in a transdermal patch.

So, yet again, a person of ordinary skill in the art would not have had any motivation to combine the aqueous solutions for injection in Elmalem with the rivastigmine transdermal patches in GB 040.

Turning then to Noven's structural theories and they are based on rivastigmine's benzylic carbon hydrogen bond, the amine, and its alleged inclusion in a class of compounds called

alkaloids, although it's not clear whether Noven's expert will actually advance the third theory at trial.

As Dr. Klibanov will explain, Your Honor, oxidation reactions are complex and mechanicistically, they were not well understood in 1998. And, in fact, they're still not understood even today.

And as such, a person of ordinary skill in the art could not have reasonably predicted from rivastigmine's structure that it would undergo oxidative degradation under pharmaceutically relevant conditions. Pharmaceutically relevant conditions is the key because any organic compounds can be oxidized if you expose it to harsh enough conditions.

So the relevant questions here are whether rivastigmine would undergo oxidative degradation under the types of conditions that are encountered during manufacture and storage of pharmaceuticals.

And if some degradation did occur, questions remain as to whether the rate and extent of that degradation under those

pharmaceutically relevant conditions would give rise to a stability problem. The only way to answer those questions would have been by testing.

And that means that the problem would not have been known in advance. And absent knowledge of the problem, Your Honor, there would not have been a motivation to try to solve it.

Indeed, the inventors of the '031 patent were not able to predict rivastigmine's instability and they had far more experience with rivastigmine and were more skilled than a person of ordinary skill in the art.

Now, tellingly, only one of Noven's structural theories is even advanced by the chemistry expert, Dr. Schoneich. He alleges that a person of ordinary skill in the art would have known that rivastigmine had the potential to undergo oxidative degradation based on the presence of a benzylic carbon hydrogen bond in the rivastigmine molecule.

And in support of this theory, Dr. Schoneich relies on only one compound nicotine, which was known to potentially undergo oxidative

degradation under some pharmaceutically relevant conditions.

But, Your Honor, the universe of compounds with benzylic carbon hydrogen bonds is large. And in contrast to Dr. Schoneich's theory, the reality is that there were many drugs with benzylic carbon hydrogen bonds that were not reported to undergo oxidative degradation and were not reported to contain an antioxidant in the FDA approved commercially available formulations.

And in light of this real world evidence, the mere presence of a carbon hydrogen -- sorry, a benzylic carbon hydrogen bond in the molecule would not have told a person of ordinary skill that rivastigmine was unstable. Your Honor, Dr. Klibanov will further explain that to a person of ordinary skill in the art, rivastigmine is not structurally similar to nicotine.

And despite nicotine's known potential to undergo oxidative degradation, as of 1998, none of the commercially available nicotine transdermal patches were reported to include an

antioxidant.

It simply cannot be the case that knowledge of nicotine's potential instability would have led a person of ordinary skill to add an antioxidant to rivastigmine in a transdermal patch when that knowledge didn't even lead to the addition of an antioxidant to nicotine in a transdermal patch.

And the story is the same for Noven's second structural theory based on rivastigmine. Noven relies on an unexamined patent application called Sasaki. And that tested two amine containing drugs in one transdermal formulation. But a person of ordinary skill in the art would not have believed based on these two compounds in one formulation that all amines would undergo oxidative degradation in all transdermal formulations.

Again, Your Honor, the universe of amine containing drugs is large and the reality is that there were many drugs with amines that were not reported to undergo oxidative degradation under pharmaceutically relevant conditions and were not reported to contain an

antioxidant in the FDA approved transdermal formulations.

So yet again, the real world evidence contradicts Noven's theoretical argument.

And that brings us to Noven's third structural theory based on alkaloids, which isn't really a structural theory at all. And indeed Noven's chemical expert hasn't even addressed it. Noven's other expert has not identified any chemical structure that would have enabled a person of ordinary skill in the art to determine whether a compound was or was not an alkaloid. Certainly there was nothing in the prior art that taught a person of ordinary skill that rivastigmine was an alkaloid and that it would undergo oxidative degradation under pharmaceutically relevant conditions for that reason. Indeed Noven's own references demonstrate that there were known alkaloid that did not undergo oxidative degradation in transdermal patches.

Turning then to Noven's remaining references relating to antioxidants or

antioxidants in transdermal patches with other drugs. Your Honor, these references contain no teaching relating to rivastigmine or its oxidative instability. As Your Honor will hear from Dr. Klibanov, Noven's principal reference Ebert discloses a nonconventional transdermal manufacturing process to address problems specific to nicotine, and in particular, that nicotine is volatile. And that means that it evaporated at low temperatures and it cannot be manufactured into a transdermal device by conventional processes, because those processes include heating and drying in an oven.

But Your Honor will hear no evidence from Noven's experts that rivastigmine was known to suffer from any of the problems associated with nicotine that were addressed by Ebert. To the contrary, GB '040 teaches that rivastigmine can be manufactured into a transdermal patch by conventional processes, and that would include drying in an oven. And so again there would have been no motivation to combine GB '040 with Ebert.

Now, no doubt Noven picked Ebert from the available prior art on transdermals

because Ebert added an antioxidant, but that antioxidant was added to stabilize nicotine during Ebert's nonconventional manufacturing process.

As I noted before, unlike rivastigmine, as of 1998, nicotine was known to potentially undergo oxidative degradation, but Ebert is silent with respect to rivastigmine and its instability, and so Ebert cannot provide the motivation to add an antioxidant to a rivastigmine transdermal patch that is missing from the rest of Noven's prior art.

Finally, Noven pointed to the Watson decision and specifically to Your Honor's holding that if a person of ordinary skill in the art would have known that rivastigmine was susceptible to oxidation, then the '031 patent would have been invalid because the addition of an antioxidant to a pharmaceutical composition that oxidatively degrades is one of several known obvious solutions.

Your Honor's holding is entirely consistent with the pharmaceutical reality, that a person of ordinary skill in the art would not add an antioxidant just because there was a

theoretical possibility that rivastigmine could undergo oxidative degradation. Instead, a person of ordinary skill in the art would only add an antioxidant if one was actually needed. And one would only be needed if it was known that rivastigmine oxidatively degrades in the pharmaceutical composition in question.

As before, the evidence will show that none of the prior art taught or suggested that rivastigmine undergoes oxidative degradation in any formulation, let alone a transdermal patch. And, thus, Noven will not be presenting clear and convincing evidence that these valid claims should be found invalid. Because the problem of oxidative degradation of rivastigmine in a pharmaceutical composition was not known or suggested in the prior art, and a person of ordinary skill in the art would not have been motivated to combine rivastigmine with an antioxidant to try to solve the problem that he or she did not know existed.

Thank you, Your Honor.

THE COURT: All right. Thank you, Ms. Jacobsen.

Mr. Levy.

MR. LEVY: May it please the Court, Your Honor, for the record, Mike Levy of Kenyon & Kenyon on behalf of Noven Pharmaceuticals.

In that regard, Noven calls as its first witness Dr. Christian Schoneich of the University of Kansas.

May I approach, Your Honor.

THE COURT: Sure.

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

THE WITNESS: Christian Schoneich.

THE CLERK: Can you spell that please.

THE WITNESS: S-C-H-O-N-E-I-C-H.

CHRISTIAN SCHONEICH, PH.D.,

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

DIRECT EXAMINATION.

BY MR. LEVY:

Q. Good morning, Dr. Schoneich.

A. Good morning.

Q. Please turn to DTX 4 in your binder, please?

A. Yes.

Q. What is exhibit DTX 4?

A. This is a copy of my curriculum vitae.

Q. And does this copy of your CV accurately reflect your educational and professional experience?

A. It does.

Q. Does this copy of your CV accurately list your awards, publications and invited lectures?

A. It does.

MR. LEVY: Your Honor, defendants offer DTX 4 into evidence.

THE COURT: Admitted without objection.

BY MR. LEVY:

Q. What is your present position, Dr. Schoneich?

A. I am professor and am chair of the Department of Pharmaceutical Chemistry at the University of Kansas. I also hold the title of Takeru Higuchi Distinguished Professor for Bioanalytical Chemistry at the University of

Kansas. And I hold the title of professor in chemistry at the University of Kansas.

Q. Doctor, could you please briefly describe your educational background?

A. Yes. I obtained the equivalent of a masters in Germany in 1987 in chemistry at the Free University of Berlin. And obtained my Ph.D. with honors in chemistry in 1990 at the Technical University in Berlin.

Q. And briefly, Dr. Schoneich, could you please describe your positions that you have held professionally?

A. Yes, between 1991 and '92, I was a postdoctoral associate in the Department of Pharmaceutical Chemistry at the University of Kansas. In '92, I became assistant professor in the same department. And in '98 I was promoted to associate professor. And in 2003 to full professor in the same department. Since 2005, I am the chair of the Department of Pharmaceutical Chemistry.

Q. And what is your field of expertise generally?

A. My field of expertise is oxidation and

free radical reactions, mostly regarding proteins, but also small molecules. We studied oxidation reactions, we study the behavior of proteins and solutions and in the solid state. We studied stability issues with proteins and small molecules. We studied instability and also how to stabilize proteins in these formulations.

Q. Dr. Schoneich, have you received any awards in the field?

A. Yes. I was very fortunate to receive a couple of awards. I was awarded the Young Investigator Award for the Society For Free Radical Research in 1990 and '94. I obtained a Pfizer research scholar award in the years 2001, 2002, 2003 and 2004. In 2005 I was elected as a fellow of the American Association of Pharmaceutical Scientists. And then in 2010, I received the Dolph Simons Award in Biomedical Sciences.

Q. Dr. Schoneich, do you serve on any editorial boards?

A. Yes, I do, on five. I served on the editorial board of the Journal Experimental Gerontology, and Free Radical Biology and

Medicine. I serve on the editorial advisory boards on the General Journal of Pharmaceutical Science and also of Chemical Research and Toxicology, and I'm also the review editor of the Journal For Free Radical Research.

Q. Are you an author on any journal articles relating to pharmaceutical chemistry?

A. Yes, I have more than 200 journal articles in this field.

Q. Do you have experience with pharmaceutical drug formulation?

A. I do have experience with pharmaceutical drug formulation.

Q. Could you briefly describe that for the Court?

A. Yes. I have consulted over many years with the pharmaceutical industry. I have long-term and short-term consulting agreements with the pharmaceutical industry. In our laboratory we make formulations regarding stability issues. I am on the scientific advisory board of a pharmaceutical company in Munich. The name of the company is Coriolis Pharma, my work with them includes issues on

stability and formulation. And also I'm teaching a graduate course in pharmaceutical chemistry and that course is called mechanisms of drug deterioration and stabilization.

In this course

.

A. In this course, I teach students issues on stability, hydrogen oxidative and particularly teach students how to recognize science and molecules, which are susceptible to degradation.

Q. Dr. Schoneich, do you have any experience in dealing with oxidative degradation of pharmaceutical products during the drug development process?

A. Yes, I do. Through my consulting work, I have experience in that.

MR. LEVY: Your Honor, defendants offer Dr. Schoneich as an expert in the field of pharmaceutical chemistry including oxidative degradation of pharmaceuticals.

MR. MINION: No objection, Your Honor.

THE COURT: You may proceed.

BY MR. LEVY:

Q. Dr. Schoneich, what were you asked to do in this case?

A. I was asked to provide an analysis and expert opinion on what a person of ordinary skill in the art in 1998 would have expected about the chemical reactivity, if any, of rivastigmine in view of his or her understanding of organic chemistry and also disclosures in the prior art.

Q. And did you form such an opinion?

A. I did form such an opinion.

Q. And what is that opinion?

A. My opinion is that a person of ordinary skill in the art in 1998 would have recognized that the drug rivastigmine is susceptible to oxidative degradation.

Q. How would a person of ordinary skill in the art have arrived at the expectation that rivastigmine was susceptible to oxidation?

A. The person of ordinary skill in the art would have arrived at this by looking at the structure of the molecule and by general knowledge of organic chemistry.

Person of ordinary skill in the art would have also consulted references with that.

Q. And I believe you brought a slide showing the structure of rivastigmine.

A. Yes.

Q. And what does this slide show?

A. That is the structure of rivastigmine.

Q. Dr. Schoneich, what is the basis for your understanding that this is the structure of rivastigmine?

A. I reviewed a published reference which displayed the structure.

Q. Could you please turn in your binder to Tab JTX019, please?

A. Yes.

Q. And what is JTX019?

A. This is a published U.K. patent application GB 2,203,040.

Q. And when did JTX019 publish?

A. That was published in 1988.

Q. Did you review this reference in connection with your work here?

A. I did so.

Q. And what does JTX019 disclose?

A. It discloses the structure of rivastigmine.

MR. LEVY: Your Honor, defendants offer Exhibit JTX019 into evidence.

THE COURT: All right. Admitted without objection.

MR. LEVY: Can we please bring up in JTX019, Page 1, please, and bring up that middle paragraph.

BY MR. LEVY:

Q. On Page 1 of JTX019 and specifically at the structure text at the top of the page, what is shown here, Dr. Schoneich?

A. That that is the structure of Rivastigmine, and with a name which is displayed above it is clear that it is clearly of rivastigmine.

Q. Can we go back now to the slide?

A. Yes.

Q. Does this slide, Dr. Schoneich, show all of the atoms that make up the rivastigmine molecule?

A. Yes, it does. But there is some important shorthand which organic chemists usually use.

Q. And what do you mean by "shorthand"?

A. So if you look at the structure, and I'm

using my pointer now, but what is here is solid lines. And these solid lines meet at certain vertices. Now, in general, we display atoms by symbols, by letters. But sometimes we don't. And if you don't, these vertices, that means that here that is a carbon atom.

Now, the other thing is carbon atoms usually make four bonds. But what you see here in this ring, and we'll talk about this structure of the ring later, that here the carbon makes only three bonds. One has been omitted for clarity, but it's still there.

This is then implied to be a carbon hydrogen bond. So that ring here contains four carbon hydrogen bonds, but they're not explicitly shown.

Q. Do you have a slide explicitly showing all the atoms in rivastigmine identified by a chemical symbol?

A. Yes, I do on the next slide. So what you see here is a slide depicting the structure of rivastigmine with all the atoms and all bonds shown. But you easily see that it's not very easy on the eyes, so we prefer to work with a

structure which I have shown previously.

Q. Dr. Schoneich, a moment ago you stated your opinion that one of ordinary skill in the art would have expected that rivastigmine would be susceptible to oxidation. Can you please explain your opinion based on the chemical structure of rivastigmine?

A. Well, if you go back to the next slide, and now I would like to highlight one particular bond here. Rivastigmine has a carbon hydrogen bond and this is highlighted in red.

Now, this carbon hydrogen bond is surrounded by three distinct features which makes this carbon hydrogen bond particularly susceptible. First of all, this carbon hydrogen bond is immediately adjacent to an aromatic ring. And that aromatic ring here is highlighted in blue.

In this blue ring you see an alternating system of double bonds illustrated by these two lines and single bonds illustrated by these single lines. And that will become very important later.

Now, this carbon hydrogen bond is

also immediately adjacent to a tertiary amine. And to explain what an amine is, an amine is a nitrogen compound here, which has three bonds to other substituents. The carbon atom is also immediately adjacent to another carbon substituent here.

And altogether that makes this carbon here a tertiary carbon. And that is also very important to remember.

So these are the structured features a person of ordinary skill in the art would have immediately recognized based on organic chemistry knowledge.

Q. When you were forming your opinion, what information did you rely upon?

A. Well, I relied on the structure of rivastigmine and generally organic chemistry knowledge. I reviewed the patent which we refer to as the '031 patent and also some references.

Q. Did you review the prosecution history of the '031 patent or any documents from Noven, Hisamitsu (phonetic) or Novartis before forming your opinion?

A. I did not review the prosecution history,

and I did not review any documents which you just mentioned.

Q. Would a person of ordinary skill in the art have also consulted any literature in conducting the analysis?

A. Of course, a person of ordinary skill in the art would have consulted literature to make a really informed decision beyond about what to expect from the structure like rivastigmine.

Q. Dr. Schoneich, let's now discuss in more detail the basis of your opinion. You mentioned a person of ordinary skill in the art.

Dr. Schoneich, I believe you brought a slide explaining your understanding of such a person?

A. Yes, and that is illustrated on our next slide.

Q. Could you explain what is shown?

A. Yes. It it's a definition which is also present in our opening report.

A person of ordinary skill in the art would have been a collaborative team of individuals in which each person would have been able to draw upon the experiences and knowledge

of others. And the collaborative aspect is important.

In particular, the person of ordinary skill in the art at the time of the alleged invention would have been a chemist, a chemical engineer, or a polymer chemist or a pharmaceutical chemist working to develop pharmaceutical formulations. And that includes transdermal drug delivery systems.

Again, important as to the collaborative aspect here. The person of ordinary skill in the art would have been familiar with testing that accompanies the development of any pharmaceutical formulation, that includes testing for efficacy and stability.

And the person of ordinary skill in the art would have been familiar with excipients, which is typically employed in pharmaceutical formulations and that includes transdermal devices.

Now, the person of ordinary skill in the art would have had knowledge of organic chemistry, either on his or her own, or through collaboration with other people in the group or

team having knowledge of organic chemistry. And together they would have been able to predict physical properties of a compound based upon the chemical structure.

Q. Dr. Schoneich, did you formulate this definition on your own?

A. Well, I reviewed the '031 patent and came up with a very similar definition. But the wording of this definition was provided to me by counsel and I totally agree with that.

Q. And did you perform your analysis from the perspective of such a person?

A. I did so.

Q. And did you perform your analysis from the perspective of such a person as of January 1998?

A. I did so.

Q. Dr. Schoneich, can you please now assist the Court by explaining the chemical principles that allowed you to conclude that the ordinary skilled artisan would have formed an expectation that rivastigmine was susceptible to oxidation?

A. Yes. So in order to understand how a person of ordinary skill in the art in 1998 would have arrived at the conclusion of susceptibility

to oxidation, there are four important principles which we need to appreciate.

And I would like to walk you carefully through the four principles here. And I would also like to alert you that each of these principles will come back in the successive slides, so we'll talk back about those.

So, first of all, oxidation often involves the breaking of a covalent chemical bond. And that break of a covalent chemical bond results in formation of a radical.

Radicals --

THE COURT: I'm sorry. Just remind me what does covalent mean?

THE WITNESS: I have that on another slide, but --

THE COURT: All right.

THE WITNESS: Do you want me to --

THE COURT: If you're going to cover it some time, that's fine.

THE WITNESS: Please. Radicals are reactive molecules with an unpaired electron.

Some chemical bonds are weaker than others and that depends on the structural context

of the molecule.

Now the structural context defines the electronic neighborhood of an atom or a bond. And, thus, those chemicals bonds are more prone to oxidation.

And, finally, a drug molecule containing a chemical bond prone to oxidation can lead to degradation of the drug.

BY MR. LEVY:

Q. Dr. Schoneich, what is oxidation that's been referred to in this slide?

A. Oxidation, in general, refers to the loss of an electron from a molecule. But in drug development or pharmaceutical you mostly consider carbon-bearing organic molecules and these molecules, oxidation very frequently is affected by the loss of a hydrogen bond, the breakage of a carbon hydrogen bond.

Q. Can you explain an example illustrating oxidation over an organic compound?

A. Yes. That is on the next slide.

And here I also list what is a covalent length bond. This is the molecule butane.

Now, butane is not a drug. It's a very simple compound. It's the primary ingredient of lighter fluid and serves a perfect purpose to explain oxidation.

First of all, please look at these symbols here. We have carbons and hydrogens and you see solid lines between carbon and hydrogens. These are covalent bonds.

Now, this basically makes up the bonding structure of a molecule. We see that some carbons have three bonds to hydrogens. And we see that some carbons have two bonds to hydrogens.

Q. Can you explain a covalent bond is?

A. Yes. So I have initially shown you this covalent bond.

Here is a solid line. What these solid lines really represent is a shared electron pair. And that is shown on the right-hand side.

Now, you see there are no lines here anymore, but you see that between every atom and the other, there are two dots. And each of those dots represents an electron. A covalent bond is made up of a shared electron pair between two

atoms.

Q. Doctor, can you explain oxidation of that molecule?

A. Yes. So if you go back to the previous structure, and what I would like to do now, I would like to replace one carbon hydrogen solid line, one of these covalent bonds by a shared electron pair.

Oxidation now happens when the hydrogen takes one of those electrons and the carbon takes the other one. And these two atoms move apart from each other. And that is shown in the progression of the reaction.

Basically what we have done here we have broken this carbon hydrogen bond and that breakage of the bond leads to two radicals where the two final products here, each of them retain one electron. And that is represented now by the red dots.

It is important to understand that this process here is called a homolysis process. So if you break this bond homolytically.

Q. Dr. Schoneich, what happens when the carbon hydrogen bond is broken?

A. When the carbon hydrogen bond is broken in any organic molecule such as this, the organic molecule has become oxidized. Now, if this were a drug molecule, this could undergo further reactions and ultimately convert into a different chemical entity and become irreversibly degraded.

Q. And what are the resulting species called upon breakage of the carbon hydrogen bond?

A. The resulting species here are called radicals.

Q. And how are radicals represented in your diagram?

A. Radicals are represented exactly as molecules which have these under -- basically single electrons associated with the atoms.

Q. What re the implications of forming a radical?

A. The implications of forming a radical, I think I said this before, when this molecule gets oxidized and forms a radical, it then can undergo additional reaction, further reaction which converts this vertical into other chemical entities. And ultimately, in this case, a butane molecule. But that is representative for any

drug that becomes chemically modified, chemically changed and basically degraded.

Q. What determines if a chemical bond in a drug can be broken to form a radical?

A. There's a very important concept that is the strength of the bond. We have strong bonds and weak bonds.

The strength of the bond dictates how much energy we have to put in here in order to cleave this bond. And this energy we have to put in here is called the bond dissociative energy.

Q. Do all covalent bonds have the same strength?

A. Some bonds are weaker, some bonds are stronger. Now this depends very much on which atoms make up these bonds, it depends on which chemical neighborhood these atoms are, and generally the ease of, the ease of breaking the bond depends on how stable the final product, in this case the radicals, are.

Q. What do you mean by how stable the resulting radical is?

A. What I really mean is how reactive the

resulting radicals are.

Q. And how does radical stability affect bond strength?

A. Well, there are some simple concept, the more stable the product radical is, the weaker the bond which we have to break in order to form it. Or even simpler, the more stable the radical is to form, the easier it is to form.

Q. What makes a radical more or less stable?

A. It is the structural context in which this radical is placed. That is the neighborhood of this current atom. And what you have to understand is that in a drug, not every carbon atom is in the same neighborhood, so there will be sites in the drug which forms radicals easier and there will be sites in the drug which forms radicals harder.

Q. You mentioned the stability of radicals. Are radicals actually stable?

A. No radicals are usually reactive. When I refer to a stable radical, what I really mean is the relative stability of a radical in comparison to another radical.

Q. You mentioned before the structural

context of an atom. Do you have a slide illustrating the effects of structural context?

A. Yes. I will carefully walk you through. What you see here is four radicals. Remember a radical is a compound which has an unshared electron on an atom, here it is always the carbon atom. On the left-hand side you see a carbon atom which is having another three bonds to hydrogen atoms and this is a methyl radical. You see that this methyl radical is the least stable radical in this series. As you move to the right-hand side you see that successively you replace a hydrogen by a group which is called R, and R is an alkyl group, for example you can see it could be a methyl group. Here one alkyl group here, we have three, going from the left to the right, the radical becomes successively more stable. The radical on the right-hand side here because it has three additional covalent bonds is called a tertiary radical. This is the most stable radical in this series.

Q. So, Doctor, you have explained that a radical can be stabilized being adjacent to other carbon atoms. Are there other structural context

that stabilize a carbon radical?

A. Yes. Another structural context would be if that carbon radical would be adjacent to a tertiary amine. Another structure would be if that carbon radical would be immediately adjacent to an aromatic ring.

Q. What effect, if any, would an aromatic ring provide?

A. We have a slide which illustrates that. First what you see in here is the compound called toluene. Toluene is an ingredient of the gasoline which we run our cars with. What you see is an aromatic ring and this aromatic ring is the same system we talked about before, a ring where we have alternating double and single bonds. Immediately adjacent to that ring here is a carbon atom. That carbon atom adjacent to the ring is called a benzylic carbon. And we have three hydrogen bonds, the carbon hydrogen bond here is benzylic carbon hydrogen bond, it's important to remember that that benzylic carbon is immediately adjacent to an aromatic ring.

Q. How does the aromatic ring effect the stability of the carbon radicals?

A. In order to illustrate this, what you see is the molecule toluene. I would like to do what we do with butane, I replace one of those covalent bonds with one of these lines where there is a shared pair and I break this bond so I move the hydrogen away and generate the radical on the carbon. Now this is called a benzylic radical. And the way that it's stabilized is illustrated on the next slide.

So what we have again here is our radical, and in order to understand how this is stabilized, we need to introduce the concept of electron delocalization. This means that that carbon centered radical can be handed over to the ring and generate resonance structures. We see the carbon centered radical here, and we see it here and here. These resonance four are all possible with a benzylic radical.

Now, the result of it is, first of all, we can compare these delocalization here pretty much to handing a hot potato around a circle of people, nobody wants to hold a hot potato in their hand, so it gets passed around the ring without anybody having a lot of time

with it, and that is the concept of electron delocalization.

But the concept of this is, especially radicals of benzylic carbon hydrogen atom bonds are extremely easy to make and a person of ordinary skill in the art would have recognized this.

Q. Does the presence of an aromatic ring stabilize any radical in a molecule?

A. No. An aromatic ring can be located far away from the site of oxidation and then it would not necessarily stabilize that radical. In order to stabilize this carbon centered radical here, the carbon radical has to be immediately adjacent to this aromatic ring.

