

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS )  
CORPORATION, et al., ) Trial Volume 1  
)  
Plaintiffs, )  
) C.A. No. 13-527-RGA  
v. )  
)  
NOVEN PHARMACEUTICALS, INC., )  
)  
Defendant. )

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 APPEARANCES CONTINUED:  
2  
3

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

6 -and-

7 KENYON & KENYON  
8 BY: STEVEN J. LEE, ESQ.  
9 BY: MICHAEL K. LEVY, ESQ.  
10 BY: CHRISTOPHER J. COULSON, ESQ.

11 Counsel for the Defendants  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 THE CLERK: All rise.

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

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

5 MR. LEE: I am, Your Honor.

6 THE COURT: All right. Yeah.

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

14 Can we put up Slide 2?

15 The Court found that Watson had not  
16 met its burden of proof that those claims were  
17 invalid, and explained that, the obvious  
18 determination in this case turns on whether a  
19 person of ordinary skill in the art in January of  
20 1998, looking at all of the prior art, would have  
21 known rivastigmine was susceptible to oxidative  
22 degradation. If the answer is yes, the asserted  
23 claims of the '023 and '031 patents are invalid  
24 because the addition of an antioxidant to a

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

4 In this case, Noven will prove by  
5 clear and convincing evidence that a person of  
6 ordinary skill would have known that rivastigmine  
7 was susceptible to oxidation, that Claims 7 and  
8 16 of the '031 patent are invalid and will do it  
9 based largely on evidence that was not before the  
10 Court in those earlier cases.

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

17 Put up Slide 3.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 explain that the Weinstock 1981 article shows  
2 that Elmalem would have been understood by one of  
3 ordinary skill in the art as teaching that  
4 rivastigmine was susceptible to oxidative  
5 degradation. Unlike any of the experts in the  
6 Watson case, either for plaintiffs or defendants,  
7 Dr. Kydonieus has spent the bulk of his  
8 40-plus-year career formulating and developing  
9 transdermal delivery systems.

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

15 Can we put up Slide 5.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

17 Let's put up Slide 6.

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

24 When describing their work in

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

21 Put up Slide 8.

22 On the left here we have the  
23 structure of rivastigmine as it appears in GB  
24 040, and on the right, we have the structure of

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

16 Put up slide nine.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

9 Put up slide ten.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 would have known that rivastigmine would be  
2 susceptible to oxidation.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

13 Dr. Kydonieus will testify that  
14 rivastigmine is an amine compound within the  
15 meaning of Sasaki, and that the transdermal patch  
16 of example two of GB 040 is made with an acrylic  
17 adhesive. Thus, one of ordinary skill in the art  
18 would have been motivated to employ an  
19 antioxidant with a rivastigmine transdermal  
20 patch. He will testify that the amount of the  
21 tocopherol antioxidant which Sasaki recommends,  
22 when used in the formulation of example two of GB  
23 040, would fall within the scope of the claimed  
24 antioxidant ranges of claim 7.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

24 Regarding the presence of BHA and

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

3 We have a second defense which was  
4 not brought up in the prior litigations, the  
5 defense of double patenting. Novartis's patent  
6 5,602,176 is the U.S. equivalent of GB 040, it  
7 claims priority from the same German application  
8 as GB 040; it identifies the same inventor,  
9 Albert Enz, and contains substantially the same  
10 disclosure. It is owned by Novartis. It claims  
11 rivastigmine, a pharmaceutical composition  
12 containing rivastigmine, a method of treating  
13 Alzheimer's disease with such a composition, and  
14 a systemic, transdermal patch containing  
15 rivastigmine and a carrier. Like GB 040, it does  
16 not disclose the use of an antioxidant. For the  
17 reasons claim 7 and 16 are obvious in view of GB  
18 040 and the other prior art which I referred to,  
19 including the structure of rivastigmine, claim 7  
20 and 16 are obvious variants of the claims of the  
21 '176 patent, and not patentably distinct.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

8 Thank you, Your Honor.

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

11 MS. JACOBSEN: Good morning, Your  
12 Honor.

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 of degradation in every formulation.

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 any compound, including RA7.

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

9 To the contrary, to the extent the  
10 '807 patent mentions stability, it portrays RA7  
11 in a positive light. And as a result, the '807  
12 patent cannot provide the motivation to add an  
13 antioxidant to rivastigmine and the transdermal  
14 patch formulations of GB '040.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

6 Noven, however, points to another  
7 paper published by one of the authors of the  
8 Elmalem study called Weinstock 1981. Weinstock  
9 1981 did not report any stability testing on  
10 rivastigmine. In fact, Weinstock 1981 did not  
11 report any study result on rivastigmine or RA7  
12 because those compounds didn't even exist in  
13 1981.

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

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

24 Unlike Elmalem, the purpose of the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 protocols.

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 degradation under some pharmaceutically relevant  
2 conditions.

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

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

21 And despite nicotine's known  
22 potential to undergo oxidative degradation, as of  
23 1998, none of the commercially available nicotine  
24 transdermal patches were reported to include an

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 antioxidant.

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 antioxidant in the FDA approved transdermal  
2 formulations.

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

22 Thank you, Your Honor.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Mr. Levy.

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

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

8 May I approach, Your Honor.

9 THE COURT: Sure.

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

12 THE WITNESS: Christian Schoneich.

13 THE CLERK: Can you spell that  
14 please.

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

16

17 CHRISTIAN SCHONEICH, PH.D.,

18 the deponent herein, having first

19 been duly sworn on oath, was

20 examined and testified as follows:

21 DIRECT EXAMINATION.

22 BY MR. LEVY:

23 Q. Good morning, Dr. Schoneich.

24 A. Good morning.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

3 A. Yes.

4 Q. What is exhibit DTX 4?

5 A. This is a copy of my curriculum vitae.

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

9 A. It does.

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

12 A. It does.

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

15 THE COURT: Admitted without  
16 objection.

17 BY MR. LEVY:

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

22 Q. And what is your field of expertise  
23 generally?

24 A. My field of expertise is oxidation and

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

10 A. Yes. I was very fortunate to receive a  
11 couple of awards. I was awarded the Young  
12 Investigator Award for the Society For Free  
13 Radical Research in 1990 and '94. I obtained a  
14 Pfizer research scholar award in the years 2001,  
15 2002, 2003 and 2004. In 2005 I was elected as a  
16 fellow of the American Association of  
17 Pharmaceutical Scientists. And then in 2010, I  
18 received the Dolph Simons Award in Biomedical  
19 Sciences.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

10 Q. Do you have experience with pharmaceutical  
11 drug formulation?

12 A. I do have experience with pharmaceutical  
13 drug formulation.

14 Q. Could you briefly describe that for the  
15 Court?

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

5 In this course

6

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

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

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

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

21 MR. MINION: No objection, Your  
22 Honor.

23 THE COURT: You may proceed.

24 BY MR. LEVY:

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

9 Q. And did you form such an opinion?

10 A. I did form such an opinion.

11 Q. And what is that opinion?

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

3 A. Yes.

4 Q. And what does this slide show?

5 A. That is the structure of rivastigmine.

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

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

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

13 A. Yes.

14 Q. And what is JTX019?

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

17 Q. And when did JTX019 publish?

18 A. That was published in 1988.

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

21 A. I did so.

22 Q. And what does JTX019 disclose?

23 A. It discloses the structure of  
24 rivastigmine.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

3 THE COURT: All right. Admitted  
4 without objection.

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

8 BY MR. LEVY:

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

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

16 Q. Can we go back now to the slide?

17 A. Yes.

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 structure which I have shown previously.

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

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

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

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

24 Now, this carbon hydrogen bond is

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

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

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

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

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

24 A. I did not review the prosecution history,

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

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

18 Q. Could you explain what is shown?

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 of others. And the collaborative aspect is  
2 important.

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

13 A. I did so.

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

16 A. I did so.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

12 Radicals --

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

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

17 THE COURT: All right.

18 THE WITNESS: Do you want me to --

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 of the molecule.

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

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

9 BY MR. LEVY:

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

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

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

21 A. Yes. That is on the next slide.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

14                 Q. Can you explain a covalent bond is?

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 atoms.

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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

9           A. The resulting species here are called  
10          radicals.

11          Q. And how are radicals represented in your  
12          diagram?

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

16          Q. What re the implications of forming a  
17          radical?

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

13 Q. Do all covalent bonds have the same  
14 strength?

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

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

24 A. What I really mean is how reactive the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 resulting radicals are.

2 Q. And how does radical stability affect bond  
3 strength?

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

9 Q. What makes a radical more or less stable?

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

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

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

24 Q. You mentioned before the structural

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 that stabilize a carbon radical?

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

5 A. Yes.

6 Q. Do you recognize DTX 32?

7 A. Yes.

8 Q. Can you describe what that is?

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

12 Q. What does this chapter in the textbook  
13 disclose?

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

17 Q. Is this a standard textbook in organic  
18 chemistry?

19 A. This is a standard textbook in organic  
20 chemistry.

21 Q. When did DTX 32 publish?

22 A. This was in 1990.

23 MR. LEVY: Your Honor, we offer DTX  
24 32.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 THE COURT: Admitted without  
2 objection.

3 BY MR. LEVY:

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

24 If we go one step down, we have now

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

24 Q. Okay. Doctor, how do the different bond

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

24 Now, this oxygen has a very easy

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

21 MR. MINION: I'll withdraw my  
22 objection.

23 THE COURT: Thank you.

24 You may continue, Mr. Levy.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

14           A. They are, sure.

15           Q. Dr. Schoneich, please turn to exhibit DTX  
16 91 in your binder, please.

17           A. Yes.

18           Q. What is DTX 91?

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

22           Q. Is this a standard pharmaceutical  
23 textbook?

24           A. That is a standard pharmaceutical

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 textbook.

2 Q. When was DTX 91 published?

3 A. That was published in 1985.

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

6 A. Yes, I did so.

7 Q. What does DTX 91 disclose?

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

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

13 MR. MINION: No objection.

14 THE COURT: Admitted without  
15 objection.

16 BY MR. LEVY:

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

21 A. And this process rivastigmine has become  
22 oxidized.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 what happens next?

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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 degradation?

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

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

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

14 A. They're all generally susceptible to  
15 oxidation.

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

5 A. No, it would not.

6 Q. And why is that?

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

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

19 A. I recall that.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 degradation?

2 A. I recall that.

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

9 A. I have an opinion.

10 Q. And what is that opinion?

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

16 Q. Did you bring a slide explaining that?

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

23 A. Yes.

24 Q. And to what do you refer?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. I refer to the molecule of nicotine.

2 Q. And have you brought a slide showing that?

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

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

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

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

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

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

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

23 A. Yes.

24 Q. What is JTX032?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

3           Q. And what does JTX032 disclose?

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

8           Q. And when did JTX032 publish?

9           A. It was published in 1960.

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

12          A. I did so.

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

15                   MR. MINION: No objection.

16                   THE COURT Admitted into evidence  
17          without objection.

18          BY MR. LEVY:

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 immediately adjacent to aromatic ring systems.

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

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

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

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

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

23 A. That does not affect my opinion.

24 Q. And why is that?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

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

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

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

24          A. Well, the person of ordinary skill in the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

7 A. Yes.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 conditions would not show that it's not  
2 susceptible.

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

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

8 All right.

9 MR. MINION: Thank you.

10 THE CLERK: All rise.

11 (A brief recess was taken.)

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

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

16 BY MR. MINION:

17 Q. Good morning, Dr. Schoneich.

18 A. Good morning.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

10 A. Yes.

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

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

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

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

22 MR. MINION: Your Honor, may I  
23 approach?

24 THE COURT: Yeah.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 BY MR. MINION:

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

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

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

11 A. Yeah.

12 Q. Is that the question and answer --

13 A. Yeah.

14 Q. -- at your deposition?

15 A. Yes.

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

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

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

24 A. Well, as I mentioned before, the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

13      A.  I have not reviewed any such data.

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

16      A.  I have not.

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

18      A.  I have not.

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

23      A.  I don't recall that.

24      Q.  And you agree with the general principle

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

9 A. That's true for every drug.

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

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

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

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

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

17 A. Yes.

18 Q. And you said your definition was  
19 important?

20 A. Yes.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

12          A. Yes.

13          Q. Like a modern pharmaceutical company?

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

19 A. Yes.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

16          A. Correct.

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

10 Q. There may have been other terms?

11 A. Yes.

12 Q. But you searched those terms?

13 A. Yes.

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

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

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

24 A. I have not given you any reference or any

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 number, that's correct.

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

6 A. I have not.

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Exactly.

2 A. I am aware of these compounds.

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

7 A. I did cite two examples.

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

11 A. That's correct.

12 Q. You only focused on the compound nicotine?

13 A. That's correct.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

9 Q. But it's not a benzylic compound?

10 A. It's not a benzylic compound.

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

16 A. Yes.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 immediately adjacent to an aromatic ring. We  
2 have --

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

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

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

10 A. It does.

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

13 A. Yes.

14 Q. And nicotine does not have a carbamate  
15 substituent?

16 A. Yes.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

6 A. Yes.

7 Q. That's the paper from 1960?

8 A. Yes.

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

10 A. Yes.

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

13 A. Yes.

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

21 Do you see that?

22 A. Yes.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1       oxidation of nicotine by Linnell or anyone else?

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

5           Q. One article?

6           A. Yeah.

7           Q. From 1960?

8           A. Yes.

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

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

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

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

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

24          A. I think that specific article does not

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 refer to pharmaceutical formulation.

2 Q. He studied nicotine in its pure liquid  
3 state?

4 A. I think so.

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

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

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

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

18 Q. So you're not aware of any?

19 A. Okay.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 regarding nicotine transdermal formulations;  
2 correct?

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

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

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

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

17 A. I take your word.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

16 A. Yes.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

8                   A. Yes.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 therefore an antioxidant was not necessary?

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

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

8 A. Yes.

9 Q. "Question: So with respect to ProStep,  
10 Nicotrol and Habitrol, you agree that the POSA in  
11 1998 would not have known whether any steps to  
12 reduce oxidative degradation were taken in those  
13 formulations?

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

24 A. Yes.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

8 A. Yes.

9 Q. In your opinion, Dr. Schoneich, a POSA in  
10 1998 could have formulated rivastigmine in a  
11 pharmaceutical composition without the addition  
12 of an antioxidant?

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

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

18 A. I have not reviewed these formulations.

19 MR. MINION: No more questions, Your  
20 Honor.

21 THE COURT: Any redirect?

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

24 THE COURT: All right.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

## 1 RE-CROSS-EXAMINATION

2 BY MR. LEVY:

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

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

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

13 BY MR. LEVY:

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

17 A. Yes.

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

22 A. Yes.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

6 A. Yes.

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

9 A. Yes.

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

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

14 All right, I assume you have another  
15 witness?

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 swear the witness.

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

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

6  
7 AGIS KYDONIEUS, PH.D.,  
8 the deponent herein, having first  
9 been duly sworn on oath, was  
10 examined and testified as follows:

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

14 MR. CONDE: Yes, Your Honor.

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

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

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

21 MR. COULSON: Thank you, Your Honor.

22 DIRECT EXAMINATION

23 BY MR. LEE:

24 Q. Dr. Kydonieus, have you ever testified

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 before in court?

2 A. No, this is my first time.

3 Q. Have you ever worked or consulted for  
4 Noven?

5 A. No, I have not.

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

8 A. No, I have not.

9 Q. How did you first learn about this case?

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

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

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

17 MR. LEE: May I hand it up?

18 THE COURT: Yes. Sure.

19 BY MR. LEE:

20 Q. You have DTX 5 in front of you?

21 A. Yes. Tab one, right.

22 Q. Yes. And can you identify that?

23 A. Yeah, that's my curriculum vitae.

24 Q. Does it accurately reflect your

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

7 MR. CONDE: No objection, Your  
8 Honor.

9 THE COURT: Admitted without  
10 objection.

11 BY MR. LEE:

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

15 A. I received my Ph.D. in chemical  
16 engineering from the University of Florida in  
17 1964.

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

20 A. Around 1970, '72.

21 Q. Can you briefly describe your industry  
22 experience?

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

7 A. Yes. I started that kind of work in late  
8 '70s, maybe '77, 1977. And that was basically  
9 the time that transdermal delivery was being  
10 initiated. It was just the start of transdermal  
11 delivery. And I have been doing that since that  
12 time up to today.

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 sent it to the FDA for approval.

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

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

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

13 We developed at least, I would say,  
14 20 formulations, early-stage formulations in  
15 transdermal delivery at that time.

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

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

24 Q. Did you --

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

9           A. Yes.

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Have you written any other books on  
2 transdermals?

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

6 Q. Can we highlight the last one?

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

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

13 A. That's two now.

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

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

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

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

21 I see from your resume that you have  
22 60 patents and applications, but how many are in  
23 the area of transdermal delivery?

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

6 A. Yes. The Controlled Release Society is  
7 the Scientific Society for Controlled Release of  
8 Drugs and now has thousands of members. But in  
9 1973, I was a co-founder of the Controlled  
10 Release Society with a few other guys. We  
11 started it as a symposium, which officially was  
12 incorporated in 1977 as the Controlled Release  
13 Society.

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 did a lot of work with antioxidants in the area.

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

7 MR. CONDE: No objection, Your  
8 Honor.

9 THE COURT: All right. You may  
10 proceed.

11 BY MR. LEE:

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

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

24 Q. When is the stability considered in the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 formulation process?

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

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

11 A. Yes, of course.

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

16 A. Yes, I was.

17 Q. And is that your experience?

18 A. Yes, it is.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 have two opinions regarding the invalidity of the  
2 '031 patent.

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

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

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

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

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

18 A. Yes, I am.

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

21 A. Yes, I did.

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

24 A. Yeah, they are.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Can we put up DDX 369?

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

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

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

13 THE COURT: All right.

14 BY MR. LEE:

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

15           A. Yes, I was.

16           Q. And is your definition the same?

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 had a team.

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

4 A. No, absolutely not.

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

8 A. Please repeat that. I'm sorry.

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

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

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

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

24 So a POSA would have been motivated

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 to develop a transdermal system.

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

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

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

10 A. The date is 9, February 1996.

11 Q. Who is the lead author on this article?

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

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

16 A. That is rivastigmine.

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

19 MR. CONDE: No objection, Your  
20 Honor.

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

23 MR. LEE: Tab 8.

24 THE COURT: All right. Admitted

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 without objection.

2 BY MR. LEE:

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

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

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

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

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

18 A. I believe there were three milligrams to  
19 12 milligrams per day.

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

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

24 Q. Can we highlight on the summary the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

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

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

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

23 A. That is rivastigmine.

24 MR. LEE: Your Honor, I move to

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 admit JTX 25 into evidence.

2 MR. CONDE: No objection, Your  
3 Honor.

4 THE COURT: Admitted without  
5 objection.

6 BY MR. LEE:

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

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

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

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

24 A. Right. Well, the donepezil was another

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 second-generation inhibitor and it was approved  
2 already.

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

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

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

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

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

24 A. It was one milligram to 12 milligrams per

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 day.

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

4 A. Yes.

5 Q. This is already in evidence.

6 A. Yes.

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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

3 What does that refer to?

4 A. That is rivastigmine.

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

7 A. That's the rivastigmine structure.

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

11 What is that?

12 A. RA7 is the racemic mixture of  
13 rivastigmine.

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

4 What is the (-) enantiomer of  
5 formula I?

6 A. That's rivastigmine.

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

10 Is that a good thing or a bad thing?

11 A. That's a very good thing.

12 Q. And why is that?

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

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

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

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

22 A. Yes, it does as well. Yes.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

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

17 Q. Would one of ordinary skill --

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

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

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

24 MR. LEE: May I approach?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 THE COURT: Yeah, bring him some  
2 water.

