

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

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

844 King Street
Wilmington, Delaware

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

APPEARANCES:

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

-and-

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

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Counsel for the Plaintiffs

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APPEARANCES CONTINUED:

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

-and-

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

Counsel for the Defendants

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1 THE CLERK: All rise. All right.

2 Good morning, everyone. Please be
3 seated.

4 Are we ready to begin?

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

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

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

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

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

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

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

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

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

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

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

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

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

4 MS. JACOBSEN: Right.

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

7 MR. LEVY: No, Your Honor.

8 THE COURT: All right.

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

11 THE COURT: Okay. All right.

12 MS. JACOBSEN: Thank you.

13 THE COURT: You may proceed, Ms.
14 Jacobsen.

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

22 THE WITNESS: Good morning, Your
23 Honor.

24 THE COURT: Good morning. Is his

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1 Ph.D. in 1977?

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

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

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

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

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

15 THE WITNESS: Yes, I do.

16 ALEXANDER M. KLIBANOV, Ph.D.,
17 having first been duly sworn on oath, was
18 examined and testified as follows:

19 THE CLERK: Thank you. Please be
20 seated.

21 MS. JACOBSEN: May I approach,
22 Your Honor?

23 THE COURT: Yeah. Sure.

24 DIRECT EXAMINATION

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1 BY MS. JACOBSEN:

2 Q. Good morning, Dr. Klibanov.

3 A. Good morning.

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

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

10 THE COURT: All right. Thank you.

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

13 BY MS. JACOBSEN:

14 Q. And Dr. Klibanov, you have a book
15 of documents there. Will you please turn to Tab
16 1 and you will find PTX 8. Can you identify
17 that document?

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

21 MS. JACOBSEN: Plaintiffs move
22 into evidence PTX 8.

23 MR. LEVY: No objection.

24 THE COURT: Admitted without

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1 objection.

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

6 THE COURT: All right.

7 MR. LEVY: No objection.

8 THE COURT: You may proceed.

9 MS. JACOBSEN: Thank you.

10 BY MS. JACOBSEN:

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

14 A. Yes, I was.

15 Q. And what were your overall
16 conclusions?

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

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

24 A. Yes, I was.

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1 Q. Do you agree with their invalidity
2 opinions?

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

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

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

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

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

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

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

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

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

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

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

24 Q. And are there other types of

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

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

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

17 Q. And how did that apply in this
18 case?

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

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1 formulations.

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

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

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

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1 consistent with the available experimental data.

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

9 THE COURT: Mr. Levy.

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

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

21 THE COURT: Can you just cite me a
22 paragraph?

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

24 THE COURT: Well, usually one is

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1 better than a slew.

2 MS. JACOBSEN: Well, 79, and 94 to
3 97 was also at his deposition discussed at
4 length about the importance of the molecule as a
5 whole.

6 THE COURT: Right. Well, proceed.

7 BY MS. JACOBSEN:

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

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

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

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1 had been possible to reasonably predict in
2 advance?

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

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

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

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

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1 degradation in a pharmaceutical formulation?

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

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

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

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

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

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

24 Q. What was the time of the invention

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1 of the '031 patent?

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

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

9 Q. Dr. Klibanov, why did you put
10 yourself in the position of a POSA as of January
11 12, 1998?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 And these references include GB
5 '040, so Great Britain patent application, the
6 U.S. '807 patent and the Elmalem reference.
7 These were the very same references that I
8 already discussed before this Court in the
9 Watson case.

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

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

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

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

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

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

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

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

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1 pharmaceutical formulation?

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

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

15 Q. Do all drugs undergo oxidative
16 degradation?

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

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

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1 oxidative degradation under pharmaceutically
2 relevant conditions.

3 Q. And what are pharmaceutically
4 relevant conditions?

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

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

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

13 Degradation by heat called
14 pyrolysis. Degradation by -- I'm sorry,
15 degradation by light called photochemical
16 degradation. Degradation by water called
17 hydrolysis. Degradation by acids and oxygen, as I
18 already mentioned, and a number of
19 others.

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

24 Q. So, focusing on oxidative

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 A. Yes, the U.S. counterpart of GB
19 '040, the '176 patent, was considered by the PTO
20 during the prosecution of the '031 patent.

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

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

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

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

6 A. No, not at all. What is shown on
7 the screen now is an amendment taken from the
8 '031 patent prosecution history, and as the
9 Court can see on the screen now, it says, among
10 other things, "As acknowledged by the fact that
11 the office action contains no rejection over the
12 prior art, the composition and method related to
13 this aspect of applicants' invention are both
14 novel and obvious."

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

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

19 A. I'm sorry. Novel and unobvious.

20 Q. Thank you.

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

24 MR. LEVY: No objection.

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1 THE COURT: All right. Admitted
2 without objection.

3 BY MS. JACOBSEN:

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

6 A. Yes, it does.

7 Q. What kind of drug is rivastigmine?

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

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

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

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

24 A. No, not at all.

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1 Q. Why do you say that?

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

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

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

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

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

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

23 A. Yes.

24 Q. Are any of those ingredients an

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1 antioxidant?

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

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

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

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

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

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

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

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

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

9 A. No.

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

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

20 Q. Does example two require Brij 97?

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

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

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

8 A. Yes, it was, because even if Brij
9 97 did contain an antioxidant, the use of Brij
10 97 is by no means compulsory, and therefore,
11 other plasticizers could have been used as well,
12 and there is certainly no evidence that they
13 would have an antioxidant present.

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

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

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

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

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

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

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

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

23 THE COURT: All right. Thank you.

24 BY MS. JACOBSEN:

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

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

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

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

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

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

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

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

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

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

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

23 MR. LEVY: No objection.

24 THE COURT: Admitted without

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1 objection.

2 BY MS. JACOBSEN:

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

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

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

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

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

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1 essential.

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

7 MS. JACOBSEN: For the record, Dr.
8 Klibanov, referred to PTX 184 at Column 2, Lines
9 60 to 68, and Column 3, Lines 3 to 7. And
10 plaintiffs move to introduce into evidence PTX
11 184.

12 MR. LEVY: No objection.

13 THE COURT: Admitted without
14 objection.

15 BY MS. JACOBSEN:

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

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

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

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

5 And a relevant excerpt here states
6 that obvious sources of pharmaceutical
7 instability include the incompatibility of
8 various ingredients with formulations -- within
9 a formulation. And then it states numerous
10 examples are described in other sections of the
11 book -- of this book and the literature is
12 replete with illustrations.

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

21 Q. And what happens if there is an
22 incompatibility?

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

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

4 MS. JACOBSEN: For the record, Dr.
5 Klibanov referred to JTX 5 at Page 1507 and
6 plaintiffs move to introduce into evidence JTX
7 5.

8 MR. LEVY: No objection.

9 THE COURT: Admitted without
10 objection.

11 BY MS. JACOBSEN:

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

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

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

20 And it illustrates -- it says
21 sulfites which is a type of antioxidant, can
22 readily form inactive addition compounds, as with,
23 for example, epinephrine, which is a drug. And
24 then it says, thus, not all antioxidants can be

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1 used with all drugs.

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

7 MS. JACOBSEN: For the record, Dr.
8 Klibanov referred to PTX 156 at Page 97. And
9 plaintiffs move to introduce into evidence PTX
10 156.

11 MR. LEVY: No objection.

12 THE COURT: Admitted without
13 objection.

14 BY MS. JACOBSEN:

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

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

22 Q. And does that include antioxidant
23 incompatibilities?

24 A. It certainly does, yes.

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

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

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

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

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

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

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

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

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

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

21 MR. LEVY: No objection.

22 THE COURT: Admitted without
23 objection.

24 BY MS. JACOBSEN:

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

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

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

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

20 And what is shown on this
21 timeline, this is the timeline with respect to
22 the '031 patent. So the Court --obviously, the
23 1998, as I discussed earlier, is the
24 patent-in-suit, which discloses rivastigmine

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1 plus an antioxidant in a transdermal device.

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

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

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

13 A. Yes.

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

16 A. Yes, I certainly did.

17 Q. And what was your overall
18 conclusion?

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

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

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1 combine it with any reference to solve a
2 nonexistent problem.

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

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

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

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

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

9 A. Yes, he did.

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

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

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

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

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1 this screen.

2 Q. How large is that class of
3 carbamates?

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

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

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

24 MS. JACOBSEN: For the record,

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

3 BY MS. JACOBSEN:

4 Q. Does that class of compounds
5 include RA7?

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

9 Q. And is rivastigmine different from
10 RA7?

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

19 Q. Does the '807 patent disclose
20 transdermals?

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

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1 types of formulations that are taught by the
2 '807 patent.

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

6 BY MS. JACOBSEN:

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

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

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

19 A. Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 MS. JACOBSEN: For the record,
23 Dr. Klibanov referred to JTX 17, column 3, lines
24 37 to 39, and column 11, lines 21 to 29.

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1 BY MS. JACOBSEN:

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

4 A. Yes, I did.

5 Q. Did it change your opinion?

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

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

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

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

2 MS. JACOBSEN: And for the record,
3 Dr. Klibanov referred to JTX 17 Column 7, Lines
4 15 to 53.

5 BY MS. JACOBSEN:

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

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

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

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

20 A. By testing. A person would
21 proceed with pharmaceutical formulation
22 development.

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

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1 for example, adding such inactive ingredients.

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

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

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

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

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

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

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

10 BY MS. JACOBSEN:

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

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

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

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

24 In fact, would understand -- it

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9 A. Yes.

10 Q. And do you recognize this
11 document?

12 A. Tab 5.

13 Q. Sorry, Tab 9.

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

16 Q. What does this patent relate to?

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

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

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1 physostigmine.

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

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

11 A. No, none.

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

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

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

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1 MR. LEVY: No objection.

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

4 BY MS. JACOBSEN:

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

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

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

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

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

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

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

14 A. Yes, it does.

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

17 A. Yes, it does.

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

20 And, Dr. Klivanov, can you turn to
21 Tab 10 of your witness binder?

22 A. Yes.

23 Q. Do you recognize that document?

24 A. Yes. That's that European

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

3 Q. And when was that application
4 published?

5 A. It was published in 1986.

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

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

15 But, nonetheless, Dr. Enz in GB
16 '040 made no efforts and made no statement or
17 indicated no evidence that either there was an
18 instability oxidative degradation problem of
19 rivastigmine or any need to add an antioxidant.

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

24 A. It was published in 1986. Yes,

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1 sorry.

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

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

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

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

15 MS. JACOBSEN: Your Honor,
16 plaintiffs move to introduce into evidence PTX
17 194.

18 MR. LEVY: No objection.

19 THE COURT: All right. Admitted
20 without objection.

21 BY MS. JACOBSEN:

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

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1 A. Yes, of course.

2 Q. And what was your overall
3 conclusion?

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

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

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

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

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

19 Q. Please can I have the next slide.

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

24 A. I agree with Dr. Kydonieus that an

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

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

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

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

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

8 A. Elmalem was published in 1991.

9 Q. What drugs did Elmalem study?

10 A. Elmalem studied several drugs.
11 And what Elmalem did is Elmalem compared the
12 physiological effects of these drugs in a
13 head-to-head format. So, in other words, what
14 was done in Elmalem was that morphine was used
15 to induce respiratory depression in rabbits. So
16 morphine was used to depress breathing of
17 rabbits, and then several drugs, RA6, RA7, RA15,
18 physostigmine, and the saline placebo drug. So
19 these five drugs were used to assess their
20 ability to reverse this morphine-induced
21 respiratory depression. So it was a
22 head-to-head study, quantitative study of the
23 effects of these drugs on this physiological
24 condition, morphine-induced respiratory

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1 depression.

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

4 BY MS. JACOBSEN:

5 Q. Dr. Klibanov, did Elmalem study
6 rivastigmine?

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

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

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

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

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

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

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

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

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

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1 H5C2, which is called an ethyl group.

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

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

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

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

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

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

9 BY MS. JACOBSEN:

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

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

17 Q. Would an antioxidant reduce
18 hydrolysis?

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

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

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

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

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

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

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

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

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

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

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

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1 MS. JACOBSEN: For the record,
2 Dr. Klibanov referred to JTX 18 at page 456, and
3 plaintiffs introduce into evidence Exhibit JTX
4 18.

5 MR. LEVY: No objection.

6 BY MS. JACOBSEN:

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

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

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

24 And the reason for that is not

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

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

12 MR. LEVY: No objection.

13 THE COURT: Admitted without
14 objection.

15 BY MS. JACOBSEN:

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

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

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1 formulations.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 MR. LEVY: No objection.

23 THE COURT: Admitted without
24 objection.

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1 BY MS. JACOBSEN:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 And that explains
8 mechanicistically why dialkyl carbamates, as was
9 known even then in particular, was known even in
10 1994, it explains mechanicistically why dialkyl
11 carbamates are much more stable against
12 hydrolysis than monomethyl carbamates.

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

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

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

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

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

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

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

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

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

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

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1 degradants.

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

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

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

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

21 Early on, there was some
22 prosecution history from 2009; right, on the
23 '031 patent? Or there was prosecution history.
24 What was the date on it?

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1 THE WITNESS: It was 2009.

2 MS. JACOBSEN: It does say 2009.

3 We can check the date on that, Your Honor.

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

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

8 MR. KALLAS: May I speak, Your
9 Honor? The patent, the '031 patent, if that's
10 what we're discussing, issued on January 1st,
11 2002. So that date must be wrong or you're
12 thinking of another date. But --

13 THE COURT: All right.

14 MS. JACOBSEN: We'll correct it
15 after.

16 THE COURT: Okay. I just -- okay.

17 All right. Well, we'll be in
18 recess.

19 THE CLERK: All rise.

20 (A brief recess was taken.)

21 THE CLERK: All rise.

22 THE COURT: All right. Let's
23 continue.

24 MS. JACOBSEN: Your Honor, just on

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

3 THE COURT: Okay. All right.

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

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

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

11 MS. JACOBSEN: Okay.

12 BY MS. JACOBSEN:

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

15 A. Yes.

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

20 A. Yes.

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

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

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

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

14 And specifically says --

15 MS. JACOBSEN: May I approach,
16 Your Honor?

17 THE COURT: Sure.

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

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

3 BY MS. JACOBSEN:

4 Q. How were the drugs in Elmalem
5 prepared?

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

11 Q. What is saline?

12 A. Saline is simply solution of
13 sodium chloride in water. So it's essentially a
14 solution of table salt at a concentration of
15 4.15 molar in water.

16 Q. And what is sodium metabisulphite?

17 A. It's an antioxidant.

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

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

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1 injected simultaneously with morphine.

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

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

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

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

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

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

20 Q. Does Elmalem use the actual
21 amount of antioxidant used?

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

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1 equal weight of sodium metabisulphite.

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

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

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

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

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

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

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

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

23 Q. Why would it have been done that
24 way?

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

8 Q. Is this way of doing it also
9 easier?

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

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

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

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

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

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

20 Q. Did Elmalem control for any other
21 variables?

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

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

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

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

22 BY MS. JACOBSEN:

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

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

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

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

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

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

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

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

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

24 A. RA7 would do nothing of the sort.

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

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

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

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

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1 as of 1998 that would have contradicted that
2 reading?

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

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

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

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1 bioavailability and a longer duration of action
2 than physostigmine."