Q. How would a person of ordinary skill in the art know the relative bond strengths of a drug compound?

A. Well, first of all, bond strengths are tabulated in organic textbooks. We can look at bond dissociation energies and look at these, but the person of ordinary skill in the art can also look at the structures and features around a potential bond and decide whether they are

structural features which support formation of the radical and make a decision about that.

Q. Dr. Schoneich, please turn in your binder to tab DTX 32.

A. Yes.

Q. Do you recognize DTX 32?

A. Yes.

Q. Can you describe what that is?

A. That's a chapter out of an organic textbook authored by Francis Carey and Richard Sundberg.

Q. What does this chapter in the textbook disclose?

A. This chapter just discloses all the principles I have recently illustrated on these slides.

Q. Is this a standard textbook in organic chemistry?

A. This is a standard textbook in organic chemistry.

Q. When did DTX 32 publish?

A. This was in 1990.

MR. LEVY: Your Honor, we offer DTX 32.

THE COURT: Admitted without objection.

BY MR. LEVY:

Q. Doctor, does DTX 32 provide information on the relative bond strengths of carbon hydrogen bonds?

A. Yes, it does. The chapter actually provides a table and that table is shown on this slide. And again, I now have to walk you carefully through here.

What you see on the left-hand side of column, you see a number of organic compounds and you see covalent bonds highlighted between certain atoms, carbon and hydrogen, but also between other atoms which are not of consideration today.

Now, if I highlight the first compound on the top, this is methane, the gas methane. If you break methane by the way of a compound which has one carbon and four carbon hydrogen bonds. Now if you break one of those carbon hydrogen bonds, you generate a methyl radical, and that methyl radical is the same radical which we had shown in the series of three

radicals in one of these previous slide. That methyl radical is one of the least stable radicals in the series and consistent with this it takes a lot of energy to form this radical.

In fact, it takes a lot of energy to break the carbon hydrogen bond. It takes 104 kilocalories per mole. If you highlight the second compound, we have replaced one carbon hydrogen bond with one carbon alkyl bond. I have told you in the series of free radicals before, as we replace hydrogen with carbon substituents, the radicals become more stable and consistent with this it will take less energy to generate. And consistent with that the carbon hydrogen bond energy here is now lower than the carbon hydrogen bond here, we are dealing with 98 kilocalories per mole.

If you go to the next compound below, we have now replaced two carbon hydrogen bonds with alkyl substituents and consistent with our expectation, the bond dissociation energy of this carbon hydrogen bond is even lower. It's only 94-and-a-half kilocalories per mole.

If we go one step down, we have now

have replaced all but one carbon hydrogen bonds with alkyl substituents. If you break that one remaining carbon hydrogen bond, we generate a tertiary carbon radical, exactly the radical on the previous slide we had seen on the right-hand side which was the most stable radical, and consistent that the energy requires to break that bond is only 91 kilocalories per mole.

Now, we have to go a few steps down and I want to highlight the example of a benzyl radical. This is again a methane gas except that we have replaced one carbon hydrogen bond with now a phenyl substituent with an aromatic ring. And this aromatic ring present at this carbon here makes breakage of that carbon hydrogen bond even easier. The energy required to break this bond is now only 85 kilocalories per mole.

So in summary, these energies which have been measured, these are experimental values are very consistent, above what we have seen in the slides before that by putting the radicals which we make, and immediately adjacent to certain substituents they are easier to make.

Q. Okay. Doctor, how do the different bond

strengths of carbon hydrogen bonds relate to the stability of drugs like rivastigmine?

A. Well, as I say there are weaker and stronger carbon hydrogen bonds and the weaker a carbon hydrogen is the easier it is to oxidize it and to make a radical. Now, if you do make a radical as I have said before, this radical can then undergo further reactions and basically change into a different compound.

In the case of a rivastigmine that means if you have a carbon hydrogen bond which is easy to break, when we make the radical, it is easy to oxidize rivastigmine at this place and convert it into a different chemical entity, meaning degraded drug.

Q. What causes the carbon hydrogen bond to actually break leading to the formation of a radical?

A. So for this we have to understand another important concept, and if you can go to the next slide please, I have now to talk about initiation. What you see on the slide in short is an organic molecule and this is depicted as R-H, that may be a drug molecule. You see on the

left-hand side an a initiator. This is a free radical initiator. We will talk later about how this can form in a formulation.

This initiating radical is a reactive radical, and if that radical sees a weak carbon hydrogen bond such as present in rivastigmine, that initiating radical will abstract that hydrogen and convert into a covalent bond compound where we generate now the radical of the drug, or of the organic compound. This is the initiation of oxidation of the drug.

Q. Dr. Schoneich, after an initiator abstracts a hydrogen from a drug forming a radical, what happens?

A. Well, after that reaction happens, this radical here will be able to react with other components in the formulation. Now, as one component we can take oxygen. That is illustrated on the next reaction. Oxygen here is presented as a di-radical. That means every of these oxygen atoms contains an unshared electron. This is actually how electron is present in the air we breathe.

Now, this oxygen has a very easy

time to react with this radical, and the reason being we have two radicals reacting with each other. And when this reaction happens, our initial, our current set of radical here converts into another radical which we now to refer to as a peroxy radicals.

Now, these peroxy radicals are not stable themselves, they're formed but then they look for other reactants. This peroxy radical here sees that there a drug present which has a weak carbon hydrogen bond, this further reacts with drug molecules and even convert more drug compound by this radical pathway.

So we have initiated the reaction, but then we trigger a chain reaction process by which very much of the drug can decompose in a relatively short time.

Q. Do these reactions occur in a time frame relevant to pharmaceuticals?

A. Absolutely. We have to recall that pharmaceutical formulations are formulated in order to last for two years. Two years shelf life is typical. So these reactions have ample time to proceed in these two years.

Q. Dr. Schoneich, where do initiators come from?

A. That is an important topic. Initiators can come from various components in the formulation. If you think about formulations contained excipients, excipients frequently contain peroxides which can trigger formulation of initiating radicals. Excipients can also contain transition metals such as iron or copper and these metals can reacted with the drug to oxidize the drug. And ultimately some formulations may contain polymers, and these polymers are frequently made --

MR. MINION: Objection, Your Honor. This is outside the scope of the witness's expert report.

MR. LEVY: I beg to differ. I believe in Dr. Schoneich's opening report of paragraphs 38 and 39 there is a discussion of the subject matter that he's testifying to right now.

MR. MINION: I'll withdraw my objection.

THE COURT: Thank you.

You may continue, Mr. Levy.

A. I refer to, I mean polymers, and these polymers are frequently made by free radical reactions themselves. In order to make these polymers, initiators have to be added to the monomers that are finally converted into polymers. And if the final drug formulation still contains some of these initiating molecules, that can trigger also radical formulation and the initiators of these radical into pharmaceutical formulation.

Q. Dr. Schoneich, are the concepts that you just discussed regarding free radical oxidations disclosed in pharmaceutical textbooks?

A. They are, sure.

Q. Dr. Schoneich, please turn to exhibit DTX 91 in your binder, please.

A. Yes.

Q. What is DTX 91?

A. It's a textbook on the Introduction to Pharmaceutical Dosage Forms authored by Dr. Howard Ansel.

Q. Is this a standard pharmaceutical textbook?

A. That is a standard pharmaceutical

textbook.

Q. When was DTX 91 published?

A. That was published in 1985.

Q. Did you review this document as part of your work?

A. Yes, I did so.

Q. What does DTX 91 disclose?

A. It discloses general concepts of formulation design and also concepts of stability issues including oxidation.

MR. LEVY: Your Honor, defendants offer DTX 91 into evidence.

MR. MINION: No objection.

THE COURT: Admitted without objection.

BY MR. LEVY:

Q. Doctor, let's turn to back to rivastigmine now. When you considered what the ordinarily skilled artisan would have expected by the chemical reactivity of rivastigmine, what did you do first?

A. Well, I looked at the structure of rivastigmine and, of course, I applied organic textbook knowledge.

Q. Would a person of ordinary skill in the art in 1998 have looked at the chemical structure of a drug when undertaking formulation development?

A. Of course, a person of ordinary skill in the art would have looked at the structure of rivastigmine as part of a routine preformulation process. That's an absolutely fundamental process. And the person of ordinary skill in the art would have realized that there is a particular feature of rivastigmine, which makes it susceptible to oxidation.

First of all, there is this benzylic carbon hydrogen which we talked about and secondly there are the other structure features which we are to talk about.

Q. Stepping back for a moment, would a person of ordinary skill in the art look at a chemical structure of a drug as part of a formulation development?

A. The person of ordinary skill in the art would look at the structure in order to gain insight into some of the drug's properties or characteristics such as, for example, stability,

solubility, and when the person of ordinary skill in the art would have gained insight into these, the person of ordinary skill in the art would have made rational decisions about formulation design.

Q. Are there any features in particular about the rivastigmine molecule that a person of ordinary skill in the art would consider as relevant to the stability question?

A. Yes. And for this I would like to highlight a few bonds here, and we have seen one before. We have seen these benzylic carbon hydrogen bonds which is highlighted in red. Now the benzylic carbon hydrogen bond is immediately adjacent to the aromatic ring. We have seen that the presence of an aromatic ring next to a carbon like this could stabilize the radical here.

The aromatic ring is again the system which contains these alternating double and single bonds. The carbon hydrogen bond is also immediately adjacent to a tertiary amine highlighted in green and also to these other alkyl substituents highlighted in purple. All together it shows the person of ordinary skill in

the art would have recognized that there are multiple features which support a very good oxidation at these carbon hydrogen bond here of rivastigmine.

Now, with regard to formulation development, the person of ordinary skill in the art would have immediately recognized that an antioxidant could be added to these type of compounds in order to prepare an oxidation stable formulation.

Q. So rivastigmine has a carbon hydrogen bond that is susceptible to oxidation. How does that relate to the degradation of rivastigmine?

A. So when rivastigmine is oxidized, and I have a slide, please, rivastigmine can oxidize in the same way as I had just presented to you a few slides ago. If you have initiating radicals present in a formulation, they can abstract a hydrogen from the carbon hydrogen bond here and convert the rivastigmine now into a radical here.

A. And this process rivastigmine has become oxidized.

Q. If initiators are present and a radical is formed at the benzylic carbon in rivastigmine,

what happens next?

A. What happens next is that this radical can react further. And if you go to the next slide, I will illustrate that this radical now can react in the formulation with various constituents.

And, again, one of them will be oxygen. Now, this oxygen to which the character can add very efficiently to this carbon. And in this way, the rivastigmine molecule is converted into a peroxide radical.

With this process now, the rivastigmine molecule has been completely changed. It's not rivastigmine anymore. It's a complete chemical structure.

And by the way, this peroxyl radical again here can react with additional molecules or additional components of the formulation to trigger additional oxidation processes like the chain reaction which I've presented before.

Q. Is this the only reaction that could occur once a rivastigmine radical is formed?

A. No, that is one possibility. The possibility here is that rivastigmine reacts with oxygen.

But the radical of rivastigmine can react by various pathways in the formulation. And these pathways depend on the ingredients of the formulation, that is, the chemical environment present.

Q. If the actual reaction pathway can take different routes, how would a person of ordinary skill reasonably expect that oxidative degradation of rivastigmine would occur?

A. Well, it's important here not to confuse two concepts. The first concept is that rivastigmine is susceptible to oxidation. And that's an inherent property of rivastigmine.

The second concept is once rivastigmine is oxidized such as here, it can react by a various path, but that's irrelevant to the initial step. It's irrelevant to the susceptibility.

The different paths the rivastigmine radical can take later can lead to various different products.

Q. Are there other sites on rivastigmine that a person of ordinary skill in the art would expect to be susceptible to oxidative

degradation?

A. Yes, they are. And if you can go to the next slide, please.

What you see here is the structure of rivastigmine. And you talked about oxidation, other sites. But if you see here, it's a tertiary amine, and it's very well known that tertiary amines are susceptible to oxidation.

Q. Are all drug molecules that contain a benzylic carbon hydrogen bond at a tertiary carbon, that is also eight immediately adjacent to tertiary amine susceptible to oxidative degradation?

A. They're all generally susceptible to oxidation.

Q. Do all drugs that contain a benzylic carbon hydrogen bond that is adjacent to a tertiary amine necessarily degrade by oxidative degradation?

A. No, they do not necessarily degrade. It depends very much on the makeup of the formulation whether they degrade or not.

Q. And what do you mean by the "makeup of the formulation"?

A. So, for example, we can design formulations in different ways. We can design formulations which are totally devoid, let's say, of initiator of oxidation. We can design formulations which are devoid of oxygen.

We can design formulations in which we produce salt forms such as with the tertiary amine here for rivastigmine.

We can also design formulations in solids. And in general, reactions in solid are slower than in liquids. And, ultimately, we can add an antioxidant. So all these five possibilities would lead practically to less oxidation.

Q. Would a person of ordinary skill in the art expect that rivastigmine would be susceptible to oxidative degradation in transdermal formulation?

A. Oh, yes. Again, it's important, the susceptibility of the molecule doesn't change no matter in what formulation we put it.

The susceptibility to oxidation is an inherent property of the molecule and that goes into every formulation.

Q. Dr. Schoneich, would a person of ordinary skill in the art in 1998 have been surprised if he or she observed oxidative degradation of rivastigmine?

A. Not at all. A person would have not been surprised.

Q. Dr. Schoneich, I'm putting a structure of rivastigmine back central on the screen. We've talked a lot about susceptibility to rivastigmine and oxidation.

Would a person of ordinary skill in the art expect rivastigmine to be susceptible to any other degradation issue?

A. So, yes, potentially. What we have done so far, we have inspected only the right-hand side here of the molecule. But if you look to the left-hand side, and that is highlighted in orange, we see a carbamate function.

Now, in general, carbamates are susceptible to hydrolysis. But specifically with rivastigmine, that is less of an issue because in this carbamate, the nitrogen contains two alkyl substituents and such carbamates are less susceptible to hydrolysis.

Q. Would the presence of the carbamate group on the left-hand side of rivastigmine affect a person of ordinary skill's opinion regarding the susceptibility of rivastigmine to oxidation?

A. No, it would not.

Q. And why is that?

A. The presence of the carbamate here would not change the concepts which I had illustrated before, which are basically the adjacency to the aromatic ring, the electron delocalization and the adjacencies to these other function groups which support oxidation.

Q. Dr. Schoneich, are you aware that Novartis' expert has asserted that the compound called physostigmine bears on the person of ordinary skill's understanding of whether or not rivastigmine is susceptible to oxidative degradation?

A. I recall that.

Q. And are you also aware that Novartis' expert has asserted that the compound called neostigmine bears on the person of ordinary skill's understanding of whether or not rivastigmine is susceptible to oxidative

degradation?

A. I recall that.

Q. And do you have an opinion whether information on the stability or instability of physostigmine or neostigmine would have affected a person of ordinary skill in the art's understanding of whether rivastigmine would be susceptible or not to oxidative degradation?

A. I have an opinion.

Q. And what is that opinion?

A. My opinion is that the structures of physostigmine and neostigmine are sufficiently different to rivastigmine and have no direct impact on the oxidation susceptibility of rivastigmine.

Q. Did you bring a slide explaining that?

A. Yes. So, again, we need to walk through this carefully.

What you see here are the three structures of concern. Rivastigmine on the top, physostigmine on the left-hand side bottom and neostigmine here.

Now, all three molecules contain these carbamate groups, but I had already

outlined that in the case of rivastigmine these two alkyl substituents would make hydrolysis not so easy. The same is true for neostigmine.

And physostigmine, hydrolysis would be easy here because there's only one alkyl group. However, most importantly, and in the past slides I've illustrated that the carbon hydrogen bond, the benzylic carbon hydrogen bond in rivastigmine, which makes it so susceptible to oxidation because of the structured features here, and that benzylic carbon hydrogen bond is not present in physostigmine and it's not present in neostigmine.

That's why a meaningful comparison of these compounds with regard to oxidation is not possible.

Q. Dr. Schoneich, other than the basic chemical principles you've discussed, was there anything else in the prior art that may have informed a person of ordinary skill's expectation that rivastigmine would be susceptible to oxidative degradation?

A. Yes.

Q. And to what do you refer?

A. I refer to the molecule of nicotine.

Q. And have you brought a slide showing that?

A. Yes. So you see here the structure of nicotine.

Do you want me to walk you through the special features?

Q. Yes, that would be helpful, I think, to the Court.

A. The important thing is nicotine has a carbon hydrogen bond, which is very similar to the carbon hydrogen bond which we find in rivastigmine.

Q. Now, would a person of ordinary skill in the art look to structurally similar drugs when undertaking formulation development?

A. Yes, of course. Looking at structurally similar drugs would inform the person of ordinary skill in the art of potential problems which could come up with the development of the drug of interest.

Q. Dr. Schoneich, can you please turn to Tab JTX032 in your binder?

A. Yes.

Q. What is JTX032?

A. It is a paper by Robert Linnell on the oxidation of nicotine.

Q. And what does JTX032 disclose?

A. It discloses, and that's illustrated on the next slide, some experiment which Robert Linnell has done towards what's the mechanism of oxidation.

Q. And when did JTX032 publish?

A. It was published in 1960.

Q. Did you review this publication in your analysis of rivastigmine?

A. I did so.

MR. LEVY: Your Honor, Defendants offer JTX032 into evidence.

MR. MINION: No objection.

THE COURT Admitted into evidence without objection.

BY MR. LEVY:

Q. What would a person of ordinary skill in the art have understood from JTX032 of the Linnell paper?

A. Well, if you go to the next slide, please. Here is what Dr. Linnell did. Linnell exposed nicotine to oxygen in the presence of an

initiator. And that initiator here is referred to by AIBN.

Now, under this condition, nicotine was oxidized. Importantly, Linnell concluded that this oxidation of nicotine follows the general mechanism of olefin oxidation and he refers to another paper here.

Now, also importantly, when Linnell added an antioxidant such as butylated hydroxytoluene, nicotine oxidation was inhibited. So, clearly, the addition of an antioxidant was able to inhibit the oxidation of the drug of interest.

Q. Can you explain the chemical similarities between nicotine and rivastigmine?

A. Yes. If you go to the next slide, it's done here.

First of all, please let me outline these carbon hydrogen bonds, benzylic carbon hydrogen bonds, which we have now seen many times. This is highlighted in red.

And a similar carbon hydrogen bond is present in nicotine. Why do I say this? Because both of these carbon hydrogen bonds are

immediately adjacent to aromatic ring systems.

Both these carbon hydrogen bonds are also immediately adjacent to a tertiary amine highlighted in green. And both these carbon hydrogen bonds are also immediately adjacent to another alkyl substituent.

In short, there are so many similarities in the structure between nicotine and rivastigmine that a person of ordinary skill in the art would have clearly taken this as an example for drug development.

Q. Do rivastigmine and nicotine have the same aromatic ring?

A. No, really not. What you see in rivastigmine, this aromatic ring. This is a benzene ring. Whereas in nicotine, this is a pyridine ring.

Q. Does this difference affect your opinion as to whether nicotine is relevant to the ordinary skilled artisan's expectation of rivastigmine's susceptibility to oxidative degradation?

A. That does not affect my opinion.

Q. And why is that?

A. That is illustrated on the next slide. I had previously introduced the concept of electron delocalization. And you remember this was a compound toluene.

Now, if you make that radical here, in nicotine, we have exactly the same possibility of this. We can delocalize the electron, like the hot potato before, into the ring, pass it around the ring and generate these resonance structures.

Q. Would a person of ordinary skill in the art, Doctor, in 1998 draw conclusions about the susceptibility of rivastigmine to oxidation from the nicotine molecule?

A. Oh, absolutely. There are so many structural similarities that the person of ordinary skill in the art would draw conclusions; however, we have to understand these are not identical compounds, but similar enough that these conclusions can be drawn.

Q. Dr. Schoneich, once a person of ordinary skill in the art determines that rivastigmine was susceptible to oxidative degradation, what then?

A. Well, the person of ordinary skill in the

art would have immediately taken precautions in formulation development. And one of the precautions would have been the addition of an antioxidant.

Q. Would a person of ordinary skill add an antioxidant?

A. Well, in 1998, it was well known from the pharmaceutical, but also from the food literature, that antioxidants can prevent oxidation.

Q. And how would the addition of an antioxidant prevent the oxidative degradation of rivastigmine?

A. Well, if you recall the mechanism of oxidation, which we have done, so the initiating radical, and again I would like to walk you through. We have our carbon hydrogen bond. We have our initiating radical. That abstracts the hydrogen from the carbon-hydrogen bond and generates the rivastigmine radical.

Now, an antioxidant principally would be able to react with this initiating radical in competition. That means it would take the initiating radical away from the reaction

with rivastigmine and, in this way, prevent the oxidation of rivastigmine.

Q. Would a person of ordinary skill in the art in 1998 have expected that adding an antioxidant to rivastigmine would prevent oxidative degradation of the drug?

A. Yes.

Q. Would the fact that a drug is actually marketed in a formulation that does not contain an antioxidant as a listed ingredient indicate to a person of ordinary skill in the art that the drug is not susceptible to oxidation?

A. No, it would not. So, as I said before, formulations can be designed in various ways. And if a formulator would prohibit oxidation by other means, and I've said for sure we could remove initiating radicals or initiating compounds from formulations, we could omit oxygen from formulations. We could omit, let's say, metals from formulations. We could formulate in a solid state or we could prepare salt form. Then the formulator could have taken these precautions to prevent oxidation. So the fact that the drug did not show oxidation in those

conditions would not show that it's not susceptible.

MR. LEVY: Thank you, Dr. Schoneich. Noven has no further questions at this time.

THE COURT: All right. Why don't we take our morning break for 15 minutes and come back and do cross-examination.

All right.

MR. MINION: Thank you.

THE CLERK: All rise.

(A brief recess was taken.)

THE COURT: All right. Let's go ahead here.

MR. MINION: It's Daniel Minion, Your Honor.

BY MR. MINION:

Q. Good morning, Dr. Schoneich.

A. Good morning.

Q. There are a few things I would like to make sure I have clear about your testimony today.

And, first, with respect to your opinion that rivastigmine is susceptible to oxidative degradation, am I correct that that

opinion is based on the structure of rivastigmine and what you refer to as general chemical principles?

A. Rivastigmine to oxidation can be deduced from its structure and from general organic chemistry principle.

Q. But your opinion is based on the structure of rivastigmine and general chemical principles, nothing else?

A. Yes.

Q. And when you use the phrase susceptible to oxidative degradation, you mean there is the potential for oxidative degradation at a site in the molecule?

A. What I mean is susceptible is the likelihood of oxidation.

Q. I'm asking you -- you say it's the potential for oxidation; correct?

A. Well, if you translate likelihood as potential, we could say that, but it really means it's the likelihood of oxidation at that place.

MR. MINION: Your Honor, may I approach?

THE COURT: Yeah.

BY MR. MINION:

Q. Dr. Schoneich, I've handed you the transcript of your deposition in this case. If you could turn to Page 18, Line 7 through 13.

"Question: When you use the term "susceptible to oxidative degradation", can you give me a little more of a sense of what that term means to you?

Answer: It means to me there is the potential for oxidative degradation at the site."

A. Yeah.

Q. Is that the question and answer --

A. Yeah.

Q. -- at your deposition?

A. Yes.

Q. You are not aware of any prior art suggesting that rivastigmine is susceptible to oxidative degradation?

A. When I gave my opinion, I was not aware of any prior art.

Q. And you do not know whether rivastigmine is susceptible to oxidative degradation in pharmaceutical compositions?

A. Well, as I mentioned before, the

susceptibility of oxidation is an inherent property of the molecule. Drugs will always be susceptible.

However, whether it actually degrades and at which rate, that depends on how the formulation is made up.

Q. Right. Let's talk about a specific example.

You haven't seen any data that would allow you to answer the question of whether rivastigmine is susceptible to oxidative degradation in a transdermal formulation?

A. I have not reviewed any such data.

Q. You haven't reviewed any of Novartis' stability testing data?

A. I have not.

Q. Nor any of Noven's stability testing data?

A. I have not.

Q. And you're not aware of any prior art? You're not aware of any published articles reflecting stability testing of rivastigmine formulations?

A. I don't recall that.

Q. And you agree with the general principle

that the extent of degradation depends on the chemical environment in which a drug is formulated?

A. So if you have a drug which is susceptible to degradation, the extent to which it actually happens, that depends on the environment.

Q. And that's true with respect to rivastigmine as well?

A. That's true for every drug.

Q. So whether rivastigmine oxidatively degrades in a specific formulation is something that has to be shown?

A. Well, whether rivastigmine is susceptible to degradation that can be deduced from the structure, whether it actually happens, that needs to be shown experimentally and the extent to what it happens needs to be shown experimentally.

Q. And you're not aware of anyone in the prior art testing to determine whether rivastigmine is susceptible to oxidative degradation?

A. Well, you don't need to test for the rivastigmine whether rivastigmine is susceptible

to oxidation. What you need to test for is to what extent it degrades.

Q. But you're not aware of anyone in the prior art testing to determine whether rivastigmine is susceptible to oxidative degradation?

A. I think I just answered that question. The susceptibility is an inherent property.

I'm not aware of any prior art whether someone has actually experimentally verified to what extent rivastigmine degrade.

Q. All right. Let's turn to how you formed your opinion in this case.

In your direct examination, you discussed the person of ordinary skill in the art?

A. Yes.

Q. And you said your definition was important?

A. Yes.

Q. And I just want to be clear: When you contemplate the person of ordinary skill in the art, you do not envision a single individual; right?

A. No. I said a person of ordinary skill in the art can be or is a collaborative team of individuals. And some of them may be chemists, polymer chemists, chemical engineers, pharmaceutical chemists.

There are multiple qualifications. And this team, this group works together to design pre-formulation and formulation.

