IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS, CORPORATION, Plaintiff,	Trial Volume 1
v.	C.A. No. 11-1077-RGA
PAR PHARMACEUTICAL, INC., Defendants.	

Thursday, May 1, 2014
8:10 a.m.

844 King Street
Wilmington, Delaware

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

APPEARANCES:

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

-and-

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

Counsel for the Plaintiff

APPEARANCES CONTINUED:

RICHARDS LAYTON & FINGER, P.A.
BY: STEVEN J. FINEMAN, ESQ.

-and-

LATHAM & WATKINS, LLP
BY: DANIEL G. BROWN, ESQ.
BY: JENNIFER KOH, ESQ.
BY: ROGER CHIN, ESQ.

Counsel for the Defendant

THE CLERK: All rise.

THE COURT: Good morning. Please be seated.

I just wanted to come out and see if there was anything we need to deal with before our official start.

Mr. Silver.

MR. SILVER: Good morning. I'd offer to make introductions if Your Honor wants, but I think Your Honor knows all the relevant players.

THE COURT: I think I know all the people. I'm not sure of you, sir.

MR. CHIN: Roger chin.

THE COURT: Roger Chin. I think I've heard you on the phone. Maybe I met you in person, too.

Everyone else, I think I recognize. Anything else?

Mr. Fineman.

MR. FINEMAN: Good morning, Your Honor.

THE COURT: Good morning.

MR. FINEMAN: There are a few, at

least one major housekeeping issues we'd like to take up from the start. Certain of the documents that are going to be used today were produced by 3M Company.

THE COURT: Okay.

MR. FINEMAN: And they are designated highly confidential in the Protective Order. And I believe --

THE COURT: Okay. So I'm sympathetic to keeping 3M's products, since they're not actually a party here. How would you like to handle this?

MR. FINEMAN: We've come up with a couple different ways, Your Honor. One of the documents that would be used is what is known as the DMF. The DMF contains trade secrets and very very confidential information, as I understand it.

We spoke with Novartis last night and I believe the parties are in contextual agreement. I believe 3M is in agreement that for the DMF, what we're going to do is we're going to use a redacted version as the actual trial exhibit.

THE COURT: Okay.

MR. FINEMAN: Neither party will argue at any point that it's an incomplete document or that both parties get the opportunity to put in those pages that they believe they need. We'll redact the rest.

And if Your Honor is okay with that.

THE COURT: I'm okay with that if the parties are.

Mr. Silver.

MR. SILVER: That's fine, Your Honor.

THE COURT: All right. That's good.

MR. FINEMAN: Now, even though we do that, that will protect some of the trade secrets. But even the remaining pages, we will need to close the courtroom or at least ask Your Honor to close the courtroom while that document is being discussed.

THE COURT: How much discussion of that document do you expect to have occur?

MR. FINEMAN: From our side, Your Honor, not much. It will probably be under 15 minutes.

THE COURT: Is it something -- I kind of vaguely remember. I might be getting one trial mixed up with another trial. Yeah, I probably am.

Is it possible that whatever is being shown on, I guess, the screen can just be sort of tilted toward me and -- because I really, if at all, prefer not to close the courtroom.

MR. FINEMAN: Your Honor, we certainly understand and we are cognizant of that. And we tried to make arrangements for this and what we're proposing is that we only close the courtroom when we're discussing the DMF because that's the, if you will, the crown jewels of the trade secret.

So we want to close the courtroom just for that limited period. We might even make it less than ten minutes, a very short period of time.

There will be other documents which are similarly designated, but we've spoken to -- 3M, Your Honor, is present in the courtroom and is represented by Mr. McCann, so that he's able to speak.

THE COURT: All right. I know Mr. McCann.

MR. FINEMAN: So if they want to speak for themselves, Your Honor, they certainly can. But as I understand it, what we'll do with the rest of the documents is we won't ask Your Honor to close the courtroom. But we will not publish on the screen the documents while they're being used. And we'd like to reserve the right, Your Honor, to redact the transcript.

THE COURT: Well, why don't I -- you don't even have to reserve the right to redact the transcript. If you mean reserve the right to ask to have the transcript redacted, yeah, you got that one, whether you reserve it or not. Whether or not -- I mean, I think -- I hope that everyone knows that I hate to do that.

So that, you know, the best thing is if you can avoid littering the transcript with stuff that 3M rightfully regards as secret.

Then the second best thing is because 3M is actually not a party, you know. There's not that much they can do to prevent what you all say so I would be more sympathetic to

either 3M itself or to you later on or some combination, but remembering that it is a public trial and there is a value to redacting as little as possible.

MR. FINEMAN: That's right, Your Honor. And the three parties have tried to coordinate --

THE COURT: Right. And I do appreciate that.

MR. FINEMAN: That's how we propose to address --

THE COURT: When do you think this closing of the courtroom is because I see, you know, maybe twenty people sitting behind the bench, I have no idea who they are. I know a lot of them are associated with one or the other side. I guess what I'm wondering is how do I actually close the courtroom? Do I require that anyone that you all don't vouch for identify themselves or what?

MR. FINEMAN: Yes, Your Honor, the DMF was designated outside counsel only, I believe, Your Honor, and someone in this room will correct me if I'm wrong, I don't think the

parties to this case have had access to this information, it's outside counsel.

THE COURT: So basically what you're saying is people sitting at the table, everyone else except for the person on the computers leaves.

MR. FINEMAN: I think that's right, Your Honor, and we would as I said be very studious to let Your Honor know precisely when we need to close it and when we need to open it and minimize any disruption and minimize the absence of the public to the proceedings.

THE COURT: Okay. Is there anyone in the courtroom who objects to this?

All right. We'll do that. And if you can, do you have an idea of when in the proceedings that might be?

MR. FINEMAN: Your Honor, I can't speak for whether Novartis is going to use it. From our side I think at the earliest it will come up late in the afternoon today.

THE COURT: Okay. Well, all right. Well, in any event, Mr. Silver, do you have anything to add on that.

MR. SILVER: No, Your Honor. We'll confer to see when we need to be prepared to close the courtroom.

THE COURT: Okay. All right. Well, I will do that upon request and again, we just ask that you all in the first instance be judicious in what you're requesting.

MR. FINEMAN: Absolutely, Your Honor.

THE COURT: All right. And Mr. McCann, does 3M have anything to add?

MR. McCANN: Not at this time, Your Honor.

THE COURT: When we close the courtroom for this portion, does that mean that Mr. McCann or somebody associated with him stays or does he leave, too?

MR. FINEMAN: You know we have no objection to the representative from 3M or their counsel staying because it's, in fact, their confidential information.

THE COURT: I just wanted to make sure we're all on the same page there.

All right. Anything else?

MR. FINEMAN: Your Honor, the second issue is we had last night what I would call a significant difference of opinion regarding objections to deposition designations, and the propriety of certain counter-designations. I participated in the meet and confer last night myself, Your Honor, and tried to work it out. We were unsuccessful.

I understand from counsel they would like to speak to us at lunch today in a further effort. My concern, Your Honor, is these deposition designations in all likelihood will be played this afternoon and we would like to work it out and play the clips. We're happy as always, Your Honor, to try to work this out. How would you like to address this at this juncture?

THE COURT: How much volume are you talking about?

MR. FINEMAN: Your Honor, the number of objections to the number of designations was overwhelming. It was frankly incredible, Your Honor. Some of the designations had as many as seven or eight different objections, so it's tremendous.

THE COURT: Okay. And so the objections are to the so to speak the underlying forms of the question or are they to relevance or to what?

MR. FINEMAN: Your Honor, they cover the broad spectrum. It almost looks like a law school hypothetical with how many objections are lodged.

THE COURT: All right. Do you have a proposal, Mr. Fineman?

MR. FINEMAN: Your Honor, it's their objections, their objections to our testimony, so if they would like to maintain objections, as of last night, I specifically asked are they going to drop any of the objections. Their response was no, they are pressing all their objections.

I would ask, Your Honor, that they argue their objections and then get charged with the time. We'll meet with them, I'm happy to discuss with them, I'll meet with them right now after we're done. The second issue --

THE COURT: I'm sorry, the second issue.

MR. FINEMAN: The second issue, Your

Honor, and again, this is something we can talk about, but I want to flag it for Your Honor so it's not a surprised, it is they have counter-designated and a fair amount of their counter-designations were not in the pretrial order and they were required to be in the pretrial order. There is a good cause standard for why they could be added. I asked what the basis was last night. There was no good cause, Your Honor. And we can try to address this, but this is something I want to flag with Your Honor because this is going to come up today.

THE COURT: Thank you, Mr. Fineman.

Mr. Silver.

MR. SILVER: Your Honor, I hate to take up time arguing over things that can likely be resolved this morning. I would suggest that we meet and confer at the first break in the trial and if issues are still lingering at that point we can bring that to Your Honor's attention. There are several objections that we consider to be valid. We are going to trim those down a little. Mr. Fineman says there were not in the pretrial order. We'll take a look at that

and hope to resolve that issue as well.

THE COURT: Okay. It seems like there is probably not a whole lot I can do about it right now, so having you all try to narrow down what's in dispute seems like a productive use of my time.

Okay. So anything else?

MR. FINEMAN: That's all from our side, Your Honor.

THE COURT: Mr. Silver.

MR. SILVER: That's it for us, Your Honor.

THE COURT: So we'll take a roughly ten-minute recess and come back and be prepared to start.

All right.

MR. SILVER: Thank you, Your Honor.

THE COURT: Thank you.

(A brief recess was taken.)

THE CLERK: All rise.

THE COURT: All right. Good morning.

Let's be seated. Are we prepared to proceed?

MR. SILVER: Your Honor, one more housekeeping issue that was just brought to my attention. I apologize.

The defendants do have one fact witness present that we would ask him to be sequestered until he testifies.

THE COURT: All right. And I take it there's no objection to that?

MR. BROWN: None, Your Honor.

THE COURT: All right. So is the witness sequestered?

MR. BROWN: He's not here.

MR. FINEMAN: Who is he?

THE COURT: Well, even better.

All right. So go ahead.

Ms. Jacobsen.

MS. JACOBSEN: Good morning, Your Honor. I have some books of slides.

May I approach?

THE COURT: Sure.

MS. JACOBSEN: Your Honor, Par seeks approval from the FDA to market three Rivastigmine transdermal products.

For the purposes of Your Honor's

infringement analysis, there's no difference between their products. They contain the same ingredients and they're just simply different size patches that deliver different size doses of Rivastigmine.

The only claim at issue is Claim 7 of the '031 patent. As Your Honor is aware, the claims of the '031 patent fall into two categories. The first category requires proof that the accused product contain an amount of antioxidant that functions to significantly reduce oxidative degradation over a prolonged period of time in the accused product.

And those are the function claims. And they're not at issue in this case.

The second category of claims require an affirmative proof that the presence of an antioxidant, but not affirmative proof that it's functioning as such in the accused product for there to be a finding of infringement.

And those are the presence claims. And Claim 7 of the '031 patent, the claim at issue, is a presence claim.

So with respect to infringement of

Claim 7, there are two questions. The first: Is acetaldehyde an antioxidant? That is, is it an agent that reduces objection day active degradation?

The second question is: Do Par's ANDA products contain about 0.01 to about 0.5 percent by weight of acetaldehyde? And, Your Honor, we will present evidence, and of course it is our burden to prove infringement by a preponderance of the evidence, that the answer to both of those questions is yes.

Now, I'll start with the second question, because as Your Honor observed at the pretrial conference, there's really no factual dispute here. The controlling case is a Federal Circuit decision in Sunovion. And in Sunovion, if an ANDA filer seeks FDA approval to market a generic product that falls within the scope of a valid claim, it's an act of infringement as a matter of law.

So how then does the court determine whether Par is seeking approval to manufacture a generic product that falls within the scope of Claim 7 of the '031 patent? Well, according to

the Federal Circuit in the Sunovion, it's by looking at the ANDA specification. Because that describes the product that Par is asking for approval to manufacture and sell. It's essentially the blueprint for their products.

Par concedes that its ANDA specification commits its ANDA products to contain not more than 1,000 part per million of acetaldehyde. One thousand parts per million is 0.1 percent of acetaldehyde.

And that means that if Par's's ANDA products are approved, Par will be permitted to make a product with anywhere between 0 and 0.1 percent of acetaldehyde. So if we now compare Par's specification with the '031 patent, we can see that 90 percent of Par's ANDA specification, that's between 0.1 and -- 0.01 and 0.1 fall within the claims range. And that's without even considering the scope of the claims are about.

And, Your Honor, that's dispositive with respect to infringement of the amount of limitation.

Par will allege that it uses an adhesive that has undergone a rigorous washing

process that minimizes the amount of acetaldehyde in its adhesive. So Par argues that even though its ANDA specification permits it, it won't actually make a product with an amount of acetaldehyde that falls within the claim numeric range.

But in Sunovion, the Federal Circuit rejected what the Court called "but I won't do it" defense. And that's at 731 F.3rd at 1218.

And that's once this case is over, there will be nothing to stop Par from going out and making that washing process less rigorous, less time consuming or less expensive and making a product with a hundred, 500, or even a thousand parts per million of acetaldehyde. And that's entirely acceptable given Par's ANDA specification, but it's not permissible and it's not acceptable given the '031 patent. And that's because all of those amounts fall within the claimed numeric range.

The plaintiffs should not have to go out and test a product that Par actually puts on the market to determine whether or not to bring a second infringement action.

The Federal Circuit explained in Sunovion that the Hatch Waxman Act made filing an ANDA a technical act of infringement precisely so that infringement disputes were resolved before approved.

Now, Your Honor, at the pretrial conference Par argued that Sunovion was distinguishable because the FDA in that case had mandated infringement. And, Your Honor, that's not right.

The patents claim in issue in Sunovion required that the drug contain not more than 0.25 percent of a particular impurity. The FDA had requested that the ANDA filing in Sunovion narrow its specification to provide for not more than 0.3 percent. But even the FDA's range allowed for amounts outside of the claimed range and those are the amounts from 0.25 to 0.3 percent.

Now, in fact, the ANDA filer hadn't done that, they amended their specification to allow for not more than 0.6 percent, and they said the ANDA specification provided that the product could contain between 0 and 0.6 percent

of the impurity.

And the ANDA filer had actually represented that all of its products would contain more than 0.3 percent of impurity, so everything that it made would have between 0.3 and 0.6 percent of that impurity and none of them would have less than .25, which was what was required by the claim.

And nevertheless, the Federal Circuit found infringement as a matter of law because the ANDA specification included products with an amount of impurity that fell within the claimed range, and that's exactly the case here. Par's ANDA specification includes products with amounts of acetaldehyde that fall within the claimed range.

And during the pretrial conference, Par also argued that the controlling case was Glaxo v. Novopharm and that in this case, as in that case, Your Honor should consider the ANDA batch products.

The Federal Circuit explained in Sunovion that reference to actual samples of a generic composition in Glaxo was necessary

because the ANDA specification itself did not resolve the question of infringement in the first instance.

And that's at 731 F.3rd at 1279 to 80. And here is why, Your Honor. The drug at issue in Glaxo split in two crystalline forms, those were form one and form two. The patent claimed form two as defined by a very specific set of 29 infrared peaks. The ANDA applicant was seeking to market the other form of the drug, form one, and that drug had 90 percent purity.

The ANDA specification revealed the presence of an impurity and that impurity had one of the 29 peaks required by the claim in form two, but the ANDA specification said nothing about whether or not that impurity would have any of the other 28 peaks required by the claim for there to be form two present. And that's why the ANDA specification did not resolve the question of infringement in the first instance, and why reference to the actual products was necessary. And that's not what we have here.

Here as in Sunovion we have a simple matter of comparing the numeric ranges in the

'031 patent with Par's ANDA specification. And Par's ANDA specification alone resolves the question of infringement in the first instance. It describes

MS. JACOBSEN: It describes a product that contains acetaldehyde in the claimed range. And Your Honor, that should be the end of the infringement inquiry for this claim element.

So turning then to the first question: Is acetaldehyde an antioxidant? Your Honor has twice construed the term antioxidant to require the presence of an agent that reduces oxidative degradation.

And plaintiffs contend that acetaldehyde is just that, an agent that reduces oxidative degradation. And before I outline plaintiff's proofs, I want to first acknowledge a few things.

Acetaldehyde is not listed as an antioxidant in the '031 patent. It's not listed as an antioxidant in the Handbook of Pharmaceuticals, and it's also not listed in the FDA's inactive ingredient list.

And Your Honor will hear Par call

acetaldehyde things like an impurity and a residual solvent. You'll also hear about efforts that Par has taken to try to develop a product without an antioxidant.

And, finally, Your Honor will hear about batches of Par's ANDA products that contain no detectable acetaldehyde.

But, at the end of the day, as Dr. Davies will testify, there are two facts that, as a matter of basic chemistry, cannot be credibly disputed.

The first is that acetaldehyde is a known reducing agent. And the second is that reducing agents can act as antioxidants. And Dr. Davies will go over the definition of a reducing agent.

But, in a nutshell, reducing agents are agents that are capable of undergoing sacrificial oxidation. They are more readily oxidized than other compounds in the system. And that means that they are sacrificially oxidized and can protect other compounds in the system from oxidation. And that's how they reduce oxidative degradation of other compounds.

And there's no dispute that the '031 patent, the exemplary antioxidant in the '031 patent includes antioxidants that are known to function as reducing agents. And those are the two highlighted here, ascorbyl palmitate and ascorbic acid.

So we know, as a matter of basic chemistry, that acetaldehyde is capable of functioning as an antioxidant. The question Dr. Davies will address is: How do we confirm whether it is, in fact, an antioxidant?

And Dr. Davies' answer will be simple: You test it. And that's exactly what Dr. Davies did.

He ran a controlled head-to-head stress test in the presence and absence of acetaldehyde. And he demonstrated that acetaldehyde causes a statistically significant reduction in the oxidative degradation of Rivastigmine.

And before I outline Dr. Davies' testing in more detail, let's go over a few words of terminology. The first is stress tests.

As Dr. Davies will explain, stress

tests are a type of test that are designed to speed up the degradation of a drug, so that the degradation can be studied in a relatively short period of time.

Stress tests are standard in the pharmaceutical industry. And, indeed, Par's manufacturing partner, 3M, conducted a stress test during development of Par's ANDA products.

Dr. Davies will show Your Honor that the '031 patent confirms that stress tests can be used to test whether an agent reduces oxidative degradation.

And second, a head-to-head test, that's one that compares two equivalent compositions that are identical in all respects, safe for one, such as the presence or absence of an antioxidant.

Now, Dr. Davies will explain that in designing his test, the first step was to create an oxidizing environment. And that's because without an oxidizing environment that results in appreciable degradation of Rivastigmine, it's not possible to test whether the agent in question reduces that oxidative degradation.

And once Dr. Davies had determined experimentally the proper conditions, he ran the head-to-head stress test. And that's outlined on this slide.

So, first, Dr. Davies adds Rivastigmine and an oxidizing agent to a solution. That's the oxidizing environment.

An then he splits that solution into two equal parts. And he added acetaldehyde to only one of them. And that meant that he had two identical solutions with only one difference between them, that being the presence of acetaldehyde in one of them.

And then Dr. Davies heated up the samples to speed up the degradation and he studied the degradation oxidative degradation of Rivastigmine over time. And he showed that acetaldehyde causes statistically significant reduction in oxidative degradation of Rivastigmine. The result, consistent with the literature, calling acetaldehyde a reducing agent and recognizing that reducing agents can act as antioxidants.

Now, Your Honor will hear Par

criticize the type of test that Dr. Davies conducted, the way that he conducted his test and complain that he didn't conduct additional tests. None of those criticisms will stand close to Rivastigmine.

As Dr. Davies will show, Your Honor, literature demonstrating that stress tests are standard in the pharmaceutical industry, and he will show you literature demonstrating that the conditions he used for his test are within the range of conditions that are commonly used, including by 3M.

Now, of course, Dr. Davies had to tailor his stress test to the exact drug and antioxidant in issue in this case, but that's standard in the pharmaceutical industry. Because every drug is different, and not all drugs undergo the same degradation in the same conditions.

So Dr. Davies will explain to Your Honor why he selected each of the conditions he did for his stress test and how he determined that those were the proper conditions for his test.

Dr. Davies will also explain that the type of head-to-head experiment that he did is really the purist form of scientific experiment. And that's because it tests only one variable and nothing else.

And that allows Dr. Davies and scientists to be certain that the observed difference is due to that one variable. So his, with only one difference being acetaldehyde, that allowed Dr. Davies to be certain that the reduction in oxidative degradation that he observed was due to acetaldehyde and nothing else. There's no scientific explanation, other scientific explanation for it.

Now, of course, Par's experts could have easily repeated Dr. Davies' stress test. It's a standard experiment and it requires no specialized equipment.

And Par's experts could have run any one of these other tests that they say are necessary, but Par's experts ran no experiments.

So, finally, Your Honor, Par will point to the long term and accelerated stability testing on batches of the ANDA products with

acetaldehyde and with no detectable acetaldehyde and say that there's no reduction in oxidative degradation in the presence of acetaldehyde.

But, importantly, those tests are not head-to-head studies where there was only one variable, the presence of acetaldehyde.

So it's impossible to draw any conclusions about whether acetaldehyde is an antioxidant from Par's stability data for at least two reasons.

The first is Dr. Davies will explain that each of the batches of Par's ANDA products was made with different lots of ingredients. And that gives rise to batch-to-batch variation, and it means that there are many variables that could have impacted the stability data.

And the second reason is that Par only tested one patch at each time point he studied the amount of oxidative degradation and studied the amount of oxidative degradation in one patch at each time. And as Dr. Davies will explain because of the patch to patch variation we just don't know to what extent the one patch that Par tested is representative of the whole

batch which contains tens of thousands of patches.

It could be that the patch that Par tested had the lowest amount of degradation or it could have had the highest amount of degradation or it could have been somewhere in the middle, we just don't know.

So that brings us back to Dr. Davies' test, which is the only test that will be in this case and was designed to and was capable of assessing whether acetaldehyde is an antioxidant and that test demonstrated that acetaldehyde consistent with the literature produces the oxidative degradation and is now an antioxidant.

Just a few words then on validity. Par alleges that if acetaldehyde is an antioxidant and the Claim 7 of the '031 patent is invalid for failing to meet the written description enablement and definiteness requirement of Section 112. Your Honor, the plaintiff submits that Par will not be able to meet its burden of proving invalidity by clear and convincing evidence.

Now, as plaintiffs understand it, Par's case appears to be that Claim 7 is limited to the antioxidants specifically named in the '031 patent. And if it includes any other antioxidants, then it fails under 112.

So first, Par says that if a claim term antioxidants includes antioxidants not named in the specification, the term is indefinite. But for a claim term to be indefinite, it has to be incapable of definition. And plaintiffs, Par and the Court have all provided a definition for the term antioxidants. And there is no evidence that whether or not a compound meets that definition depends on specific tests used to determine it.

In fact, in this case, the only test that will address whether or not acetaldehyde is an antioxidant will be Dr. Davies' stress test and that confirmed that it is.

So second, Par says that there is no written description for Claim 7 beyond those antioxidants specifically named in the '031 patent. But Your Honor will hear from Dr. Klibanov that the '031 patent provides a

written description of inventors' discovery that is susceptible to antioxidants and a written description of a rivastigmine transdermal device containing antioxidants as recited in Claim 7.

And Dr. Klibanov will testify that there is nothing in the '031 patent from a scientific standpoint that will cause a person of ordinary skill in the art to limit antioxidants to those specifically named in the '031 patent.

Dr. Klibanov will explain that a person of ordinary skill in the art in January of 1998 would have known that there are many different antioxidants, and the person of ordinary skill in the art would have recognized that the '031 patent does not try to list them all. And instead, it provides examples of the different types of antioxidants. And those include some that function as free radial scavengers such as BHD and some that function as reducing agents such as ascorbic acid and ascorbic compound. The '031 patent also discloses that antioxidants can be experimentally determined to reduce oxidative degradation by stress stability test and as I outlined a moment

ago, Dr. Davies will explain that that's exactly what he did, he confirmed using a stress test that acetaldehyde is an antioxidant.

Now, while Par's experts may now try to argue that the invention is limited to the antioxidants specifically named in the '031 patent, the weakness of Par's case is revealed by the fact that it never made that argument during claim construction.

Finally, Par argues that antioxidants beyond those named in the specification are not inadequate.

And Dr. Klibanoff will explain that Claim 7 is fully enabled because whether or not a compound is an agent that reduces oxidative degradation can be determined by reference to the '031 patent itself and the scientific literature or testing with and without an antioxidant to determine whether or not it reduces oxidative degradation. The fact that some testing may be necessary does not mean that the patent is not enabled.

As a matter of law, the patent need only set forth one way to make and use the

invention. And there is no dispute that the '031 patent describes one test that can be used to test whether a compound reduces oxidative degradation and those are the stress stability test.

And so in conclusion, Your Honor, we specific fully submit that Par will not present clear and convincing evidence that this presumptively valid claim is invalid. And we respectfully submit that we will present evidence that it is more likely than not the Par infringes Claim 7 of the '031 patent.

Thank you.

THE COURT: Thank you, Ms. Jacobsen.

Mr. Brown.

MR. BROWN: Good morning, Your Honor.

THE COURT: Good morning.

MR. BROWN: So Par's case here is pretty simple. Par's ANDA product does not contain about .01 percent to about .5 percent of antioxidants as required by Claim 1.

Could I have Claim 1 up here with this element highlighted.

Now, Par's ANDA product, the transdermal patch, was developed through a partnership with 3M Corporation. And actually could I get a slide. 3M is famous for its expertise in adhesives. They make many, many, both commercial and industrial adhesives. They're one of the top companies in this field, and besides these commercial products they have a very, very strong expertise in adhesives for medical purposes including transdermal patches.

And the adhesive is the major ingredient besides rivastigmine in Par's product. I think you recall, you'll see the side-by-side comparison with plaintiff's patch they have a whole bunch of ingredients in there that was necessitated because they couldn't have the same adhesives that delivers the drugs, it sticks to the skin and it contains the drug and it controls all the necessary processes. An innovated technology, and they succeeded in developing a product that did not use an antioxidant.

You're going to hear testimony from Jim DiZio who is an inventor of the washing procedure that's used for purifying 3M adhesive

and he's the first named inventor on the patent application in the process.

The Court may recall in the August Watson trial Dr. Klibanov testified that he used the 3M patent application that Jim DiZio is the inventor on as evidence that the Watson product infringed. And Dr. Klibanov specifically testified about the effect that the 3M washing process had on stability.

And so this process reliably and demonstrably results in a product that is essentially free of all impurities. It gets rid of all of the things that are used in the process of making a polymer that are reactive and can cause damage to the product. And it gets rid of the vast majority of the acetaldehyde and for both, for all of the impurities including acetaldehyde, it seems very, very small amounts in all of the processes that have been made following the ANDA process.

And I want to put up two excerpts from the ANDA where Par's ANDA clearly stated to the FDA that they do not use antioxidants. Here is the side-by-side comparison with the

plaintiff's commercial patch and the middle one is the Par product, the transdermal system. And you can see there is the adhesive, there is something called a pacifier which is isopropyl and there are the components that sticks to the edges of the patch that make it a patch. And they don't use the rivastigmine modifier, they don't have antioxidant and they don't use an adhesive because they're polymer drug adhesive, they don't have separate drug loading and they don't have the other modifier, so the Par 3M product is a much simpler patch, it doesn't create the problems the plaintiff's patch does and it doesn't use an antioxidant. In fact, within the ANDA they say the primary pathway pursued by 3M in the development was formulate without an antioxidant.

So plaintiff's infringement theory they came up with long into this case was that, that acetaldehyde and antioxidant that's measured in some of the batches of Par's product, sorry, the acetaldehyde, an impurity is measured in some of the batches of Par's product is an antioxidant.

So Par and 3M have extensively tested the stability of their products following the well-known validated and standardized FDA stability testing protocols. This testing corresponds to one of the two testing methods identified in the '031 patent. I would like to pull up the column here, this is at column four, lines 20 to 30. Plaintiff's counsel in opening argument says the patent describes one way to test for I believe it was for antioxidant behavior. This column, she pointed to this, the general description of stress stability test. This column provides the only parameters for stress stability tests that are described in the patent.

MR. BROWN: And, first of all, they are all performed on pharmaceutical compositions. They're not performed as Dr. Davies did his test in a test tube under different conditions.

Second, they define the time period and temperature. So, the first one they describe is a two-month stress test at 60 degrees C. And the last one they describe as a three-month stress test at 40 degrees C at 75 percent room

humidity.

And the second one of these tests corresponds to a well-known accelerated stability protocol that all pharmaceutical companies use. It's one of the FDA mandated ones.

And so -- and Par has followed this test faithfully or actually 3M followed the test faithfully. And I want to point out that the plaintiffs are going to be arguing, Well, you should ignore this and you should listen to Dr. Davies' test, and that Davies' test is actually the purist science.

But we did not. There's no dispute we didn't come up with these test parameters for this litigation. These test parameters were set beforehand, set by the FDA. And these are generally accepted and reliable in the industry and I'd like to have a look at Par's data for a second to show.