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

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

9 THE COURT: Admitted without
10 objection.

11 BY MS. JACOBSEN:

12 Q. Do either of Enz 1991 or Weinstock
13 1994 discuss adding an antioxidant to
14 rivastigmine?

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

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

21 A. No, they do not.

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

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1 A. Yes, I did.

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

4 A. It does not.

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

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

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

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

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

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

4 And, of course, it is the goal of
5 the experiment that dictates what experimental
6 protocol is to be employed. As I will explain
7 in a moment, the goals of the two studies in
8 question, Elmalem on the one hand and Weinstock
9 '81 on the other, were very different.

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

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

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

21 A. Well, the goal of the Weinstock
22 '81 study, it was not a head-to-head comparison
23 of drug study. In fact, there were no
24 head-to-head comparisons at all.

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

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

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

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

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

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

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

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

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

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

15 MS. JACOBSEN: For the record, Dr.
16 Klibanov referred to JTX 30 at Pages 504 and
17 507.

18 BY MS. JACOBSEN:

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

22 A. Yes.

23 Q. -- to test the hypothesis?

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

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

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

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

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

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

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

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1 system.

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

4 BY MS. JACOBSEN:

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

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

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

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

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

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

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

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

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

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

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

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

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

6 Q. And is that different from
7 Elmalem?

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

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

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

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

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

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

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1 differences.

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

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

8 A. I don't believe so.

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

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

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

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

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

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

9 A. No. I don't think that there
10 would be a motivation to combine GB '040 with
11 Elmalem simply because there was no problem that
12 one of skill in the art would understand in GB
13 '040 that needed a solution. But even if one
14 were to combine them, then they -- obviously,
15 the invention of the, for example, Claim 7 of
16 the patent-in-suit still wouldn't be obvious
17 because it specifically requires transdermal
18 formulation, whereas undeniably Elmalem does not
19 deal with transdermal formulations.

20 Q. Thank you, Dr. Klibanov.

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

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1 oxidative degradation based on its structure?

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

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

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

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

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

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

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

4 And the second reference, it's
5 1996, Modern Pharmaceutics, says the mechanisms
6 of oxidation reactions are usually complex. So
7 one of skill in the art would have known that,
8 and would have known on the basis of these and
9 other references that oxidation reactions were
10 not well understood. And I might add are not
11 well understood even today.

12 MS. JACOBSEN: For the record, Dr.
13 Klibanov referred to JTX 22 at Page 82 and PTX
14 153 and Page 183. And plaintiffs move to
15 introduce into evidence JTX 22 and PTX 153.

16 MR. LEVY: No objection.

17 THE COURT: All right. Admitted
18 without objection.

19 BY MS. JACOBSEN:

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

23 A. Yes, with potentially being the
24 key term.

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

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

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

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

21 BY MS. JACOBSEN:

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

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

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

6 A. That's correct.

7 Q. Does rivastigmine have any of the
8 functional groups in table two of Modern
9 Pharmaceuticals?

10 A. No, it does not.

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

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

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

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

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

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

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

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

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1 amines.

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

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

24 MS. JACOBSEN: For the record,

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

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

10 Q. Thank you, Dr. Klibanov.

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

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

15 THE COURT: It's admitted without
16 objection.

17 MS. JACOBSEN: Thank you. And
18 Dr. Klibanov referred to column 3, lines 51 to
19 61.

20 BY MS. JACOBSEN:

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

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1 A. Yes, I did.

2 Q. And why did you do that?

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

16 Q. What did you discover?

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

23 Q. How was that relevant to your
24 analysis?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24 MS. JACOBSEN: And for the record,

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

4 MR. LEVY: No objection.

5 THE COURT: Admitted without
6 objection.

7 BY MS. JACOBSEN:

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

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

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

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

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

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

19 MS. JACOBSEN: For the record,
20 Dr. Klivanov referred to PTX 246 at page 70 and
21 Plaintiffs move to introduce into evidence PTX
22 246.

23 MR. LEVY: No objection.

24 THE COURT: Admitted without

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1 objection.

2 BY MS. JACOBSEN:

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

5 A. Again, Dr. Tiemessen at the trial
6 here was asked that question, he was asked, so,
7 you see the word stability, that is this word
8 stability that's highlighted, that's referred to
9 in this document. Is that a reference to
10 oxidative degradation? And he said no. This is
11 referencing to stability in general. He says
12 then, the chemical stability in general, and
13 also the physical stability in general. So this
14 15 percent wasn't even his -- their expectation
15 of encountering oxidative instability, that was
16 their expectation of encountering any type of
17 instability, whether it's chemical or physical
18 combined.

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

21 BY MS. JACOBSEN:

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

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

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

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

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1 discovered how to prevent it from happening.

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

5 BY MS. JACOBSEN:

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

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

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

15 A. Yes, I did.

16 Q. What was your overall conclusion?

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

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

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

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

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

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

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

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

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

14 A. Yes.

15 Q. Can you give some examples?

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

24 And these drugs include

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

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

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

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

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

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1 2007, 2015, 2035, 2044, and 2872. And
2 Plaintiffs move to introduce into evidence PTX
3 157.

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

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

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

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

12 BY MS. JACOBSEN:

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

16 A. No, because they were both liquid
17 and solid dosage forms. And
18 besides, all dosage

19 forms are known to undergo oxidative
20 degradation. It's just a question of rates.

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

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1 pharmaceutical formulation as of 1998?

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

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

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

18 MS. JACOBSEN: And for the record,
19 Dr. Klibanov referred to PTX 157 and Pages 890
20 and 1336. PTX 185, Column 5, Line 55 to Column
21 7, Line 10, and PTX 186 at Column 6, Line 15 to
22 Column 8, Line 32.

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

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1 MR. LEVY: No objection.

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

4 BY MS. JACOBSEN:

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

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

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

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

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

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

6 MR. LEVY: Objection, Your Honor.

7 THE COURT: Is this your earlier
8 objection?

9 MR. LEVY: Yes.

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

12 MR. LEVY: Thank you, Your Honor.

13 BY MS. JACOBSEN:

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

16 A. Yeah. These are later examples.

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

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

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1 antioxidant.

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

5 A. Yes, it does.

6 MS. JACOBSEN: For the record, Dr.
7 Klibanov referred to PTX 188 at Page 903 and PTX
8 189, at 2684.

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

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

13 BY MS. JACOBSEN:

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

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

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

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

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

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

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

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

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

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

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1 And plaintiffs move to introduce into evidence
2 JTX 24.

3 MR. LEVY: No objection.

4 THE COURT: Admitted without
5 objection.

6 BY MS. JACOBSEN:

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

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

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

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

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

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

8 That's a direct quote.

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

13 MR. LEVY: In objection.

14 THE COURT: Admitted without
15 objection.

16 BY MS. JACOBSEN:

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

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

24 And what I list on the next slide

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

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

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

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

17 BY MS. JACOBSEN:

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

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

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

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

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

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

18 A. I did.

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

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

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

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

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

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

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

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1 in rivastigmine. It is undeniably not present
2 in nicotine.

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

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

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

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

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

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

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

24 It is this bond right here. And

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

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

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

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

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

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

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

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

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

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

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

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

23 At the time of the invention in
24 1998, there were three commercial transdermal

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

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

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

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

18 BY MS. JACOBSEN:

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

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

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

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

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

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

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

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

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

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

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

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

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1 advance?

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

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

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

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

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10 BY MS. JACOBSEN:

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

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

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

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

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

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

15 A. I did.

16 Q. What did you conclude?

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

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

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

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

11 Q. Is Sasaki a peer reviewed
12 reference?

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

17 Q. Does Sasaki disclose rivastigmine?

18 A. It does not.

19 Q. What does Sasaki relate to?

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

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

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

13 A. No, it does not.

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

16 BY MS. JACOBSEN:

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

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

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

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

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

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

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

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

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

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

7 BY MS. JACOBSEN:

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

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

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

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

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1 physostigmine as I discussed earlier.

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

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

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

17 Q. Do these compounds contain
18 tertiary amines like rivastigmine?

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

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1 just like rivastigmine.

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

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

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

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

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

5 THE COURT: I will note Mr. Levy's
6 objection to this as being I guess irrelevant
7 because it post dates the invention, but I will
8 overrule the objection.

9 MR. LEVY: That's correct, Your
10 Honor. Thank you.

11 BY MS. JACOBSEN:

12 Q. And one of these compounds is
13 selegiline; is that right?

14 A. Yes.

15 Q. Is selegiline a tertiary amine?

16 A. Yes, it is.

17 Q. And is selegiline also a compound
18 with a benzylic carbon hydrogen bond?

19 A. Yes, it is. This carbon here is a
20 benzylic carbon and there is a hydrogen attached
21 to it.

22 MS. JACOBSEN: For the record,
23 Dr. Klivanov referred to PTX 187 at 59, PTX 188
24 at 903, and PTX 189 at 2864. Plaintiffs move to

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1 introduce into evidence PTX 187.

2 MR. LEVY: No objection.

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

5 MR. LEVY: I'm sorry, subject to
6 the prior objections.

7 THE COURT: Good point. Thank
8 you.

9 BY MS. JACOBSEN:

10 Q. Dr. Klibanov, was there any
11 suggestion in the prior art that rivastigmine
12 was unstable in an acrylic adhesive?

13 A. No. In fact, there was
14 suggestions to the contrary, because if we go
15 back to GB '040, which we discussed in the
16 beginning of my direct testimony, and that
17 example two that I also talked about, it
18 specifically says that with respect to
19 composition of this transdermal it specifically
20 says -- so it's compound A which is -- the
21 compound A which is rivastigmine, it also says
22 that among other components, other ingredients,
23 inactive ingredients is acrylate polymer. So
24 example two of GB '040 is an example of an amine

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1 drug compound in a transdermal formulation
2 containing acrylate polymers.

3 Q. Is the amine-containing compound
4 in example two rivastigmine?

5 A. Yes, it is, it could be
6 rivastigmine.

7 Q. Is there any suggestion that that
8 would have given rise to a stability problem?

9 A. No. As I mentioned earlier, GB
10 '040 gives no indication, in fact gives opposite
11 indications, but gives no indication to one of
12 ordinary skill in the art that rivastigmine
13 needed an antioxidant or that rivastigmine
14 undergoes oxidative degradation.

15 MS. JACOBSEN: So for the record,
16 Dr. Klibanov referred to JTX 19 at page 19.

17 BY MS. JACOBSEN:

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

20 A. No, I see no such motivation,
21 because GB '040 didn't identify any oxidative
22 degradation problem and, therefore, a person of
23 ordinary skill in the art wouldn't look for a
24 reference to combine GB '040 with Sasaki to

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1 solve an unknown problem. But even aside from
2 this lack of motivation, even if one of skill in
3 the art were to combine GB '040 with Sasaki, in
4 my opinion, this combination doesn't make the
5 invention of the patent-in-suit obvious because
6 Sasaki doesn't deal with rivastigmine, doesn't
7 deal even with RA7, it deals with just two
8 particular amine compounds in one particular
9 transdermal formulation, and therefore, I don't
10 see how it can possibly make the invention of
11 the patent-in-suit obvious.

12 Q. Dr. Kydoniues also discussed the
13 Ebert reference?

14 A. Yes.

15 Q. Did you consider that reference in
16 your analysis?

17 A. Yes, of course.

18 Q. What was your overall conclusion?

19 A. Well, again, my overall conclusion
20 is that a POSA would not have combined Ebert
21 with GB '040, and briefly, the reasons for that
22 are outlined on this slide that's on the screen
23 now.

24 First of all, Ebert does not

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1 disclose rivastigmine or even RA7. Ebert solves
2 problems that are not related to rivastigmine,
3 meaning it solves problems that do not exist with
4 rivastigmine.

5 And also, Ebert discloses, and
6 that's important, nonconventional manufacturing
7 of a transdermal device, whereas GB '040
8 expressly prefers conventional manufacturing for
9 rivastigmine, and reiterates that.

10 Q. So what problem does Ebert address
11 in the prior art?

12 A. It follows from what is shown on
13 the screen now, so there were several problems
14 that Ebert addressed that were present with
15 nicotine. So as the citation from Ebert says,
16 an object of the present invention, that's
17 Ebert's invention, is to provide a method of
18 fabricating transdermal devices with volatile or
19 heat-sensitive drugs, and as a result of their
20 volatility and sensitivity to heat, such
21 components cannot be subjected to drying or
22 heating.

23 And there is no evidence that
24 rivastigmine is either volatile or heat

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1 sensitive. And, in fact, there is evidence that
2 transdermal devices containing rivastigmine can
3 be subjected to drying and heating because they
4 are both in the Novartis manufacturing process
5 and in the Noven manufacturing process.

6 Q. Does Ebert identify any particular
7 drugs that are heat sensitive or volatile?

8 A. Yes. There are a number of drugs
9 that are mentioned, but all of the
10 experimentation is done with just one particular
11 drug, namely nicotine.

12 Q. And does Ebert suggest that
13 rivastigmine would be heat sensitive or
14 volatile?

15 A. No. As I said, it doesn't mention
16 rivastigmine at all.

17 MS. JACOBSEN: For the record,
18 Dr. Klivanov referred to JTX 28 at page 5, line
19 16 to 21.

20 BY MS. JACOBSEN:

21 Q. And did Ebert address any other
22 problems?

23 A. Yes. Ebert addressed some other
24 manufacturing problems, but again, problems that

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1 were specific for nicotine. So as the Court can
2 see on the screen now, these are two other
3 excerpts from Ebert, the first one says with
4 above about 50 percent nicotine by weight, the
5 polymer fails to solidify. This is the polymer
6 that is used to make the transdermal device.

7 And then it continues, common
8 materials used to make transdermal devices, such
9 as backing layers, adhesives and release liners,
10 are dissolved or degraded by nicotine.

11 So Ebert specifically identifies a
12 couple of other problems with nicotine in
13 transdermal devices in terms of manufacturing
14 issues, one is prevention of the polymer from
15 solidification, and another one is degradation
16 by nicotine or dissolution. And again, there is
17 no evidence presented that rivastigmine will
18 have any of these problems. So these were all
19 the problems that were specific for nicotine.

20 Q. And you mentioned the polymer
21 that's used to make the transdermal device. Is
22 that a reference to the adhesive?

23 A. Yes.

24 MS. JACOBSEN: Just for the

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1 record, Dr. Klibanov referred to JTX 28 at page
2 3, lines 17 to 25, and page 4, lines 1 to 4.

3 BY MS. JACOBSEN:

4 Q. Now, how did Ebert address these
5 problems with nicotine?

6 A. Well, basically what Ebert did,
7 Ebert prepared -- he employed a very unusual
8 manufacturing process. So what Ebert did, he
9 first extruded the polymer, which didn't contain
10 a drug, and then -- this polymer was dissolved
11 in the solvent and the solvent was evaporated in
12 an oven. And then subsequent to that, Ebert
13 extruded a mixture of nicotine with a polymer,
14 with another polymer, in this particular case,
15 and in this particular case as the Court can see
16 it was hydroxy propyl cellulose, and this mixture
17 which was very thick, it required stirring for
18 as I recall twenty-four hours. And since
19 nicotine as I mentioned earlier, Your Honor,
20 under some conditions undergoes oxidative
21 degradation, to prevent this degradation of
22 nicotine while stirring, Ebert added the
23 antioxidant BHT due to the fact that nicotine
24 was stirred over an extended period of time.