Q. So your person of ordinary skill in the art is actually a team of scientists with complementary expertise?

A. Yes.

Q. Like a modern pharmaceutical company?

A. Well, like you would have in a team which nowadays develops pharmaceutical formulations.

Q. And it's your opinion that a POSA, your collaborative team of scientists with complementary expertise seeking to formulate rivastigmine in a pharmaceutical composition would choose to incorporate an antioxidant before conducting any testing?

A. So what I've said before when -- and you called it POSA. I think POSA is short for person of ordinary skill in the art. When a POSA is

charged with developing a pre-formulation, the POSA would look at the structure first.

If the POSA recognizes any susceptibility to any degradation, the POSA must immediately include in the formulation development experiments, which would address this issue. In other words, the POSA would design a matrix of experiments to rapidly verify whether degradation such as oxidation is an issue. And the reason for this is that the POSA needs to save time. The POSA cannot do an experiment, wait for the result to come out and then do another experiment. So much time is not given to the POSA in the pharmaceutical company anymore.

Q. You're saying that your pharmaceutical company, your person of ordinary skill in the art would choose to add an antioxidant before doing any testing in order to save the company time?

A. Yes.

Q. And you didn't cite any literature to support your opinion that a person of ordinary skill in the art would choose to add an antioxidant to a formulation prior to determining whether an antioxidant was necessary?

A. I don't cite any references, but these days, we have terms like design of experiments, quality by design, where actually much of these are generated very early on in formulation development in order to make that process rationale and more efficient.

Q. So you didn't cite to a single piece of literature to support that opinion?

A. I did not cite, I think that's well understood.

Q. Now, as I understand it, you were first presented with the structure of rivastigmine and from that structure, you formed your opinion that rivastigmine is susceptible to oxidative degradation?

A. Correct.

Q. Then you looked to see if there were any examples in the literature that supported your opinion?

A. I looked at -- I reviewed the '031 patent and also some references, and some of the references are given in my original declaration and opening report.

Q. We'll get to those in a minute, but you

also did a search of the literature for compounds having a benzylic hydrogen that were susceptible to oxidative degradation?

A. That was after I formulated my opinion, yes, I did a search.

Q. And specifically you searched the terms benzylic, oxidation and stability?

A. I think in the deposition I cite that's what I recall. I think that's what I did, yeah.

Q. There may have been other terms?

A. Yes.

Q. But you searched those terms?

A. Yes.

Q. And you haven't given an opinion in this case as to how many compounds existed as of 1998 that contained a benzylic carbon hydrogen bond?

A. That was not necessary, because again, if I come back to the first principles, just by the structure alone of rivastigmine --

Q. That's not my question, Doctor. My question is you haven't given an opinion as to how many compounds existed as of 1998 that contained a benzylic carbon hydrogen bond?

A. I have not given you any reference or any

number, that's correct.

Q. And you also have not given an opinion as to how many compounds with a benzylic carbon hydrogen bond have been formulated in a pharmaceutical composition as of 1998?

A. I have not.

Q. You are aware, Doctor, that as of 1998, there were several commercially available pharmaceutical formulations of compounds having a benzylic hydrogen carbon that were not reported to contain an antioxidant?

A. Well, I need to go back to my testimony. If a formulation doesn't contain an antioxidant, that doesn't mean that a compound is not susceptible to oxidation. I think I presented before that there are other ways to prevent oxidation.

Q. But you are aware that as of 1998 there were several commercially available formulations of compounds having a benzylic carbon hydrogen bond that were not reported to contain an antioxidant?

A. Are you referring to the compounds listed in Dr. Klibanov's rebuttal?

Q. Exactly.

A. I am aware of these compounds.

Q. In your expert reports, you only cited to two examples of compounds having a benzylic carbon hydrogen bond that are susceptible to oxidative degradation?

A. I did cite two examples.

Q. One of those examples was dextromethorphan, and you didn't mention that today; correct?

A. That's correct.

Q. You only focused on the compound nicotine?

A. That's correct.

Q. And you agree, Dr. Schoneich, that technically speaking, nicotine does not have a benzylic hydrogen?

A. Technically speaking nicotine has a carbon hydrogen bond which is immediately adjacent to a pyridine, so if I can to say the nomenclature, it wouldn't be a benzopyridine or something, I don't know anyway, the aromatic ring is immediately adjacent to the carbon, and I outlined the principles of how electron delocalization can stabilize a radical. So

whether we have pyridine in there or a benzene ring doesn't change the principle.

Q. When you discuss nomenclature, if you look at the IUPAC nomenclature, that's the naming system that chemists use to name compounds, the nicotine is not a benzylic compound?

A. Well, it has features of a benzylic compound.

Q. But it's not a benzylic compound?

A. It's not a benzylic compound.

Q. When you were discussing the benzylic hydrogen, the benzylic carbon hydrogen bond in rivastigmine, you referred to quote, three distinct features around that carbon hydrogen bond. Do I recall that correctly?

A. Yes.

Q. And you agree that those features in rivastigmine are chemically distinct from the three features around the carbon hydrogen bond of nicotine?

A. So I would like to outline, first of all, the three main features are very similar. I said they're not identical, but they're very similar. We have our carbon hydrogen bond here which is

immediately adjacent to an aromatic ring. We have --

Q. Dr. Schoneich, my question wasn't whether they were similar, my question was whether they were distinct?

A. So the chemical features around each of these carbons are distinct.

Q. And rivastigmine also has a carbamate substituent on its benzylic ring?

A. It does.

Q. That's the part of the molecule here that you have grayed out?

A. Yes.

Q. And nicotine does not have a carbamate substituent?

A. Yes.

Q. And you agree that carbamate substituent affects the electronic characteristics of the aromatic ring?

A. The carbamate substituents might have minor interferences on the electronic density in this aromatic ring. I would also like to point out that the carbamate appears in the three position compared to the carbon substituent here,

this means it would have at most an inductive effect and no delocalization effect.

Q. Let's talk about nicotine. And the only document that you cited on nicotine was the Linnell paper?

A. Yes.

Q. That's the paper from 1960?

A. Yes.

Q. And it's from the journal Tobacco Science?

A. Yes.

Q. And that paper was provided to you by your counsel?

A. Yes.

Q. If I could get slide 21. And you cited to the last paragraph of Linnell, if we look, if we blow it up, now, if we look at the conclusion of that paragraph, the last sentence the author states, "Further work is underway to isolate the proposed hydroperoxide and provide more details on the mechanism of this reaction."

Do you see that?

A. Yes.

Q. And you didn't find anything in the literature regarding additional studies on the

oxidation of nicotine by Linnell or anyone else?

A. I did not do a very detailed search on this. I think this article is well sufficient to illustrate the principle.

Q. One article?

A. Yeah.

Q. From 1960?

A. Yes.

Q. And you have never studied the oxidation of nicotine?

A. I have never studied the oxidation myself of nicotine.

Q. And you agree that very few detailed studies in regard to oxidative mechanisms of specific pharmaceuticals have been performed as of 1998?

A. I would say very few detailed mechanistic studies have been performed, but the problem of oxidation was very well-known, very well established by 1998.

Q. Linnell, the author, did not study the stability of nicotine in a pharmaceutical composition; correct?

A. I think that specific article does not

refer to pharmaceutical formulation.

Q. He studied nicotine in its pure liquid state?

A. I think so.

Q. And you're not aware of any prior art studies that demonstrate the oxidative degradation of nicotine in a pharmaceutical composition?

A. I have not reviewed this prior art, but coming back to the article you're talking about, I think it's very well shown that nicotine is subjected to --

Q. Again, that wasn't my question, Doctor. You are not aware of any prior art studies that demonstrate the oxidative degradation of nicotine in a pharmaceutical composition?

A. As I have said, I have not reviewed that.

Q. So you're not aware of any?

A. Okay.

Q. And when you cited Linnell for the proposition that the person of ordinary skill in the art in 1998 would have understood nicotine to be susceptible to oxidative degradation, you did not search the literature for information

regarding nicotine transdermal formulations; correct?

A. I think I briefly searched for nicotine oxidation, but I don't think I looked for nicotine transdermal.

Q. But you are now aware that there were commercially available nicotine transdermal formulations in 1998 that did not contain an antioxidant?

A. Yes. But as I said before, that doesn't indicate whether the oxidated compound is susceptible to oxidation or not.

Q. Those three commercially available compounds, sorry, commercially available nicotine transdermal formulations in 1998 were ProStep, Nicotrol and Habitrol?

A. I take your word.

Q. And you will agree that the person of ordinary skill in the art in 1998 presented with the product labels for ProStep, Nicotrol and Habitrol, nicotine transdermal patches would conclude that in those particular formulations an antioxidant was not necessary?

A. Well, in order to conclude this, I would

like really to see the prescription. If you can show them to me, that would be great, but as I said before, a person of ordinary skill in the art from the mere fact that an oxidation issue is not reported in the form of formulation, cannot conclude whether it is susceptible or not because the susceptibility is an inherent property and the formulator may have taken steps to avoid oxidation in another way.

Q. You reviewed the PDR entries for ProStep, Nicotrol and Habitrol in this case; correct?

A. I don't think so. I don't recall. I don't think so.

Q. If you could turn to page 188 of your deposition transcript. Line five to line 20.

A. Yes.

Q. "Question: Well, will you agree with me that the POSA, looking at the formulations of ProStep, Nicotrol and Habitrol can either conclude one of two things: That either nicotine does not require an antioxidant in transdermal formulations or two, that there are other means aside from including an antioxidant from preventing oxidative degradation of nicotine?

"Answer: So from the information given the POSA can only conclude that this particular formulations an antioxidant was not necessary. But the POSA can not conclude anything else."

That was the question I asked and the answer you gave at your deposition; right?

A. Yes.

Q. So in spite of the known susceptibility of nicotine, the compound itself, to oxidative degradation, when it comes to transdermal formulations of nicotine, an antioxidant is not necessary?

A. Well, as I said before, the compound itself is susceptible to oxidation, and the formulation environment will decide whether the actual oxidation happens or not, so in the formulation, a formulator can take steps to avoid oxidation different from adding an antioxidant, for example, the formulator can exclude oxygen, the formulator can avoid the presence of anything that can initiate oxidation. In those cases an antioxidant may not be necessary but the drug is still susceptible to oxidation.

Q. And you agree with regard to the ProStep, Nicotrol and Habitrol formulations in their product labels there was no indication that any means were undertaken to provide oxidation?

A. Well, if I don't have an antioxidant and I don't have oxygen, I don't necessarily need to describe whether I omit oxygen or not, right. And again, before going ahead with this, I have not seen the detailed insert of these packages or these prescriptions, so if you show them to me, I think we can discuss this in more detail.

Q. You agree that a POSA in 1998 could have concluded that the extent of oxidation of nicotine in the ProStep, Nicotrol and Habitrol formulations was at a tolerable level and therefore an antioxidant was not necessary?

A. So in that regard, though, I think in the application process the pharmaceutical company would have probably indicated that oxidation happened. But oxidation if it happens to a very low extent may be tolerable, that is sure.

Q. And a POSA in 1998 could have concluded that the extent of oxidation of nicotine in those formulations was at a tolerable level and

therefore an antioxidant was not necessary?

A. So from the information you're giving me, I cannot conclude that. But again, if you look at the details, I think we can discuss that further.

Q. Can you turn to page 190 of your deposition transcript, line 4 to 19?

A. Yes.

Q. "Question: So with respect to ProStep, Nicotrol and Habitrol, you agree that the POSA in 1998 would not have known whether any steps to reduce oxidative degradation were taken in those formulations?

"Answer: I think what the POSA would have deduced from the structure is that there is an oxidation susceptible site. The fact that antioxidants were not added to these formulations only means that for some reason, they were not necessary, which can include various reasons, either oxidation was prevented by any other means or -- and I haven't seen the details on this, on these studies -- or that oxidation was tolerated for some reason."

A. Yes.

Q. That's the question I gave and the answer you gave at your deposition?

A. Yeah, and I think I just said the same thing.

Q. And you agree that a person of ordinary skill in the art in 1998 could have selected other means?

A. Yes.

Q. In your opinion, Dr. Schoneich, a POSA in 1998 could have formulated rivastigmine in a pharmaceutical composition without the addition of an antioxidant?

A. For example, yes, they could have taken any other means to prevent oxidation.

Q. And aside from Novartis's Exelon product, you're not aware of any marketed transdermal formulations that contain an antioxidant?

A. I have not reviewed these formulations.

MR. MINION: No more questions, Your Honor.

THE COURT: Any redirect?

MR. LEVY: Yes, Your Honor, just a moment.

THE COURT: All right.

RECROSS-EXAMINATION

BY MR. LEVY:

Q. Dr. Schoneich, a moment ago Mr. Minion directed you to page 18 of your deposition transcript, August 15th of this year. I now want to direct you to the following page, page 19, in which the question --

MR. MINION: Your Honor, is Mr. Levy reading from the expert deposition transcript on redirect?

THE COURT: I think he is going to -- he might be. Let's see what he's doing.

BY MR. LEVY:

Q. I would like to direct your attention to page 19 of your deposition transcript, line 8 through 14. Do you see that?

A. Yes.

Q. Is that refresh your recollection that when you were asked about the potential for oxidative degradation, you clarified that you understood that to mean likelihood?

A. Yes.

Q. And a moment ago when Mr. Minion was asking you questions, you mentioned that the

ordinary skilled artisan perhaps as a collaborative team would have generated as part of the reformulation process matrixes involving different experiments. Did I capture your testimony correctly?

A. Yes.

Q. Is that true for the person of ordinary skill in the art as of 1998?

A. Yes.

MR. LEVY: Thank you. Noven has no further questions.

THE COURT: Thank you. Doctor, you may step down.

All right, I assume you have another witness?

MR. LEE: Yes, Your Honor. Noven calls Dr. Agis Kydonieus.

MR. LEE: Your Honor, there are some outstanding objections to some of the demonstratives that we propose and perhaps we should address them now so as to not impede the flow of his testimony.

THE COURT: All right. What's the nature of the objections? First off, let's just

swear the witness.

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

THE WITNESS: Agis Kydonieus. A-G-I-S, K-Y-D-O-N-I-E-U-S.

AGIS KYDONIEUS, PH.D.,
the deponent herein, having first been duly sworn on oath, was examined and testified as follows:

THE COURT: All right. First off, who are you?

MR. CONDE: Dominick Conde for Novartis. I was at the last iteration of the trials as you may recall.

Our particular objection relates to slide 325 and then there is a series of other slides that have basically the same objection. And -- I'm sorry, I have got the wrong slide. I meant to go to 361. And perhaps you could put that on the screen so we could see. Thank you.

So if you look at the second entry for GB '040, it says rivastigmine composition; structure of rivastigmine suggest susceptibility

to oxidation. Dr. Kydonieus never made in his expert report the opinion that GB '040 discloses or has a statement in it saying the structure of rivastigmine suggest susceptibility to oxidation. And this statement goes throughout the slides, there are several other instances, a series of slides, it's said in other instances.

THE COURT: Sounds to me like he's relied on the last witness.

MR. CONDE: If that's the case, the slide should say --

THE COURT: The slide isn't in evidence; right?

MR. CONDE: Yes, Your Honor.

THE COURT: So that's your only objection to this series.

MR. CONDE: That's the objection to the series.

THE COURT: All right. I'm going to overrule it. Good job, Mr. Coulson.

MR. COULSON: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. LEE:

Q. Dr. Kydonieus, have you ever testified

before in court?

A. No, this is my first time.

Q. Have you ever worked or consulted for Noven?

A. No, I have not.

Q. Have you ever worked for consulted for Kenyon & Kenyon?

A. No, I have not.

Q. How did you first learn about this case?

A. I believe that since I have been around for a very long time in transdermal delivery, somebody recommended me to you, and you got me.

Q. Can you turn to tab one in your binder, DTX 5?

A. I don't have anything here. I think these are Dr. Schoneich's.

MR. LEE: May I hand it up?

THE COURT: Yes. Sure.

BY MR. LEE:

Q. You have DTX 5 in front of you?

A. Yes. Tab one, right.

Q. Yes. And can you identify that?

A. Yeah, that's my curriculum vitae.

Q. Does it accurately reflect your

educational and professional experience and your list of publications and patents?

A. To the best of my knowledge it does accurately show this.

MR. LEE: Your Honor, I would like to move exhibit DTX 5 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MR. LEE:

Q. Let's highlight a few aspects of your qualifications. When and where did you receive your Ph.D. and in what area?

A. I received my Ph.D. in chemical engineering from the University of Florida in 1964.

Q. When did you begin working in the pharmaceutical industry?

A. Around 1970, '72.

Q. Can you briefly describe your industry experience?

A. Right after 1964, I went to work in industry. And I was initially in the laboratory

doing the actual performance with my hands type of work. And later on I moved up the ladder. I was an assistant director, vice-president and then president of several companies.

Q. Can you explain your experience with transdermal drug delivery systems?

A. Yes. I started that kind of work in late '70s, maybe '77, 1977. And that was basically the time that transdermal delivery was being initiated. It was just the start of transdermal delivery. And I have been doing that since that time up to today.

Q. What transdermal products did you work on at that time?

A. We worked in Hercon was my first real job in transdermals. We worked with nitroglycerin patch was one of the first patches that came to the market. We did all the work, sent it to the FDA, we got approval and it was marketed and it's still marketed.

Q. Did you work on any other products that were also submitted to the FDA for approval?

A. Yes. We worked with Clonidine, which is an antihypertensive. We did all the work and we

sent it to the FDA for approval.

Q. While you were at Hercon, did you work on any other transdermal formulations?

A. Yes, part of Hercon was to develop products for the pharmaceutical industry in general.

So we were developing our own products, but most of our work really was in developing products for the pharmaceutical industry. And if you look at my resume, I have all the companies which we work with, which is the main companies in the United States.

We developed at least, I would say, 20 formulations, early-stage formulations in transdermal delivery at that time.

Q. On your resume, it says that you worked at Bristol-Myers Squibb Corporation in 1988 to 1988. What was your experience at Bristol-Myers?

A. At Bristol-Myers, I was vice president of corporate R and D for one of the divisions by the name of Compa Tech. And I was in charge of the group in drug delivery, polymer chemistry, analytical chemistry and a few other things.

Q. Did you --

A. And I was also -- excuse me. I was also a consultant to the pharmaceutical group in the area of transdermal and backup delivery systems.

Q. How many publications have you authored on the subject of transdermals?

A. In general, the total would be about 125.

Q. Can we turn in the DDX 5 to the page of books?

A. Yes.

Q. And can we highlight the three entries there. Yes, those three entries, please.

Can you describe the entries transdermal delivery of drugs Volumes 1, 2 and 3. What was that?

A. I was lucky to be involved right in the beginning when transdermal delivery was being developed. So I basically decided at this point, which was about '83, '84 to publish this volume. I was the editor. So that I can put transdermal delivery in a more scientific basis.

It's a treatise of all known information in transdermal delivery at that time. And it is the first book ever published in transdermal delivery.

Q. Have you written any other books on transdermals?

A. Yes. I have written other books. The last book on my -- you know, here, the last one there.

Q. Can we highlight the last one?

A. That's also in transdermal delivery and it's to modulate skin reactions in transdermals because this has been a major problem that was not addressed in my original books.

Q. And what's the date of this most recent book?

A. That's two now.

Q. And what was the date of your other three books, the first books on transdermal?

A. 1986, I think. '96 -- '86 and '87.

Q. If we turn to the patent section of his resume.

Sorry. I think it's up above or down below. Yes. Okay.

I see from your resume that you have 60 patents and applications, but how many are in the area of transdermal delivery?

A. Last time I looked at it, it was at 35.

Q. On Page 4 of your resume, there's a reference to something called the Controlled Release Society.

Can you explain what that is and what your involvement in it is?

A. Yes. The Controlled Release Society is the Scientific Society for Controlled Release of Drugs and now has thousands of members. But in 1973, I was a co-founder of the Controlled Release Society with a few other guys. We started it as a symposium, which officially was incorporated in 1977 as the Controlled Release Society.

Q. And what is the subject matter of this society?

A. It's to increase the collaboration between scientists in the area of drug delivery including transdermal.

Q. In the course of your work, have you had any experience in dealing with oxidative degradation of pharmaceutical products?

A. On many occasions, especially early on in my Hercon days when we developed a lot of transdermal products for different companies. We

did a lot of work with antioxidants in the area.

MR. LEE: Your Honor, Noven offers Dr. Kydonieus as an expert in pharmaceutical formulation, including transdermal delivery systems and including use of antioxidants to reduce oxidative degradation.

MR. CONDE: No objection, Your Honor.

THE COURT: All right. You may proceed.

BY MR. LEE:

Q. Before we get to the '031 patent prior art, I'd like to generally discuss pharmaceutical formulation. In the context of pharmaceutical formulation, what is stability of a product or formulation?

A. Stability relates to the ability of the formulation to be able to remain stable, which means to have the same efficacy and safety for the life of the product. So if your product is a two-year product, you want -- stability will tell you basically that your product is effective and safe for that two-year period.

Q. When is the stability considered in the

formulation process?

A. It's considered very, very early on as soon as you have some formulation prepared, because you've got to look at the chemical structure of the molecule and see if it is susceptible to oxidation or hydrolysis, and take the precaution of what you have to do to establish a formulation that's stable.

Q. And in January of 1988, was testing for stability required by the FDA?

A. Yes, of course.

Q. Were you here in Court when Dr. Schoneich testified about the practice of formulators to make a matrix of formulations and to test them early on in the formulation development?

A. Yes, I was.

Q. And is that your experience?

A. Yes, it is.

Q. Let's talk more specifically about transdermal formulation. So what is the role of product stability in the context of transdermal products?

A. The stability in transdermals is the same really as other pharmaceutical formulations

except perhaps in transdermals, it's a little more stringent or more difficult because the drug has to remain in solution in the transdermal patch. So you cannot have crystals or something like that which are less susceptible to oxidation or susceptible to breaking down.

So it's a little bit more difficult but similar to other pharmaceutical formulation.

Q. Are there advantages of transdermal formulation as opposed to other methods of drug delivery such as oral or injectables?

A. Yes, of course. With transdermals, the drug goes directly into the systemic circulation and it bypasses the liver, which we call the first pathway and delivers the drugs and metabolizes. So you may lose in the case of advancing it.

I don't know if I should say that but you lose 66 percent of your drug going through the delivery. So in transdermals, you put all of your drug right into the systemic circulation. So that's one advantage.

A second advantage would be that you bypass any issues directly to the stomach like

ulcers and so on or nausea. And the transdermals you don't have to worry about that.

And another major advantage is that you deliver the drug very slowly so you eliminate the peaks and valleys of oral delivery or the bolus delivery of injections, which usually cause the problems of side effects. Because when you put a bolus, you get a lot of drug immediately and that causes a problem.

In transdermal delivery, as I said, you deliver the very slowly for a very long period of time, so that you have patches from one day to as long as seven days.

Q. Are there any particular advantages of transdermal administration in the context of patients with dementia?

A. Probably they will be a little bit more important because dementia people don't have the memory to take their pills, and also, they can't swallow, as I understand it. So it would be very good for the patient to be able to put a patch on once a day.

Q. With that brief background, let's turn to your opinions in this case. I understand you

have two opinions regarding the invalidity of the '031 patent.

A. Yes. There are two and we have a demonstrative for that.

Q. Can we put up DDX 302? And what are your opinions?

A. Well, my opinions are that the asserted claims 7 and 16, which are the only ones that we have now of the '031 patent, would be obvious to a POSA by the date of the filing of the '031 patent.

And the second one is basically that the same claims would have been obvious to a POSA because of patent '176.

Q. Okay. Are you aware that the Court has construed several of the claims of the '031 patent?

A. Yes, I am.

Q. Did you apply those claim constructions in reaching your opinions?

A. Yes, I did.

Q. Can we put up DDX 356? Are these the claim constructions, the ones that you applied?

A. Yeah, they are.

Q. Can we put up DDX 369?

Are you aware of the following four factors and did you apply them in rendering your obviousness opinions as to claims 7 and 16?

A. Yes, I did. I checked the scope and content of the prior art and then I checked the differences between the claims and the prior art. And I used the level of ordinary skill in the art at the time that the patent was filed.

MR. LEE: Your Honor, by agreement, the parties are not going to put on a secondary consideration case.

THE COURT: All right.

BY MR. LEE:

Q. So regarding the third point, the level of ordinary skill in the art, what are the skill or skills that are relevant to pharmaceutical formulation?

A. Excuse me. Could you repeat that, please?

Q. Yeah. What are the skills that are relevant to pharmaceutical formulation?

A. Yes. Again, I think as Dr. Schoneich also mentioned and I think that just happens to be in agreement with what I think is basically a team

of people that have complementary skills to be able to develop the pharmaceutical composition. And certainly one of them has to be an organic chemist to be able to see what is the structure of the molecule and mechanism perhaps of the degradation.

And one has to be a formulation expert for being able to know all the ingredients, excipients and so on, and combinations thereof that could make the product a better formulation.

Q. Were you here in court when Dr. Schoneich testified regarding the definition of one of ordinary skill in the art?

A. Yes, I was.

Q. And is your definition the same?

A. It just happens to be the same because I honestly never heard from him that definition before.

Q. Have you worked as a member of a collaborative team in your experience in the industry?

A. Yes, always. It happens, for example, we developed a lot of transdermal formulations. We

had a team.

Q. On that team, were you the organic chemist?

A. No, absolutely not.

Q. Would one of ordinary skill in the art have been motivated to develop a rivastigmine transdermal system in January of 1998?

A. Please repeat that. I'm sorry.

Q. Would one of ordinary skill in the art have been motivated to develop a rivastigmine transdermal system in January of 1998?