3 THE WITNESS: Thank you.

4 BY MR. LEE:

5 Q. Okay. Are you okay now?

6 A. I'm okay.

7 Q. Would one of ordinary skill in the art  
8 aware of the Sramek and formulary article have  
9 been motivated to do further development the  
10 transdermal formulation that is disclosed in GB  
11 '040?

12 A. Of course.

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

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

20 Q. That's fine.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



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

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

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

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

22          A. Yes, I have.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. Yes.

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

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

12 And then I would like to indicate  
13 several prior art references like Elmalem, the  
14 '807 patent, Sasaki, Ebert, and GB '040, which in  
15 effect tell us that an antioxidant was used or it  
16 has to be used.

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

20 A. Yes, I was.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 oxidative degradation?

2 A. Yes, I do.

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

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

10 A. Very, very early in the process.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Can you turn in your binder to tab 14, JTX  
2 28.

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

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

7 MR. CONDE: No objection, Your  
8 Honor.

9 THE COURT: Admitted without  
10 objection.

11 BY MR. LEE:

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 including butylated hydroxyanisole,  
2 metabisulfate, EDTA and others, and it also gives  
3 us the ranges at which the BHT would work, and  
4 those ranges are overlapping the ranges of the  
5 '031 patent.

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

13 A. Of course not.

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

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

20 A. Yes.

21 Q. Can you identify this?

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

3 MR. CONDE: No objection.

4 THE COURT: It's admitted without  
5 objection.

6 BY MR. LEE:

7 Q. Who are the authors of Elmalem?

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

10 Q. Okay. Who is Marta Weinstock?

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

13 Q. Who is the lead author on this article?

14 A. Marta Weinstock.

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

4 Q. Did they also include morphine?

5 A. Yes, it includes morphine.

6 Q. And what would this signify -- I'm sorry.

7 What would have been the significance of this  
8 disclosure to a person of ordinary skill in the  
9 art?

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

17 Q. Now, let's turn to tab 15 which is JTX 30.

18 And can you identify this?

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 MR. CONDE: No objection.

2 THE COURT: Admitted without  
3 objection.

4 BY MR. LEE:

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

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

9 Q. What did these two studies have in common?

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

14 Q. Nicotine?

15 A. Excuse me. Of morphine, my apologies.

16 Q. What are the differences between those two  
17 studies?

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

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

17 A. Yes, I did.

18 Q. Can we put up DDX 306.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

6 A. Yes.

7 Q. Can you explain when this shows?

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

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

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

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

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

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

19 A. Sodium metabisulfate.

20 Q. And she did not use that in Weinstock  
21 1981?

22 A. She used ascorbic acid.

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

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 antioxidant as to any of the drugs listed in  
2 Elmalem?

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

5 Q. '807?

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

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

16 MR. CONDE: No objection.

17 THE COURT: Admitted without  
18 objection.

19 BY MR. LEE:

20 Q. Can you read that into the record?

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

23 Q. Tab nine.

24 A. Nine. Yes. This is a patent number

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 4,948,807, with a date of August 1990.

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

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

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

13 A. Column seven. My apologies.

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

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

20 Q. So can we highlight claim three, please.  
21 Claim three says N-ethyl,  
22 N-methyl-3-{1-(dimethylamino)ethyl}phenyl  
23 carbamate and pharmacologically acceptable salts  
24 thereof. Is that RA7?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. Yes, that's RA7.

2 Q. Let's go back to Elmalem. What is the  
3 ratio of rivastigmine to antioxidants in the RA7  
4 composition of Elmalem?

5 A. Give me a second because I have to find --  
6 that's 12. Right. I'm going back to 12. Yes,  
7 please ask me the question.

8 Q. Can we put up page 1060 from Elmalem,  
9 again. Can we highlight the same passage again.  
10 So my question again is what was the ratio of  
11 rivastigmine to antioxidant in the RA7 compound?

12 A. She indicates as I read before, that they  
13 were freshly prepared and included an equal  
14 weight of sodium metabisulfate, and we have at  
15 the top of that same page that RA7, we had one  
16 milligram per kilogram of, so one milligram she  
17 uses one milligram of sodium metabisulfate to  
18 make one to one. However, RA7 is half  
19 rivastigmine, so the ratio of antioxidant to  
20 rivastigmine would be one divided by .5, which is  
21 two.

22 Q. Can we put up DDX 314. Does this slide  
23 illustrate the calculation that you just gave?

24 A. Yeah, that's exactly what I said before.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 The ratio of the RA7 to antioxidant is one to  
2 one, that's what she's telling us. And since RA7  
3 is only half rivastigmine, the other half being  
4 the enantiomer, then the ratio of antioxidant  
5 used in her formulations were one antioxidant to  
6 half rivastigmine, which then give us two parts  
7 antioxidant per part of rivastigmine.

8 Q. You also referred to Sasaki. Let's  
9 identify Sasaki for the record. Can you please  
10 turn to tab two and identify this document?

11 A. Yes. This is a certified translation of a  
12 Japanese patent that was dated 1984, and inventor  
13 is Sasaki.

14 MR. LEE: Your Honor, I move DTX 12  
15 into evidence.

16 MR. CONDE: No objection, Your  
17 Honor.

18 THE COURT: Admitted without  
19 objection.

20 BY MR. LEE:

21 Q. How does Sasaki suggest to a person of  
22 ordinary skill in the art that rivastigmine would  
23 be susceptible to oxidation?

24 A. Yes. Sasaki indicates that drugs that

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 have amino groups on them are susceptible to  
2 oxidation if they're blended with acrylics. Of  
3 course we know that rivastigmine has nitrous  
4 amino molecules, amino substances on it, trying  
5 to find the right word, but I think I found it,  
6 so the Sasaki patent --

7 Q. Let me ask you a question, then. Is it  
8 your opinion that rivastigmine is an amino  
9 compound or an amine compound?

10 A. Right, it's an amino compound.

11 Q. As that term is used by Sasaki?

12 A. As the term is used by Sasaki. We'll talk  
13 about that in a minute, I guess. So rivastigmine  
14 would have been a product that would oxidize  
15 according to Sasaki if you put it together with  
16 acrylic adhesives.

17 Q. Does Sasaki disclose that there are other  
18 methods of preventing oxidation?

19 A. Yes. He basically says that to protect  
20 from oxidation for this kind of products that  
21 he's talking about our invention, you have to use  
22 antioxidants and his preferred antioxidant was  
23 tocopherol.

24 Q. Can we put up on the board page one, and

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 can we highlight the last paragraph on the  
2 right-hand side. Thank you. I'm going to read  
3 part of this into the record. Says here it is  
4 possible to prevent the dissipation and  
5 photodecomposition of the drug by way of sealing  
6 and light shielding with aluminum laminate  
7 packaging or the like. First of all, what does  
8 he mean by dissipation?

9 A. Of course, if you need to compactly state  
10 it means oxidation.

11 Q. And what is aluminum laminate packaging?

12 A. It is one of the best packaging materials  
13 we have because the aluminum which is part of the  
14 packaging, have aluminum in the middle, and  
15 outside you have two layers of the polymer, and  
16 that does not allow oxygen and moisture to enter  
17 because of the aluminum.

18 Q. But then he says, so after saying that it  
19 is possible to prevent oxidation with aluminum  
20 laminate packing, but then he says but with drugs  
21 blended with a plaster comprising an adhesive  
22 substance as described above. What does he mean  
23 by plaster?

24 A. Plaster is the type of packs.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. What is the adhesive substance?

2 A. The acrylic adhesives.

3 Q. And then he says, amine compounds and the  
4 like, breakdown of the drug will still proceed  
5 even with aluminum laminate packaging. What does  
6 he mean by that?

7 A. That means that you don't have to get in  
8 his invention, you don't have to get oxygen from  
9 the air going into the package, somehow the drug  
10 breaks down even if you don't have air coming  
11 into the package.

12 Q. And he says, they are more than a few  
13 drugs that cannot withstand usage involving  
14 storage for two or three years in the aluminum  
15 packaging. Correct?

16 A. Correct.

17 Q. And does he describe what kind of drugs  
18 those are?

19 A. Yes, he does. The bottom he does that,  
20 but I think it goes on to the next page as well,  
21 I believe.

22 Q. And what kind of compounds, or amino --

23 A. Amino compounds, he's talking about two  
24 compounds, phenolic and amino.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Can we highlight DDX 3, the portion that  
2 starts in particular, it's around 15 lines down  
3 on the left-hand side. It's on page three. I  
4 don't know how to use a laser. In particular,  
5 starting there, and going to here. Going to "And  
6 the like." A combination of high tech and low  
7 tech.

8 So what does this passage describe  
9 relating to amine compounds?

10 A. It basically tells you the amine compounds  
11 that he feels that are, that you know basically  
12 or he has tested that are susceptible, and it  
13 includes a lot of antihistamines like  
14 diphenhydramine as well as Lidocaine, which have  
15 the amino groups from what I have looked at  
16 similar to rivastigmine.

17 Q. Thank you.

18 Can we turn to page two of Sasaki.  
19 Can you highlight the paragraph that says, "Under  
20 such circumstances." So this paragraph says,  
21 "Under such circumstances the present inventors  
22 undertook various investigations and discovered  
23 that if tocopherol is blended in a plaster  
24 comprising an acrylic adhesive substance, if a

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 drug is blended in said plaster the drug will be  
2 stably present without breaking down."

3 What does he mean by breaking down?

4 A. Oxidizing, if you use tocopherol as an  
5 antioxidant so he uses it to prevent oxidation.

6 Q. Does Sasaki describe the amount of  
7 tocopherol that will solve the oxidation?

8 A. Yes, he does, that is on page two.

9 Q. And what is the amount of tocopherol that  
10 Sasaki recommends?

11 A. The amount of tocopherol that he talks  
12 about is .005 to 5, and preferably from .05 to 1,  
13 with overlap of the amounts in.

14 Q. Here in Sasaki he's describing these  
15 percentages relative in the acrylic adhesives;  
16 right?

17 A. Right. And you have to be able to compare  
18 it directly to the '031, you have to transform or  
19 translate those numbers to the complete  
20 composition in '031.

21 Q. And when you translate those numbers, how  
22 do the ratios described in Sasaki, how do they  
23 compare to the ratios in claim one?

24 A. They are right in the middle of claim one,

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 yes.

2 Q. We'll get to that later.

3 A. Okay.

4 Q. Let's discuss the first of the two  
5 asserted claims, claim seven. Have you prepared  
6 an exhibit listing which combinations of prior art  
7 render claim seven obvious.

8 A. Yes, I have.

9 Q. Can we put up DDX 327? Okay. And can you  
10 explain what's shown here?

11 A. Right. Your Honor, GB 040 we already  
12 talked about and the handbook. And optionally  
13 with Ebert, Elmalem and the '807 patent. And then  
14 the last one is GB 040 with Sasaki.

15 Q. Can we put up Claim 7 on the board?  
16 That's at DDX 334.

17 And what does Claim 7 claim?

18 A. Well, Claim 7 claims a transdermal device  
19 but is dependent on claim one. So we're  
20 talking about a pharmaceutical composition as  
21 well containing the -- we can look at that, but  
22 basically the two items here that are different  
23 is the transdermal device and supported by a  
24 substrate.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. So let's look at Claim 1. What are the  
2 elements of Claim 1?

3 A. Claim 1 says that a pharmaceutical  
4 composition comprising rivastigmine with a  
5 diluent or carrier and a percentage of  
6 antioxidant from .01 to .5 percent.

7 Q. And have you prepared a combination of the  
8 two showing the elements --

9 A. I have prepared.

10 Q. -- of Claim 7?

11 A. Claim 7 combines both elements.

12 Q. Can we put that up on the display?

13 This is DDX 335. Does this exhibit  
14 show the combined elements of both Claim 7  
15 incorporating the elements of Claim 1.

16 A. Correct.

17 MR. LEE: The '031 patent, Your  
18 Honor, is JTX 1 and it is -- it's Tab 4 in the  
19 book.

20 THE COURT: Yeah.

21 MR. LEE: And I move it into  
22 evidence.

23 MR. CONDE: No objection.

24 THE COURT: All right. Admitted

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 without objection.

2 By MR. LEE:

3 Q. Now, the first combination that you  
4 referred to on your previous slide was GB 040 and  
5 the handbook?

6 A. Yes.

7 Q. What elements of Claim 7 does GB 040  
8 disclose?

9 A. Well, it discloses a transdermal device in  
10 example two. It discloses a pharmaceutical  
11 composition again in example two.

12 It discloses a therapeutic effective  
13 amount that is in the specification. It  
14 discloses a diluent or carrier in the example two  
15 and it discloses it's supported by a substrate  
16 because example two indicates so.

17 So the only one that it does not  
18 disclose is the about .01 to .5 weight of  
19 antioxidant.

20 Q. Let's put up example two of JTX 19, the GB  
21 040. It's Page 19.

22 And where do you see the diluents?

23 A. Diluents are Eudragit E 100, Durotack 280,  
24 2416 and Brij 97 as well.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 Q. Where do you find the substrate?

2 A. The substrate is on the bottom. That says  
3 spread on top of an aluminized polyester foil.  
4 The aluminized polyester foil is a substrate of  
5 the patch, transdermal patch.

6 Q. Where does it disclose a transdermal  
7 device?

8 A. Well, it discloses right at the top, the  
9 Example 2 transdermal. But down there is where  
10 you cut.

11 Now, the samples, it says that the  
12 film is allowed to dry at room temperature over  
13 four to six hours. It is then cut up into  
14 patches. Patches, of course, are transdermal  
15 devices.

16 Q. And where does it discuss a pharmaceutical  
17 composition?

18 A. Well, it says composition and talks about  
19 compound A, which is rivastigmine. And when you  
20 blend the rivastigmine with the other three  
21 components, the hydrophilic polymer, the acrylate  
22 polymer and the plasticizer, that is a  
23 composition.

24 Q. Can we put up Page 9? You mentioned the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 specification disclosed the therapeutically  
2 effective amount of rivastigmine. Okay. We have  
3 to go down a bit.

4 A. Yes.

5 Q. Is this the passage from the specification  
6 you referred to?

7 A. Right. As indicated, daily dosage is in  
8 the range from .1 to about 25 milligrams. So .1  
9 to 25 milligrams per day. That's the therapeutic  
10 dose that he is indicating.

11 Q. Does GB 040 disclose an antioxidant?

12 A. Not explicitly.

13 Q. Does it implicitly disclose an  
14 antioxidant?

15 A. Yes, it does because Brij 97 at that time  
16 contained two antioxidants, BHA and citric acid.

17 Q. Let's go back to example two on Page 19  
18 and highlight the Brij. Can we highlight the  
19 Brij 97? Okay.

20 How would one of ordinary skill in  
21 the art know that Brij 97 included an  
22 antioxidant?

23 A. At that time, when you use Brij or any  
24 chemical, you would get a data sheet and that

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 tells you the components. And that would tell  
2 you that it contained the BHA and the citric acid,  
3 two antioxidants.

4 Q. Can we turn to --

5 A. However --

6 Q. I'm sorry.

7 A. However -- okay. I'm sorry. Go ahead.

8 Q. Let me just direct you to Tab 7, which is  
9 JTX 9 in your book. Can you identify this?

10 A. Yes. This is a patent 5,061, 480 titled  
11 Tanning Composition dated October 1991 and which  
12 basically gives us information on Brij 97 with  
13 the two antioxidants.

14 MR. LEE: I'd like to admit JTX 9  
15 into evidence, Your Honor.

16 MR. CONDE: No objection, Your  
17 Honor.

18 THE COURT: Admitted without  
19 objection.

20 BY MR. LEE:

21 Q. Can you show me the portion of JTX 9 that  
22 is relevant?

23 A. If you look at Column 3, a little bit  
24 below halfway --

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. The portion around Line 37?

2 A. Oh, yeah, Line 36 or something. Yeah, or  
3 37 maybe.

4 Q. Can you read the relevant portion?

5 A. Maybe 38. Maybe 38.

6 Q. Can you read the relevant portion into the  
7 record?

8 A. Yeah, for the polyoxyethylene 10 oleyl  
9 ether with .01 percent BHA and .05 percent citric  
10 acid known by the CTFA name of Oleth-10  
11 (Tradenname BRIJ 97 and polyoxyethylene.

12 Q. And what would a person of ordinary skill  
13 in the art have understood that sentence to mean?

14 A. That sentence indicates that Brij 97  
15 contains the two antioxidants, BHA and citric  
16 acid and at the levels of .01 percent and .005  
17 percent.

18 Q. So what would a person of ordinary skill  
19 in the art of the disclosures of DTX 20 -- sorry  
20 -- of what is this? JTX, JTX 9 -- have  
21 understood about the composition of example two  
22 of GB 040?

23 A. That example two contained some  
24 antioxidants or BHA, citric acid antioxidants.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Can you please turn to Tab 3, DTX 89?

2 Can you please identify this?

3 A. Yes. This is a manufacturing document for  
4 Brij 97.

5 Q. In your career, have you used documents  
6 such as this in the regular part of your  
7 business?

8 A. Yes, I have.

9 Q. Is this the kind of document that you  
10 normally relied on?

11 A. Yes.

12 MR. LEE: Your Honor, I move to  
13 admit DTX 89 into evidence.

14 MR. CONDE: No objection, Your  
15 Honor.

16 THE COURT: All right. Admitted  
17 without objection.

18 BY MR. LEE:

19 Q. Is there a disclosure of Brij 97 on this  
20 document?

21 A. Yes. On the upper right-hand corner, it  
22 shows Brij 97.

23 Q. Okay. And there's a reference to plant in  
24 the upper left-hand corner. What does that refer

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 to?

2 A. That is the Atlas Point plant where the  
3 product is made.

4 Q. Do you know what the Atlas Point plant is?

5 A. Atlas Point plant was a plant in Delaware  
6 that was owned by Atlas Chemical Industry.

7 Q. Where does DTX 89 disclose an antioxidant?

8 A. Right in the ingredients list, down on the  
9 fifth column, it says antioxidant solution 4.8  
10 pounds.

11 Q. What was the total amount of that, of the  
12 Brij 97?

13 A. It was 12,000 pounds.

14 Q. And there is some asterisks there next to  
15 the antioxidant?

16 A. Right.

17 Q. What does that mean?

18 A. You have to go down to the note and where  
19 you have the two stars, it says that particular  
20 solution contained 25 percent BHA and 12.5  
21 percent citric acid.

22 Q. Have you calculated percentage of  
23 antioxidants that were included in Brij 97  
24 according to DTX 89?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. Yes, I did.

2 Q. Have you prepared an exhibit to explain  
3 your calculation?

4 A. Right. I have.

5 Q. Can we display DDX 355?

6 A. I have.

7 Q. What does this show?

8 A. Okay. The total weight of the ingredients  
9 as we talked about was 12,000 pounds. The  
10 antioxidant solution weight was 4.8 pounds.

11 So 25 percent was BHA and 12.5 was  
12 citric acid. So for BHA, you have 4.8 pounds  
13 times .25 is 1.2 pounds of BHA. So the  
14 percentage of BHA is 1.2 divided by 12,000 times  
15 a hundred to make a percent. And it's .01  
16 percent.

17 And you do the same calculation for  
18 citric acid and you get .005 percent.

19 Q. How does the weight percent of the  
20 antioxidants in the Brij 97 manufactured at the  
21 Atlas plant compare to the weight percentage of  
22 antioxidants in Brij 97, according to JTX 7 of  
23 the '480 patent?

24 A. They're identical.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. There's a reference in GB 040 to Atlas  
2 Chemie, West Germany?