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1 So the rationale for this unusual
2 manufacturing process is that unlike rivastigmine
3 that can and is heated during the manufacturing,
4 nicotine cannot be because it is heat sensitive
5 and therefore it had to undergo this laborious
6 procedure and requiring lengthy stirring and to
7 prevent its oxidation during this lengthy
8 stirring the antioxidant was added.

9 Q. And the mixture of hydroxy propyl
10 cellulose and nicotine, is that the active gel
11 that's discussed?

12 A. Yes, that's what Ebert calls the
13 active gel, yes.

14 Q. And is this how transdermal
15 devices are conventionally made?

16 A. No, that's not how they are
17 conventionally made. They are conventionally
18 made using a matrix method where you basically
19 mix the adhesive with the drug and then subject
20 it to drying. Ebert couldn't use it with
21 nicotine because nicotine is heat sensitive and,
22 therefore, doesn't tolerate drying.

23 Q. And is the mixing for the extended
24 period of time, say twenty-four hours, a

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1 conventional manufacturing step?

2 A. No, it's obviously, you know,
3 wasteful, takes a long period of time, there are
4 all kinds of issues, that is not how it's
5 usually done. Ebert was forced to employ this
6 method because of the specific features of
7 nicotine as a drug.

8 MS. JACOBSEN: For the record
9 Dr. Klivanov referred to JTX 28 at page 1, lines
10 13 to 20, and page 19, lines 34 to page 20, line
11 3.

12 BY MS. JACOBSEN:

13 Q. You mentioned that Ebert disclosed
14 the use of an antioxidant. Why was that
15 antioxidant added in Ebert?

16 A. Ebert explains that, and
17 specifically says another trait of nicotine that
18 can be problematic is its tendency to oxidize
19 readily in the presence of light and air. So
20 that's the problem that nicotine was known to
21 have.

22 And then Ebert says during
23 fabrication of nicotine patches, oxidation is
24 controlled by addition of an antioxidant to the

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1 active gel. So the purpose of the antioxidant
2 was to prevent this oxidation during the lengthy
3 stirring that Ebert had to employ.

4 MS. JACOBSEN: For the record,
5 Dr. Klibanov referred to JTX 28 at page 19,
6 lines 17 to 19, and lines 23 to 24.

7 BY MS. JACOBSEN:

8 Q. If a POSA didn't prepare the
9 active gel as in Ebert, would a POSA have been
10 motivated by Ebert to add an antioxidant?

11 A. No, then there would be no reason
12 to do that.

13 Q. And if a POSA didn't already know
14 the drug would potentially undergo oxidative
15 degradation, would Ebert have told the POSA that
16 an antioxidant was required?

17 A. No. Again, the answer is no.

18 Q. Does Ebert suggest that any drug
19 other than nicotine is sensitive to oxidative
20 degradation?

21 A. No the focus is on nicotine with
22 nicotine's specific problems and issues, as I
23 just explained.

24 Q. Would a POSA have been motivated

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1 to use the teaching in Ebert with rivastigmine?

2 A. I mean, I see no such motivation.

3 Again, GB '040 didn't report any oxidative
4 degradation problem of rivastigmine, hence there
5 was no motivation to combine rivastigmine -- to
6 combine GB '040 with any other reference to
7 solve this unknown problem, but in any event,
8 even if one of skill in the art were to combine
9 GB '040 with Ebert, given that Ebert doesn't
10 deal with rivastigmine, it employs a
11 nonconventional manufacturing process as opposed to
12 conventional processes in the case of GB '040,
13 certainly this combination wouldn't make the
14 invention of the patent-in-suit obvious in my
15 opinion.

16 Q. Is there any evidence that
17 rivastigmine suffered from any of the problems
18 with nicotine that were addressed by Ebert?

19 A. No. In fact, if rivastigmine was
20 known to -- not to have these problems, for
21 example, as I mentioned previously, Your Honor,
22 nicotine was known to be volatile, so to have
23 very high vapor pressures, so that would be very
24 susceptible to evaporation. In contrast -- this

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1 is nicotine. In contrast to that, rivastigmine
2 was not known to be volatile. Also, nicotine
3 has a very low viscosity. It's only a few fold
4 more viscous than water, whereas rivastigmine
5 has a very high viscosity, much, much higher
6 than water.

7 So that once again confirms that
8 what you -- you have to consider the molecule as
9 a whole to understand or predict its physical
10 properties, and chemical properties because here
11 we have some similarity as was explained
12 yesterday between rivastigmine structure and
13 nicotine structure, although I think it's very
14 modest as I explain in my testimony, and yet
15 their properties are very different, and
16 therefore, in my opinion, one would not
17 extrapolate mechanically what's known for
18 nicotine to rivastigmine. There was just no
19 good reason for doing that.

20 Q. And just for the record, what does
21 GB '040 say about the methods that can be used
22 to manufacture rivastigmine formulations?

23 A. Well, as the Court can see on the
24 screen, there are several excerpts from the GB

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1 '040, and basically it says that rivastigmine
2 transdermal system may be manufactured in
3 conventional manner, active agents may be
4 administered in any conventional liquid or solid
5 transdermal pharmaceutical composition. And
6 then finally that the rivastigmine transdermal
7 formulation is prepared using a conventional
8 apparatus.

9 So the key word here is
10 conventional, whereas Ebert is anything but. So
11 whereas Ebert due to the specific properties of
12 nicotine was forced to employ nonconventional
13 manufacturing, rivastigmine in fact not only
14 allowed, but indeed with rivastigmine
15 conventional manufacturing were employed.

16 Q. Were those conventional apparatus
17 included an oven and did the process include
18 heating?

19 A. Yes.

20 MS. JACOBSEN: For the record,
21 Dr. Klibanov referred to JTX 19, at 10, 16 and
22 19.

23 BY MS. JACOBSEN:

24 Q. Dr. Klibanov, does GB '040 make

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1 any reference to Ebert?

2 A. No, it does not.

3 Q. Does GB '040 refer to any other
4 references concerning manufacturing of
5 transdermal devices?

6 A. It does. GB '040 specifically
7 refers to the European Patent Application Number
8 155,229 with respect to how the transdermal
9 formulation may be prepared.

10 MS. JACOBSEN: For the record,
11 Dr. Klibanov referred to JTX 19 at 16, and JTX
12 29, which is the '229 patent, plaintiffs move to
13 introduce into evidence JTX 29.

14 MR. LEVY: No objection. I'm
15 sorry, 29.

16 MS. JACOBSEN: 29 is the EP '229.

17 THE COURT: Admitted without
18 objection.

19 BY MS. JACOBSEN:

20 Q. Dr. Klibanov, does EP '229 disclose
21 the use of an antioxidant in a transdermal?

22 A. No, it does not.

23 Q. What's your overall conclusion
24 with respect to Ebert?

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1 A. Well, my overall conclusion as I
2 mentioned earlier would be that first of all, a
3 person of ordinary skill in the art would not be
4 motivated to combine GB '040 with Ebert. If
5 anything, one of skill in the art would be
6 motivated to combine GB '040 with European
7 Patent Application '229 which expressly cites,
8 which discloses conventional as opposed to
9 unconventional as in Ebert manufacture of a
10 transdermal device.

11 Q. Dr. Klibanov, I would like to turn
12 to the Handbook of Pharmaceutical Excipients
13 next.

14 MS. JACOBSEN: Before I do that,
15 Your Honor, may I approach? We just had some
16 replacement slides because Dr. Klibanov's
17 testimony was shortened and they didn't find
18 their way into the binder.

19 THE COURT: Sure.

20 BY MS. JACOBSEN:

21 Q. So, Dr. Klibanov, would the
22 Handbook of Pharmaceutical Excipients have told
23 the POSA that rivastigmine undergoes oxidative
24 degradation and requires an antioxidant?

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1 A. It certainly does not. I mean,
2 the Handbook of Pharmaceutical Excipients
3 doesn't mention rivastigmine, doesn't talk about
4 drugs. It's simply a handbook that list
5 pharmaceutical excipients that have previously
6 been used in pharmaceutical products. It in no
7 way specifically relates to rivastigmine.

8 Q. And would the Handbook of
9 Pharmaceutical Excipients have told a POSA that
10 rivastigmine could be combined with an
11 antioxidant?

12 A. Again, it's in no way related
13 specifically to rivastigmine. It does list a
14 number of antioxidants, but it certainly doesn't
15 talk about rivastigmine, doesn't talk about
16 other drugs, so it would be -- there would be no
17 motivation for one of skill in the art to
18 combine a rivastigmine reference with the
19 Handbook of Pharmaceutical Excipients.

20 Q. And would the '807 patent have
21 told the POSA that rivastigmine can be combined
22 with or is compatible with antioxidants?

23 A. The '807 patent would not suggest
24 anything of the sort.

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1 Q. And why not?

2 A. Well, because, as I said, the '807
3 patent doesn't even deal with transdermal
4 formulations. And, in any event, it only talked
5 about antioxidants in the context of
6 injectables. And even then, only as required.

7 Q. Did the '807 patent specifically
8 combine RA7 with an antioxidant?

9 A. It certainly did not.

10 Q. What about Elmalem, would that
11 have told a POSA that rivastigmine was
12 compatible with antioxidants?

13 A. No. Again, there are no evidence,
14 no tests of compatibility, no information with
15 respect to that at all.

16 Q. And is the time over which the
17 Elmalem formulations existed relevant to whether
18 or not it discloses compatibility?

19 A. Yes, in some way, because it
20 specifically says that the formulations of
21 Elmalem, when prepared freshly, which, I mean, I
22 guess one of skill in the art would understand
23 means that they were used either right away or
24 shortly thereafter.

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1 So there was certainly no
2 prolonged storage, otherwise, they wouldn't say
3 freshly prepared.

4 Q. Finally, would GB '040 have shown a
5 POSA that rivastigmine is compatible with
6 antioxidants?

7 A. Again, there was no information
8 with respect to that at all. So no
9 compatibility information. No compatibility
10 conclusion, in my judgment, can be drawn
11 whatsoever.

12 Q. And I'd just like to briefly
13 discuss the documents that Dr. Kydonieus cited
14 relating to Brij 97.

15 A. Okay.

16 Q. Where was the Brij 97 that was
17 used in GB '040 obtained from?

18 A. Well, again, as I already
19 discussed earlier today, and the Court can see,
20 that it's highlighted on the screen, it was
21 expressly obtained from Atlas Chemie and the
22 company which at that time was called West
23 Germany which, of course, is Germany now. And
24 from Atlas Chemie in West Germany.

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1 Q. And did Dr. Kydonieus cite any
2 documents relating to Brij 97 from Atlas Chemie?

3 A. No.

4 Q. And where were the documents that
5 he cited from obtained from?

6 A. Well, he specifically cited -- Dr.
7 Kydonieus specifically cited two references.
8 So, one of them, as the Court can see on the
9 screen, JTX 9. That particular Brij 97 was
10 obtained from ICI Americas, Incorporated.

11 And that was as of 1991. So what
12 we know from that is that in 1991, Brij 97
13 obtained from ICI Americas contained 0.01
14 percent antioxidant, namely BHA.

15 I might also add that after 1991,
16 they stopped adding antioxidants. So there was
17 certainly no antioxidant in Brij 97 as of 1998,
18 which is the priority date of the
19 patent-in-suit.

20 The second thing that is there is
21 that the reference DTX 89, which they indicated
22 that as of 1972, a Brij 97 from Atlas Point.
23 So, again, a different company, according to the
24 tentative specifications, contained an

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1 antioxidant solution.

2 So, as I understand it, and I
3 think that's the way one of skill in the art
4 would look at it, would know that in 1991, but
5 not thereafter, Brij 97 from ICI Americas
6 contained an antioxidant, this particular
7 antioxidant.

8 We know that tentatively Brij 97
9 from Atlas Chemie in 1972 also contains some
10 antioxidant solution without explaining what the
11 antioxidant was or what the concentration was.

12 And, in my judgment, therefore,
13 these data provide no evidence that, as of 1988,
14 Brij 97 from Atlas Chemie in West Germany
15 contain an antioxidant, let alone in 1998.

16 Q. Thank you, Dr. Klibanov.

17 Turning, finally, to Dr.
18 Kydonieus' argument that the '031 patent is --
19 Dr. Klibanov, I'm told you said
20 Atlas -- you made reference to Brij 1997
21 obtained from Atlas Point in West Germany.

22 A. Oh, I'm sorry. So Atlas Point is
23 a company where it doesn't say where it was
24 located, so I don't know.

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1 And I was talking about Brij 97,
2 of course. Okay.

3 And so the conclusion that one of
4 skill in the art would have made, and I hope
5 that I made, but maybe I didn't, was that one of
6 skill in the art from these data could not, in
7 my opinion, legitimately conclude that, as of
8 1998, Brij 97 obtained -- from Atlas Chemie in
9 West Germany contained an antioxidant.

10 And, likewise, the same applies,
11 as I said -- what I just said about 1998 equally
12 applies to 1988. So, at none of those dates,
13 that is, whether we're talking about the
14 publication date of GB '040 or the priority date
15 of the patent-in-suit, was there any evidence
16 that an antioxidant was present in Brij 97.

17 Q. Thank you.

18 And did you see any documents that
19 originated from Atlas Chemie in West Germany?

20 A. I did not.

21 Q. So turning to Dr. Kydonieus'
22 argument that the '031 patent is invalid over
23 the '176 patent for double patenting.

24 A. Yes.

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1 Q. Did you consider that argument?

2 A. Yes, I did.

3 Q. Did the patent examiner consider
4 the '176 patent?

5 A. Yes. As I mentioned in the
6 beginning of my testimony before the break, that
7 the patent examiner did not reject the
8 patent-in-suit over the '176 patent.

9 Q. What does the '176 patent claim?

10 A. The '176 patent claims, as is
11 shown on the screen now -- it provides the
12 (S)-{N-ethyl-3-[(1-dimethylamino)ethyl-N-methyl-
13 phenyl-carbamate]enantiomer. That is what we
14 now call rivastigmine.

15 And Claim 7 claims a method of
16 systematically administering rivastigmine which
17 comprises administering the active agent
18 transdermally through the skin.

19 Q. And do any of the claims of the
20 '176 patent disclose an antioxidant?

21 A. No.

22 Q. Would the prior art have suggested
23 to a POSA to add an antioxidant to the claims of
24 the '176 patent?

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1 A. No. As I just explained, with
2 respect to obviousness, the same applies here.

3 There was no motivation to this
4 effect. In fact, if anything, there was an
5 opposite motivation.

6 Q. So all of your opinions with
7 respect to obviousness apply here?

8 A. In my opinion, they do everything
9 I just said with respect to obviousness, and my
10 judgment fully applies to the double patenting
11 argument.

12 MS. JACOBSEN: Thank you, Dr.
13 Klibanov. I have no further questions at this
14 time, but I do have one housekeeping matter. I
15 may not have moved PTX 242 and 246 into
16 evidence.

17 MR. LEVY: No objection.

18 THE COURT: All right. Okay.
19 They're admitted without objection.

20 MS. JACOBSEN: Thank you, Your
21 Honor.

22 THE COURT: Mr. Levy, can I see
23 you and Ms. Jacobsen over here for a second?

24 (A conference was held at side-bar

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1 off the transcript record:)

2 THE COURT: So we'll break for
3 lunch. And as I've said, or as I just told the
4 attorneys, I have something at one o'clock and
5 I'm not sure how long it's going to take.