A. Yes, they would have been. And I think we have a demonstrative, too.

Q. Can we put up DDX 322? What does DDX 322 show?

A. This shows the motivations for developing a rivastigmine transdermal system and it shows basically that, up to that point, it was known that transdermal delivery was useful in the treatment of Alzheimer's disease. It was known that the existing formulations needed improvement, that a transdermal system was shown and it was expected to solve these problems.

So a POSA would have been motivated

to develop a transdermal system.

Q. Let's discuss the bases for those opinions. Can we turn to Tab 8, JTX 11. And can you please identify it?

A. Yes. This is Safety /Tolerability Trial of SDZ ENA 713 In Patients with Probable Alzheimer's Disease.

Q. Okay. And what is the date of this article?

A. The date is 9, February 1996.

Q. Who is the lead author on this article?

A. The lead author is Sramek and I recall his article. This is the Sramek article.

Q. In the title of the article, it refers to a trial of SDZ ENA 713. What is that?

A. That is rivastigmine.

MR. LEE: Your Honor, I move JTX 11 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Hold on a second. Which tab is that?

MR. LEE: Tab 8.

THE COURT: All right. Admitted

without objection.

BY MR. LEE:

Q. We have the first page of this up on the screen. It talks about -- the title is there. And can you tell me what the purpose of the study is, which is described in Sramek as SDZ ENA 713?

A. The purpose of the trial was a phase two clinical trial which was to determine the safety and tolerability of rivastigmine on humans.

Q. Would Sramek have motivated a person of ordinary skill to work with rivastigmine?

A. Yes, of course. It is indicated that it was being tested, rivastigmine was being tested for Alzheimer's Disease. And it also indicated that tolerability was okay.

Q. What was the dosage amount being indicated in the Sramek study?

A. I believe there were three milligrams to 12 milligrams per day.

Q. And how many times a day was rivastigmine administered in that study?

A. In that study, they said two to three times per day.

Q. Can we highlight on the summary the

sentence that starts, "Fifty AD patients"? It says there, that rivastigmine was administered bid or tid. What does that mean?

A. In oral delivery, bid means twice a day, and tid means three times a day.

Q. Were there any drawbacks to the rivastigmine formulation studied by Sramek?

A. Yeah. Well, this, what we just said, is a very big drawback. Taking a pill three times a day is certainly not optimum.

The patient compliance would be next to zero. So that's a major problem, yes.

Q. Let's turn to another reference. Can you turn to Tab 13 in your binder. JTX 25. And please identify that.

A. Yeah. This is the Formulary article. And the title is New acetylcholinesterase inhibitor shows promise in largest Alzheimer's trial to date.

Q. What is the new inhibitor that is referred to in the formulary article that showed such promise?

A. That is rivastigmine.

MR. LEE: Your Honor, I move to

admit JTX 25 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MR. LEE:

Q. Would the formulary article have motivated a person of ordinary skill to work with rivastigmine?

A. Yes, it would have. It's the largest trial in Alzheimer's trials. So, by itself, it would give an incentive to work on it.

There are other items in there. It shows that the project was filed with the FDA for approval as a to-date product, I believe. And several other items that are in this article that would make a POSA interested in developing the product.

Q. Can we highlight the last paragraph on that page? And there's a reference that says, "To date, there have been no head-to-head comparisons of the two drugs." What drugs are we talking about there?

A. Right. Well, the donepezil was another

second-generation inhibitor and it was approved already.

And the advantage of that product was that it was once-per-day dosage versus the rivastigmine, which, in this particular trial, was twice a day. But both drugs had been shown to be more effective than the first-generation formulation, acetylcholinesterase inhibitor tacrine.

Q. Would one of ordinary skill in the art have been motivated to work with rivastigmine on the basis of the advantages over the first-generation drugs and the disadvantage compared to donepezil?

A. Yes, of course. It shows that it is a very good drug except that it has a problem in the delivery of it.

Q. Can we highlight a paragraph on the first column, the one starting with the reported findings? Yeah, that one.

What was the dose of rivastigmine that was used in this study of the effectiveness of rivastigmine?

A. It was one milligram to 12 milligrams per

day.

Q. Can you turn to tab ten in your binder, which is JTX 019?

A. Yes.

Q. This is already in evidence.

A. Yes.

Q. Let's see. This is the GB 040 patent application.

So what does GB 040 disclose that's in interest in this case?

A. First of all, it gives the motivation to really modify these doses issued with rivastigmine to give us a better product with a transdermal delivery product. But this document has a lot of advantages where we can talk about, but the first document that shows rivastigmine and the structure of rivastigmine, which is shown in the document there.

And, also, it shows how to obtain the rivastigmine from the racemic nature of RA7, which is a very simple chemical separation.

Q. Let's turn to Tab 10. Let's see.

Page 1 of GB 040 and there is a chemical name there,

(S)-N-ethyl-3-(1-dimethylamino)ethyl-N-methyl-phenyl-carbamate.

What does that refer to?

A. That is rivastigmine.

Q. And there's a structure there. And what is that structure?

A. That's the rivastigmine structure.

Q. Let's turn to Page 2 and let's highlight the first paragraph there. There's a reference to RA7.

What is that?

A. RA7 is the racemic mixture of rivastigmine.

Q. And what does the GB 040 teach about the relative advantage of rivastigmine and RA7?

A. Well, first of all, it indicates that rivastigmine is a better inhibitor than the racemic as well as the positive, as the plus, the enantiomer. And it also indicates that it has marked and selective inhibition of the acetylcholinesterase.

Q. So I've highlighted on the screen a passage from Page 2 of GB 040. It says, It has now surprisingly been found that the (-)

enantiomer of formula I exhibits a particularly marked and selective inhibition of the acetylcholinesterase.

What is the (-) enantiomer of formula I?

A. That's rivastigmine.

Q. And it says here that it exhibits a particularly marked and selective inhibition of the acetylcholinesterase.

Is that a good thing or a bad thing?

A. That's a very good thing.

Q. And why is that?

A. Because that's the way those drugs work, by inhibiting the acetylcholinesterase activity.

Q. Does GB 040 disclose methods of administration of rivastigmine?

A. Yes, it does on example two. It shows a transdermal delivery system.

Q. Does GB 040 discuss the relative advantages or disadvantages of transdermal delivery?

A. Yes, it does as well. Yes.

Q. Can we turn to Page 13 of GB 040 and can we highlight the paragraph at the bottom?

The paragraph that starts, "Moreover, it has been found that transdermal administration of the compounds for administration according to the invention induces a long-lasting and constant inhibition of acetylcholinesterase activity as indicated in standard tests, with a slow onset of action, which is particularly advantageous with respect to the tolerability of these compounds", does that relate to the advantages or disadvantages of transdermal delivery?

A. It is the advantages of transdermal delivery. And as I mentioned before, transdermal delivery is long lasting and it's constant delivery.

Q. Why is that an advantage that it's long lasting?

A. Well, long lasting because you can make a one-day product, which up to now rivastigmine did not have such a product.

Q. And why is it an advantage that there is constant inhibition?

A. It's a constant inhibition because it gives you lower levels to be inhibiting enough

without giving you the peaks and valleys, as I mentioned, that is the case with oral or the bolus system, which is the case with injectables.

Q. Why is it an advantage that you have slow onset of action?

A. Because you get less side effects. Tolerability is better.

Q. Let's turn to example one, which is on Page 11. Blow that up, please.

What does this teach one of ordinary skill in the art?

A. This is the method that he used to separate rivastigmine from the racemate, the RA7. And he used -- he indicated something in the specification that was a simple and standard kind of method of doing it.

Q. Would one of ordinary skill --

A. Can I -- excuse me. Could I have some water because I'm getting --

Q. Of course. Is there water in that pitcher there?

A. But there is nothing else to drink it from.

MR. LEE: May I approach?

THE COURT: Yeah, bring him some water.

THE WITNESS: Thank you.

BY MR. LEE:

Q. Okay. Are you okay now?

A. I'm okay.

Q. Would one of ordinary skill in the art aware of the Sramek and formulary article have been motivated to do further development the transdermal formulation that is disclosed in GB '040?

A. Of course.

Q. And why would they have been motivated to further develop it?

A. Because the formulation that we have in example two is not a finished formulation, it is an initial formulation, so they would have to continue developing that formulation. I don't know if I answered your question.

Q. That's fine.

Do you have an opinion as to whether a person of ordinary skill in the art would have been motivated to add an antioxidant to a rivastigmine formulation device?

A. Yes, that's the first thing we do if we know that the molecule is susceptible, and the molecule that GB '040 shows us, which was on the first page, indicates that that molecule is susceptible to oxidation.

Q. Can we put up DDX 323. Does DDX 323 set forth reasons why a person of ordinary skill would have been motivated to add an antioxidant to a rivastigmine transdermal system?

A. Right. Because the system was known from example two. Also prior art that we have not discussed yet, it shows that an antioxidant was used in rivastigmine formulations, and the molecules rivastigmine as Dr. Schoneich talked about this morning is susceptible to oxidation, so the POSA would have been motivated to do that.

Q. Let's turn to your susceptible to oxidation point, point two. And have you prepared a summary of the reasons why a person would have considered rivastigmine to be susceptible to oxidative degradation?

A. Yes, I have.

Q. Can we display the reasons. Does 325 set forth those reasons?

A. Yes.

As I mentioned, and I don't want to talk more than that because Dr. Schoneich is better than me in the area, the chemical structure of rivastigmine tells us that rivastigmine is susceptible to oxidation.

Secondly, another molecule, nicotine, again, Dr. Schoneich told us, has great similarities to rivastigmine. And I will try to show you some aspects of that in transdermal delivery.

And then I would like to indicate several prior art references like Elmalem, the '807 patent, Sasaki, Ebert, and GB '040, which in effect tell us that an antioxidant was used or it has to be used.

Q. Were you in the courtroom when Dr. Schoneich testified regarding the chemical structure of rivastigmine?

A. Yes, I was.

Q. In your opinion, would one of ordinary skill in the art in 1998, namely a team including an organic chemist as you have defined it have known about the susceptibility of rivastigmine to

oxidative degradation?

A. Yes, I do.

Q. What use would the team of ordinary skill in the art have made of the chemist prediction regarding rivastigmine?

A. Well, as I mentioned before, the first thing we do is we use an antioxidant. Now, we also mentioned experimentation, and I can say here that when you want to do some experiment, you use your product without the antioxidant and then you use your product again with two, three levels of antioxidant, different levels, and looking always at the handbook to make sure that you use the right amounts of antioxidant. And you do one week study at accelerated conditions and that tells you if you need the antioxidant or not in that particular formulation. It doesn't say the susceptibility, but in the formulation that you're using the way you're going to do it, do you need it. And it's basically a week or two weeks kind of work.

And if your product doesn't show major oxidation, if you get oxidation of two percent while you heat it at 80 degrees for a

week, then you know that you can use that formulation without antioxidants. If it shows you eight or ten percent, then you look at the formulations that you use antioxidant and you pick up the one that gave you the best results at the lower, lowest amount of antioxidant.

Q. When would the team have done such testing, when in the pharmaceutical development process?

A. Very, very early in the process.

Q. Moving to your second point on DDX 325, can you explain how knowledge of the similarity between the structure of nicotine and rivastigmine would have been used by a person of ordinary skill in the art?

A. Yes. I mean, you look at other structures of other drugs to see if you learn anything about different aspects, not only oxidation. In this particular case nicotine will tell us there is a big similarity between nicotine and rivastigmine as far as oxidation is concerned. So I would be looking to find references that tell me if there is any way that I would understand better how to treat rivastigmine.

Q. Can you turn in your binder to tab 14, JTX 28.

A. Yes. I'm sorry, this is the Ebert patent, the WO 95/24172. And the date is 1995.

MR. LEE: Your Honor, I move JTX 28 be admitted into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MR. LEE:

Q. Let's put up JTX 28 on the display at page 19. And can we highlight the first full paragraph there. What does this page teach a person of ordinary skill in the art regarding the susceptible of nicotine to oxidative degradation?

A. Well, this says the trait of nicotine that was problematic it has a tendency to oxidize in light and air, so immediately you know that nicotine has an oxidation problem. Further down he tells us, he uses an antioxidant to eliminate the problem, and his preferred antioxidant was butylated hydroxyanisole, although he mentioned others at the bottom, all the way to the bottom

including butylated hydroxyanisole, metabisulfate, EDTA and others, and it also gives us the ranges at which the BHT would work, and those ranges are overlapping the ranges of the '031 patent.

Q. Can we highlight the sentence that says during fabrication. Now, Ebert discloses adding an antioxidant during the fabrication of the nicotine patches. Would one of ordinary skill in art have understood from Ebert that antioxidant patches were only used on nicotine during the production process?

A. Of course not.

Q. Let's go back to 325, DDX 325.

In your third point here, you refer to certain prior art, including Elmalem, the '807 patent, Sasaki, Ebert and GB '040. Let's start with Elmalem. Can you turn to page 12 in your binder.

A. Yes.

Q. Can you identify this?

A. Yes. This is the Antagonism of Morphine-Induced Respiratory Depression by Novel Anticholinesterase. And it's dated May 1991.

MR. LEE: Your Honor, I move that JTX 21 be admitted into evidence.

MR. CONDE: No objection.

THE COURT: It's admitted without objection.

BY MR. LEE:

Q. Who are the authors of Elmalem?

A. Elmalem, Chorev, and Weinstock, Marta Weinstock.

Q. Okay. Who is Marta Weinstock?

A. Marta Weinstock was a professor at the Hebrew University Pharmacy College in Israel.

Q. Who is the lead author on this article?

A. Marta Weinstock.

Q. Okay. How does Elmalem suggest to a person of ordinary skill that rivastigmine would be susceptible to oxidation?

A. If we look on page two at the bottom of page two on the left-hand side, it tells us that this study he used RA6, RA7 which is the rivastigmine, and RA15 as well as rivastigmine, physostigmine. On the bottom it tell us all drugs were made up freshly in sterile saline, which included an equal weight of sodium

metabisulfate to prevent oxidation. And to me it indicates that the metabisulfate was to prevent the oxidation.

Q. Did they also include morphine?

A. Yes, it includes morphine.

Q. And what would this signify -- I'm sorry. What would have been the significance of this disclosure to a person of ordinary skill in the art?

A. To me, and I have been a POSA for many years, it would tell me that RA7, which means rivastigmine, because as far as that oxidation is concerned RA7 and rivastigmine have the same properties, that Weinstock used sodium metabisulfate to prevent oxidation in those RA compounds.

Q. Now, let's turn to tab 15 which is JTX 30. And can you identify this?

A. Yes. Antagonism of the cardiovascular respiratory depressant effects of morphine in the conscious rabbit by physostigmine. And it's dated 1981.

MR. LEE: Your Honor, I move JTX 30 into evidence.

MR. CONDE: No objection.

THE COURT: Admitted without objection.

BY MR. LEE:

Q. Let's put up the first page of JTX 30. Can we look at the authors?

A. The lead author is Marta Weinstock which I mentioned before is a professor in Israel.

Q. What did these two studies have in common?

A. They had in common that the group, which is the same group of investigators, tried to see could cholinesterase inhibit some of the side effects of nicotine.

Q. Nicotine?

A. Excuse me. Of morphine, my apologies.

Q. What are the differences between those two studies?

A. The difference is that in the 1991, or the Elmalem study, the cholinesterase inhibitors were RA6, RA7, which is again the rivastigmine, and R15 are other compounds because they were invented by that time. And in 1981 she used four different cholesterase inhibitors because the RAs were not invented yet.

Q. Can we put up page 505 of Weinstock. And focus on the second to last full paragraph on the left-hand side. What does this paragraph disclose?

A. This paragraphs tells us what are the drugs she used in the 1981 study which is ATMN, hyosine, neostigmine, physostigmine, morphine.

Q. How does she describe making up the solution for the study?

A. She says that morphine and physostigmine were made up especially for each experiment in sterile saline which included an equal weight of ascorbic acid to prevent oxidation, and the other she did not use an antioxidant.

Q. Have you prepared a demonstrative exhibit to explain the use of antioxidant in these two?

A. Yes, I did.

Q. Can we put up DDX 306.

A. And here in the Elmalem which is in 1991, she used the antioxidant in all the drugs that she tested with. And it's my opinion it's because she knew that RA6, RA7, RA15 were susceptible to oxidation. And then in the 1981, she only used it in morphine and physostigmine,

and in the others did not, and again, I presume she did that because she knew which drugs needed antioxidant and which ones did not.

Q. Do you have a demonstrative which compares the disclosure of Weinstock in 1981 and Emalem?

A. Yes.

Q. Can you explain when this shows?

A. At the top, let's look at Elmalem first. At the top it shows the drugs that were tested, RA6, RA7, RA15, and physostigmine. And underneath it is morphine. And underneath it says all drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulfate to prevent oxidation. On the one Weinstock 1981 side which is to the right, at the top again we see the drugs that's used, atropine, hyosine, neostigmine, physostigmine, I don't know if I'm going to miss any here, morphine, and then it says morphine and physostigmine were made up freshly for each experiment in sterile saline which included an equal weight of ascorbic acid to prevent oxidation.

So as you can see here, the wording is almost the same after ten years except that

the Weinstock, she uses the antioxidant for the two drugs, morphine and physostigmine, and the Elmalem she uses for all the drugs, including morphine and physostigmine, but specifically RA7.

Q. What conclusion would one of ordinary skill in the art draw regarding the meaning of which included an equal weight of metabisulfite to prevent oxidation in Elmalem, in view of which included an equal weight of ascorbic acid to prevent oxidation in Weinstock?

A. It would mean to me that she knew that she had to add sodium metabisulfate in RA7 to prevent oxidation, and since basically in that solution there is nothing else but saline, sodium metabisulfate and RA7, it was used to prevent oxidation of RA7.

Q. What was the antioxidant that was used in Elmalem?

A. Sodium metabisulfate.

Q. And she did not use that in Weinstock 1981?

A. She used ascorbic acid.

Q. Is there any teaching in the prior art that sodium metabisulfate was a preferred

antioxidant as to any of the drugs listed in Elmalem?

A. Yes, Marta Weinstock obtained a patent which we called 087, if I'm not mistaken.

Q. '807?

A. '807. I was mistaken. '807. And that was in 1988, again if I'm not mistaken, but I think it's 1988. And in that patent she indicates that she has -- you can use with the RA compounds, including RA7, you can use stabilizers which are antioxidants. And farther down she says that the preferred antioxidants are sodium metabisulfate and ascorbic acid.

Q. JTX '807 is at tab 9 and I would like to move it into evidence?

MR. CONDE: No objection.

THE COURT: Admitted without objection.

BY MR. LEE:

Q. Can you read that into the record?

A. Can you tell me what tab it is? I'm still looking trying to find it.

Q. Tab nine.

A. Nine. Yes. This is a patent number

4,948,807, with a date of August 1990.

Q. So the question I have for you now is whether the -- what is disclosed on column 11 starting around line 49 regarding the use of antioxidants with any of the drugs listed in Elmalem? What is disclosed there?

A. Well, the prefer antioxidants for use with the compounds of the invention which are the RA compounds, includes sodium metabisulfate and ascorbic acid.

Q. Sorry, I may have misspoke. That was column seven I was referring to.

A. Column seven. My apologies.

Q. And what are the compounds that are claimed in the '807 patent?

A. The RA compounds. The compounds are RA6, RA7, and RA15, and the one of interest to us is the RA7, and that was singularly shown, claimed in claim number three.

Q. So can we highlight claim three, please. Claim three says N-ethyl, N-methyl-3-{1-(dimethylamino)ethyl}phenyl carbamate and pharmacologically acceptable salts thereof. Is that RA7?

A. Yes, that's RA7.

Q. Let's go back to Elmalem. What is the ratio of rivastigmine to antioxidants in the RA7 composition of Elmalem?

A. Give me a second because I have to find -- that's 12. Right. I'm going back to 12. Yes, please ask me the question.

Q. Can we put up page 1060 from Elmalem, again. Can we highlight the same passage again. So my question again is what was the ratio of rivastigmine to antioxidant in the RA7 compound?

A. She indicates as I read before, that they were freshly prepared and included an equal weight of sodium metabisulfate, and we have at the top of that same page that RA7, we had one milligram per kilogram of, so one milligram she uses one milligram of sodium metabisulfate to make one to one. However, RA7 is half rivastigmine, so the ratio of antioxidant to rivastigmine would be one divided by .5, which is two.

Q. Can we put up DDX 314. Does this slide illustrate the calculation that you just gave?

A. Yeah, that's exactly what I said before.

The ratio of the RA7 to antioxidant is one to one, that's what she's telling us. And since RA7 is only half rivastigmine, the other half being the enantiomer, then the ratio of antioxidant used in her formulations were one antioxidant to half rivastigmine, which then give us two parts antioxidant per part of rivastigmine.

Q. You also referred to Sasaki. Let's identify Sasaki for the record. Can you please turn to tab two and identify this document?

A. Yes. This is a certified translation of a Japanese patent that was dated 1984, and inventor is Sasaki.

MR. LEE: Your Honor, I move DTX 12 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MR. LEE:

Q. How does Sasaki suggest to a person of ordinary skill in the art that rivastigmine would be susceptible to oxidation?

A. Yes. Sasaki indicates that drugs that

have amino groups on them are susceptible to oxidation if they're blended with acrylics. Of course we know that rivastigmine has nitrous amino molecules, amino substances on it, trying to find the right word, but I think I found it, so the Sasaki patent --

Q. Let me ask you a question, then. Is it your opinion that rivastigmine is an amino compound or an amine compound?

A. Right, it's an amino compound.

Q. As that term is used by Sasaki?

A. As the term is used by Sasaki. We'll talk about that in a minute, I guess. So rivastigmine would have been a product that would oxidize according to Sasaki if you put it together with acrylic adhesives.

Q. Does Sasaki disclose that there are other methods of preventing oxidation?

A. Yes. He basically says that to protect from oxidation for this kind of products that he's talking about our invention, you have to use antioxidants and his preferred antioxidant was tocopherol.

Q. Can we put up on the board page one, and

can we highlight the last paragraph on the right-hand side. Thank you. I'm going to read part of this into the record. Says here it is possible to prevent the dissipation and photodecomposition of the drug by way of sealing and light shielding with aluminum laminate packaging or the like. First of all, what does he mean by dissipation?

A. Of course, if you need to compactly state it means oxidation.

Q. And what is aluminum laminate packaging?

A. It is one of the best packaging materials we have because the aluminum which is part of the packaging, have aluminum in the middle, and outside you have two layers of the polymer, and that does not allow oxygen and moisture to enter because of the aluminum.

Q. But then he says, so after saying that it is possible to prevent oxidation with aluminum laminate packing, but then he says but with drugs blended with a plaster comprising an adhesive substance as described above. What does he mean by plaster?

A. Plaster is the type of packs.

Q. What is the adhesive substance?

A. The acrylic adhesives.

Q. And then he says, amine compounds and the like, breakdown of the drug will still proceed even with aluminum laminate packaging. What does he mean by that?

A. That means that you don't have to get in his invention, you don't have to get oxygen from the air going into the package, somehow the drug breaks down even if you don't have air coming into the package.

Q. And he says, they are more than a few drugs that cannot withstand usage involving storage for two or three years in the aluminum packaging. Correct?

A. Correct.

Q. And does he describe what kind of drugs those are?

A. Yes, he does. The bottom he does that, but I think it goes on to the next page as well, I believe.

Q. And what kind of compounds, or amino --

A. Amino compounds, he's talking about two compounds, phenolic and amino.

Q. Can we highlight DDX 3, the portion that starts in particular, it's around 15 lines down on the left-hand side. It's on page three. I don't know how to use a laser. In particular, starting there, and going to here. Going to "And the like." A combination of high tech and low tech.

So what does this passage describe relating to amine compounds?

A. It basically tells you the amine compounds that he feels that are, that you know basically or he has tested that are susceptible, and it includes a lot of antihistamines like diphenhydramine as well as Lidocaine, which have the amino groups from what I have looked at similar to rivastigmine.

Q. Thank you.

Can we turn to page two of Sasaki. Can you highlight the paragraph that says, "Under such circumstances." So this paragraph says, "Under such circumstances the present inventors undertook various investigations and discovered that if tocopherol is blended in a plaster comprising an acrylic adhesive substance, if a

drug is blended in said plaster the drug will be stably present without breaking down."

What does he mean by breaking down?

A. Oxidizing, if you use tocopherol as an antioxidant so he uses it to prevent oxidation.

Q. Does Sasaki describe the amount of tocopherol that will solve the oxidation?

A. Yes, he does, that is on page two.

Q. And what is the amount of tocopherol that Sasaki recommends?

A. The amount of tocopherol that he talks about is .005 to 5, and preferably from .05 to 1, with overlap of the amounts in.

Q. Here in Sasaki he's describing these percentages relative in the acrylic adhesives; right?

A. Right. And you have to be able to compare it directly to the '031, you have to transform or translate those numbers to the complete composition in '031.

Q. And when you translate those numbers, how do the ratios described in Sasaki, how do they compare to the ratios in claim one?

A. They are right in the middle of claim one,

yes.

Q. We'll get to that later.

A. Okay.

Q. Let's discuss the first of the two asserted claims, claim seven. Have you prepared an exhibit listing which combinations of prior art render claim seven obvious.

A. Yes, I have.

Q. Can we put up DDX 327? Okay. And can you explain what's shown here?

A. Right. Your Honor, GB 040 we already talked about and the handbook. And optionally with Ebert, Elmalem and the '807 patent. And then the last one is GB 040 with Sasaki.

Q. Can we put up Claim 7 on the board? That's at DDX 334.

And what does Claim 7 claim?

A. Well, Claim 7 claims a transdermal device but is dependent on claim one. So we're talking about a pharmaceutical composition as well containing the -- we can look at that, but basically the two items here that are different is the transdermal device and supported by a substrate.