3 A. Yes.

4 Q. And this document is from the Atlas Point  
5 plant of Atlas, I think you testified Atlas  
6 Chemical Company?

7 A. Atlas, yes.

8 Q. Is there a relationship between those two?

9 A. Yes. I do know that they're -- at the  
10 time, they were one company.

11 Q. Is there any evidence that you're aware of  
12 that there was more than one Brij 97 in  
13 existence?

14 A. Not that I know of. I believe --

15 Q. The '480 patent --

16 A. Okay.

17 Q. -- refers to bridge as a trade name of ICI  
18 Americas, Inc. Do you know if there's a  
19 relationship between Atlas Chemical Industry and  
20 ICI Americas, Inc.?

21 A. Yeah, that I know from personal experience  
22 because I'm an old guy, I guess. ICI bought the  
23 Atlas Chemical Industries and it was operating  
24 under ICI.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1                   So when they bought the product, it  
2                   was an ICI product. Now the product really  
3                   belongs to Croda because ICI gave that up.

4                   Q. Novartis contends that one of ordinary  
5                   skill in the art would have been concerned that  
6                   antioxidants may have been incompatible with  
7                   rivastigmine. What is the significance of the  
8                   fact that Brij 97 included in example two of GB  
9                   040 antioxidants?

10                  A. It would show that there is no reason to  
11                  believe that antioxidants are a problem.

12                  Q. Are you aware of any teaching in the prior  
13                  art that would suggest that antioxidants would be  
14                  incompatible with rivastigmine?

15                  A. No, none.

16                  Q. Can we put up DDX 342?

17                                 Can you tell us whether DDX 342  
18                                 accurately reflects the disclosure of GB 040?

19                  A. Again, can you repeat that, please?

20                  Q. Yeah. Can you tell us whether DDX 342,  
21                  the slide that's up on the board accurately  
22                  reflects the disclosure of GB 040?

23                  A. Yes, I'm sure that it does. Yes.

24                  Q. Does GB 040 disclose the structure of

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 rivastigmine?

2 A. Yeah. I can go through it if you want me  
3 to or whatever you want to do. Yes, of course,  
4 it does on the first page. It shows the  
5 structure.

6 Q. Is rivastigmine a promising treatment for  
7 Alzheimer's?

8 A. Absolutely.

9 Q. Does it disclose a therapeutic effective  
10 amount of rivastigmine?

11 A. Yes, it does and we talked about that.

12 Q. Does it disclose how to separate  
13 rivastigmine from RA7?

14 A. Right. We did in example one.

15 Q. And does it disclose a transdermal  
16 composition containing rivastigmine?

17 A. Example two.

18 Q. And does it disclose the superiority of  
19 transdermal over oral or injectable delivery?

20 A. Right. Two or three places I think we  
21 talked about, but I'd be happy to go over it if  
22 anybody wants to.

23 Q. We may have to. Let's move on.

24 Would one of ordinary skill be aware

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 of GB 040 and recognize that the transdermal  
2 system disclose there be required further  
3 development?

4 A. Well, absolutely. The initial kind of  
5 product, transdermal product because it doesn't  
6 show any work on human skin in vitro or vivo. So,  
7 you don't know exactly if you will get the  
8 permeation you want.

9 It does not show even a release  
10 liner, which every transdermal product has a  
11 release liner to protect the adhesive, to prevent  
12 the adhesive from sticking to everything. And it  
13 doesn't even contain or talk about packaging film  
14 to package this product.

15 So all of those things indicate that  
16 this is an early-stage development and needs a  
17 lot more work.

18 Q. Does GB 040 describe any stability testing  
19 of any transdermal system?

20 A. No, it does not.

21 Q. Can you turn to Tab 6 and please identify  
22 this?

23

24

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. Excuse me?

2 Q. Can you please identify it?

3 A. Yes. The Handbook of Pharmaceutical  
4 Excipients. Maybe I'm a little bit hard of  
5 hearing, too.

6 Q. Maybe I spoke too softly.

7 Your Honor, we'd like to move JTX 8,  
8 which is Tab 6 into evidence.

9 MR. CONDE: No objection.

10 THE COURT: Admitted without  
11 objection.

12 BY MR. LEE:

13 Q. So what is the Handbook of Pharmaceutical  
14 Excipients?

15 A. The Handbook of Pharmaceutical Excipients  
16 contains excipients of different kinds that can  
17 be used in the pharmaceutical field or they have  
18 been used in the pharmaceutical field and in the  
19 food area. And they are a source for the  
20 pharmaceutical scientists to look and see, hey,  
21 this has been used. And it gives you also the  
22 ranges you can use, hundred milligrams or  
23 whatever.

24 So the tells you if they have been

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 used and at what levels for pharmaceutical and  
2 food applications.

3 Q. Let's look at an example of a monograph.  
4 Can we turn to JTX 8 at 45?

5 So this is the monograph for  
6 butylated hydroxyanisole or BHA?

7 A. Right.

8 Q. Okay. What is disclosed in Section 6 of  
9 the monograph?

10 A. Right. The butylated -- we talked about  
11 it a couple of times already. It's an  
12 antioxidant.

13 Q. What is described in or disclosed in  
14 Section 7 of the monograph?

15 A. Well, in Section 7, we see the  
16 concentrations that BHA can be used to protect  
17 what we have on the left-hand side.

18 Q. Okay.

19 A. So essentially oils and we also have  
20 topical formulations. And the BHA would be in  
21 the range of .005 to .02.

22 Q. What is the relationship -- let's see. Is  
23 the use of antioxidants in transdermal delivery  
24 systems disclosed in the handbook?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. Topical formulations encompass those  
2 topics.

3 Q. And what, again, is the concentration of  
4 BHA to be used in topical formulations including  
5 transdermal delivery systems?

6 A. Including transdermal formulation.

7 Q. What is the concentration?

8 A. Oh .005 to .02, which really is in the  
9 range of the '031 patent.

10 Q. Remind us: What is the range in Claim 1  
11 of the '031 patent?

12 A. .01 to .05. .5, excuse me.

13 Q. Thank you.

14 Let's highlight Section 12 in the  
15 monograph. What does that disclose about BHA?

16 A. Yeah. It discloses incompatibilities and  
17 it does for every antioxidant that I looked at.  
18 And it tells you what you can use it with and  
19 what you have to worry about.

20 In this case, it tells you --  
21 undergoes reactions characteristic of phenols.  
22 It is incompatible with oxidizing agents and  
23 ferric salts.

24 Q. Does it disclose any incompatibilities

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 with amine compounds?

2 A. No, it does not.

3 Q. Are there monographs in the handbook for  
4 all of the antioxidants that are in Claim 16 of  
5 the '031 patent?

6 A. Yes, they are.

7 Q. Have you prepared a summary chart of the  
8 amount of antioxidants that are claimed in Claim  
9 16 as recommended by the handbook?

10 A. Yes, I have done that.

11 Q. Can we put up DDX 354?

12 What does DDX 354 show?

13 A. Okay. On the left-hand side, we have five  
14 antioxidants that are used in Claim 16. And the  
15 first one is ascorbic acid and you have the  
16 ranges. The range is .01 to .1.

17 Weight of volume is basically the  
18 same as weight to weight. And BHT -- let's look  
19 at the topical formulation .0075 to .1.  
20 A-tocopherol .001 to .05.

21 BHA in topical formulations .005 to  
22 .02. And propyl gallate less than .1.

23 Q. And, again, how did those ranges compare  
24 to the ranges that are claimed in Claim 1?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1           A. All of these ranges overlap the ranges  
2 disclosed in the patent '031.

3           Q. Have you prepared a summary of how GB 040  
4 and the handbook teach the elements of Claim 7?

5           A. Yes, I have done that.

6           Q. Can we put up DDX 364? And can you  
7 explain using DDX 364 where the elements of Claim  
8 7 are found in GB 040 and the handbook?

9           A. Correct. The GB 040, as I mentioned,  
10 example two, talks about transdermal  
11 administration. So we have that.

12                         And it also talks about  
13 pharmaceutical composition. We talked about  
14 that.

15                         The combination of rivastigmine with  
16 the three components that are there, the adhesive  
17 and the E 100. It also talks about the  
18 therapeutic effective amount that was in the  
19 specification section. It is from .1 to 25  
20 milligrams per day.

21                         Let's go to diluent. It describes  
22 diluent and as I mentioned Duratack and Eudragit  
23 E 100 with diluent and supported by substrate. We  
24 talked about that as well. That is the aluminum

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 foil at the bottom of example two.

2 Now, going back into the  
3 antioxidant, as I mentioned, the structure of  
4 rivastigmine, it suggests susceptibility to  
5 degradation. And we have the two antioxidants,  
6 but not at the level of .01 to .5.

7 But the handbook now tells us that  
8 we can use it in all of the antioxidants that are  
9 claimed at that particular level.

10 Q. Why would a person of ordinary skill in  
11 the art have been motivated to combine the  
12 handbook with GB 040?

13 A. GB 040 has the structure rivastigmine  
14 right on the first page. And Dr. Schoneich told  
15 you that it's susceptible to oxidation.

16 And because of that, it knows that  
17 this is susceptible to oxidation. It will  
18 consider as the first option at least in  
19 transdermal delivery, the first option being an  
20 antioxidant.

21 Q. Thank you.

22 What does Ebert add to the  
23 combination of GB 040 and the handbook?

24 A. Ebert describes transdermal patch for the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 delivery of nicotine, which as Dr. Schoneich told  
2 us, again, is similar to the rivastigmine.  
3 And it also shows us that to protect the nicotine  
4 from breaking down, he uses an antioxidant. And  
5 he shows several antioxidants in his patent.

6 Q. Now, let's turn to Elmalem and let me turn  
7 to Elmalem and the '807 patent. They both  
8 describe solutions of RA7, not transdermal  
9 delivery systems?

10 A. Correct.

11 Q. Why are the '807 patent and Elmalem  
12 relevant to Claim 7?

13 A. They're relevant because in transdermal  
14 compositions, the drug has to be in solution. It  
15 is in solution. It's not in water solution, but  
16 it is in a solution.

17 And we know that solutions -- we  
18 know the susceptibility as Dr. Schoneich told us  
19 before, that is a part of the molecule. But it  
20 degrades. I mean, if we had it in a crystalline  
21 form, the rate of oxidation would be lower. But  
22 we have it in solution, so the data that would be  
23 obtained from solutions would be optimum to  
24 transdermal delivery.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Now, have you prepared a demonstrative to  
2 explain the disclosures of Elmalem that are  
3 relevant?

4 A. Yes, I think I have.

5 Q. Can we put up DDX 341? And please tell us  
6 what is disclosed on this slide?

7 A. It shows that RA7 is susceptible to  
8 oxidation and we know that from the structure of  
9 the molecule, rivastigmine molecule. RA7 can be  
10 prevented from oxidizing by an antioxidants. And  
11 that -- we discussed that also.

12 And RA7, as far as oxidation is  
13 concerned, is the same thing as rivastigmine.  
14 And the compatibility of RA7 to an antioxidant is  
15 very good because they both -- both data, the  
16 experiments, and they have not acknowledged any  
17 incompatibility.

18 Q. So let's turn back to the '807 patent, JTX  
19 17 at 9. Given that Elmalem already discloses  
20 RA7, what does the '807 patent add to the  
21 disclosure of Elmalem?

22 A. Well, it does not -- does not add very  
23 much because it -- they both use sodium  
24 metabisulphite.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1           The only thing that it adds is if  
2           somebody has a question about Elmalem, which I  
3           understand it was a question about how and why  
4           the sodium metabisulphite was used. And the '807  
5           patent makes sure that everybody should  
6           understand that the rivastigmine alone was  
7           susceptible to oxidation and it needed an  
8           antioxidant.

9           Q. How would the person of ordinary skill in  
10          the art determine the amount of antioxidant to  
11          put into rivastigmine transdermal formulation to  
12          stabilize it?

13          A. Well, there are a couple of ways. One is  
14          to go back into the handbook and see what kind of  
15          ranges they're talking for your particular  
16          antioxidant. And the other one would be to look  
17          at patent literature and some of similar  
18          molecules to see what amounts they used. And if  
19          you use those, you would have a great probability  
20          of success.

21          Q. In view of the teachings of the '807  
22          patent, Elmalem and Ebert, how would a person of  
23          ordinary skill in the art have addressed  
24          rivastigmine's susceptibility to oxidative

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 degradation? What would they have done?

2 A. Yes. They would have used an antioxidant.  
3 That's the first thing that all of these guys  
4 did.

5 They used an antioxidant. And I  
6 believe because of my experience that there would  
7 not be any problem in having good probability of  
8 success.

9 I honestly have used BHT for many  
10 years and I never had any problem with  
11 compatibilities with B H T.

12 Q. Another combination of prior art that you  
13 referred to was GB 040 and Sasaki.

14 A. Yes.

15 Q. Have you prepared a summary slide  
16 regarding the teaching of Sasaki?

17 A. Yes, I think I have.

18 Q. Can we put up DDX 343? And can you  
19 explain the relevant disclosures of Sasaki?

20 A. Right. Sasaki discloses that amino  
21 compounds are susceptible to oxidation when  
22 they're blended or in addition added to acrylic  
23 adhesives in transdermal systems.

24 And the oxidative degradation is not

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 prevented by packaging impervious to oxygen, but  
2 is prevented by an antioxidant. And his  
3 preferred antioxidant was tocopherol. And as I  
4 mentioned, he had tocopherol. The amount of  
5 tocopherol is per unit of acrylic adhesive.

6 And I calculated the range to the  
7 total formulation and those are the numbers that  
8 are shown on the bottom bullet.

9 Q. Before we get to the.

10 A. .022 to .44.

11 Q. Before we get to that, can we put Claim 1  
12 up on the board? In Claim 1, it says that the  
13 range is 0.01 to about 0.5 percent based on the  
14 weight of the composition?

15 A. Right.

16 Q. In Sasaki, it says that the antioxidant  
17 ratio is based on the amount of the adhesive?

18 A. Right. So you have to change it to the  
19 total composition to be able to compare it apples  
20 to apples.

21 Q. And have you prepared a demonstrative  
22 showing that calculation based on the total  
23 amount of a transdermal delivery system?

24 A. Right.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. And by which transdermal delivery system  
2 did you use as an example?

3 A. I used the example two of GB 040.

4 Q. Let's put up DDX 329 and please explain  
5 what this shows?

6 A. This sounds ominous, but it's very simple.  
7 Sasaki tells us that we have -- he uses .05 to  
8 one percent tocopherol relative to the amount of  
9 acrylate adhesive. Now, we have to be able to  
10 compare it to the '031 patent that talks about  
11 the percent antioxidant to the percent oxidation.

12 So I took the GB 040, example two,  
13 how much acrylic adhesive they use. That  
14 was 44 percent. This is an approximate number  
15 and could be 50 percent, or 52 or 55. But that's  
16 a real number in transdermal delivery. And the  
17 only thing I did, I multiply the tocopherol  
18 numbers.

19 Multiply .005, by .44 and got  
20 translated to .022 antioxidant to the complete  
21 pharmaceutical composition.

22 And the same thing for the upper  
23 limit of tocopherol, which was one percent and  
24 that gives you .44.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Why would a person of ordinary skill in  
2 the art be motivated to combine the teachings of  
3 GB 040 and Sasaki?

4 A. Well, Sasaki teaches that you use -- first  
5 of all, that if you use a material or a drug  
6 which is an amino compound like rivastigmine, you  
7 use it with acrylic adhesives, you can have the  
8 degradation, oxidative problems. And we know that  
9 rivastigmine is a compound, amino compound.

10 And we also know that both GB 040  
11 and the patent '031 use acrylic adhesive, so it's  
12 a good reason to combine the two.

13 Q. Would a person of ordinary skill in the  
14 art have had a reasonable expectation that in  
15 combining GB 040 and Sasaki they would be able to  
16 make a stable rivastigmine transdermal device?

17 A. Yes, I believe so because he has done that  
18 in example one, for example, and -- well, in his  
19 examples, example one, two and three. But he saw  
20 in tocopherol reduced the oxidation 84 or 95,  
21 big, big reduction in oxidation.

22 Q. Have you prepared a summary to show the  
23 combined teaching of Sasaki in GB 040?

24 A. Yes, I have.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 Q. Can we put up DDX 12. Can you use this to  
2 explain your opinion?

3 A. Yes. I think we talked a lot about this.  
4 I don't know if I should go into detail, but  
5 basically GB 040 talks about a transdermal  
6 device. It talks about pharmaceutical  
7 composition that discloses the effective amounts  
8 of rivastigmine. It discloses the diluent and  
9 the support of a substrate and it discloses two  
10 antioxidants that Sasaki teaches us that for  
11 amino drugs like rivastigmine, the ratio at which  
12 at least tocopherol would be successful and  
13 that's within the range of the '031 patent.

14 Q. In your opinion is claim seven of the '031  
15 patent obvious in view of GB 040 and Sasaki?

16 A. Yes.

17 Q. Now, less turn to claim 16.

18 A. Okay.

19 Q. The only other asserted claim. What are  
20 the elements of claim 16?

21 A. Claim 16 is based on claim 15.

22 Q. Can we put 15 up on the board, claim 15.

23 What does claim 15, what are the elements of  
24 claim 15?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1           A. Right. Claim 15 is a method for  
2 stabilizing rivastigmine by mixing the  
3 rivastigmine with an antioxidant to stabilize the  
4 rivastigmine.

5           Q. And what does claim 16 add to claim 15?

6           A. Claim 16 adds a list of antioxidants, all  
7 of them well-known and presented in the handbook,  
8 so a list of antioxidants.

9           Q. Can we put up DDX 339. What does this  
10 show?

11          A. These are all the elements of claim 16 and  
12 encompassing the claims of -- the elements of  
13 claim 15 as well.

14          Q. What prior art combinations render claim  
15 16 obvious?

16          A. I have a demonstrative of that.

17          Q. Can we put up 328. What are those  
18 combinations?

19          A. GB 040 and the handbook and optionally in  
20 view of Ebert or '807 patent, GB 040 and Sasaki,  
21 and then Elmalem and the handbook.

22          Q. Let's talk about GB 040 and the handbook.  
23 How does the combination of GB 040 and the  
24 handbook, let's put that, the elements of claim

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 16, which is DDX 339, how does the combination of  
2 GB 040 and the handbook render claim 16 obvious?

3 A. Yes. A method of stabilizing, we have a  
4 method, a transdermal method from GB 040, and we  
5 have the antioxidant from the handbook, and the  
6 mixture would stabilize the product, forming a  
7 composition, we have a composition again in  
8 example two, and adding the antioxidant from the  
9 handbook, we have that.

10 Again, the amount of antioxidant  
11 effective to stabilize, we know this from  
12 several-from the handbooks, we are talking about  
13 the handbook here, several antioxidants and the  
14 amounts that would stabilize the product.

15 And the antioxidants from the last  
16 element, tocopherol, ascorbic acid and all that,  
17 they're disclosed in the handbook and the amounts  
18 that you have to use to get stability are shown  
19 there as well.

20 Q. Have you prepared a summary -- I'm sorry,  
21 I didn't mean to interrupt.

22 A. I said and they are encompassed in the  
23 limits of the '031 patent.

24 Q. Have you prepared a summary of your

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 opinions regarding the teachings of this  
2 combination?

3 A. Yes. And that would be better described.

4 Q. Would you put up DDX 361. And can you  
5 tell us your opinions based on the summary set  
6 forth on DDX 361?

7 A. Right. Similar to what I mentioned  
8 before, GB 040 is a rivastigmine composition,  
9 together with handbook, the common antioxidants.  
10 We have that element.

11 Forming a composition by combining  
12 rivastigmine with the antioxidant, we have GB 040  
13 with the rivastigmine composition, and it suggest  
14 susceptible to oxidation, so the use of  
15 antioxidant used or recommended by the handbook  
16 would be obvious. The amount of antioxidants we  
17 use, they are delineated in the handbook with  
18 different antioxidants. And also the  
19 antioxidants list on the last element, all of  
20 them are disclosed in the handbook.