6 So let's plan to reconvene at
7 1:45, but I may be late. All right?

8 We'll stand in recess.

9 THE CLERK: All rise.

10 (A brief recess was taken.)

11 THE CLERK: All rise.

12 THE COURT: All right. Please be
13 seated. Are we ready to proceed?

14 MR. LEE: Your Honor, before we
15 begin our cross-examination, we have a request
16 to make.

17 THE COURT: Okay.

18 MR. LEE: We have reviewed the
19 information that Novartis has provided us as to
20 the support for the testimony of Dr. Klibanov as
21 to the mechanism of the oxidation, and whether
22 we now know today that there is -- oxidation
23 does not occur at the benzylic compound. This
24 is a very important point and it is not

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1 addressed in either his deposition or in the
2 paragraphs that they've cited to us.

3 There is the paragraph that
4 they've cited to us in the opening report that
5 refers to an Exhibit 15, but not to the page
6 that Dr. Klibanov is relying on. There is a
7 paragraph in his reply report.

8 THE COURT: Well, wait. Just so I
9 understand that.

10 MR. LEE: Yeah.

11 THE COURT: His opening report
12 says something and it cites an Exhibit 15 and --

13 MR. LEE: Cites to Page 2401.

14 THE COURT: Yeah.

15 MR. LEE: But that is not the page
16 that, I believe, Dr. Klibanov is relying on in
17 his testimony.

18 THE COURT: What page do you
19 believe he's relying on?

20 MR. LEE: Page 2403. His opening
21 report, of course, is on infringement, not on
22 invalidity. And he, of course, doesn't address
23 this issue.

24 And his reply report is also on

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1 infringement and doesn't address the issues of
2 validity.

3 Frankly, I've looked at the
4 deposition transcript that we've been pointed to
5 and I don't see this issue there at all. And we
6 have not been pointed to a particular line
7 number in the three-page sequence that they say
8 supports this point.

9 I believe that we have been
10 sandbagged about this point, Your Honor, because
11 it was not in his expert report. We could not
12 reasonably expect he would testify about it and
13 we had no reason to put it on in our direct
14 case.

15 Dr. Schoneich is here. He is
16 ready to testify about this issue, and we would
17 ask permission for a very short rebuttal, a
18 matter of a few minutes on this one point.

19 THE COURT: Well, does he address
20 it in his reports?

21 MR. LEE: Yes, he does. Well, let
22 me say this: He addresses -- he has in his
23 expert report in the appendix a list of the
24 oxidation products, the final products of

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1 oxidation. One of them is the product that is
2 shown on Page 2403.

3 Dr. Schoneich's opinion is
4 consistent with the Novartis page and I expect
5 that Dr. Schoneich will testify to that. He
6 will also testify that on the page that Dr.
7 Klibanov is relying on, or I believe he is
8 relying on, it does not show the initial point
9 of oxidation which, as Dr. Schoneich testified
10 on direct, is a radical.

11 There are no radicals shown on
12 Page 2403. That's not the purpose of Page 2403.
13 Page 2403 shows degradation products, not
14 radicals.

15 THE COURT: All right. Anything
16 else you want to say?

17 MR. LEE: No, Your Honor.

18 THE COURT: All right. Ms.
19 Jacobsen.

20 MS. JACOBSEN: Your Honor, in Dr.
21 Klibanov's opening report, he sets out the
22 oxidative degradation products that are now
23 known to be generated through the degradation of
24 rivastigmine and he pointed to the document in

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1 which rivastigmine -- sorry, Novartis identified
2 the degradation pathway. And in his --

3 THE COURT: And is this Exhibit
4 15?

5 MS. JACOBSEN: It is, yes, Your
6 Honor. And that includes the degradation
7 pathway.

8 And in his reply report, he
9 specifically points to that page where the 2403
10 which shows the degradation pathway, that shows
11 that it proceeds through the formation of the N
12 oxide, which is the product of oxidation of the
13 amine and then forms to the styrene and the
14 ketone degradants, which is what Novartis
15 measures in its products and what Noven measures
16 in its products to check whether oxidative
17 degradation is occurring.

18 And that's what Dr. Klibanov
19 relied on in his opening report and also in his
20 reply report on infringement.

21 THE COURT: So in the opening
22 report, did he cite to Page 2401?

23 MS. JACOBSEN: He did, yes.

24 THE COURT: All right. But in his

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1 reply report, he cites to Page 2403?

2 MS. JACOBSEN: He did, yes. And
3 then at his deposition, he was asked in the
4 context of validity of the stability of amines.
5 And what Dr. Klibanov said is there are some
6 that are stable and some that undergo oxidative
7 degradation.

8 And he said before 1998, a person
9 of ordinary skill in the art would have believed
10 that rivastigmine was stable, even though it has
11 an amine. And now we know that's not the case.
12 And that it's an amine compound that degrades
13 oxidatively.

14 THE COURT: So it sounds to me
15 from what you just said about his deposition
16 that, at least the way you just said it, maybe
17 this is -- maybe you're not being entirely
18 precise, I don't know. It sounded like it
19 wasn't exactly a direct head on addressing the
20 issue in the deposition.

21 MS. JACOBSEN: It was addressing
22 whether or not you could predict from the
23 structure whether or not rivastigmine was stable
24 and where the degradation occurred, the fact

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1 that it's an amine that undergoes degradation
2 for that reason.

3 THE COURT: All right. Is there a
4 page or two that I can look at?

5 MR. LEE: I'm sorry, Your Honor?

6 THE COURT: I was just going to
7 say, you know, maybe it's time for me to look at
8 the page or two and see if I can figure it out.

9 MS. JACOBSEN: It's over a couple
10 of questions. Do you have a copy of it?

11 Okay.

12 MR. LEE: We can put it up on the
13 screen, Your Honor.

14 THE COURT: All right. Put it up
15 on the screen.

16 So, but just while you're doing
17 that, Mr. Lee, so what you want is to be able to
18 recall Dr. Schoneich and ask him some questions
19 about the same topic; is that right?

20 MR. LEE: Same topic.

21 THE COURT: And Ms. Jacobsen,
22 what's your point on that?

23 MS. JACOBSEN: Well, if it's in
24 his report, he could have reasonably anticipated

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1 that this was coming. He's responded on how he
2 believes that it undergoes oxidative
3 degradation.

4 And, in fact, during direct, he
5 was asked: Are there other sites on
6 rivastigmine that a person of ordinary skill in
7 the art would expect to be susceptible to
8 oxidative degradation? And he says, yes, there
9 are.

10 And if you go to the next slide,
11 and he discusses the tertiary amine. So, Your
12 Honor, to the extent that he wanted to discuss
13 it on his direct, he's already had the
14 opportunity to do so.

15 MR. LEE: I think maybe, Your
16 Honor --

17 THE COURT: Yes.

18 MR. LEE: I think we're confusing
19 two amines. Part of the discussion is whether
20 the amine group would influence the
21 susceptibility of a carbon-hydrogen bond to
22 oxidize. What Dr. Klibanov was talking about
23 was whether the oxidation takes place on the
24 amine.

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1 The testimony in his deposition, I
2 think, is Page 153 to 155 was about the first
3 issue about whether amine compounds, not the
4 amine itself, are susceptible to oxidation. So
5 the portion of his deposition doesn't go to this
6 same issue of the mechanism.

7 As far as whether we had a
8 reasonable basis to believe this, there is no
9 statement in his report that he believes that
10 Dr. Schoneich was wrong in saying that oxidation
11 takes place at the hydrolytic carbon. And
12 that's why we had no reason to address that
13 issue, whether it takes place at some other
14 position because there was no counter testimony.

15 And, now they've put in this
16 testimony and we will need to recount it and we
17 need Dr. Schoneich to do it.

18 THE COURT: And what's the
19 relevance of which one it takes place out of?

20 MR. LEE: Well, so our case relies
21 on the fact that the structure of rivastigmine
22 is very special. It has a carbon-hydrogen bond,
23 which is surrounded by three groups, each of
24 which renders that carbon hydrogen bond weak and

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1 susceptible to oxidation.

2 If, in fact, oxidation takes place
3 at a different position, then our whole argument
4 about why one of ordinary skill in the art would
5 have relied on this basic structure rivastigmine
6 to show that it was susceptible to oxidation,
7 that falls apart.

8 THE COURT: And so what is it that
9 Dr. Schoneich is going to testify to again?

10 MR. LEE: What Dr. Schoneich is
11 going to testify to, Your Honor is that the
12 evidence to which Dr. Klibanov replied is
13 completely consistent with his opinion that the
14 initial oxidation takes place at the
15 carbon-hydrogen bond and that the evidence that
16 Dr. Klibanov is relying on, if I am correct that
17 this is what he's relying on, that it does not
18 disclose at all the initial point of oxidation,
19 which is, as Dr. Schoneich testified on direct,
20 was the formation of a radical.

21 There are no radicals in the flow
22 chart that Dr. Klibanov, I believe, is relying
23 on.

24 THE COURT: All right. Yes, Ms.

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1 Jacobsen.

2 MS. JACOBSEN: Your Honor, you
3 know, we believe the testimony is fairly
4 supported by his reports, but if Your Honor is
5 minded to allow a reply, then we'll withdraw the
6 question and answer. And we don't see that
7 there's any need for recalling a witness here.

8 THE COURT: What do you think
9 about that?

10 MR. LEE: That's fine, Your Honor.

11 THE COURT: All right.

12 Okay. All right.

13 So maybe just put on the record so
14 that it will be easy for me to figure out later
15 on what question and answer do we think is
16 withdrawn? It was your question, Ms. Jacobsen,
17 so why don't you tell us.

18 MR. KALLAS: It may be difficult
19 for us to do that without the transcript.

20 THE COURT: Well, do your best.
21 You know, you don't have to do it literally,
22 just basically the topic of whether the tertiary
23 amine has something to do with the actual
24 oxidation process in rivastigmine is withdrawn.

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1 MS. JACOBSEN: Yeah. The question
2 is whether it, in fact, undergoes oxidative
3 degradation at the tertiary amine, and Dr.
4 Klibanov's testimony that that's now known to be
5 the site of oxidation.

6 THE COURT: All right. Well, that
7 testimony of Dr. Klibanov will be struck by
8 agreement of the parties.

9 So go ahead with
10 cross-examination.

11 MR. LEVY: May it please the
12 Court, Your Honor, Mike Levy on behalf of Noven.

13 CROSS-EXAMINATION.

14 BY MR. LEVY:

15 Q. Good afternoon, Dr. Klibanov.

16 A. Good afternoon, Mr. Levy.

17 Q. Pleasure to meet you.

18 May I please have PDX 11? Dr.
19 Klibanov, earlier today you testified about an
20 Exhibit PTX 162, which was some guidelines from
21 an organization called EMEA.

22 Do you recall that?

23 A. Yes.

24 Q. Now, this Exhibit PTX 162, which

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1 supports this slide, that's just a set of
2 guidelines; isn't that right?

3 A. It's a set of guidelines by the
4 European equivalent of the FDA for
5 pharmaceutical formulators. Yes.

6 Q. Do these guidelines have any
7 authority in the United States?

8 A. I don't think so, but I don't
9 know.

10 Q. Were you confining your person of
11 ordinary skill in the art to just the European
12 jurisdiction?

13 A. I mean, I'm just relying on all
14 the documents that were public documents that
15 one of skill in the art would have access to,
16 and this was one of these documents.

17 Q. There is no rule or provision in
18 this document proscribing the use of
19 antioxidants; isn't that right?

20 A. As I just said, these are
21 guidelines that one of skill in the art would
22 read in the context of the entire prior art.

23 Q. And there is no rule or provision
24 in that document, those guidelines, that

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1 proscribes the use of antioxidants in
2 pharmaceutical formulations; isn't that right?

3 A. If you don't consider these
4 excerpts rules or guidelines, then
5 that's what's
6 more pertinent to that issue.

7 Q. Now, these guidelines aren't
8 limited to transdermals; correct?

9 A. That's correct.

10 Q. In fact, they also address perhaps
11 eyedrops that are given to infants; isn't that
12 right?

13 A. They address a number of
14 formulations as I said in my direct testimony.

15 Q. So there could be incompatibility
16 or toxicity issues related to
17 formulations that

18 have nothing to do with transdermals such as
19 infant eyedrops; right?

20 A. Well, these are general
21 statements, they're not limited to any
22 particular formulation, so I don't agree with
23 you.

24 Q. When you cut out that excerpt that

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1 antioxidants should only be included in a
2 formulation if it has been proved that their use
3 cannot be avoided, are you saying that is what
4 people always do in the field of pharmacy
5 formulation?

6 A. This is sort of the general sort
7 of state of mind at the time and even now of one
8 of skill in the art in this area.

9 Q. I believe that document had a
10 publication date on its face of 1997. Was that
11 the same guidance that ordinarily skilled
12 artisans followed prior to 1997?

13 A. I mean, I don't know. These seem
14 to be sort of general principles that are
15 consistent with what I explained in my testimony
16 as how formulations scientists work.

17 Q. So for all you know it wasn't
18 until 1997 that this type of advice was given by
19 a regulatory authority?

20 A. That's not true.

21 Q. So it was possible that was true
22 before 1997; is that right?

23 A. It is definitely true that that
24 was the case before 1997 because I was working

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1 in the field long before 1997, and I knew and
2 regular practitioners knew that you don't add an
3 excipient such as an antioxidant unless needed.

4 Q. Now, the Exelon patch marketed by
5 Novartis has an antioxidant; isn't
6 that right?

7 A. Yes.

8 Q. Was Novartis aware of these
9 guidance points when they developed
10 the Exelon
11 patch?

12 A. I cannot speak for Novartis.
13 Again, one of skill in the art of this is a
14 mythical person who is expected to be familiar
15 with all the literature that was available.
16 People who work with Novartis are real people,
17 so I don't know what they were aware of, what
18 they were not aware of.

19 Q. But you spoke very eloquently this
20 morning about the development of the Exelon
21 patch; right?

22 A. I just relied on the evidence that
23 was before, that's in this case. I'm glad that
24 you found it eloquent, but I just relied on the

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1 documents that I showed on the slides.

2 Q. Did Novartis to your knowledge try
3 any other solutions before it decided on an
4 antioxidant consistent with that guidance?

5 A. I don't recall.

6 Q. People don't always follow such
7 guidelines, do they?

8 A. People don't always follow
9 guidelines, that's true. Such guidelines and
10 any other guidelines, yes.

11 MR. LEVY: May I have PTX 13,
12 please.

13 BY MR. LEVY:

14 Q. In this slide, Doctor, you pointed
15 out by excerpts that excipient incompatibility
16 may cause degradation. Is that right?

17 A. Yes.

18 Q. Did you intend for your testimony
19 to explain that persons of ordinary skill in the
20 art would have been reluctant to even consider
21 antioxidants?

22 A. No, I don't think there is any
23 harm considering, but in doing so a person of
24 ordinary skill in the art would be aware that

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1 there are downsides of doing that.

2 Q. You didn't testify this morning
3 that the person of ordinary skill in the art
4 could not run routine stability testing to
5 identify an appropriate compatible antioxidant;
6 correct?