Q. So let's look at Claim 1. What are the elements of Claim 1?

A. Claim 1 says that a pharmaceutical composition comprising rivastigmine with a diluent or carrier and a percentage of antioxidant from .01 to .5 percent.

Q. And have you prepared a combination of the two showing the elements --

A. I have prepared.

Q. -- of Claim 7?

A. Claim 7 combines both elements.

Q. Can we put that up on the display?

This is DDX 335. Does this exhibit show the combined elements of both Claim 7 incorporating the elements of Claim 1.

A. Correct.

MR. LEE: The '031 patent, Your Honor, is JTX 1 and it is -- it's Tab 4 in the book.

THE COURT: Yeah.

MR. LEE: And I move it into evidence.

MR. CONDE: No objection.

THE COURT: All right. Admitted

without objection.

By MR. LEE:

Q. Now, the first combination that you referred to on your previous slide was GB 040 and the handbook?

A. Yes.

Q. What elements of Claim 7 does GB 040 disclose?

A. Well, it discloses a transdermal device in example two. It discloses a pharmaceutical composition again in example two.

It discloses a therapeutic effective amount that is in the specification. It discloses a diluent or carrier in the example two and it discloses it's supported by a substrate because example two indicates so.

So the only one that it does not disclose is the about .01 to .5 weight of antioxidant.

Q. Let's put up example two of JTX 19, the GB 040. It's Page 19.

And where do you see the diluents?

A. Diluents are Eudragit E 100, Durotack 280, 2416 and Brij 97 as well.

Q. Where do you find the substrate?

A. The substrate is on the bottom. That says spread on top of an aluminized polyester foil. The aluminized polyester foil is a substrate of the patch, transdermal patch.

Q. Where does it disclose a transdermal device?

A. Well, it discloses right at the top, the Example 2 transdermal. But down there is where you cut.

Now, the samples, it says that the film is allowed to dry at room temperature over four to six hours. It is then cut up into patches. Patches, of course, are transdermal devices.

Q. And where does it discuss a pharmaceutical composition?

A. Well, it says composition and talks about compound A, which is rivastigmine. And when you blend the rivastigmine with the other three components, the hydrophilic polymer, the acrylate polymer and the plasticizer, that is a composition.

Q. Can we put up Page 9? You mentioned the

specification disclosed the therapeutically effective amount of rivastigmine. Okay. We have to go down a bit.

A. Yes.

Q. Is this the passage from the specification you referred to?

A. Right. As indicated, daily dosage is in the range from .1 to about 25 milligrams. So .1 to 25 milligrams per day. That's the therapeutic dose that he is indicating.

Q. Does GB 040 disclose an antioxidant?

A. Not explicitly.

Q. Does it implicitly disclose an antioxidant?

A. Yes, it does because Brij 97 at that time contained two antioxidants, BHA and citric acid.

Q. Let's go back to example two on Page 19 and highlight the Brij. Can we highlight the Brij 97? Okay.

How would one of ordinary skill in the art know that Brij 97 included an antioxidant?

A. At that time, when you use Brij or any chemical, you would get a data sheet and that

tells you the components. And that would tell you that it contained the BHA and the citric acid, two antioxidants.

Q. Can we turn to --

A. However --

Q. I'm sorry.

A. However -- okay. I'm sorry. Go ahead.

Q. Let me just direct you to Tab 7, which is JTX 9 in your book. Can you identify this?

A. Yes. This is a patent 5,061, 480 titled Tanning Composition dated October 1991 and which basically gives us information on Brij 97 with the two antioxidants.

MR. LEE: I'd like to admit JTX 9 into evidence, Your Honor.

MR. CONDE: No objection, Your Honor.

THE COURT: Admitted without objection.

BY MR. LEE:

Q. Can you show me the portion of JTX 9 that is relevant?

A. If you look at Column 3, a little bit below halfway --

Q. The portion around Line 37?

A. Oh, yeah, Line 36 or something. Yeah, or 37 maybe.

Q. Can you read the relevant portion?

A. Maybe 38. Maybe 38.

Q. Can you read the relevant portion into the record?

A. Yeah, for the polyoxyethylene 10 oleyl ether with .01 percent BHA and .05 percent citric acid known by the CTFA name of Oleth-10 (Tradename BRIJ 97 and polyoxyethylene.

Q. And what would a person of ordinary skill in the art have understood that sentence to mean?

A. That sentence indicates that Brij 97 contains the two antioxidants, BHA and citric acid and at the levels of .01 percent and. 005 percent.

Q. So what would a person of ordinary skill in the art of the disclosures of DTX 20 -- sorry -- of what is this? JTX, JTX 9 -- have understood about the composition of example two of GB 040?

A. That example two contained some antioxidants or BHA, citric acid antioxidants.

Q. Can you please turn to Tab 3, DTX 89?

Can you please identify this?

A. Yes. This is a manufacturing document for Brij 97.

Q. In your career, have you used documents such as this in the regular part of your business?

A. Yes, I have.

Q. Is this the kind of document that you normally relied on?

A. Yes.

MR. LEE: Your Honor, I move to admit DTX 89 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: All right. Admitted without objection.

BY MR. LEE:

Q. Is there a disclosure of Brij 97 on this document?

A. Yes. On the upper right-hand corner, it shows Brij 97.

Q. Okay. And there's a reference to plant in the upper left-hand corner. What does that refer

to?

A. That is the Atlas Point plant where the product is made.

Q. Do you know what the Atlas Point plant is?

A. Atlas Point plant was a plant in Delaware that was owned by Atlas Chemical Industry.

Q. Where does DTX 89 disclose an antioxidant?

A. Right in the ingredients list, down on the fifth column, it says antioxidant solution 4.8 pounds.

Q. What was the total amount of that, of the Brij 97?

A. It was 12,000 pounds.

Q. And there is some asterisks there next to the antioxidant?

A. Right.

Q. What does that mean?

A. You have to go down to the note and where you have the two stars, it says that particular solution contained 25 percent BHA and 12.5 percent citric acid.

Q. Have you calculated percentage of antioxidants that were included in Brij 97 according to DTX 89?

A. Yes, I did.

Q. Have you prepared an exhibit to explain your calculation?

A. Right. I have.

Q. Can we display DDX 355?

A. I have.

Q. What does this show?

A. Okay. The total weight of the ingredients as we talked about was 12,000 pounds. The antioxidant solution weight was 4.8 pounds.

So 25 percent was BHA and 12.5 was citric acid. So for BHA, you have 4.8 pounds times .25 is 1.2 pounds of BHA. So the percentage of BHA is 1.2 divided by 12,000 times a hundred to make a percent. And it's .01 percent.

And you do the same calculation for citric acid and you get .005 percent.

Q. How does the weight percent of the antioxidants in the Brij 97 manufactured at the Atlas plant compare to the weight percentage of antioxidants in Brij 97, according to JTX 7 of the '480 patent?

A. They're identical.

Q. There's a reference in GB 040 to Atlas Chemie, West Germany?

A. Yes.

Q. And this document is from the Atlas Point plant of Atlas, I think you testified Atlas Chemical Company?

A. Atlas, yes.

Q. Is there a relationship between those two?

A. Yes. I do know that they're -- at the time, they were one company.

Q. Is there any evidence that you're aware of that there was more than one Brij 97 in existence?

A. Not that I know of. I believe --

Q. The '480 patent --

A. Okay.

Q. -- refers to bridge as a trade name of ICI Americas, Inc. Do you know if there's a relationship between Atlas Chemical Industry and ICI Americas, Inc.?

A. Yeah, that I know from personal experience because I'm an old guy, I guess. ICI bought the Atlas Chemical Industries and it was operating under ICI.

So when they bought the product, it was an ICI product. Now the product really belongs to Croda because ICI gave that up.

Q. Novartis contends that one of ordinary skill in the art would have been concerned that antioxidants may have been incompatible with rivastigmine. What is the significance of the fact that Brij 97 included in example two of GB 040 antioxidants?

A. It would show that there is no reason to believe that antioxidants are a problem.

Q. Are you aware of any teaching in the prior art that would suggest that antioxidants would be incompatible with rivastigmine?

A. No, none.

Q. Can we put up DDX 342?

Can you tell us whether DDX 342 accurately reflects the disclosure of GB 040?

A. Again, can you repeat that, please?

Q. Yeah. Can you tell us whether DDX 342, the slide that's up on the board accurately reflects the disclosure of GB 040?

A. Yes, I'm sure that it does. Yes.

Q. Does GB 040 disclose the structure of

rivastigmine?

A. Yeah. I can go through it if you want me to or whatever you want to do. Yes, of course, it does on the first page. It shows the structure.

Q. Is rivastigmine a promising treatment for Alzheimer's?

A. Absolutely.

Q. Does it disclose a therapeutic effective amount of rivastigmine?

A. Yes, it does and we talked about that.

Q. Does it disclose how to separate rivastigmine from RA7?

A. Right. We did in example one.

Q. And does it disclose a transdermal composition containing rivastigmine?

A. Example two.

Q. And does it disclose the superiority of transdermal over oral or injectable delivery?

A. Right. Two or three places I think we talked about, but I'd be happy to go over it if anybody wants to.

Q. We may have to. Let's move on.

Would one of ordinary skill be aware

of GB 040 and recognize that the transdermal system disclose there be required further development?

A. Well, absolutely. The initial kind of product, transdermal product because it doesn't show any work on human skin in vitro or vivo. So, you don't know exactly if you will get the permeation you want.

It does not show even a release liner, which every transdermal product has a release liner to protect the adhesive, to prevent the adhesive from sticking to everything. And it doesn't even contain or talk about packaging film to package this product.

So all of those things indicate that this is an early-stage development and needs a lot more work.

Q. Does GB 040 describe any stability testing of any transdermal system?

A. No, it does not.

Q. Can you turn to Tab 6 and please identify this?

A. Excuse me?

Q. Can you please identify it?

A. Yes. The Handbook of Pharmaceutical Excipients. Maybe I'm a little bit hard of hearing, too.

Q. Maybe I spoke too softly.

Your Honor, we'd like to move JTX 8, which is Tab 6 into evidence.

MR. CONDE: No objection.

THE COURT: Admitted without objection.

BY MR. LEE:

Q. So what is the Handbook of Pharmaceutical Excipients?

A. The Handbook of Pharmaceutical Excipients contains excipients of different kinds that can be used in the pharmaceutical field or they have been used in the pharmaceutical field and in the food area. And they are a source for the pharmaceutical scientists to look and see, hey, this has been used. And it gives you also the ranges you can use, hundred milligrams or whatever.

So the tells you if they have been

used and at what levels for pharmaceutical and food applications.

Q. Let's look at an example of a monograph. Can we turn to JTX 8 at 45?

So this is the monograph for butylated hydroxyanisole or BHA?

A. Right.

Q. Okay. What is disclosed in Section 6 of the monograph?

A. Right. The butylated -- we talked about it a couple of times already. It's an antioxidant.

Q. What is described in or disclosed in Section 7 of the monograph?

A. Well, in Section 7, we see the concentrations that BHA can be used to protect what we have on the left-hand side.

Q. Okay.

A. So essentially oils and we also have topical formulations. And the BHA would be in the range of .005 to .02.

Q. What is the relationship -- let's see. Is the use of antioxidants in transdermal delivery systems disclosed in the handbook?

A. Topical formulations encompass those topics.

Q. And what, again, is the concentration of BHA to be used in topical formulations including transdermal delivery systems?

A. Including transdermal formulation.

Q. What is the concentration?

A. Oh .005 to .02, which really is in the range of the '031 patent.

Q. Remind us: What is the range in Claim 1 of the '031 patent?

A. .01 to .05. .5, excuse me.

Q. Thank you.

Let's highlight Section 12 in the monograph. What does that disclose about BHA?

A. Yeah. It discloses incompatibilities and it does for every antioxidant that I looked at. And it tells you what you can use it with and what you have to worry about.

In this case, it tells you -- undergoes reactions characteristic of phenols. It is incompatible with oxidizing agents and ferric salts.

Q. Does it disclose any incompatibilities

with amine compounds?

A. No, it does not.

Q. Are there monographs in the handbook for all of the antioxidants that are in Claim 16 of the '031 patent?

A. Yes, they are.

Q. Have you prepared a summary chart of the amount of antioxidants that are claimed in Claim 16 as recommended by the handbook?

A. Yes, I have done that.

Q. Can we put up DDX 354?

What does DDX 354 show?

A. Okay. On the left-hand side, we have five antioxidants that are used in Claim 16. And the first one is ascorbic acid and you have the ranges. The range is .01 to .1.

Weight of volume is basically the same as weight to weight. And BHT -- let's look at the topical formulation .0075 to .1.

A-tocopherol .001 to .05.

BHA in topical formulations .005 to .02. And propyl gallate less than .1.

Q. And, again, how did those ranges compare to the ranges that are claimed in Claim 1?

A. All of these ranges overlap the ranges disclosed in the patent '031.

Q. Have you prepared a summary of how GB 040 and the handbook teach the elements of Claim 7?

A. Yes, I have done that.

Q. Can we put up DDX 364? And can you explain using DDX 364 where the elements of Claim 7 are found in GB 040 and the handbook?

A. Correct. The GB 040, as I mentioned, example two, talks about transdermal administration. So we have that.

And it also talks about pharmaceutical composition. We talked about that.

The combination of rivastigmine with the three components that are there, the adhesive and the E 100. It also talks about the therapeutic effective amount that was in the specification section. It is from .1 to 25 milligrams per day.

Let's go to diluent. It describes diluent and as I mentioned Duratack and Eudragit E 100 with diluent and supported by substrate. We talked about that as well. That is the aluminum

foil at the bottom of example two.

Now, going back into the antioxidant, as I mentioned, the structure of rivastigmine, it suggests susceptibility to degradation. And we have the two antioxidants, but not at the level of .01 to .5.

But the handbook now tells us that we can use it in all of the antioxidants that are claimed at that particular level.

Q. Why would a person of ordinary skill in the art have been motivated to combine the handbook with GB 040?

A. GB 040 has the structure rivastigmine right on the first page. And Dr. Schoneich told you that it's susceptible to oxidation.

And because of that, it knows that this is susceptible to oxidation. It will consider as the first option at least in transdermal delivery, the first option being an antioxidant.

Q. Thank you.

What does Ebert add to the combination of GB 040 and the handbook?

A. Ebert describes transdermal patch for the

delivery of nicotine, which as Dr. Schoneich told us, again, is similar to the rivastigmine. And it also shows us that to protect the nicotine from breaking down, he uses an antioxidant. And he shows several antioxidants in his patent.

Q. Now, let's turn to Elmalem and let me turn to Elmalem and the '807 patent. They both describe solutions of RA7, not transdermal delivery systems?

A. Correct.

Q. Why are the '807 patent and Elmalem relevant to Claim 7?

A. They're relevant because in transdermal compositions, the drug has to be in solution. It is in solution. It's not in water solution, but it is in a solution.

And we know that solutions -- we know the susceptibility as Dr. Schoneich told us before, that is a part of the molecule. But it degrades. I mean, if we had it in a crystalline form, the rate of oxidation would be lower. But we have it in solution, so the data that would be obtained from solutions would be optimum to transdermal delivery.

Q. Now, have you prepared a demonstrative to explain the disclosures of Elmalem that are relevant?

A. Yes, I think I have.

Q. Can we put up DDX 341? And please tell us what is disclosed on this slide?

A. It shows that RA7 is susceptible to oxidation and we know that from the structure of the molecule, rivastigmine molecule. RA7 can be prevented from oxidizing by an antioxidants. And that -- we discussed that also.

And RA7, as far as oxidation is concerned, is the same thing as rivastigmine. And the compatibility of RA7 to an antioxidant is very good because they both -- both data, the experiments, and they have not acknowledged any incompatibility.

Q. So let's turn back to the '807 patent, JTX 17 at 9. Given that Elmalem already discloses RA7, what does the '807 patent add to the disclosure of Elmalem?

A. Well, it does not -- does not add very much because it -- they both use sodium metabisulphite.

The only thing that it adds is if somebody has a question about Elmalem, which I understand it was a question about how and why the sodium metabisulphite was used. And the '807 patent makes sure that everybody should understand that the rivastigmine alone was susceptible to oxidation and it needed an antioxidant.

Q. How would the person of ordinary skill in the art determine the amount of antioxidant to put into rivastigmine transdermal formulation to stabilize it?

A. Well, there are a couple of ways. One is to go back into the handbook and see what kind of ranges they're talking for your particular antioxidant. And the other one would be to look at patent literature and some of similar molecules to see what amounts they used. And if you use those, you would have a great probability of success.

Q. In view of the teachings of the '807 patent, Elmalem and Ebert, how would a person of ordinary skill in the art have addressed rivastigmine's susceptibility to oxidative

degradation? What would they have done?

A. Yes. They would have used an antioxidant. That's the first thing that all of these guys did.

They used an antioxidant. And I believe because of my experience that there would not be any problem in having good probability of success.

I honestly have used BHT for many years and I never had any problem with compatibilities with B H T.

Q. Another combination of prior art that you referred to was GB 040 and Sasaki.

A. Yes.

Q. Have you prepared a summary slide regarding the teaching of Sasaki?

A. Yes, I think I have.

Q. Can we put up DDX 343? And can you explain the relevant disclosures of Sasaki?

A. Right. Sasaki discloses that amino compounds are susceptible to oxidation when they're blended or in addition added to acrylic adhesives in transdermal systems.

And the oxidative degradation is not

prevented by packaging impervious to oxygen, but is prevented by an antioxidant. And his preferred antioxidant was tocopherol. And as I mentioned, he had tocopherol. The amount of tocopherol is per unit of acrylic adhesive.

And I calculated the range to the total formulation and those are the numbers that are shown on the bottom bullet.

Q. Before we get to the.

A. .022 to .44.

Q. Before we get to that, can we put Claim 1 up on the board? In Claim 1, it says that the range is 0.01 to about 0.5 percent based on the weight of the composition?

A. Right.

Q. In Sasaki, it says that the antioxidant ratio is based on the amount of the adhesive?

A. Right. So you have to change it to the total composition to be able to compare it apples to apples.

Q. And have you prepared a demonstrative showing that calculation based on the total amount of a transdermal delivery system?

A. Right.

Q. And by which transdermal delivery system did you use as an example?

A. I used the example two of GB 040.

Q. Let's put up DDX 329 and please explain what this shows?

A. This sounds ominous, but it's very simple. Sasaki tells us that we have -- he uses .05 to one percent tocopherol relative to the amount of acrylate adhesive. Now, we have to be able to compare it to the '031 patent that talks about the percent antioxidant to the percent oxidation.

So I took the GB 040, example two, how much acrylic adhesive they use. That was 44 percent. This is an approximate number and could be 50 percent, or 52 or 55. But that's a real number in transdermal delivery. And the only thing I did, I multiply the tocopherol numbers.

Multiply .005, by .44 and got translated to .022 antioxidant to the complete pharmaceutical composition.

And the same thing for the upper limit of tocopherol, which was one percent and that gives you .44.

Q. Why would a person of ordinary skill in the art be motivated to combine the teachings of GB 040 and Sasaki?

A. Well, Sasaki teaches that you use -- first of all, that if you use a material or a drug which is an amino compound like rivastigmine, you use it with acrylic adhesives, you can have the degradation, oxidative problems. And we know that rivastigmine is a compound, amino compound.

And we also know that both GB 040 and the patent '031 use acrylic adhesive, so it's a good reason to combine the two.

Q. Would a person of ordinary skill in the art have had a reasonable expectation that in combining GB 040 and Sasaki they would be able to make a stable rivastigmine transdermal device?

A. Yes, I believe so because he has done that in example one, for example, and -- well, in his examples, example one, two and three. But he saw in tocopherol reduced the oxidation 84 or 95, big, big reduction in oxidation.

Q. Have you prepared a summary to show the combined teaching of Sasaki in GB 040?

A. Yes, I have.

Q. Can we put up DDX 12. Can you use this to explain your opinion?

A. Yes. I think we talked a lot about this. I don't know if I should go into detail, but basically GB 040 talks about a transdermal device. It talks about pharmaceutical composition that discloses the effective amounts of rivastigmine. It discloses the diluent and the support of a substrate and it discloses two antioxidants that Sasaki teaches us that for amino drugs like rivastigmine, the ratio at which at least tocopherol would be successful and that's within the range of the '031 patent.

Q. In your opinion is claim seven of the '031 patent obvious in view of GB 040 and Sasaki?

A. Yes.

Q. Now, less turn to claim 16.

A. Okay.

Q. The only other asserted claim. What are the elements of claim 16?

A. Claim 16 is based on claim 15.

Q. Can we put 15 up on the board, claim 15. What does claim 15, what are the elements of claim 15?

A. Right. Claim 15 is a method for stabilizing rivastigmine by mixing the rivastigmine with an antioxidant to stabilize the rivastigmine.

Q. And what does claim 16 add to claim 15?

A. Claim 16 adds a list of antioxidants, all of them well-known and presented in the handbook, so a list of antioxidants.

Q. Can we put up DDX 339. What does this show?

A. These are all the elements of claim 16 and encompassing the claims of -- the elements of claim 15 as well.

Q. What prior art combinations render claim 16 obvious?

A. I have a demonstrative of that.

Q. Can we put up 328. What are those combinations?

A. GB 040 and the handbook and optionally in view of Ebert or '807 patent, GB 040 and Sasaki, and then Elmalem and the handbook.

Q. Let's talk about GB 040 and the handbook. How does the combination of GB 040 and the handbook, let's put that, the elements of claim

16, which is DDX 339, how does the combination of GB 040 and the handbook render claim 16 obvious?

A. Yes. A method of stabilizing, we have a method, a transdermal method from GB 040, and we have the antioxidant from the handbook, and the mixture would stabilize the product, forming a composition, we have a composition again in example two, and adding the antioxidant from the handbook, we have that.

Again, the amount of antioxidant effective to stabilize, we know this from several-from the handbooks, we are talking about the handbook here, several antioxidants and the amounts that would stabilize the product.

And the antioxidants from the last element, tocopherol, ascorbic acid and all that, they're disclosed in the handbook and the amounts that you have to use to get stability are shown there as well.

Q. Have you prepared a summary -- I'm sorry, I didn't mean to interrupt.

A. I said and they are encompassed in the limits of the '031 patent.

Q. Have you prepared a summary of your

opinions regarding the teachings of this combination?

A. Yes. And that would be better described.

Q. Would you put up DDX 361. And can you tell us your opinions based on the summary set forth on DDX 361?

A. Right. Similar to what I mentioned before, GB 040 is a rivastigmine composition, together with handbook, the common antioxidants. We have that element.

Forming a composition by combining rivastigmine with the antioxidant, we have GB 040 with the rivastigmine composition, and it suggest susceptible to oxidation, so the use of antioxidant used or recommended by the handbook would be obvious. The amount of antioxidants we use, they are delineated in the handbook with different antioxidants. And also the antioxidants list on the last element, all of them are disclosed in the handbook.

Q. Why would one of ordinary skill in the art have been motivated to combine these references?

A. Because the GB 040 discloses the rivastigmine molecule which tells us that the

rivastigmine is susceptible to oxidation, and so using the antioxidants of the handbook is something that will motivate a POSA to do.

Q. What does Ebert add to the combination of GB 040 and the handbook?

A. As I mentioned before, Ebert describes a transdermal patch where he delivers nicotine and he shows that he can use antioxidants to eliminate the oxidation, because nicotine is susceptible to oxidation, so he uses antioxidants to eliminate the oxidation issue.

So it teaches us -- and since the nicotine has similar structures with rivastigmine, he will tell us basically that the antioxidants he uses and the amounts he uses will be something that we have to consider in our determination of what to use in our formulations to get a better probability of success in the antioxidant, a probability of success that we will not get oxidation.

Q. Does Ebert disclose any of the specific antioxidants in claim 16?

A. Yes, he discloses tocopherol, it discloses butylhydroxytoluene, I think it discloses

butylhydroxyanisole. I just don't remember the orders.

Q. Can we put DDX 362 up on the screen. Can you explain what this shows?

A. Right. This is basically the summary of what I was just trying to say. And again --

Q. If you could just focus on the additional elements of Ebert?

A. Ebert, right. Ebert shows us the effective ranges of nicotine, and that is an advantage, and also it shows us the tocopherol, BHT, and BHA are being used in his patent, which are similar to the ones used in claim 16.

Q. Let's turn to the combination of GB 040 and Sasaki with respect to claim 16. Is it your opinion that that combination renders claim 16 obvious?

A. Yes, I believe that it does.

Q. Did you prepare a demonstrative exhibit to explain where the elements of claim 16 are disclosed?

A. Yes, that would be a better way to do it.

Q. Could we put up DDX 370. Can you explain where the elements of claim 16 are found in GB

040 and Sasaki?

A. Yes. Sasaki says that the antioxidants stabilize amino drugs with acrylic adhesive compositions. So that is a method of stabilizing.

Forming a composition by combining rivastigmine with antioxidant, GB 040 talks about the acrylic adhesive in rivastigmine, composition, and Sasaki talks about antioxidants with amino drugs and acrylic adhesives, so there is a motivation to combine those two.

The amount of antioxidants effective, as I mentioned, I did the calculation as a percentage to the total transdermal delivery and they are at the levels of 0.22 and .44 which are effective to stabilize rivastigmine. And finally Sasaki teaches tocopherol, which is one of the antioxidants of claim 16.

Q. Why would one of ordinary skill in the art have been motivated to combine GB 040 and Sasaki?

A. Well, because as I mentioned before, Sasaki teaches antioxidants can be used to prevent the oxidation of amino drugs when they're used with acrylic adhesives. And that's what

patent '031 shows, and we do know that rivastigmine appears susceptible to oxidation, so it is the motivation is there. All the elements are there, acrylic adhesives, the amino groups under the rivastigmine, the susceptibility of rivastigmine, I believe that all the elements are there for the motivation.