21 Q. Why would one of ordinary skill in the art  
22 have been motivated to combine these references?

23 A. Because the GB 040 discloses the  
24 rivastigmine molecule which tells us that the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 rivastigmine is susceptible to oxidation, and so  
2 using the antioxidants of the handbook is  
3 something that will motivate a POSA to do.

4 Q. What does Ebert add to the combination of  
5 GB 040 and the handbook?

6 A. As I mentioned before, Ebert describes a  
7 transdermal patch where he delivers nicotine and  
8 he shows that he can use antioxidants to  
9 eliminate the oxidation, because nicotine is  
10 susceptible to oxidation, so he uses antioxidants  
11 to eliminate the oxidation issue.

12 So it teaches us -- and since the  
13 nicotine has similar structures with  
14 rivastigmine, he will tell us basically that the  
15 antioxidants he uses and the amounts he uses will  
16 be something that we have to consider in our  
17 determination of what to use in our formulations  
18 to get a better probability of success in the  
19 antioxidant, a probability of success that we  
20 will not get oxidation.

21 Q. Does Ebert disclose any of the specific  
22 antioxidants in claim 16?

23 A. Yes, he discloses tocopherol, it discloses  
24 butylhydroxytoluene, I think it discloses

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 butylhydroxyanisole. I just don't remember the  
2 orders.

3 Q. Can we put DDX 362 up on the screen. Can  
4 you explain what this shows?

5 A. Right. This is basically the summary of  
6 what I was just trying to say. And again --

7 Q. If you could just focus on the additional  
8 elements of Ebert?

9 A. Ebert, right. Ebert shows us the  
10 effective ranges of nicotine, and that is an  
11 advantage, and also it shows us the tocopherol,  
12 BHT, and BHA are being used in his patent, which  
13 are similar to the ones used in claim 16.

14 Q. Let's turn to the combination of GB 040  
15 and Sasaki with respect to claim 16. Is it your  
16 opinion that that combination renders claim 16  
17 obvious?

18 A. Yes, I believe that it does.

19 Q. Did you prepare a demonstrative exhibit to  
20 explain where the elements of claim 16 are  
21 disclosed?

22 A. Yes, that would be a better way to do it.

23 Q. Could we put up DDX 370. Can you explain  
24 where the elements of claim 16 are found in GB

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 040 and Sasaki?

2 A. Yes. Sasaki says that the antioxidants  
3 stabilize amino drugs with acrylic adhesive  
4 compositions. So that is a method of  
5 stabilizing.

6 Forming a composition by combining  
7 rivastigmine with antioxidant, GB 040 talks about  
8 the acrylic adhesive in rivastigmine,  
9 composition, and Sasaki talks about antioxidants  
10 with amino drugs and acrylic adhesives, so there  
11 is a motivation to combine those two.

12 The amount of antioxidants  
13 effective, as I mentioned, I did the calculation  
14 as a percentage to the total transdermal delivery  
15 and they are at the levels of 0.22 and .44 which  
16 are effective to stabilize rivastigmine. And  
17 finally Sasaki teaches tocopherol, which is one  
18 of the antioxidants of claim 16.

19 Q. Why would one of ordinary skill in the art  
20 have been motivated to combine GB 040 and Sasaki?

21 A. Well, because as I mentioned before,  
22 Sasaki teaches antioxidants can be used to  
23 prevent the oxidation of amino drugs when they're  
24 used with acrylic adhesives. And that's what

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 patent '031 shows, and we do know that  
2 rivastigmine appears susceptible to oxidation, so  
3 it is the motivation is there. All the elements  
4 are there, acrylic adhesives, the amino groups  
5 under the rivastigmine, the susceptibility of  
6 rivastigmine, I believe that all the elements are  
7 there for the motivation.

8 Q. In your last answer you said the '031  
9 patent. Did you mean GB 040?

10 A. GB 040.

11 Q. Let's turn to the last prior art  
12 combination.

13 THE COURT: Mr. Lee, even though we  
14 are near the end of this line of questioning, I  
15 think it's time to take our lunch break. So why  
16 don't we come back at two o'clock and we'll pick  
17 up with more direct examination of Dr. Kydonieus.

18 MR. LEE: Thank you, Your Honor.

19 (Lunch break taken:)

20 THE COURT: All right. Please be  
21 seated. Let's continue on.

22 MR. LEE: Your Honor, my staff has  
23 asked me to go back over something, but just  
24 briefly. Can we put up DDX 369.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 THE COURT: Why don't you wait for  
2 your witness.

3 MR. LEE: Good idea, Your Honor.

4 THE COURT: All right. Now you may  
5 proceed.

6 MR. LEE: Thank you.

7 BY MR. LEE:

8 Q. I didn't ask this one question, but did  
9 you in your obvious analysis, did you consider  
10 any secondary considerations of nonobviousness?

11 A. No, I did not. I did in the beginning,  
12 but then it was dropped.

13 THE COURT: I thought the parties  
14 have stipulated that was out of the case.

15 MR. LEE: Just for appeals, Your  
16 Honor, I just wanted to make sure that it's clear  
17 this is something that has been considered and  
18 then dropped.

19 THE WITNESS: I did, but then it's  
20 no more, as I understand.

21 THE COURT: All right.

22 BY MR. LEE:

23 Q. Let's consider the prior art combination  
24 which is Elmalem and then the handbook. Can you

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 explain how the elements of claim 16 are found in  
2 Elmalem and then the handbook?

3 A. We have a demonstrative, that would be the  
4 best way.

5 Q. Can we put up DDX 358.

6 A. Okay.

7 Q. Using 358, can you explain your opinion?

8 A. Yes. Elmalem shows us that the use of an  
9 antioxidant added to RA7 saline solution to  
10 prevent oxidation, so that's a method of  
11 stabilizing rivastigmine. For a composition, RA7  
12 is combined with sodium metabisulfite so that's a  
13 formulating a composition. The amount of  
14 antioxidant effective to stabilize rivastigmine  
15 from degradation, I think as I indicated before  
16 is two parts antioxidant to one part rivastigmine  
17 which is substantially higher than it's shown in  
18 '031, the patent, for example.

19 So it should be effective to  
20 stabilize rivastigmine. And the last element,  
21 it's a list of some antioxidants all of which are  
22 shown in the handbook, they're common  
23 antioxidants.

24 Q. You mentioned the ratio of antioxidant to

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 rivastigmine from the '031 patent. Let's put up  
2 the '031 patent, that's JTX 1. And can we turn  
3 to example one.

4 Is this a portion of the '031 patent  
5 that discloses an effective amount of antioxidant  
6 to rivastigmine?

7 A. Right. This is the one I used, and it  
8 says there that alpha-tocopherol was .15 percent  
9 and the compound A was 30 percent.

10 Q. How do you know that was an effective  
11 amount?

12 A. It says insignificant degradation is  
13 detected after storage of up to six months at  
14 room temperature.

15 Q. And have you compared that ratio to the  
16 ratio disclose in Elmalem?

17 A. Yes, because the ratio here would be .15  
18 divided by 30, so that's .005, and I think we  
19 have that in the demonstrative.

20 Q. Let's display that, DDX 330. What does  
21 DDX 330 show?

22 A. It shows that the Elmalem has a ratio of  
23 antioxidant to rivastigmine of two, and the '031  
24 patent has a ratio of .005. So basically we're

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 saying that the amount of antioxidant in Elmalem  
2 is sufficient to stabilize the product.

3 Q. Why would a person of ordinary skill in  
4 the art have had an expectation that the addition  
5 of an antioxidant would prevent oxidative  
6 degradation of rivastigmine?

7 A. Well, there are several reasons for that.  
8 '176 shows the structure of rivastigmine, and as  
9 Dr. Schoneich told us already it's susceptible to  
10 oxidation, and there are several prior art pieces  
11 that we already talked about that use  
12 antioxidants to protect from oxidation,  
13 specifically for rivastigmine and similar  
14 compounds as in the case of nicotine. So looking  
15 at all these in total it would be obvious that  
16 the addition of an antioxidant is not something  
17 unique.

18 Q. Can we put up DDX 368, please.

19 MR. CONDE: Objection, Your Honor.  
20 Outside the scope of his report.

21 MR. LEE: Your Honor, he reviewed  
22 the '031 patent, I'm just going to ask him  
23 whether these references are disclosed on the  
24 front page of the '031 patent.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 THE COURT: All right. Whether it's  
2 inside or outside the report, I can look at the  
3 patent itself and probably figure that out, so  
4 why don't you do that so I don't have to do that.

5 MR. LEE: Exactly.

6 BY MR. LEE:

7 Q. Are any of these references that we've  
8 discussed this today, the Sramek, Formulary Art,  
9 Ebert, Sasaki, Weinstock, any of those before the  
10 examiner during prosecution?

11 A. None of them was.

12 Q. I now would like to turn to the second  
13 opinion that the asserted claims would have been  
14 obvious to one of ordinary skill in the art over  
15 the '176 patent. Can you please turn to tab 11  
16 in your book and identify that. Do you have tab  
17 11 there?

18 A. Tab 11?

19 Q. Yes, tab 11.

20 A. Yes.

21 Q. JTX 20?

22 A. Yes, that's patent 5,602,176, Phenyl  
23 Carbonate, February, 1977.

24 MR. LEE: Your Honor, I moved to

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 admit JTX 20 into evidence.

2 MR. CONDE: No objection, Your  
3 Honor.

4 THE COURT: All right. Admitted  
5 without objection.

6 BY MR. LEE:

7 Q. Can we put up the '176 patent.  
8 Dr. Kydonieus, can we focus on the assignee part  
9 of the first page. Who does it list as the  
10 assignee?

11 A. Sandoz, Limited.

12 Q. Who is the current owner of the '176  
13 patent?

14 A. Novartis AG.

15 Q. Please turn to tab five in your exhibit  
16 binder.

17 A. Yes.

18 Q. Can you identify this?

19 A. Yes. This is a patent assignment for  
20 patent number 5,602,176.

21 MR. LEE: Your Honor, I move exhibit  
22 PTX 210 into evidence.

23 MR. CONDE: No objection, Your  
24 Honor.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 THE COURT: All right. Admitted  
2 without objection.

3 BY MR. LEE:

4 Q. On the first page of the assignment  
5 history, can we look at assignment two, and who  
6 are the assignor and assignee listed?

7 A. They are -- the assignor is Sandoz LTD,  
8 and the assignee is Novartis AG.

9 Q. Now, if we can put back on the screen JTX  
10 20. Who is the inventor of the '176 patent?

11 A. Albert Enz.

12 Q. What is the relationship between the '176  
13 patent and GB 040 that you previously testified  
14 about?

15 A. I believe that they are the same patent,  
16 that the GB '040 was filed in the UK, and this is  
17 what was filed in the US.

18 Q. Have you compared the disclosures of the  
19 '176 patent and GB 040?

20 A. Yes, I have, and they're very, very  
21 similar.

22 Q. Which claims of the '176 patent render  
23 claim 7 and 16 obvious?

24 A. One, three, eight and eleven.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. So let's go through these claims. Can we  
2 look at Claim 1?

3 What does Claim 1 cover?

4 A. Claim 1 is the molecular structure of  
5 rivastigmine.

6 Q. Please explain what Claim 3 covers.

7 A. The Claim 3 covers a composition  
8 comprising rivastigmine with pharmaceutical  
9 carrier or diluent.

10 Q. What does Claim 8 cover?

11 A. Again, Claim 8 is dependent on Claim 3,  
12 which is dependent on Claim 1. But this one  
13 covers a systemic transdermal therapeutic  
14 pharmaceutical composition containing  
15 rivastigmine and a carrier suitable for  
16 transdermal delivery.

17 Q. And let's look at Claim 11. What does  
18 that cover?

19 A. That is, again, based on Claim 8 and it's  
20 a systemic transdermal pharmaceutical composition  
21 of Claim 8 with an acceptable carrier.

22 Q. Let's put up the slide, DDX 355 with the  
23 elements of Claim 7 and the claims of the '176  
24 patent. And can you identify which elements of

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 Claim 7 are found in Claim 11 of the '176 patent  
2 and its parent claims?

3 A. Yes, I can do that.

4 Let's see, transdermal device that  
5 would be covered by Claim 11. Should I continue?

6 Q. Yeah.

7 A. Okay. Pharmaceutical composition is shown  
8 in, for example, Claim 3 because it's talking  
9 about rivastigmine combined with the carrier or  
10 diluent.

11 Therapeutic amount of rivastigmine  
12 is shown in Claim 8. And I can read that in  
13 there. It's comprising a therapeutically  
14 effective amount of rivastigmine.

15 Diluent or carrier is in, of course,  
16 three and eight and supported by substrate. That  
17 would be something that -- oh, it's not there  
18 distinctly, so...

19 Q. Okay. Regarding the therapeutically  
20 effective amount of rivastigmine, is a  
21 therapeutically effective amount of rivastigmine  
22 disclosed in the specification?

23 A. Yes, that was discussed before and that's  
24 .1 to 25 milligrams per day.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Can we put up Column 5 of the '176 patent?  
2 This is going to be JTX 20.

3 And this sentence at Line 10 to 15,  
4 is that the disclosure of the therapeutically  
5 effective amount of rivastigmine?

6 A. Yes. .1 to about 25 milligrams a day is  
7 the dosage that was mentioned.

8 Q. So what are the differences, if we can go  
9 back to the previous -- yes.

10 What are the differences between  
11 Claim 7 of the '031 patent and Claim 7 of the  
12 '176 patent?

13 A. The differences are two. Supported by  
14 substrate and about .01 to about .5 weight  
15 percent of antioxidant.

16 Q. Would the differences between Claim 7 of  
17 the '031 patent and Claim 11 of the '176 patent  
18 have been obvious to a person skilled in the art?

19 A. Yes, I believe that they should be.  
20 Certainly, support for substrate in a transdermal  
21 device is. Every transdermal device has a  
22 support, a substrate, so that you don't even need  
23 to -- because there's no transdermal patch,  
24 there's no substrate.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1                   So the last one that is mentioned  
2                   there is the antioxidant, and in that particular  
3                   range and we know from Claim 1 that shows  
4                   rivastigmine -- that the rivastigmine is  
5                   susceptible to oxidation. We all know now and  
6                   there are several other prior art pieces that I  
7                   have discussed like the Sasaki patent that in all  
8                   of these are overlap, the range of .01 to .5. So  
9                   it would be obvious to a POSA to do those things.

10                  Q. Would a person of ordinary skill in the  
11                  art rely on the structure of rivastigmine which  
12                  was shown in Claim 1 of the '176 patent?

13                  A. For?

14                  Q. For considering whether Claim 7 would have  
15                  been obvious?

16                  A. Yes, one. One of the items.

17                  Q. Let's turn to Claim 16. How does Claim 16  
18                  of the '031 patent differ from the claims of the  
19                  '176 patent? Maybe we can put up on the board  
20                  the elements of Claim 16.

21                  A. So tell me the question again.

22                  Q. How does Claim 16 of the '031 patent  
23                  differ from the claims of the '176 patent?

24                  A. Okay. The difference is that the '176

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 patent does not show an antioxidant. And this  
2 basically carries through these elements.

3           However, as I indicated before, a  
4 POSA would be -- it would be secondhand for the  
5 POSA to really use an antioxidant with the  
6 elements found in '176.

7           Q. So let's make sure I have this answer on  
8 the record. Would the difference between Claim  
9 16 of the '031 patent and the claims of the '176  
10 patent have been obvious to a person of ordinary  
11 skill in the art?

12           A. Yes. It would be obvious to a POSA.

13           Q. And please explain again why.

14           A. Because, again, we know that in '176, the  
15 rivastigmine structure is shown. And we know  
16 that it is susceptible to oxidation.

17                       And we have also several patents  
18 that we talked about and -- other articles and  
19 other patents that we show that they provide  
20 antioxidants for stabilizing rivastigmine.

21                       So all of that together will tell a  
22 POSA that it's obvious that he has to use an  
23 antioxidant.

24                       And the last one -- by the way, just

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 to complete this, the last one is several  
2 antioxidants, which are well-known standard  
3 antioxidants or the most common ones.

4 MR. LEE: Your Honor, I have no  
5 further questions.

6 THE COURT: All right. That's good.  
7 Any cross-examination?

8 MR. CONDE: Yes, Your Honor. May we  
9 approach the witness, Your Honor.

10 THE COURT: Sure.

11 CROSS-EXAMINATION

12 BY MR. CONDE:

13 Q. Good afternoon, Dr. Kydonieus. We haven't  
14 met before, but my name is Dominick Conde and  
15 I'll be asking you a few questions this  
16 afternoon.

17 A. Sure.

18 Q. Dr. Kydonieus, you're not an expert in  
19 organic chemistry; correct?

20 A. Correct.

21 Q. And with regard to organic chemistry  
22 issues, you would defer to an expert in that  
23 field; right?

24 A. Yes, I would.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. In this case, you're deferring to  
2 Dr. Schoneich?

3 A. Correct.

4 Q. And it's your opinion that a person of  
5 ordinary skill in the art would be able to make  
6 reasonable predictions about the physical  
7 properties of a drug based on its chemical  
8 structure; right?

9 A. Well, of course it depends on what  
10 properties you're talking about, but yes.

11 Q. But you have not provided your own  
12 analysis of the general chemistry principles that  
13 would have let a person of ordinary skill in the  
14 art to reasonably expect that rivastigmine would  
15 be susceptible to oxidative degradation; right?

16 A. No, I have not done that.

17 Q. And that's something you left for  
18 Dr. Schoneich; right?

19 A. Yes, I think he is better than I am.

20 Q. Under your definition of a person of  
21 ordinary skill in the art, to the extent that  
22 they would make reasonable predictions based on  
23 the structure, you would not be included in that  
24 definition; right?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1           A. Well, I think I mentioned, I just want to  
2           make sure that we understand the same thing. I  
3           mentioned that the POSA in my definition is a  
4           group of scientists which include a person that  
5           is a Ph.D. or chemist that can do this.

6           Q. To the extent that the POSA includes that  
7           part as a definition, you're not a POSA?

8           A. I'm not part of the POSA, correct.

9           Q. So now, Dr. Kydonieus, I would like to  
10          discuss with you what knowledge a person of  
11          ordinary skill in the art would obtain from  
12          reading some of the references that you relied  
13          on.

14          A. Okay.

15          Q. Let's start by assuming that a person of  
16          ordinary skill in the art were reading a prior  
17          art reference that mentions a rivastigmine  
18          formulation. Are you with me so far?

19          A. That was doing what?

20          Q. The reference mentions a rivastigmine  
21          formulation.

22          A. Correct. Yes.

23          Q. So to know if any oxidative degradation is  
24          taking place in that prior art rivastigmine

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 formulation, a person of ordinary skill would need  
2 to see data showing what degradation would take  
3 place, if  
4 any, and on what time scale in the absence of an  
5 antioxidant; right?

6 A. Can I say a couple of things?

7 Q. Is that a correct, statement,  
8 Dr. Kydonieus?

9 A. Not really. Not hundred percent. If you  
10 want me, I can try to explain.

11 Q. I just want to know, do you agree with the  
12 statement or not, and then we can move on?

13 A. Not totally, no.

14 Q. And so I want to go another step in my  
15 analysis here. Let's further assume that the  
16 prior art reference mentions rivastigmine  
17 formulation containing an antioxidant. Are you  
18 with me on that?

19 A. Yes.

20 Q. So to know that antioxidant was having an  
21 effect on that prior art rivastigmine  
22 formulation, a person of ordinary skill in the  
23 art would need to see data showing what effect,  
24 if any, the antioxidant has in the formulation.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 Do you agree with that statement, Dr. Kydonieus?