So this is -- this slide is the 25 degree C, 60 percent room humidity. That is what's generally to be considered ambient conditions. This is where the patch sits in the drug store.

And Par and 3M have produced tests over the entire course of the shelf life of their product. And the first two batches I've highlighted up there are batches with no detectable acetaldehyde, and then we have about six other batches that have detectable acetaldehyde.

And there's one batch that we gray out for which the room temperature wasn't measured. So, as you can see, after 24 months at room temperature with no acetaldehyde, there's no degradation.

Less than 0.01, when you see the less than sign, what that means is that that's below the measurement level of the device. And so they couldn't measure any impurities after 24 months of the product.

And as you go down, as you descend through the different levels of acetaldehyde that was measured in the rollstock for the product, you can see in three of these examples, you have some oxidative degradation in the -- so there's a batch 11280 has .3 and .2.

That's a very low level of

impurities, but they're forming and there's acetaldehyde. So it's not stopping that from happening.

Then, at the next batch, you have a .1 instead of a less than .1. That means it was detected. At one and two batches down, you have another .1.

So at room temperature, acetaldehyde is not an agent that reduces oxidative degradation. But let's look at the exact test that's described in the patent. This is the next slide.

This is the 40 degree C, 75 percent room humidity. And so now, if you look at the six-month data, one of the two batches with no acetaldehyde has a tiny bit of an impurity showing up under these sort of more extreme conditions. And as you walk down, you can see very clearly that the addition that's acetaldehyde that is appearing in some of these batches is doing nothing to reduce oxidative degradation.

And so this is an objective standard test. It's the test referenced in the patent.

And it shows what we submit very clearly that acetaldehyde is not an agent that reduces oxidative degradation.

And plaintiff's counsel noted in opening argument, also, the difference between when we were here last August, they were asserting that the function claims that require a specific proof that the purported antioxidant is working in the product producing oxidative degradation, they're not saying those claims anymore. And I think in looking at this data, I think the Court can see why.

So plaintiffs support their theory that acetaldehyde is an antioxidant with testimony by their expert, Martyn Davies. He's a pharmaceutical formulator.

And the pharmaceutical literature simply does not support the assertion that acetaldehyde is an antioxidant. And I want to talk a little bit about: What is acetaldehyde and go through that for a few minutes. What are the chemical properties?

Acetaldehyde is a volatile chemical. If there was a dish of acetaldehyde sitting on

the table here, it would probably be boiling because its boiling point is about 68 degrees Fahrenheit.

It's also known to be an oxidizing agent, not an antioxidant. Our expert, Dr. Ganem, is going to testify that when acetaldehyde is exposed to air, it forms peroxides. It also does not stop the oxidation reaction.

The oxidation process is a chain reaction that's propagated by radicals. And one of the reasons oxidation is a bad reaction for pharmaceuticals and otherwise is because it's a propagated reaction. It grows and it becomes a chain reaction that causes a lot of damage.

And when acetaldehyde reacts with radicals and in an oxidative environment, it forms more radicals. That is not what an antioxidant does. And Dr. Ganem is going to tell you about that.

So how does Dr. Davies get to his opinion that acetaldehyde is an antioxidant? It was summarized very well in opening.

The first position is that it's known in the literature as a reducing agent. And

it's sort of this logical chain.

Acetaldehyde is sometimes referred to in the literature as a reducing agent. Some antioxidants work as reducing agents; therefore, according to Dr. Davies, acetaldehyde is an antioxidant.

We think that position doesn't have much merit. First of all, being a reducing agent just means that here's something that can be oxidized. The term is usually used in a very, very specific context, in a particular situation, this compound acts as a reducing agent.

And the paint on your car can be oxidized. That doesn't make it an antioxidant. Lots and lots and lots of compounds can be oxidized.

The vast majority of them are not antioxidants. Just being a reducing agent doesn't provide, we think, a good evidence that something is an antioxidant.

Dr. Davies' second argument is based on his experimentation and we think this wholly fails to show that acetaldehyde is an antioxidant, i.e. an agent that reduces oxidative

degradation.

The type of test that Dr. Davies conducted is called a forced degradation study. He basically, as the schematics showed, he dissolved Rivastigmine in a solvent in a flask with none of the other ingredients that would be found in a pharmaceutical formulation. And he purported to measure the effect of acetaldehyde.

But forced degradation studies are not designed or used in the pharmaceutical field to determine whether a compound is an antioxidant. They are not standard in the industry for that purpose.

A standard test is standardized precisely so that results from one test can be compared to results from another test, and you can interpret those results and draw conclusions. The principal purpose in a forced degradation study used for in the pharmaceutical industry and the purpose of the 3M test that plaintiffs are pointing to is to seriously degrade the compounds at very extreme conditions to make the impurities that happen when the drug breaks down.

It's almost like a synthetic

process. I want to get large quantities of these so that my analytical group can do all of the experimental work that they need, so I can now prove I can detect very minute amounts of them in my final process.

It's also used to get very general basic chemical information about the drug, but plaintiffs aren't going to be able to point to a single instance in the reported literature where this kind of test that's been used to evaluate an oxidant behavior. And it's simply not an analytical test. It's not a test used to measure anything.

It's a test used to break your product down, see what happens when it's exposed to extreme conditions. But that's all it's used for.

And we believe that Dr. Davies' test results and testimony are squarely contradicted by the 3M testing that I went through at the beginning here. And our expert, Dr. Buckton, is going to talk about the validity of those.

And, in particular, plaintiff's batch-to-batch variability argument, we don't

think that that holds merit, either. The purpose of an antioxidant is to reduce oxidative degradation. And if it doesn't do that under normal conditions that are experienced, then it's not an antioxidant.

As plaintiff's counsel mentioned, we are going to be allege that Dr. Davies' testing methodology has serious detection and I want to take a minute to explain why, even if you disregard or if you don't believe our criticism of the test, why his test is not credible evidence that acetaldehyde is an antioxidant.

This is a little example. When I was growing up, my older brother used to do this trick for the neighborhood kids. He would pour gasoline into a dish. He would light a match and he would extinguish the match into the gasoline. He would take the match, throw it into the gasoline.

The doesn't light on fire. A lot of reasons why that happens.

But I would submit that my brother's experiment did not establish that gasoline is flame retardant. And this is analogous to what

Dr. Davies' test is.

It's a single experiment under extreme non-standard conditions. And even if you credit as being a test as being carried out directly, which we seriously dispute Dr. Davies' conditions are not predictive of what will happen in a pharmaceutical product or under any conditions, any other conditions whatsoever or even in a repeat of the same test.

And you may recall that before the August trial, we made a Daubert motion regarding Dr. Davies' testing and the Court denied that without prejudice. And we would submit that, in addition to their relevance as far as admissibility of testing, the Daubert factor is quite a good framework to evaluate the weight that the test should be given.

And using this test for this purpose has never been peer-reviewed or published. It's a single experiment.

And Dr. Davies has not established the results repeatable, and he has not established any known or potential rate of error for this test. There are no standards

controlling the operation.

Plaintiffs will assert this is a standard test. But what Dr. Davies will testify to is that it's standard not to conduct a standard test, that everybody does their own thing in the literature, that he sites shows that basically there are no standard procedures in the industry and people do whatever they want because they don't care about reproducibility of the results.

Because they're not using the test for purposes of making an evaluation of anything other than identifying the chemical compounds that result in the break up of the drug product.

And so the next problem we have with this test, conceptually before you get into details of it is he didn't validate the test, and validating a test means you provide some evidence that it works for its intended purpose, that it's capable of showing, in this case that it would separate antioxidants from things that aren't antioxidants, and he hasn't done that. He didn't test alpha-tocopherol, he didn't test any antioxidants. He didn't see what this test does

when it stays with the presence of something that's wildly believed to be an antioxidant.

So in short we believe Dr. Davies' forced degradation study is exactly the type of litigation test that shouldn't be given much weight and at the end of the day the Court is going to be balancing the test data that 3M did which is under the FDA standard and it's the test identified in the patent versus Dr. Davies' test using conditions that have never been done before for any purpose outside of this litigation.

On top of it all, Dr. Davies' results at the very best for plaintiffs show barely any difference. Nothing like the effect shown in the patent. In the patent using the standard accelerated stability testing, the amount of degradation products are reduced by approximately four fold, and our expert, Dr. Michniak-Kohn is going to testify that Dr. Davies' experimental results are not statistically significant, Dr. Davies is going to say they are. His methodology which he establishes statistical significance was established after the fact and that is a serious

no no in statistics. But we think beyond the statistics when I look at the results there is hardly any difference and given the other problems that we have sort of with the test, we think the Court shouldn't give it very much weight.

Now, I would like to put back Claim 1 back up on the screen with the highlighted element and I want to take a minute to, a brief minute to address plaintiff's Sunovion argument that the Court raised during the pretrial conference. It's a legal issue. We're going to address it extensively in posttrial briefing, but I want to address a factor that we believe to be a major distinguishing factor in that case, which is Par's ANDA does not have a specification for an antioxidant. In fact, our specification says we're not going to have an antioxidant. And Sunovion addresses the situation, I think the words plaintiff's counsel used was where the ANDA directly addresses the question of infringement, what that means is you look at the ANDA and if you can see infringement without leaving the ANDA you're going to apply the Sunovion standard and

you don't consider other evidence.

But that doesn't apply here and plaintiffs admitted it doesn't apply here because when I sit down Dr. Davies is going to stand up and say something that's not been described in the patent or otherwise as ******an antioxidant is an antioxidant. So this is very different. In fact, if you look at the Glaxo case, the only reason Sunovion distinguished Glaxo was that from the 90 percent to 0 was form one and they didn't put a label on what was from 90 percent to a hundred percent. The facts of the case there were only two forms and so they're very well, that very well could be effectively a specification permitting up to ten percent of form two, but the ANDA specification didn't say form two, you had to go outside the ANDA specification to find out if that was or was not in fact form two. And once you did, you had to consider all the relevant evidence about what the ANDA applicant would likely sell.

So we submit that, and we think there is a lot of other reasons to distinguish Sunovion in this case, but we submit that since

your ANDA specification does not resolve the question of infringement because we say we don't have an antioxidant ******and, therefore, the plaintiffs, and you have to look at other evidence to make that determination, we think that is a significant distinguishing factor of Sunovion.

Now another big difference is that case was based on a piece of paper somebody put into the Court and I believe in that case they actually spike their sample with the other product. I did want to point in the ANDA specification identified a particular chemical, it was levetiracetam, the specification and the claim element identified the exact same thing. And here, this is different because our ANDA specifications are acetaldehyde, the claim element is for an antioxidant. And that is something different.

Another different is there are now batches of Par ANDA product that have been manufactured using the ANDA product for which acetaldehyde measurements have been taken, two batches have no detectable acetaldehyde, the

other six batches the acetaldehyde was measured to be between eight parts per million and 30 parts per million.

And to cover our actual ANDA product plaintiffs have to resort to the term in the claim and they got to stretch their claim pretty far if they're going to cover the actual product made using the ANDA process, and when we were heading to trial in August, the court in ruling on our Daubert motion cited a case called Cohesive Technologies that the Court believed was relevant to the interpretation, so I wanted to address that case for a couple of minutes.

So essentially in the Cohesive Technologies case the Federal Circuit said when you're addressing the lower end of a numerical range you need to look at the function that the numerical range has in the invention. And here, so if we're going to look at the function of the numerical portion of this element, this was added during prosecution, in response to a rejection by the patent office that the patentees had not enabled all antioxidants at all concentrations so they added the about language to the limitation.

And the specification here describes experimental data from only one antioxidant and at two concentration, .1 and .15 and those are both well within the claim, so from the prosecution history, the function of the range is to enable a person of ordinary skill in the art to stabilize a pharmaceutical composition, and if we look at the specification, I would like to pull up column four, line 16 to 30. Here is the only place in the specification that the numerical range appears and immediately following it, they give two examples where the pharmaceutical compositions of the invention are reducing degradation in one case from 4.46, from 1.09 to .25 percent. While we realize that the Court has construed antioxidants that it does not have to function in the formulation, we submit that when plaintiff's resort to the about limitation to try to capture something that's not within the numerical range, they're bringing back functionality in the claim through the Cohesive Technology, then they have to show that our amount of acetaldehyde functions like the amount, the claimed amounts of antioxidants.

And we submit that this again, same stability data shows unequivocally acetaldehyde doesn't do anything in our product.

And then on infringement, I think the Court knows, discussed in the pretrial conference we also have our declaratory judgement claim for the '023 patent that's in the case, and I want to then jump ahead and talk briefly about our 112 invalidity case that the plaintiffs address in their opening.

If the Court were to credit Dr. Davies's study, that presents a different problem for plaintiffs. Since those results at least according to plaintiffs are different from the results of 3M's FDA approved stability testing using a test that is specified in the patent, that means using different test methods yields different results.

And the crux, an important components of our indefiniteness test is that under plaintiff's interpretation of how you show infringement, there is no principal way to determine what is or is not an antioxidant. Competitors are entitled to know the scope of the

patent. And even if Dr. Davies' test is one way, there are infinitely other ways and references he cited and otherwise to conduct a forced degradation. Even if we did ten tests that showed no effect, Dr. Davies can design an eleventh test with some unknown chemical in it, he can come up with some new set of test circumstances that he says show some minor effect, he now can wave that around and say, I discovered a new antioxidant, and that's not a legitimate scope of a claim. The public is entitled to know and to be able to determine if they're inside or outside the claim, and the case we cite for that and Amagen versus Herch 314 F.3rd 1313, the enablement defense is similar. Like the patent office rejection during prosecution we are asserting the full scope of this claim is not enabled and particularly the full scope the plaintiffs are asserting that that the compound doesn't have to be established according to them to be an antioxidant by any established test, nor does it have to be an antioxidant for anything in particular, you know, according to my previous example, I think, you

know, the paint on your car can be oxidized, I think the plaintiff's definition would encompass Turtle Wax because I can put Turtle Wax on my car and it can stop oxidizing. They have really not been able since the scope of their claim that they're asserting is not limited by reducing oxidation of any particular thing under any particular environment, we think they clearly have not enabled a person of ordinary skill in the art to use that scope of compound as an antioxidant in a pharmaceutical formulation.

The written description defense is similar, the difference between the written description and the enablement defense conceptually is the written description you look only at what's in the specification and you use ask the question whether the inventors were in possession of the invention as it's claimed, and here, they have described data for one antioxidant, we know in fact they tested one other one, and it didn't work, they have data from two, one worked, one didn't work and from that, they extrapolated to claim any chemical compound in their words capable of reducing

oxidation of any other compound any other circumstances in any test and we would submit they don't have written description enablement or definiteness support for that scope.

Thank you, Your Honor.

THE COURT: Thank you, Mr. Brown.

Novartis, call your first witness.

MS. JACOBSEN: Plaintiff's first witness is Martyn Davies. And he'll be providing the infringement testimony.

THE COURT: Thank you.

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

THE WITNESS: My name is Martyn, M-A-R-T-Y-N, Christopher Davies, D-A-V-I-E-S.

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

THE COURT: Could I just ask both counsel to move the microphone a little closer to your mouth. You're both very soft spoken and I heard what you said, but it's a challenge. It

shouldn't be a challenge.

MS. JACOBSEN: Yes, Your Honor.

Your Honor, can we approach?

THE COURT: Yes.

MR. FINEMAN: Your Honor, quick housekeeping before we start, does Your Honor want to address objections as they come along or would Your Honor want to wait to the end?

THE COURT: You should objection as we come along.

MR. FINEMAN: Thank you.

DIRECT EXAMINATION

BY MS. JACOBSEN:

Q. Good morning, Dr. Davies.

A. Good morning.

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

A. My name is Martyn Christopher Davies.

Q. And Dr. Davies, do you have a binder of documents in front of you there?

A. I do.

Q. And can you turn to tab one, you'll find PTX 50A. Can you please identify that document for the Court?

A. That's my curriculum vitae.

MS. JACOBSEN: Your Honor, plaintiffs moved to introduce into evidence PTX 50A.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

MS. JACOBSEN: And, Your Honor, based on your comments at the pretrial conference, we don't plan to go through his qualifications.

THE COURT: I'm satisfied. Is there any objection to him testifying as an expert?

MR. BROWN: No, Your Honor.

THE COURT: You may proceed.

MS. JACOBSEN: Thank you, Your Honor.

BY MS. JACOBSEN:

Q. Dr. Davies, can you please summarize what you were asked to do with respect to Par ANDA products?

A. Yes. I was asked to see whether Par's ANDA products meet the elements of Claim 7 of the '031 patent. And in particular I was asked if

the acetaldehyde is an antioxidant. Is it an agent that reduces oxidative degradation. And also I was asked if acetaldehyde was present in the amounts that are in the claims of Claim 7.

Q. Can you summarize your analysis with respect to the first issue, whether acetaldehyde is an antioxidant?

A. Yes. It was a matter of, if one looks simply first at the basic chemistry of acetaldehyde, acetaldehyde is firstly known as a reducing agent, and reducing agents act as antioxidants. And with that basic chemistry understanding, I then undertook an experiment to show that acetaldehyde is an antioxidant.

Q. What type of experiment did you run?

A. I ran a controlled head to head stress test where I created an oxidative environment, I placed the rivastigmine within that environment in the presence or absence of acetaldehyde. So I created an experiment which in many ways is the simplest form of experiment where there is only one variable. That one variable being the presence or absence of acetaldehyde

A. And I monitored the degradation that

occurred in the assay of the drug in the presence or absence of acetaldehyde.

Q. And what did that experiment show?

A. That experiment showed that acetaldehyde is an agent which reduces oxidative degradation. And it also showed that acetaldehyde is an antioxidant.

Q. Can you summarize your analysis with respect to the second issue, whether Par's ANDA product contains about 0.01 to about 0.5 weight percent of acetaldehyde?

A. Yes. If you look at Par's specification, the specification cites for acetaldehyde that it can be present in up to a thousand parts per million. That is 0.1 percent which falls directly within the range of the claim.

Q. Is that the specification for all three of Par's ANDA products?

A. That's correct.

Q. What was the basis for Par's ANDA specification for acetaldehyde?

A. Par ran its own evaluation of the toxicity of acetaldehyde and they also measured the levels in their prototype batches at -- they set the

specification to up to a thousand parts per million.

Q. Thank you, Dr. Davies.

Let's discuss briefly Par's ANDA products and their structure. And can you please describe Par's ANDA products for the Court?

A. Yes. A very simple diagram which just illustrates the point.

Par has three products. It has an -- excuse my tremor -- 4.6, a 9.5 and a 13.3 milligram per 24-hour patches. These all contain the same ingredients.

They have a backing layer. They have a release liner. And they have a single drug-in-adhesive layer. And that single drug-in-adhesive layer contains Rivastigmine. It contains the isopropyl myristate, which is the tackifier. And it contains the acrylate copolymer adhesive, which contains acetaldehyde.

Q. And can you please turn to Tab 2 of your witness book and there you'll find PTX 344. Can you identify that document for the Court?

A. This is a portion of Par's ANDA which highlights the structure and also the composition

of the three different dosage strengths of Par's ANDA products.

MS. JACOBSEN: And, Your Honor, plaintiff moves to introduce into evidence PTX 344.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

MS. JACOBSEN: And for the record Dr. Davies referred to PTX 344 at Page 231.

BY MS. JACOBSEN:

Q. Dr. Davies, can you describe how you determined whether Par's ANDA products meet the elements of Claim 7?

A. Yes. I broke the claim down into the key elements and then I compared those elements with Par's ANDA product to come to my opinion.

Q. And can you walk us through those elements, please, Dr. Davies?

A. Yes, certainly.

It is a transdermal device -- sorry. A transdermal device, which has pharmaceutical composition comprising of therapeutically effective amounts of -- this is Rivastigmine.

Has an antioxidant with about 0.01 to about 0.5 percent by weight. A diluent or carrier and wherein the pharmaceutical composition is supported by a substrate.

Q. Dr. Davies, can you please turn to Tab 3 of your witness binder? And there you'll find JTX 1.

Can you please identify that document?

A. That's the '031 patent from which Claim 7 shown here is drawn.

MS. JACOBSEN: And, Your Honor, plaintiff moves to introduce into evidence JTX 1, the '031 patent.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Dr. Davies, do you have an understanding as to which elements are actually in dispute in this case?

A. Yes. It's whether or not there's an antioxidant present in Par's products and whether it's present in about 0.01 to about 0.5 percent

by weight in the three.

Q. And Dr. Davies, I'd like to start with the first issue, whether Par's ANDA products contain an antioxidant. Are you aware of how this Court has construed the term antioxidant?

A. Yes. It says that the antioxidant requires the presence of an agent that reduces oxidative degradation as shown on this slide.

MS. JACOBSEN: And for the record, Dr. Davies is referring to the '031 patent in JTX 1 and the Court's claim construction DI-250.

BY MS. JACOBSEN:

Q. Do Par's ANDA products contain an antioxidant under the Court's claim construction?

A. Yes, I believe they do. They contain acetaldehyde.

Acetaldehyde, which I will show is known as a reducing agent. Reducing agents can be antioxidants. And my test shows that it is an antioxidant.

Q. And how do you know that Par's ANDA products contain acetaldehyde?

A. Well, the specification states quite clearly that it contains acetaldehyde. Contains

acetaldehyde up to the order of a thousand parts per million.

3M, who is Par's manufacturer, also detected the acetaldehyde and makes the adhesive.

Q. Dr. Davies, what is an ANDA specification?

A. An ANDA specification is a document submitted to the FDA where a company is seeking regulative approval to market a particular product. The ANDA specification is a blueprint of all the information the FDA requires for it to be able to assess the products and its suitability for regulatory approval.

That includes information related to the manufacture, the properties of the compounds present, and it also includes information pertinently related to the specification.

And the company, when it submits its ANDA with those specifications, if that particular ANDA is approved and the product approved for marketing the company can actually manufacture their product to meet those specifications.

Q. Dr. Davies, can you please turn to Tabs 4, 5 and 6 of your witness book? And there you'll

find documents marked PTX 348, 349 and 350.

And can you please identify those documents?

A. These are the specification for the finished product for the 4.6, the 9.5 and the 13.3 milligram, the three different dosage strengths for Par's product respectively.

Q. Can you identify where in Par's ANDA specification the limit for acetaldehyde is set?

A. Yes. This slide shows -- this is taken from a portion of a finished product specification. It shows the one for the 13.3 milligram per 24 hours.

And you see that it has here NMT 1000 parts per million acetaldehyde. The NMT means not more than.

And you see the same specification in all three dosage strengths.

Q. What does the parenthetical monomer-related mean?

A. That means that the acetaldehyde is in the adhesive -- it's present within the adhesive. The adhesive that Par mixes with its drug and to create its drug-in-adhesive layer.

MS. JACOBSEN: Plaintiffs move to introduce PTX 348, 349, and 350 into evidence.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

MS. JACOBSEN: And for the record, the pages referred to by Dr. Davies are PTX 348 at Page 780, PTX 349 at Page 788, and PTX 350 at Page 796.

BY MS. JACOBSEN:

Q. Dr. Davies, how did you analyze whether acetaldehyde is an antioxidant?

A. As I explained, I -- firstly, I looked at the chemistry. I looked at the chemistry of acetaldehyde. It's a well-known reducing agent.

And reducing agents can act as antioxidants. And so then I took tests -- a test that demonstrated that acetaldehyde is an agent which reduces oxidative degradation.

Q. Dr. Davies, can you please explain what reducing agents are?

A. It's -- yes. Reducing agents are agents that will undergo sacrificial oxidation in a mixture such that they help to protect other

agents that -- other compounds such as drugs that may be present. So they're more susceptible, in that sense, to oxidation.

So reducing agents can act -- will undergo sacrificial oxidation reducing the level of the oxidative environment; and therefore, helping to protect the drug.

Q. And after you considered the basic chemistry, what was the next step in your analysis?

A. The next step in my analysis was to create an experiment where I undertook a stress test, a controlled stress test which was a head-to-head stress test where I created an oxidative environment where an oxidative environment which would degrade the drug. And then I compared that oxidation, what would happen if I had a sample with and without acetaldehyde.

Q. And what do you mean with a controlled head-to-head test?

MR. BROWN: Your Honor, in your order denying our Daubert motion, you mentioned that at trial to preserve that, we should renew our Daubert request. So I'm issuing a Daubert

objection to Dr. Davies' testimony and I would request that the Court grant me a continuing objection, so I don't need to do this further during the trial.

THE COURT: Well, I'll grant you a continuing objection to at least this particular testing --

MR. BROWN: Correct.

THE COURT: -- which I think, as I understand, is what you're objecting to. And basically I think, based on the pretrial ruling, the pretrial ruling, I'll expect Dr. Davies will explain what it's in the test. And then probably your expert will explain why it's not.

And I'll figure that out later on.

MR. BROWN: Thank you, Your Honor.

THE COURT: All right. You may proceed, Ms. Jacobsen.

MS. JACOBSEN: Thank you.

BY MS. JACOBSEN:

Q. So, Dr. Davies, you used the term controlled head-to-head test. Can you please explain what you meant by that?

A. Yes. When I'm saying it's a head-to-head

test, what I'm saying there is that this is a test where there's only one variable in play. In this case, it's the presence or absence of acetaldehyde. Everything else remains the same.

So if there -- if I show between these two sets of samples, one of which has no acetaldehyde, one of which has acetaldehyde present, the only difference between these two samples is the absence or presence of acetaldehyde.

So if there's any difference between these two samples related to the oxidative degradation of the drug, it could be attributable directly to the presence of just that one variable, i.e. the absence or presence of acetaldehyde.

Q. And what were the results of your stress test?

A. The results of my stress test showed that acetaldehyde reduced the oxidative degradation. It was also -- my stress test showed that acetaldehyde is an antioxidant.

Q. Did you conduct any statistical analysis on your results?

A. Yes, I did. I conducted statistical analysis to show that the difference between the two samples, the two sets of samples, the only variable in play with or without acetaldehyde was statistically significant. I showed that it was statistically significant.

Q. And did you draw any conclusions from your experiment?

A. I did. I drew the conclusion that, based on my experiment, that acetaldehyde is an agent which reduces oxidative degradation. That backed up what I knew from the literature.

And what I knew about acetaldehyde is it is a known reducing agent, and reducing agents can be antioxidants. And my data clearly shows in this very simple and very straight forward, very pure, in a sense, experiment, that it is. Acetaldehyde is an antioxidant.

Q. Thank you, Dr. Davies.

Does the '031 patent list acetaldehyde as an antioxidant?

A. No, it does not. It lists exemplary examples. Sorry.

I show this slide here, which lists

them, a number of examples in, I believe, it's Column 4.

Q. Did the fact that acetaldehyde is not listed in the '031 patent influence your infringement analysis in any way?

A. No, it does not. It's not -- this list is not limited to be -- it's not -- pardon. It doesn't limit the antioxidants that can be used to this specific list.

The claims are quite clear that it -- they relate to antioxidants. They're not limited to specific antioxidants in Claim 1 or Claim 7.

Q. Does the '031 patent describe any reducing agents as antioxidants?

A. Yes, it does. It describes ascorbic acid and ascorbyl palmitate, both of which are both reducing agents.

MS. JACOBSEN: And for the record, the passage from the '031 patent, JTX 1 that Dr. Davies is referring to is at Column 4, Lines 10 to 19.

BY MS. JACOBSEN:

Q. Dr. Davies, are you aware of any

literature calling acetaldehyde a reducing agent?

A. This is at slide -- a page from Van Nostrand's Concise Encyclopedia of Science. There's a monograph here for acetaldehyde.

And it says the compound also is used as a reducing agent.

MS. JACOBSEN: And, Your Honor, Plaintiffs move to introduce into evidence JTX 61.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

MS. JACOBSEN: And for the record, Dr. Davies referred to JTX 61 at Page 5.

BY MS. JACOBSEN:

Q. Is there any other evidence that acetaldehyde is capable of being oxidized itself to protect other compounds from oxidation?

A. Yes. This is a slide, again, from a page taken from a pharmaceutical textbook called Modern Pharmaceutics.

And there's a section here on oxidation. And in the section on oxidation, it talks about, in pharmaceutical dosage forms, oxidation is usually mediated through reaction

with atmospheric oxygen and under ambient conditions, a process commonly referred to as autoxidation.

And the next paragraph, it goes on to talk about many autoxidation reactions are initiated by trace amounts of impurities, such as metal ions or hydroperoxides.

Now, if you look below, there's a table where it talks about some functional groups subject to autoxidation. And it highlights acetaldehydes here. Sorry, it highlights aldehydes here.

And acetaldehyde is one of the simplest forms of aldehyde.

Q. Why is this relevant to your analysis?

A. It's relevant to my analysis because it demonstrates that -- it shows that aldehydes are, such as acetaldehyde, are subject to autoxidation. In other words, aldehydes act as reducing agents.

MS. JACOBSEN: Your Honor, plaintiffs move to introduce into evidence JTX 106.

MR. BROWN: No objection, Your

Honor.

THE COURT: Admitted without objection.

MS. JACOBSEN: And for the record, Dr. Davies referred to JTX 106 at Page 183.