Q. In your last answer you said the '031 patent. Did you mean GB 040?

A. GB 040.

Q. Let's turn to the last prior art combination.

THE COURT: Mr. Lee, even though we are near the end of this line of questioning, I think it's time to take our lunch break. So why don't we come back at two o'clock and we'll pick up with more direct examination of Dr. Kydonieus.

MR. LEE: Thank you, Your Honor.

(Lunch break taken:)

THE COURT: All right. Please be seated. Let's continue on.

MR. LEE: Your Honor, my staff has asked me to go back over something, but just briefly. Can we put up DDX 369.

THE COURT: Why don't you wait for your witness.

MR. LEE: Good idea, Your Honor.

THE COURT: All right. Now you may proceed.

MR. LEE: Thank you.

BY MR. LEE:

Q. I didn't ask this one question, but did you in your obvious analysis, did you consider any secondary considerations of nonobviousness?

A. No, I did not. I did in the beginning, but then it was dropped.

THE COURT: I thought the parties have stipulated that was out of the case.

MR. LEE: Just for appeals, Your Honor, I just wanted to make sure that it's clear this is something that has been considered and then dropped.

THE WITNESS: I did, but then it's no more, as I understand.

THE COURT: All right.

BY MR. LEE:

Q. Let's consider the prior art combination which is Elmalem and then the handbook. Can you

explain how the elements of claim 16 are found in Elmalem and then the handbook?

A. We have a demonstrative, that would be the best way.

Q. Can we put up DDX 358.

A. Okay.

Q. Using 358, can you explain your opinion?

A. Yes. Elmalem shows us that the use of an antioxidant added to RA7 saline solution to prevent oxidation, so that's a method of stabilizing rivastigmine. For a composition, RA7 is combined with sodium metabisulfite so that's a formulating a composition. The amount of antioxidant effective to stabilize rivastigmine from degradation, I think as I indicated before is two parts antioxidant to one part rivastigmine which is substantially higher than it's shown in '031, the patent, for example.

So it should be effective to stabilize rivastigmine. And the last element, it's a list of some antioxidants all of which are shown in the handbook, they're common antioxidants.

Q. You mentioned the ratio of antioxidant to

rivastigmine from the '031 patent. Let's put up the '031 patent, that's JTX 1. And can we turn to example one.

Is this a portion of the '031 patent that discloses an effective amount of antioxidant to rivastigmine?

A. Right. This is the one I used, and it says there that alpha-tocopherol was .15 percent and the compound A was 30 percent.

Q. How do you know that was an effective amount?

A. It says insignificant degradation is detected after storage of up to six months at room temperature.

Q. And have you compared that ratio to the ratio disclose in Elmalem?

A. Yes, because the ratio here would be .15 divided by 30, so that's .005, and I think we have that in the demonstrative.

Q. Let's display that, DDX 330. What does DDX 330 show?

A. It shows that the Elmalem has a ratio of antioxidant to rivastigmine of two, and the '031 patent has a ratio of .005. So basically we're

saying that the amount of antioxidant in Elmalem is sufficient to stabilize the product.

Q. Why would a person of ordinary skill in the art have had an expectation that the addition of an antioxidant would prevent oxidative degradation of rivastigmine?

A. Well, there are several reasons for that. '176 shows the structure of rivastigmine, and as Dr. Schoneich told us already it's susceptible to oxidation, and there are several prior art pieces that we already talked about that use antioxidants to protect from oxidation, specifically for rivastigmine and similar compounds as in the case of nicotine. So looking at all these in total it would be obvious that the addition of an antioxidant is not something unique.

Q. Can we put up DDX 368, please.

MR. CONDE: Objection, Your Honor. Outside the scope of his report.

MR. LEE: Your Honor, he reviewed the '031 patent, I'm just going to ask him whether these references are disclosed on the front page of the '031 patent.

THE COURT: All right. Whether it's inside or outside the report, I can look at the patent itself and probably figure that out, so why don't you do that so I don't have to do that.

MR. LEE: Exactly.

BY MR. LEE:

Q. Are any of these references that we've discussed this today, the Sramek, Formulary Art, Ebert, Sasaki, Weinstock, any of those before the examiner during prosecution?

A. None of them was.

Q. I now would like to turn to the second opinion that the asserted claims would have been obvious to one of ordinary skill in the art over the '176 patent. Can you please turn to tab 11 in your book and identify that. Do you have tab 11 there?

A. Tab 11?

Q. Yes, tab 11.

A. Yes.

Q. JTX 20?

A. Yes, that's patent 5,602,176, Phenyl Carbonate, February, 1977.

MR. LEE: Your Honor, I moved to

admit JTX 20 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: All right. Admitted without objection.

BY MR. LEE:

Q. Can we put up the '176 patent. Dr. Kydonieus, can we focus on the assignee part of the first page. Who does it list as the assignee?

A. Sandoz, Limited.

Q. Who is the current owner of the '176 patent?

A. Novartis AG.

Q. Please turn to tab five in your exhibit binder.

A. Yes.

Q. Can you identify this?

A. Yes. This is a patent assignment for patent number 5,602,176.

MR. LEE: Your Honor, I move exhibit PTX 210 into evidence.

MR. CONDE: No objection, Your Honor.

THE COURT: All right. Admitted without objection.

BY MR. LEE:

Q. On the first page of the assignment history, can we look at assignment two, and who are the assignor and assignee listed?

A. They are -- the assignor is Sandoz LTD, and the assignee is Novartis AG.

Q. Now, if we can put back on the screen JTX 20. Who is the inventor of the '176 patent?

A. Albert Enz.

Q. What is the relationship between the '176 patent and GB 040 that you previously testified about?

A. I believe that they are the same patent, that the GB '040 was filed in the UK, and this is what was filed in the US.

Q. Have you compared the disclosures of the '176 patent and GB 040?

A. Yes, I have, and they're very, very similar.

Q. Which claims of the '176 patent render claim 7 and 16 obvious?

A. One, three, eight and eleven.

Q. So let's go through these claims. Can we look at Claim 1?

What does Claim 1 cover?

A. Claim 1 is the molecular structure of rivastigmine.

Q. Please explain what Claim 3 covers.

A. The Claim 3 covers a composition comprising rivastigmine with pharmaceutical carrier or diluent.

Q. What does Claim 8 cover?

A. Again, Claim 8 is dependent on Claim 3, which is dependent on Claim 1. But this one covers a systemic transdermal therapeutic pharmaceutical composition containing rivastigmine and a carrier suitable for transdermal delivery.

Q. And let's look at Claim 11. What does that cover?

A. That is, again, based on Claim 8 and it's a systemic transdermal pharmaceutical composition of Claim 8 with an acceptable carrier.

Q. Let's put up the slide, DDX 355 with the elements of Claim 7 and the claims of the '176 patent. And can you identify which elements of

Claim 7 are found in Claim 11 of the '176 patent and its parent claims?

A. Yes, I can do that.

Let's see, transdermal device that would be covered by Claim 11. Should I continue?

Q. Yeah.

A. Okay. Pharmaceutical composition is shown in, for example, Claim 3 because it's talking about rivastigmine combined with the carrier or diluent.

Therapeutic amount of rivastigmine is shown in Claim 8. And I can read that in there. It's comprising a therapeutically effective amount of rivastigmine.

Diluent or carrier is in, of course, three and eight and supported by substrate. That would be something that -- oh, it's not there distinctly, so...

Q. Okay. Regarding the therapeutically effective amount of rivastigmine, is a therapeutically effective amount of rivastigmine disclosed in the specification?

A. Yes, that was discussed before and that's .1 to 25 milligrams per day.

Q. Can we put up Column 5 of the '176 patent? This is going to be JTX 20.

And this sentence at Line 10 to 15, is that the disclosure of the therapeutically effective amount of rivastigmine?

A. Yes. .1 to about 25 milligrams a day is the dosage that was mentioned.

Q. So what are the differences, if we can go back to the previous -- yes.

What are the differences between Claim 7 of the '031 patent and Claim 7 of the '176 patent?

A. The differences are two. Supported by substrate and about .01 to about .5 weight percent of antioxidant.

Q. Would the differences between Claim 7 of the '031 patent and Claim 11 of the '176 patent have been obvious to a person skilled in the art?

A. Yes, I believe that they should be. Certainly, support for substrate in a transdermal device is. Every transdermal device has a support, a substrate, so that you don't even need to -- because there's no transdermal patch, there's no substrate.

So the last one that is mentioned there is the antioxidant, and in that particular range and we know from Claim 1 that shows rivastigmine -- that the rivastigmine is susceptible to oxidation. We all know now and there are several other prior art pieces that I have discussed like the Sasaki patent that in all of these are overlap, the range of .01 to .5. So it would be obvious to a POSA to do those things.

Q. Would a person of ordinary skill in the art rely on the structure of rivastigmine which was shown in Claim 1 of the' '176 patent?

A. For?

Q. For considering whether Claim 7 would have been obvious?

A. Yes, one. One of the items.

Q. Let's turn to Claim 16. How does Claim 16 of the '031 patent differ from the claims of the '176 patent? Maybe we can put up on the board the elements of Claim 16.

A. So tell me the question again.

Q. How does Claim 16 of the '031 patent differ from the claims of the '176 patent?

A. Okay. The difference is that the '176

patent does not show an antioxidant. And this basically carries through these elements.

However, as I indicated before, a POSA would be -- it would be secondhand for the POSA to really use an antioxidant with the elements found in '176.

Q. So let's make sure I have this answer on the record. Would the difference between Claim 16 of the '031 patent and the claims of the '176 patent have been obvious to a person of ordinary skill in the art?

A. Yes. It would be obvious to a POSA.

Q. And please explain again why.

A. Because, again, we know that in '176, the rivastigmine structure is shown. And we know that it is susceptible to oxidation.

And we have also several patents that we talked about and -- other articles and other patents that we show that they provide antioxidants for stabilizing rivastigmine.

So all of that together will tell a POSA that it's obvious that he has to use an antioxidant.

And the last one -- by the way, just

to complete this, the last one is several antioxidants, which are well-known standard antioxidants or the most common ones.

MR. LEE: Your Honor, I have no further questions.

THE COURT: All right. That's good. Any cross-examination?

MR. CONDE: Yes, Your Honor. May we approach the witness, Your Honor.

THE COURT: Sure.

CROSS-EXAMINATION

BY MR. CONDE:

Q. Good afternoon, Dr. Kydonieus. We haven't met before, but my name is Dominick Conde and I'll be asking you a few questions this afternoon.

A. Sure.

Q. Dr. Kydonieus, you're not an expert in organic chemistry; correct?

A. Correct.

Q. And with regard to organic chemistry issues, you would defer to an expert in that field; right?

A. Yes, I would.

Q. In this case, you're deferring to Dr. Schoneich?

A. Correct.

Q. And it's your opinion that a person of ordinary skill in the art would be able to make reasonable predictions about the physical properties of a drug based on its chemical structure; right?

A. Well, of course it depends on what properties you're talking about, but yes.

Q. But you have not provided your own analysis of the general chemistry principles that would have let a person of ordinary skill in the art to reasonably expect that rivastigmine would be susceptible to oxidative degradation; right?

A. No, I have not done that.

Q. And that's something you left for Dr. Schoneich; right?

A. Yes, I think he is better than I am.

Q. Under your definition of a person of ordinary skill in the art, to the extent that they would make reasonable predictions based on the structure, you would not be included in that definition; right?

A. Well, I think I mentioned, I just want to make sure that we understand the same thing. I mentioned that the POSA in my definition is a group of scientists which include a person that is a Ph.D. or chemist that can do this.

Q. To the extent that the POSA includes that part as a definition, you're not a POSA?

A. I'm not part of the POSA, correct.

Q. So now, Dr. Kydonieus, I would like to discuss with you what knowledge a person of ordinary skill in the art would obtain from reading some of the references that you relied on.

A. Okay.

Q. Let's start by assuming that a person of ordinary skill in the art were reading a prior art reference that mentions a rivastigmine formulation. Are you with me so far?

A. That was doing what?

Q. The reference mentions a rivastigmine formulation.

A. Correct. Yes.

Q. So to know if any oxidative degradation is taking place in that prior art rivastigmine

formulation, a person of ordinary skill would need to see data showing what degradation would take place, if any, and on what time scale in the absence of an antioxidant; right?

A. Can I say a couple of things?

Q. Is that a correct, statement, Dr. Kydonieus?

A. Not really. Not hundred percent. If you want me, I can try to explain.

Q. I just want to know, do you agree with the statement or not, and then we can move on?

A. Not totally, no.

Q. And so I want to go another step in my analysis here. Let's further assume that the prior art reference mentions rivastigmine formulation containing an antioxidant. Are you with me on that?

A. Yes.

Q. So to know that antioxidant was having an effect on that prior art rivastigmine formulation, a person of ordinary skill in the art would need to see data showing what effect, if any, the antioxidant has in the formulation.

Do you agree with that statement, Dr. Kydonieus?

A. If I understand what you are saying, that you put an antioxidant in there and you're going to look at data to see how well the antioxidant did.

Q. That's not exactly my question, no. My question is: You're reading a prior art reference on a piece of paper, you're just reading a piece of paper, and it's got a formulation in it with rivastigmine and an antioxidant. Okay?

A. Just --

Q. Just looking at the paper.

A. Right.

Q. Just looking at the paper, you would need to know -- to know that antioxidant that's disclosed in that piece of paper was having an effect on the formulation, a POSA would need to see data showing what effect, if any, the antioxidant was having on the formulation?

A. Let me say a couple of things.

Q. I just want to know, do you agree with that or not?

A. But these questions are not yes or no.

Q. So if you don't agree, just let me know.

A. I don't agree. I would like to discuss it.

Q. So you know that in this litigation, Noven produced documents which disclosed the formulation of its patch; right?

A. Right.

Q. And in that information, they would disclose the actual ingredients and the list, and the amount of ingredients that were used in the patch; right?

A. Yes.

Q. And this is similar to the type of information you would see in a reference, for example, in GB 040, example two provided the ingredients and the amounts of ingredients; right?

A. Yes.

Q. So you would read Noven's list of ingredients and the amounts of ingredients similar to the way that you could read a piece of prior art; right?

A. Yes.

[redacted]

[redacted]

[redacted]

Q. You're very familiar with that antioxidant?

A. Very familiar.

Q. Do you recall that you submitted a report regarding whether Noven's product infringes in this litigation?

A. Yes.

Q. And in that report, you commented on the expert report of Dr. Davies, Novartis' expert; right?

A. Yes.

Q. So can we go to slide two, which is paragraph 51 of Dr. Kydonieus's rebuttal report regarding Noven's product.

So you would agree with me that despite the fact that Noven said it used a well-known antioxidant in its formulation, you stated in paragraph 51 of your rebuttal report that Dr. Davies presents no data to show what effect, if any, [redacted] has in the context of Noven's products, right, you said that?

A. I said that, but you don't let me say

anything, so yeah, I said that.

Q. So as to Noven's product that contained a known antioxidant, you took the position that absent data, a person of ordinary skill in the art could not tell whether the antioxidant in Noven's formulation was having an antioxidant effect; right?

A. No. I mean, you got to let me speak because you can't just tell me no, no, yes, yes, and I just say yes and no.

Q. Isn't it correct in paragraph 51 in discussing Noven's product, you criticized Dr. Davies because he didn't have data showing the [redacted] was having an effect on Noven's product?

A. There is -- Dr. Schoneich described this morning and I think I discuss it, too, there is a susceptibility to oxidation and then there is a formulation that is formulation dependent, so you can't tell me about something without -- okay. You're going to say yes.

Q. Dr. Kydonieus, the whole context of this is how you would read a piece of prior art that was available. And would you agree with me that

absent -- if you have a piece of prior art that has a rivastigmine formulation plus an antioxidant, you would not know that antioxidant was having an effect on that formulation absent data?

A. I would have to look to see if the molecule was susceptible.

Q. Would you agree that without having data, when you have a piece of prior art that has a rivastigmine formulation and an antioxidant, you cannot definitively say that the antioxidant was having an effect?

A. No, in general I would say that the antioxidant will have an effect, in general.

Q. But when Dr. Davies said that [redacted] was having an effect on Noven's product, you required data; correct?

A. Because for infringement, you have to show me, as I understood from the lawyers, if I'm wrong, I'm wrong, you have to show me that this was happening, and you did not show anything. In infringement you have to show to me it was happening, and you did not do it.

Q. So with regard to GB 040 -- let me back

up. So in regard to a piece of Elmalem, in regard to Elmalem, without any data, it would be fair to say that the antioxidant used in Elmalem was having an antioxidant effect, is that fair to say?

A. Yes. I'm saying -- you compare it to the handbook, and the numbers that you have in the handbook and what you used in a particular formulation, the probability of doing something good, because we are saying that sometimes the formulations are such that you don't need the antioxidant.

Q. So sometimes you don't need the antioxidant?

A. No, you don't need it, you need it very little.

Q. Let me go back to my question, which is that with regard to Elmalem, you could just read the formulation and see it had an antioxidant and you concluded that that antioxidant was having an effect on the formulation; am I correct?

A. No. I concluded after I checked out the antioxidant used was in amounts that were at least as much as it was in the handbook.

Q. Right. But with respect to the Noven product, [redacted] right?

A. Yes.

Q. And the amount of antioxidant used by Noven was within the handbook right?

A. Yes, but you have to show me an infringement.

Q. Let me finish my question, Dr. Kydonieus.

A. The only thing that I'm saying here is that you have to show me that infringement. You have to show me that something happened and you have not shown me what happened. That's what that says.

Q. Okay. So in regard --

A. If you want to ask different questions, I'll be happy to answer.

Q. So with regard to --

A. That's --

Q. So with regard to analyzing the prior art, we don't have to show you -- you don't have to show us what happened?

A. Me analyzing this?

Q. So, with regard to Elmalem, you don't have to show us that it's having an antioxidant

effect; is that your testimony?

A. I have to show you that the amount is sufficient, as I understand it. It is sufficient as compared to the numbers that I see.

Q. I just want you to focus on my question. So when you're doing your obviousness analysis and you're reviewing Elmalem, it's your position that you don't need to have data showing that the antioxidant used in Elmalem had an antioxidant effect?

A. Yes, if I calculate it and I saw that there was enough antioxidant to meet the requirement, then I would say that probability is that I have a good sign that the antioxidant is working.

Q. So Dr. Kydonieus, the second part of Paragraph 51, you criticized Dr. Davies because you say he presents no data to show what degradation would take place, if any, and on what time scale based on just looking at the formulation of Noven's product; right?

A. Yes.

Q. And so when you're reading the prior art, you would want to see data to show what

degradation would take place, if any, and on what time scale; correct?

A. No. Wrong again.

The idea here is that you have to show me --

Q. Okay.

A. -- that this phenomena were happening. Not -- and I'm saying you haven't shown me anything.

Q. Okay.

A. Show me something because infringement you're supposed to show me, as I understand it. And if I'm wrong, please tell me.

You have to show me that something is happening. And Dr. Davies did not show me.

Q. So when you're reviewing the prior art in the obviousness analysis, you don't have to show me that the formulation that's at issue would actually have degradation and how much?

A. Yeah, I did.

Q. Did you show how much degradation and how much took place in the Elmalem formulations without an antioxidant?

A. No, I don't -- I didn't show you --

Q. So with regard to Elmalem, you are using a different standard than what you used for Dr. Davies on infringement?

A. I don't use different standards. I use the same standards.

Q. And, of course, you know that Noven said that [redacted] was needed to prevent the API from oxidizing; right?

A. Well, I mean, I don't know what they said.

Q. That's what they said; right?

A. They could have said that. I'm not saying that antioxidants are not used to prevent oxidation. You don't understand me.

I'm trying to tell you three times and you don't want to get it. I'm not saying that the antioxidants are not used to reduce oxidation.

If that is -- if it is -- we should be on the same page on that. I'm saying that you are supposed to show me that these effects are happening in infringement and you have not shown me any of this.

That's all I'm saying. And all these statements you're making --

Q. So, Dr. Kydonieus, let's go a little further with this. Absent experiments, a person of ordinary skill in the art would not know if an antioxidant was having an effect on the prior art formulation; right?

A. Would you repeat that?

Q. Sure. We're back into our hypothetical.

A. Yeah.

Q. Okay. And we've got a rivastigmine formulation --

A. Yes.

Q. -- with an antioxidant in it; right?

A. Right.

Q. And my question is: Absent experimental data, a person of ordinary skill would not know if an antioxidant was having an effect on that formulation, right?

A. On that specific formulation?

Q. Right?

A. I don't know the answer.

Q. Okay. Well isn't it true that the mere possibility of an effect by an antioxidant is very different from showing that there is an actual effect in the specific -- in the specific

formulation?

A. Not really. I have a good confidence in myself. If I use an antioxidant in -- at least with a drug that has some susceptibility to oxidation that I would get --

Q. Let's go back to your report. Let's go to Slide 7, please.

So, again, you stated in your rebuttal report "the mere possibility of an effect is very different from showing an actual effect in a specific transdermal system."

Do you see that?"

A. I'm saying that a -- specific to a formulation.

Q. Right. And so with regard to the prior art formulations, the mere possibility of an effect is very different from showing an actual effect; right?

A. It depends. We don't know. The answer is it depends on the formulation. That's what I'm saying.

Q. Your statements --

A. Your statement was in the susceptibility of oxidation of a drug, and the formulation that

is dependent on the formulation, how much you have. You could have degradation that is two percent and that's acceptable.

Q. So, Dr. Kydonieus, let's go --

A. You can get four percent and that's acceptable.

Q. So what you're saying is you would need to know, as a formulator, how much degradation was in the formulation without an antioxidant; right.

A. Without an antioxidant?

Q. Right.

A. Yeah, I will do that.

Q. Right.

A. If you heard what I said today, if you remember that, I said the high temperature test that I said it was one week or two weeks, you will test your product without an antioxidant in the particular formulation.

Q. Right.

A. So with three antioxidant formulations with three antioxidants to compare to see where --

Q. And, Dr. Kydonieus, I'd like to stick to my question again.

So with regard to a prior art formulation, you would want -- the mere possibility of an effect in that formulation is different from showing an actual effect?

A. I don't -- I cannot agree with that because you are telling me, for example, with Elmalem that Elmalem or Dr. Weinstock got the Nobel prize in Israel. Maybe not the Nobel prize, but some prize in Israel, the highest prize in medicine in Israel. She got the prize. That she does not -- she uses -- she uses an antioxidant for no reason.

Q. So you hold Dr. Elmalem to a different standard than you held Dr. Davies for his infringement report; is that what you're saying?

A. No, I'm not saying that. I'm saying that in the case with Dr. Davies, because of infringement, he had to tell me that something was happening, as I understand it, to prove to me that something was going. That's infringement as I understand it.

Q. Okay. So --

A. In the case of Elmalem -- it is a scientific journal of super experts in Elmalem's

case. Dr. Weinstock, and when she tells me that I use an antioxidant, I know that, especially when there is nothing else in it except RA7, she's using that antioxidant so that RA7 does not degrade.

Q. Okay. So, Dr. Kydonieus, an experiment must be conducted to know what effect a specific antioxidant will have and in any particular specific transdermal device. Do you agree with that?

A. What I agree with is that you don't know if a particular formulation, transdermal or otherwise, will be even if you have a susceptible molecule, if a particular formulation would allow you to get the required antioxidant effect, or the required known degradation so that you would have a product that would be accepted by the FDA.

Q. So just looking at whether a formulation as you put it is susceptible to -- let me start over.

So just saying that a compound may be susceptible to oxidation doesn't tell you how much oxidation would occur with that compound in any specific formulation or for any specific

time; right?

A. Forget about the time. The time is the same thing. We are talking about drugs that go for two years. So for two-year period of time, that's what you're looking for.

Q. So let me go back to my question. Just knowing that a compound as you put it is susceptible to oxidation doesn't tell you how much oxidative degradation will occur over any particular time; right?

A. Over any particular time? It doesn't tell you how much degradation you will get period depending on that formulation.

Q. So it could be even if a compound is as you put it susceptible to oxidation, the oxidation was so low that it may not need any special treatment; right?

A. Well, what we're saying here again is if the drug is susceptible to --

Q. Doctor, I just want to you stick to my question. It's a hypothetical.

You agree that it's possible that even if a compound was as you put it susceptible to oxidative degradation, that the amount of

degradation would be so low that it would not need an antioxidant or any other special treatment for oxidation?

A. In that particular formulation, it may be.

Q. So now you agree that none of the prior art references that you cited provided any stability data on rivastigmine or RA7 formulations; right?

A. Stability data. Actual stability data?

Q. Yes.

A. I can't think of any at the moment.

Q. And even if the prior art showed that there was some -- excuse me. Even if the prior art showed from some stability data that there was some impurity, a person of ordinary skill in the art would need to identify the structure to know if that impurity was caused by oxidation; right?

A. Sure. If you have oxidation, you have to look at the -- let me --

Q. Stay to my question. In order to know --

A. You're talking about science, you're talking about words. That's what bothers me.

Q. I'm talking about science.

A. You're not.

Q. In order to know whether the impurity was caused by oxidative degradation, you would need to know the structure of the impurity; right?

A. You would have to know that if it is larger than one percent and you have to test it.

Q. So if it's not larger than one percent, you don't really have to worry about it?

A. You have to look to see if it is in the literature, and that's sufficient to let the FDA to allow your product.

Q. Dr. Kydonieus, you have not cited any prior art disclosing the structure of any of the oxidative degradation products of rivastigmine, have you?