2 A. If I understand what you are saying, that  
3 you put an antioxidant in there and you're going  
4 to look at data to see how well the antioxidant  
5 did.

6 Q. That's not exactly my question, no. My  
7 question is: You're reading a prior art  
8 reference on a piece of paper, you're just  
9 reading a piece of paper, and it's got a  
10 formulation in it with rivastigmine and an  
11 antioxidant. Okay?

12 A. Just --

13 Q. Just looking at the paper.

14 A. Right.

15 Q. Just looking at the paper, you would need  
16 to know -- to know that antioxidant that's  
17 disclosed in that piece of paper was having an  
18 effect on the formulation, a POSA would need to  
19 see data showing what effect, if any, the  
20 antioxidant was having on the formulation?

21 A. Let me say a couple of things.

22 Q. I just want to know, do you agree with  
23 that or not?

24 A. But these questions are not yes or no.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. So if you don't agree, just let me know.

2 A. I don't agree. I would like to discuss  
3 it.

4 Q. So you know that in this litigation, Noven  
5 produced documents which disclosed the  
6 formulation of its patch; right?

7 A. Right.

8 Q. And in that information, they would  
9 disclose the actual ingredients and the list, and  
10 the amount of ingredients that were used in the  
11 patch; right?

12 A. Yes.

13 Q. And this is similar to the type of  
14 information you would see in a reference, for  
15 example, in GB 040, example two provided the  
16 ingredients and the amounts of ingredients;  
17 right?

18 A. Yes.

19 Q. So you would read Noven's list of  
20 ingredients and the amounts of ingredients  
21 similar to the way that you could read a piece of  
22 prior art; right?

23 A. Yes.

24

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1

2

3

[REDACTED]

Q. You're very familiar with that antioxidant?

4

5

A. Very familiar.

6

Q. Do you recall that you submitted a report regarding whether Noven's product infringes in this litigation?

7

8

9

A. Yes.

10

Q. And in that report, you commented on the expert report of Dr. Davies, Novartis' expert; right?

11

12

13

A. Yes.

14

Q. So can we go to slide two, which is paragraph 51 of Dr. Kydonieus's rebuttal report regarding Noven's product.

15

16

17

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?

18

19

20

21

22

23

24

A. I said that, but you don't let me say

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 anything, so yeah, I said that.

2 Q. So as to Noven's product that contained a  
3 known antioxidant, you took the position that  
4 absent data, a person of ordinary skill in the  
5 art could not tell whether the antioxidant in  
6 Noven's formulation was having an antioxidant  
7 effect; right?

8 A. No. I mean, you got to let me speak  
9 because you can't just tell me no, no, yes, yes,  
10 and I just say yes and no.

11 Q. Isn't it correct in paragraph 51 in  
12 discussing Noven's product, you criticized Dr.  
13 Davies because he didn't have data showing the  
14 [REDACTED] was having an effect on Noven's  
15 product?

16 A. There is -- Dr. Schoneich described this  
17 morning and I think I discuss it, too, there is a  
18 susceptibility to oxidation and then there is a  
19 formulation that is formulation dependent, so you  
20 can't tell me about something without -- okay.  
21 You're going to say yes.

22 Q. Dr. Kydonieus, the whole context of this  
23 is how you would read a piece of prior art that  
24 was available. And would you agree with me that

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 absent -- if you have a piece of prior art that  
2 has a rivastigmine formulation plus an  
3 antioxidant, you would not know that antioxidant  
4 was having an effect on that formulation absent  
5 data?

6 A. I would have to look to see if the  
7 molecule was susceptible.

8 Q. Would you agree that without having data,  
9 when you have a piece of prior art that has a  
10 rivastigmine formulation and an antioxidant, you  
11 cannot definitively say that the  
12 antioxidant was having an effect?

13 A. No, in general I would say that the  
14 antioxidant will have an effect, in general.

15 Q. But when Dr. Davies said that [REDACTED] was  
16 having an effect on Noven's product, you required  
17 data; correct?

18 A. Because for infringement, you have to show  
19 me, as I understood from the lawyers, if I'm  
20 wrong, I'm wrong, you have to show me that this  
21 was happening, and you did not show anything. In  
22 infringement you have to show to me it was  
23 happening, and you did not do it.

24 Q. So with regard to GB 040 -- let me back

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 up. So in regard to a piece of Elmalem, in regard  
2 to Elmalem, without any data, it would be fair to  
3 say that the antioxidant used in Elmalem was  
4 having an antioxidant effect, is that fair to  
5 say?

6 A. Yes. I'm saying -- you compare it to the  
7 handbook, and the numbers that you have in the  
8 handbook and what you used in a particular  
9 formulation, the probability of doing something  
10 good, because we are saying that sometimes the  
11 formulations are such that you don't need the  
12 antioxidant.

13 Q. So sometimes you don't need the  
14 antioxidant?

15 A. No, you don't need it, you need it very  
16 little.

17 Q. Let me go back to my question, which is  
18 that with regard to Elmalem, you could just read  
19 the formulation and see it had an antioxidant and  
20 you concluded that that antioxidant was having an  
21 effect on the formulation; am I correct?

22 A. No. I concluded after I checked out the  
23 antioxidant used was in amounts that were at  
24 least as much as it was in the handbook.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Right. But with respect to the Noven  
2 product, [REDACTED] right?

3 A. Yes.

4 Q. And the amount of antioxidant used by  
5 Noven was within the handbook right?

6 A. Yes, but you have to show me an  
7 infringement.

8 Q. Let me finish my question, Dr. Kydonieus.

9 A. The only thing that I'm saying here is  
10 that you have to show me that infringement. You  
11 have to show me that something happened and you  
12 have not shown me what happened. That's what  
13 that says.

14 Q. Okay. So in regard --

15 A. If you want to ask different questions,  
16 I'll be happy to answer.

17 Q. So with regard to --

18 A. That's --

19 Q. So with regard to analyzing the prior art,  
20 we don't have to show you -- you don't have to  
21 show us what happened?

22 A. Me analyzing this?

23 Q. So, with regard to Elmalem, you don't have  
24 to show us that it's having an antioxidant

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 effect; is that your testimony?

2 A. I have to show you that the amount is  
3 sufficient, as I understand it. It is sufficient  
4 as compared to the numbers that I see.

5 Q. I just want you to focus on my question.  
6 So when you're doing your obviousness analysis  
7 and you're reviewing Elmalem, it's your position  
8 that you don't need to have data showing that the  
9 antioxidant used in Elmalem had an antioxidant  
10 effect?

11 A. Yes, if I calculate it and I saw that  
12 there was enough antioxidant to meet the  
13 requirement, then I would say that probability is  
14 that I have a good sign that the antioxidant is  
15 working.

16 Q. So Dr. Kydonieus, the second part of  
17 Paragraph 51, you criticized Dr. Davies because  
18 you say he presents no data to show what  
19 degradation would take place, if any, and on what  
20 time scale based on just looking at the  
21 formulation of Noven's product; right?

22 A. Yes.

23 Q. And so when you're reading the prior art,  
24 you would want to see data to show what

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 degradation would take place, if any, and on what  
2 time scale; correct?

3 A. No. Wrong again.

4 The idea here is that you have to  
5 show me --

6 Q. Okay.

7 A. -- that this phenomena were happening.  
8 Not -- and I'm saying you haven't shown me  
9 anything.

10 Q. Okay.

11 A. Show me something because infringement  
12 you're supposed to show me, as I understand it.  
13 And if I'm wrong, please tell me.

14 You have to show me that something  
15 is happening. And Dr. Davies did not show me.

16 Q. So when you're reviewing the prior art in  
17 the obviousness analysis, you don't have to show  
18 me that the formulation that's at issue would  
19 actually have degradation and how much?

20 A. Yeah, I did.

21 Q. Did you show how much degradation and how  
22 much took place in the Elmalem formulations  
23 without an antioxidant?

24 A. No, I don't -- I didn't show you --

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. So with regard to Elmalem, you are using a  
2 different standard than what you used for Dr.  
3 Davies on infringement?

4 A. I don't use different standards. I use  
5 the same standards.

6 Q. And, of course, you know that Noven said  
7 that [REDACTED] was needed to prevent the API from  
8 oxidizing; right?

9 A. Well, I mean, I don't know what they said.

10 Q. That's what they said; right?

11 A. They could have said that. I'm not saying  
12 that antioxidants are not used to prevent  
13 oxidation. You don't understand me.

14 I'm trying to tell you three times  
15 and you don't want to get it. I'm not saying  
16 that the antioxidants are not used to reduce  
17 oxidation.

18 If that is -- if it is -- we should  
19 be on the same page on that. I'm saying that you  
20 are supposed to show me that these effects are  
21 happening in infringement and you have not shown  
22 me any of this.

23 That's all I'm saying. And all  
24 these statements you're making --

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. So, Dr. Kydonieus, let's go a little  
2 further with this. Absent experiments, a person  
3 of ordinary skill in the art would not know if an  
4 antioxidant was having an effect on the prior art  
5 formulation; right?

6 A. Would you repeat that?

7 Q. Sure. We're back into our hypothetical.

8 A. Yeah.

9 Q. Okay. And we've got a rivastigmine  
10 formulation --

11 A. Yes.

12 Q. -- with an antioxidant in it; right?

13 A. Right.

14 Q. And my question is: Absent experimental  
15 data, a person of ordinary skill would not know  
16 if an antioxidant was having an effect on that  
17 formulation, right?

18 A. On that specific formulation?

19 Q. Right?

20 A. I don't know the answer.

21 Q. Okay. Well isn't it true that the mere  
22 possibility of an effect by an antioxidant is  
23 very different from showing that there is an  
24 actual effect in the specific -- in the specific

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 formulation?

2 A. Not really. I have a good confidence in  
3 myself. If I use an antioxidant in -- at least  
4 with a drug that has some susceptibility to  
5 oxidation that I would get --

6 Q. Let's go back to your report. Let's go to  
7 Slide 7, please.

8 So, again, you stated in your  
9 rebuttal report "the mere possibility of an  
10 effect is very different from showing an actual  
11 effect in a specific transdermal system."

12 Do you see that?"

13 A. I'm saying that a -- specific to a  
14 formulation.

15 Q. Right. And so with regard to the prior  
16 art formulations, the mere possibility of an  
17 effect is very different from showing an actual  
18 effect; right?

19 A. It depends. We don't know. The answer is  
20 it depends on the formulation. That's what I'm  
21 saying.

22 Q. Your statements --

23 A. Your statement was in the susceptibility  
24 of oxidation of a drug, and the formulation that

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 is dependent on the formulation, how much you  
2 have. You could have degradation that is two  
3 percent and that's acceptable.

4 Q. So, Dr. Kydonieus, let's go --

5 A. You can get four percent and that's  
6 acceptable.

7 Q. So what you're saying is you would need to  
8 know, as a formulator, how much degradation was  
9 in the formulation without an antioxidant; right.

10 A. Without an antioxidant?

11 Q. Right.

12 A. Yeah, I will do that.

13 Q. Right.

14 A. If you heard what I said today, if you  
15 remember that, I said the high temperature test  
16 that I said it was one week or two weeks, you  
17 will test your product without an antioxidant in  
18 the particular formulation.

19 Q. Right.

20 A. So with three antioxidant formulations  
21 with three antioxidants to compare to see  
22 where --

23 Q. And, Dr. Kydonieus, I'd like to stick to  
24 my question again.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1                   So with regard to a prior art  
2                   formulation, you would want -- the mere  
3                   possibility of an effect in that formulation is  
4                   different from showing an actual effect?

5                   A. I don't -- I cannot agree with that  
6                   because you are telling me, for example, with  
7                   Elmalem that Elmalem or Dr. Weinstock got the  
8                   Nobel prize in Israel. Maybe not the Nobel  
9                   prize, but some prize in Israel, the highest  
10                  prize in medicine in Israel. She got the prize.  
11                  That she does not -- she uses -- she uses an  
12                  antioxidant for no reason.

13                  Q. So you hold Dr. Elmalem to a different  
14                  standard than you held Dr. Davies for his  
15                  infringement report; is that what you're saying?

16                  A. No, I'm not saying that. I'm saying that  
17                  in the case with Dr. Davies, because of  
18                  infringement, he had to tell me that something  
19                  was happening, as I understand it, to prove to me  
20                  that something was going. That's infringement as  
21                  I understand it.

22                  Q. Okay. So --

23                  A. In the case of Elmalem -- it is a  
24                  scientific journal of super experts in Elmalem's

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 case. Dr. Weinstock, and when she tells me that  
2 I use an antioxidant, I know that, especially  
3 when there is nothing else in it except RA7,  
4 she's using that antioxidant so that RA7 does not  
5 degrade.

6 Q. Okay. So, Dr. Kydonieus, an experiment  
7 must be conducted to know what effect a specific  
8 antioxidant will have and in any particular  
9 specific transdermal device. Do you agree with  
10 that?

11 A. What I agree with is that you don't know  
12 if a particular formulation, transdermal or  
13 otherwise, will be even if you have a susceptible  
14 molecule, if a particular formulation would allow  
15 you to get the required antioxidant effect, or  
16 the required known degradation so that you would  
17 have a product that would be accepted by the FDA.

18 Q. So just looking at whether a formulation  
19 as you put it is susceptible to -- let me start  
20 over.

21 So just saying that a compound may  
22 be susceptible to oxidation doesn't tell you how  
23 much oxidation would occur with that compound in  
24 any specific formulation or for any specific

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 time; right?

2 A. Forget about the time. The time is the  
3 same thing. We are talking about drugs that go  
4 for two years. So for two-year period of time,  
5 that's what you're looking for.

6 Q. So let me go back to my question. Just  
7 knowing that a compound as you put it is  
8 susceptible to oxidation doesn't tell you how  
9 much oxidative degradation will occur over any  
10 particular time; right?

11 A. Over any particular time? It doesn't tell  
12 you how much degradation you will get period  
13 depending on that formulation.

14 Q. So it could be even if a compound is as  
15 you put it susceptible to oxidation, the  
16 oxidation was so low that it may not need any  
17 special treatment; right?

18 A. Well, what we're saying here again is if  
19 the drug is susceptible to --

20 Q. Doctor, I just want to you stick to my  
21 question. It's a hypothetical.

22 You agree that it's possible that  
23 even if a compound was as you put it susceptible  
24 to oxidative degradation, that the amount of

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 degradation would be so low that it would not  
2 need an antioxidant or any other special treatment  
3 for oxidation?

4 A. In that particular formulation, it may be.

5 Q. So now you agree that none of the prior  
6 art references that you cited provided any  
7 stability data on rivastigmine or RA7  
8 formulations; right?

9 A. Stability data. Actual stability data?

10 Q. Yes.

11 A. I can't think of any at the moment.

12 Q. And even if the prior art showed that  
13 there was some -- excuse me. Even if the prior  
14 art showed from some stability data that there  
15 was some impurity, a person of ordinary skill in  
16 the art would need to identify the structure to  
17 know if that impurity was caused by oxidation;  
18 right?

19 A. Sure. If you have oxidation, you have to  
20 look at the -- let me --

21 Q. Stay to my question. In order to know --

22 A. You're talking about science, you're  
23 talking about words. That's what bothers me.

24 Q. I'm talking about science.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. You're not.

2 Q. In order to know whether the impurity was  
3 caused by oxidative degradation, you would need  
4 to know the structure of the impurity; right?

5 A. You would have to know that if it is  
6 larger than one percent and you have to test it.

7 Q. So if it's not larger than one percent,  
8 you don't really have to worry about it?

9 A. You have to look to see if it is in the  
10 literature, and that's sufficient to let the FDA  
11 to allow your product.

12 Q. Dr. Kydonieus, you have not cited any  
13 prior art disclosing the structure of any of the  
14 oxidative degradation products of rivastigmine,  
15 have you?

16 A. No, I have not.

17 Q. So now let's go to GB 040.

18 A. Okay.

19 Q. And GB 040 is the only reference you cite  
20 that discloses rivastigmine or RA7 in a  
21 transdermal device; right?

22 A. Well, also the '176 patent.

23 Q. The '176?

24 A. Yes.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. We're going to assume the '176 and GB 040  
2 are the same unless I say otherwise. Are you  
3 okay with that?

4 A. I'm okay, the claims are different.

5 Q. And GB 040 is not limited to transdermal  
6 formulations of rivastigmine; right?

7 A. Not specifically.

8 Q. So, for example, GB 040 includes  
9 formulations that can be administered orally or  
10 subcutaneously; right?

11 A. Sure.

12 Q. And GB 040 does not expressly disclose an  
13 antioxidant; right?

14 A. It does not explicitly, implicitly.

15 Q. I just wanted an answer to my question,  
16 which is GB 040 does not expressly disclose an  
17 antioxidant?

18 A. Expressly or explicitly, yes.

19 Q. I'm sorry, I just want to make sure the  
20 record is clear. GB 040 does not expressly  
21 disclose an antioxidant; correct?

22 A. Is the word expressly the same thing as  
23 explicitly?

24 Q. Yes.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. Okay. That's what I said.

2 Q. I thought you said something else. Thank  
3 you.

4 Now, in your slides, do you recall  
5 that you did not contend that GB 040 disclosed  
6 the use of antioxidants to prevent oxidation.

7 A. Yes.

8 Q. That's correct, you didn't disclose that?

9 A. GB 040, yes.

10 Q. In fact, you relied on a handbook for the  
11 use of antioxidants to prevent oxidation, do you  
12 recall that?

13 A. Yes.

14 Q. And you have not cited any reference that  
15 says the first thing you would do with a drug you  
16 believe is susceptible to oxidative degradation  
17 would be to add an antioxidant; correct?

18 A. No, I indicated that.

19 Q. That's not my question. My question is  
20 you haven't cited a reference that says the first  
21 thing you would do with a drug --

22 A. My reference is my forty years doing  
23 transdermal patches.

24 Q. I need to have a clear record.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1                   So you agree you haven't cited a  
2                   reference that says the first thing you would do  
3                   is to add an antioxidant?

4                   A. Yeah, there is no reference.

5                   Q. You know some of the formulations that Dr.  
6                   Klibanov pointed to that had a benzylic carbon  
7                   hydrogen bond, for example, did not include an  
8                   antioxidant; right?

9                   A. Yeah, but as Dr. Schoneich --

10                  Q. Am I correct. Some of the commercial  
11                  products you have seen that did not have an  
12                  antioxidant, but had a benzylic carbon hydrogen  
13                  bond?

14                  A. I don't know that, but I know there are  
15                  some like nicotine that have oxidation, and the  
16                  product in the market does not have an  
17                  antioxidant. But as we said before --

18                  Q. So are you saying that they took the  
19                  antioxidant out after they tried it?

20                  A. No.

21                  Q. So it's not always the first thing that  
22                  someone would do would be to add an antioxidant?

23                  A. They may have done it, probably they have  
24                  done work with antioxidant and then they did the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 experiments that I mentioned with you before, the  
2 accelerated experiments and they say that the  
3 formula that they were using was okay, so they  
4 stuck with that without the antioxidant because  
5 you don't want to put any chemicals including  
6 antioxidants into something that you don't need.

7 Q. With regard to that nicotine product you  
8 referred to, you have no personal knowledge about  
9 how that product was formulated and the work that  
10 was done for it; right?

11 A. That particular product, no.

12 Q. Now, GB 040 does not suggest adding an  
13 antioxidant to any of the rivastigmine  
14 formulations disclosed therein; right?

15 A. Yes.

16 Q. And GB 040 did not measure the stability  
17 of rivastigmine; correct?

18 A. Right.

19 Q. And GB 040 does not disclose the rate or  
20 extent of oxidation of rivastigmine in general or  
21 in a formulation; correct?

22 A. In anything.

23 Q. I'm sorry?

24 A. In anything. We didn't do any stability

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 work.