BY MS. JACOBSEN:

Q. And Dr. Davies, is there any other evidence that reducing agents can act as antioxidants?

A. Yes. This is a slide from, again, a page taken from the EMEA Note for Guidance. EMEA is the European equivalent to the FDA.

And there's a section here on antioxidants. And it shows antioxidants are used to reduce the oxidation of active substances and excipients in the finished product.

And it highlights, there are three different types of antioxidants, one of which is reducing agents. And it says these have a lower redox potential than the drug or excipient they are protecting. What that means is that the more susceptible to oxidation and they'll sacrificially undergo oxidation so that they're able to protect the drug excipient.

It gives an example of ascorbic acid and ascorbic acid is one of the examples that we seen in the '031 patent.

MS. JACOBSEN: Your Honor, plaintiffs move to introduce into evidence JTX 105.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

MS. JACOBSEN: And for the record, Dr. Davies referred to JTX 105 at page one of four.

BY MS. JACOBSEN:

Q. And Dr. Davies, have you seen any other evidence of reducing agents can act as antioxidants?

A. Yes. This is another section from Modern Pharmaceutics, and it's a section again dealing with in this case antioxidants. And talks about mechanistically some antioxidants such as ascorbic acid and ascorbic palmitate, those are the two that I highlighted again from the examples in the '031 patent, act as reducing agents. They are easily oxidized, preferentially

undergo autoxidation, thereby consuming oxygen and protecting the drug or excipient.

MS. JACOBSEN: For the record, Dr. Davies referred to JTX 106 at page 203.

BY MS. JACOBSEN

Q. Is acetaldehyde listed in the FDA inactive ingredient list?

A. No, it is not.

Q. Are you aware of acetaldehyde being used in pharmaceuticals?

A. Yes, this is the specialty chemicals sourcebook and, again, it's got a monograph for acetaldehyde. And under the uses, it cites synthetic flavoring agent in foods, beverages and pharmaceuticals. And it also cites that it's used in the manufacture of pharmaceuticals.

And if you look at its regulatory status, its status is GRAS, which is general, the term for generally regarded as safe. And as given by the FDA --

Q. And Dr. Davies, I think you misspoke, you said generally regarded as safe. Is it generally recognized as safe?

A. I believe that's true, yes. Sorry.

Q. Thank you.

And are you aware of any products in which acetaldehyde is permitted to be present?

A. Yes. The Par product where it's present.

MS. JACOBSEN: Your Honor, plaintiff move to introduce into evidence JTX 63.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

MS. JACOBSEN: And for the record, Dr. Davies referred to JTX 63 at page 7.

BY MS. JACOBSEN:

Q. So focusing on rivastigmine specifically, can you explain what happens when rivastigmine is oxidized?

A. Yes. This is the generally recognized by Par, I don't think there is any dispute about this regarding rivastigmine oxidative degradation pathway. Here is the rivastigmine molecule, it can undergo oxidation by oxygen or peroxides to form what is called an N-oxide here. The N-oxide has a very short half life, and it degrades to form, the styrene molecule here. The styrene molecule is referred to as ECAV by Par. That

molecule can undergo further oxidation by oxygen or peroxides to form the ketone, and that's known as impurity 4.

Q. Are oxidative degradation products different if rivastigmine is oxidized by oxygen or peroxide?

A. No, they're the same. In fact, these are the two key degradation products that are seen for the oxidative degradation of rivastigmine, whether by oxygen or by peroxides.

Q. Can you explain how an agent, reducing agent such as acetaldehyde can act as an antioxidant?

A. Yes. I have shown it on this slide. Reducing agents such as acetaldehyde will sacrifice themselves and react with the oxygen or peroxides so reducing the oxidative degradation, and they will do that in this case block the conversion of the rivastigmine to the, they'll react with the oxygen or peroxides, they'll also at this point with the conversion of the styrene to ketone, acetaldehyde will sacrifice itself and react with the oxygen and peroxide thereby reducing the oxidative degradation.

Q. Dr. Davies, can you please turn to tabs 11 and 12 of your witness book and there you'll find JTX 85 and PTX 125. Can you please identify those documents?

A. Again, they're part of the Actavis technical documents, the first, and then there is also you said 12.

Q. Tab 12, should be PTX 125?

A. I'm sorry, I'm looking at the wrong document. I apologize. Tab 12, yes, that's an E-mail correspondence from Actavis. I'm happy to talk about it, if you wish me to talk about it.

Q. I will.

MS. JACOBSEN: We'll move to introduce as exhibits into evidence JTX 85 and PTX 125.

MR. BROWN: We have an objection to PTX 125 as hearsay. This is an Actavis E-mail. They're not a party to the litigation, and they're introducing it for I believe statements that are in for the truth of the matter asserted and we would object to PTX 125 on those grounds.

THE COURT: Ms. Jacobsen.

MS. JACOBSEN: This is an E-mail

from Actavis. Actavis used to own Par's ANDA. It's an admission against interest by Par's predecessor so it's admissible under 801(d)2(b).

THE COURT: All right. Do you agree that Actavis was Par's predecessor?

MR. BROWN: Actavis was the previous owner of the ANDA, that is correct.

THE COURT: All right. I'm going to tentatively admit it. If it turns out that you want to present in posttrial briefing that this was a mistake, go ahead, but I think it's admissible. Go ahead.

MS. JACOBSEN: Thank you, Your Honor.

For the record, Dr. Davies referred to JTX 85 at page 2403 and PTX 125 at page 33980.

BY MS. JACOBSEN:

Q. Dr. Davies, I would like to transition now to the experiment that you conducted. Just so the record is clear, Dr. Davies, can you go to Tab 12 again in your witness book, and that's where PTX 125 is?

A. Yes.

Q. And can you turn to page 980, page ending

in 980, and can you explain what this document relates to?

A. Yes. This is called the E-mail from Dale Martin at Actavis, and in the third paragraph down, he's talking about an impurity is an oxidation impurity and its formation is promoted by the presence of oxygen, especially peroxides and like. So he's recognizing that oxygen and peroxides are responsible for the oxidative degradation of rivastigmine.

Q. Thank you, Dr. Davies.

Now I would like to transition to the experiment that you conducted.

MS. JACOBSEN: Sorry, Your Honor. One other matter. On JTX 85, I understand it's not clear whether that was admitted.

THE COURT: I'm sorry. It was admitted without objection, or it is now admitted without objection.

MS. JACOBSEN: Thank you, Your Honor.

BY MS. JACOBSEN:

Q. Now, I would like to transition to your testing. Can you briefly explain how you

approached the design of your experiment?

A. First thing I wanted to do was create conditions where -- such that I created an oxidizing environment such that I could monitor the oxidative degradation of rivastigmine.

Q. Why did you want to create an oxidizing environment?

A. Well, the reason I wanted to do it because I wanted to be able to create an environment where I am replicating the oxidative degradation pathway of rivastigmine so I'm able to show the presence of these two key degradation products, and I wanted to do that at a sufficient level such that I could then undertake an experiment, undertake an experiment where I compared two sets of solutions, one with and without the presence of acetaldehyde to see whether or not acetaldehyde had any influence on the formation of those two degradation products of the oxidative degradation pathway.

Q. What did you do once you established the conditions for an oxidizing environment?

A. Once I established that, I then set up the experiment in a way that I created an experiment

where I created two sets of samples, one of which had no acetaldehyde present, one set, another set which had acetaldehyde present. So I was creating my head to head stress test.

The one without acetaldehyde acted as the control for the samples with acetaldehyde. There is only one variable here, the presence or absence of acetaldehyde, therefore, any differences in the levels of these two key components could be attributable to the presence or absence of acetaldehyde.

Q. Dr. Davies, you used the term stress test. What is a stress test?

A. A stress test is a test used widely within the pharmaceutical industry. And they're used to accelerate the degradation of a drug or excipient so that you can monitor that degradation over a short period of time.

Q. Can stress tests be used to study different degradation pathways?

A. Yes, it can. And it is used, and it's widely used for that effect. So, for example, one can study the influence of light, you could study the influence of acid or basic conditions.

You could study the influence of oxidation. There are a number of things that one could do.

Q. Can stress tests be used to determine whether something is an antioxidant?

A. Yes, it can. Because having established with the stress test that you are able to -- a particular pathway as we have shown here, as I will show -- you can in the kind of experiment that I have undertaken, a controlled head to head study, you can show whether or not a molecule is an antioxidant by doing the controlled head to head study by having a control and then having a sample with say in this case acetaldehyde in that stress test. Any differences in the rate of the degradation could be attributable to the one key variable that's changing, the presence or absence of acetaldehyde.

Q. And is it necessary for all the conditions to be the same to run a head to head test?

A. It is for this, I believe it is, because in that controlled stress test you have a test where there is only one variable in play, so any differences between the two sets of samples could be directly attributable to that one variable.

However, if you have multiple variables occurring, the multiple differences between the samples, then you can't be sure that any differences that you do observe could be attributable to the presence or absence in this case of acetaldehyde.

Q. Are stress tests standard in the pharmaceutical industry?

A. Yes, it is. This is a paper by Alsante. It talks of stress testing is a critical component of drug development. It says by generating key stress-testing samples (i.e., partially degraded samples stressed under various conditions), predictive degradation information can be obtained early in the process. Stress testing can help in the selection of more stable drug substance salt forms and drug formulations.

So that can help in the selection of the most appropriate drug forms to use and also which excipients to use to make a stable composition.

Q. Are there any other references discussing the use of stress tests in the pharmaceutical industry?

A. Yes. There is a reference by Aubry, it talks about the development of stability indicating methods. And here, it says forced degradation studies typically involve the exposure of representative samples of drug substance or drug product to the relevant stress conditions of light, heat, humidity, acid/base hydrolysis and oxidation. These experiments play an important role in the drug development process.

The results of forced degradation studies can facilitate drug formulation design, in other words, sorting out your formulation such that it's stable, what excipients one would include to be sure that you have stable formulation. And it's also used with solving of stability-related problems.

Q. Dr. Davies, can you turn to tab 13 and 14 of your witness book, and there you will find JTX 75 and JTX 221. Can you identify those documents?

A. Yes, these are the two documents that I have just highlighted pages from, Alsante and the Aubry reference.

MS. JACOBSEN: Your Honor,

plaintiffs move to introduce into evidence JTX 75 and JTX 221.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

MS. JACOBSEN: For the record, Dr. Davies referred to Alsante as JTX 75 at page 60, and JTX 221, that's the Aubry reference, at page 141.

BY MS. JACOBSEN:

Q. Dr. Davies, have you conducted stress tests prior to your involvement in this case?

A. Yes, I have.

Q. Can you give me a simple example?

A. The example I conducted such test at both the university and also at Molecular Profiles, for example, recently we were working on a new drug that we were helping to prepare the drug for the formulation for a clinical trial. The drug is acid labile, the stress test we saw that it was acid labile and through further stress tests we were able to use those stress tests to look at the most appropriate pH modifying excipient to use within that formulation.

Q. Dr. Davies, what does it mean to be acid labile?

A. It means that the drug degrades in a particular environment, such as say for example in your stomach is an acidic environment. The drug degrades in the acidic environment so we include excipients such that they would help stabilize the drug by acid modifying.

Q. I would like you to take a closer look at the Alsante reference that you discussed a moment ago. Can you generally describe what this paper is about?

A. Yes. The Alsante paper was a stress testing benchmarking study, and the authors say to better understand current stress testing practices in the pharmaceutical industry, the authors conducted a benchmarking survey to which twenty pharmaceutical companies responded. And the authors themselves are from the pharmaceutical industry, they're from Pfizer and they're also from Eli Lily.

Q. Does this paper discuss the use of stress tests to study oxidative degradation?

A. Yes, it does. It has a section on

oxidation, and that section shown again on this page on the slide, here we see that under oxidation it says nineteen companies perform oxidative stress testing on the drug substance. Approximately 65 percent perform oxidative, which I think is about 13, perform oxidative stress testing on the drug product.

So that's both on the drug substance and on the drug product. If you look below, it shows here, that a range of conditions are used, a range of conditions are used or, it shows that you could use peroxide, use radical initiator, pressurized oxygen, transition metal and bubbled oxygen.

When you look at below in the figure six from the paper, it shows that those companies, it shows the peroxide, the typical peroxide used is hydrogen peroxide, and it shows a range of typical concentrations, study duration and temperatures are used by those 19 companies.

So it's illustrating there are a number of ways that one could conduct oxidative stress tests. But the objective is the same in all cases, it's to create an oxidative

degradation environment that one could study for the drug.

Q. Why is it the object

Q. Why is that the objective to create an oxidizing environment?

A. Such that one can study the oxidative degradation of the drug and of the drug products that's recited here.

Q. And why does the variability exist?

A. Variability exists because each drug is different. Each drug has different physicochemical properties and drugs undergo -- and kind of undergo oxidative degradation in different ways.

So the scientist within the pharmaceutical industry designed their experiments in a way with an understanding that each drug is different. And they designed their experiments such that they're able to -- that's why there is this variability.

And they design their experiments. But in each case, it's the same objective. Its objective -- the goal is the same, to be able to create an oxidative environment, study the

oxidative degradation of the drug or the drug product.

Q. Is any particular level of oxidative degradation necessary to conduct a stress test?

A. Once you achieve a sufficient level such that you're able to monitor the key degradation products over the time scale of the experiment. So, in my particular stress test, I wanted to achieve sufficient degradation such that I was able to distinguish between the samples which had a -- control samples which had no acetaldehyde present and the samples which had acetaldehyde present, to be able to distinguish between those two.

Q. What if there isn't enough degradation to distinguish between the two samples?

A. If you don't generate enough oxidative degradation of the sample then you can't make the -- you can't undertake the experiments to -- to distinguish between these two sets of samples in this head-to-head stress test.

Q. And is the variability in the ways that stress tests can be conducted recognized in the Alsante reference?

A. Yes, it is. The point goes to the conclusion. It says, Although the benchmarking survey shows significantly diversified approaches among the participating companies, the diversity is not as great as one might expect based on the lack of clear guidance in literature or in regulatory guidelines.

What that's basically saying is that the benchmarking survey is recognizing that there is this diversified approach, but ultimately, the scientists within the pharmaceutical industry that design the experiments within these parameters, because the differently -- because there are all types of differences and you have to tailor your test to the different drugs.

Q. Does Alsante discuss the stress test to study the effect of potential antioxidants?

A. Yes, it does. Not -- sorry, not explicitly, I should say, but it does talk about the fact that one can undertake stress testing, look at pharmaceutical formulations.

So, in addition, it says stress testing can help in the selection of more-stable drug substances, salt forms and drug

formulations. Well, what that's talking about there are excipients. And if one looks at Figure 1 shown here, it shows that there is a -- here it shows predominant reasons for performing the stress test studies and it showed here preformulation and excipient compatibility.

Seventeen of twenty companies use stress testing to test the effect of an excipient compatibility on the drug. And what it's talking about there is that one could use that -- exactly that approach to study the effect of an antioxidant on a drug or an excipient, for that matter.

MS. JACOBSEN: For the record, the portions of Alsante that Dr. Davies referred to in the previous set of slides occur at JTX 75 on Pages 60, 64, 67, 68 and 72.

BY MS. JACOBSEN:

Q. Dr. Davies, does the FDA issue guidance on how to perform stress tests?

A. It does. It's very general guidance and I think that's recognized and cited in this Aubry paper, which I've highlighted on the next slide. And that recognizes this, although it's FDA

guidance. And ICH guidelines provide useful definitions and general comments about forced degradation studies there.

And forced degradation studies are another term for stress tests. Their direction concerning the scope, timing and best practices is very general and lacking in details.

That's recognizing what we saw in Alsante, that there are a range of ways to achieve -- that one can undertake stress tests and achieve the same goal, the goal of studying the oxidative degradation of the drug.

MS. JACOBSEN: For the record, Dr. Davies referred to JTX 221 at Page 141.

BY MS. JACOBSEN:

Q. Dr. Davies, were you aware of Par ever having performed a stress test?

A. Yes, I am. They undertook a stress test when they -- they noticed in some accelerated stability and long-term stability studies on their products that prototype batches or other -- they noticed the emergent degradation product.

Now, they -- they reasoned that that degradation product was the product of an

oxidative degradation. So Par undertook a stress test where they stressed Rivastigmine in an oxidative environment. And they -- in doing so, they identified the two key degradation products that I highlighted in my schematic.

It showed that one of those key degradation products was, indeed, the degradation product that they were observing.

Q. Did 3M or Par use that test to determine whether any compound was an antioxidant?

A. No, they didn't. But they could have undertaken such a test because they created an oxidative degradation environment and they could have looked to see the effect of adding an antioxidant to that environment.

Q. And can you please turn to Tab 15 of your witness book? And there you'll find JTX 162.

Can you identify that document?

A. Yes. This is the work undertaken by 3M, Par's manufacturer where they -- this is a portion that includes the stress test.

MS. JACOBSEN: Your Honor, plaintiff's move to introduce into evidence JTX 162.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. Dr. Davies, I'd like you to turn now to the detail of your stress test. And can you please give us an overview of your stress test?

A. Yes. This is a very simple, straightforward schematic which illustrates what I've done here in creating an oxidative environment for Rivastigmine by adding an oxidizing agent in with Rivastigmine.

I then split that stock solution into two to create a control and create a sample where I add acetaldehyde. I then split those samples further into three and I labeled them showing here one, two, three. C for control, A for acetaldehyde samples.

And then I stressed them. I stressed them at a particular temperature for over a period of time.

Q. And did you analyze what was happening in those samples?

A. Yes. I took samples at key time points

and measured the degradation products. And I then compared the two sets of data. I compared the degradation products of the drug levels in control and compared that to the acetaldehyde-added forms.

Q. And who designs the stress test you conducted?

A. I did.

Q. And who carried out the stress test?

A. The stress test was carried out by experienced scientists, Ph.D.-level scientists with molecular profiles under my supervision.

Q. And is the exact stress test with the combination of conditions used described in a single published literature?

A. There is more -- there are many of such tests, stress tests, but it does fall within the framework of the parameters that we saw in Alsante and the like.

So the conditions that I used, and I'm going to explain, fall within the same parameters that are used, range of parameters that are used within the pharmaceutical industry, as described -- as highlighted by Alsante.

Q. So I'd like to walk through the test step-by-step now. What was the first step?

A. The first step was to create a stock solution. And to create a stock solution, I dissolved the Rivastigmine in a solvent ethyl acetate. I added T-butyl hydroperoxide, the oxidizing agent to that solution.

Q. And how many stock solutions did you prepare?

A. I prepared a single stock solution. Now, the reason I did that is because I wanted that single stock solution to be the source of the solutions for the entirety of my test. And the reason I did that, I wanted to eliminate any variability that may occur if I make multiple solutions.

So all these samples come from that single stock solution to eliminate any variability that may occur by preparation of multiple solutions.

Q. And how much Rivastigmine was present in your test samples?

A. It was in the order approximately of .36 percent.

Q. And is that the same amount that's present in Par's ANDA products?

A. No, it's not. When you're doing a stress test, you use a concentration which is sufficient for you to be able to monitor the oxidative degradation of the drug. And I showed in my preliminary test that using .36 percent was a suitable level such that I could monitor the oxidative degradation in the time scale of the experiment and achieve significant amounts of oxidative degradation such that I could undertake this head-to-head stress test.

Par uses a different concentration in their products because their products are designed to achieve a therapeutic effect. But therapeutic effect is important there.

So the amount that Par uses in its product is determined by its need to produce the therapeutic effect.

Q. You indicate on the slide there that you added T-butyl hydroperoxide you added. Is that also called TBHP?

A. Yes, it is.

Q. And what is TBHP?

A. TBHP is an oxidizing agent. It's a hydroperoxide. And I included it in here to create an oxidizing environment. I particularly included TBHP and I selected TBHP because I wanted to create an anhydrous oxidizing environment.

The reason for that is that Rivastigmine also undergoes hydrolysis in water. So I wanted to be sure that I was only watching monitoring, should I say, the oxidative degradation of the drug.

To do that, I selected TBHP because it's anhydrous. It's free from water.

Q. And could you also use hydrogen peroxide?

A. I think -- well, one could have done that experiment, but I think it would not have been the right experiment to do because you would have had two competing degradation processes occurring. You'd have hydrolysis as well as oxidative degradation.

So I wouldn't have done that experiment. That's why I did the experiment with TBHP because I was able to do that in an anhydrous environment.

Q. And why would you have two competing degradation pathways if you had used hydrogen peroxide?

A. Because hydrogen peroxide is not -- would not be free from available -- free from water. And, in that context, one would -- if one was undertaking an analysis where there was water present, one would see that there were not only oxidative degradation occurring, but the presence of hydrolysis occurring.

And I wanted to look just simply at oxidative degradation and that's why I chose an anhydrous environment.

Q. And what does anhydrous mean, Dr. Davies?

A. It's free from water.

Q. And how did you know that you could use a peroxide as the oxidizing agent?

A. Because peroxide -- it's well known that Rivastigmine undergoes oxidative degradation in the presence of peroxides.

Q. Is there any evidence in the literature of the use of peroxide in stress tests?

A. Yes, there is. I show in this slide a number of examples.

Alsante talks about using peroxides. Aubry talks about using peroxide concentrations. Bianchini talks about using T-butyl hydroperoxide the one that I used. And the U.S. patent, the '498 patent talks about using T-butyl hydroperoxide as well. So a number of these papers talk about using peroxide.

MS. JACOBSEN: Your Honor, plaintiffs move to introduce into evidence JTX 74 and JTX 77.

MR. BROWN: No objection, Your Honor.

THE COURT: Admitted without objection.

MS. JACOBSEN: And for the record, Dr. Davies referred to JTX 74 at Column 5, Lines 61 to 65. JTX 75 at Pages 67 to 68. JTX 77 at Pages 1,056 and JTX 221 at Page 149.

BY MS. JACOBSEN:

Q. Dr. Davies, how much TBHP did you use?

A. I used approximately 1.3 percent TBHP in this solution.

Q. And why did you use that amount?

A. That was the amount that I saw in my

preliminary work that showed that I could -- could obtain sufficient levels of Rivastigmine degradation for my test. It also falls within the range that is cited within some of these references, for example, the Alsante reference.

It talks about one to three percent peroxide levels. So it falls within such ranges.

Q. Now, you also noted that you added TBHP and Rivastigmine to ethyl acetate. Why did you use ethyl acetate?

A. Again, because ethyl acetate is anhydrous. Ethyl acetate is free from water.

I wanted to just purely look at oxidative degradation, so I chose ethyl acetate for that reason. So I dissolved Rivastigmine and T-butyl hydroperoxide into ethyl acetate so I would only be watching and observing the oxidative degradation of Rivastigmine, not any other process.

Q. Do you know what solvent 3M and Par used in the stress test that we looked at a moment ago?

A. It used the same, the ethyl acetate.

Q. What was the next step?

THE COURT: Ms. Jacobsen, would this be a convenient time to take a break?

MS. JACOBSEN: Yes, Your Honor.

THE COURT: All right. Let's take a 15-minute break. And could I just ask the defendants, you know, I said at the pretrial conference, I was familiar with Dr. Davies and Dr. Klibanov, and so therefore, skip going through their background.

If you could get me the CVs of your three experts in advance of when they take the stand, then when you admit them, maybe we could skip over their backgrounds, too. Okay?

MR. BROWN: We can do that, Your Honor.

THE COURT: All right. We'll be in recess.

THE CLERK: All rise.

(A brief recess was taken.)

THE COURT: All right. You may all be seated. For what it's worth I'm going to try to go to about quarter of 1:00 for lunch. Okay?

MS. JACOBSEN: Thank you, Your Honor.

THE COURT: Good ahead, Ms. Jacobsen.

BY MS. JACOBSEN:

Q. Dr. Davies, before the break, we were about to move to the second step in your stress test. And can you please explain what that second step was?

A. Yes. The second step was to separate that stock solution into two parts. So the one I'm going to -- I have as a control one half I have as a control, the other half I have as the acetaldehyde. And the way I do that is that I dissolved acetaldehyde in the ethyl acetate solvent and I add it back to this half of the stock solution.

I then created a control by adding exactly the same amount of the solvent, ethyl acetate to the control so I maintained the concentrations between the two samples and the only difference between the two samples is the presence or absence of acetaldehyde.

Q. How much acetaldehyde did you add to the test samples?

A. I added approximately 0.0017 percent by

weight to the second mixture.

Q. What is the relevance of that amount of acetaldehyde in your stress test?

A. That is the level that was reported in Par's ANDA product, that's the reason why I chose that particular level.

Q. What was the next step?

A. I then separated each of the controls into three separate samples, label them C1, C2, C3. And I did the same for the acetaldehyde, I separated them into three samples labeling, A1, A2, A3.

I did that because I wanted to be sure that I was creating a statistically significant test so I could monitor the effect in triplicate measurements for each sample, so that I had undertaken an appropriate statistically significant experiment.

Q. And what did you do next?

A. What I did next is then I stressed those samples. And I stressed those samples at 60 degrees centigrade.

Q. Why did you use an elevated temperature?

A. I used an elevated temperature because in

preliminary experiments I had looked at room temperature, I looked at 40 degrees, I looked at 60 degrees, and I chose to use 60 degrees because that gave me the greatest amount, the largest amount of the oxidative degradation of the drug.

As you increase the temperature, you increase the rate at which the drug degrades, so over the time period of my experiment I was getting more degradation with the higher temperature than I was at 40 and with room temperature, and that's why I chose 60 degrees.

Q. Could you have used room temperature or 40 degrees Celsius for your stress test?

A. I could have, but that would taken longer, and the point of the stress test is that one can look at -- one can increase the rate of that degradation and look at it over a shorter period of time. The same mechanism, the same chemistries occur, although it's just occurring slower at lower temperatures, so you're seeing the same degradation product.

Q. Did you see enough degradation product at room temperature at 40 degrees Celsius to run the stress test in the time that you conducted your

stress test at?

A. I didn't think so, and that's why I chose the 60 degrees. I thought 60 degrees would be over the time frame that I wanted to run the experiment, and I thought that was appropriate, I thought it was sufficient at 60 degrees.

Q. Why was it appropriate to use a temperature that generated sufficient degradation?

A. Over the time scale of the experiment because I used that temperature, I saw as I will show you, I saw the same two key degradation products that one sees for oxidative degradation of rivastigmine, and I saw them in sufficient amounts over the time period of the experiment such that I could then compare the levels of those degradation products in the control sample without acetaldehyde and the samples with acetaldehyde, certain level you had to undertake that head to head stress test.

Q. Could you have done that comparison if you had not seen sufficient levels of degradation?

A. No, I could not have done that.

Q. And why not?

A. Because if you don't see sufficient levels of degradation, then you can't deduce whether or not that this head to head study, the only variable that's changing, the presence or absence of acetaldehyde, and you wouldn't be able to distinguish that affect whether or not acetaldehyde did indeed have an affect, did indeed prevent the oxidative degradation, you got to induce oxidative degradation before you can see the effect of reducing it.

Q. Are there examples in the literature of the use of peroxides at 60 degrees Celsius in stress tests?

A. There is a range of temperatures in the literature and 60 degrees falls within those ranges. So, for example, Alsante talks about peroxide stress testing ranging from room temperature to greater than 50 degrees centigrade. The Bianchini testing talks about room temperature up to 100 degrees centigrade. Singh talks about peroxide stress testing up to a hundred degrees centigrade. And the US patent '498 talks about taking stress testing up to around 60 degrees centigrade.

Q. And what oxidizing agent was used at 60 degrees Celsius in the '498 patent?

A. It's the same, the TBHP, the hydroperoxide that I used.

MS. JACOBSEN: Your Honor, plaintiffs introduce into evidence JTX 78.

MR. BROWN: No objection, Your Honor.

THE COURT: Admitted without objection.

MS. JACOBSEN: For the record, Dr. Davies referred to JTX 74 in column five lines 61 to 65, JTX 75 at page 68, JTX 77 at pages 1056 and 1058, and JTX 78 at page four.

BY MS. JACOBSEN:

Q. What was the next step, Dr. Davies?

A. The next step, once I incubated my samples, stressed them at 60 degrees C, I then took samples at key time points. I took samples at three time points, 6, 15 and 21 hours. I took the samples of those time points because I wanted to see what was happening to the oxidative degradation over a period of time. I wanted to see how the level of the degradation product was

changing as the function of time, over the time scale of my experiment.

I then wanted to see whether or not acetaldehyde had any influence over that as a function of time. My experiment was designed, the only differences, the presence of acetaldehyde.

So is acetaldehyde reducing the level of oxidative degradation products at 6, 15 and 21 hours across the board, that's what I wanted to see.

Q. Why did you choose those time points?

A. Those time points allow me to as I say, watch the change in the levels of the oxidative degradation as a function of time. They also allowed me to undertake a good statistical analysis of my data.

Q. And did you conduct any preliminary stress testing to determine whether those were appropriate time points?

A. Yes, I did. In my preliminary test, I looked at the -- I looked at I think up to around 14-and-a-half hours, and after -- with the three different temperatures, and I showed that up to

that time point I was getting sufficient degradation, so these three time points were good to use for my stress test as I will go on to show.