7 A. There was no law against trying
8 routine tests. I was talking about whether one
9 of skill in the art would add excipients that
10 are not necessary to a pharmaceutical
11 formulation.

12 Q. So this would not discourage an
13 ordinary skilled artisan from running a routine
14 test with a desired antioxidant if one was so
15 desired; right?

16 A. It may.

17 Q. Is it your testimony, sir, that
18 persons of ordinary skill in the art will not
19 even attempt to test for an appropriate
20 antioxidant?

21 A. No, that is not my testimony.

22 Q. May I have PTX 61, please.

23 This morning, Doctor, you
24 testified about the inventors having a

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1 particular level of skill that matched the
2 person of ordinary skill that you have talked
3 about; correct?

4 A. Not quite correct, no.

5 Q. Is there any evidence on this
6 slide, Dr. Klibanov, that the inventors knew
7 about the Ebert reference, the Elmalem
8 reference, the Sasaki reference and the Handbook
9 of Pharmaceuticals?

10 A. There is no evidence on this slide
11 one way or another.

12 Q. In fact, you have cited no
13 evidence that any of the inventors alone or
14 collectively had knowledge of all of the
15 relevant prior art; correct?

16 A. I cited no such evidence. And it
17 wasn't probative with respect to the opinions
18 that I was asked to opine on. These were the
19 inventors. I was asked to opine on one of
20 ordinary skill in the art and what this person
21 would do.

22 Q. And you through that slide allowed
23 the inventors to meet that qualification; isn't
24 that right?

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1 A. That's not right.

2 Q. With this slide, you were saying
3 that the inventors had the level of ordinary
4 skill in the art that you applied to your
5 validity analysis; isn't that right?

6 A. No, that's not correct.

7 Q. You offered no testimony in your
8 direct that any of the inventors was actually an
9 organic chemist; isn't that correct?

10 A. I did not offer any testimony with
11 respect to that.

12 Q. May I have PDX 12, please.

13 Dr. Klibanov, you also had a slide
14 talking about the use of antioxidants in which
15 you cited the Evans '376 patent; isn't that
16 right?

17 A. Yes.

18 Q. Now, are you saying that the
19 person of ordinary skill in the art would have
20 regarded most antioxidants as toxic, therefore
21 to be avoided?

22 A. I made no such statement.

23 Q. Then could you please -- strike
24 that.

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1 And you cited the Handbook of
2 Pharmaceutical -- I'm sorry, strike that.

3 Can we bring up JTX 008, page 12.
4 The entry for tocopherol. Do you see that,
5 Dr. Klibanov?

6 A. I do.

7 Q. This is an antioxidant; right?

8 A. Yes.

9 Q. In fact, this is one of the
10 antioxidants of claim 16; right?

11 A. Yes.

12 Q. Could we please go to the
13 regulatory status on the next page in the left
14 column, entry 16.

15 Alpha-tocopherol is identified as
16 being GRAS listed; is that right?

17 A. Yes.

18 Q. And that means generally regarded
19 as safe; isn't that correct?

20 A. That's correct.

21 Q. In fact, this is accepted in
22 Europe as a food additive; right?

23 A. That's what it says.

24 Q. Can I also go up a paragraph

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1 above, the paragraph beginning the use of
2 tocopherol. The third from the bottom. I'm
3 highlighting a sentence from that entry.

4 It says the use of tocopherols in
5 pharmaceuticals and food products is unlikely to
6 pose any hazard to human health since the daily
7 intake from such uses is small compared to the
8 intake of naturally occurring tocopherols in the
9 diet. Do you see that?

10 A. I do.

11 Q. Is there anything in that entry
12 that I have shown you about tocopherol that
13 would discourage a generally skilled artisan
14 from using it in a pharmaceutical formulation?

15 A. With respect to tocopherol, which
16 is one of many FDA approved
17 antioxidants, with
18 respect to tocopherols, the
19 statement speaks for
20 itself.

21 Q. There is no toxicity issues that
22 would discourage the use of tocopherols by an
23 ordinarily skilled artisan; is that right?

24 A. You know, in the passages that you

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1 specifically asked me to look at.

2 Q. And you didn't testify this
3 morning contradictory to that; correct?

4 A. I wasn't talking specifically
5 about tocopherol. I was talking about
6 antioxidants in general.

7 Q. Can we please go to page 15. This
8 is the entry for ascorbic acid?

9 A. Yes.

10 Q. Do you see that on the screen
11 doctor?

12 A. I do.

13 Q. And ascorbic acid is also one of
14 the claim 16 recited antioxidants; isn't that
15 correct?

16 A. That's correct.

17 Q. And I'm referring to claim 16 in
18 the '031 patent. We're in agreement there?

19 A. Yes.

20 Q. Can we go to the regulatory
21 status, please, on page 17.

22 And here this is also identified
23 as GRAS listed; is that right?

24 A. Yes, this is the second

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1 antioxidant that's identified as such, yes.

2 Q. And, in fact, this is also
3 accepted as a food additive in Europe; isn't
4 that right?

5 A. That's what it says.

6 Q. And there is nothing there
7 teaching the ordinarily skilled artisan to avoid
8 that particular antioxidant based on toxicity
9 issues; is that right?

10 A. That's right, ascorbic acid is
11 vitamin C. In fact, we take it when we get sick
12 or are sick, so I don't think there is any
13 problem with vitamin C. I certainly wasn't
14 talking about that.

15 Q. Can we please bring up PDX 14.

16 This is another slide I believe
17 you discussed this morning entitled Antioxidants
18 May Unpredictably Increase Degradation. Do you
19 recall that?

20 A. I do.

21 Q. You didn't refer to any reference
22 in your direct testimony confirming an instance
23 where formulators could not formulate a drug
24 with an antioxidant; correct?

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1 A. I'm sorry, could you repeat -- are
2 you asking me about sulfites or are you asking
3 me a more general question.

4 Q. I'm asking a question based on
5 this reference, this slide, and your citation to
6 Connors. You didn't refer to any reference in
7 your direct testimony confirming any instance
8 where formulators could not formulate a drug
9 with an antioxidant; correct?

10 A. I mean, I was just mentioning this
11 as an example. There are many references like
12 that. The Sasaki reference specifically says
13 that you should not use BHT, which is also
14 mentioned in claim 16 of the '031 patent,
15 because it says that it is believed to cause
16 cancer, so BHT, which is also a claimed
17 antioxidant, is just one of those. So yes,
18 there are some good ones and there are some not
19 so good ones.

20 Q. You didn't cite any reference
21 confirming there is a drug that couldn't be
22 matched to a compatible antioxidant; correct?

23 A. I mean, I can only say that I
24 specifically presented this reference, the

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1 Connors reference, and I stand by that
2 reference.

3 Q. Can we bring up claim 7 of the
4 '031 patent, please. Claim 7 depends from claim
5 1. I'm sure you know those requirements from
6 memory. This claim 7 is not limited to any
7 particular antioxidant; correct?

8 A. That's correct.

9 Q. Can we look at claim 16, please.

10 And here in claim 16, none of
11 these antioxidants are of the sulfite variety
12 that was warned against in your citation to
13 Connors in your testimony this morning; correct?

14 A. That's correct, but that is
15 butylhydroxytoluene, and Sasaki says it
16 shouldn't be used because it causes cancer.

17 Q. Persons of ordinary skill in the
18 art don't need all antioxidants to work with all
19 drugs; correct?

20 A. A person of ordinary skill in the
21 art may not need any antioxidants to work with
22 any drugs if drugs do not undergo oxidative
23 degradation.

24 Q. If they do select an antioxidant

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1 to address that issue, they just need one to
2 work properly; right?

3 A. Could be one, could be
4 combination, but there are other considerations
5 that go into creating pharmaceutical
6 formulations.

7 Q. Can we please go back to PDX 14.
8 And despite this warning about sulphites, we
9 know that sodium metabisulfate was compatible
10 with RA7 in the Elmalem reference; right?

11 A. We do not know that, first of all
12 it's not sodium metabisulfate, it's sodium
13 metabisulfite.

14 Q. Thank you for correcting me.

15 A. Second of all, we don't know that,
16 we only know that sodium metabisulphite was
17 added. What the consequence of that was, we
18 don't know.

19 Q. Can we have PDX 49, please.

20 Now, you testified that because
21 RA7 is a dialkyl carbamate, a person of ordinary
22 skill would have had an expectation of
23 stability in water; correct?

24 A. A greater stability in the case of

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1 monomethyl carbamate, yes.

2 Q. In making this, and in sharing
3 that opinion with the Court today, you focused
4 us on the left side of the molecule; correct?

5 A. I focused on the entire molecule,
6 but since the carbamate moiety is located in the
7 left-hand side molecule, that is what I circled,
8 but I presented the structure of the entire
9 molecule.

10 Q. And you're saying here, aren't
11 you, that the property of water stability is
12 affected by the left side of the molecule and
13 the right side you did not testify about any
14 contribution it makes to that; correct?

15 A. No, that's not correct.

16 Q. I don't recall hearing any
17 testimony that the right side of the molecule
18 contributes to water stability; is that right?

19 A. Well, I'm sorry that you don't
20 recall it, but if you go to the slide where I
21 specifically talked about the effect of the
22 amine moieties of physostigmine on the carbamate
23 moiety, that is exactly what the point of that
24 slide was.

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1 Q. I understand. This isn't
2 physostigmine, is it?

3 A. This is not, this is RA7.

4 Q. And those amino moieties that you
5 pointed to this in the physostigmine slide
6 aren't present here, are they?

7 A. They're not present here. One of
8 the other amines is present. The point of what
9 I demonstrated was to show that it is the entire
10 molecule that determines the stability of the
11 compound.

12 Q. Dr. Klibanov, in so testifying
13 about the impact of the alkyl groups on
14 stability in water, aren't you confirming that a
15 person of ordinary skill in the art can look at
16 the structure of a chemical compound and make a
17 reasoned prediction about a physical property,
18 yes or no?

19 A. No.

20 Q. That was not the substance of your
21 testimony regarding the -- regarding the title,
22 the title of your slide, because RA7 is a
23 dialkyl carbamate, a POSA would expect it to be
24 stable in water. Did I say that correctly?

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1 A. You read the title correctly, yes.

2 Q. Your testimony about that
3 expectation was based on looking at the
4 structure and making a reasoned judgment about
5 what was known about those functional groups of
6 that particular structure as disclosed in the
7 prior art; correct?

8 A. That's not correct.

9 Q. So is it your testimony that a
10 person of ordinary skill in the art would not
11 harbor the expectation of water stability by
12 looking at the structure of the molecule?

13 A. It is my testimony that one of
14 skill in the art relying on the vast amount of
15 experimental studies that were carried out with
16 monomethyl and dialkyl carbamates would know
17 from those experimental studies that in general,
18 dialkyl carbamates are much more stable against
19 hydrolysis than monomethyl.

20 Q. I think we agree with each other
21 that when you take that information that would
22 have been available to the person of ordinary
23 skill in the art as you just articulated, you
24 look at a structure and make an informed

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1 prediction about behavior; correct?

2 A. That's not correct.

3 Q. May I have PTX 59, please.

4 You testified this morning,
5 Dr. Klibanov, about a table containing
6 functional groups subject to autooxidation; is
7 that correct?

8 A. You misstate what the table shows,
9 but I did testify about this table and I did
10 show this slide.

11 Q. I misstated the purpose of the
12 table when I said it contains functional groups
13 subject to autooxidation?

14 A. First of all, it doesn't talk
15 about autooxidation at all. Second of all, it
16 talks about potentially oxidized, and as I
17 specifically emphasized during my testimony, the
18 word potentially is a key word here.

19 Q. And this is from the Modern
20 Pharmaceuticals text; correct?

21 A. Yes.

22 Q. PTX 153?

23 A. Yes.

24 Q. That's an authoritative text in

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1 pharmaceuticals; correct?

2 A. Yes.

3 Q. Perhaps you and I aren't meeting
4 eye to eye on what this table is because I think
5 your slide elected to show some of the table.
6 Can we show some of the complete table, please.

7 On the left is your slide, on the
8 right is the table that's actually taken from
9 there. And I think you cut off the title. It
10 says, "Table 2, Some Functional Groups Subject
11 to Autooxidation." Do you see that?

12 A. Yes.

13 Q. And I think you testified that
14 look, here is a list of functional groups that
15 are known to be susceptible to oxidation; is
16 that right?

17 A. These are some functional groups
18 that are susceptible to oxidation, that is
19 correct.

20 Q. And I think your slide -- strike
21 that.

22 That's not an exhaustive list;
23 isn't that right?

24 A. It's not an exhaustive list, which

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1 is what the word some signifies. This is a
2 table that with respect to the data and the
3 statements is taken verbatim from Modern
4 Pharmaceuticals. And I specifically said that
5 these are some functional groups that have been
6 known to potentially oxidize in pharmaceutical
7 compounds.

8 Q. You're not saying, are you,
9 Doctor, that a person of ordinary skill
10 undertaking the task of inspecting a chemical
11 structure for susceptibility to oxidative
12 degradation would consult this table only to the
13 exclusion of any other information, are you?

14 A. No, I think that one of skill in
15 the art would examine the prior art as a whole
16 as I have been emphasizing during my direct
17 testimony.

18 Q. Doesn't the very existence of a
19 table like this in an authoritative text in the
20 field confirm that the person of ordinary skill
21 in the art could make reasonable predictive
22 judgements about a molecule's susceptibility to
23 oxidation based on chemical structure?

24 A. Certainly not.

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1 Q. This table is giving guidance to
2 the ordinarily skilled artisan in the text
3 Modern Pharmaceuticals to help spot and I'll
4 quote, some functional groups subject to
5 autooxidation; is that correct?

6 A. The groups that can potentially
7 undergo oxidative degradation, that's correct.

8 Q. And we agree it's not an
9 exhaustive list; right?

10 A. We do agree it's not an exhaustive
11 list and I never claimed it to be one.

12 Q. And that table does not say
13 potentially; correct?

14 A. That table does not say that, but
15 if you read the text that precedes this table,
16 that in the context of the entire chapter, this
17 is what one of skill in the art would
18 understand.

19 Q. Dr. Klibanov, wouldn't a person of
20 ordinary skill in the art in 1998 undertaking to
21 formulate a drug look at the structure of the
22 molecule and make educated assessments about the
23 molecules potential for degradation?

24 A. As I already explained in my

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1 direct testimony, any organic molecule has a
2 potential for degradation under sufficiently harsh
3 condition. Any organic molecule will oxidize,
4 such as in burning, for example.

5 That, by itself, has no bearing on
6 what will happen in the pharmaceutical
7 formulation or under pharmaceutically relevant
8 conditions.

9 Q. That really wasn't my question.
10 Let me rephrase or ask it again.

11 A. Please.

12 Q. Wouldn't a person of ordinary
13 skill in the art in 1998, undertaking to
14 formulate a drug, look at the structure of the
15 molecule and make educated assessments about the
16 molecule's potential for degradation?

17 A. No.

18 Q. Wasn't a person of ordinary skill
19 in the art in 1998 instructed to look at a
20 molecule's features in order to anticipate
21 potential modes of degradation?

22 A. Person was instructed to look at
23 the molecule as a whole without ignoring any
24 parts of that molecule. The molecule as a

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1 whole.