2 Q. And GB 040 does not provide any data that  
3 would suggest that rivastigmine would undergo  
4 oxidative degradation under pharmaceutically  
5 relevant conditions; right?

6 A. It didn't do any work, no.

7 Q. And you would equate pharmaceutically  
8 relevant conditions to what you testified on  
9 direct, that the product has to remain stable for  
10 two years?

11 A. Yes, you have to do that, if your product  
12 is for two years. If you decided you wanted a  
13 product for one year, then you have to do the  
14 stability for one year.

15 Q. Could you please go to Noven's slide 11.  
16 I don't know if we have that. Do we have that?  
17 It's DDX 361.

18 Now, you see on one of these slides  
19 that you used on direct, DDX 361, on the second  
20 box on the right, it says for GB 040 that it  
21 discloses structure of rivastigmine susceptible  
22 to oxidation. Do you see that?

23 A. Yes.

24 Q. So just to be clear, GB 040 does not

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 actually state that the structure of rivastigmine  
2 suggest susceptibility to oxidation; right?

3 A. It shows the structure.

4 Q. My question is different. My question is  
5 the reference itself does not state that the  
6 rivastigmine -- the structure of rivastigmine  
7 suggest susceptibility to oxidation?

8 A. No.

9 Q. No, it doesn't?

10 A. No, it does not say that.

11 Q. Thank you.

12 And, in fact, none of the references  
13 you cite specifically state that the structure of  
14 rivastigmine suggest susceptibility to oxidation;  
15 correct?

16 A. No. Any references? I'm trying to think.  
17 No, I don't think so.

18 Q. And none of the references you cite  
19 specifically state that a benzylic carbon  
20 hydrogen group makes a compound susceptible to  
21 oxidation; right?

22 A. I have not looked at that, and I --

23 Q. None of the references you cite say that;  
24 right?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1           A. None of the references that I cite state  
2           that. I haven't looked to know which of all these  
3           things are.

4           Q. As you sit here today, you're not aware of  
5           any of the references stating, specifically  
6           stating that a benzylic carbon group makes a  
7           compound susceptible to oxidation?

8           A. No, I depend on my chemists to do that for  
9           me.

10          Q. So my statement was correct?

11          A. Your statement as far as the projects -- I  
12          mean the projects, the prior art that I saw, it  
13          doesn't, it does not show that.

14          Q. Thank you.

15                        I apologize for asking the question  
16                        a second time, because sometimes your answer, I  
17                        wasn't clear which way you were answering. So I  
18                        may have to do that as we go along here.

19                        And GB 040 does not provide a person  
20                        of ordinary skill in the art any information as  
21                        to whether its composition would be stable for  
22                        weeks or whether it would be stable for years;  
23                        right?

24          A. That was from a formulation that was

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 totally uncompleted. You're talking about example  
2 two.

3 Q. I'm talking about the reference GB 040  
4 does not provide a person of ordinary skill any  
5 information as to whether any of its compositions  
6 including example two would be stable for weeks  
7 or whether it would be stable for years; correct?

8 A. No. It is not correct. Because it  
9 provides the rivastigmine which tells the organic  
10 chemist that that's susceptible to oxidization.

11 Q. That wasn't my question, Dr. Kydonieus.  
12 Let's focus on my question. GB 040 does not  
13 provide a person of ordinary skill in the art any  
14 information as to whether example two would be  
15 stable for weeks or whether it would be stable  
16 for years; right?

17 A. Well, you're assuming that the POSA is a  
18 dumb person; right?

19 Q. I'm just asking you what's in the  
20 reference, Dr. Kydonieus. Is it correct, there  
21 is no data in that reference that would allow,  
22 that would provide a POSA any information whether  
23 --

24 A. But you're saying any information; right?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Let me finish the question.

2 A. And I'm saying yes, it does provide  
3 information.

4 Q. Let me ask the question differently, then.  
5 GB 040 does not provide any data as to whether  
6 example two would be stable for weeks or whether  
7 it would be stable for years; correct?

8 A. That is correct.

9 Q. So can we go to paragraph 96 of  
10 Dr. Kydonieus' opening report.

11 So you recall in your opening  
12 report, you talked about GB 040?

13 A. Not really, but you tell me, which part?  
14 Which part?

15 Q. Okay. And this is Paragraph 96 from your  
16 opening report. And in this paragraph, you talk  
17 about a lot of different things. But at the very  
18 end of it --

19 A. Yeah.

20 Q. -- you say -- and you know Enz is GB 040;  
21 right?

22 A. Right.

23 Q. You say Enz also lacked any stability  
24 data, which one of -- I'm sorry, which is one of

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 the first considerations addressed in the early  
2 drug product development. One of ordinary skill  
3 in the art would be unable to determine, for  
4 example, whether Enz's composition would be  
5 stable for weeks or whether it would be stable  
6 for years.

7 Do you see that?

8 A. Yeah.

9 Q. You don't say in that paragraph that you  
10 would be able to make that determination just  
11 based on the susceptibility of rivastigmine to  
12 oxidation, do you?

13 A. Because I do not know the formulation. I  
14 did not look at the formulation.

15 Q. Okay. Let's turn our attention to the  
16 '807 patent which is JTX 17.

17 A. Mm-hmm.

18 Q. And can we go to Slide 15, please? And  
19 you see we've highlighted a portion of the '807  
20 patent from Column 1, Lines 32 to 34 which says  
21 -- and it's referring to Physostigmine. You  
22 agree with that?

23 A. I have not looked at that. Yes, I read  
24 that.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. So the '807 patent says that a  
2 physostigmine is chemically unstable and must be  
3 prepared in a solution with an antioxidant and  
4 protected from light. And you agree with that  
5 statement; right?

6 A. The words, I have -- I have to agree  
7 with.

8 Q. I'm sorry?

9 A. I have to agree.

10 Q. You agree with it?

11 A. I have to. They did the work; right? So  
12 I have to agree with it.

13 Q. But they did the stability testing?

14 A. I believe that when people say things like  
15 the '807 says, we are talking -- since we are  
16 talking about '807 that they recommend preferred  
17 antioxidants being for the RA component, I  
18 believe that. I believe that they have done the  
19 work and they should have shown that it's  
20 stable --

21 Q. Okay.

22 A. -- when you use the antioxidant.

23 Q. And the purpose of the '807 patent was to  
24 identify alternatives to physostigmine because

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 physostigmine lacks the desired chemical  
2 stability; right?

3 A. Chemical stability, plus many other  
4 things.

5 Q. And you do not dispute that there are  
6 millions of compounds disclosed in the '807  
7 patent; right?

8 A. I do. I do.

9 I disagree with that.

10 Q. You didn't provide your own number of  
11 compounds that --

12 A. Well, there are three.

13 Q. Dr. Kydonieus --

14 A. Claim 1 says -- the claims say three  
15 compounds.

16 Q. But I'm talking about the specification in  
17 general. You know Dr. Klibanov did an analysis.

18 A. I don't care what he says. I'm -- in  
19 POSA, in the people -- I'm trying to -- I don't  
20 care what Dr. Klibanov says with 3,000 molecules.

21 Q. Okay.

22 A. I'm looking at RA7 and I'm looking at the  
23 claims. And I see Claim 3 being RA7, which is --  
24 and I am developing a transdermal for

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 rivastigmine and that's what I care --

2 Q. Dr. Kydonieus, let's stick to my question.

3 A. Yes.

4 Q. My question was a very simple one. You do  
5 not dispute that there's millions of compounds  
6 that are disclosed in the '807 patent; right?

7 A. I don't care how many.

8 Q. You don't care because when you started  
9 with the claimed invention that said rivastigmine  
10 and then you went back and you looked at the '807  
11 for disclosure for rivastigmine, is that why you  
12 don't care because you're only focused on  
13 rivastigmine?

14 A. No, because, I mean, if you have a  
15 chemical compound, you have R1, and R2, and R3  
16 and R5. You have a million compounds.

17 What does that mean?

18 Q. Okay.

19 A. It doesn't mean anything.

20 Q. And, Doctor, just bear with me for a  
21 minute.

22 A. I'm trying.

23 Q. You agree there's more than rivastigmine  
24 disclosed in the '807 patent; right?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1           A. There are at least three compounds, RA6,  
2 RA7, RA16.

3           Q. And there's more than that disclosed?

4           A. And there are more than that. Could be.

5           Q. And you cannot answer the question of  
6 whether all of the compounds of the invention of  
7 the '807 patent would undergo oxidative  
8 degradation under pharmaceutically relevant  
9 conditions; right?

10          A. Would you repeat that?

11          Q. Sure. You cannot answer the question of  
12 whether all of the compounds that are disclosed  
13 in the '807 patent would undergo oxidative  
14 degradation under pharmaceutically relevant  
15 conditions; right?

16          A. I concede it's meaningless what you're  
17 telling me.

18          Q. Am I correct, though, that you cannot do  
19 that?

20          A. No. I know that there are three compounds  
21 that Elmalem and '807 -- Marta Weinstock looked  
22 at them. She tested them and she said the  
23 preferred antioxidants, if you tell me one  
24 billion compounds, I cannot tell you yes or no

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 because I don't know the billion compounds.

2 Q. So you just can't answer that question?

3 You couldn't answer that question?

4 A. I could not answer. I couldn't even --

5 Q. All right. So --

6 A. It's improper to answer.

7 Q. Dr. Kydonieus, the '807 patent discusses  
8 the use of RA7 in tablets, capsules and elixirs  
9 for oral administration as well as sterile  
10 solutions and suspensions for parenteral  
11 administration; right?

12 A. Which someone that --

13 Q. The '807 patent --

14 A. Oh. I don't remember that, but I accept  
15 that.

16 Q. Okay. It does not -- the '807 patent does  
17 not discuss transdermal formulations; right?

18 A. No, it does not discuss.

19 Q. And you recall you had a slide up on your  
20 direct which showed that for sterile  
21 compositions, the '807 patent says "buffers,  
22 preservatives, antioxidants and the like can be  
23 incorporated as required." Do you recall that  
24 from the patent?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. Yes, I remember that.

2 Q. And that means buffers, preservatives,  
3 antioxidants --

4 A. Right.

5 Q. -- may or may not be needed; right?

6 A. Could be used, but --

7 Q. It means it may or may not be needed;  
8 right?

9 A. But a couple of --

10 Q. Just answer my question. It means that  
11 those may or may not be needed; right?

12 A. But a sentence below it says that  
13 preferred antioxidants are sodium metabisulfate  
14 and ascorbic acid, so...

15 Q. We'll get to that, but I'd like to start  
16 with just an answer to my question.

17 A. But you're asking me questions that you  
18 want me to answer half of the question.

19 Q. Okay. So --

20 A. Because -- but you're asking me could be  
21 the buffers, that may or may not use.

22 Q. Dr. Kydonieus, let's turn to your  
23 deposition, Page 237. Could you put that on the  
24 screen actually? It will be easier.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1                   And if you look starting at about  
2                   Line 4 or Line 5, you were asked: My question  
3                   was that: The statement in the '807 patent is  
4                   that antioxidants and the like can be  
5                   incorporated as required. It does not say that  
6                   they must be incorporated, correct?

7                   "Answer: No. You don't need  
8                   perhaps to put buffers in there or  
9                   preservatives."

10                  THE WITNESS: Right. That's what I  
11                  said.

12                  Q. So you agree, Dr. Kydonieus -- I'm not  
13                  done.

14                  "So you agree that a buffer may or  
15                  may not be required?

16                  Answer: May or may not be required,  
17                  yes."

18                  THE WITNESS: I'm not an expert, but  
19                  I said it may or may not be required.

20                  BY MR. CONDE:

21                  Q. So all of those things may or may not be  
22                  required; right?

23                  A. Not all. I don't say all, I say that  
24                  antioxidants are required because a sentence

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 below where you mentioned before there are  
2 antioxidants and there are preferred  
3 antioxidants, which means it's a lot of work to  
4 find out what the preferred antioxidants are.

5 And she mentions it, so the answer  
6 is I don't say that the antioxidants in that  
7 statement is may or may not.

8 Q. So, Dr. Kydonieus, is there any stability  
9 data in the '807 patent?

10 A. Not yet.

11 Q. And have you talked to Dr. -- it's Dr.  
12 Weinstock; right? It's her patent?

13 A. Yes.

14 Q. Did you talk to her about whether she did  
15 a lot of work to determine whether any of the  
16 compounds need an antioxidant?

17 A. She tells me preferred antioxidants are --

18 Q. I'm just asking you a question: Do you  
19 have any knowledge --

20 A. Do you want me to speak with her?

21 Q. Do you have any knowledge that Dr.  
22 Weinstock actually did a lot of work to support  
23 her statement as to the preferred antioxidants?

24 A. Well, I assume that Dr. Weinstock with her

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 credentials is not lying.

2 Q. That wasn't my question.

3 A. That's what you're asking me to say.

4 Q. No, I'm not. What I'm asking you is  
5 simply do you know if Dr. Weinstock did any work,  
6 any stability work to support the statement in  
7 her patent that certain antioxidants are  
8 preferred?

9 A. When somebody tells me that I have  
10 preferred antioxidants, and these are the two  
11 preferred antioxidants, I believe those people  
12 have done the work.

13 Q. But you don't actually know whether they  
14 did?

15 A. No. I didn't talk to her.

16 Q. That's my question. It's that simple.

17 And the '807 patent doesn't report  
18 any stability data on RA7 or rivastigmine; right?

19 A. Stability data, no.

20 Q. And so it doesn't tell us the rate or  
21 extent of any oxidative degradation for  
22 rivastigmine RA7; right?

23 A. I calculate the numbers and I said, I  
24 think in my testimony, that the numbers weren't

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 very high of antioxidants. So they would be  
2 effective oxidative degradation for a long period  
3 of time.

4 Q. But, Dr. Kydonieus, you know that the '807  
5 patent doesn't provide any ranges for the  
6 antioxidants that it says is preferred --

7 A. Well --

8 Q. You have to let me finish my question.

9 A. Sorry.

10 Q. You know that the '807 patent doesn't  
11 provide any ranges for any of the antioxidants  
12 that it says are preferred; right?

13 A. Right.

14 Q. And the patent itself does not provide any  
15 data regarding the rate or extent of oxidative  
16 degradation of degradation of RA7 or  
17 rivastigmine; right?

18 A. You have to repeat that, please.

19 Q. I'm sorry?

20 A. Can you repeat it, please?

21 Q. Sure. Absolutely.

22 The '807 patent does not report any  
23 data regarding the rate or extent of oxidative  
24 degradation of RA7 or rivastigmine; right?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. No, they have not done any work or they  
2 haven't shown any.

3 Q. And the examples of '807 do not include an  
4 antioxidant; right?

5 A. I don't remember, but probably, yes,  
6 you're right.

7 Q. You think I'm right. Okay.

8 Do you recall at your deposition  
9 stating that the examples of the '807 patent  
10 containing RA7 did not include an antioxidant?

11 A. I don't remember, but I accept what you  
12 said. I mean, I trust you.

13 Q. And the '807 patent does not disclose any  
14 information relating to what amount of  
15 antioxidant would be effective at stabilizing RA7  
16 from oxidative degradation; right?

17 A. '807?

18 Q. '807.

19 A. Yes.

20 Q. Am I correct?

21 A. Yeah, I believe so, the amount.

22 Q. Okay. So now let's turn our attention to  
23 Elmalem. Elmalem's not a stability study; right?

24 A. Stability study. No, it was a study to

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 determine the effect of cholinesterase inhibitors  
2 on the side effects of morphine.

3 Q. Elmalem was designed to compare the effect  
4 of physostigmine versus three investigational  
5 drugs; right?

6 A. Yes, these are all inhibitors --

7 Q. And they were trying to find out, and what  
8 Elmalem was studying is how much inhibition there  
9 was of a cholinesterase enzyme; right?

10 A. Right.

11 Q. And Elmalem does not disclose any data  
12 regarding the rate or extent of oxidative  
13 degradation of RA7; right?

14 A. It shows the amounts that they have used.

15 Q. My question is very simple. Elmalem does  
16 not disclose any data regarding the rate or  
17 extent of oxidative degradation of RA7; right?

18 A. The data, no, they have not shown any  
19 data.

20 Q. And Elmalem does not include any data  
21 showing that RA7 is actually undergoing  
22 oxidation; right?

23 A. Well, you're asking me to tell you the  
24 answers that don't make any sense.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 Q. There is no data in Elmalem that would  
2 tell a POSA whether RA7 is actually undergoing  
3 oxidation; right?

4 A. Yes. No. But I tell you one thing, when  
5 I have a solution that is only a saline solution  
6 with RA7 and I put an antioxidant, I know that  
7 the antioxidant is put there because there is  
8 nothing else to protect RA7.

9 Q. Back to my question. Do you agree that  
10 there is no data showing that RA7 is undergoing  
11 oxidation; right?

12 A. I have to believe Marta Weinstock that  
13 says yes, there is oxidation going on.

14 Q. Now, you know that all the formulations in  
15 Elmalem were solutions; right?

16 A. Yes.

17 Q. And Elmalem did not prepare any  
18 transdermal formulations; right?

19 A. Right.

20 Q. And if I heard you on direct, you said  
21 that information regarding a solution formulation  
22 was applicable to a transdermal patch. Did I get  
23 that correct?

24 A. Yes, I said that.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Let me ask this question. Would you agree  
2 that information regarding a patch formulation is  
3 not probative to a solution formulation?

4 A. Well, the reason I can say that any  
5 formulation is not -- you cannot extrapolate  
6 directly from one formulation to the other, but  
7 --

8 Q. So if you have oxidative degradation in a  
9 solution, you cannot conclude that it would also  
10 be a problem, for instance, in a transdermal  
11 patch; right?

12 A. I said that many times. That is  
13 formulation dependent.

14 Q. And, in fact, transdermal patches are wet  
15 for a matter of hours before being coated; right?

16 A. Say again, now.

17 Q. Transdermal patch formulations are only  
18 wet for a matter of hours; right?

19 A. Right.

20 Q. The stability we're concerned with here  
21 during this litigation is stability over a year  
22 or two; right?

23 A. Correct.

24 Q. Now, the solutions in Elmalem were

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 prepared to be used soon after?

2 A. I didn't get that.

3 Q. The solutions in Elmalem were prepared and  
4 then used soon after; correct?

5 A. It says freshly, so I really don't know  
6 what that means. I can't tell you the time  
7 element.

8 Q. So you would agree they were probably used  
9 shortly thereafter?

10 A. I don't know what shortly thereafter  
11 means. I don't know the answer. Freshly, so  
12 whatever freshly means.

13 Q. Freshly made and then they use them right  
14 away; right?

15 A. I don't know. I don't know what freshly  
16 means.

17 Q. So that's a possibility, though?

18 A. You're saying freshly is there, and  
19 everybody can see freshly.

20 Q. And it's not uncommon to make a solution  
21 freshly and then use it shortly thereafter,  
22 right, in an experiment?

23 A. I don't know. I don't know that.

24 Q. Well, there is nowhere in Elmalem that it

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 says that the solutions were stored for a  
2 prolonged or pharmaceutically relevant period of  
3 time; right?

4 A. No.

5 Q. Am I correct?

6 A. Yes, you are correct.

7 Q. Let's go to our slide 19, I think. This  
8 was one of your slides on direct. It shows the  
9 parts antioxidant to parts of rivastigmine  
10 disclosed in Elmalem?

11 A. Right.

12 Q. And I did the math, but you probably can  
13 do the math, but you can do it in your head.  
14 There is a 400 parts difference between the  
15 amounts used in Elmalem and '031; right?

16 A. Right.

17 Q. And you didn't address on direct whether  
18 by adding a 400 parts more antioxidant it would  
19 create any issues in the formulation, did you?