Q. Are there examples in the literature of stress tests conducted over this time period?

A. Yes, there are. So Alsante talks about maximum duration ranging from a day to seven days. Bianchini talks about stressing anywhere from 7.2 hours to 30 days. Singh talks about the API was stressed typically between one and 24 hours, so the time frame that I'm looking at is typical of what would be employed by scientists undertaking a stress test.

MS. JACOBSEN: For the record, Dr. Davies referred to JTX 75 at pages 67 to 68, JTX 77 at page 1058, and JTX 78 at page four.

BY MS. JACOBSEN:

Q. And what did you do with the samples that you collected at each time point?

A. What I did was I then used the technique of high performance liquid chromatography. High performance liquid chromatography is a standard technique used in the pharmaceutical industry to

separate and to identify and quantify the level of drug and drug degradation product.

Q. How does HPLC work?

A. HPLC or high performance liquid chromatography, this is very simple schematic to illustrate the point and I'll show a little video related to that.

You have a test sample, your test sample contains a mixture of compounds. That's injected into the HPLC system where it's carried along by fluid into an HPLC column. The HPLC column is designed to separate different components of the mixture. And these will come and pass through the column depending on how they interact with the column at different rates.

And then, they will be separated, come off the column and be detected in some way. In this case, I have used light, UV lights as a detection. And then what you see, you see is a chromatogram where the chromatogram is time as a function of coming off the column, and then detection is the level of detection in the UV detector.

A. And the time at which it comes off the column helps to identify the compounds as the level of detection, also helps you to understand how much is present in the sample. So if we run them in the video, here's a mixture. It separates it.

One comes off the column. You see it in this chromatogram. Next one comes off the column. You see it in the chromatogram.

Finally the last one comes off the column the slowest. You see this in the chromatogram. As I said, we can use the position that it comes off the column to help identify compounds.

We can use also the amount, the area or the peak helps you establish how much is present, sorry, coming off the column.

Q. And what did your HPLC results look like?

A. This is an example of an HPLC printout and it's taken from, excuse me, Control-2 sample at 21 hours. And here we have the chromatogram. We have time along here in minutes, time it takes to come off the column.

We have the response of the

detection shown here. We have three main peaks that I've highlighted.

The main peak in the center here is Rivastigmine. We're actually looking at the base of the peak. The peak actually extends beyond what I've shown here.

And on the side of that, we have a peak here, which is Impurity 4. There's a peak here, which is ECAV.

Now, how do I know each one of those is other chemicals that I've stated? Well, I have a standard for Rivastigmine and that standard comes off of this time point.

I also was able to obtain a standard for Impurity 4. And that, again, comes off -- the standard came off of this time port. So that's the standard where the scientists within the pharmaceutical industry use to establish the identity of the peak in this way.

I also then looked at this peak. I didn't have a standard for ECAV.

ECAV is -- excuse me. What I was able to do is take a UV spectrum of the compounds in that peak and the UV spectrum was identical to

the same UV spectrum undertaken by Par and their scientists. So that demonstrated to me that this was ECAV.

Now, this is one of my typical HPLC printouts and I just want to point something out. I'm seeing the drug and I'm seeing the two key degradation products in my stress test.

And the point of that -- this is the control and the point's sample. And the point I want to make is I've replicated what is known about the oxidative degradation of Rivastigmine.

I've replicated this in a way that I've identified the two key degradation products of Rivastigmine. So, in my stress test, I'm replicating what is known, the known mechanism for oxidative degradation of Rivastigmine.

Q. And the Rivastigmine and Impurity 4 standards that you referred to, was that something you were able to purchase?

A. That's correct.

Q. And do you understand that Dr. Ganem has asserted that other compounds could have been formed by side reactions with TBHP in your stress test?

A. That's correct.

Q. And do you agree?

A. I don't. Dr. Ganem doesn't go -- doesn't tell us what those compounds are equally. And I've shown in my test and my results. I've shown that I've identified two key degradation products of -- for the known -- for Rivastigmine undergoing oxidative degradation.

But I also undertook a mass-balance analysis where I, through that mass-balance analysis, that these three peaks account for over 99 percent of the peaks that come off the column. That demonstrates to me that I am looking at the two key degradation products and the drug in this analysis.

And as I will show you, those two key degradation products change as a function of time in a manner which is consistent with the oxidative degradation of Rivastigmine. So I don't think there's any basis for Dr. Ganem's position there could be other key degradation products formed. In fact, he doesn't identify what those are.

Q. And when you ran your stress test, what

did you observe?

A. When I ran my stress test, what I observed that, as a function of time in the control samples, the key degradation products increased as a function of time. When I compared those samples, control samples to the samples that contain acetaldehyde, I saw that, as a function of time, less of these impurities in degradation products were formed.

That demonstrates to me -- and I quite want to show statistically -- there's a statistical significance between the control and the acetaldehyde samples demonstrating that acetaldehyde is reducing the oxidative degradation of Rivastigmine.

Q. And --

A. I have a little figure to demonstrate that. Okay.

So this is the start point. And at the start point, you see there's the peak for Rivastigmine here. And I'm going to -- in this short video, I'm going to show -- I'm going to show the control samples in orange and the acetaldehyde samples in purple.

And for the purpose of this, I'm just going to overlay them, so you can see how they rise as a function of time. So if we start the video when you're ready.

If we go up, the -- the sample is taken up to the first time point at six minutes. And you see that there's a rise in the levels of these two impurities.

And the rise in the level of the two impurities is different for the control samples relative to the samples with acetaldehyde. The acetaldehyde samples are shown in purple. The control samples are shown in orange.

And you see that the control samples are higher than the levels reported for the samples with acetaldehyde actually if you look at the level of Rivastigmine. There's more Rivastigmine present in the sample shown here with acetaldehyde than there is without acetaldehyde.

If we continue onwards, this goes on to the 15-hour mark. And, again, you're seeing the same effect. You're seeing the difference becoming more pronounced.

You're seeing the level of the control are higher than that for the two key degradation products that acetaldehyde -- you're also seeing when one looks at the drug, you're seeing high levels of the drug relative to that with acetaldehyde present and then without.

If one continues onwards to the final time point, there's the 21 hours. You see that stark difference between the two sets of samples.

The control samples are higher in terms of the two impurities relative to that acetaldehyde sample. And the level of the drug is also higher, as one would expect, in the acetaldehyde sample, because the acetaldehyde compound is reducing the oxidative degradation of the drug.

Q. Thank you, Dr. Davies. I think you misspoke when you said the first time point was six minutes.

A. I thought I did. I apologize.

Q. Not at all. What was the first time point?

A. I wondered if I had said minutes. It's

six hours.

Q. Thank you.

Dr. Davies, can you summarize your test results?

A. Yes. This is a table where I tried to summarize the results and it does show the results.

These, I'm showing it in bar charts, and I've done it for the six-hour time, the 15-hour time and the 21-hour time. And in accordance with the bar chart for the six-hour time, what I've done is I've added together the percentages for the two key oxidative degradation products.

And, again, I've cut -- color-coded the two sets of samples. Orange is the control, the without acetaldehyde.

The purple is the control -- is the sample with acetaldehyde present in my head-to-head study.

And I've given you the total percentages here for comparison and I've done that for each of the time points. And as you can see, at each point, there's more of the

degradation compounds in the sample without acetaldehyde in the control sample.

There's less degradation products in each one of the samples with acetaldehyde. So there's direct evidence. There's only one variable occurring here, the presence or absence of acetaldehyde.

And it's showing in each case at each time point, there's less degradation products in the samples with acetaldehyde.

Q. And approximately how much less is there at each time point?

A. It's approximately 30 percent.

Q. Were you able to draw any conclusions from your test results?

A. Yes. I was able to draw the conclusion that acetaldehyde reduces -- is an agent which reduces the oxidative degradation. It confirms that acetaldehyde is an antioxidant.

Q. Did you measure whether there was any acetaldehyde left in your test samples after six, 15 and 21 hours?

A. No, I did not.

Q. And how did you know the reduction in

oxidative degradation was due to acetaldehyde?

A. Well, I know it because the data shows me. There's only one variable in play here, the presence or absence of acetaldehyde. And I designed the experiments in a way that I know acetaldehyde is a known reducing agent. Reducing agents can act as antioxidants.

My test clearly demonstrates that acetaldehyde is an antioxidant.

Q. And Dr. Davies, there is a notation on this slide, P less than 0.05 for all samples. What does that indicate?

A. What that indicates is that one could look at this data, as we have done, and you can consistently see that looking at the bar charts that there is always less in the samples with acetaldehyde relative to the control. But you can also undertake a statistical analysis. And I undertook a statistical analysis to see whether or not the data between these two sets of samples at each time point, does it come from the same population, or is it different. Can I say these two sets of data are statistically different.

So I ran what is called a two sample

T-test. This is a standard test used to look at, to see whether or not two samples are the same or are they different. And I showed that -- the P value here is the notation that's used. And I showed with my data, related to the probability and I showed in my data that there is 95 percent confidence that these two sets of data are different. So I have 95 percent confidence levels that the samples without acetaldehyde, the control samples, are different than the samples with acetaldehyde.

Q. Do you understand that Par's expert, Dr. Michniak-Kohn disagrees that your results are statistically significant?

A. Yes, I understand that. I don't think Dr. Michniak-Kohn disagreed with the use of the T-test. She just disagrees with the way in which I have undertaken that.

If we go to the next slide, I can explain that.

I undertook this test where I had used what is called a T-test, it's a one-tailed T-test. What that means is that you have some understanding of the test at the direction at

which the change may occur. So I had some expectation that acetaldehyde would either not or it would reduce the oxidative degradation of rivastigmine.

Now, I based that on my knowledge of the molecules -- of the reducing agent. That a reducing agent's known to act as an antioxidant. They reduce the level of oxidative degradation. Dr. Michniak-Kohn suggested that well, you can't assume that. She suggested that acetaldehyde could not only reduce -- that it not only reduces oxidative degradation, but it could increase the oxidative degradation, the so-called two-tail test.

I don't agree with that, but anyway I undertook that test. One undertakes that test where it could either decrease or increase the oxidative degradation. I get values of 90 -- greater than 90 percent confidence that the two sets of data are statistically significantly different.

Q. And what does that mean if you have 90 percent confidence that the two data sets are different?

A. It means that acetaldehyde is an antioxidant for rivastigmine using that approach.

Q. Have you seen any evidence that acetaldehyde can promote oxidative degradation?

A. No, I have not.

Q. Did you consider the Albano and McNesby articles raised by Dr. Ganem?

A. Yes, I did.

Q. Does the Albano reference teach that acetaldehyde promotes oxidation?

A. Well, this paper shows about the free radical activation of acetaldehyde and its role in protein alkylation. This is a process occurring in vivo in the body. And the acetaldehyde is oxidized using an enzyme, xanthine oxidase. Xanthine oxidase is a particular enzyme in the body that is known to change compounds such as acetaldehyde. And in the case of acetaldehyde forms -- that occurs in the body as an important process that occurs in the body in vivo. There is no xanthine oxidase in my test and there are no such conditions in my test.

Q. What about the McNesby article?

A. Yes, the McNesby article talks about when exposed to oxygen or air, an aldehyde is slowly oxidized to the corresponding peracid which further reacts with the aldehyde to form the normal acid and the peracid. But if you read further into the article, it talks about Kagan and Lubarksy were the first to isolate a complex using acetaldehyde and peracid, and their complex were stable at minus 30 degrees centigrade and decomposed to normal acid that would be acetic acid on heating or on treatment with catalyst.

So the point is this peracid of acetaldehyde is only stable at minus 30 degrees centigrade, it only exist at that temperature it doesn't exist at temperatures at say above that, so it's not relevant to this particular case.

Q. And is minus 30 degrees Celsius, do you know what that is in Fahrenheit?

A. I think it's -- I'm not really good on Fahrenheit, but I think it's around minus 20. Is that right? I'm not very good at that.

Q. If we go back to your statistical analysis, what happens if you run a two-tailed

T-test?

A. So if you run the two-tailed T-test, so if you run this two-tailed T-test where you don't -- you assume you go either reduce oxidation or increase oxidation, you get a confidence of greater than 90 percent that acetaldehyde is an antioxidant for rivastigmine.

Q. There is a reference there to unequal variance. What is that?

A. Yes, Dr. Michniak-Kohn suggested that I couldn't assume that the two sets of samples have equal variance. And here variance relates to this is a statistical term. It relates to the variation of the data around the mean.

Now, I actually set up my experiment in such a way that I used the same number of samples in each data set. I also only had one variable changing, the presence or absence of acetaldehyde. In such circumstances the use of equal variance is appropriate.

However, I did calculate based on the two-tailed test using unequal variance what the confidence would be, and it showed that the confidence would range from 87 to 94 percent

confidence that acetaldehyde is an antioxidant for rivastigmine.

Q. Did you confirm whether your assumption of equal variance was appropriate?

A. Yes. I did a further test called the statistical test called the F-test. Using the F-test you can test whether or not two sets of samples, whether the variances are equal or different. And again, using the F-test I was able to show that, in fact, the two sets of samples had equal variance.

Q. Did you draw any conclusion from that?

A. Yes. Sorry. I drew the conclusion that my use of equal variance is appropriate, and it showed that I was getting, even if I used the two-tail test which I don't think is appropriate, I was getting 90 percent or greater confidence that acetaldehyde is an antioxidant for rivastigmine.

Q. Did you conduct any other statistical analysis on your data?

A. I did. Then I went on to use the technique used linear regression analysis. In linear regression analysis it looks at the rate

in which the two sets of samples form the key degradation products. And it compares those rates using residuals. And when you use that approach, I found that I had greater than 99 percent confidence that acetaldehyde is an antioxidant for rivastigmine, whether I used a one-tail or a two-tail approach.

Q. Dr. Davies, can you please turn to tab 19 in your witness book. And there you will find JTX 66.

A. Yes. That's appendix E from my opening report, describing my stress test.

MS. JACOBSEN: Your Honor, plaintiffs move to introduce JTX 66 into evidence. I believe there was an objection, but I think we have resolved it.

MR. BROWN: Yes, Your Honor, we will not object to this coming in for the data that's in it as long as it doesn't come in for the opinions that are provided in it. And we have conditioned that on Novartis also introducing into evidence an underlying laboratory notebook and some underlying raw HPLC data, as long as it all comes in.

THE COURT: So basically the numbers are in, the opinions are not.

MR. BROWN: Correct.

THE COURT: Okay. It's admitted with that stipulation.

MS. JACOBSEN: Thank you, Your Honor.

MS. JACOBSEN: Thank you, Your Honor.

BY MS. JACOBSEN:

Q. And, Dr. Davies, can you turn to Tab 20 in your witness book? And there you'll find PTX 103.

A. Yes. That's my laboratory notebook and also some -- the HPLC column chromatograms column.

Q. Is that the data underlying stress tests and the data in Appendix E that we just looked at, JTX 66?

A. That's correct.

MS. JACOBSEN: And, Your Honor, plaintiff would move to introduce into evidence PTX 103.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. And then, Dr. Davies, can you please turn to Tab 43 of your witness book? It should be the last tab.

And you should have JTX 170.

A. Yes.

Q. Do you recognize that document?

A. This is my laboratory notebook.

MS. JACOBSEN: And, Your Honor, plaintiffs move to introduce JTX 170 into evidence.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. And then, Dr. Davies, can you please turn to Tab 21 of your witness book? And there you'll find PTX 365.

A. Yes. This is the -- this is a copy of the slide that we were just looking at of the stress test confirming acetaldehyde is an antioxidant.

MS. JACOBSEN: And, Your Honor,

plaintiffs move to introduce into evidence PTX 365.

MR. BROWN: Your Honor, we object to this as an improper summary. It contains, among other things, opinions about the list of statistical significance. And the way the data is presented, we move is argumentative.

And while we wouldn't object to a proper summary, but we do object to this data.

THE COURT: Ms. Jacobsen.

MS. JACOBSEN: It's a summary chart of and you see a great deal of numbers and raw data that are provided in Dr. Davies' Appendix E from his report. The data is just reporting the numbers, and the statistical notation is reporting the results of Dr. Davies' test.

THE COURT: All right. Well, I'm going to sustain the objection. I will submit it as a court exhibit, so there is a demonstrative exhibit in the record.

It seems to me that Dr. Davies has essentially testified at one time or another to all of these numbers, so I think, I don't know, by not having this as an exhibit, I don't think

you're actually losing anything.

MS. JACOBSEN: We haven't read all the percentages into the record and that would be a way of providing all of those percentages to the Court.

MR. BROWN: Your Honor, the Appendix E exhibit that we talked about a minute ago provides all of the data and in a convenient chart form. This is not providing a summary of the data.

The data is readily readable within that document.

THE COURT: I presume you've looked and saw the numbers that are actually in this exhibit that are, in fact, reflected in the record somewhere.

MR. BROWN: I believe. Well, the numbers that are not reflected in the record somewhere are the totals, the 2.49 and the 3.55. He didn't provide those in his report.

THE COURT: That's the total. But, for example, the 2.49, the 1.57 and the 0.92 are in the record?

MR. BROWN: Those are in the record.

THE COURT: I can understand I can get the 2.49 from those two numbers. Okay. So I think we're arguing about something that's actually not terribly important here.

So let's move it on. But I will sustain the objection to it coming in as having some independent value.

MS. JACOBSEN: Thank you, Your Honor.

BY MS. JACOBSEN:

Q. So, Dr. Davies, before we move on, can you briefly summarize your opinions with respect to the first issue, which is whether acetaldehyde is an antioxidant?

A. Yes. I believe acetaldehyde is an agent which reduces oxidative degradation.

I believe my test has shown that and I believe acetaldehyde is an antioxidant. That confirms the literature that I have cited in terms of acetaldehyde being a reducing agent. Reducing agent is a known antioxidant.

Q. Dr. Davies, did you perform any stress testing on Par's ANDA products?

A. No, I did not.

Q. Why not?

A. I was not able to do that because, in my test, I was able to perform a head-to-head test where there's only one variable change. But in Par's ANDA products, I wasn't able to obtain a product where I was able to compare products with and without acetaldehyde where that was the only variable that they would be changing.

Q. And why were you not able to obtain that product?

A. Because I wasn't able to obtain products where they were adhesive, for instance, with and without acetaldehyde. I wasn't able to obtain those products.

I was also not able to make the products. The only people who could actually make those products is Par with or without the presence of acetaldehyde, keeping everything else the same.

Q. And, Dr. Davies, did you consider Par's stability data relating to the ANDA products?

A. I did.

Q. And what data did you consider?

A. I considered the data performed, their

accelerated stability and also their long-term stability studies on their batches.

Q. And which batches did you consider?

A. There were nine of them. One of the batches, they didn't test for acetaldehyde.

There were two of the batches where it was said there is none detected meaning below limits of detection of acetaldehyde. And there was six batches where they did detect acetaldehyde.

Q. And what do you understand Par's position to be with respect to this data?

A. I believe Par's position is -- I believe their expert, Dr. Buckton believes that if you compare the level of the degradation products in Par's ANDA batches, those batches which contain no acetaldehyde and compared to the levels of degradation products with those that do contain acetaldehyde, he believes you can conclude that, in fact, acetaldehyde is not an agent to reduce oxidative degradation.

Q. And you mentioned batches of Par's ANDA products where there was no acetaldehyde?

A. Sorry. Non-detectable.

Q. And do you agree with Dr. Buckton's opinion with respect to this data?

A. I don't because I don't think you can make that determination. There are two reasons why I believe that's the case.

The first reason is important is that you can't set up this head-to-head study where the only variable changing is acetaldehyde. There's nine different batches.

The different components of those batches, the dry adhesive, the tackifier, et cetera, there's no batch that's made with the same components. Different -- different lot numbers are used. Different lots of the components are used to make those batches.

Because of that batch-to-batch variation in the lots used for the different components, there are other variables in play. So, therefore, you can't say, based on that, that -- you can't exclude the effect of other components on the degradation properties that are formed.

Q. And can you illustrate that point by reference to the next slide?

A. Yeah. I have a slide which illustrates that point.

This is a very bright, colorful slide, but I've done it to illustrate a point. What I've done is that I've shown here the ANDA batch numbers shown here. And on the right-hand side, I'm showing this is the batch where acetaldehyde was not tested.

There's a line drawn and then there's two batches here. These are batches where acetaldehyde is not detected.

And then, finally, below that further line, these are the batches where acetaldehyde is detected. Now, what I've done, I'm just showing here the backing layer, the drug-in-adhesive layer and the release liner.

And within the drug-in-adhesive layer, I'm showing three key components: The adhesive, the Rivastigmine, the tackifier.

And what I've done is I'm showing here lot numbers of the components. I'll highlight on the drug adhesive layer.

And I've given each lot number, a combination of lot numbers or different color.

And if you just look at the colors to illustrate the point, no batch is made with the same combination across the board for the backing layer right through the release liner.

No batch is made with the same combination of colors. And that illustrates the point. There's batch-to-batch variability in the lots that are used to manufacture the product.

So, for this reason, that one cannot -- and it's for this reason that one cannot use -- rule out the effect on the variation in the lots used to manufacture the product of the data.

Q. And, Dr. Davies, can you please turn to Tab 24 of your witness book. You'll find PTX 364.

A. Yes. This is the table from which these lot numbers are drawn. And that's correct.

MS. JACOBSEN: And, Your Honor, plaintiff's move to introduce into evidence PTX 364.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

MS. JACOBSEN: And for the record,

Dr. Davies is referring to PTX 364 discussing the batch variability. And the information on this slide also comes from JTX 180, JTX 181, JTX 192, JTX 197, JTX 198, JTX 199, PTX 352 and PTX 353.

BY MS. JACOBSEN:

Q. And, Dr. Davies, why was the batch-to-batch variability relevant to your analysis?

A. It's relevant to my analysis because of that batch-to-batch variability. You cannot conclude from the stability data that acetaldehyde is not an agent that reduces oxidative degradation.

Because of this batch-to-batch variability, there are multiple variables at play here. So, for that reason, you cannot draw that conclusion.

Q. And is there any batch in which acetaldehyde was not detected that is made with the same components as one made with one in which acetaldehyde was detected?

A. Yes. If one looks at -- I'll show this, if one looks at these top two batches, here, you see --

Q. Dr. Davies, sorry to interrupt you, but I think you misheard my question. Can we just go back to the previous slide just so we're clear. And I was asking you about the batches with acetaldehyde not detected, and acetaldehyde detected.

And is there any batch made with the same components or any two batches made with the same component one in which acetaldehyde was detected and one in which acetaldehyde was not detected?

A. There is no -- for these two sets, if we look at the colors, it illustrates the point as I have said before, that no batch has been made with the same combination of lot numbers. That's important. That's important because it shows that there is batch-to-batch variable in the lots that one uses, therefore, in the samples which have been tested for acetaldehyde, therefore, one cannot use this information -- there are other variables that are going to be in play that can influence the interpretation of the stability data. It's not a direct head-to-head comparison.

Q. Thank you, Dr. Davies.

And other than the batch-to-batch variability, is there any other reason that you disagree with Par's position regarding its stability data?

A. Yes. If one looks at -- I was going to talk about it. If one looks at these two, top two patches, if we move to the next slide I'll explain it. If you look at these top two patches, these are patches which are produced wherein this case they do have the same combination of lots for the drug-in-adhesive layer, all be it, that one of them, acetaldehyde was not tested.

Now, if you look at the stability of these two, these are made with exactly the same ingredients that I have shown, if you look at that stability data, for the 110177, you get for the two impurities values of .2 which is a total of .4 over a six-month period.

If you look at the 110110 lot, you getting values of less than .1.

Now, that's important because that's illustrating the point. Even with the same level, same -- using the same lots, we're getting

batch-to-batch variability of the components in terms of their stability.

There is also another important point to make here is that these values as shown here actually come from a single patch. And if I go to my next slide I'll show that point.

Only one patch is used to determine degradation products. So you can see here it talks about the impurities and the method test one patch so here you have the data that's generated for the stability data is simply from one patch out of the thousands that are in that particular batch.

In that case, I don't think you can use the data from one patch. Together with my concerns of the lot variability, you can't use that information to draw conclusions about whether acetaldehyde is acting to reduce the oxidative degradation, or is an antioxidant in Par's products.

MS. JACOBSEN: Your Honor, for the record, Dr. Davies referred to PTX 348, page 778, PTX 349 at page 786, and PTX 350 at page 796. And those are the excerpts from Par's ANDA

specifications. And I'm told I misspoke. The reference to PTX 350 was page 794. Dr. Davies also referred to the stability data.

BY MS. JACOBSEN:

Q. And Dr. Davies, if you can turn to tab 25 in your witness book, can you identify that document?

A. Yes, this is a portion of 3M's documents, again, part of their ANDA highlighting stability.

Q. Was that the data that you relied on in preparing the slide on patch-to-patch variability?

A. That's correct.

MS. JACOBSEN: Your Honor, plaintiffs move to introduce into evidence JTX 200.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

MS. JACOBSEN: For the record, Dr. Davies referred to JTX 200 at pages 3M 9355 and 3M 9357.

BY MS. JACOBSEN:

Q. Dr. Davies, let's move to the second

issue, whether Par's ANDA describes products that contain about .01 to about 0.5 percent by weight of an antioxidant.

Can you explain the dispute with respect to this claim element?

A. Yes. The dispute is whether or not the acetaldehyde that's present in Par's product falls within that claimed range.

Q. And does it?

A. It does based on the specification that Par sets for acetaldehyde, the specification states that there could be up to a thousand parts per million which is .1 percent by weight.

Q. Did you compare the amount in Par's specification with the '031 patent?

A. Yes, I did.

As I said, Paris shown on the left on this slide, Par's own specification permits not more than a thousand parts per million or 0.1 percent by weight of acetaldehyde. If you think, that falls within the range of the '031 patent claim of about 0.01 to about 0.5 percent by weight of an antioxidant.

Q. What amounts that are permitted by Par's

ANDA specification fall within the claim range of about 0.01 to about 0.5 percent by weight?

A. That would fall -- that would be from a hundred to a thousand parts per million.

Q. And what's that in weight percent?

A. That is 0.01 to 0.1 percent by weight.

MS. JACOBSEN: For the record, Dr. Davies referred to JTX 1, that's the '031 patent, and PTX 348, page 780, 349 and 788, 350, and 796?

Q. And Dr. Davies, in providing your answer of what amounts within Par's ANDA specification fall within the claim range, were you also considering in that answer the claim, scope of the claim term about, or was that leaving that aside?

A. Leaving that aside.

Q. And on Par's ANDA specification submitted to the FDA?

A. Yes, they were.

Q. What was the basis for Par's ANDA specification for acetaldehyde?

A. The basis was a scientific evaluation of the acetaldehyde and also measurements of the

levels in prototype batches and what amount of acetaldehyde were observed in Par's prototypes.

As this slide shows, in the prototype patches they measured up to 402 parts per million for one patch, and 224 parts per million for others. That's 0.04 and 0.02 percent by weight.

Q. And Dr. Davies, could you please turn to tab 26 in your witness binder where you'll find JTX 65?

A. Yes.

Q. Can you identify that document?

A. Yes, this is the document from which the table is drawn.

MS. JACOBSEN: Your Honor, plaintiffs move to introduce into evidence JTX 65.

MR. BROWN: No objection.

THE COURT: All right. Admitted without objection.

MS. JACOBSEN: For the record, Dr. Davies referred to JTX 65 at page 721.

BY MS. JACOBSEN:

Q. Dr. Davies, earlier you mentioned that 3M

detected the presence of acetaldehyde in Par's ANDA products. What did they report?

A. Yes. This is a slide that I prepared to show the acetaldehyde content in Par's representative ANDA batches. I'm showing it for the three dosing strengths. Two of the batches they had levels that were not detected. The remainder, six batches show levels ranging from eight through to 30 parts per million of acetaldehyde.

Q. And if Par gains FDA approval, is 300 -- sorry, is 30 parts per million the maximum amount of acetaldehyde that Par's ANDA products are permitted to contain?

A. No. If they gain FDA approval, they would be able to manufacture batches up to a thousand parts per million. That is up to .1 percent by weight.

MS. JACOBSEN: And Your Honor, for the record, Dr. Davies referred to JTX 180, 181, 196, 197, 198, 199, and PTX 352 and 353. And Your Honor, we move to introduce those exhibits into evidence.

MR. BROWN: No objection, Your

Honor.

THE COURT: All right. So those eight exhibits are admitted without objection.

BY MS. JACOBSEN:

Q. Dr. Davies, can you summarize your opinions relating to whether Par's ANDA products meet the disputed elements of Claim 7?

A. I believe I have shown through my analysis of my tests that Par's ANDA products contain an antioxidant acetaldehyde, and I believe that acetaldehyde in Par's ANDA product is present within the claimed ranges of 0.01 to about 0.5 percent by weight.

Q. Thank you.

Dr. Davies, I would like to turn now to the claim elements that are not in serious disputed.

MS. JACOBSEN: Unfortunately we stipulate that Par stipulated to infringement as Your Honor requested that the parties meet and we weren't able to reach an agreement so we'll make this as quick as possible.

THE COURT: All right.