2 Q. Let's turn to Page 181 of this
3 exhibit that supported that slide.

4 A. Yes.

5 Q. Sorry Page 181, first full
6 paragraph, third sentence.

7 MS. JACOBSEN: What's the exhibit
8 number? We haven't gotten cross books.

9 MR. LEVY: It was the -- I think
10 it was Modern Pharmaceuticals. I'm sorry.

11 MS. JACOBSEN: Do you have it?
12 153.

13 Exhibit PTX 153.

14 BY MR. LEVY:

15 Q. Can I please have the third
16 sentence highlighted beginning, Yet through the
17 application? Dr. Klibanov, I've highlighted a
18 sentence from this text, this authoritative text
19 that you cited --

20 A. Yes.

21 Q. -- to the Court. And I want to
22 find out if you agree with this.

23 It says, "Yet through the
24 application of functional group chemistry, it is

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1 possible to anticipate the potential modes of
2 degradation that drug molecules will likely
3 undergo. Do you agree with it?

4 A. I do. And in particular, I want
5 to again emphasize the word potential, which is
6 found in this sentence. With the word potential
7 there, I do agree with this sentence.

8 Yes, sir.

9 Q. Can we please have PDX 105 up,
10 please?

11 I just want to clarify the record.
12 Dr. Klibanov, I don't think you and I will have
13 a dispute here at all.

14 Your slide says GB '040 references
15 EP '229, not Ebert; is that right?

16 A. Yes.

17 Q. Were you trying to show through
18 your testimony that the inventors chose not to
19 refer to Ebert?

20 A. The inventor of GB '040 did not
21 refer to Ebert. Yes.

22 Q. Okay. It was your testimony,
23 wasn't it -- I'm sorry.

24 Was it the intent of your

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1 testimony to communicate to the Court that the
2 inventor made a conscious decision not to refer
3 to Ebert?

4 A. I have never spoken with the
5 inventor. Actually, in this case, it's
6 singular. One inventor, Albert Enz.

7 I have never spoken with him, have
8 never met the man. I don't know what his
9 intention was.

10 I can only look at this prior art
11 reference as one of skill in the art would, and
12 the fact of the matter is that this reference GB
13 '040 references the European application, the
14 '229 application and does not reference Ebert.

15 Q. In fact, it couldn't reference
16 Ebert;

17 right? Wasn't Ebert published in 1995?

18 A. That's right. It doesn't -- it
19 doesn't refer to either Ebert or another
20 publication that deals with unconventional,
21 unusual methods of manufacturing of transdermal
22 devices, but it clearly does not cite Ebert.

23 Q. And it couldn't, right, because GB
24 '040 published in 1988; correct?

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1 A. That's right. It could not cite
2 Ebert, but it certainly could cite another
3 Ebert-like reference. But it didn't do that,
4 either.

5 Q. Well, in any event, Doctor, you
6 and I can certainly agree that by 1998, the
7 person of ordinary skill in the art would have
8 had the benefit of both references; correct,
9 Ebert and GB '040?

10 A. That's right. That's correct.

11 Q. Can we please bring up PDX 85?

12 Thank you. You had a slide today
13 that talked about Sasaki. Does that slide -- do
14 you recall this slide that I've brought up on
15 the screen?

16 A. Yes, I do.

17 Q. And it's titled Sasaki Broadly
18 States Amines Undergo Oxidation in Acrylic
19 Adhesives; is that right?

20 A. Well, you said adhesives. It
21 actually says adhesive --

22 Q. I appreciate again the correction.

23 A. -- singular. No problem.

24 Q. The call out from Sasaki that you

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1 discuss with the Court talked about acrylic
2 adhesive substances; correct?

3 A. Again, it's not plural, it's
4 singular.

5 Q. Are acrylic adhesives made by a
6 free radical reaction, Doctor?

7 A. They may be, but don't have to be.

8 Q. Can we please bring up PTX 183?

9 Dr. Klibanov, you testified this
10 morning that I believe you relied on this
11 exhibit, which is testimony taken in this
12 courtroom in 2013, the testimony of Dr. Harry
13 Tiemessen; is that correct?

14 A. That's right.

15 Q. And PTX 138 is a collection of
16 excerpts from the testimony of Dr. Tiemessen; is
17 that right?

18 A. Yes.

19 Q. And it's not the whole testimony
20 of Dr. Tiemessen; is that correct?

21 A. That's right.

22 Q. In fact, it contains almost none
23 of the cross-examination that Dr. Tiemessen
24 received on this day when he was sitting in the

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1 same chair that you are; is that right?

2 A. I didn't cite it because I only
3 cited what was relevant to my testimony this
4 morning.

5 Q. Were you here on that day in 2013
6 and hear Dr. Tiemessen's testimony?

7 A. No, I was not.

8 Q. Well, do you recall, Doctor,
9 reading whether or not Dr. Tiemessen was asked
10 about how Novartis started with a salt form of
11 rivastigmine and not the free base?

12 A. What I recall is that they started
13 -- well, first of all, it's not clear what they
14 started with.

15 Second of all, what they started
16 with, what they at some point used was a salt.
17 But they also used an ion exchanger there that
18 would, as they stated in those documents that I
19 recall, convert that salt into a free base.

20 Q. I want to show you just a couple
21 excerpts that you may not have reviewed.
22 Perhaps you did and you can confirm for me
23 otherwise.

24 A. Sure.

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1 Q. Can we please see Page 794,
2 beginning at Line 14 and going through 795, 10.
3 I want to know if you considered the following
4 question and answer testimony in your analysis
5 when you testified this morning based on the
6 Tiemessen testimony.

7 The question was: "And so base
8 drugs can exist either as the free base or in
9 the acid addition salt form?"

10 "Answer: That's correct."

11 A. I'm sorry. Where are you reading?

12 Q. I'm reading from the top.

13 A. Oh, okay.

14 Q. This is still Dr. Harry Tiemessen,
15 the guy you cited to.

16 "Question: And so base drugs can
17 exist either as the free base or in the acid
18 addition salt form?"

19 "Answer: That's correct.

20 "Question: And you were using the
21 acid addition salt form during that first
22 several years of your development program?"

23 "Answer: Mm-hmm. That's correct.

24 Question: And you were aware at

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1 the time that, in general, the flux of a basic
2 drug through skin is much better with the base
3 form of the drug than with the salt form of the
4 drug; correct?

5 "Answer: That's correct.

6 Question: And you were trying a
7 rather unique approach of freeing that base
8 using this Eudragit polymer; correct?

9 "Answer: That's correct.

10 Question: But in the final
11 analysis, that just didn't work out?

12 "Answer: That didn't work out
13 because we always had to add so much of the
14 Eudragit that we could not increase the drug
15 load as we would like to."

16 Do you see that?

17 A. I do see that.

18 Q. Did you consider that testimony
19 this morning before you answered -- you
20 discussed the inventorship story today?

21 A. I don't specifically recall this
22 particular testimony. But during my deposition,
23 I had a very substantive discussion about this
24 very issue with your former partner, Ms.

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1 Hardman. And she showed me a number of
2 development documents which revealed expressly
3 that, in fact, when they used salts of
4 rivastigmine, due to the fact that they used
5 Eudragit, which is an ion exchanger, the salt
6 was converted into free base.

7 And whether or not that ultimately
8 resulted in a workable pharmaceutical
9 formulation, in my judgment, is not relevant to
10 this particular fact.

11 Q. Can we go to Page 796, please,
12 beginning at Line 6?

13 A. By the way, could I see just the
14 pages, so I can read them, so I can actually see
15 the context of what you're reading?

16 Q. I'm just asking: You presented
17 certain excerpts this morning. I just want to
18 show you a couple at -- one more excerpt and
19 then I'll move on.

20 A. Okay.

21 Q. And there is -- can you see it on
22 your screen?

23 A. Yes.

24 Q. -- 796 to Line 6 through 797, Line

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1 8. This, again, is the testimony in Court of
2 Dr. Harry Tiemessen. Another excerpt that I
3 want to find out if you considered it.

4 "Question: And the formula that
5 you developed after you got those unfavorable
6 results with the tartrate form of rivastigmine,
7 that formulation contained the rivastigmine free
8 base, the Duro-tak 280-2516 adhesive and
9 Blastoid B; is that correct?

10 "Answer: That's correct.

11 "Question: And that's essentially
12 the same formula that you used, then, throughout
13 the development of the project?

14 "Answer: That's correct. It was
15 the second lead formulation, and that was then
16 developed further.

17 "Question: So, Doctor, in the
18 book I gave you, could you turn to Exhibit DTX
19 129? Withdrawn."

20 The question then became: "I
21 think you've already talked about some of this,
22 and we might be able to short circuit this.

23 So if I understand, with the
24 second formulation, you discovered there was a

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1 stability problem in June of 1995?

2 "Answer: Yes, that's correct.

3 "Question: And in July of 1995 is
4 when you wrote your memo including as a possible
5 solution the addition of an antioxidant?

6 "Answer: Mm-hmm that's correct."

7 Did you consider that testimony?

8 A. I read the entire testimony of Dr.
9 Tiemessen and I certainly considered it in the
10 context of the entirety of the information
11 available to me, including the Novartis
12 development documents, including those that I
13 discussed with your former partner, Ms. Hardman
14 during my deposition. Yes, sir.

15 Q. Can we please bring up Slide DDX
16 222 from yesterday?

17 Now, Doctor, you gave testimony
18 this morning that rivastigmine is not
19 structurally similar to nicotine; is that
20 correct?

21 A. I explained and substantiated that
22 they are not structurally similar molecules.
23 Correct.

24 Q. Okay. And I thought -- if you and

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1 I go through it, I think you and I will probably
2 be able to agree on some things that are
3 similar. So let's see if we can do that.

4 Using the slide from yesterday,
5 were you here in the courtroom for this
6 presentation?

7 A. I certainly was.

8 Q. And I'm using the slide I used
9 because it has the colors, and it makes it easy
10 for you and I to communicate better. Is that
11 okay?

12 Have I presented the structures
13 accurately?

14 A. The colors don't bother me. Sure.

15 Q. You will agree that rivastigmine
16 and nicotine both have a tertiary carbon that is
17 identified as the red carbon; correct?

18 A. They both have a tertiary carbon,
19 as I said in my direct testimony. But in one
20 case, it's part of a ring and another case it is
21 not.

22 Q. But in both cases, it's a tertiary
23 carbon; right?

24 A. It's not a tertiary carbon you're

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1 talking about.

2 Q. In both molecules?

3 A. Yeah.

4 Q. It's simply a tertiary carbon?

5 A. You're talking about the carbon
6 that's right next to the arm?

7 Q. Yes, it's the red C.

8 A. Yes.

9 Q. And in rivastigmine, that is a
10 tertiary carbon; is that right?

11 A. That is correct.

12 Q. And nicotine, that's a tertiary
13 carbon; is that correct?

14 A. That is correct as well.

15 Q. Now, in both compounds, that red
16 C, the tertiary carbon is bonded to another
17 carbon atom shown in purple; is that right?

18 A. Well, that is what makes it a
19 tertiary carbon. Otherwise, it wouldn't be a
20 tertiary carbon.

21 Q. So we agree; is that right?

22 A. I'm not sure I understand the
23 question.

24 Q. The question is: The red carbon,

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1 the tertiary carbon --

2 A. Yes.

3 Q. -- in both cases is bonded to
4 another carbon atom that is shown in purple?

5 A. That's correct.

6 Q. And that tertiary carbon in both
7 cases is bonded to a tertiary amine shown in
8 green; isn't that correct?

9 A. Yes. As I said, one of these
10 amines is a part of a ring. Another one is not.

11 But in both cases, it's bound --
12 it's bonded to a nitrogen atom thereby making
13 the resulting structure a tertiary amine.

14 Q. And you'll agree with me, won't
15 you, that the tertiary carbon in both cases is
16 also bonded to an aromatic ring system; is that
17 right?

18 A. To a different or aromatic ring
19 structure, yes.

20 Q. But they're both aromatic rings in
21 rivastigmine and nicotine; correct?

22 A. Yes. They're both aromatic rings,
23 just as I said in my direct testimony.

24 Q. Now, will you also agree with me

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1 that the pyridine ring, it undergoes --

2 A. I'm sorry. Which ring?

3 Q. The pyridine in nicotine. I'm
4 sorry, pyridine. I apologize for my
5 pronunciation.

6 A. No problem.

7 Q. It's the nitrogen-containing
8 aromatic ring in this picture for the record.

9 A. Pyridine ring, yes.

10 Q. Will you agree with me that the
11 pyridine ring in nicotine can undergo resonance
12 stabilization?

13 A. It depends on the conditions in
14 which it is placed. If it is placed in an
15 aqueous solution and it is in a protonated
16 state, then resonance stabilization will be
17 almost non-existent.

18 Q. Will you agree with me that a
19 person of ordinary skill in the art would
20 conclude that information about nicotine is
21 relevant to the development of a transdermal
22 product?

23 A. Which transdermal product?

24 Q. Rivastigmine.

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1 A. I don't see any particular
2 relevance of that. I mean, certainly one of
3 skill in the art wouldn't disregard anything.
4 But I don't see any particular relevance, no.

5 Q. Going back to the question I asked
6 about resonance stabilization, absent the
7 condition that you mentioned, will the pyridine
8 ring undergo resonance stabilization?

9 A. Yes. If it's not in an acidic
10 aqueous solution, it will undergo resonance
11 stabilization.

12 Q. Can we please bring up PDX 71?

13 You testified earlier this morning
14 about the compound dextromethorphan. Do you
15 recall that?

16 A. Yes.

17 Q. And you testified about the
18 alleged stability regarding dextromethorphan; is
19 that right?

20 A. No, I testified about stability,
21 not alleged stability.

22 Q. And you discussed with the Court a
23 Boccardi article as I recall; is that right?

24 A. That's right.

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1 Q. Let's look at what you have
2 highlighted here in this article. Can we please
3 bring up Exhibit JTX 04?

4 Actually before we do that -- I'm
5 sorry, but before we do that, you've highlighted
6 two sentences here in your slide that you've
7 discussed with the Court. One, that
8 dextromethorphan hydrobromide is very stable.

9 Do you see that?

10 A. Yes.

11 Q. And a second sentence in the case
12 of dextromethorphan, the low reactivity in the
13 free radical test reflects good stability of the
14 substance; correct?

15 A. Yes. You didn't read the first
16 sentence in its entirety, but that's correct.

17 Q. And I think you took these
18 sentences from the same paragraph. I want to go
19 look at the actual exhibit where we got that
20 paragraph.

21 A. May I also see it, please?

22 Q. I'm sorry?

23 A. May I also see this?

24 Q. Sure.

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1 A. Just hard copy of this.

2 Q. Well, I'll bring it up on the
3 screen for you right now.

4 A. Could I see a hard copy, please.

5 MS. JACOBSEN: Dr. Klibanov, you
6 have it in your binder. It's at Tab 30.

7 THE WITNESS: Which one?

8 MS. JACOBSEN: Tab 30.

9 THE WITNESS: Thank you.

10 BY MR. LEVY:

11 Q. Can we bring up the paragraph on
12 Page 433, the second from the bottom?

13 A. Just a second. Just a second.

14 Let me orient myself. What page
15 is that?

16 Q. We are on Page 433.

17 A. Okay.

18 Q. I've blown up the paragraph, and
19 I'd like to highlight the third sentence
20 beginning, The same impurity was found.