20 A. Can I explain?

21 Q. Did you talk about that on direct?

22 A. Excuse me?

23 Q. You didn't address whether adding 400  
24 times more antioxidant?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. That's the wrong comment.

2 Q. Let me ask you this question, then. It is  
3 not always the case that adding a higher  
4 concentration of an antioxidant will improve or  
5 keep the same the stability of the formulation.  
6 Do you agree with that?

7 A. You don't let me answer. Let me answer  
8 the first question.

9 Q. Let starts with my question.

10 A. You're asking me questions that don't make  
11 any sense.

12 Q. Let me try --

13 A. This thing here is based on the amounts of  
14 rivastigmine to antioxidant, it is not on the  
15 formulation. If you want me to explain the  
16 formulation, I'll be happy to do that.

17 Q. You presented this chart to the Court and  
18 you agree --

19 A. Yes, and there was a lot of antioxidant,  
20 that's what I said.

21 Q. 400 times more antioxidant?

22 A. Yeah.

23 Q. And then my question is, it's not always  
24 the case that adding a higher concentration of an

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 antioxidant will improve or keep the same the  
2 stability of the formulation. Do you agree with  
3 that?

4 A. I don't understand. Tell me again,  
5 please.

6 Q. Do you agree that it's not always the case  
7 that adding a higher concentration of antioxidant  
8 will improve or keep the same the stability of  
9 the formulation?

10 A. Well, I have seen where -- well, let me  
11 explain for this, because that's what we're  
12 talking about. I have to explain. I have to  
13 explain it because you're making comments that  
14 don't make any sense. There is not here 400  
15 difference in the formulation. In the  
16 formulation they're exactly the same. And if you  
17 want me to show you, I'll be happy to show you,  
18 but before in the deposition you didn't let me  
19 show it.

20 Q. So, Dr. --

21 A. The numbers are the same and you're making  
22 an issue out of something that is wrong.

23 Q. So this slide that you presented to the  
24 Court, it does not correctly show the relative

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 amounts of antioxidant in Elmalem versus the '031  
2 patent?

3 A. No, it says what it says up there. It  
4 shows the antioxidant to rivastigmine ratios in  
5 both cases.

6 Q. So that was important to your direct,  
7 right, that was an important slide?

8 A. Everything is important.

9 Q. Your slide, I'm just looking at your  
10 slide, and what it shows me is there 400 fold  
11 more antioxidant in Elmalem than the '031 patent?

12 A. No, wrong.

13 Q. Go back to my question. Do you agree that  
14 it is not always the case that adding a higher  
15 concentration of antioxidant will improve or keep  
16 the same the stability of the formulation?

17 A. I have to explain.

18 Q. I just want to know, do you agree with  
19 that statement?

20 A. Let me explain. I have to explain because  
21 you see you're always trying to say yes and no  
22 and there are no yes and no in science.

23 Q. Let me go to slide 68 which is from your  
24 rebuttal report again. I'm sorry, slide 24. And

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 this is a statement that you made in the rebuttal  
2 report. You said, "It is not always the case  
3 that adding a higher concentration of an  
4 antioxidant will improve (or keep the same) the  
5 stability of the formulation."

6 Did I read that directly?

7 A. You read that correctly. And I have to  
8 explain it to you.

9 Q. Let's go to Elmalem, and this time, let's  
10 go to the document itself. Let's go to slide 26  
11 and this is from a section of Elmalem that you  
12 read this morning that's from the bottom of the  
13 page under drugs, and you went to the section  
14 this morning where it says all drugs were made up  
15 freshly in a sterile saline, which included an  
16 equal weight of sodium metabisulfite to prevent  
17 oxidation. Do you see that?

18 A. Yes.

19 Q. It's your interpretation that this  
20 sentence means that the weight of sodium  
21 metabisulfite included in the solution equalled  
22 the weight of the drug in solution; right?

23 A. Right.

24 Q. But it doesn't actually say those words in

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 that section; right? It does not say, it does  
2 not literally say the weight of metabisulfite is  
3 the same as the weight of the drug, does it?

4 A. To me it says that, yes.

5 Q. And in your opinion, Elmalem made up a  
6 different saline solution for each drug  
7 formulation that was tested; right?

8 A. Yes.

9 Q. And under your interpretation of Elmalem,  
10 each formulation contained an amount of  
11 antioxidant equal to the weight of the drug in  
12 the formulation; right?

13 A. Correct.

14 Q. So every formulation contained a different  
15 amount of antioxidant; right?

16 A. Yeah. The ratio of the antioxidant to the  
17 drug is the same.

18 Q. But that wasn't my question. Each  
19 formulation had a different --

20 A. You always want a half answer, you want a  
21 half answer so you get half answers.

22 Q. So let's see what that means. So let's go  
23 to slide 27, please. So the lowest amount of  
24 drug used in Elmalem was .05 milligrams per

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 kilogram for physostigmine?

2 A. Right.

3 Q. And the highest amount drug used in the  
4 study was 2.5 milligrams per kilogram for RA7;  
5 right?

6 A. Okay.

7 Q. That's a 40-fold difference between the  
8 amount of antioxidant used in physostigmine and  
9 RA7?

10 A. Right. Want me to tell you what it means?

11 Q. Let's go to Weinstock. I'm on a clock and  
12 if your counsel wants you to explain it.

13 A. I'll be here forever.

14 Q. Unfortunately we don't have time forever.

15 Let's go to Weinstock, which is JTX 30, and  
16 that's the Weinstock 1981 reference. You  
17 remember talking about that this morning. There  
18 is no mention of rivastigmine or RA7 in Weinstock  
19 1981, right?

20 A. Right.

21 Q. And there is no stability data for  
22 rivastigmine or RA7 in Weinstock 1981; right?

23 A. Data, no.

24 Q. There is none, because they didn't exist

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 at the time; right?

2 A. For RA7, yes.

3 Q. But the compounds that were used in this  
4 study were well-known?

5 A. Yes.

6 Q. And I think you, maybe you misspoke, but  
7 we think what you said on direct is that  
8 Weinstock used four cholinesterase inhibitors, did  
9 you say that?

10 A. Maybe I did, four drugs, ATMN,  
11 neostigmine, hydrazine and something else.

12 Q. So they're not -- do you know whether  
13 they're all cholinesterase inhibitors --

14 A. I don't know that they're all  
15 cholinesterase inhibitors.

16 Q. You don't know that much about the drugs  
17 that were used in the Weinstock formulation?

18 A. I know that some of these are used on  
19 opioids, opioids to move --

20 Q. But you're not familiar with the mechanism  
21 of those drugs, how they act?

22 A. Not necessarily, no. I'm not a  
23 pharmacologist.

24 Q. You're not a biologist, either; right?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. No.

2 Q. You're not here testifying as a  
3 pharmacologist or biologist; right?

4 A. No.

5 Q. All right. Prior to this litigation, had  
6 you ever seen either the Weinstock paper or the  
7 Elmalem paper?

8 A. Before the litigation?

9 Q. Yes.

10 A. No.

11 Q. Because they're not in your area of  
12 expertise and work; right?

13 A. Well, my work is mainly transdermals.

14 Q. So these two, Elmalem and Weinstock aren't  
15 in your expertise or your area?

16 A. Right. You may say that, yeah, I look at  
17 literature, but I had never seen those.

18 Q. So let's -- so I want to talk a little bit  
19 about the Brij 97 documents. Let me turn to that  
20 next.

21 Now, so let's assume for the moment  
22 that you're right that there is antioxidant in  
23 Brij 97 was manufactured by Atlas Chemie out of  
24 West Germany. You would agree that the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 antioxidant in Brij 97 was used to protect the  
2 plasticizer?

3 A. That's what it's used for, to start with.

4 Q. To protect the plasticizer?

5 A. That's my presumption.

6 Q. And you didn't testify about the amount of  
7 antioxidant, assuming that Brij 97 has an  
8 antioxidant, you didn't testify about how much  
9 antioxidant would be in the final formulation of  
10 example two of the '040 patent, did you?

11 A. No, I did not.

12 Q. So let's go to slide 44 to see if we can  
13 do that analysis. You looked at the '480 patent  
14 on direct, you looked at this very sentence;  
15 right?

16 A. Again, please.

17 Q. Sure, this slide is from the 480 patent,  
18 and you went to this patent on your direct and  
19 you pointed to this very sentence which says that  
20 there is .01 percent BHA and .005 percent citric  
21 acid --

22 A. Correct.

23 Q. -- in Brij 97; right?

24 A. Right.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. And you know that the '480 patent does not  
2 identify Atlas Chemie, West Germany as the  
3 inventor?

4 A. ICI.

5 Q. It says ICI, but it doesn't say Atlas  
6 Chemie?

7 A. It says Atlas Chemical was bought by ICI.

8 Q. That was based on your personal knowledge,  
9 you didn't bring any documents that show that ICI  
10 bought the manufacturer of Brij 97?

11 [REDACTED]  
12 [REDACTED]  
13 [REDACTED]  
14 [REDACTED]  
15 [REDACTED]  
16 [REDACTED]

17 Q. But none of those documents show that ICI  
18 actually purchased Atlas Chemie in West Germany;  
19 right?

20 A. I don't know if the documents say that,  
21 but basically what it says is that Atlas Chemie  
22 was bought by ICI. ICI have sold the Brij 97 to  
23 somebody else and in the end was bought by Croda,  
24 and now it's owned by Croda.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Let's continue on with this. It says on  
2 slide 44, we added up the amount of BHA and  
3 citric acid and got .015 percent; do you see  
4 that?

5 A. Okay.

6 Q. Let's go to the next slide. Then we look  
7 at example two, and we did the calculation to  
8 find out how much in total there was of BHA and  
9 citric acid, and you can see the calculation we  
10 did. It's very similar to the one you did on our  
11 earlier slide, and we end up with nine parts per  
12 million?

13 A. Right.

14 Q. Would you agree with that?

15 A. Yes.

16 Q. So when Brij 97 is made, it contains --  
17 and assuming it has an antioxidant, it contains  
18 nine parts per million; right?

19 A. For the formulation, that formulation,  
20 example two contains this antioxidant.

21 Q. So example two contains nine parts per  
22 million. And you don't know whether all of the  
23 citric acid in BHA actually made it into example  
24 two, do you?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. Why not?

2 Q. For example, the BHA and citric acid could  
3 have been used up because it was protecting the  
4 plasticizer; right?

5 A. I have no idea of that, but neither here  
6 nor there. We never -- I mean, I can maybe help  
7 you, not to ask me this line of question, because  
8 we never -- I never said that the amount of  
9 antioxidants in Brij 97 was the amount required  
10 to give us effective antioxidation effect, that's  
11 why I used the handbook and so on to help me in  
12 saying, we never said that Brij 97 was the one  
13 that gave us another antioxidant to protect this  
14 formulation.

15 Q. Thank you for that explanation.

16 Now, you also did not testify  
17 whether nine parts per million is a sufficient  
18 amount for a person of ordinary skill to make the  
19 compatibility determination with the BHA and  
20 citric acid with example two formulation; right?

21 A. I just told you that we didn't use this  
22 part here to make a point that it was  
23 therapeutically -- not therapeutically, but in an  
24 amount adequate to stabilize the oxidation, so

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 there was no need for me to go farther in saying  
2 anything else.

3 Q. Can we go to the next slide, 46. This is  
4 defendants' exhibit 89, another document that you  
5 looked at in your direct. Do you remember that  
6 document, Dr. Kydonieus?

7 A. Yes, I remember it very well.

8 [REDACTED]  
9 [REDACTED]  
10 [REDACTED]  
11 [REDACTED]  
12 [REDACTED]  
13 [REDACTED]  
14 [REDACTED]  
15 [REDACTED]  
16 [REDACTED]  
17 [REDACTED]  
18 [REDACTED]  
19 [REDACTED]  
20 [REDACTED]

21 Q. Thank you. And this document is a  
22 document you relied on for your slide which is  
23 DDX 355, do you remember that?

24 A. Yes.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. And there is a lot of redactions on the  
2 document; right?

3 A. Yeah.

4 Q. There is so many things removed that you  
5 really couldn't make much sense of it; right?

6 A. No.

7 Q. That's what you said at your deposition,  
8 do you recall?

9 A. I don't think so.

10 Q. Let's look at 272, go to page 272 of your  
11 deposition. So go to line 18. Are you with me?  
12 You were asked the question, [REDACTED]

13 [REDACTED]

14 [REDACTED]

15 [REDACTED]

16 "Answer: Yeah, I looked at this  
17 particular page. There was so many things  
18 removed, I couldn't really make much sense of  
19 this document. But go ahead."

20 Were you asked that question and did  
21 you give that answer?

22 A. I asked the question and what?

23 Q. Did you give that answer?

24 A. Yes. Because I don't know what it was.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 You have to put in proper perspective --

2 Q. Dr. Kydonieus, I just wanted to know, you  
3 answered my question.

4 A. But you're asking me on what, what point  
5 did I make that statement there, because now  
6 you're making it sound like I couldn't calculate.  
7 That's not true.

8 THE COURT: Dr. Kydonieus, quiet for  
9 a second.

10 MR. LEE: I think for completeness,  
11 we need to have the next question and answer.

12 THE COURT: Let's have the next  
13 question and answer.

14 MR. CONDE: Sure.

15 THE COURT: I'm sorry. So  
16 Dr. Kydonieus, we're just going to go over that  
17 again, but with not only the question you were  
18 just asked about, but also the following one.

19 BY MR. CONDE:

20 Q. So I will go to the next part.

21 "So it's not possible to tell from  
22 this document the percent of antioxidant in the  
23 product; correct?

24 "Answer: Well, it says something

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 down here double star, 25 percent BHA, 12.5  
2 percent citric acid monohydrate, 62.5 USP  
3 propylene glycol. If you look at the double  
4 star, it's the antioxidant solution that was used  
5 in the formulation."

6 That's what you said; right,  
7 Dr. Kydonieus.

8 A. Right. ?

9 A. Right.

10 Q. Okay. So, now let's keep going.

11 Let me keep going.

12 Question: Right. But we don't know  
13 how much of the other ingredients were added to  
14 this product, correct?

15 Answer: Well, quantities are  
16 removed, so it's very difficult to tell what the  
17 other numbers are."

18 And you also gave that answer?

19 A. The point is there so I can calculate.  
20 Right.

21 Q. I'm just -- that was the full testimony,  
22 so let's move on.

23 A. Well, okay. I mean, as long as you are  
24 not telling me that I'm not able to calculate the

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 amount that is there, we're okay.

2 Q. Okay. So let's move on. Let's go to  
3 Slide 47.

4 This is another document that you  
5 relied on; correct?

6 A. This Brij 96?

7 MR. LEE: No, Your Honor.

8 THE COURT: Not earlier today.

9 MR. CONDE: My apologies. That's  
10 okay.

11 BY MR. CONDE:

12 Q. We'll just -- oh, so now, Dr. Kydonieus,  
13 as of 1998, Brij 97 no longer contained any  
14 antioxidant; right?

15 A. It was removed January 1, 1991.

16 Q. And a person of ordinary skill would have  
17 known that; right?

18 A. Ordinary skill in the art?

19 Q. Yes.

20 A. Yes, they would know that because they  
21 received the data any time that they order the  
22 material.

23 Q. So let's turn our attention to Sasaki.

24 A. Okay.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Now, you agree with me that Sasaki --  
2 excuse me one second. You agree with me that  
3 Sasaki --

4 THE COURT: I'm sorry, Mr. Conde.  
5 The last question and answer went by kind of fast  
6 for me.

7 The antioxidants, the BHT or  
8 ascorbic acid or whatever it was that was in Brij  
9 97 was removed from the product in 1991?

10 THE WITNESS: Correct.

11 THE COURT: Okay.

12 BY MR. CONDE:

13 Q. Now, Dr. Kydonieus, Sasaki does not  
14 disclose or discuss rivastigmine; right?

15 A. No. It discussed molecules of similar  
16 structures.

17 Q. They're only similar in the regard that  
18 they have an amino group?

19 A. They have amino groups.

20 Q. And that's the only similarity that you  
21 pointed to on direct; right?

22 A. Right, because that's what Sasaki claims  
23 in his patent.

24 Q. So Sasaki does not include any

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 rivastigmine stability data; right?

2 A. No, rivastigmine was not even available at  
3 the time.

4 Q. So can we go to Sasaki DTX 12, and I think  
5 I need to go to Page 3. Down on the -- put that  
6 on the screen.

7 Page 3, please. And on direct you  
8 testified -- you noted that there's a several  
9 different drugs in the left-hand column.

10 A. Right.

11 Q. Right? And I think you said that Sasaki  
12 had tested all of those compounds he listed to  
13 see whether they had an oxidative degradation  
14 problem?

15 A. No. I don't know what I said, but I never  
16 would say that he tested all of them. He  
17 probably tested a lot of them to make this  
18 statement.

19 Q. But you don't know whether he tested any  
20 of them on any of the drugs on the left-hand  
21 column on that page?

22 A. Well, I presume that he tested a lot of  
23 them to be able to make those comments.

24 Q. Well --

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1           A. Usually the stuff that comes in patents or  
2 in articles, that doesn't mean that you've tested  
3 everything.

4           Q. Right. So you know that patents sometimes  
5 disclose things because they want to make the  
6 claims as broad as they can, but they may not  
7 have actually tested for that property; right?

8           A. Some cases maybe, but --

9           Q. So now --

10          A. You cannot in patents claim things or put  
11 down things are not correct, either. So you've  
12 got to put -- I mean, if you want to get your  
13 patent -- I have 61 patents, so I know.

14          Q. If you want to get an extensive range, you  
15 have to do some work to get that extensive range.  
16 But you don't have to test everything that you  
17 disclose in the patent, all the compounds that  
18 you disclose; right?

19          A. No, you don't have to.

20          Q. So let's go to Slide 60. And this is a  
21 table from Sasaki; right?

22          A. Right.

23          Q. And there's only two compounds that have  
24 amine structures; right?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 A. Yes.

2 Q. Okay. And those two compounds are the  
3 diphenhydramine; right?

4 A. Diphenhydramine.

5 Q. And the ethyl aminobenzoate?

6 A. Yes.

7 Q. And neither of those compounds have a  
8 benzylic carbon hydrogen connected to the amine;  
9 right?

10 A. Sasaki is not talking about any benzylic  
11 hydrogen carbons or anything like that.

12 Q. So neither one of those compounds have a  
13 benzylic carbon compound as far as you know; am I  
14 correct?

15 A. I don't know the answer. Maybe, I'm not  
16 sure. I have to look at the structure if you  
17 want me to answer that question.

18 Q. You did not testify as to how many  
19 pharmaceutical compounds have an amine group, did  
20 you?

21 A. An amine group?

22 Q. Yeah. Out of all the pharmaceutical  
23 compounds, how many of them have an amine group?

24 A. No. I don't think I testified to that.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. And if you saw a tertiary amine compound  
2 on a compound, you would not be able to know  
3 whether or not that compound was susceptible to  
4 oxidative degradation; correct?

5 A. Are you talking about Sasaki or we're  
6 talking generalities now?

7 Q. We're talking generalities.

8 A. So if it was an amine compound, if I would  
9 know or if it is susceptible to oxidation? Tell  
10 me the question again, please.

11 Q. Okay. If you saw a tertiary amine on a  
12 compound, you would not be able to know whether  
13 or not that compound was susceptible to oxidative  
14 degradation; correct?

15 A. As I mentioned, I'm not an organic  
16 chemist. I would leave that question to the  
17 organic chemist to tell me.

18 Q. Now, you cited Sasaki in part because it  
19 uses an acrylic adhesive; right?

20 A. Well, that's the main thesis of this  
21 patent that you have an acrylic adhesive and you  
22 have drug molecules that contain amino groups.  
23 He says oxidation.