BY MS. JACOBSEN:

Q. So starting with the first claim element, a transdermal device, under the parties' agreed upon construction, are Par's ANDA products transdermal devices?

A. Yes. It's a medical device for systemic drug administration through intact skin. Par's product clearly is a transdermal device, a device that's meant to be applied to the skin with a systemic drug administration through the skin.

Q. Can you turn to tab 27, PTX 343. Do you recognize that document?

A. Yes. It's the patient prescribing information that shows at the top there, a transdermal system.

MS. JACOBSEN: Your Honor plaintiffs move to introduce into evidence PTX 343.

MR. BROWN: No objection.

THE COURT: Admitted without objection.

BY MS. JACOBSEN:

Q. And then the next claim element is a pharmaceutical composition and do Par ANDA products contain a pharmaceutical composition under the agreed upon construction of that term?

A. Yes, it is, it's a composition suitable for pharmaceutical use. Par represents that it submitted to the FDA ANDA information which, it's about a product that's suitable for pharmaceutical use, for the treatment of patients.

Q. And then the next element, therapeutically effective amount of rivastigmine, is one of those present in Par's ANDA products?

A. Yes. It's an amount sufficient to produce the desired therapeutic effect. Par has represented to the FDA that the dose is suitable for treatment of dementia, Alzheimer and associated with Parkinson's disease, of those three dosage strengths.

Q. The next element is a diluent or carrier. Do Parties' ANDA products contain a diluent or carrier under the Par's agreed upon construction?

A. Yes. The inactive ingredient aids in the administration of the drug. It contains an adhesive. The adhesive is highlighted in the patent as a diluent or carrier.

Q. And how does the adhesive aid in the

administration of Rivastigmine in Par's ANDA products?

A. It aids in the administration because the drug is contained within the adhesive and the drug is released from the adhesive into the skin and for systemic circulation.

Q. And then the last element is: Did Par's ANDA products meet the limitation: Wherein the pharmaceutical composition is supported by a substrate?

A. That is supported structurally. The pharmaceutic backing layer providing structural support for the pharmaceutical. Par's patch has a backing layer.

Q. And does that backing layer provide structural support?

A. It does.

MS. JACOBSEN: Thank you, Dr. Davies. We have no more questions at this time.

THE COURT: All right. Thank you.

Mr. Brown.

MR. BROWN: We have some binders and things to hand up, Your Honor.

THE COURT: Surely.

MR. FINEMAN: Your Honor, permission to approach?

THE COURT: Sure.

MR. BROWN: Permission to approach the witness, Your Honor?

THE COURT: Sure. Yes.

CROSS-EXAMINATION

BY MR. BROWN:

Q. Good morning, Dr. Davies.

A. Good morning to you.

Q. I'm Dan Brown. We met at your deposition.

I'm representing Par. I have a few questions to ask you today regarding your testimony on direct.

You just testified on direct examination that part of your basis for concluding that acetaldehyde is an antioxidant is that it is, in your words, a known reducing agent; correct?

A. That's correct.

Q. And I'd like to turn to Exhibit JTX 060. It's one of the binders that we provided to you.

Doctor, it's one that has JTX exhibits in it. Can you find JTX 060?

And this is the Van Nostrand dictionary that you cited in support of your assertion that acetaldehyde is a known reducing agent. And can we have that entry blown up on the screen, please?

A. I don't seem to have it.

MR. KALLAS: We don't have it, either.

BY MR. BROWN:

Q. In that case, I'll just go to -- can I have Davies' Slide 8 up?

And this is a slide that you used on direct examination for JTX 061, which is Van Nostrand's Concise Encyclopedia of Science.

And am I correct that Van Nostrand's Concise Encyclopedia of Science, despite referring to acetaldehyde as a reducing agent, never uses the term antioxidant to refer to acetaldehyde?

A. That's correct.

Q. And if you could also turn in your original binder that you used on direct examination to Tab 10, which is JTX 063.

And I'd like to have actually

Davies' Slide 12 up. And that is the Specialty Chemicals Sourcebook that you relied on on direct examination; correct?

A. That's correct.

Q. And despite limited -- despite enumerating a variety of possible uses for acetaldehyde here, the Specialty Chemicals Sourcebook does not identify acetaldehyde as an antioxidant; correct?

A. That's correct.

Q. And, Dr. Davies, if I see a particular chemical compound referred to in the literature as a reducing agent, isn't it correct that you have no opinion as to whether that means it's an antioxidant?

A. I believe -- I think I've said in my depositions, it can be an antioxidant. Correct.

Q. Well, Dr. Davies, without conducting an experiment on a reducing agent, you don't know whether it's an antioxidant or a prooxidant; correct?

A. I'm not sure that's correct.

Q. Well, you don't have an opinion, one way or the other; correct?

A. Well, for acetaldehyde, I certainly do.

Acetaldehyde is a reducing agent, a known reducing agent. And I've shown that it is an antioxidant.

Q. My question is more general. It relates to the relationship between reducing agents and antioxidants. And if I see a compound referred to in the literature as a reducing agent, without conducting an experiment, you don't have an opinion, one way or the other, about whether that compound going to be an antioxidant or a prooxidant; correct?

A. I think, as I've said, reducing agents can be antioxidants, as I've said it at my deposition.

Q. Can they also be prooxidants?

A. I don't think so, in the context of the work that I've undertaken here. No.

Q. Well, Doctor, could you find your deposition transcript in front of you? You recall when I took your deposition in this matter and I'd like you to find the June 5th version of your deposition transcript and go to Page 177.

A. Thank you.

Q. And I'm reading from Page 177, Lines 5 to

19. And the question: "So, before you conduct -- let me start over. Before you conduct any experiment on a reducing agent, can you determine whether it is an antioxidant or a prooxidant?

"Answer: Again, I have not been asked to consider that in the context of what I did. You're talking very generally there. But in the context of what I did, acetaldehyde, a known reducing agent, which is subject to oxidation-reducing agents known to be antioxidants in the context of my experiment, I had every expectation that acetaldehyde would act as an antioxidant and I've shown that."

Was that the correct question and answer?

A. That's correct.

Q. And while you have provided an opinion that acetaldehyde is a known reducing agent, you also have no opinion about whether it is a known oxidizing agent; correct?

A. Well, it depends what you mean by opinion. In the context of the work I've done, I believe it's a reducing agent.

Q. But you don't have an opinion about

whether it's also a known oxidizing agent; correct?

A. You mean as a prooxidant; I don't believe it is in the context of the work.

Q. Well, if you can turn ahead in your June 5th deposition transcript to Page 180.

And I'm reading from Page 180, Line 14.

"Question: Are there different conditions under which acetaldehyde is a known oxidizing agent that is subject to being reduced?

"Answer: Again, you know, I've not been asked to consider that. I have been asked to consider the conditions, the kind of conditions that the stress test, which demonstrates the acetaldehyde, a known reducing agent acts as an antioxidant that is susceptible to oxidization and that is able to inhibit the degradation of Rivastigmine in an oxidizing environment."

So as of the day of your deposition, you did not have an opinion about whether acetaldehyde is also a known oxidizing agent; correct?

A. I wasn't asked to consider that. That's correct.

MS. JACOBSEN: Sorry. I object.

That was an incomplete -- the previous question and answer of Dr. Davies' deposition was specifically on this topic, and he gave complete answers. And the two questions -- and Mr. Brown didn't show the Court those.

THE COURT: I'm sorry. Your objection is?

MS. JACOBSEN: That was an incomplete part of the deposition testimony. The previous question and answer addresses this issue.

THE COURT: All right. Well, on -- actually why don't we take care of this now. Can you ask him about the previous question and answer?

MR. BROWN: Certainly, Your Honor.

MS. JACOBSEN: Page 80, Lines 5 to 13.

BY MR. BROWN:

Q. And from Page 180, Lines 5 to 13.

"Question: Is acetaldehyde also a

known oxidizing agent that is subject to being reduced?

"Answer: Acetaldehyde is a known reducing agent that is susceptible to oxidation in the context of the work that we're doing here in the context of this experiment. I have shown that and proven it -- that it acts as an antioxidant in the context of the work of my experiments."

THE COURT: All right. For what it's worth, I don't actually think that needed to be read to be complete, but it also causes no harm.

Go ahead, Mr. Brown.

BY MR. BROWN:

Q. I'd like you to turn to JTX 1, the '031 patent. Now, you studied this patent carefully in forming your opinions in this case; am I correct?

A. Correct.

Q. And I'd like to put up a section of the patent. This is at Column 4, Lines 10 to 19. And this is the section of the patent where they list the particular antioxidants that they

describe. And I'd like to look at the first compounds listed here as an antioxidant tocopherol acetate.

You agree that tocopherol acetate is an antioxidant; correct?

A. It's listed in the patent. Correct.

Q. But you don't have any opinion as to whether it's a reducing agent; correct?

A. I don't believe it is an reducing agent.

Q. At the time of your deposition, you didn't have an opinion, one way or the other; correct?

A. That's correct.

Q. And looking at this list of antioxidants, I'd next like to focus on ascorbyl palmitate. Ascorbyl palmitate being listed as an antioxidant, you have no opinion whether ascorbyl palmitate would increase the oxidative degradation of acetaldehyde in a transdermal patch, isn't that correct?

A. I do. It depends which patch you're talking about.

Q. In any rivastigmine transdermal patch, do you have an opinion one way or the other whether adding ascorbyl palmitate could cause an increase

in oxidative degradation in that patch?

A. I have an opinion based on the reading of the patent that ascorbyl palmitate will act as an antioxidant to reduce oxidative degradation.

Q. Let's look at page 161 of your June 5th deposition transcript. And I'm reading from page 161 line 15 to page 162 line nine.

"QUESTION: Is it possible for ascorbyl palmitate to increase the oxidation of an active ingredient in a particular pharmaceutical formulation?

"ANSWER: Again, I have not been asked to consider that. I have not considered that. That's not what I was asked to do, but I believe Dr. Klibanov has talked at length about these things. Please tell me, give me an example, show me.

"QUESTION: Well, is it possible that ascorbyl palmitate even though it's listed here as an antioxidant could increase the oxidation of rivastigmine and a transdermal patch.

"ANSWER: Again, I have not been asked to give an opinion on that."

That was your answer; correct?

A. You read it correct, but what you said summarized what I just said, you're asking me very general questions. You're asking me about a specific issue, but I go on to talk about if you go read down page 162, the patent is teaching me, the patent is teaching me that, so it's clear that I'm relying on the patent to teach you that, and the antioxidants that are listed in this list, you are trying to steer me to some other issue, but I didn't know what you were talking about.

Q. Dr. Davies, if you continue on to the next page at the top, line three to ten:

"QUESTION: So based on that teaching, if I put ascorbyl palmitate into a formulation, is it possible that the ascorbyl palmitate will increase the oxidation of rivastigmine?

"ANSWER: Again, you have asked me this before, and I say I have not been asked to consider that."

Isn't that, in fact, the answer you gave me?

A. Yes. And I also said it's a very really

vague question, doesn't make sense, based on the teaching of the patent. I go on to say the patent clearly teaches you that antioxidants can have a positive effect on these two formulations. That's what I say. And you go on to ask me that question over and over again.

Q. Doctor, I would like now to go to DTX 526. And this is Van Nostrand's Encyclopedia of Chemistry. You're familiar with this reference; correct?

Let me know when you find it. And I want to blow up an entry that's on the bottom second column and going to the first line of the second page. Can you pull that up, Bill. And I want to read this section into the record.

An antioxidant ties up the peroxy radicals so that they are incapable of propagating the reaction chain or to decompose the hydroperoxides in such a manner that carbonyl groups and additional free radicals are not formed. The former, which are called chain-breaking antioxidants, free-radical scavengers, or inhibitors, are usually hindered phenols or amines. The latter, called peroxide

decomposers, are generally sulfur compounds or organophosphites.

I just have a few questions for you about this discussion. Now, alpha-tocopherol is a well-known antioxidant; correct?

A. I'm sorry.

Q. Alpha-tocopherol is a well-known antioxidant; correct?

A. It's listed in the patent.

Q. That's one of the categories of antioxidants Dr. Klibanov testified in the Watson trial was a quintessential antioxidant; right?

A. I don't recall him saying that.

Q. Well, alpha-tocopherol is the only antioxidant for which there is data provided in the '031 patent; correct?

A. I believe that's correct, specific data, but the patent talks about the range of antioxidants.

Q. But the data all comes from alpha-tocopherol; correct?

A. I believe that's correct.

Q. And isn't it correct that you have no opinion about whether alpha-tocopherol is a

hindered phenyl or an amine?

A. I believe it is, yeah, based on my definition, that's correct.

Q. And, in fact, you have no opinion about whether alpha-tocopherol functions as an antioxidant by working as a free radical scavenger or by working as a peroxide decomposer; isn't that correct?

A. Based on my deposition, I believe it is a free radical scavenger.

Q. That's a opinion you didn't have at your deposition that you have today?

A. That's correct, I was tired, correct.

Q. And, in fact, for the list of compounds in the '031 patent that we looked at a few minutes ago at column four, lines 11 to 19, going down that list, you haven't formed an opinion as to whether each one of those compounds would be a hindered phenyl, an amine, a sulphur compound or an organophosphites, isn't that correct?

A. I wasn't asked, correct.

Q. Dr. Davies, I would like to ask you some questions about first about the experiment that you conducted that you testified about on direct

examination, JTX 66. Can you find JTX 66, Dr. Davies?

A. I don't have it.

MR. BROWN: Permission to approach.

THE COURT: Yes.

BY MR. BROWN:

Q. Dr. Davies, you agree that this type of test that's reported here in JTX 66 can be referred to as a forced degradation study?

A. Yes.

Q. And you also refer to it as a stress test; correct?

A. Sorry, I apologize. It's known as a forced degradation study as well as a stress test; correct.

Q. And Dr. Davies, isn't it true that you are not aware of a single instance in the published literature where a forced degradation study was used to evaluate whether a particular chemical compound served as an antioxidant in a finished pharmaceutical dosage form?

A. I disagree.

Q. Well, Dr. Davies, do you recall at your deposition that I asked you several times to

identify any literature reference of which you are aware in which a forced degradation study was used to evaluate whether or not a particular compound served as an antioxidant?

A. I do, and I replied at length. I replied that I rely on the literature that I cited in my reports. I talked about it at length.

Q. Do you recall that I asked you to prepare a list for me of every published literature reference of which you were aware that described using a forced degradation study to evaluate whether a compound was an antioxidant?

A. I do, indeed.

Q. And could you turn to DTX 105, which is Davies 17.

Now, Dr. Davies, DTX 105 is, in fact, a list you prepared for me at the deposition of every literature reference of which you are aware where a forced degradation study was used to evaluate whether a compound was an antioxidant; correct?

A. This is the sheet. As I told you at the time, I provided a list of -- I provided many references which I relied on in my reports. I

told you at the time and on a number of occasions on a repeated questioning that I relied on those papers from my reports.

MR. BROWN: Your Honor, Par would move to admit DTX 105 into evidence.

MS. JACOBSEN: No objection.

THE COURT: Admitted without objection.

BY MR. BROWN:

Q. Can you give me a citation right now, Doctor?

A. I can give you examples that I described in my reports and depositions, the example, the example of the Alsante.

Q. Thank you, Doctor. We'll get to that in a minute.

Now, I would like to look for a minute at JTX 1, the '031 patent, at column four, line 20 to 30. And now here, Doctor, am I correct that the '031 patent describes conditions for two stress tests?

A. I'm sorry, I didn't hear you.

Q. Am I correct that this section of the '031 patent, column four, lines 20 to 30, describes

two different sets of conditions for stress tests; correct?

A. That's correct.

Q. One of those tests was conducted at three months at 40 degrees C and 75 percent room humidity; correct?

A. Correct.

Q. And the other test was run for two months at 60 degrees C; correct?

A. Correct.

Q. And both of these tests were conducted on quote, the pharmaceutical composition of the present invention; correct?

A. That's correct.

Q. Now, I would like to refer now back to JTX 66. Your forced degradation study. You were the person who designed this forced degradation study; correct?

A. I was.

Q. And in addition to the forced degradation study, you have done a total of two other tests that you relied on over the course of this action for your opinions regarding Par's ANDA products; correct?

A. You mean the peroxide and the oxygen level?

Q. That's exactly what I mean.

A. I see. Okay. Yes, correct.

Q. And the peroxide value test and the oxygen saturation test, are those the two tests you're referring to?

A. I believe so.

Q. And you designed and conducted the peroxide value test and the oxygen saturation test in February of 2013 in response to opinions that Par's experts provided in the case; correct?

A. That's correct.

Q. And could you please turn to DTX 111. And DTX 111 is the laboratory notebook work -- let me restate the question.

DTX 111 is the laboratory notebook that reports all of the work done in connection with the peroxide value test and the oxygen saturation tests that you conducted in February of 2013; correct?

A. I believe that's the case.

MR. BROWN: Par would move to admit DTX 111.

MS. JACOBSEN: No objection.

THE COURT: Admitted without objection.

MS. JACOBSEN: No objection.

THE COURT: Admitted without objection.

BY MR. BROWN:

Q. Now, if you could now turn to JTX 170 in your binder.

Now, JTX 170 is the laboratory notebook that records the laboratory work that went into your forced degradation study that we looked at at JTX 066; correct?

A. I'm sorry. I'm trying to find it.

That's correct.

Q. And the cover, the date on the cover of this notebook tells you that it was generated on October 29th, 2012; correct?

A. Correct.

Q. So I'm going to start a timeline that we've put together and I want to put that date up on the timeline.

MR. BROWN: So, Bill, can you put up the timeline with that date showing?

BY MR. BROWN:

Q. Now, it didn't take you very long to design the forced degradation study; correct?

A. In what sense? Once I decided to do that test, correct. About a week.

Q. And in your opinions in this case regarding the forced degradation study, JTX 066, you were not relying on any testing that you or anyone on your behalf conducted prior to October 29th, 2012; correct?

A. No, I'm not.

Q. And when you designed the forced degradation study, you expected that it would take about a week or so; correct?

A. That's correct. When I made that decision to do it, yes.

Q. And the process of conducting the experimental testing for the forced degradation study took about ten days running from October 29th to November 7th, 2012; correct?

A. Correct. That's running the experiment. Then I had to analyze the data.

Q. So I want to add that November 7th date to our timeline. Now, the Rivastigmine active

ingredient that you used in the forced degradation study was shipped directly to you in the United Kingdom from the 3M Company; correct?

A. That's correct.

Q. And if you could find JTX 33. JTX 33 is a chain of custody document that you prepared in this case; correct?

A. That's correct.

Q. And if you could turn to Page 4, there's a section entitled Actavis' Rivastigmine sample. Do you see that?

A. That's correct.

Q. And you understand that Par now owns the ANDA that previously belonged to Actavis; correct?

A. That's correct.

Q. And so this chain of custody document demonstrates that you received the sample of Rivastigmine active ingredient from 3M on September 10th, 2012; correct?

A. That's correct.

Q. And I'd like to put that date onto the timeline. And after you received the sample on September 10th, you stored that sample at

Molecular Profiles until you used it beginning around October 29th; correct?

A. That's correct.

Q. Now, in addition to the Rivastigmine active ingredient that you received on September 10th, you received a number of other samples in this matter from 3M Corporation relating to the Par product; correct?

A. That's correct.

Q. In fact, before you conducted any work in this case, you requested a variety of samples relating to the Par 3M patch; correct?

A. I believe that's correct.

Q. Could you please look at DTX 113 in the binder in front of you?

DTX 113 is an April 20th, 2012 letter from Novartis' counsel, Chris Loh; correct?

A. That's correct.

Q. And now I'd also like you to turn to DTX 120. This is a document Entitled Plaintiffs' Third Set of Requests to Actavis for the Production of Documents and Things. And it's dated May 1st, 2012.

I'm going to come back to DTX 113 and 120 in a second. I'd like to go now to DTX 112.

Now, this is a letter dated June 1, 2012 from Novartis' counsel, Chris Loh. And I'd like to blow up the first sentence in the second paragraph of DTX. The first sentence in the second paragraph, please.

And there it says, As I mentioned during that call, our April 20, 2012 and May 1, 2012 requests for samples of Actavis' ANDA products and the active ingredients, excipients and materials used therein were determined in consultation with our expert.

And now I want to blow up -- if we can leave that on there, I want to blow up the rest of it. The following paragraph continues: "To clarify matters, our expert, Martyn Davies, believes that the requested sample quantities are reasonable and necessary in view of three enumerated items; correct?

A. That's correct. That's what it says.

Q. And number three is the number of tests he has in mind; correct?

A. Correct.

Q. And, in fact, you believed, based on your experience in undertaking work on pharmaceutical formulations, that you required the sample quantities referenced in the April 20th and May 1st requests shown in DTX 113 and DTX 120?

A. That's correct. Because I didn't know what experiments I would be doing, so I wanted to have sufficient numbers so I could do the experiments if they were required.

Q. Dr. Davies, your research and work at Molecular Profiles relates to the development and characterization of pharmaceutical dosage forms in drugs; correct?

A. That's correct.

Q. And isn't it true that in view of your experience in undertaking work on pharmaceutical formulations, you thought that the samples identified in DTX 113 and DTX 120 were reasonable and necessary?

A. Oh, absolutely, of that type. When I was -- before so I'd have sufficient samples, so if I wanted to do some experiments.

Q. Well, let's look back at DTX 113 and see

what you thought were reasonable and necessary, and if I can blow up the list provided there.

It included 200 patches of the 4.6 milligram product. Another 200 patches of the 9.5 milligram product. 200 empty pouches.

Five square meters of the 3M Scotchpak laminate backing. Five square meters of Scotchpak release liner.

Another five square meters of the 3M Scotchpak in process release liner. One kilogram of the 3M R-27149 solvated acrylate copolymer adhesive.

One kilogram is about 2.2 pounds; correct?

A. I have no idea what it is in pounds.

Q. And a hundred grams of the Cognis isopropyl myristate tackifier. Ten grams of the Rivastigmine API and one five-gallon core carboy.

Those are the materials that you thought were reasonable and necessary in this case; correct?

A. That's correct.

Q. Now, could you please turn to DTX 114?

Now, this is a letter dated August

3, 2012 from 3M to yourself at your address at Molecular Profiles in the U.K.; correct?

A. That's correct.

Q. And 3M sent you by FedEx the samples you requested; isn't that correct?

A. I believe that's correct. They were requested by counsel. That's correct.

Q. And you, in fact, received the items listed here, one to ten in this letter?

A. That's correct.

Q. And after you received the ten enumerated items here from 3M, you put them in your store room at Molecular Profiles; correct?

A. I did.

Q. And do you see at the top of this letter, DTX 114, that 3M designated the materials that it gave you Highly Confidential Outside Counsel Only?

A. Yes.

Q. And you, in fact, honored that designation; correct?

A. Yes.

Q. And from the time you received the samples in August 2012 until February 2013, when your

experiments in this case were complete, none of the samples that 3M shipped to you ever left the premises of Molecular Profiles; correct?

A. That's my understanding. Correct.

Q. Now, turning to the second page of DTX 114 at the very end, it states that 3M is not enclosing the requested Rivastigmine active ingredient samples.

Do you see that?

A. I do.

Q. And you received those as we looked at a minute ago on September 10th; correct?

A. That's correct.

Q. So I'd like to add this August 3rd shipment to the time line.

Now, Doctor, isn't it correct that in the forced degradation study that you relied on for your infringement positions in this case you, in fact, used none of the materials that were shipped to you with the August 3rd, 2012 3M shipment?

A. That's correct.

Q. And am I correct that at no time between August 3rd, 2012 and October 29th, 2012 were you

in the process of conducting any experiments that you are relying on in this case for your opinions regarding the Par ANDA Rivastigmine patch?

A. That's correct.

Q. I'd like you to turn in your binder to DTX 568. This document is entitled Plaintiffs' Second Supplemental Responses to Actavis' Interrogatories Number 1 and 2.

And I'd like you to first turn to Page 15 of this document. And do you see the document is dated August 23rd, 2012?

A. I do.

Q. And this is before you received the active ingredient Rivastigmine from 3M; correct?

A. That's correct.

Q. And I'd like you to turn back to Page 11. And do you see at Page 11 purports a claim chart with the '031 patent claim elements in the first column, and in the second column it states how claim elements are met by the Actavis' ANDA product, which is now the Par ANDA product; correct?

A. I see that.

Q. And I'd like to blow up Element B all the

way through to the second column.

And under Element B, the interrogatory response states, "Plaintiffs are in the process of testing Actavis' ANDA products to identify and quantify the antioxidant(s) expect such testing to be complete in two to two-and-one-half months, and will provide supplemental responses at that time or earlier, if the testing is completed sooner than expected.

So I have some questions for you about this statement. Now, as of the August 23rd date of this response, none of the testing that you have disclosed and relied on in this litigation regarding the Par ANDA product was in the process of being conducted; correct?

A. That's correct.

Q. Regarding the Par ANDA products was in the process of being conducted; correct?

A. That's correct.

Q. So the testing of Actavis' ANDA products to identify and identify the antioxidant referenced in this response does not refer to any of the testing that you referred to in this case; correct?

A. Correct. I don't know what this refers to.

Q. I would like to focus on the next statement that plaintiffs quote, expect such testing to be complete in two to two-and-a-half months.

I would like to go back to the timeline. And you will agree with me, will you not, the very beginning of the first experiment you were relying on in this litigation, specifically the October 29th date of your laboratory notebook occurred two to two-and-a-half months after the August 23rd date of this interrogatory response?

A. I accept that.

Q. Well, I would like to see if we can shed a little more light about what might have been referred to in this interrogatory response since you said you don't seem to know.

MR. BROWN: Permission to approach.

THE COURT: Sure.

BY MR. BROWN:

Q. Now, what I have handed you, Doctor, is a transcript of a discovery proceeding that

occurred in this court. This is DI-77 in this action. It occurred on July 1st, 2012. And I want to put up a section of the discovery proceeding that runs from page 13 line 19 to page 14 line 9. And in this section of the transcript, Novartis' counsel, Mr. Prugo, is telling the Court that Novartis needs extra time for discovery in the case because of the testing of the ANDA products will take about three months.

And, in fact, he says, The testing will take about three months. And there are the three months that are talked about in this specification, so the whole point here is that you have to have a stable active ingredient, and the accelerated stability testing described in the specification is three months long.

So, Doctor, I want to ask you about that statement. Isn't it true that as of August 23rd, 2012, you believe that the correct test for antioxidant behavior was the three-month stability testing described in the '031 patent specification?

A. No. But I didn't say this, this is

somebody else's words, not mine.

Q. Isn't it a fact, Doctor, that you designed and conducted your forced degradation study only after you knew the results of whatever testing is described in the August 23rd interrogatory response?

A. No. I designed my testing as I described in my direct, because I couldn't do that head-to-head study.

Q. Doctor, did you or did you not know the results of the testing that's being described in the August 23rd, 2012 discovery response when you designed your October 29th test?

A. No. Sorry, you mean at this time, in this -- how could I?

Q. My question relates to the time that you designed your October 29 test, and my question for you is: Did you or did you not know the results of the testing that's described in the August 23rd, 2012 discovery response when you designed your test?

A. I don't know what that test is. This is somebody else's words, not my test.

Q. Doctor, since you were the only person

that had Actavis' ANDA products that had been shipped to plaintiffs, who else could have been doing that test?

A. I have no idea. I don't know what this is related to. It's nothing to do with me, it has to do with the lawyers.

Q. Now, Doctor, on direct examination, you said you did not see enough degradation at 40 degrees C or room temperature to do the forced degradation experiment on the time schedule you had in mind; correct?

A. That's correct.

Q. And your opening expert reports in this case were due November 19th, 2012; correct?

A. That's correct.

Q. And so isn't the lack of time that you're complaining about something that happened because we don't have any evidence of what you were doing before October 29th, 2012 with all of these materials?

A. No. It's purely come down to the design of the experiment. Over the time scale I wanted to study the experiment, that's why I chose 60 degrees, again, faster.

Q. So it only took you a week to design it; right?

A. That's about right.

Q. And it took you about another week to do it?

A. Correct.

Q. So if you started it back in September when you got the active ingredient, you would have had months and months to look for the results; correct?

A. But then as you know, I was doing lots of things at that time. I was also doing the work for the other; art -- what was the other part of the case, the Watson case. I also had my other work to do, my university work and the like. So I designed that test and I did that test I think in an appropriate manner.

Q. So, Doctor, you're telling us that the reason you didn't start your test until October 29th, 2012 is because of the testing you were doing in the Watson case and other work at the university and not because you were awaiting results of a different test?

A. Correct. Due to the fact that I was doing

multiple things at that time, and I was -- made the decision to run that specific test based on what I saw in the ANDA, what I saw in the -- for the information that I had related to the products, and I decided to run that test.

Q. I would like to go to your -- I would like to switch topics now, Doctor, and go to your slide 26.

THE COURT: Mr. Brown, if you're switching topics, would this be a good time to break for lunch?

MR. BROWN: It would be perfect. Thank you, Your Honor.

THE COURT: So we'll take an approximately one-hour recess. And, Dr. Davies, you can't talk with your lawyers during this break. And do you have these resumes that I want to look at?