A. No, I have not.

Q. So now let's go to GB 040.

A. Okay.

Q. And GB 040 is the only reference you cite that discloses rivastigmine or RA7 in a transdermal device; right?

A. Well, also the '176 patent.

Q. The '176?

A. Yes.

Q. We're going to assume the '176 and GB 040 are the same unless I say otherwise. Are you okay with that?

A. I'm okay, the claims are different.

Q. And GB 040 is not limited to transdermal formulations of rivastigmine; right?

A. Not specifically.

Q. So, for example, GB 040 includes formulations that can be administered orally or subcutaneously; right?

A. Sure.

Q. And GB 040 does not expressly disclose an antioxidant; right?

A. It does not explicitly, implicitly.

Q. I just wanted an answer to my question, which is GB 040 does not expressly disclose an antioxidant?

A. Expressly or explicitly, yes.

Q. I'm sorry, I just want to make sure the record is clear. GB 040 does not expressly disclose an antioxidant; correct?

A. Is the word expressly the same thing as explicitly?

Q. Yes.

A. Okay. That's what I said.

Q. I thought you said something else. Thank you.

Now, in your slides, do you recall that you did not contend that GB 040 disclosed the use of antioxidants to prevent oxidation.

A. Yes.

Q. That's correct, you didn't disclose that?

A. GB 040, yes.

Q. In fact, you relied on a handbook for the use of antioxidants to prevent oxidation, do you recall that?

A. Yes.

Q. And you have not cited any reference that says the first thing you would do with a drug you believe is susceptible to oxidative degradation would be to add an antioxidant; correct?

A. No, I indicated that.

Q. That's not my question. My question is you haven't cited a reference that says the first thing you would do with a drug --

A. My reference is my forty years doing transdermal patches.

Q. I need to have a clear record.

So you agree you haven't cited a reference that says the first thing you would do is to add an antioxidant?

A. Yeah, there is no reference.

Q. You know some of the formulations that Dr. Klibanov pointed to that had a benzylic carbon hydrogen bond, for example, did not include an antioxidant; right?

A. Yeah, but as Dr. Schoneich --

Q. Am I correct. Some of the commercial products you have seen that did not have an antioxidant, but had a benzylic carbon hydrogen bond?

A. I don't know that, but I know there are some like nicotine that have oxidation, and the product in the market does not have an antioxidant. But as we said before --

Q. So are you saying that they took the antioxidant out after they tried it?

A. No.

Q. So it's not always the first thing that someone would do would be to add an antioxidant?

A. They may have done it, probably they have done work with antioxidant and then they did the

experiments that I mentioned with you before, the accelerated experiments and they say that the formula that they were using was okay, so they stuck with that without the antioxidant because you don't want to put any chemicals including antioxidants into something that you don't need.

Q. With regard to that nicotine product you referred to, you have no personal knowledge about how that product was formulated and the work that was done for it; right?

A. That particular product, no.

Q. Now, GB 040 does not suggest adding an antioxidant to any of the rivastigmine formulations disclosed therein; right?

A. Yes.

Q. And GB 040 did not measure the stability of rivastigmine; correct?

A. Right.

Q. And GB 040 does not disclose the rate or extent of oxidation of rivastigmine in general or in a formulation; correct?

A. In anything.

Q. I'm sorry?

A. In anything. We didn't do any stability

work.

Q. And GB 040 does not provide any data that would suggest that rivastigmine would undergo oxidative degradation under pharmaceutically relevant conditions; right?

A. It didn't do any work, no.

Q. And you would equate pharmaceutically relevant conditions to what you testified on direct, that the product has to remain stable for two years?

A. Yes, you have to do that, if your product is for two years. If you decided you wanted a product for one year, then you have to do the stability for one year.

Q. Could you please go to Noven's slide 11. I don't know if we have that. Do we have that? It's DDX 361.

Now, you see on one of these slides that you used on direct, DDX 361, on the second box on the right, it says for GB 040 that it discloses structure of rivastigmine susceptible to oxidation. Do you see that?

A. Yes.

Q. So just to be clear, GB 040 does not

actually state that the structure of rivastigmine suggest susceptibility to oxidation; right?

A. It shows the structure.

Q. My question is different. My question is the reference itself does not state that the rivastigmine -- the structure of rivastigmine suggest susceptibility to oxidation?

A. No.

Q. No, it doesn't?

A. No, it does not say that.

Q. Thank you.

And, in fact, none of the references you cite specifically state that the structure of rivastigmine suggest susceptibility to oxidation; correct?

A. No. Any references? I'm trying to think. No, I don't think so.

Q. And none of the references you cite specifically state that a benzylic carbon hydrogen group makes a compound susceptible to oxidation; right?

A. I have not looked at that, and I --

Q. None of the references you cite say that; right?

A. None of the references that I cite state that. I haven't looked to know which of all these things are.

Q. As you sit here today, you're not aware of any of the references stating, specifically stating that a benzylic carbon group makes a compound susceptible to oxidation?

A. No, I depend on my chemists to do that for me.

Q. So my statement was correct?

A. Your statement as far as the projects -- I mean the projects, the prior art that I saw, it doesn't, it does not show that.

Q. Thank you.

I apologize for asking the question a second time, because sometimes your answer, I wasn't clear which way you were answering. So I may have to do that as we go along here.

And GB 040 does not provide a person of ordinary skill in the art any information as to whether its composition would be stable for weeks or whether it would be stable for years; right?

A. That was from a formulation that was

totally uncompleted. You're talking about example two.

Q. I'm talking about the reference GB 040 does not provide a person of ordinary skill any information as to whether any of its compositions including example two would be stable for weeks or whether it would be stable for years; correct?

A. No. It is not correct. Because it provides the rivastigmine which tells the organic chemist that that's susceptible to oxidization.

Q. That wasn't my question, Dr. Kydonieus. Let's focus on my question. GB 040 does not provide a person of ordinary skill in the art any information as to whether example two would be stable for weeks or whether it would be stable for years; right?

A. Well, you're assuming that the POSA is a dumb person; right?

Q. I'm just asking you what's in the reference, Dr. Kydonieus. Is it correct, there is no data in that reference that would allow, that would provide a POSA any information whether --

A. But you're saying any information; right?

Q. Let me finish the question.

A. And I'm saying yes, it does provide information.

Q. Let me ask the question differently, then. GB 040 does not provide any data as to whether example two would be stable for weeks or whether it would be stable for years; correct?

A. That is correct.

Q. So can we go to paragraph 96 of Dr. Kydonieus' opening report.

So you recall in your opening report, you talked about GB 040?

A. Not really, but you tell me, which part? Which part?

Q. Okay. And this is Paragraph 96 from your opening report. And in this paragraph, you talk about a lot of different things. But at the very end of it --

A. Yeah.

Q. -- you say -- and you know Enz is GB 040; right?

A. Right.

Q. You say Enz also lacked any stability data, which one of -- I'm sorry, which is one of

the first considerations addressed in the early drug product development. One of ordinary skill in the art would be unable to determine, for example, whether Enz's composition would be stable for weeks or whether it would be stable for years.

Do you see that?

A. Yeah.

Q. You don't say in that paragraph that you would be able to make that determination just based on the susceptibility of rivastigmine to oxidation, do you?

A. Because I do not know the formulation. I did not look at the formulation.

Q. Okay. Let's turn our attention to the '807 patent which is JTX 17.

A. Mm-hmm.

Q. And can we go to Slide 15, please? And you see we've highlighted a portion of the '807 patent from Column 1, Lines 32 to 34 which says -- and it's referring to Physostigmine. You agree with that?

A. I have not looked at that. Yes, I read that.

Q. So the '807 patent says that a physostigmine is chemically unstable and must be prepared in a solution with an antioxidant and protected from light. And you agree with that statement; right?

A. The words, I have -- I have to agree with.

Q. I'm sorry?

A. I have to agree.

Q. You agree with it?

A. I have to. They did the work; right? So I have to agree with it.

Q. But they did the stability testing?

A. I believe that when people say things like the '807 says, we are talking -- since we are talking about '807 that they recommend preferred antioxidants being for the RA component, I believe that. I believe that they have done the work and they should have shown that it's stable --

Q. Okay.

A. -- when you use the antioxidant.

Q. And the purpose of the '807 patent was to identify alternatives to physostigmine because

physostigmine lacks the desired chemical stability; right?

A. Chemical stability, plus many other things.

Q. And you do not dispute that there are millions of compounds disclosed in the '807 patent; right?

A. I do. I do.

I disagree with that.

Q. You didn't provide your own number of compounds that --

A. Well, there are three.

Q. Dr. Kydonieus --

A. Claim 1 says -- the claims say three compounds.

Q. But I'm talking about the specification in general. You know Dr. Klibanov did an analysis.

A. I don't care what he says. I'm -- in POSA, in the people -- I'm trying to -- I don't care what Dr. Klibanov says with 3,000 molecules.

Q. Okay.

A. I'm looking at RA7 and I'm looking at the claims. And I see Claim 3 being RA7, which is -- and I am developing a transdermal for

rivastigmine and that's what I care --

Q. Dr. Kydonieus, let's stick to my question.

A. Yes.

Q. My question was a very simple one. You do not dispute that there's millions of compounds that are disclosed in the '807 patent; right?

A. I don't care how many.

Q. You don't care because when you started with the claimed invention that said rivastigmine and then you went back and you looked at the '807 for disclosure for rivastigmine, is that why you don't care because you're only focused on rivastigmine?

A. No, because, I mean, if you have a chemical compound, you have R1, and R2, and R3 and R5. You have a million compounds.

What does that mean?

Q. Okay.

A. It doesn't mean anything.

Q. And, Doctor, just bear with me for a minute.

A. I'm trying.

Q. You agree there's more than rivastigmine disclosed in the '807 patent; right?

A. There are at least three compounds, RA6, RA7, RA16.

Q. And there's more than that disclosed?

A. And there are more than that. Could be.

Q. And you cannot answer the question of whether all of the compounds of the invention of the '807 patent would undergo oxidative degradation under pharmaceutically relevant conditions; right?

A. Would you repeat that?

Q. Sure. You cannot answer the question of whether all of the compounds that are disclosed in the '807 patent would undergo oxidative degradation under pharmaceutically relevant conditions; right?

A. I concede it's meaningless what you're telling me.

Q. Am I correct, though, that you cannot do that?

A. No. I know that there are three compounds that Elmalem and '807 -- Marta Weinstock looked at them. She tested them and she said the preferred antioxidants, if you tell me one billion compounds, I cannot tell you yes or no

because I don't know the billion compounds.

Q. So you just can't answer that question? You couldn't answer that question?

A. I could not answer. I couldn't even --

Q. All right. So --

A. It's improper to answer.

Q. Dr. Kydonieus, the '807 patent discusses the use of RA7 in tablets, capsules and elixirs for oral administration as well as sterile solutions and suspensions for parenteral administration; right?

A. Which someone that --

Q. The '807 patent --

A. Oh. I don't remember that, but I accept that.

Q. Okay. It does not -- the '807 patent does not discuss transdermal formulations; right?

A. No, it does not discuss.

Q. And you recall you had a slide up on your direct which showed that for sterile compositions, the '807 patent says "buffers, preservatives, antioxidants and the like can be incorporated as required." Do you recall that from the patent?

A. Yes, I remember that.

Q. And that means buffers, preservatives, antioxidants --

A. Right.

Q. -- may or may not be needed; right?

A. Could be used, but --

Q. It means it may or may not be needed; right?

A. But a couple of --

Q. Just answer my question. It means that those may or may not be needed; right?

A. But a sentence below it says that preferred antioxidants are sodium metabisulfate and ascorbic acid, so...

Q. We'll get to that, but I'd like to start with just an answer to my question.

A. But you're asking me questions that you want me to answer half of the question.

Q. Okay. So --

A. Because -- but you're asking me could be the buffers, that may or may not use.

Q. Dr. Kydonieus, let's turn to your deposition, Page 237. Could you put that on the screen actually? It will be easier.

And if you look starting at about Line 4 or Line 5, you were asked: My question was that: The statement in the '807 patent is that antioxidants and the like can be incorporated as required. It does not say that they must be incorporated, correct?

"Answer: No. You don't need perhaps to put buffers in there or preservatives."

THE WITNESS: Right. That's what I said.

Q. So you agree, Dr. Kydonieus -- I'm not done.

"So you agree that a buffer may or may not be required?

Answer: May or may not be required, yes."

THE WITNESS: I'm not an expert, but I said it may or may not be required.

BY MR. CONDE:

Q. So all of those things may or may not be required; right?

A. Not all. I don't say all, I say that antioxidants are required because a sentence

below where you mentioned before there are antioxidants and there are preferred antioxidants, which means it's a lot of work to find out what the preferred antioxidants are.

And she mentions it, so the answer is I don't say that the antioxidants in that statement is may or may not.

Q. So, Dr. Kydonieus, is there any stability data in the '807 patent?

A. Not yet.

Q. And have you talked to Dr. -- it's Dr. Weinstock; right? It's her patent?

A. Yes.

Q. Did you talk to her about whether she did a lot of work to determine whether any of the compounds need an antioxidant?

A. She tells me preferred antioxidants are --

Q. I'm just asking you a question: Do you have any knowledge --

A. Do you want me to speak with her?

Q. Do you have any knowledge that Dr. Weinstock actually did a lot of work to support her statement as to the preferred antioxidants?

A. Well, I assume that Dr. Weinstock with her

credentials is not lying.

Q. That wasn't my question.

A. That's what you're asking me to say.

Q. No, I'm not. What I'm asking you is simply do you know if Dr. Weinstock did any work, any stability work to support the statement in her patent that certain antioxidants are preferred?

A. When somebody tells me that I have preferred antioxidants, and these are the two preferred antioxidants, I believe those people have done the work.

Q. But you don't actually know whether they did?

A. No. I didn't talk to her.

Q. That's my question. It's that simple.

And the '807 patent doesn't report any stability data on RA7 or rivastigmine; right?

A. Stability data, no.

Q. And so it doesn't tell us the rate or extent of any oxidative degradation for rivastigmine RA7; right?

A. I calculate the numbers and I said, I think in my testimony, that the numbers weren't

very high of antioxidants. So they would be effective oxidative degradation for a long period of time.

Q. But, Dr. Kydonieus, you know that the '807 patent doesn't provide any ranges for the antioxidants that it says is preferred --

A. Well --

Q. You have to let me finish my question.

A. Sorry.

Q. You know that the '807 patent doesn't provide any ranges for any of the antioxidants that it says are preferred; right?

A. Right.

Q. And the patent itself does not provide any data regarding the rate or extent of oxidative degradation of degradation of RA7 or rivastigmine; right?

A. You have to repeat that, please.

Q. I'm sorry?

A. Can you repeat it, please?

Q. Sure. Absolutely.

The '807 patent does not report any data regarding the rate or extent of oxidative degradation of RA7 or rivastigmine; right?

A. No, they have not done any work or they haven't shown any.

Q. And the examples of '807 do not include an antioxidant; right?

A. I don't remember, but probably, yes, you're right.

Q. You think I'm right. Okay.

Do you recall at your deposition stating that the examples of the '807 patent containing RA7 did not include an antioxidant?

A. I don't remember, but I accept what you said. I mean, I trust you.

Q. And the '807 patent does not disclose any information relating to what amount of antioxidant would be effective at stabilizing RA7 from oxidative degradation; right?

A. '807?

Q. '807.

A. Yes.

Q. Am I correct?

A. Yeah, I believe so, the amount.

Q. Okay. So now let's turn our attention to Elmalem. Elmalem's not a stability study; right?

A. Stability study. No, it was a study to

determine the effect of cholinesterase inhibitors on the side effects of morphine.

Q. Elmalem was designed to compare the effect of physostigmine versus three investigational drugs; right?

A. Yes, these are all inhibitors --

Q. And they were trying to find out, and what Elmalem was studying is how much inhibition there was of a cholinesterase enzyme; right?

A. Right.

Q. And Elmalem does not disclose any data regarding the rate or extent of oxidative degradation of RA7; right?

A. It shows the amounts that they have used.

Q. My question is very simple. Elmalem does not disclose any data regarding the rate or extent of oxidative degradation of RA7; right?

A. The data, no, they have not shown any data.

Q. And Elmalem does not include any data showing that RA7 is actually undergoing oxidation; right?

A. Well, you're asking me to tell you the answers that don't make any sense.

Q. There is no data in Elmalem that would tell a POSA whether RA7 is actually undergoing oxidation; right?

A. Yes. No. But I tell you one thing, when I have a solution that is only a saline solution with RA7 and I put an antioxidant, I know that the antioxidant is put there because there is nothing else to protect RA7.

Q. Back to my question. Do you agree that there is no data showing that RA7 is undergoing oxidation; right?

A. I have to believe Marta Weinstock that says yes, there is oxidation going on.

Q. Now, you know that all the formulations in Elmalem were solutions; right?

A. Yes.

Q. And Elmalem did not prepare any transdermal formulations; right?

A. Right.

Q. And if I heard you on direct, you said that information regarding a solution formulation was applicable to a transdermal patch. Did I get that correct?

A. Yes, I said that.

Q. Let me ask this question. Would you agree that information regarding a patch formulation is not probative to a solution formulation?

A. Well, the reason I can say that any formulation is not -- you cannot extrapolate directly from one formulation to the other, but --

Q. So if you have oxidative degradation in a solution, you cannot conclude that it would also be a problem, for instance, in a transdermal patch; right?

A. I said that many times. That is formulation dependent.

Q. And, in fact, transdermal patches are wet for a matter of hours before being coated; right?

A. Say again, now.

Q. Transdermal patch formulations are only wet for a matter of hours; right?

A. Right.

Q. The stability we're concerned with here during this litigation is stability over a year or two; right?

A. Correct.

Q. Now, the solutions in Elmalem were

prepared to be used soon after?

A. I didn't get that.

Q. The solutions in Elmalem were prepared and then used soon after; correct?

A. It says freshly, so I really don't know what that means. I can't tell you the time element.

Q. So you would agree they were probably used shortly thereafter?

A. I don't know what shortly thereafter means. I don't know the answer. Freshly, so whatever freshly means.

Q. Freshly made and then they use them right away; right?

A. I don't know. I don't know what freshly means.

Q. So that's a possibility, though?

A. You're saying freshly is there, and everybody can see freshly.

Q. And it's not uncommon to make a solution freshly and then use it shortly thereafter, right, in an experiment?

A. I don't know. I don't know that.

Q. Well, there is nowhere in Elmalem that it

says that the solutions were stored for a prolonged or pharmaceutically relevant period of time; right?

A. No.

Q. Am I correct?

A. Yes, you are correct.

Q. Let's go to our slide 19, I think. This was one of your slides on direct. It shows the parts antioxidant to parts of rivastigmine disclosed in Elmalem?

A. Right.

Q. And I did the math, but you probably can do the math, but you can do it in your head. There is a 400 parts difference between the amounts used in Elmalem and '031; right?

A. Right.

Q. And you didn't address on direct whether by adding a 400 parts more antioxidant it would create any issues in the formulation, did you?

A. Can I explain?

Q. Did you talk about that on direct?

A. Excuse me?

Q. You didn't address whether adding 400 times more antioxidant?

A. That's the wrong comment.

Q. Let me ask you this question, then. It is not always the case that adding a higher concentration of an antioxidant will improve or keep the same the stability of the formulation. Do you agree with that?

A. You don't let me answer. Let me answer the first question.

Q. Let starts with my question.

A. You're asking me questions that don't make any sense.

Q. Let me try --

A. This thing here is based on the amounts of rivastigmine to antioxidant, it is not on the formulation. If you want me to explain the formulation, I'll be happy to do that.

Q. You presented this chart to the Court and you agree --

A. Yes, and there was a lot of antioxidant, that's what I said.

Q. 400 times more antioxidant?

A. Yeah.

Q. And then my question is, it's not always the case that adding a higher concentration of an

antioxidant will improve or keep the same the stability of the formulation. Do you agree with that?

A. I don't understand. Tell me again, please.

Q. Do you agree that it's not always the case that adding a higher concentration of antioxidant will improve or keep the same the stability of the formulation?

A. Well, I have seen where -- well, let me explain for this, because that's what we're talking about. I have to explain. I have to explain it because you're making comments that don't make any sense. There is not here 400 difference in the formulation. In the formulation they're exactly the same. And if you want me to show you, I'll be happy to show you, but before in the deposition you didn't let me show it.

Q. So, Dr. --

A. The numbers are the same and you're making an issue out of something that is wrong.

Q. So this slide that you presented to the Court, it does not correctly show the relative

amounts of antioxidant in Elmalem versus the '031 patent?

A. No, it says what it says up there. It shows the antioxidant to rivastigmine ratios in both cases.

Q. So that was important to your direct, right, that was an important slide?

A. Everything is important.

Q. Your slide, I'm just looking at your slide, and what it shows me is there 400 fold more antioxidant in Elmalem than the '031 patent?

A. No, wrong.

Q. Go back to my question. Do you agree that it is not always the case that adding a higher concentration of antioxidant will improve or keep the same the stability of the formulation?

A. I have to explain.

Q. I just want to know, do you agree with that statement?

A. Let me explain. I have to explain because you see you're always trying to say yes and no and there are no yes and no in science.

Q. Let me go to slide 68 which is from your rebuttal report again. I'm sorry, slide 24. And

this is a statement that you made in the rebuttal report. You said, "It is not always the case that adding a higher concentration of an antioxidant will improve (or keep the same) the stability of the formulation."

Did I read that directly?

A. You read that correctly. And I have to explain it to you.

Q. Let's go to Elmalem, and this time, let's go to the document itself. Let's go to slide 26 and this is from a section of Elmalem that you read this morning that's from the bottom of the page under drugs, and you went to the section this morning where it says all drugs were made up freshly in a sterile saline, which included an equal weight of sodium metabisulfite to prevent oxidation. Do you see that?

A. Yes.

Q. It's your interpretation that this sentence means that the weight of sodium metabisulfite included in the solution equalled the weight of the drug in solution; right?

A. Right.

Q. But it doesn't actually say those words in

that section; right? It does not say, it does not literally say the weight of metabisulfite is the same as the weight of the drug, does it?

A. To me it says that, yes.

Q. And in your opinion, Elmalem made up a different saline solution for each drug formulation that was tested; right?

A. Yes.

Q. And under your interpretation of Elmalem, each formulation contained an amount of antioxidant equal to the weight of the drug in the formulation; right?

A. Correct.

Q. So every formulation contained a different amount of antioxidant; right?

A. Yeah. The ratio of the antioxidant to the drug is the same.

Q. But that wasn't my question. Each formulation had a different --

A. You always want a half answer, you want a half answer so you get half answers.

Q. So let's see what that means. So let's go to slide 27, please. So the lowest amount of drug used in Elmalem was .05 milligrams per

kilogram for physostigmine?

A. Right.

Q. And the highest amount drug used in the study was 2.5 milligrams per kilogram for RA7; right?

A. Okay.

Q. That's a 40-fold difference between the amount of antioxidant used in physostigmine and RA7?

A. Right. Want me to tell you what it means?

Q. Let's go to Weinstock. I'm on a clock and if your counsel wants you to explain it.

A. I'll be here forever.

Q. Unfortunately we don't have time forever. Let's go to Weinstock, which is JTX 30, and that's the Weinstock 1981 reference. You remember talking about that this morning. There is no mention of rivastigmine or RA7 in Weinstock 1981, right?

A. Right.

Q. And there is no stability data for rivastigmine or RA7 in Weinstock 1981; right?

A. Data, no.

Q. There is none, because they didn't exist

at the time; right?

A. For RA7, yes.

Q. But the compounds that were used in this study were well-known?

A. Yes.

Q. And I think you, maybe you misspoke, but we think what you said on direct is that Weinstock used four cholinesterase inhibitors, did you say that?

A. Maybe I did, four drugs, ATMN, neostigmine, hydrazine and something else.

Q. So they're not -- do you know whether they're all cholinesterase inhibitors --

A. I don't know that they're all cholinesterase inhibitors.

Q. You don't know that much about the drugs that were used in the Weinstock formulation?

A. I know that some of these are used on opioids, opioids to move --

Q. But you're not familiar with the mechanism of those drugs, how they act?

A. Not necessarily, no. I'm not a pharmacologist.

Q. You're not a biologist, either; right?

A. No.

Q. You're not here testifying as a pharmacologist or biologist; right?

A. No.

Q. All right. Prior to this litigation, had you ever seen either the Weinstock paper or the Elmalem paper?

A. Before the litigation?

Q. Yes.

A. No.

Q. Because they're not in your area of expertise and work; right?

A. Well, my work is mainly transdermals.

Q. So these two, Elmalem and Weinstock aren't in your expertise or your area?

A. Right. You may say that, yeah, I look at literature, but I had never seen those.

Q. So let's -- so I want to talk a little bit about the Brij 97 documents. Let me turn to that next.

Now, so let's assume for the moment that you're right that there is antioxidant in Brij 97 was manufactured by Atlas Chemie out of West Germany. You would agree that the

antioxidant in Brij 97 was used to protect the plasticizer?

A. That's what it's used for, to start with.

Q. To protect the plasticizer?

A. That's my presumption.

Q. And you didn't testify about the amount of antioxidant, assuming that Brij 97 has an antioxidant, you didn't testify about how much antioxidant would be in the final formulation of example two of the '040 patent, did you?

A. No, I did not.

Q. So let's go to slide 44 to see if we can do that analysis. You looked at the '480 patent on direct, you looked at this very sentence; right?

A. Again, please.

Q. Sure, this slide is from the 480 patent, and you went to this patent on your direct and you pointed to this very sentence which says that there is .01 percent BHA and .005 percent citric acid --

A. Correct.

Q. -- in Brij 97; right?

A. Right.

Q. And you know that the '480 patent does not identify Atlas Chemie, West Germany as the inventor?

A. ICI.

Q. It says ICI, but it doesn't say Atlas Chemie?

A. It says Atlas Chemical was bought by ICI.

Q. That was based on your personal knowledge, you didn't bring any documents that show that ICI bought the manufacturer of Brij 97?