24 Q. But you don't know if rivastigmine -- let

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 me start over -- if rivastigmine is in an acrylic  
2 adhesive, you don't know whether it will  
3 necessarily undergo oxidative degradation, do  
4 you?

5 A. Well, it is an amine group and, honestly,  
6 this morning that I mentioned diphenhydramine was  
7 one of them. Amino was another one. And  
8 Lidocaine was another one.

9 In the amine groups, in those three  
10 compounds that you mentioned Sasaki mentioned are  
11 similar to the amine compounds in rivastigmine.

12 Q. Could you turn to your deposition, Page  
13 89?

14 Let's put it on the screen. It will  
15 be easier. Page 89, and 18, Line 18. And you  
16 were asked the question: "So am I right that  
17 it's your opinion that when rivastigmine's in an  
18 acrylic adhesive, it will not necessarily undergo  
19 oxidative degradation?"

20 "Answer: I don't know the answer."

21 A. Absolutely correct. Yes.

22 Q. Now, Dr. Kydonieus --

23 A. May I finish. It is formulation  
24 dependent.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. So you know the structure of rivastigmine;  
2 right?

3 A. Right.

4 Q. And you know about nicotine; right?

5 A. Right.

6 Q. And according to Sasaki, acrylic polymers  
7 would also create a problem; right?

8 A. With amino group compounds.

9 Q. All right. But in your infringement  
10 report, even though you knew all those three  
11 things, you said that the drug doesn't  
12 necessarily go through oxidative degradation even  
13 though it has rivastigmine and an acrylic  
14 adhesive; right?

15 A. I think I keep on saying the same thing.  
16 As far as the degradation is concerned, it is  
17 formulation dependent.

18 Q. Okay.

19 A. Okay.

20 Q. So now, excuse me a second.

21 Now, you agree that Sasaki teaches  
22 adding .05 to one percent of tocopherol; right?

23 A. Right.

24 Q. And that's relative to the adhesive?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. Relative to the adhesive.

2 Q. And the adhesive is the oxidative  
3 environment for the drugs in the formulation  
4 disclosed in Sasaki; right?

5 A. I think that's what you said.

6 Q. So Sasaki teaches that the amount of  
7 antioxidants should be chosen based on the  
8 concentration of the oxidizing agents in the  
9 environment of the formulation, not based on the  
10 amount of drug; right?

11 A. Well, I think you said in the amount of  
12 drug because -- give us a ratio between point --  
13 I forget the number, but .01 to .3 ratio of drug.  
14 Excuse me, drug to acrylic adhesive.

15 Q. So Sasaki's saying you determine the  
16 amount of antioxidant based on the amount of the  
17 adhesive; right?

18 A. Right.

19 Q. Let's go to --

20 THE COURT: Actually why don't we  
21 take our afternoon break. All right.

22 So we'll take a 15-minute break.

23 THE CLERK: All rise.

24 (A brief recess was taken.)

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 THE COURT: All right. Let's be  
2 seated and back to Kydonieus. Yes.

3 BY MR. CONDE:

4 Q. Dr. Kydonieus let's talk about the Ebert  
5 reference that you rely on. You agree that the  
6 Ebert reference addresses a manufacturing issue  
7 with nicotine formulations for transdermals;  
8 right?

9 A. Yes, I did.

10 Q. And Ebert does not discuss rivastigmine at  
11 all; right?

12 A. No.

13 Q. So it doesn't discuss or state using an  
14 antioxidant with rivastigmine, does it?

15 A. No. I mean --

16 Q. Okay. So it doesn't?

17 A. I don't know how to answer these things  
18 because, honestly, they're half --

19 Q. But I, just as a matter of fact, Ebert  
20 does not include any stability data for a  
21 rivastigmine formulation, right?

22 A. No.

23 Q. And so can we go to our Slide 43.

24 And I think you, in general, went to

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 -- it's in the Ebert reference and it's -- I  
2 think it's at Page 5 at the top of the page. And  
3 in Ebert it says an object of the present  
4 invention is to provide a method of fabricating  
5 laminated TDD devices that is compatible with  
6 volatile or heat-sensitive drugs, enhancers or  
7 other components that cannot be subjected to  
8 drying or heating, such as would occur in an  
9 oven.

10 Do you see that?

11 A. Yes, I see that.

12 Q. And the way that Ebert solved that problem  
13 was to extrude the drug as a gel onto the  
14 adhesive layer to avoid having to expose the drug  
15 to drying; right?

16 A. He did that, yes.

17 Q. And you agree that a person of ordinary  
18 skill in the art would not have added an  
19 antioxidant to protect against degradation caused  
20 by heat; right?

21 A. He talks about oxidation as well.

22 Q. You agree that a person of ordinary skill  
23 in the art would not have added an antioxidant to  
24 protect against degradation caused by heat?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. Okay. Let me explain.

2 Q. Would you agree that --

3 A. No. I don't agree with this.

4 Q. So let's look at your deposition, let's go  
5 to Page 38 of your deposition. Can you put that  
6 on?

7 Thank you. Look at Line 12.

8 And at Line 12, you were asked: "A  
9 person of ordinary skill in the art wouldn't have  
10 added an antioxidant to protect against  
11 degradation caused by heat?

12 "Answer: I would think so.

13 "Question: You would think they  
14 would or you would think they would not?

15 "Answer: I think they would not."

16 Were you asked that question and did you give  
17 those answer?

18 A. Yes, I did.

19 Q. Okay.

20 A. But heat is one thing and oxidation at a  
21 higher heat is a different thing. Oxidation  
22 takes place at higher heat and faster.

23 So if you told me that you're going  
24 to put it in a container and you heat it at

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1       whatever temperature you want, I would say that  
2       that doesn't have anything to do with oxidation.  
3       But if you put it in an oven to make a  
4       transdermal patch, you have heat and you have  
5       oxygen, then it's a different situation.

6                   When you heat it up, every ten  
7       degrees you double the degree of oxidation.

8       Q.   So let's go on.

9                   You have not cited any literature  
10       showing that rivastigmine is heat sensitive or a  
11       volatile drug, have you?

12       A.   I want you to know that it's a liquid and  
13       liquids are really more volatile than solid.

14       Q.   So let me ask the question again: You do  
15       not cite any literature showing that rivastigmine  
16       is a heat sensitive or volatile drug, do you?

17       A.   I have not formulated it myself. No.

18       Q.   And to make a transdermal patch, it is  
19       common to mix the drug with the adhesive in  
20       solvent; right?

21       A.   Mix the adhesive in?

22       Q.   It's common to mix the drug with the  
23       adhesive in solvents?

24       A.   The adhesive has solvent already.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. Let me try that again. And that's called  
2 the matrix-type patch; right?

3 A. Where you -- when you finally make the  
4 product.

5 Q. It's a matrix, matrix patch?

6 A. Correct. Or a drug-in-adhesive patch.

7 Q. And after the drug is mixed with the  
8 adhesive, it's conventional to use elevated  
9 temperatures to drive out the solvent when making  
10 a matrix-type patch; right?

11 A. Correct.

12 Q. And that's the conventional method of  
13 making a patch formulation; right?

14 A. Well, that's one method. There are  
15 different kinds of methods.

16 Q. In fact, you said at your deposition 90  
17 percent of the patches are of the matrix type;  
18 right?

19 A. Yes.

20 Q. And you also cite Ebert because it  
21 discloses a transdermal delivery device; right?

22 A. Right.

23 Q. And by the way, the rivastigmine patches  
24 that are at issue here, they're matrix type of

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 patches; right?

2 A. They're three types. Now, on all three or  
3 the actual product?

4 Q. Noven's product.

5 A. Oh, Noven's product. I'm sorry.

6 Noven's product is a drug-in-adhesive  
7 patch. Yes.

8 Q. And you cited Ebert because it discloses a  
9 transdermal device; right?

10 A. One of the reasons.

11 Q. But Ebert was not the only patent relating  
12 to nicotine in a transdermal device as of 1998,  
13 right?

14 A. Right.

15 Q. And there were patents as of 1998 that  
16 talked about nicotine transdermal devices that  
17 did not use an antioxidant; right?

18 A. I don't know that.

19 Q. You saw Dr. Klibanov gave a list of such  
20 products; right?

21 A. Yeah. Yeah, of course.

22 Q. So, as of 1998, there existed transdermal  
23 patches using nicotine that did not include an  
24 antioxidant?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1           A. Nobody says that they couldn't do it. I  
2 keep on coming to the same thing. It's  
3 formulation dependent.

4           Q. Okay.

5           A. You keep on asking me the same question.

6           Q. And you did not do a patent search on  
7 nicotine transdermals to see how many transdermal  
8 nicotine formulations were out there and whether  
9 they included an antioxidant; right?

10          A. No, I did not do that.

11          Q. And the one patent that you relied on, the  
12 Ebert patent, was provided to you by Noven's  
13 lawyers; right?

14          A. K & K. Kenyon & Kenyon.

15          Q. Right. Now, Dr. Kydonieus, you worked on  
16 a product and I may mispronounce it, so bear with  
17 me, called Selegiline.

18          A. Selegiline.

19          Q. Thank you. Right?

20          A. Yes.

21          Q. And that has a benzylic carbon bond;  
22 right?

23          A. No.

24          Q. What's that?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 A. No, I don't think so.

2 Q. Well, let's go to Slide 65.

3 A. Yeah.

4 Q. Does Selegiline have a benzylic carbon  
5 bond?

6 A. I don't think so, but we have the expert  
7 here. He can tell us --

8 Q. Well --

9 A. -- whether it has a carbon or not.

10 Q. So, and when you --

11 A. There's a carbon between -- before the  
12 other carbons, so I don't think that it is  
13 benzylic carbon. But I'm not the organic chemist  
14 and I don't want to say one way or another. But  
15 I don't think it is.

16 Q. Well, when you formulated Selegiline into  
17 a transdermal patch, you did not use an  
18 antioxidant; right?

19 A. I did not use an antioxidant because the  
20 formulation that we developed was -- mainly  
21 evolved around another product that was already  
22 in the market and had patents. And we decided to  
23 use an unrelated adhesive, which they said that  
24 it would not work with Selegiline.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Q. So let me try --

2 A. A long way to -- the only way to make it  
3 work with Selegiline and that's when we found the  
4 patent.

5 Q. And it did not have an antioxidant in your  
6 patent, either, did it?

7 A. No, because that's -- we did ten days'  
8 worth of work.

9 Q. Okay. And Selegiline has a tertiary  
10 amine; right?

11 A. Yeah.

12 Q. Just like the tertiary amine in Sasaki?

13 A. I'm not saying that it was not oxidized at  
14 some point, I'm saying that we made a formulation  
15 for other purposes to show that some adhesives  
16 that the literature said it would not work with  
17 Selegiline would work with Selegiline and that's  
18 why we filed a patent.

19 Q. I just want to make sure it's clear on the  
20 record that the patent that you filed on  
21 Selegiline for a transdermal patch in which  
22 Selegiline has a tertiary amine did not include  
23 any examples that had an antioxidant in them, did  
24 they?

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1           A. And I have to say that's true, but I have  
2 to say also that this is a very preliminary work.  
3 This is based on few hours of work.

4           MR. CONDE: I have no further  
5 questions at this time, Your Honor.

6           THE COURT: All right. Any  
7 redirect?

8           MR. LEE: Yes, Your Honor.

9                                 REDIRECT EXAMINATION

10          BY MR. LEE:

11           Q. Do you recall your testimony on  
12 cross-examination of when BHA was removed from  
13 Brij 97?

14           A. The date was January 1, 1991.

15           Q. So as of the date of the GB 040, was there  
16 antioxidant in the Brij?

17           A. Yes, there was antioxidant in the Brij.

18           Q. Would one of ordinary skill in the art  
19 have been aware of that?

20           A. Of course.

21           Q. Can you look in front of you, Plaintiff's  
22 Exhibit 231.

23           A. Where is that.

24           Q. In the book in front of you, Plaintiff's

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 Exhibit 231.

2 A. 231? Okay.

3 Q. Is that your patent application that you  
4 were discussing on cross-examination?

5 A. Yeah, on Selegiline, yes.

6 Q. Is there any stability data in this patent  
7 application at all?

8 A. No.

9 Q. Did you do any stability testing for this  
10 patent application?

11 A. No.

12 Q. And can you explain to us again why you  
13 filed this patent application, what was novel  
14 about it?

15 A. Well, what was novel was that there were a  
16 lot of patents saying that this type of adhesives  
17 would not work with transdermal delivery of  
18 Selegiline. And we needed some protection if we  
19 were to develop this and we looked at this and my  
20 philosophy is yeah, they can be made to work and  
21 we made them work. So it is basically  
22 developing, using the polymers of a patch that  
23 would be around the inventions of other people so  
24 that we can try to make a Selegiline patch.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



1 Q. When you say you were trying to see if it  
2 would work, did you mean you were trying to see  
3 if it would be stable for an extended period of  
4 time?

5 A. No, if it would work -- first of all if we  
6 could formulate it. Basically they said you  
7 cannot formulate it and you cannot deliver it  
8 through human skin, it would not work.

9 Q. And you mentioned that you were trying to  
10 protect yourself with this patent?

11 A. Correct.

12 Q. And why did you need protection?

13 A. Why did we need protection?

14 Q. Yes.

15 A. Because if you do not have protection, you  
16 don't make a product.

17 Q. So once you got this patent on file, were  
18 you then prepared to see if you could develop a  
19 formulation for the marketplace?

20 A. We are three people, including myself,  
21 that is Samos Pharmaceuticals, we own that  
22 company and we put our own money into developing  
23 this, so our philosophy is we're going to develop  
24 it, as we did file the patent, get the patent,

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 and then try to out license, because if it needs  
2 an antioxidant, there is nothing to it, we'll put  
3 an antioxidant. If it needs something else,  
4 we'll do something else, but we develop the  
5 patent, we got protection, and we got to show  
6 that it permeates through skin at the levels that  
7 are required to give us therapeutic level, and  
8 that's what you need to sell it to somebody.

9 Q. When you were being questioned about  
10 Elmalem, I believe you testified that the patches  
11 were only wet for a matter of hours?

12 A. What was wet?

13 Q. I think you testified that the patches  
14 were only wet for a matter of hours?

15 A. I don't know if that's exactly the words  
16 he used, but I think he meant -- I may be wrong  
17 what he meant. I thought you meant the solution  
18 that you make before you put it on to the coater,  
19 you try to minimize those hours.

20 Q. When you have a drug in an adhesive  
21 matrix, and it's already been formulated, is it  
22 in solution?

23 A. Yes, it is in solution.

24 MR. LEE: That's all, Your Honor.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 THE COURT: Thank you.

2 Dr. Kydonieus, you may step down.

3 Thank you.

4 Mr. Lee, do you have anything more?

5 MR. LEE: No, Your Honor, we have  
6 nothing more.

7 THE COURT: All right. Thank you  
8 very much. Do you have a case.

9 MS. JACOBSEN: Yes, we do, Your  
10 Honor. We move for a judgment as a matter of  
11 law. Both of Noven's experts admitted that even  
12 if a drug is susceptible to oxidative  
13 degradation, potentially theoretically  
14 susceptible, that doesn't mean it's going to  
15 undergo oxidative degradation in a formulation,  
16 and the rate and the extent cannot be predicted.  
17 And that means whether or not you have a problem  
18 cannot be predicted.

19 And both of Noven's experts admitted  
20 that degradation is formulation dependent, and  
21 that means Noven hasn't proven that a person of  
22 ordinary skill in the art would have been  
23 motivated to combine rivastigmine with an  
24 antioxidant and a transdermal patch.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 THE COURT: I'm going to deny the  
2 motion. Let's go ahead.

3 MR. JACOBSEN: Your Honor,  
4 plaintiff's only witness is Dr. Klibanov. It's  
5 up to Your Honor if you want to start today. We  
6 disclosed our slides last night and we have just  
7 been given some objections and the parties  
8 haven't had an opportunity to work through.

9 THE COURT: Well, I don't know how  
10 much time, how much time you're planning on doing  
11 with Dr. Klibanov. I don't know how much time  
12 there is for cross. I don't mind stopping for  
13 today as long as we finish tomorrow.

14 MR. KALLAS: I'm certain that we'll  
15 finish tomorrow. Noven has dropped some of its  
16 case so we can work with Dr. Klibanov to shorten  
17 some of his direct examination.

18 THE COURT: Are you confident,  
19 Mr. Lee, that we'll finish tomorrow?

20 MR. LEE: Yes. Before I say that --

21 THE COURT: Roughly speaking the  
22 plaintiff has used three hours and fifteen  
23 minutes and you have used two hours and seventeen  
24 minutes.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 MR. LEE: Right. So if we use  
2 another four hours tomorrow, I'm sure we'll be  
3 finished.

4 THE COURT: They have less than four  
5 hours. All right. In any event, I hear  
6 agreement. Just for bookkeeping purposes if it's  
7 all right, we'll just charge each side  
8 twenty-five minutes to make sure we finish  
9 tomorrow. Okay? You can use it to work out your  
10 objections or whatever else. Are we good with  
11 that?

12 MS. JACOBSEN: Yes, Your Honor,  
13 except according to our time keeping, we have  
14 only used two hours and twenty minutes.

15 THE COURT: I've gotten the people  
16 reversed.

17 MS. JACOBSEN: Then I think that's  
18 all right.

19 MR. KALLAS: We guesstimate we have  
20 four hours and thirty-eight minutes left.

21 THE COURT: All decisions of the  
22 judge are final, but we're in the same ballpark,  
23 but I do have the parties reversed, because --  
24 Mr. Lee, with this additional information we're

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 still good?

2 MR. LEE: I've tried to do the  
3 calculation in my head.

4 THE COURT: You have got three hours  
5 and ten minutes left.

6 MR. LEE: I'm only concerned with  
7 how much time they have left, because if they use  
8 up all the time, then I won't be able to -- so if  
9 they have four hours and a half, that will give  
10 me two-and-a-half hours and that's more than  
11 enough.

12 THE COURT: I think we have a deal  
13 here.

14 MS. JACOBSEN: Sorry, Your Honor,  
15 did you say we will be charged twenty-five  
16 minutes.

17 THE COURT: I'm going to charge you  
18 each twenty-five minutes so in case either or  
19 another you start going really long tomorrow, you  
20 got to stop. In other words, there is some time  
21 that we're not going to use, it seems to me fair  
22 to split it between the two of you.

23 MR. KALLAS: We're in the ballpark  
24 of four hours, Your Honor.

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 THE COURT: Well, that's no problem  
2 because you have -- even if I give you another  
3 twenty-five minutes, you still will have more  
4 than four hours left.

5 MR. KALLAS: We'll shave it down to  
6 three hours.

7 THE COURT: So we'll be finished. I  
8 will be back here tomorrow morning ready to go at  
9 8:30, and presumably you all will, too, and we'll  
10 have fun tomorrow. Thank you very much. We'll  
11 be in recess.

12 (Court recessed at 4:10 p.m.)

13

14

15

16

17

18

19

20

21

22

23

24

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1 State of Delaware)  
 )  
2 New Castle County)

3  
4 CERTIFICATE OF REPORTER

5 I, Heather M. Triozzi, Certified  
6 Professional Reporter and Notary Public in the  
7 State of Delaware, do hereby certify that the  
8 foregoing record, Pages 1 to 304 inclusive is a  
9 true and accurate record of the above-captioned  
10 proceedings on the 1st day of December, 2014, in  
11 Wilmington.

12 IN WITNESS WHEREOF this 1st day of  
13 December, at Wilmington.

14  
15 Heather M. Triozzi, CSR, RPR  
16 Cert. No: 184-PS  
17 Exp: Permanent  
18  
19  
20  
21  
22  
23  
24

DATED: December 1, 2014

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801



- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24

Hawkins Reporting Service  
715 N. King Street - Wilmington, Delaware 19801