MR. FINEMAN: Yes.

MR. BROWN: Your Honor, we have the CV's for two of our experts, the third one won't be testifying until tomorrow.

THE COURT: That will be fine. All right. Thanks. We'll be in recess. See you

again at quarter to 2:00.

(A brief recess was taken.)

THE CLERK: All rise.

THE COURT: All right. Good afternoon, everybody. Be seated, please.

Are we ready to continue, Mr. Brown?

MR. BROWN: Yes. And, Your Honor, during the examination before lunch, there were a few exhibits that I had neglected to move for admission.

I'd like to go ahead and move for admission of JTX 33, DTX 112, 113, 114, 120, 526 and 568.

MS. JACOBSEN: No objection.

THE COURT: All right. They're all admitted without objection.

BY MR. BROWN:

Q. Good afternoon, Dr. Davies.

A. Good afternoon.

Q. Could I have Slide 26 up from the direct examination?

Now, I want to ask you just a couple questions about the stock solution that's referenced there in the left-hand column. And

the Rivastigmine concentration that you have there is approximately .36 percent; correct?

A. That's correct.

Q. And in your stock solution, you have 1.3 percent approximately of T-butyl hydroperoxide; correct?

A. That's correct.

Q. And that's roughly three times as much of the peroxide as there is of the active ingredient Rivastigmine; correct?

A. Correct.

Q. And you would agree that in a normal pharmaceutical product, you're not likely to encounter three times as many peroxides as the active ingredients?

A. I am not sure of that. Well, of course, there would be less peroxides, of course.

Q. Now, Doctor, in your forced degradation study, you didn't test any known antioxidant such as alpha tocopherol using the same experimental protocol to see if it would prove effective under the conditions of your experiments; correct?

A. That's correct. I didn't need to.

Q. And, in fact, you didn't test any of the

compounds listed in Column 4, Lines 11 to 19 to see if your test would demonstrate an antioxidant effect for those known antioxidant compounds; correct?

A. That's correct.

Q. Can I have up Davies' Slide 22?

And I believe you testified on direct that for all of the vials that you have here, C1 C2, C3, A1, A2 and A3, you never measured the amounts of acetaldehyde in any of those vials at any of the time points in your study; correct?

A. That's correct.

Q. And you never did a control experiment where you measured the amount of acetaldehyde in a vial stored at 60 degrees C over 21 hours to see what happens to the acetaldehyde under those conditions?

A. Well, I did a control. I did do that experiment.

Q. And in your experiment, you also did not measure the oxygen content of any of the six vials that you were measuring; correct?

A. That's correct.

Q. And, Doctor, are you aware that the reaction of acetaldehyde with oxygen or air produces peroxides?

A. I am aware. It can produce peroxides. Correct.

Q. Now, in this litigation, you did measure -- you did conduct an oxygen saturation measurement on Par's ANDA product to see if there was oxygen there; correct?

A. That's correct.

Q. And you provided the opinion that Par's product does, in fact, have oxygen in it; correct?

A. That's correct.

Q. Now, I'd like to look at one of your experiments in particular and can you find JTX 066 in the binder?

A. I've got it.

Q. And I'd like to look at Pages 8 and 9. Can we go forward to that?

And I'd like to focus particularly on Sample A3 at the 15-hour time point and sample A3 at the 21-hour time point.

And so, in looking at these data,

the middle value there is the value for Rivastigmine and I want to ask you about that.

So, at the 15-hour time point, the raw area value you measured for Rivastigmine was 6,937 units; correct?

A. Correct.

Q. And at the 21-hour time period time point, the raw area of Rivastigmine that you measured was 10,185 area units; correct?

A. That's correct.

Q. And so the raw area for the Rivastigmine peak actually increased by approximately 50 percent in the experiment; correct?

A. That particular volume, that's correct. But, of course, I explained that in the context of this work, that all the other peaks increased pro rata. And I say that for that A3 sample, the 21 hours that I believe the top of the vial may have been not sealed properly in the HPLC system, so we may have lost some solvent.

Q. Because it's not possible that the amount of Rivastigmine would increase in that time period; correct?

A. That's correct.

Q. And --

A. That's why all the degradants relative to each other stay the same.

Q. And the conclusion you drew upon looking at the data was that it is possible that this increase in the raw data was due to evaporation of a portion of the solvent in that vial upon loosening of the seal for that vial; correct?

A. That's correct.

Q. Now, if you could turn to JTX 170, that's the laboratory notebook for this experiment. There is no reference to any loosened seal or evaporated solvent recorded in the lab notebook for this experiment; correct?

A. There is a record that we subsequently re-analyzed that Sample three times just to double-check.

Q. Understood. But no one wrote down that the seal was loose and the solvent evaporated; correct?

A. I would have to check it, but I don't have it in front of me.

Q. 170 is in the Davies cross exhibit binders of JTX and PTX exhibits. Can you confirm that

for me?

A. That's correct, it just says it's done in triplicate.

Q. So now at the various time points of your experiment including the end, you also didn't measure the amount of solution that was left in each vial; correct?

A. That's correct, I didn't need to.

Q. And so there is no way of knowing if any of the other seals also allowed some of the solvent to evaporate; correct?

A. No. That's incorrect. Consistency of the data shows as I explained in my reports, shows that they were sealed.

Q. Doctor, you were not physically present in the lab the day the vials were placed in the oven and the day the measurements were taken; correct?

A. That's correct.

Q. Acetaldehyde boils at around 20 degrees Celsius; correct?

A. Pure acetaldehyde does, correct.

Q. And in your experiment at 60 degrees C, you were 40 degrees above acetaldehyde's boiling point; correct?

A. Correct, the boiling point of pure acetaldehyde.

Q. So if we assume that your supposition that the result in the A3 vial was caused by solvent evaporation, do you know if all the solvent had evaporated out when the seal broke -- sorry. Do you know if all of the acetaldehyde had evaporated out when the seal broke?

A. No, because if you look at the data, you look at the data relative to degradation relative to the drug on that particular sample, it's the same relative ratios that you see in the other two vials for that time point, so, no.

Q. So you're inferring the presence of acetaldehyde from your results; correct?

A. I know it's there because we put it in there, and it's in a sealed system. It's there. The results show that.

Q. Thank you, Doctor.

I want to move on and ask you a little -- a couple of questions about the statistical discussion that you provided on direct examination.

Doctor, you first provided the

results of your forced degradation study in your opening expert report that was served on November 19, 2012; correct?

A. That's correct.

Q. At that time the only statistical analysis you provided was a T-test using a one-tailed distribution; correct?

A. That's correct, I felt that was appropriate.

Q. And you subsequently provided the statistical analysis using the two-sided T-test and the linear regression model that you discussed here; correct?

You didn't give an audible answer, but I think you nodded your head yes?

A. Sorry, I can't hear you.

Q. I'm sorry. After the November 19th report, at a subsequent time you provided the statistical analysis using the two-sided T-test and the linear regression model; correct?

A. That's correct, in response to Dr. Michniak-Kohn's comments.

Q. And a one-tailed T-test is appropriate only when the investigator has an a priori

expectation of the direction of the result; correct?

A. I think that's correct. And I did have -- as I explained on direct, I did have that expectation.

Q. And in this case you used the one-tailed T-test rather than a two-tailed test because you had an a priori expectation that acetaldehyde would reduce the oxidative degradation of rivastigmine rather than increase it; correct?

A. Not quite correct. I had the expectation either it has no effect or it would reduce the oxidative degradation, so it's in one direction.

Q. And you based your a priori expectation that acetaldehyde would reduce or have no effect on the degradation of rivastigmine in part on your knowledge that acetaldehyde was a known reducing agent; correct?

A. In part, correct.

Q. So a couple of questions about that.

Dr. Davies, you provided opinions in the August trial against Watson about the compound BHT; correct?

A. Correct.

Q. And BHT is a known antioxidant; correct?
A. Correct.
Q. And ascorbyl palmitate is another known antioxidant; correct?
A. They are listed in the patent, that's correct.
Q. And ascorbyl palmitate is one of the antioxidants that you call a reducing agent; right?
A. That's correct.
Q. Let's go to JTX 187. Can find that in the binder?
MR. BROWN: We would move to admit JTX 170 if it wasn't already admitted.
MS. JACOBSEN: No objection.
THE COURT: Admitted without objection.
BY MR. BROWN:
Q. You have seen JTX 187 before; correct?
A. I'm not sure I have.
Q. Well, Doctor, JTX 187 is the pharmaceutical development report prepared by one of the plaintiffs here, LTS Lohmann, and I believe you testified that a pharmaceutical

development report is a document that is often included in an ANDA to give the regulatory authority a general idea of how a formulation was developed; correct?

A. That can be done, absolutely, I agree.

Q. I would like you to turn to page 504454. I'm putting it up on the screen now. This page shows the oxidative degradation pathway that you testified about on direct examination; correct?

A. Correct.

Q. And the two oxidation impurities that you measured in your forced degradation study are the ones identified here as 802-95 and 213-95; correct?

A. That's correct.

Q. 213-95 is the compound known as Impurity 4?

A. Correct.

Q. And 802-95, also called styrene, is the compound known as ECAV; correct?

A. Correct.

Q. And I'd like to turn ahead in JTX 187 to Page N504460.

And I want to blow up Table 5 from

this report on the screen, along with the text immediately above the table. And in the text above the table, it says two antioxidants ascorbyl-palmitate and tocopherol have been added as single substances in a concentration of 0.1 percent and in combination to formulation 2200. The TDS have been packed in Barex-pouches and stored at 60 degrees C for eight weeks.

In Table 5, the detected amounts of the two main degradation products are listed. And you understand TDS means transdermal system; correct?

A. I believe that's the case.

Q. I'd like to look at what they found out about ascorbyl-palmitate in this study. So I'd first like to look at the first two lines of the study, the formulation 2200 with no antioxidants and the addition of .1 percent tocopherol.

Can you describe the effect that adding .1 percent tocopherol had on formulation 2200?

A. Again, I -- well, I haven't been asked to comment on this, but it appears to reduce the level, the overall levels of the ketone or

styrene.

Q. In fact, it substantially reduces the ketone and the styrene; correct?

A. Well, I agree it's reducing significantly. Yeah.

Q. So now I'd like to compare the second line. Excuse me.

Yeah. I'd like to compare the second line with the fourth line. And the only difference between those two formulations, Doctor, is the addition of .1 percent ascorbyl-palmitate; correct?

A. Actually, I don't -- well, that's what it says here. I haven't read this document. So that's what it says here.

Q. Well, let's look at the effect that they observed in this experiment between those two formulations. The amount of the 213-95 ketone approximately doubled; correct?

A. It goes -- I agree.

Q. And the amount of ECAV 802-95 went from .66 to 2.18 percent; correct?

A. That's correct.

Q. So it basically tripled?

A. Of that order.

Q. So, Doctor, if you had formed an a priori expectation before this experiment that adding ascorbyl-palmitate could only reduce rather than increase the oxidation of Rivastigmine, you would have been wrong; correct?

A. No, because if you look at the total amount of the two key degradation amounts, irrespective of the three examples shown, they're much lower than the degradation products of the 2200.

So if you add up the degradation products for the 2200, that's of the order of five percent. Then if you add up the other degradants, then it's much lower in each case.

Q. But, Doctor --

A. So I wouldn't make that assumption.

Q. But, Doctor --

A. Make the assumption -- three compounds are all acting as antioxidants because they're reducing the oxidative degradation to the compounds.

I mean, I haven't read this in detail, so you're just showing me a small portion

of this. But just as a scientist just sitting here, you know, you've got three, three antioxidants.

So, and they're all reducing the level of oxidative degradation of the two degradation products.

Q. Doctor, the only difference between the second experiment and the fourth experiment is the addition of the ascorbyl palmitate; correct?

A. I don't know that in detail, but I -- you know, I can see it over here. Ascorbyl palmitate is ascorbyl palmitate.

Q. I'd like you to turn to JTX 91.

And this is a document that you cited in your surreply report in this case and you've read this document; correct?

A. I have. That's correct.

Q. And this reference reports work done by researchers at Pfizer to evaluate the effect of an antioxidant BHT on their drug formulation; correct?

A. Yes, on their coatings. That's correct.

Q. And I want to go to Page 123 of the reference and I want to blow up a section where

they're reporting their conclusions.

Yes. And I'm highlighting a sentence there where they reported a conclusion that I'm going to read, "Surprisingly, the core containing BHT at a concentration equivalent to the two percent BHT coating had higher levels of the sulfoxide degradant. Due to the instability of BHT and the stability of the BHT radical species, BHT radicals can enhance its oxidation in the core.

So, Dr. Davies, if these researchers had formed an a priori expectation that the known antioxidant BHT could only decrease oxidation rather than enhance it, they would have been wrong; isn't that correct?

A. I don't agree.

Q. You don't agree with the conclusion the researchers reached here?

A. No. I don't agree with your comments. That's supposition.

Q. Dr. Davies, I'd now like to go and talk about the parameters for the stress test that you talked about on direct examination.

First, I'd like to turn to DTX 591.

This is a document published by the U.S. Department of Health and Human Services; correct?

A. Yes, I agree.

Q. And this document sets forth guidelines for stability testing of new drug substances and products; correct?

A. That's what it says.

Q. And I would like to turn to Page 7 of DTX 591 and I'm going to blow up the tables on the bottom of the page. And this table in this document is describing two different tests; correct?

A. Sorry, which page are you on? Sorry.

Q. Page seven.

A. Thank you. Yes, it is.

Q. One test is called long-term testing; correct?

A. That's correct.

Q. And the other test is called accelerated testing; correct?

A. That's correct.

Q. And for each of those tests the guidance specifies a temperature at which it is to occur; correct?

A. That's correct.

Q. And for each test the guidance also specifies a relative humidity?

A. That's correct.

Q. And the guidance also specifies a minimum time period; correct?

A. That is correct.

Q. And you agree that the tests set forth in this table are standard tests; correct?

A. I agree they're one form of test.

Q. And, in fact, you believe that these are standard tests within the meaning of the '031 patent; correct?

A. They're a type of test, I agree.

Q. And within the meaning of the '031 patent; correct?

A. Depends what you mean by that. They're certainly the kind of tests one can use and as I described the process.

Q. And, in fact, the lower test called accelerated testing, those conditions match one of the two stress tests that we saw earlier that were described in column four of the '031 patent; correct?

A. That's correct, the temperature and the humidity.

Q. But it's your opinion that the standard tests that may be used for purposes of the '031 patent are broader than those shown in the patent; is that correct?

A. I believe somebody skilled would understand reading the patent that stress tests that are described would describe such tests but also would describe other tests that are known stress tests that are known to pharmaceutical scientists; correct.

Q. And if you could turn to DTX -- well, I believe -- could you find JTX 75 in the binder that you used on direct examination.

A. Thank you.

Q. This is the Alsante reference you talked about; correct?

A. That's correct.

Q. And when I asked you earlier about identifying a reference that described using a forced degradation study to determine if a compound was an antioxidant, you referenced the Alsante reference. I would like you to tell me

if you can find the word "antioxidant" anywhere in this document?

A. Well, the document doesn't mention the word antioxidant. As we discussed at my deposition, it does mention the word excipient, and antioxidant is an excipient and it talks about using stress tests as I indicated in my direct for the selection of more stable drugs and drug formulation. It talks about drug excipient compatibilities.

Q. Doctor, I want to blow up a section of the first page of the Alsante reference in the middle portion there. And there is a section within this paragraph that I want to highlight. It starts at the beginning, because the ICH definition leaves the details of the investigation to the pharmaceutical researcher, the practices that companies use to conduct stress testing studies can vary tremendously and, therefore, have a significant effect on the quality of the analytical methodology used throughout the industry.

You believe that what Alsante has reported here is a correct characterization of

the use of the stress testing; correct?

A. Well, I think it's saying what I indicated with that, with guidance from the ICH, but the details are left to the individual researchers, but ultimately all achieving the same objective, and that's what's accepted by the FDA when they review such tests.

Q. I would like to look at some of the parameters that you went through on direct examination. First on page 62 of the reference, there is a sentence in here that says, pull it up, the second sentence under the heading how stress testing studies are conducted, says most companies attempt to induce at least five to 20 percent degradation of the drug substance before considering stress testing to be complete.

My question for you, Doctor, is, you did not induce at least five percent degradation in any of the vials in your forced degradation study; correct?

A. That's correct, I induced about three-and-a-half percent. That was sufficient for me to be able to compare the two samples, the control versus the acetaldehyde.

Q. I would like to move forward to page 67 of the reference, below the heading oxidation.

And I would like to blow up the last sentence before the heading peroxides, and that sentence says, For example, in the peroxide pie chart that shows typical temperatures, 84 percent of the companies selected ambient to 30 degrees C, 11 percent selected 31 to 50 degrees C, and only five percent selected greater than 50 degrees C.

And my question for you is, Doctor, in your forced degradation study, you did not use a temperature that falls within what 95 percent of the companies in this review selected, namely a temperature somewhere between ambient and 50 degrees C; correct?

A. I agree. It fell in the range that was cited within the publication.

Q. Now, proceeding to the first sentence under the heading peroxides, the first sentence says all companies use hydrogen peroxide.

A. That's correct.

Q. And you did not use hydrogen peroxide in your forced degradation experiment; correct?

A. That's correct. That doesn't mean all companies used it in every experiment, of course, it just means that it's available for them to use.

Q. The Alsante reference doesn't refer to tocopherol as hydrogen peroxide; correct?

A. That's correct.

Q. Now, the last sentence of this section states that the maximum study duration selected was the same for one and seven days, 37 percent for both. And your study duration was for less than one day; correct?

A. It's approximately one day. It was twenty-one hours, I accept that, just under one day. That was sufficient for my experiment.

Q. The next heading on page 67 is radical initiator. You did not use a radical initiator in your forced degradation study; correct?

A. That's correct. And 15 of the companies also didn't use it. You see N equals five, it doesn't mean that you use it every time.

Q. Doctor, do you know how many different radical initiators there are that you would consider standard in the industry for a stress

test?

A. There could be a number. I don't know the exact number.

Q. The next heading on page 67 is transition metals. And this section describes transition metals that could be used because they promote oxidative degradation; correct?

A. That's correct.

Q. And there are two more categories of stress tests described here for oxidation purposes, pressured oxygen and bubbled oxygen; correct?

A. That's correct.

Q. And you didn't use either pressured oxygen or bubbled oxygen in your study; correct?

A. That's correct.

Q. Dr. Davies, if you were testing a proposed antioxidant called compound X to evaluate whether or not it was an antioxidant, isn't it a fact that you have not considered whether doing a peroxide test, a radical initiator test, a transition metal test, a pressured oxygen test and a bubbled oxygen test would all give you the same result?

A. No, I don't think that's the case. I think I considered that, but as I have said, you design the test to address the specific drug that you're looking at. And all achieve the same objective if they're suitably designed. In other words, they generate the oxidative degradation drug.

Q. Doctor, I would like you to turn in your deposition binder to the April 2nd, 2014 deposition.

Q. And turn to -- please turn to Page 361. And I'm reading from Line 12.

"Question: So if you were testing a proposed antioxidant, Compound X, to evaluate whether or not it was an antioxidant, would doing a peroxide test, a radical initiator test, a transition metal test, a pressure oxygen test and a bubble oxygen test all give you the same result?

"Answer: Again, as a scientist, one would -- if one doesn't know that, one would have to think about that, give it some thought. It's not something that I have been asked to consider.

But clearly these documents, as I've

highlighted, there's a number of different ways the industry uses to undertake oxidation stress tests. And the diversity reflects the diversity of drugs and the different susceptibility to oxidation and the different formulations."

Is that the answer you gave me?

A. Yes, absolutely. It's absolutely correct.

Q. And I'd like to switch topics for a moment.

Doctor, for the batches of Par's rollstock where no acetaldehyde has been measured, you believe that one possible explanation for why those batches contain no detectable acetaldehyde is that the acetaldehyde may have been consumed in an oxidation reaction; correct?

A. Maybe I missed your question. Are you saying there was a batch which -- where the acetaldehyde wasn't measured, in other words?

Q. Let me restate the question. You remember there were two batches that you talked about on direct where there was not a detectable amount of acetaldehyde present; correct?

A. Yes.

Q. And you believe that one possible explanation for why those batches contained no detectable acetaldehyde is that the acetaldehyde may have been consumed in an oxidation reaction; correct?

A. That's possible.

Q. It's also possible that acetaldehyde evaporates; correct?

A. It depends. In that context, I think it would be difficult because it's in the patch.

Q. Dr. Davies, after the Par product is manufactured, isn't it true that you don't have the information to know if there's any acetaldehyde in the patch a month later?

A. Well,.

At one month later.

Q. Yes.

A. Certainly, there was an example of a patch that I highlighted in my reports which was made and then packaged one month later.

And that was represented to the FDA as the final formulation had a level of acetaldehyde. So the FDA has represented the final finished product has that level of

acetaldehyde.

Q. Well, Doctor, during your direct testimony, you provided testimony regarding Par's specification for acetaldehyde from PTX 348. Do you recall that?

A. Thank you. Yeah.

Q. And could you find Page Par 780, which is where I think you got your information from? Now, I'd like to blow up the entire top section. Not that, the second chart, but the top section.

And in the method column, do you see where it says Report three sample results?

A. I do.

Q. And below that, it says report results from rollstock?

A. It does.

Q. And Dr. Davies, isn't it correct that you have never seen a specification that requires Par or 3M to measure the amount of acetaldehyde directly in their finished patches?

A. I think this shows that it's measured in the rollstock, but then Par -- Par then says to the FDA -- if you look at the front of this document, it says the finished product

specification, in other words, the finished final product in the patent, in the pouch specification, and it's representing that's the boundaries of acetaldehyde.

Q. Doctor, you have never seen any data for an acetaldehyde measurement taken on a finished patch; correct?

A. I disagree. These are -- this is data that is represented to the FDA on the finished final products.

Q. My question is: You have never seen data for an acetaldehyde measurement taken on a finished patch; correct?

A. That's been taken on a finished patch. This is the rolls of the stock that is then cut and put into the patches. And they measure it there.

Q. Well, let's go to your deposition, your April 2nd deposition, Page 320.

And I'm reading from Line 6 to 12.

"Question: Have you seen any acetaldehyde measurements that were taken on finished patches?

"Answer: I believe the results that

I have seen are based on rollstock."

Is that the question and answer from the deposition?

A. That's correct. That is what I said.

And then I go on to say, if you look underneath, I've relied on Par's representations of the FDA based on the acetaldehyde they measured in their product. And that's what they represented to the FDA.

That's what I just told you -- talked to you about. So, if you read further on down the line, you know, you see exactly what I just told you.

Q. And, Doctor, even though you asked for and received 400 patches of Par's ANDA product, you haven't produced any testing of the acetaldehyde content of any of those patches, have you?

A. That's correct. I've relied on Par's testing.

MR. BROWN: Thank you. Par has no further questions.

THE COURT: All right. Thank you.

Any redirect, Ms. Jacobsen?

REDIRECT EXAMINATION

BY MS. JACOBSEN:

Q. Just a couple of questions, Dr. Davies.

Dr. Davies, do you recall Par's counsel asking you questions on cross-examination regarding whether you had a positive control in your stress test?

A. Yes, I do.

Q. And I believe you said that you didn't need to include one?

A. That's correct.

Q. And why was that?

A. Well, I already knew that Rivastigmine would degrade, undergo oxidative degradation in the presence of peroxides.

So I already knew that from the data. And I -- my own data shows that, in fact, that's exactly what happens.

The two key degradation products that I observed are the key degradation products that result from the presence of peroxide. I already knew -- if I placed something, another antioxidant against that system, that antioxidant would have reduced the level of degradation, just like acetaldehyde would. I wouldn't have any

other expectation because I was creating the right kind of oxidative degradation.

Q. Dr. Davies, do you recall Par's counsel asking you questions about your stress test containing oxygen?

A. Yes.

Q. And would the presence of oxygen have altered the results of your stress test?

A. No. Whether it's by oxygen or peroxides, you see the same effect. You see the same two key degradation products. That's what I showed in my direct, that's what Par believed based on their documentation as well.

Q. And finally --

A. It won't change the oxidative degradation of the drug.

Q. And Dr. Davies, do you recall Par's counsel asking you questions on cross-examination about the temperature at which you conducted your stress test?

A. Yes.

Q. And I believe he asked you if it was at 40 degrees Celsius above the boiling point of acetaldehyde, do you recall?

A. Yes.

Q. Would acetaldehyde in your opinion have been a gas in your stress test?

A. No. It would have been -- it's very much present in the solution. The reason for that is that acetaldehyde on its own is a pure material at that particular boiling point. However, when you mix it in with a solvent, it then takes the -- it then alters the boiling point of the material, and it's somewhere between the two materials' boiling point.

Now, that's important because that means that acetaldehyde would have stayed within the solvent of my test. But then you have to look at the results. Two key degradation products formed and there is less formed in the solvent with acetaldehyde present, showing that it is present, it is acting as an antioxidant.

MS. JACOBSEN: Thank you, Dr. Davies. I have no further questions.

THE COURT: Thank you. Dr. Davies, you can step down.

Does Novartis have anything more on this infringement case?

MS. JACOBSEN: No, Your Honor.

THE COURT: All right. So you rest?

MS. JACOBSEN: We rest.

THE COURT: All right. Mr. Brown.

MR. BROWN: Two quick things, Your Honor, from Dr. Davies' cross. I again neglected to admit a couple of exhibits, JTX 91 and DTX 591, we would like to move those for admission now. It's the article and the FDA guidance.

MS. JACOBSEN: We have no objection.

THE COURT: Admitted without objection.

MR. BROWN: DTX 591.

Par now calls Dr. Bruce Ganem.

THE COURT: All right.

MR. SILVER: Your Honor, one housekeeping matter. We have swapped out some team members. Sitting at the counsel table with me will be Daniel Minion and Dominick Conde. I don't know if they have been before Your Honor before.

THE COURT: Welcome gentleman.

MR. SILVER: Thank you.

THE CLERK: Please state and spell

your full name for the ready.

THE WITNESS: Yes. My name is Bruce, B-R-U-C-E, Ganem, G-A-N-E-M.

BRUCE GANEM, PH.D.,

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

MR. CHIN: Your Honor, may I approach to pass up a pen?

THE COURT: Yes.

MR. CHIN: Your Honor, may we also approach to hand up a couple of binders?

THE COURT: Sure.

DIRECT EXAMINATION.

BY MR. CHIN:

Q. Good afternoon, Dr. Ganem.

A. Good afternoon.

Q. Could you please introduce yourself to the Court?

A. Yes. My name is Bruce Ganem. I hold an endowed chair at the Department of Chemistry and Chemical Biology at Cornell University in Ithaca, New York. I held that chair and I also serve as

chair of my department.

Q. What is your particular focus within the field of chemistry?

A. I'm an organic chemist and I'm particularly interested in developing reaction pathways to biologically active natural products. That often involves developing new oxidation and reduction reactions which are a core part of organic chemistry.

Q. Could you turn to DTX 524 in your book.

A. Yes.

Q. Could you identify this document?

A. Yes. This is my current CV.

Q. Does DTX 524 provide an accurate description of your professional credentials?

A. I believe it does.

MR. CHIN: Your Honor, Par moves the admission of DTX 524.

MR. MINION: No objection.

BY MR. CHIN:

Q. Dr. Ganem, has any of your work involved the development of pharmaceutical products?

A. Yes, it has. Several years ago my lab discovered and developed a new reduction reaction

that has been used to greatly amplify and improve the synthesis for the important anticancer drug Taxol which is used in treating almost all solid tumors. The drug used to come from a very rare plant that was threatened biologically. We can use make the drug from ordinary garden variety trees, it accounts for about a third of the world's supply today.

MR. CHIN: Your Honor, Par offers Dr. Ganem as an expert in organic chemistry including oxidation and reduction reactions.

MR. MINION: No objection, Your Honor.

THE COURT: All right. You may proceed.

BY MR. CHIN:

Q. I would like to turn to some of the issues in this case. Can you explain to the Court what is oxidation?

A. Yes. Simply put, oxidation is the process by which electrons are removed from a chemical compound.

Q. Can you generally describe how oxidation occurs?

A. Yes. Typically when a compound loses one or more electrons, it transfers those compounds, those electrons to another compound, a different substance which accepts those electrons and is thus reduced. So the process of oxidating, oxidizing one compound goes hand in hand with a concomitant reduction of some other substance and that tandem process is generally referred to as a redox process.

Q. Redox is short for reduction and oxidation?

A. Yes.

Q. What is oxidative degradation?

A. So oxidative degradation is the process by which the oxidation level of chemical compound results in the decomposition.

Q. And have you prepared a slide to illustrate this?

A. Yes, I have.

Q. So --

A. So I'll explain to the Court what I call the core cycle of oxidative degradation. This process begins with some organic compounds, the organic compounds undergoing oxidative

degradation, which is oxidized by something to produce this, what we call, radical.

But it's a chemical radical different from an ordinary type of radical. It has just one electron.