21 A. Yes.

22 Q. And you, in your slide,
23 highlighted the first sentence and the last
24 sentence; isn't that correct?

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1 A. Yes.

2 Q. You didn't highlight the middle
3 sentence that I just highlighted here in the
4 courtroom. I'm going to read it.

5 It says, The same impurity was
6 found in trace amounts during preformulation of
7 an antitussive syrup combining 8. And 8 is a
8 compound that we know from reading the article
9 is one of the degradants of dextromethorphan;
10 correct?

11 A. Well, first of all, you are
12 mistaken. Dextromethorphan hydrobromide, as is
13 evident from the very first sentence, in this
14 paragraph. So when you called it a degradant.
15 That's just wrong.

16 Q. Okay.

17 A. Second of all -- may I finish?

18 Q. Yes.

19 A. Okay. Second of all, yes, it is
20 true that I did not highlight this because this
21 is, obviously, a reference to the previous
22 sentence, the second sentence, which talks about
23 photochemical meaning, oxidation meaning
24 oxidation by light, which is not relevant to the

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1 issue at hand.

2 Q. Okay. The second sentence says
3 that the impurity, which from the previous
4 sentence we learned is a degradant. The
5 ten-keto dextromethorphan compound was found in
6 trace amounts during preformulation in an
7 antitussive syrup. You see that?

8 A. I do see that.

9 Q. Now, you didn't mean to suggest
10 that the person of ordinary skill in the art
11 would understand that dextromethorphan does not
12 undergo oxidative degradation under
13 pharmaceutical relevant conditions; correct?

14 A. No, that's exactly what I meant to
15 indicate because the key element of the phrase
16 that you read was found in trace amounts. You
17 always have trace amounts of things.

18 As Dr. Kydonieus pointed out
19 yesterday, the important thing is whether you
20 have a significant concentration of the
21 degradant. This specifically talks about trace
22 amounts.

23 Q. And that's trace amounts of the
24 oxidative degradant were found in a syrup under

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1 pharmaceutically relevant conditions; correct?

2 A. Photochemical oxidation

3 degradation product, correct. So a

4 light-induced oxidation degradation product.

5 Q. Can we please go to PDX 87? Dr.

6 Klibanov, you testified earlier about some

7 amine-containing compounds or amine-containing

8 drugs in transdermals; correct?

9 A. Yes.

10 Q. And I believe you spoke from this

11 slide PDX 87 this morning and you spoke about

12 the compound dexsecoverine. And, again, please

13 permit my mispronunciation of these

14 pharmaceuticals.

15 A. Well, I'm certainly no expert.

16 It's dexsecoverine.

17 Q. Thank you. Scopolamine?

18 A. Yes.

19 Q. Fetanyl?

20 A. Yes.

21 Q. Benztropine?

22 A. Yes.

23 Q. Secoverine?

24 A. Secoverine.

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1 Q. Yes. And physostigmine?

2 A. No, physostigmine. It's the same
3 compound that I talked about quite a bit this
4 morning.

5 Q. Thank you.

6 Now, you asserted that all of
7 these are amine-containing drugs in a
8 transdermal without listed antioxidants that
9 were commercially available or disclosed in
10 patents; correct?

11 A. That's correct.

12 Q. And just so we have a clean record
13 here, you did not testify on direct that any of
14 the transdermal products that are highlighted on
15 this slide contain any of the active compounds
16 on this -- I'm sorry. Let me strike that
17 question.

18 You did not testify on direct that
19 any of the transdermal products containing any
20 of the active compounds on this page are
21 formulated with an acrylic adhesive; correct?

22 A. No. I did not testify to that
23 effect. Some of them may have been, some of
24 them may not have been.

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1 Q. In fact, you're not aware of any
2 evidence that the active compounds on the screen
3 that we just read into the record are formulated
4 in transdermal products with an acrylic
5 adhesive; right?

6 A. Yes. I don't recall at the
7 moment.

8 Q. And just so we're also clear, none
9 of the six compounds whose names we just read
10 into the record contain the same structural
11 feature of rivastigmine that includes a tertiary
12 benzylic carbon-hydrogen bond immediately
13 adjacent to a tertiary amine; correct?

14 A. These ones do not, that's correct.
15 They have benzylic -- they have benzylic
16 carbon-hydrogen bonds, but the amine is not
17 immediately adjacent.

18 Q. Right. So they don't share that
19 same important feature as rivastigmine; correct?

20 A. They do not have that feature. As
21 I said, the amine is not immediately
22 adjacent.

23 It's one carbon atom away.

24 Q. Doctor, you've testified that

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1 approved transdermal systems prior to 1998
2 contained no listed antioxidants; correct?

3 A. Not quite.

4 Q. Well, did you testify that
5 approved transdermal systems prior the 1998
6 contained no listed antioxidants in their PDR
7 entries?

8 A. That's right.

9 Q. Okay. And I think the implication
10 of that testimony was that the person of
11 ordinary skill in the art would deduce that the
12 API, the drug in that particular product is not
13 susceptible to degradation if it's not
14 accompanied by a listed antioxidant; is that
15 correct?

16 A. That was not the implication. The
17 implication was that none of these compounds,
18 although those compounds contained all the
19 structural elements mentioned by
20 Dr. Schoneich, none of them was listed to
21 contain an antioxidant. That was the statement,
22 and that was the implication.

23 Q. And the implication is that if
24 it's not accompanied by an antioxidant, there

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1 must not be an oxidation issue present; is that
2 right?

3 A. No, that's not right.

4 Q. That's right, because you didn't
5 investigate each of those drugs; correct?

6 A. I'm sorry.

7 Q. You didn't do any testing on any
8 of those products; right?

9 A. I have done no testing, but I
10 specifically indicated in my testimony this
11 morning that there are many different ways, and
12 I illustrated that, to prevent oxidative
13 degradation and some of them actually are
14 preferable to using antioxidants, so I don't
15 know how one could possibly draw the implication
16 that you drew.

17 Q. Dr. Klibanov, you didn't confine
18 your person of ordinary skill in the art to just
19 examining approved pharmaceutical products, did
20 you?

21 A. No. And, in fact, I, for example,
22 as I do on the very slide that's on the screen
23 now, it specifically says were commercially
24 available or patented.

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1 Q. Will you agree with me that a
2 commercial product that does not list an
3 antioxidant among its ingredients does not
4 necessarily tell you that the API, the active
5 drug is not subject to oxidative degradation?

6 A. Yes, I agree with that.

7 Q. Can we please go to PDX 27. You
8 testified this morning that physostigmine -- did
9 I mispronounce that again?

10 A. Yes.

11 Q. Can you correct me? What is it
12 again?

13 A. I'm not an expert, but it's
14 physostigmine. That's the way everybody...

15 Q. I mean, I just want to make sure
16 we're talking about the same compound.

17 You testified that physostigmine
18 did not require an antioxidant in a transdermal
19 device; correct?

20 A. No. What I testified on is that
21 in this example, for instance, there is a
22 transdermal device containing physostigmine, and
23 there was no antioxidant there.

24 Q. And the implication of that

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1 testimony is that physostigmine did not require
2 an antioxidant; isn't that correct?

3 A. Well, it certainly didn't require
4 it in this particular formulation.

5 Q. Now, you know that physostigmine
6 was known to be susceptible to oxidative
7 degradation; correct?

8 A. No, as a matter of fact, I know
9 just the opposite. As I said in my direct
10 testimony, what is susceptible to oxidative
11 degradation is the degradant of physostigmine.
12 Physostigmine in contrast to that under
13 pharmaceutical conditions is not undergoing
14 oxidative degradation.

15 Q. Thank you for that clarification.

16 Can we go to PDX 68. You also
17 testified today that you looked at a number of
18 commercial products containing the benzylic
19 carbon hydrogen bond; correct?

20 A. Yes, and specifically adjacent to
21 nitrogen atom.

22 Q. And your authority for that
23 testimony was the PDR; isn't that correct?

24 A. That's where this information came

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1 from, yes.

2 Q. So all you did, and correct me if
3 I'm wrong, I want to find out what you did, I
4 believe all you did was look at the entry for
5 each drug and the PDR and look to see if there
6 was a listed ingredient that was an antioxidant;
7 is that correct?

8 A. I reviewed each monograph, and I
9 presented the structural formulas for the
10 monographs where no presence of an antioxidant
11 was reported, even though all of these drugs had
12 the benzylic carbon hydrogen bond and an adjacent
13 nitrogen atom.

14 Q. Let's look at Ampicillin. Can we
15 blow that up, please. Ampicillin does not have
16 a tertiary amine bonded to the benzylic carbon;
17 is that correct?

18 A. That's right. It's a primary
19 amine.

20 Q. And this particular drug,
21 Ampicillin, is formulated as a dry powder; isn't
22 that correct?

23 A. It can be formulated in a number
24 of different ways.

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1 Q. It's also formulated as a capsule;
2 isn't that right?

3 A. It could be.

4 Q. Well, when you looked at the PDR
5 for Ampicillin drugs, did you look at the drug
6 Tunicine and Omnipen?

7 A. I don't recall.

8 Q. Why don't we go please to PDX 157,
9 and if we could bring up page 2035.

10 MS. JACOBSEN: It's tab 25.

11 THE WITNESS: Okay. What page?

12 Q. Let me move on, Doctor.

13 A. Pardon me?

14 Q. Let me move on.

15 The drug Hydroxyzine is -- the
16 drug Hydroxyzine, this is formulated as a
17 hydrochloride salt; isn't that correct?

18 A. I don't recall right now. I will
19 be happy to look up. Just a second.

20 Q. Let's look at page 1992.

21 A. Just a second.

22 Q. For the drug Atarax, A-T-A-R-A-X.

23 A. Sir, please bear with me. Okay?

24 Q. Yes, sir.

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1 A. You said 992.

2 Q. 1,992.

3 A. Okay. Sorry.

4 Q. This is all the support that was
5 on the slide. I'm finding the pages from your
6 slide.

7 A. It's okay. Just a second. Okay.

8 Q. And the entry for Atarax says it's
9 formulated as Hydroxyzine hydrochloride;
10 correct?

11 A. Yes.

12 Q. And on page 2042, we see the drug
13 Vistaril -- actually, page 2042, Vistaril. And
14 in the upper left-hand corner at the entry for
15 Vistaril, we see that it is formulated as the
16 Hydroxyzine pamoate salt; correct?

17 A. Yes.

18 Q. And if we can go on to the drug
19 Meclizine -- let's go to page 1992 for the drug
20 Antivert in the middle. And this is formulated
21 as Meclizine hydrochloride; isn't that correct?

22 A. That's correct.

23 Q. And it's in tablet form; right?

24 A. That's correct.

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1 Q. And let's go to the drug
2 mirtazapine at page 1878. And this
3 is the drug
4 Remeron in the lower right-hand corner. And
5 those are mirtazapine tablets; correct, it's
6 formulated as a tablet?

7 A. That's right.

8 Q. If you look under the drug there
9 is a paragraph beginning mirtazapine is a white
10 to creamy white crystallin powder. And that
11 list some ingredients that are in the tablet; is
12 that right? And the last ingredient after
13 lactose is quote, "and other inactive
14 ingredients." Do you see that?

15 A. Yes.

16 Q. Did you -- I'm sorry, I don't
17 believe you testified this morning that any of
18 those inactive ingredients are an antioxidant;
19 correct?

20 A. I did not testify, no. And one of
21 skill in the art looking at this language in
22 fact would have no reason to believe that they
23 are antioxidants. I mean, they wouldn't know,
24 and, therefore, would presume that that wasn't

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1 the case. And this compound by the way was a
2 freebase.

3 Q. Why would an ordinarily skilled
4 artisan simply look at that language and stop
5 right there and not investigate whether or not
6 there was an antioxidant in the formulation?

7 A. Well, I mean, there is nothing in
8 this description that would suggest to one of
9 skill in the art or to me that there is an
10 antioxidant, that there is an antioxidant. I
11 mean, they mention several ingredients that
12 presumably were more important than others and
13 then they say other inactive ingredients. I
14 don't know what they are. And one of skill in
15 the art wouldn't know what they are, but
16 certainly there is no reason for one of skill in
17 the art in my opinion to presume that they were
18 antioxidants.

19 Q. So one of skill in the art would
20 not do any further investigation to find out the
21 extent of any reported oxidation or what those
22 inactive ingredients might be?

23 A. I don't know what further
24 investigation you're referring to. This is the

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1 Physicians Desk Reference, this is the product
2 insert, so that's the description of the
3 product. So I don't know what further
4 investigation you're referring to.

5 Q. When you were talking about the
6 Elmalem article today, do you recall that?

7 A. Yes, of course.

8 Q. You had about twenty to
9 twenty-five slides explaining why one of skill
10 in the art would see language about
11 physostigmine receiving an antioxidant and that
12 ordinarily skilled artisan doing further work,
13 researching, looking at reaction kinetics of
14 physostigmine and dialkyl carbamate and reaction
15 products of physostigmine and hydrolysis, all in
16 support of understanding a one-sentence
17 discussion of how an antioxidant was delivered
18 to all the drugs, do you remember that?

19 A. I disagree with your
20 characterization.

21 Q. Now, your person of ordinary
22 skill in the art reading Elmalem, did a lot of
23 work, did a lot of stuff, did a lot of research
24 to arrive at the conclusion about how he or she

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1 would understand Elmalem; correct?

2 A. As I explained during my direct
3 testimony, one of skill in the art, and I
4 specifically showed it in the slide, one of
5 skill in the art as with any paper would
6 endeavor to understand what the state of the art
7 was at that time. And furthermore, would
8 endeavor to understand what the goals of this
9 study were. And those slides that I showed
10 aimed to illustrate answers to these two
11 questions, and that's what I did.

12 Q. And here in the PDR, your
13 ordinarily skilled artisan just looks at a bunch
14 of ingredients and just makes a decision; isn't
15 that right?

16 A. One of skill in the art doesn't
17 make a decision, one of skill in the art simply
18 looks at the description of the product, does
19 not see an antioxidant listed there, and
20 therefore, presumes that an antioxidant is not
21 there. I'm not saying that it's not there, I
22 don't know, but one of skill in the art not
23 seeing it there would have no reason to believe
24 that it is there in my opinion.

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1 Q. The drug benzquinamide is next.

2 If we could go back to PDX 68. Thank you very
3 much. Let's go to page 2008 of the PDR that you
4 still have open I believe in front of you. And
5 --

6 A. I'm just looking at the screen.

7 Q. Okay. I will take you there. I
8 believe it's on page 2007, there is the drug
9 Emete-Con. And this drug is formulated as the
10 hydrochloride salt; is that correct?

11 A. That's right.

12 Q. And it's formulated as a dry
13 dosage form; isn't that right?

14 A. Yeah, it's formulated for
15 intramuscular and intravenous use.

16 Q. Can we please bring up slide PDX
17 '81. You also testified this morning that no
18 commercial nicotine transdermal device was
19 reported to contain an antioxidant; is that
20 correct?

21 A. Not quite.

22 Q. What did I get wrong there?

23 A. No commercial device -- no
24 transdermal device commercially available as of

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1 1998, none of the three was reported to contain
2 an antioxidant, that was my testimony.