[redacted]

Q. But none of those documents show that ICI actually purchased Atlas Chemie in West Germany; right?

A. I don't know if the documents say that, but basically what it says is that Atlas Chemie was bought by ICI. ICI have sold the Brij 97 to somebody else and in the end was bought by Croda, and now it's owned by Croda.

Q. Let's continue on with this. It says on slide 44, we added up the amount of BHA and citric acid and got .015 percent; do you see that?

A. Okay.

Q. Let's go to the next slide. Then we look at example two, and we did the calculation to find out how much in total there was of BHA and citric acid, and you can see the calculation we did. It's very similar to the one you did on our earlier slide, and we end up with nine parts per million?

A. Right.

Q. Would you agree with that?

A. Yes.

Q. So when Brij 97 is made, it contains -- and assuming it has an antioxidant, it contains nine parts per million; right?

A. For the formulation, that formulation, example two contains this antioxidant.

Q. So example two contains nine parts per million. And you don't know whether all of the citric acid in BHA actually made it into example two, do you?

A. Why not?

Q. For example, the BHA and citric acid could have been used up because it was protecting the plasticizer; right?

A. I have no idea of that, but neither here nor there. We never -- I mean, I can maybe help you, not to ask me this line of question, because we never -- I never said that the amount of antioxidants in Brij 97 was the amount required to give us effective antioxidation effect, that's why I used the handbook and so on to help me in saying, we never said that Brij 97 was the one that gave us another antioxidant to protect this formulation.

Q. Thank you for that explanation.

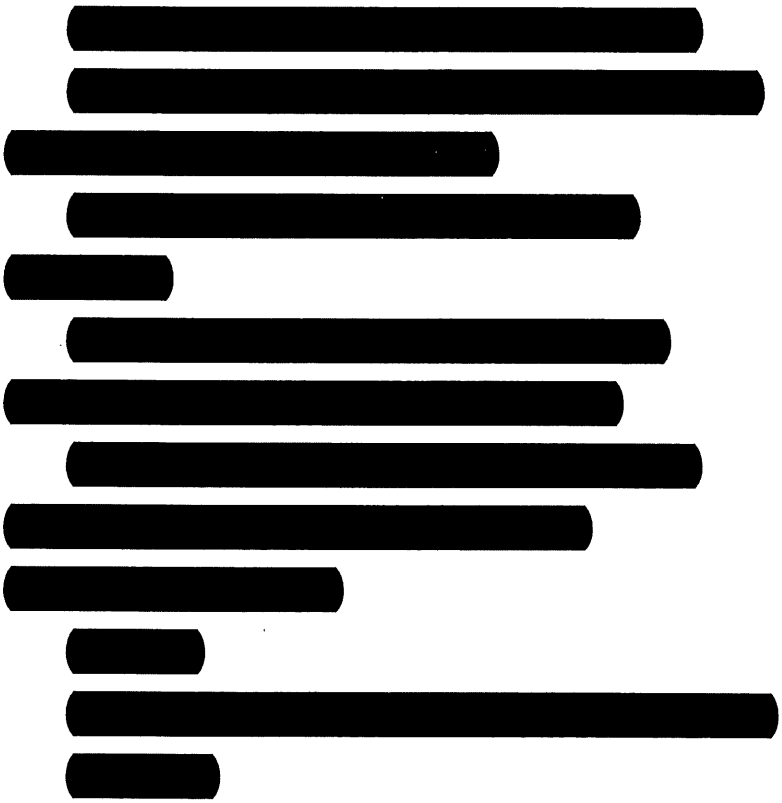
Now, you also did not testify whether nine parts per million is a sufficient amount for a person of ordinary skill to make the compatibility determination with the BHA and citric acid with example two formulation; right?

A. I just told you that we didn't use this part here to make a point that it was therapeutically -- not therapeutically, but in an amount adequate to stabilize the oxidation, so

there was no need for me to go farther in saying anything else.

Q. Can we go to the next slide, 46. This is defendants' exhibit 89, another document that you looked at in your direct. Do you remember that document, Dr. Kydonieus?

A. Yes, I remember it very well.



Q. Thank you. And this document is a document you relied on for your slide which is DDX 355, do you remember that?

A. Yes.

Q. And there is a lot of redactions on the document; right?

A. Yeah.

Q. There is so many things removed that you really couldn't make much sense of it; right?

A. No.

Q. That's what you said at your deposition, do you recall?

A. I don't think so.

Q. Let's look at 272, go to page 272 of your deposition. So go to line 18. Are you with me? You were asked the question, [redacted]

"Answer: Yeah, I looked at this particular page. There was so many things removed, I couldn't really make much sense of this document. But go ahead."

Were you asked that question and did you give that answer?

A. I asked the question and what?

Q. Did you give that answer?

A. Yes. Because I don't know what it was.

You have to put in proper perspective --

Q. Dr. Kydonieus, I just wanted to know, you answered my question.

A. But you're asking me on what, what point did I make that statement there, because now you're making it sound like I couldn't calculate. That's not true.

THE COURT: Dr. Kydonieus, quiet for a second.

MR. LEE: I think for completeness, we need to have the next question and answer.

THE COURT: Let's have the next question and answer.

MR. CONDE: Sure.

THE COURT: I'm sorry. So Dr. Kydonieus, we're just going to go over that again, but with not only the question you were just asked about, but also the following one.

BY MR. CONDE:

Q. So I will go to the next part.

"So it's not possible to tell from this document the percent of antioxidant in the product; correct?

"Answer: Well, it says something

down here double star, 25 percent BHA, 12.5 percent citric acid monohydrate, 62.5 USP propylene glycol. If you look at the double star, it's the antioxidant solution that was used in the formulation."

That's what you said; right, Dr. Kydonieus.

A. Right. ?

A. Right.

Q. Okay. So, now let's keep going.

Let me keep going.

Question: Right. But we don't know how much of the other ingredients were added to this product, correct?

Answer: Well, quantities are removed, so it's very difficult to tell what the other numbers are."

And you also gave that answer?

A. The point is there so I can calculate. Right.

Q. I'm just -- that was the full testimony, so let's move on.

A. Well, okay. I mean, as long as you are not telling me that I'm not able to calculate the

amount that is there, we're okay.

Q. Okay. So let's move on. Let's go to Slide 47.

This is another document that you relied on; correct?

A. This Brij 96?

MR. LEE: No, Your Honor.

THE COURT: Not earlier today.

MR. CONDE: My apologies. That's okay.

BY MR. CONDE:

Q. We'll just -- oh, so now, Dr. Kydonieus, as of 1998, Brij 97 no longer contained any antioxidant; right?

A. It was removed January 1, 1991.

Q. And a person of ordinary skill would have known that; right?

A. Ordinary skill in the art?

Q. Yes.

A. Yes, they would know that because they received the data any time that they order the material.

Q. So let's turn our attention to Sasaki.

A. Okay.

Q. Now, you agree with me that Sasaki -- excuse me one second. You agree with me that Sasaki --

THE COURT: I'm sorry, Mr. Conde. The last question and answer went by kind of fast for me.

The antioxidants, the BHT or ascorbic acid or whatever it was that was in Brij 97 was removed from the product in 1991?

THE WITNESS: Correct.

THE COURT: Okay.

BY MR. CONDE:

Q. Now, Dr. Kydonieus, Sasaki does not disclose or discuss rivastigmine; right?

A. No. It discussed molecules of similar structures.

Q. They're only similar in the regard that they have an amino group?

A. They have amino groups.

Q. And that's the only similarity that you pointed to on direct; right?

A. Right, because that's what Sasaki claims in his patent.

Q. So Sasaki does not include any

rivastigmine stability data; right?

A. No, rivastigmine was not even available at the time.

Q. So can we go to Sasaki DTX 12, and I think I need to go to Page 3. Down on the -- put that on the screen.

Page 3, please. And on direct you testified -- you noted that there's a several different drugs in the left-hand column.

A. Right.

Q. Right? And I think you said that Sasaki had tested all of those compounds he listed to see whether they had an oxidative degradation problem?

A. No. I don't know what I said, but I never would say that he tested all of them. He probably tested a lot of them to make this statement.

Q. But you don't know whether he tested any of them on any of the drugs on the left-hand column on that page?

A. Well, I presume that he tested a lot of them to be able to make those comments.

Q. Well --

A. Usually the stuff that comes in patents or in articles, that doesn't mean that you've tested everything.

Q. Right. So you know that patents sometimes disclose things because they want to make the claims as broad as they can, but they may not have actually tested for that property; right?

A. Some cases maybe, but --

Q. So now --

A. You cannot in patents claim things or put down things are not correct, either. So you've got to put -- I mean, if you want to get your patent -- I have 61 patents, so I know.

Q. If you want to get an extensive range, you have to do some work to get that extensive range. But you don't have to test everything that you disclose in the patent, all the compounds that you disclose; right?

A. No, you don't have to.

Q. So let's go to Slide 60. And this is a table from Sasaki; right?

A. Right.

Q. And there's only two compounds that have amine structures; right?

A. Yes.

Q. Okay. And those two compounds are the diphenhydramine; right?

A. Diphenhydramine.

Q. And the ethyl aminobenzoate?

A. Yes.

Q. And neither of those compounds have a benzylic carbon hydrogen connected to the amine; right?

A. Sasaki is not talking about any benzylic hydrogen carbons or anything like that.

Q. So neither one of those compounds have a benzylic carbon compound as far as you know; am I correct?

A. I don't know the answer. Maybe, I'm not sure. I have to look at the structure if you want me to answer that question.

Q. You did not testify as to how many pharmaceutical compounds have an amine group, did you?

A. An amine group?

Q. Yeah. Out of all the pharmaceutical compounds, how many of them have an amine group?

A. No. I don't think I testified to that.

Q. And if you saw a tertiary amine compound on a compound, you would not be able to know whether or not that compound was susceptible to oxidative degradation; correct?

A. Are you talking about Sasaki or we're talking generalities now?

Q. We're talking generalities.

A. So if it was an amine compound, if I would know or if it is susceptible to oxidation? Tell me the question again, please.

Q. Okay. If you saw a tertiary amine on a compound, you would not be able to know whether or not that compound was susceptible to oxidative degradation; correct?

A. As I mentioned, I'm not an organic chemist. I would leave that question to the organic chemist to tell me.

Q. Now, you cited Sasaki in part because it uses an acrylic adhesive; right?

A. Well, that's the main thesis of this patent that you have an acrylic adhesive and you have drug molecules that contain amino groups. He says oxidation.

Q. But you don't know if rivastigmine -- let

me start over -- if rivastigmine is in an acrylic adhesive, you don't know whether it will necessarily undergo oxidative degradation, do you?

A. Well, it is an amine group and, honestly, this morning that I mentioned diphenhydramine was one of them. Amino was another one. And Lidocaine was another one.

In the amine groups, in those three compounds that you mentioned Sasaki mentioned are similar to the amine compounds in rivastigmine.

Q. Could you turn to your deposition, Page 89?

Let's put it on the screen. It will be easier. Page 89, and 18, Line 18. And you were asked the question: "So am I right that it's your opinion that when rivastigmine's in an acrylic adhesive, it will not necessarily undergo oxidative degradation?

"Answer: I don't know the answer."

A. Absolutely correct. Yes.

Q. Now, Dr. Kydonieus --

A. May I finish. It is formulation dependent.

Q. So you know the structure of rivastigmine; right?

A. Right.

Q. And you know about nicotine; right?

A. Right.

Q. And according to Sasaki, acrylic polymers would also create a problem; right?

A. With amino group compounds.

Q. All right. But in your infringement report, even though you knew all those three things, you said that the drug doesn't necessarily go through oxidative degradation even though it has rivastigmine and an acrylic adhesive; right?

A. I think I keep on saying the same thing. As far as the degradation is concerned, it is formulation dependent.

Q. Okay.

A. Okay.

Q. So now, excuse me a second.

Now, you agree that Sasaki teaches adding .05 to one percent of tocopherol; right?

A. Right.

Q. And that's relative to the adhesive?

A. Relative to the adhesive.

Q. And the adhesive is the oxidative environment for the drugs in the formulation disclosed in Sasaki; right?

A. I think that's what you said.

Q. So Sasaki teaches that the amount of antioxidants should be chosen based on the concentration of the oxidizing agents in the environment of the formulation, not based on the amount of drug; right?

A. Well, I think you said in the amount of drug because -- give us a ratio between point -- I forget the number, but .01 to .3 ratio of drug. Excuse me, drug to acrylic adhesive.

Q. So Sasaki's saying you determine the amount of antioxidant based on the amount of the adhesive; right?

A. Right.

Q. Let's go to --

THE COURT: Actually why don't we take our afternoon break. All right.

So we'll take a 15-minute break.

THE CLERK: All rise.

(A brief recess was taken.)

THE COURT: All right. Let's be seated and back to Kydonieus. Yes.

BY MR. CONDE:

Q. Dr. Kydonieus let's talk about the Ebert reference that you rely on. You agree that the Ebert reference addresses a manufacturing issue with nicotine formulations for transdermals; right?

A. Yes, I did.

Q. And Ebert does not discuss rivastigmine at all; right?

A. No.

Q. So it doesn't discuss or state using an antioxidant with rivastigmine, does it?

A. No. I mean --

Q. Okay. So it doesn't?

A. I don't know how to answer these things because, honestly, they're half --

Q. But I, just as a matter of fact, Ebert does not include any stability data for a rivastigmine formulation, right?

A. No.

Q. And so can we go to our Slide 43.

And I think you, in general, went to

-- it's in the Ebert reference and it's -- I think it's at Page 5 at the top of the page. And in Ebert it says an object of the present invention is to provide a method of fabricating laminated TDD devices that is compatible with volatile or heat-sensitive drugs, enhancers or other components that cannot be subjected to drying or heating, such as would occur in an oven.

Do you see that?

A. Yes, I see that.

Q. And the way that Ebert solved that problem was to extrude the drug as a gel onto the adhesive layer to avoid having to expose the drug to drying; right?

A. He did that, yes.

Q. And you agree that a person of ordinary skill in the art would not have added an antioxidant to protect against degradation caused by heat; right?

A. He talks about oxidation as well.

Q. You agree that a person of ordinary skill in the art would not have added an antioxidant to protect against degradation caused by heat?

A. Okay. Let me explain.

Q. Would you agree that --

A. No. I don't agree with this.

Q. So let's look at your deposition, let's go to Page 38 of your deposition. Can you put that on?

Thank you. Look at Line 12.

And at Line 12, you were asked: "A person of ordinary skill in the art wouldn't have added an antioxidant to protect against degradation caused by heat?

"Answer: I would think so.

"Question: You would think they would or you would think they would not?

"Answer: I think they would not." Were you asked that question and did you give those answer?

A. Yes, I did.

Q. Okay.

A. But heat is one thing and oxidation at a higher heat is a different thing. Oxidation takes place at higher heat and faster.

So if you told me that you're going to put it in a container and you heat it at

whatever temperature you want, I would say that that doesn't have anything to do with oxidation. But if you put it in an oven to make a transdermal patch, you have heat and you have oxygen, then it's a different situation.

When you heat it up, every ten degrees you double the degree of oxidation.

Q. So let's go on.

You have not cited any literature showing that rivastigmine is heat sensitive or a volatile drug, have you?

A. I want you to know that it's a liquid and liquids are really more volatile than solid.

Q. So let me ask the question again: You do not cite any literature showing that rivastigmine is a heat sensitive or volatile drug, do you?

A. I have not formulated it myself. No.

Q. And to make a transdermal patch, it is common to mix the drug with the adhesive in solvent; right?

A. Mix the adhesive in?

Q. It's common to mix the drug with the adhesive in solvents?

A. The adhesive has solvent already.

Q. Let me try that again. And that's called the matrix-type patch; right?

A. Where you -- when you finally make the product.

Q. It's a matrix, matrix patch?

A. Correct. Or a drug-in-adhesive patch.

Q. And after the drug is mixed with the adhesive, it's conventional to use elevated temperatures to drive out the solvent when making a matrix-type patch; right?

A. Correct.

Q. And that's the conventional method of making a patch formulation; right?

A. Well, that's one method. There are different kinds of methods.

Q. In fact, you said at your deposition 90 percent of the patches are of the matrix type; right?

A. Yes.

Q. And you also cite Ebert because it discloses a transdermal delivery device; right?

A. Right.

Q. And by the way, the rivastigmine patches that are at issue here, they're matrix type of

patches; right?

A. They're three types. Now, on all three or the actual product?

Q. Noven's product.

A. Oh, Noven's product. I'm sorry.

Noven's product is a drug-in-adhesive patch. Yes.

Q. And you cited Ebert because it discloses a transdermal device; right?

A. One of the reasons.

Q. But Ebert was not the only patent relating to nicotine in a transdermal device as of 1998, right?

A. Right.

Q. And there were patents as of 1998 that talked about nicotine transdermal devices that did not use an antioxidant; right?

A. I don't know that.

Q. You saw Dr. Klibanov gave a list of such products; right?

A. Yeah. Yeah, of course.

Q. So, as of 1998, there existed transdermal patches using nicotine that did not include an antioxidant?

A. Nobody says that they couldn't do it. I keep on coming to the same thing. It's formulation dependent.

Q. Okay.

A. You keep on asking me the same question.

Q. And you did not do a patent search on nicotine transdermals to see how many transdermal nicotine formulations were out there and whether they included an antioxidant; right?

A. No, I did not do that.

Q. And the one patent that you relied on, the Ebert patent, was provided to you by Noven's lawyers; right?

A. K & K. Kenyon & Kenyon.

Q. Right. Now, Dr. Kydonieus, you worked on a product and I may mispronounce it, so bear with me, called Selegiline.

A. Selegiline.

Q. Thank you. Right?

A. Yes.

Q. And that has a benzylic carbon bond; right?

A. No.

Q. What's that?

A. No, I don't think so.

Q. Well, let's go to Slide 65.

A. Yeah.

Q. Does Selegiline have a benzylic carbon bond?

A. I don't think so, but we have the expert here. He can tell us --

Q. Well --

A. -- whether it has a carbon or not.

Q. So, and when you --

A. There's a carbon between -- before the other carbons, so I don't think that it is benzylic carbon. But I'm not the organic chemist and I don't want to say one way or another. But I don't think it is.

Q. Well, when you formulated Selegiline into a transdermal patch, you did not use an antioxidant; right?

A. I did not use an antioxidant because the formulation that we developed was -- mainly evolved around another product that was already in the market and had patents. And we decided to use an unrelated adhesive, which they said that it would not work with Selegiline.

Q. So let me try --

A. A long way to -- the only way to make it work with Selegiline and that's when we found the patent.

Q. And it did not have an antioxidant in your patent, either, did it?

A. No, because that's -- we did ten days' worth of work.

Q. Okay. And Selegiline has a tertiary amine; right?

A. Yeah.

Q. Just like the tertiary amine in Sasaki?

A. I'm not saying that it was not oxidized at some point, I'm saying that we made a formulation for other purposes to show that some adhesives that the literature said it would not work with Selegiline would work with Selegiline and that's why we filed a patent.

Q. I just want to make sure it's clear on the record that the patent that you filed on Selegiline for a transdermal patch in which Selegiline has a tertiary amine did not include any examples that had an antioxidant in them, did they?

A. And I have to say that's true, but I have to say also that this is a very preliminary work. This is based on few hours of work.

MR. CONDE: I have no further questions at this time, Your Honor.

THE COURT: All right. Any redirect?

MR. LEE: Yes, Your Honor.

REDIRECT EXAMINATION

BY MR. LEE:

Q. Do you recall your testimony on cross-examination of when BHA was removed from Brij 97?

A. The date was January 1, 1991.

Q. So as of the date of the GB 040, was there antioxidant in the Brij?

A. Yes, there was antioxidant in the Brij.

Q. Would one of ordinary skill in the art have been aware of that?

A. Of course.

Q. Can you look in front of you, Plaintiff's Exhibit 231.

A. Where is that.

Q. In the book in front of you, Plaintiff's

Exhibit 231.

A. 231? Okay.

Q. Is that your patent application that you were discussing on cross-examination?

A. Yeah, on Selegiline, yes.

Q. Is there any stability data in this patent application at all?

A. No.

Q. Did you do any stability testing for this patent application?

A. No.

Q. And can you explain to us again why you filed this patent application, what was novel about it?

A. Well, what was novel was that there were a lot of patents saying that this type of adhesives would not work with transdermal delivery of Selegiline. And we needed some protection if we were to develop this and we looked at this and my philosophy is yeah, they can be made to work and we made them work. So it is basically developing, using the polymers of a patch that would be around the inventions of other people so that we can try to make a Selegiline patch.

Q. When you say you were trying to see if it would work, did you mean you were trying to see if it would be stable for an extended period of time?

A. No, if it would work -- first of all if we could formulate it. Basically they said you cannot formulate it and you cannot deliver it through human skin, it would not work.

Q. And you mentioned that you were trying to protect yourself with this patent?

A. Correct.

Q. And why did you need protection?

A. Why did we need protection?

Q. Yes.

A. Because if you do not have protection, you don't make a product.

Q. So once you got this patent on file, were you then prepared to see if you could develop a formulation for the marketplace?

A. We are three people, including myself, that is Samos Pharmaceuticals, we own that company and we put our own money into developing this, so our philosophy is we're going to develop it, as we did file the patent, get the patent,

and then try to out license, because if it needs an antioxidant, there is nothing to it, we'll put an antioxidant. If it needs something else, we'll do something else, but we develop the patent, we got protection, and we got to show that it permeates through skin at the levels that are required to give us therapeutic level, and that's what you need to sell it to somebody.

Q. When you were being questioned about Elmalem, I believe you testified that the patches were only wet for a matter of hours?

A. What was wet?

Q. I think you testified that the patches were only wet for a matter of hours?

A. I don't know if that's exactly the words he used, but I think he meant -- I may be wrong what he meant. I thought you meant the solution that you make before you put it on to the coater, you try to minimize those hours.

Q. When you have a drug in an adhesive matrix, and it's already been formulated, is it in solution?

A. Yes, it is in solution.

MR. LEE: That's all, Your Honor.

THE COURT: Thank you.

Dr. Kydonieus, you may step down. Thank you.

Mr. Lee, do you have anything more?

MR. LEE: No, Your Honor, we have nothing more.

THE COURT: All right. Thank you very much. Do you have a case.

MS. JACOBSEN: Yes, we do, Your Honor. We move for a judgment as a matter of law. Both of Noven's experts admitted that even if a drug is susceptible to oxidative degradation, potentially theoretically susceptible, that doesn't mean it's going to undergo oxidative degradation in a formulation, and the rate and the extent cannot be predicted. And that means whether or not you have a problem cannot be predicted.

And both of Noven's experts admitted that degradation is formulation dependent, and that means Noven hasn't proven that a person of ordinary skill in the art would have been motivated to combine rivastigmine with an antioxidant and a transdermal patch.

THE COURT: I'm going to deny the motion. Let's go ahead.

MR. JACOBSEN: Your Honor, plaintiff's only witness is Dr. Klibanov. It's up to Your Honor if you want to start today. We disclosed our slides last night and we have just been given some objections and the parties haven't had an opportunity to work through.

THE COURT: Well, I don't know how much time, how much time you're planning on doing with Dr. Klibanov. I don't know how much time there is for cross. I don't mind stopping for today as long as we finish tomorrow.

MR. KALLAS: I'm certain that we'll finish tomorrow. Noven has dropped some of its case so we can work with Dr. Klibanov to shorten some of his direct examination.

THE COURT: Are you confident, Mr. Lee, that we'll finish tomorrow?

MR. LEE: Yes. Before I say that --

THE COURT: Roughly speaking the plaintiff has used three hours and fifteen minutes and you have used two hours and seventeen minutes.

MR. LEE: Right. So if we use another four hours tomorrow, I'm sure we'll be finished.

THE COURT: They have less than four hours. All right. In any event, I hear agreement. Just for bookkeeping purposes if it's all right, we'll just charge each side twenty-five minutes to make sure we finish tomorrow. Okay? You can use it to work out your objections or whatever else. Are we good with that?

MS. JACOBSEN: Yes, Your Honor, except according to our time keeping, we have only used two hours and twenty minutes.

THE COURT: I've gotten the people reversed.

MS. JACOBSEN: Then I think that's all right.

MR. KALLAS: We guesstimate we have four hours and thirty-eight minutes left.

THE COURT: All decisions of the judge are final, but we're in the same ballpark, but I do have the parties reversed, because -- Mr. Lee, with this additional information we're

still good?

MR. LEE: I've tried to do the calculation in my head.

THE COURT: You have got three hours and ten minutes left.

MR. LEE: I'm only concerned with how much time they have left, because if they use up all the time, then I won't be able to -- so if they have four hours and a half, that will give me two-and-a-half hours and that's more than enough.

THE COURT: I think we have a deal here.

MS. JACOBSEN: Sorry, Your Honor, did you say we will be charged twenty-five minutes.

THE COURT: I'm going to charge you each twenty-five minutes so in case either or another you start going really long tomorrow, you got to stop. In other words, there is some time that we're not going to use, it seems to me fair to split it between the two of you.

MR. KALLAS: We're in the ballpark of four hours, Your Honor.

THE COURT: Well, that's no problem because you have -- even if I give you another twenty-five minutes, you still will have more than four hours left.

MR. KALLAS: We'll shave it down to three hours.

THE COURT: So we'll be finished. I will be back here tomorrow morning ready to go at 8:30, and presumably you all will, too, and we'll have fun tomorrow. Thank you very much. We'll be in recess.

(Court recessed at 4:10 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 1 to 304 inclusive is a true and accurate record of the above-captioned proceedings on the 1st day of December, 2014, in Wilmington.

IN WITNESS WHEREOF this 1st day of December, at Wilmington.

Heather M. Triozzi, CSR, RPR
Cert. No: 184-PS
Exp: Permanent

DATED: December 1, 2014