And that radical R dot will react with a molecule of oxygen in the atmosphere to produce another radical. This is called a peroxy radical at the bottom of the slide. Both of these compounds are highlighted in red because they represent the process of oxidative degradation.

Now, continuing the process in this, peroxy radical encounters another organic molecule such as the substance being degraded RH. The peroxy radical will abstract the hydrogen and be reduced, thus forming now a peroxide, a hydroperoxide compound here and regenerating the initial radical at the top of the slide R dot.

And so this process, first of all, is a chain reaction. It can propagate itself many, many times, going around and around this cycle driving the transformation of an organic compound to the oxidative degradation products.

It's the core engine of oxidative degradation.

Q. Are you aware that the Court has given a definition of the term antioxidant in this case?

A. Yes, I am. The definition shown on the slide, I understand the Court has agreed that an antioxidant is an agent that reduces oxidative degradation. And I have adopted that definition in forming my opinions.

Q. Can you turn to JTX 1 in your book? This is the '031 patent which has already been admitted into evidence.

A. Yes, I'm there.

Q. Did you have an opportunity to study the '031 patent in connection with your work on this case?

A. I did.

Q. And I'd like to draw your attention to Column 4, Lines 10 through 19.

Do you see that this passage lists several antioxidant compounds that have been discussed today?

A. Yes, it has been several times.

Q. In your experience, do these compounds qualify as antioxidants to chemists?

A. Yes. They're all well-known antioxidants for which extensive published literature exists.

Q. And can we turn back to Slide Number 2, the cycle. Can you describe how the antioxidants that were listed in the '031 patent act to reduce oxidative degradation?

A. I can. So all of those antioxidants shown in the '031 patent have the unique ability to shut down or suppress this cycle of oxidative degradation in several ways.

One, for example, is if the radical at the top of the slide encounters a molecule of antioxidant, the antioxidant will reduce this radical by adding an H to it to form RH. That immediately shuts down the ability of this radical to drive further degradation.

But the unique ability of the antioxidant to do that is caused by the antioxidant now forming a radical, which is very stable. Typically can't do anything. It can't engage in the cycle.

So that's one example of how an antioxidant can shut down this process. And quickly another is simply that the antioxidant

can react with this red peroxy radical at the bottom, get -- radical gets reduced by accepting a hydrogen to form this peroxide. And, again, a very stable antioxidant radical, which does not contribute to oxidative degradation.

Q. Does aldehyde form a stable radical?

A. No, quite to the contrary. Acetaldehyde can form a radical, but it's a highly reactive radical that can itself contribute to oxidative degradation.

Q. Can a radical of acetaldehyde break this cycle of oxidative degradation?

A. No, quite to the contrary. An acetaldehyde radical can actually engage in much of this same process and enhance oxidative degradation.

Q. You're aware that plaintiffs are contending that acetaldehyde is an antioxidant?

A. Yes, I am.

Q. Did you find acetaldehyde listed in the '031 patent as an antioxidant?

A. No, I did not find it anywhere in the patent.

Q. How commonly is acetaldehyde used as a

reagent in chemical reactions?

A. Well, as we heard earlier today, acetaldehyde is a well-known chemical compound. And organic chemists use acetaldehyde all the time as a synthetic building block for preparing other compounds.

Q. In your 40 years of experience as a chemistry professor, have you ever heard of acetaldehyde reported as an antioxidant?

A. No, never.

Q. In your opinion, is acetaldehyde an antioxidant?

A. No, it is not and chemists do not consider it to be an antioxidant.

Q. Is acetaldehyde a reducing agent?

A. Yes, it is.

Q. What does it mean to be a reducing agent?

A. So, for a substance to be a reducing agent that simply means that it will reduce some other chemical substance and, in turn, become oxidized as would happen in any combined redox process.

Q. In your opinion, does acetaldehyde qualify as an antioxidant because it can be a reducing agent?

A. No, not at all. Lot of compounds can be reducing agents, but that does not mean that they can disrupt this engine, this cycle of oxidative degradation.

Q. In your opinion, does acetaldehyde qualify as an antioxidant because it can be oxidized itself?

A. No, not at all.

Q. What can happen if acetaldehyde is oxidized itself?

A. Well, if acetaldehyde gets oxidized, as I mentioned before, it can do so by forming a reactive free radical and in turn actually enhance oxidative degradation.

Q. Is that behavior reported anywhere?

A. Well, yes. We've heard in the courtroom today mention that acetaldehyde can form a reactive peroxide.

It turns out whenever you purchase a sample of acetaldehyde, it comes with a serious warning label that indicates the potential for peroxide formation to occur and the compound should be treated accordingly. The mechanisms by which that happens have been well worked out in

the chemical literature.

Q. Can you turn to JTX 086 in your book?

A. Yes, I'm there.

Q. Do you recognize this document?

A. I do. This is a review article I've relied on that describes the chemical mechanisms by which acetaldehyde undergoes oxidation.

Q. What journal is it from?

A. This is from the journal Chemical Reviews, which is the principal review journal of my professional society, American Chemical Society.

MR. CHIN: Your Honor, Par moves the admission of JTX 086.

MR. MINION: No objection.

BY MR. CHIN:

Q. Can we turn to Page 335 and have the chemical equations presented on the screen?

Dr. Ganem, can you describe for the Court what these equations show?

A. Yes, I can. So I direct the Court's attention to a series of chemical equations numbered four through eight. And these react -- these equations indicate that the process by which an aldehyde here shown on the left of

equation four, RCHO can undergo an oxidation using molecular oxygen to form what turns out to be a variety of reactive chemical radicals.

So with Mr. Smith's help, I'll try to highlight these for the Court. The first radical, reactive radical that's formed is a radical R dot shown here on the right side of the equation four. That radical can then react as shown in equation five with molecular oxygen to form this radical peroxy radical in equation five, which is another reactive radical.

In fact, these are the very same radicals we saw in that oxidative cycle I mentioned. But, furthermore, we see the formation of acyl RCO. That's RCO dot on equation six, and it appears again on the product side of equation eight.

Thank you.

And in addition an acyl radical can combine with molecular oxygen to form this reactive radical shown on the right side of equation seven. So we see here four different chemical radicals. One of them appears twice in the overall cascade of reactions. All of which

are reactive enough to contribute to oxidative degradation.

Q. How do all of these reactive radicals generated by acetaldehyde compare to the oxidative degradation cycle that you described earlier?

A. Well, as I mentioned, at least two of them are chemically equivalent to the two that we saw, and others, such as this peroxy radical is similar in structure, the one on equation seven is similar in reactivity and structure to the one on equation five and I think chemist consider acetaldehyde an extremely reactive radical.

Q. Do you recall that Dr. Davies mentioned a negative 30 degree threshold that's mentioned in the Chemical Reviews article in his testimony this morning?

A. Yes, I do recall that. Dr. Davies pointed out something having to do with a low temperature limit to what's possible here. But actually he was quoting from some studies that lead to this understanding of reactive pathways. That temperature threshold has nothing to do with these equations. All of these processes can

occur readily at room temperature.

Q. Are the chemical reactions that you discussed here consistent with acetaldehyde being a reducing agent?

A. Yes, they are. Because to be a reducing agent means that the compound gets oxidized. And if you look overall at what happens, an aldehyde such as acetaldehyde shown here at the start is eventually converted into a peroxy carboxylic acid shown here at the product of equation eight. So in sum the reaction is a net oxidation of the aldehyde.

Q. Are the chemical reactions that you have discussed and shown here consistent with acetaldehyde being an antioxidant?

A. No, I don't think so. As I say, this process is producing a variety of quite chemical radicals that would not suppress oxidative degradation, they would actually enhance and contribute to it.

Q. I would like to change to a slightly different topic. Were you in court -- you were in court earlier today when Dr. Davies described his experiment testing, rivastigmine and

acetaldehyde in the presence of TBHP?

A. Yes, I was here throughout that.

Q. Have you had an opportunity to study the data and records relating to Dr. Davies's experiment?

A. I did.

Q. Do you consider Dr. Davies's experiment to be an appropriate model for the oxidative degradation of rivastigmine by oxygen?

A. No, I don't. And the reason I don't is because Dr. Davies doesn't use oxygen in his study, he uses TBHP, the peroxide compound.

Q. How is TBHP different than oxygen?

A. TBHP is different from molecular oxygen in several ways. To begin with, TBHP seeks out negative charge, TBHP is also a protic, meaning slightly acidic compound whereas molecular oxygen has no property. As we heard earlier today, TBHP is a liquid whereas we're all familiar with the fact that oxygen is a highly diffusible gas.

Q. Do those differences effect the oxidation process?

A. Yes, they certainly can. Among other things, TBHP, the hydroperoxide can perform

direct oxidation of chemical compounds. For example, TBHP will directly oxidize an aldehyde such as acetaldehyde to a carboxylic acid and TBHP will directly oxidize amine such as rivastigmine to the amine oxide.

Q. Can you describe these direct reactions that you just alluded to?

A. Yes, I have them on a slide for the Court. So on the top slide I show acetaldehyde undergoing a known reaction with TBHP in which the aldehyde gets oxidized to acetic acid. And at the bottom of the slide I show rivastigmine pointing especially to the nitrogen on the right side of this molecule which undergoes an oxidation with TBHP to form the amine oxide that we heard about.

Q. How important are these direct reactions under the conditions of Dr. Davies's experiment?

A. So as I said, in Dr. Davies's experiment he used a very large excess of TBHP, so given that, I would have assumed that these are the dominant processes in his reaction, that oxidation by air would play a minimal role, if any, in his experiments.

Q. Does Dr. Davies's experiment reflect how acetaldehyde would affect oxidative degradation of rivastigmine by oxygen?

A. No, as I just said, there is very little oxygen in Dr. Davies's experiments. In fact, I was able to calculate that the amount of oxygen in the experiment he described is about approximately two orders of magnitude less than the amount of TBHP that he put into his experiments. So again, I would assume that it would be very unlikely that in the Davies experiments one is seeing very much oxidation caused by molecular oxygen.

Q. Is the Davies' experiment an appropriate model for oxidative degradation by oxygen?

A. No, for that reason, I don't think so.

Q. Have you reached any conclusions regarding the design and methodology of Dr. Davies's experiment?

A. Yes. So in my opinion Dr. Davies's experiment is not a scientifically valid way to test the oxidation of rivastigmine by oxygen. It first of all -- or the effect of acetaldehyde on that process.

Q. What is your concern about the scientific validity that you just alluded to?

A. Well, I have several concerns. To begin with, Dr. Davies does not use any method, Dr. Davies's experiment doesn't use any method I have ever encountered, any valid scientific method that I know of to test for the antioxidant capabilities of a chemical compound. But putting that aside, there are additional concerns I have in both the execution and methodology of his experiment.

Q. What would be needed for a validated scientific method in such a study?

A. Well, I think the Court has heard this already this morning, and I don't want to bore you, Your Honor, but the fact is in my opinion, a scientifically -- for a test of an antioxidant to be a scientifically valid method, the test should first of all show that known antioxidants display the expected antioxidant behavior that's been reported for them, and likewise, compounds that are known not to have any antioxidant activity should be shown in the Davies test likewise to exhibit no such activity. And absent those

controls, those validations, I don't think one can draw any conclusions from an experiment.

Q. You also referred to issues of methodology. What were you concerned about there?

A. Well, I have three main concerns and I have summarized them for the Court on a slide.

So to begin with, in my opinion, Dr. Davies fails to account for numerous other components that are produced in his reaction, and in particularly, those that might be generated by side reactions with TBHP.

Secondly, Dr. Davies in my opinion fails to account for the possibility of what is called co-elution of these other components in the HPLC. And finally, it's my opinion that Dr. Davies has improperly used a form of data normalization that I believe obscures errors in his experiments and actually represents them as real results.

Q. Perhaps we can start with the first bullet point. Can you explain why you consider failing to account for other components to be a flaw in the experiment?

A. Yes, I can. So Dr. Davies's bases his entire analysis on the assumption that only three chemical substances are involved in his experiment. The rivastigmine, which he recovers unreacted and the two impurities we have heard about, impurity 4 and ECAV.

However, when we look at Dr. Davies's data in the test samples, the A1, A2, and A3 samples and look at the HPLC chromatogram of those experiments, one sees numerous other minor compounds that show up as peaks in the chromatogram all across the chromatogram. And Dr. Davies simply ignores these other compounds and does not characterize them. He, I think to put it harshly, he pretends they don't exist and bases his analysis only on three compounds I mentioned.

Q. Did Dr. Davies attempt to address your criticism about ignoring other components?

A. I raised this concern in one of my expert reports and Dr. Davies replied as I think we heard him say today, that he could account for 99 percent of the mass in his experiment. He referred to that as a 99 percent mass balance.

When I looked at his data with that in mind, I discovered that Dr. Davies inappropriately included a large solvent peak that is used, you used solvent to inject your HPLC sample into the chromatogram. I think he inappropriately included that solvent in his mass balance.

MR. MINION: Objection.

THE COURT: Yes.

MR. MINION: It seems like Dr. Ganem is offering a sure reply to Dr. Davies's reply report. He only has one main expert report.

MR. CHIN: Your Honor, Dr.

MR. CHIN: Your Honor, Dr. Ganem had a couple of different paragraphs explaining the missing other components. Dr. Davies responded in his surreply. I think Dr. Ganem is entitled to explain why he believes it, in his opinion that he sets forth, is a valid opinion in light of Dr. Davies' response --

THE COURT: Was his response before the two professors were deposed?

MR. CHIN: All of this was prior to the deposition. There were three reports.

Dr. Davies set forth his experiment. Dr. Ganem set forth his criticisms. And then and only then did Dr. Davies say he had an appropriate mass balance.

Then depositions were taken. That's the record. If we had to have a surreply for every single response to a response, I don't think we'd ever end up submitting expert reports.

THE COURT: Well, that's probably true. So basically what you are saying, what I'm about to hear is not in any expert report.

THE COURT: Well, that's --

MR. CHIN: The substance of it is in the expert report, Dr. Ganem set forth his criticism of the lack of accounting for other components and he merely explained why that is an appropriate criticism in light of what Dr. Davies said in his rebuttal report and his last three reports before depositions.

We're not getting into any new data. They're not getting into any new substance.

THE COURT: You have something more to say?

MR. MINION: I do. I want to say

two things: That what he was going into, what Dr. Ganem was about to go into talking about, the solvent peak and that wasn't in any of the reports, not in Dr. Davies' report, not in Dr. Ganem's report.

And I would like to point out that after the depositions were over, Dr. Ganem did supplement his expert report and he did not put this new opinion in.

THE COURT: Is that right, Mr. Chin?

MR. CHIN: It was a one-page supplemental to make some minor corrections to an entirely unrelated issue. This issue did not occur and it was to correct an error that was raised during the deposition.

THE COURT: All right. Well, I think you -- what you can actually do, you can probably make a point of what he made in his report, first report. So why don't you stick to that.

So I'll sustain the objection.

MR. MINION: Thank you, Your Honor.

MR. CHIN: If you can just give me a minute to --

THE COURT: Yes.

MR. CHIN: -- find the precise language of the original report.

BY MR. CHIN:

Q. Dr. Ganem, can you describe for me approximately how much of the non-volatile analytes that Dr. Davies failed to account or correct for?

A. Yes, I think I can. In Dr. Davies' experiment, it was about 92 to 93 percent of a material that was unreactive Rivastigmine. That leaves about seven or eight percent for the impurities of the reaction product.

But what Dr. Davies failed to account for, about one-fifth of that -- 20 percent.

Q. And what conclusions do you draw from failing to account for about one-fifth of the impurities?

A. Well, my concern as a scientist is that a large amount of undocumented material, it goes unrecognized. Some of this could have been formed, as I mentioned already, by the side reactions or direct reactions of TBHP with --

with these impurities, Impurity 4 and ECAV.

The net result of that is that it would alter the -- it would distort the actual percentages of those two impurities. And I believe this is important because, as we heard earlier today, Dr. Davies experiment relies on measuring minute differences between these impurity peaks, Impurity 4, ECAV and I'm concerned that these other components could have distorted that.

Q. Dr. Ganem, have you served as an editor or a reviewer for peer-reviewed journals in the chemistry literature?

A. Yes, for over a dozen years, I was the U.S. executive editor for a journal called International Journal of Organic Chemistry.

We typically handle about 500 papers a year in that office.

Q. In your opinion, would a scientific study that fails to account for other components in the system, as you discussed, be acceptable for publication in a peer-reviewed journal?

A. No, generally not.

Q. Let's turn to your second bullet point,

the co-elution issue that you mentioned. Can you describe why you believe failure to account for co-elution of these components is a flaw in the Davies experiment?

A. Yes. Well, as I just described to the Court --

THE COURT: Can you first describe what co-elution is?

THE WITNESS: I'll describe that. Give me just a moment.

THE COURT: Okay.

THE WITNESS: So I mentioned there was about 20 percent of these other products that went uncharacterized. And when one looks at one of the HPLC chromatograms that Dr. Davies did in this experiment, these other minor things are spread across the entire spectrum frequently bracketing one on either side of a peak of interest, such as Impurity 4 of ECAV.

Now, sometimes they're so close that the tail of one peak begins to merge a rise of another peak. That is, they overlap.

And when peaks overlap like this, the possibility exists of co-elution, which means

the two different compounds are coming out together, at least in part. That's what co-elution is and it's not an uncommon experience of HPLC analysis, especially when peaks are close together.

So the concern I have about this co-elution, different compounds showing up in the same peak, is that this is another factor that can distort the actual amount of a particular impurity. It could either contribute to or detract from the actual amount of the compound that's present.

And I think any good scientist would be concerned about that when, again, the differences being measured are such minute percent differences between control experiments and the test experiments.

Did I explain co-elution for you?

THE COURT: Yes. I get it. Yes.

BY MR. CHIN:

Q. Now, you heard this morning how Dr. Davies had identified the peaks, Impurity 4 and ECAV. Does that account for collusion?

A. So I raised this concern about co-elution.

This is one of my replies to Dr. Davies and he responded, first of all, by saying in the case of ECAV, he had taken a UV spectrum. We heard him testify to that today.

Now, a UV spectrum will tell you whether you have the compounds you believe you have. But other components can be present in a sample without -- that would not distort the ultraviolet spectrum. So that's not a very good explanation or response to my concern.

It indicates of Impurity 4, pardon me, the other impurity Dr. Davies responded simply by saying that he had shown that was ECAV by using an authentic standard. And I understand that, but that doesn't diminish the possibility of co-elution. So he really did not address my concerns.

Q. And, finally, if we can turn to the third bullet point, improper data normalization. Can you explain why you find that to be a flaw in the experiments?

A. Yes, I can. And to do so, it helps if I can show Dr. Davies' summary of his own data on a slide.

Thank you.

So this is from Dr. Davies' summary of his experiment in which he reports the results of his three control experiments, the absence of acetaldehyde and in the presence of acetaldehyde.

And we see he's measuring the three compounds I have spoken about, Rivastigmine, Impurity 4 and ECAV.

Now, Dr. Davies, I've already pointed out, I think, has erroneously decided to ignore these other minor peaks. But to make matters worse, he simply shows the yields of these three compounds in a way that they all add up almost magically to a perfect hundred-percent yield. And he achieves this by a process of data normalization.

It's a simple arithmetic maneuver that takes the sum of each of the -- the sum of all the areas of these peaks and calls that 100 percent. And then you take a fraction of each of these and you guarantee that the yields will turn out to be 100 percent.

My concern about this is that this maneuver, this arithmetic maneuver can easily

hide serious flaws in the data.

Q. In actuality, accounting for all of the material, including impurities in the test tubes, has he, in fact, accounted for a hundred percent?

A. Well, I think by this mathematical slight-of-hand, it looks as though he has accounted for everything. But if you look at the chromatogram, these are these other unidentified peaks that I've mentioned.

Q. Now, you had indicated that this technique has a potential to hide significant errors. Did you see any specific examples of errors in technique?

A. Actually I did. Yes, I did.

And it's the same error Mr. Brown pointed out earlier today, but I won't insult the Court by showing the data that I'm particularly concerned about. It was the A3 sample at 15 hours.

If Mr. Smith can pull that up for me. Thank you.

This is from his Appendix E, his summary of his experiment. Here are the

individual tubes for A3 taken, I believe, at the 15-hour point where we've already heard that Dr. Davies got a raw measurement of the Rivastigmine at about 6,937 units, which he pointed out represented a 98.39 percent yield.

Then, if we compare this tube A3 data to the 21-hour point, the same tube at 21 hours, as we've already heard, has almost magically increased in the raw data, accounts for Rivastigmine by about 50 percent to 10,185.

So once sees 50 percent increase in the area for that peak. But in the normalized yield calculation, we magically see the yield go from 98.39 down to 97.74.

Now, as a journal editor or an author, if I had a data point like this, this would immediately be tossed out because clearly something went very wrong in this experiment. And yet, it was included in Dr. Davies final analysis. This is inappropriate, in my opinion.

Q. When you received Dr. Davies' final analysis with his opening expert report, did it acknowledge this problem?

A. No, but I asked him about it. I raised

this point in my reply report and he responded, as we heard mentioned earlier today, that one explanation might be a loose seal on this tube, which would lead to solvent evaporation and a concentration effect that would increase the measured area in this loosened tube.

Q. Is it appropriate to include such data in the calculations?

A. No. I think this data point should have been tossed out. But, more importantly, the concern I have is that if the tube was leaking, one could confidently assume that some acetaldehyde would escape from that tube. It would be a high vapor pressure of acetaldehyde at 60 degrees. And over a prolonged period of time, I would think a substantial amount of acetaldehyde would have escaped along with solvent. So that totally compromises this experimental data point.

Q. Taking into account the issues you've discussed about study design and methodology, in your opinion, can Dr. Davies' experiment be scientifically relied upon to show that acetaldehyde is an antioxidant?

A. In my opinion, given the concerns that I've raised, I don't think any scientifically valid conclusions could be drawn from the experiment run by Dr. Davies.

MR. CHIN: Thank you, Dr. Ganem.

THE COURT: I'm sorry, sir. Can you just tell me your name again?

MR. MINION: Dan Minion.

THE COURT: Minion. Thank you.

Mr. Minion, you may proceed

CROSS-EXAMINATION

BY MR. MINION:

Q. Good to see you again, Dr. Ganem.

A. Good afternoon, Mr. Minion. Good to see you, too.

Q. So let's you and I talk a little chemistry. Okay?

A. Happy to do so.

Q. All right. You agree that Rivastigmine is susceptible to oxidative degradation?

A. Yes.

Q. And there's no question it's established scientifically that Rivastigmine undergoes oxidative degradation to form ECAV in Impurity 4?

A. Yes, I would agree with that.

Q. Can you put -- thank you.

You recognize this slide, Dr. Ganem?

A. I think this may have been an earlier slide shown today. I certainly recognize the compounds. Yes.

Q. All right. Dr. Davies walked through this.

He talked about the pathway of oxidative degradation of Rivastigmine.

A. Yes.

Q. And you recognize the oxidative degradation impurities ECAV and Impurity 4?

A. I do recognize them.

Q. Those are the correct structures of those compounds?

A. Yes, I believe so.

Q. And the first step of the oxidative degradation pathway that Dr. Davies walked through is an oxidation of Rivastigmine to the amine oxide. That's what he has there; correct?

A. That's correct.

Q. And that is the same structure that you had in on your slide showing the reaction of

rivastigmine with tertbutyl hydroperoxide?

A. Correct, I pointed out that's the product with direct oxidation.

Q. Once the amine oxide is formed, it's eliminated to ECAV?

A. Yes, that's a good technical term. It's an elimination reaction.

Q. And then it's further oxidized to impurity 4?

A. Yes. Dr. Davies said that this is one path to ketone, to the ketone shown as impurity four.

Q. One of the ways that antioxidants work is by undergoing oxidation themselves before the compound they are protecting; correct?

A. That's one mechanism, yes.

Q. That's how reducing agents like ascorbic acid work?

A. Agreed.

Q. You noted in your direct examination you looked at the specific antioxidants that are listed in the '031 patent?

A. I acknowledged the ones that are listed there.

Q. You saw ascorbic acid on the list?
A. I believe so.
Q. That's a well-known antioxidant?
A. Yes, it is. It's vitamin C.
Q. It's a reducing agent?
A. Yes.
Q. And, of course, ascorbic acid is susceptible to oxidation?
A. Yes.
Q. And when ascorbic acid acts as an antioxidant, it sacrifices itself by being preferentially oxidized over the compound that it protects?
A. I would agree that ascorbic acid acts as an antioxidant by getting oxidized, yes.
Q. And you agree that any chemical compound that is a known reducing agent must, in fact, be subject to oxidation?
A. Well, that's a bit flowery language, but yes, all reducing agents do get oxidized.
Q. And you agree that acetaldehyde is susceptible to oxidation?
A. I do.
Q. And I believe when you were going through

the photo chemical degradation of acetaldehyde in the McNesby article, you commented that acetaldehyde is oxidized readily at room temperature?

A. I think what I said was that my opinion these reactions to form these radicals could occur at room temperature, yes, I may have said readily.

Q. That's the oxidation of acetaldehyde by air?

A. I think what I said yes, the radicals would form under air oxidation fairly readily.

Q. And acetaldehyde can be oxidized by peroxides?

A. Yes.

Q. For example, you noted that acetaldehyde can be oxidized by tertbutyl hydroperoxide?

A. That's correct.

Q. You will agree by the very fact that acetaldehyde can be oxidized, it is capable of acting as an antioxidant?

A. I'm not sure what you mean capable, counselor. We know that an antioxidant works by getting oxidized, so to be -- if a compound is a

reducing agent, it has potential to be an antioxidant.

Q. But you never actually studied the potential role of acetaldehyde as an antioxidant?

A. No, I never conducted any experiments.

Q. And in forming your opinions in this case, you did not consider whether acetaldehyde can function as an antioxidant?

A. I'm sorry, would you repeat your question?

Q. In forming your opinions, you did not consider whether acetaldehyde can function as an antioxidant?

A. Well, I think the question that you asked and can be answered by saying acetaldehyde can be oxidized, so that means that at least it meets the minimal requirement that it could function as an antioxidant. I think even Dr. Davies conceded that point.

Q. But in forming your opinions, you set out to establish that acetaldehyde cannot function as an antioxidant for rivastigmine?

A. I'm not sure. I honestly am not sure how to answer your question. I'm not sure I understand what you're driving at.

Q. We talked about this at your deposition, right, the question of whether acetaldehyde can function as an antioxidant and whether acetaldehyde cannot function as an antioxidant in your opinion, those are distinctly different questions?

A. Yes, that's fine.

Q. And the question that you set out to answer to establish was that acetaldehyde cannot function as an antioxidant for rivastigmine?

A. I think it's correct to say I did consider that question. I tried to consider both sides of the question in forming my opinion.

Q. So you did a literature search to find some basis to support your opinion that acetaldehyde cannot be an antioxidant for rivastigmine. Do you remember that search?

A. I think I do, yes.

Q. And as a result of those searches, you put forth an opinion regarding the oxidation potential of those two compounds, acetaldehyde and rivastigmine?

A. Well, I did. But as you know, I withdrew my report on that, that section of my report

because of an error I made.

Q. We're going to get to your supplemental report, but let's go back to your original opinion. We're talking about oxidation potentials. You talked a little bit about redox reactions in your direct examination?

A. I did, but I did not mention oxidation potentials in my exam.

Q. You agree that an oxidation potential is the tendency of a compound to be oxidized?

A. Yes.

Q. In other words, the higher the compounds oxidation potential, the more easily it's oxidized?

MR. CHIN: Your Honor, I have an objection. I think this is going beyond the scope of direct.

THE COURT: I'll allow it.

BY MR. MINION:

Q. Do you want me to give you that one again?

A. Yes, please.

Q. Talking about oxidation potentials. The higher, the more positive the compound's oxidation potential, the more easily the compound

can be oxidized?

A. That's generally true, yes.

Q. So if a compound has a more positive oxidation potential compared to another compound, that means it's more easily oxidized?

A. Well, as you know, counselor, we have to be concerned about these being measured under identical conditions, but if you want me to stipulate that in fact we're talking about oxidation potentials being measured under identical conditions using identical electrodes, then what you say is generally true.

Q. Now, you provided an opinion that acetaldehyde cannot function as an antioxidant for rivastigmine because acetaldehyde has a lower oxidation potential than rivastigmine?

A. You know, I don't recall exactly how I phrased it, but as I told you, I made a conversion error when I did some of my calculations and I quickly withdrew my report when I found my error.

Q. I have your report. Do you need to refresh your recollection of what your opinion was?

A. Well, since I withdrew that section of my report, I'm not sure why we're talking about it.

Q. I said we're going to get to your supplemental report in a minute, but I want to talk about the way you set out in your opinions in this case, and we'll come there eventually, but in your original opinion you looked in the literature to look at oxidation potentials and as a result of that analysis, you set forth an opinion that acetaldehyde cannot function as an antioxidant for rivastigmine because acetaldehyde has a lower oxidation potential than rivastigmine?

A. Okay. So if you allow me to stipulate again that we're talking about an opinion that I later withdrew, I think that is what I had in my original report, yes.