3 Q. Okay. Thank you.

4 It's true, isn't it, Doctor, that
5 the transdermal product Habitrol that you
6 mentioned utilizes an airtight pouch to prevent
7 oxidation of nicotine; isn't that right?

8 A. That's my recollection, yes. But
9 of course that wouldn't preclude -- as in
10 Sasaki, it won't preclude oxidation by the
11 oxidants present in the adhesive.

12 Q. Can we please bring up slide PDX
13 88. Dr. Klibanov, you testified about the
14 compounds on this screen and I'll mention them
15 for the record. Oxybutynin, buprenorphine, and
16 selegiline; is that right?

17 A. That's fine.

18 Q. We're on the same page?

19 A. Yes.

20 Q. Your basis for discussing
21 transdermals containing these compounds is
22 information contained in the Physicians Desk
23 Reference dated 2004 or later; is that right?

24 A. That's correct.

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1 Q. You're not asserting that any of
2 the information you testified about, oxybutynin,
3 buprenorphine and selegiline would have been
4 known to the person of ordinary skill in the art
5 into 1998; correct?

6 A. No, I'm not asserting that.

7 Q. Just so the record is clear, none
8 of the three compounds I just read contain the
9 same structural feature rivastigmine of a
10 tertiary benzylic carbon immediately adjacent a
11 tertiary amine; correct?

12 A. No, they're all tertiary amines,
13 but they were brought up in the context of
14 Sasaki, not in the context of the benzylic
15 carbon hydrogen bond theory. And Sasaki didn't
16 have all those benzylic carbon elements either.

17 Q. Can we bring up the compound
18 oxybutynin; please? Oxybutynin doesn't even
19 have a benzylic hydrogen; isn't that right?

20 A. That's correct.

21 Q. And certainly the tertiary amine
22 that you circled in red is not bonded adjacent
23 to a benzylic carbon; isn't that right?

24 A. That's right. As I explained,

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1 this was in reference to Sasaki and none of the
2 Sasaki amines also had a benzylic carbon
3 adjacent to an amine.

4 Q. I'm just asking a yes or no
5 question.

6 Can we bring up selegiline,
7 please. And here the amine that you have
8 circled in red is not adjacent to a benzylic
9 carbon; isn't that right?

10 A. That's right.

11 Q. And, in fact, the carbon that is
12 the benzylic carbon is only a secondary carbon
13 and not a tertiary carbon; is that right?

14 A. That's right.

15 Q. If we can go through the compound
16 of buprenorphine. The compound buprenorphine
17 only has a secondary carbon as the benzylic
18 carbon; isn't that right?

19 I'll withdraw the question.

20 The amine that you have circled in
21 red is not adjacent to any of the benzylic
22 carbons in that compound; is that right?

23 A. That is correct. Not immediately
24 adjacent. It has one carbon between there.

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1 Q. I guess it wouldn't be a
2 rivastigmine discussion if we didn't address
3 Elmalem just for a moment. Can we please bring
4 up JTX 021, page 1060, lower left paragraph.

5 A. Excuse me?

6 MS. JACOBSEN: It's tab 11.

7 THE WITNESS: Pardon me?

8 MS. JACOBSEN: 11.

9 THE WITNESS: 11.

10 MS. JACOBSEN: Yes.

11 BY MR. LEVY:

12 Q. And I would like to highlight the
13 sentence beginning, "all drugs were made up
14 freshly".

15 A. Yes.

16 Q. And I'll read that sentence, the
17 sentence I'm bringing to your attention. "All
18 drugs were made up freshly in sterile saline,
19 which included an equal weight of sodium
20 metabisulphite to prevent oxidation."

21 Do you see that?

22 A. Again. The key of this is not the
23 pronunciation, but what you pronounce is a
24 different compound. You said metabisulfate.

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1 That's a different compound from the compound
2 that's listed there. I don't want to be picky,
3 but I think the record should be clear.

4 Q. I appreciate. We both want a
5 clear record.

6 Does that language convey to a
7 person of ordinary skill in the art that all
8 drugs studied in Elmalem were prepared from the
9 same antioxidant containing sterile saline
10 solution?

11 A. This sentence taken in isolation
12 and then turning a blind eye to the rest of the
13 paper would not be indicative in this respect
14 one way or another. But when read in the
15 context of the entire paper, that is what it
16 would do.

17 Q. I think it's your position that
18 this language would permit a person of ordinary
19 skill in the art to understand that all of the
20 injection formulations tested were prepared from
21 the same stock solution with each formulation
22 containing an equal weight of sodium
23 metabisulphite; correct?

24 A. Yes.

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1 Q. And I think it's your position
2 that using the same stock sodium metabisulphite
3 containing saline solution for all injections
4 removes one variable that could potentially
5 effect the outcome of the experiment?

6 A. Not the outcome of the experiment,
7 but the interpretation of the results of the
8 experiment.

9 Q. And I believe it's your position
10 that this is consistent with a head-to-head
11 study; right?

12 A. That is correct.

13 Q. Now, can we please bring up the
14 Weinstock 1981 article next to it, if that's
15 possible, split screen.

16 JTX 030. And I would like to
17 bring up page 1981, two paragraphs above the
18 word results.

19 A. Just a second, let me find it
20 here.

21 MS. JACOBSEN: It's tab 16.

22 THE WITNESS: 16, thank you.

23 A. So where are you reading?

24 Q. I'm in two paragraphs above the

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1 word "results".

2 A. Okay. Three paragraphs, actually,
3 it seems.

4 Q. And the sentence begins -- I
5 apologize, Doctor.

6 After Garden City, New York.

7 I'm going to read this sentence
8 that it took me a while to get to. "Morphine
9 and physostigmine were made up freshly for each
10 experiment in sterile saline which included an
11 equal weight of ascorbic acid to prevent
12 oxidation."

13 Do you see that sentence?

14 A. I do.

15 Q. Dr. Klibanov, is it your position
16 that that sentence conveys to the person of
17 ordinary skill in the art that physostigmine and
18 morphine were prepared from the same antioxidant
19 containing sterile saline solution?

20 A. No, one would have to again, read
21 the paper in its entirety and assess exactly
22 what I explained in my direct testimony.

23 Q. But you'll agree with me that just
24 as in Elmalem, the words stock saline solution

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1 do not appear here; correct?

2 A. Just a second. I'm sorry, could
3 you repeat the question, please?

4 Q. Yes. In Elmalem, the word stock
5 saline solution do not appear here; correct?

6 A. No, they do not appear. That is
7 something that will be understood in the context
8 of the paper as a whole.

9 Q. Is it your testimony in Weinstock
10 they're also using a stock saline solution
11 albeit just for two drugs?

12 A. That is not -- I don't believe
13 that that's the case in the case of Weinstock
14 '81 because there was no particular reason there
15 to do it this way.

16 Q. Now, isn't it essentially the same
17 language that is used in both papers describing
18 the preparation of the solutions?

19 A. Well, obviously it's not the same
20 language. For starters, the antioxidant is
21 entirely different. The antioxidant in Elmalem
22 is sodium metabisulphite. In Weinstock '81,
23 it's ascorbic acid. The language is also
24 different because in Weinstock '81, it says

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1 morphine and physostigmine were made up freshly
2 for each experiment, whereas in the case of
3 Elmalem, it doesn't say that. It doesn't say in
4 each experiment.

5 But most importantly, the rest of
6 the papers in Elmalem and Weinstock '81 were
7 different. And one would read this particular
8 sentence in each one of them in the context of
9 the entire paper.

10 Q. Wouldn't it have been just --
11 wouldn't the easiest solution -- I'm sorry,
12 wouldn't it have been easy just to employ a
13 stock solution in the 1981 study if it didn't
14 matter whether an antioxidant was used?

15 A. No. Because it was a study which
16 aimed to obtain qualitative conclusions where
17 the morphine was exerting its effect via the
18 central nervous system or the peripheral nervous
19 system and it didn't make any difference.

20 MR. LEVY: I have no further
21 questions at this time.

22 THE COURT: All right. Thank you,
23 Mr. Levy.

24 Any redirect?

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1 MS. JACOBSEN: No, Your Honor, no
2 redirect.

3 THE COURT: All right. Thank you
4 Ms. Jacobsen.

5 Doctor, you may step down.

6 THE WITNESS: Thank you, Your
7 Honor. Once again, I apologize for my voice.

8 THE COURT: So do the plaintiffs
9 have anything more?

10 MS. JACOBSEN: No, Your Honor.

11 THE COURT: All right. So you
12 rest?

13 MS. JACOBSEN: We rest.

14 THE COURT: All right. And I take
15 it we're done with the defendants here, you have
16 nothing more?

17 MR. LEVY: Nothing more, Your
18 Honor.

19 THE COURT: All right. Okay. So
20 the evidentiary record is closed.

21 So we have an argument tomorrow at
22 two o'clock; right? So I have two things going
23 which has nothing to do with the argument, it
24 just has to do with my remembering things for

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1 the short term.

2 The interim part review proceeding
3 that's going on, is that between Noven and
4 Novartis.

5 MS. JACOBSEN: Yes, Your Honor.

6 THE COURT: And it says neither
7 party is bringing it up. Maybe I should just
8 leave well enough alone and not ask any
9 questions, but I thought that actually -- and I
10 know you all told me the other day when the
11 decision is required, or when the hearing is
12 supposed to be, something that is not too far
13 off in the future, but my recollection is that
14 the IPR proceeding, I guess if it's determined
15 before this, has some, not preclusive, but
16 doesn't it have some effect on this proceeding?

17 MR. KALLAS: I don't believe it
18 does. It would have to go up on appeal. The
19 patent office doesn't invalidate the claims,
20 doesn't give a certificate for invalidating the
21 claims, it would have to go up on appeal, and
22 only then would it come back down to the patent
23 office to invalidate the claims.

24 And as far as the timing is

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1 concerned, I think the proceeding, the oral
2 argument which they call a trial was in June of
3 next year, and they're mandated to give a
4 decision by I believe October 14th. I think
5 your decision will come out before October 14th.

6 THE COURT: I certainly hope so.

7 MR. KALLAS: Yes.

8 THE COURT: But the --

9 MR. KALLAS: There is a preclusive
10 effect to the extent that if Noven loses on
11 particular arguments, they're precluded from
12 bringing those same arguments in this Court.
13 But again, because of the nature of this, I
14 think your decision will come out after there.

15 Now whether we can move to
16 preclude them from those arguments afterward,
17 it's a good -- I don't know that there has been
18 a case on that, but we're going to look into
19 that immediately after we leave this courtroom,
20 Your Honor.

21 THE COURT: You're an optimist.

22 All right. So in any event, for
23 present purposes, I should basically put that
24 out of my mind; right?

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1 MR. KALLAS: I think so.

2 THE COURT: All right. So to the
3 more mundane that's actually related to this, I
4 was hoping that between now and tomorrow you
5 all, perhaps not the ones who are actually going
6 to give the argument, but could talk about sort
7 of the posttrial briefing schedule.

8 I would like to suggest something,
9 but I'm willing to listen to something else.
10 What I was going to suggest was that we do this
11 in two parts, and what I was going to suggest
12 was that we have some factual briefing where
13 basically Noven would go first, could have up to
14 thirty pages to write down facts one at a time,
15 you know, number them, each one limited to a
16 sentence with some citation or whatever it is
17 that supports it in the record.

18 Then after you're done with your
19 thirty pages, Novartis could add up to an
20 additional thirty pages, and basically every
21 fact that you say, you know, if they disagree
22 with it, besides disagreeing with it, they have
23 to say, you know, if what you're saying is
24 wrong, they have to say what the right version

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1 is, they can't just say disagree.

2 And then maybe you could have some
3 number of pages, I was thinking fifteen, so that
4 where basically again, you follow this same
5 pattern, you're not adding new facts but now
6 that they have said what their facts are, you
7 can just pick which ones to disagree with, you
8 know, you don't even have to actually use all
9 your pages. But something along those lines to
10 get the factual record argued.

11 And hopefully the end product that
12 I would get out of that would be one document
13 that would then be linked to whatever piece of
14 the factual record you were actually citing in
15 support.

16 And then when all that was done,
17 which I thought maybe it would be done before
18 Christmas, after January 1st, then you could
19 basically brief it and I would think that
20 twenty, twenty and ten, normal kind of briefing
21 schedule would be sufficient to basically write
22 legal briefs where you basically got the facts,
23 you already, you know, sort of put down that you
24 know what both sides are saying the facts are.

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1 In any event, I suggest this
2 because -- and I've tried doing this in a
3 different case, nonpatent case, but I didn't put
4 a sufficient page limit on the facts, so I got
5 way too many facts. So one thing I'm trying to
6 do is figure out a page limit that would
7 actually only force you to give me the relevant
8 facts or at least what you thought was relevant.

9 I don't know whether any of you
10 have any experience with doing something like
11 this, but I was thinking that might be more
12 beneficial to me than having you write a brief,
13 and a brief and a brief.

14 But I'm -- but part of the reason
15 I just wanted to suggest that if you all -- and
16 Mr. Kallas, you don't really need to -- I was
17 thinking maybe it would be better for you all to
18 talk to each other and then tomorrow we could
19 discuss it again once we're finished with the
20 argument.

21 MR. KALLAS: I just have one
22 concern I would like to address. To me it seems
23 very easy to write out the facts, Noven writes
24 out the facts it wants, but for us on this side

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1 to explain why those facts are wrong may take us
2 more if they give us thirty pages, we're only
3 limited to thirty pages, and having to explain
4 why they're wrong and include the facts we want
5 in it. So I think it would be a little unfair
6 to limit us to the same thing depending on what
7 their facts are.

8 THE COURT: Well, you know, that's
9 the kind of thing you can discuss with each
10 other. I can't remember actually the last time
11 I did it, I think because I give unlimited
12 pages, bad move, that you know, I didn't have to
13 deal with that issue. But that's something you
14 can talk with each other and maybe you'll decide
15 --

16 MR. KALLAS: I think we have all
17 had experience with this type of briefing, maybe
18 in the summary judgment context where one side
19 puts in their facts, undisputed facts and the
20 other side has to agree or disagree which is a
21 little different than that, but similar.

22 THE COURT: So in any event, why
23 don't you talk to each other, see if you can't
24 come up with some suggestion. If you come up

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1 with something like this, that would be great.
2 If you, you know, both think that it's not a
3 good idea, you come up with something else, I
4 mean, if you can agree to something, even though
5 I always agree to cut down on the number of
6 pages, you know, I'll probably go along with
7 whatever you agree, and you know, to be
8 reasonable about the holidays, in terms of the
9 demand of each other.

10 So, in any event, if you could
11 discuss that some time between now and tomorrow
12 and see what you come up, that would be good.

13 Is there anything else to talk
14 about before I see you tomorrow? Okay. Thank
15 you very much and I'll look forward to seeing
16 you tomorrow.

17 (Court recessed at 3:24 p.m.)

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CERTIFICATE OF REPORTER

I, Heather M. Triozzi, Certified Professional Reporter and Notary Public in the State of Delaware, do hereby certify that the foregoing record, Pages 305 to 275 inclusive, are a true and accurate record of the above-captioned proceedings on the 2nd day of December, 2014, in Wilmington.

IN WITNESS WHEREOF this 2nd day of December, 2014, at Wilmington.

Heather M. Triozzi, CSR, RPR
Cert. No: 184-PS
Exp: Permanent

DATED: December 2, 2014

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