Q. You were comparing standard oxidation potential, or you thought at the time you were comparing standard oxidation potentials?

A. That's correct.

Q. And you looked in the literature and you determined that the standard oxidation potential of acetaldehyde is 0.60 volts?

A. I think that may have been the number, yes.

Q. But you weren't able to find any reference providing an oxidation potential for rivastigmine?

A. That's correct. So far as I could tell, the oxidation potential for rivastigmine was not available in the literature, so I found several analogous compounds in forming my opinion.

Q. Was that the Lindsay Smith article?

A. Yes, I believe so.

Q. And the Lindsay Smith article talks about oxidation potentials of N-N dimethyl benzyl amines, substituted N-N dimethyl benzyl amines?

A. I believe that's correct.

Q. And those share a similar chemical structure to rivastigmine?

A. Yes. They would have just this, just this part right here, not that part.

Q. But in the Lindsay Smith article where rivastigmine has the carbamate functionality, the Lindsay Smith article had like trifluoromethyl and nitro and different substituted N-N dimethyl benzyl amines?

A. Honestly, counselor, I don't recall. It's been over a year since I looked at the Lindsay Smith article and as I pointed out several times, once I withdrew my opinion, I have not considered that article any further.

Q. Okay. I agree. I have your expert report if you have to refresh your recollection at any time, just let me know.

Now, you looked at the Lindsay Smith article and you calculated the oxidation potential of rivastigmine to be between 1.0 and 1.05 volts, higher than that of acetaldehyde?

A. I honestly don't remember what I calculated from a year and three months ago. As I say, this is ancient history and I assume when I withdrew my report that that would indicate that I was not offering that opinion.

Q. You recall that you calculated the oxidation potential of rivastigmine to be higher than that of acetaldehyde?

A. I think that's correct. What I was calculating was an estimate for rivastigmine based on the analogs in that paper.

Q. But your calculation was wrong?

A. I did use a conversion factor incorrectly, yes.

Q. You added when you should have subtracted?

A. It was a mistake which I quickly withdrew my opinion.

Q. When you subtracted instead of added, you discovered that the calculated oxidation potential for rivastigmine was .52 to .57?

A. Again, I don't remember the number, but the relative position of the numbers changed, yes.

Q. And as you have mentioned, subsequent to your deposition you have withdrawn the section of your expert report relating to oxidation potentials?

A. Yes, after I discovered my error, I simply withdrew that report, that opinion, that section of my report.

Q. Because the Lindsay Smith article does not provide a valid basis for comparison of rivastigmine and acetaldehyde?

A. Well, I withdrew it because in the end there was just too much uncertainty to draw any solid conclusion that I felt I could rely on.

Q. Because the Lindsay Smith article talks about oxidation peak potentials?

A. As I said, I realized I could not make a comparison that would be reliable one.

Q. Getting back to the question of whether acetaldehyde is an antioxidant, you testified that the sacrificial oxidation of acetaldehyde could promote the oxidation of other compounds?

A. That's not quite correct, counselor. I simply testified that the oxidation of acetaldehyde, I have not spoken about sacrificial oxidation today.

Q. But your opinion is that if acetaldehyde is oxidized, it might form a peracid compound?

A. If acetaldehyde is oxidized, it is known to form a peracid, yes.

Q. But you agree that acetaldehyde can also be oxidized to acetic acid?

A. Yes, that's true.

Q. And acetaldehyde?

A. And acetaldehyde can also be reduced.

Q. And acetic acid is not a known oxidizing agent; right?

A. No, that wouldn't be correctly true.

Acetic acid could be an oxidizing agent and it would in turn be reduced to, for example, acetaldehyde or even to ethyl alcohol.

Q. You agree that acetic acid is not a free radical?

A. Acetic acid per se is not a free radical, that is correct.

Q. And you're not aware of any testing that shows that acetaldehyde increases the oxidative degradation of rivastigmine?

A. No. As I said, I did not conduct any testing on my own.

Q. And you did not opine in your expert report that acetaldehyde was acting as a prooxidant based on Par's stability testing data?

A. I made no mention of prooxidants anywhere in my reports, in my report.

Q. You did not opine that acetaldehyde could promote the oxidation that -- actually let me rephrase that.

You did not opine that acetaldehyde promotes the oxidative degradation of rivastigmine based on Par's stability testing data?

A. From what I know of Par's stability testing data, acetaldehyde does absolutely nothing at all.

Q. Now, you said you acknowledge that you didn't do any testing in this case?

A. Well, first of all, I did, I did acknowledge that. I wasn't asked to consider doing that, and because of conflict rules at my university, I'm not permitted to do that.

Q. So you had several criticisms in your direct examination of Dr. Davies's methodologies?

A. Yes, these were technical criticisms.

Q. Now, you could have as a scientist gone through and repeated Dr. Davies's stress test?

A. Well, I have explained why I really can't do that at Cornell.

Q. So in this case, you were prevented from repeating Dr. Davies's stress test?

A. Well, I'll try to be as clear as I can. My university considers external consulting activities like these to be the sort of things I can't use university resources for, it's a conflict of interest and a conflict of commitment. See I just can't do it, and I'm the

head of my university's conflict committee so I have to set a good example.

Q. You could have asked someone else to do it; right?

A. I'm not sure what you mean by that. I can't ask anyone at my university to do it. I couldn't ask one of my graduate students to do it.

Q. You could have asked someone outside of the university?

A. I guess I could have. I didn't consider that.

Q. Well, let's come at it a different direction. Notwithstanding your agreement with the university, if you had permission to repeat Dr. Davies's tests, you could have done so?

A. Oh, it's not technically difficult, that's true, I could have done it.

Q. And you would have had ample time to repeat those tests?

A. Well, from what I heard about the time Dr. Davies spent doing it, if I had the protocol available, it doesn't sound like it would take a lot of time. I'm just not sure it would be the

appropriate test to do.

Q. But someone other than you could have rerun these tests to see if they could isolate and characterize any other degradation products besides ECAV and Impurity 4 in the reaction mixtures?

A. I think Dr. Davies could have done that, too, he just chose not to.

Q. Anyone on Par's side could have done that as well?

A. I can't speak for Par.

Q. And someone could have repeated Dr. Davies experiments to see -- to answer your question of whether there were any other co-eluting compounds in the peaks of ECAV and Impurity 4?

A. I think that would be straightforward.

Q. But as far as you know, that wasn't done?

A. Insofar as I know.

Q. You talked about potential errors in Dr. Davies's test. You're not a statistician, are you?

A. No, I'm not.

Q. And determining whether differences in oxidative degradation products between two

samples -- sorry, determining whether the differences in oxidative degradation products between two samples were statistically significant is not an area you have done much work in?

A. Correct.

Q. And you didn't conduct any independent statistical analyses of Dr. Davies's data?

A. That's right.

Q. But you did have the underlying data?

A. I had the data that was presented, I think it's called appendix E, Dr. Davies's experimental report.

Q. All right. So let's talk about tests to determine whether a compound in a transdermal formulation is acting as an antioxidant. Am I correct that it is your opinion that the only way to determine if a compound in a transdermal device is acting as an antioxidant is to conduct a stability experiment comparing two sets of patches, one set of patches that contain the compound and one set of patches that did not contain the compound?

A. So you asked me that question in my

deposition, and at the time it was an entirely hypothetical question. If you don't mind my reminding you, you didn't mention what we were testing. You didn't mention what the control and test would be. And I think I answered by saying it would be desirable to set up the test that way, yes.

Q. Desirable to set up the test with one set of patches that contain the compound in question and one set of patches that didn't?

A. Yes.

Q. And you testified that in your opinion to be a valid test, the two sets of samples should be made identically?

A. I believe what I said was that would be desirable, yes.

Q. At the same manufacturing site?

A. I think I said that, yes.

Q. Using the same process?

A. May I finish?

Q. Go ahead, sir.

A. I said that it would be desirable. Thank you.

Q. Using the same processes?

A. Yes, that's likely what I said.

Q. And having both sets of materials made using the same batches of starting materials?

A. I said that would also be desirable.

Q. From the same lot numbers?

A. If possible, yes.

Q. But the bottom line is that the two sets should be made under virtually identical conditions?

A. Well, just to be clear, I said you know, one is faced with designing this hypothetical test with, you know, no specific compounds being named, it was compound A I think we used at my deposition, I said it would be desirable to try to achieve those goals if possible, yes.

Q. That the patches should be made under virtually identical conditions?

A. As close as possible I said would be desirable, yes.

Q. To have a valid test to determine whether the antioxidant is functioning, whether the compound is functioning as an antioxidant?

A. Well, I think again, we were talking about testing a patch for an unspecified property and I

said that that would be desirable.

Q. And without having two identical sets of patches, one set with the compound, and one set without the compound, you cannot think of a way of determining whether the compound is acting as an antioxidant?

A. I don't recall saying that.

MR. MINION: Sorry, Your Honor. May I approach.

THE COURT: You may.

THE WITNESS: Thank you, Your Honor.

MR. MINION: I'm very sorry.

BY MR. MINION:

Q. Take a look at page 127, line five.

A. Okay.

Q. "Question: Just like your original methodology, that methodology requires a second batch of patches that do not contain the alpha tocopherol?

"ANSWER: Correct.

"QUESTION: Now, if you're not provided a second batch of patches that have no alpha tocopherol, in your opinion, is there any valid way of determining whether alpha tocopherol

is acting as an antioxidant in the composition?

"ANSWER: No, not that I can think of."

MR. CHIN: Your Honor, I think the basis of this testimony is talking about that methodology that they had discussed previously, just earlier in the deposition.

THE COURT: All right. You can bring it up on redirect.

Go ahead, Mr. Minion.

BY MR. MINION:

Q. Those are the questions and answers that you gave in your deposition?

A. Yes. Thanks for refreshing my memory.

MR. MINION: I have no more questions, Your Honor.

THE COURT: All right. Mr. Chin, how convenient.

REDIRECT EXAMINATION

BY MR. CHIN:

Q. Dr. Ganem, when Mr. Minion was asking you about that methodology in your deposition, what was he referring to?

A. I believe he was referring to a more or

less entirely hypothetical question about patches being tested. And I might have to refresh my memory.

Q. If you can just explain, in a general sense, I guess or perhaps I can --

MR. MINION: Objection, Your Honor. I object that the witness is reading from his deposition.

THE WITNESS: Well, I'm not supposed to read from the deposition?

MR. CHIN: I'll just rephrase the question.

THE COURT: All right. Go ahead, Mr. Chin.

BY MR. CHIN:

Q. Was Mr. Minion asking about Rivastigmine?

A. No.

Q. Was Mr. Minute asking about any type of Par product?

A. No.

Q. Was Mr. Minion asking about FDA guidance-related products?

A. No, he was not.

Q. Was it a hypothetical situation?

A. Yes, it was a hypothetical situation. He was careful to structure his question that way.

Q. Mr. Minion, during his cross-examination, made reference a couple times to sacrificial oxidation. Have you seen any evidence in this case or heard any evidence from Dr. Davies that acetaldehyde undergoes sacrificial oxidation?

A. I only heard Dr. Davies this morning mention that a compound that is a reducing agent undergoes sacrificial oxidation. And that is not my understanding of the definition of reducing agent and no freshman chemistry student would accept that, either.

The reducing agent refers to a compound that simply undergoes oxidation. There's no restrictive adjective that goes along with that word oxidating.

Q. Mr. Minion also asked you about the issue of oxidation potentials that was raised earlier on in this case. And you, I think, had indicated that you had made or the corrections were needed to conversion of oxidation potentials.

Based on the corrected oxidation potentials, was there any information that you

saw that suggested that acetaldehyde is an antioxidant?

A. No. And as I say, when I discovered my error, misapplying this correction factor, I withdrew my opinion on that matter.

Q. I believe Dr. Klibanov had responded to your expert report on the issue of oxidation potentials?

A. Yes, he did. Dr. Klibanov, whom I know, also -- well, perhaps I can only say that he made no mention of any misapplication or correction factor so it went undetected until my deposition.

Q. Both you and Dr. Klibanov missed the conversion?

A. Apparently so.

MR. CHIN: I have no further questions.

THE COURT: All right. Thank you, Mr. Chin.

Dr. Ganem, you can step down.

THE WITNESS: Thank you.

THE COURT: So why don't we take our afternoon break of 15 minutes and come back then at about somewhere between ten and five of 4:00

to finish out for the day.

THE CLERK: All rise.

(A brief recess was taken.)

THE CLERK: All rise. All right please be seated. Mr. Fineman.

MR. FINEMAN: Yes, Your Honor. We have a short housekeeping matter on confidentiality, Your Honor.

THE COURT: Okay.

MR. FINEMAN: I believe that during Dr. Davies' examination, two exhibits were used JTX 065 and JTX 200.

And we've conferred with 3M and we would like to place those exhibits under seal and 3M would like to reserve the right to review the transcript and then propose redactions.

THE COURT: I'm sorry, that cannot be right. What were the exhibit numbers?

MR. FINEMAN: I have written down JTX 065 and JTX 200.

THE COURT: G?

MR. FINEMAN: J, Joint Trial.

THE COURT: Sorry. Sorry.

You say 65 and 200?

MR. FINEMAN: That's correct, Your Honor.

THE COURT: All right. So we'll put them under seal.

We'll place them under seal and 3M can look at the transcript and weigh in on that in due course. Okay.

MR. FINEMAN: Yes, Your Honor. And when Dr. Dizio is testifying, there will be a use of JTX-065 again; however, this one will have -- this will not be the same copy of JTX-065 that plaintiff was using because this is with the --

THE COURT: Redactions?

MR. FINEMAN: Exactly.

THE COURT: Right.

MR. FINEMAN: More accurate, Your Honor, less than complete.

THE COURT: Okay. All right.

MR. FINEMAN: And we'll work that out.

THE COURT: Okay. Well, that's good.

MR. FINEMAN: Thank you, Your Honor. Your Honor, at this time, Par calls James DiZio.

THE COURT: All right.

MR. FINEMAN: Your Honor, I'm informed that it was not 200. It was 177.

THE COURT: Okay.

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

THE WITNESS: My name is James Dizio. It's J-A-M-E-S D-I-Z as in zebra I-O.

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

JAMES DiZIO,

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

THE CLERK: Thank you. Please be seated.

MR. FINEMAN: Your Honor, permission to approach?

THE WITNESS: Thank you.

DIRECT EXAMINATION

BY MR. FINEMAN:

Q. Good afternoon, sir.

A. Good afternoon.

Q. Could you please introduce yourself to the Court?

A. Yes. I'm James Dizio.

Q. Could you please briefly describe your educational background?

A. Yes. I have a B.S. degree in civil engineering. I worked as a mechanical engineer for about four years and then I went back to school and got a Ph.D. in organic chemistry, synthetic organic chemistry from the University of Illinois, one of the top schools in the country for that type of chemistry.

Q. Where are you currently employed?

A. 3M. It's a great company.

Q. How long have you been employed by 3M?

A. Well, since 1991, so 23 years.

Q. What position do you hold at 3M?

A. I'm a lead chemist in the materials resource division.

Q. What are your responsibilities as lead chemist in the materials resource division?

A. I -- I -- you know, I invent, develop, and I scale molecules and polymers for, you know, all of 3M's business divisions. 3M has many business

divisions.

The materials resource division is like 3M's internal chemical company.

Q. Does any of your work relate to pharmaceutical products?

A. Yes. You know, in the last few years, I've been focusing on medical products in general. You know, U.S. population is getting older. I don't want to say anybody in here, but the U.S. population is getting older, and you know, 3M is the perfect place. I mean it.

3M is the perfect place to innovate for this population and we are.

Q. Do these pharmaceutical products include transdermal drug delivery patches?

A. Yes.

Q. Can you please describe 3M's experience with transdermal drug delivery patches?

A. Yes. 3M -- 3M is an innovator in these patches. I'd say 3M has been working in transdermal patches for probably 30 years.

And so, you know, we've made single-layer patches. We've made multilayer drug in adhesive patches, and I'd say that the patches

we make are industry standards.

Q. Does 3M engage in FDA good manufacturing practices with respect to medicinal products such as transdermal drug delivery products?

A. Yes, we have. You know, yes, and we follow every FDA guideline.

We follow good manufacturing practices. And by good manufacturing practices, it's a detailed way to do procedures. You know, 3M makes a lot of products.

We make a lot of products. But when it comes to medical, there's good manufacturing practices. And that's a cut above industry practice.

You have to be very detailed so, and we actually surpassed all the requirements we're asked to do and we surpass them. You know, we surpass them because we want to. And we surpass them because it's good for the customer.

And, you know, the customer knows that and that's why they buy from 3M.

Q. Now, Dr. Dizio, I'd like to turn your attention to 3M's Rivastigmine transdermal patch and its development?

A. Yeah.

Q. Were you involved in the development of the Rivastigmine transdermal patch product that 3M developed that's the subject to this litigation?

A. Yes. Yes.

I developed the adhesive system 3M cleverly calls it R-217149.

Q. What was your role?

A. My role is to -- is to develop and scale the R-27149 for a variety of drugs that we're looking at.

Q. How did you first become involved with the Rivastigmine transdermal patch product?

A. I was approached by the drug delivery systems. So, again, 3M has many different companies, in essence, that we all work together.

One was called drug delivery systems division. And I was approached by people there and they said, "Hey, Jim, can you make an adhesive for these variety of drugs that we're looking at making patches for?" And I said, "Yes. I certainly can."

Q. What requirements, if any, did the drug

delivery systems division communicate to you about the adhesive they were looking for?

A. Well, it's a variety of requirements with a delivery patch. First and foremost, the drug has to be stable to live in the patch. It has to be compatible with the patch.

And, you know, you want to -- so that -- well, that you know you need to figure out what monomers go into that polymer, so that adhesive will be compatible. So that's number one.

Then you have to think about molecular weight. You know, when they formulate, you wouldn't want the patch slipping all around your skin. That's not going to be any good.

You have to make sure the polymer you can get of a certain molecular weight, and it's got to be a polymer, which we can sufficiently clean. You can't clean every polymer, so we know and we are very serious about this.

In 3M, if you're going to work on medical product, you're going to use an exceptionally clean adhesive. So it's got to be

an adhesive where you design this thing such that it can be cleaned. And we do that.

We do that especially because when you clean that adhesive, then you can, for drug delivery systems for formulators, they can minimize what goes into that formulation because they're quite stable.

Q. How did you go about achieving an exceptionally clean adhesive?

A. As I was -- well, you -- well, okay. So you make a polymer.

And when you say make a polymer, I mean, you start with the parts. They're called monomers. And you have an initiator.

This initiator starts the chain reaction that makes this big polymer. But when you're done with that, you know there's going to be monomers, initiators left. They're impurities. They're residuals.

And there's things, side reactions you don't know about. And you just want to get rid of them.

So we wash the material, a washing. So we clean the materials such that there's only

polymer left. And then many times, we will distill solvent, so we can get rid of any boilers or we can adjust the solvent system.

MR. FINEMAN: Your Honor, at this time, we respectfully ask that the Court close the courtroom to the public and to those not entitled to access to 3M's highly confidential information for a brief period.

THE COURT: All right. So I would ask anybody who's not sitting at counsel table or otherwise designated to please leave the courtroom. I don't think, based on what I've been told, this is going to be more than fifteen minutes.

All right. So I see outside experts on one side who I recognize, outside experts that I'm guessing on the other side, attorneys that I recognize, 3M, there is people over there, but -- so we're good; right?

MR. FINEMAN: Yes, Your Honor.

THE COURT: Go ahead, Mr. Fineman.

MR. FINEMAN: Thank you, Your Honor.

BY MR. FINEMAN:

Q. Dr. DiZio can you please turn to JTX 177

in your binder?

A. I'm there.

Q. Do you recognize this document?

A. Yes. Yes. This is the drug master file which we call the DMF. This is the DMF for solvated acrylate copolymer adhesive, R-27149.

Q. Is R-27149 the adhesive in the rivastigmine transdermal patch that 3M makes?

A. Yes.

MR. FINEMAN: Your Honor, since I not sure if JTX 177 is in the record, at this time to the extent it's not in, Par moves the admission of JTX 177.

MR. MINION: No objection.

THE COURT: If it's not admitted, it's admitted without objection.

BY MR. FINEMAN:

Q. What does this document generally describe?

A. This document would describe the adhesive R-27149 and the process it uses to make it.

Q. Did you draft any parts of this document?

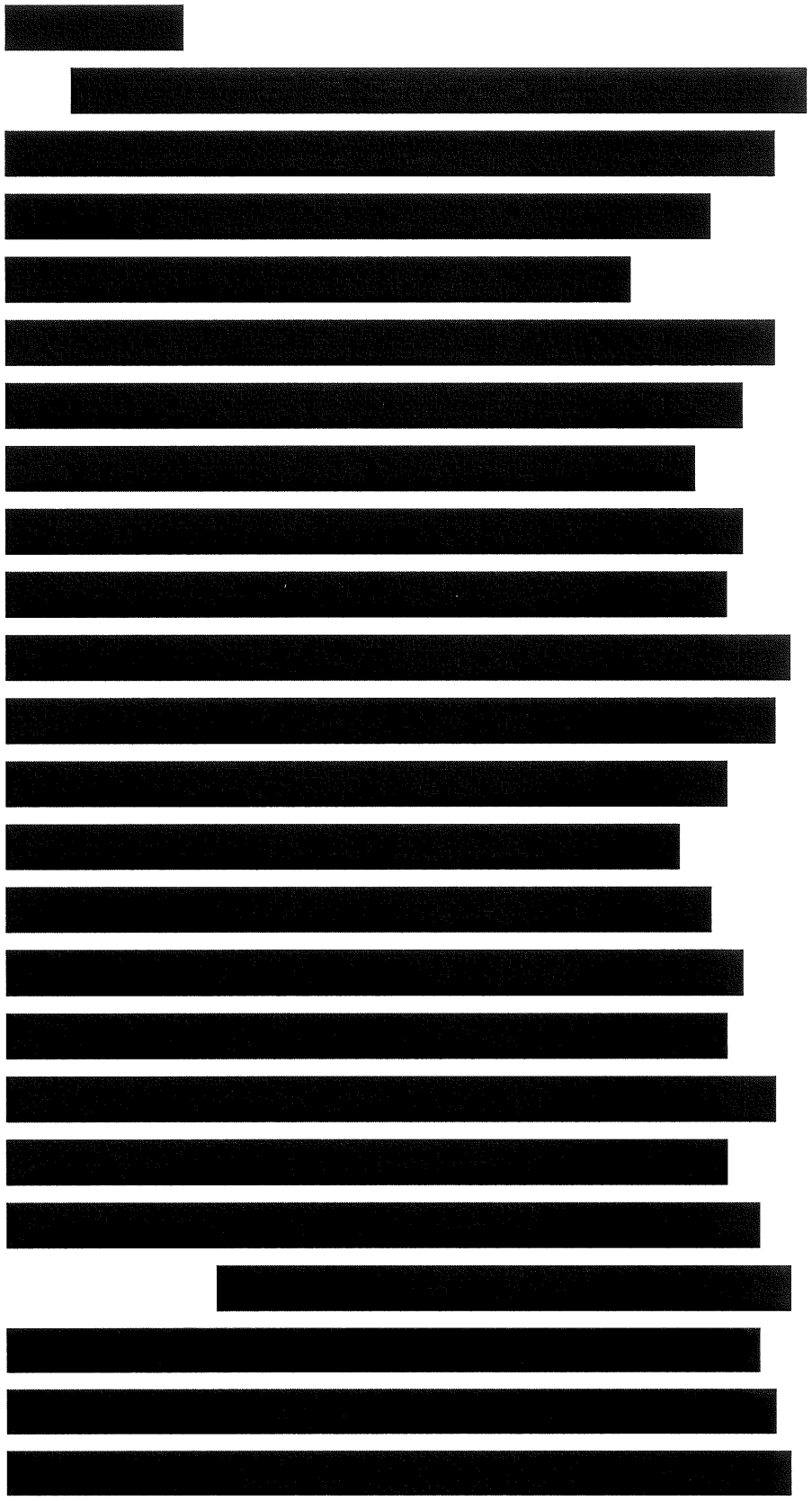
A. Yes, I submitted drafts for sections two and three.

Q. Can you please turn to section three on page 25614 entitled synthetic route of manufacture?

A. I'm there.

Q. Can you please describe the steps described in the DMF and manufacture of the R-27149 in general terms?

[redacted]



[redacted]

Q. Did you reach a conclusion of what is the effect of the washing distillation steps?

A. Yes, the effect is to clean the polymers substantially so that it meets the specs, it doesn't have residuals, doesn't have initiators, it doesn't have things you're not looking for. You're left with polymer.

Q. Is the commercial manufacturing process described in the DMF the process that 3M used to prepare the R-27149 adhesive contained in the rivastigmine transdermal patch product that 3M

developed?

A. Well, now you're getting exact. And yes, it is. It is the process. But we reserve the right to change some temperatures slightly and to change time slightly because like we said, we're looking for a certain way, we're looking for certain viscosities, we're looking for certain percent solids, so we may change some temperatures slightly to get it.

Q. Did you develop this manufacturing process?

A. Yes.

Q. Has 3M filed any patent applications on this manufacturing process?

A. Yes.

Q. Can you please turn in your binder to JTX 017, and when you get there, sir, my question is, do you recognize this document?

A. I'm there. And I do recognize the document. This is the patent application WO-2012/012417 Al, it's the patent application for the process we just discussed.

MR. FINEMAN: At this time, Your Honor, Par moves the admission of JTX 017 into

evidence.

MR. MINION: No objection, Your Honor.

THE COURT: It's admitted.

BY MR. FINEMAN:

Q. Are you a named inventor on this patent application?

A. Yes.

Q. Can you please turn to the general and detailed descriptions of the copolymer solvent washing process on page 17 of the application?

A. I'm there.

Q. Did you draft these section of the patent application?

A. Yes, I submitted drafts. These are the drafts.

Q. Do these sections describe the washing and distillation steps in the manufacturing process 3M used to prepare the R-27149 adhesive?

A. Where in general, yes, they describe the process that then went to the manufacturing plant. These actually when you look at the numbers, like if you look at line number 13, it says a hundred grams of copolymer A is added

to -- a hundred grams, that's my lab.

So it's not the manufacturing, it's not 10,000 pounds, so yes, this is a general description of what went to the manufacturing plant, but these actually describe my own bench scale or lab scale experiments.

Q. Now, do you have an understanding that there is a contention that rivastigmine transdermal patch product 3M developed contained acetaldehyde?

A. Yes. But acetaldehyde would be an impurity to us. We're looking to get rid of impurities.

Q. Where does that acetaldehyde come from?

A. It's an impurity that comes from the manufacturing of the polymer, specifically one of the parts is vinylacetate and that vinylacetate can have side reactions that create acetaldehyde, the impurity.

Q. Does 3M ever add acetaldehyde to its R-27149 adhesive for the rivastigmine transdermal patch that 3M developed?

A. No, absolutely not.

Q. I want to put JTX 065 up on the screen and

bring up table one on page 721. And I would like to walk you through some of the information here, if that's okay with you, Dr. DiZio?

A. Ready.

Q. Do you see the batch that has 300 parts per million acetaldehyde?

A. Yes.

Q. Do you see the comments in the table?

A. There is various comments. I see the comment on the right-hand side and left, yes.

Q. What, if anything, do the comments in the table tell you about this batch?

A. Well, if you -- okay. If you go to the first column, you'll see in parenthesis, 236. That is a batch number for a polymer made in the manufacturing plant. And if you go to the very right, you'll see the words unwashed adhesive. So this is, you know, how I described it, you make, you wash, and you distill. This is to make. And it means we did not wash it, nor distill it, but it is made in the manufacturing plant, it's just not washed.

Q. And what about the batches below this one that contain between 211 and 402 parts per million

adhesive lot. What if anything do the comments in the table tell you about those batches?

A. Again, if you look at the acetaldehyde, the first column, this is a suffix, ED 2. So that's me, and so that is my lab scale first ever made batch. In fact, there wasn't even a process back then. This is the first time I ever tried to make, wash the material. I didn't even distill it. So this is my first ever experiment. And so it's a lab scale, bench scale wash, but really the way I wash it, I wash it well, I got to admit, I do wash it well, but you know, this is a very viscous polymer, so when I'm washing it and trying to get the methanol to interact with the polymer, I'm shaking it by hand, I'm not doing a very good job, or I'm not doing as good a job as the manufacturing plant can do.

It's indeed a good job, but it's not like the manufacturing plant. I don't have the equipment. So this is my first ever material. It's not distilled, either.

Q. Are there any of the batches in this table representative of the process that's described in the DMF in your patent application?

A. Yes. The lots 20,007 and 20,008, if you look on the first column. So I picked those because those are manufacturing batches, they're lots seven and eight, so you know, we got pretty good at making this after a few batches, right, you can't look at the first batches, but you can certainly look at the most recent batches, and lot seven and eight, we would have gotten pretty good at washing and distilling and doing this process in the plant so they would be the most representative on this page of a manufacturing plant.

Q. How does the manufacturing scale process differ from your bench scale process?

A. Well, the manufacturing process can do much better job in intimately washing this material. Imagine, you know, when I'm in my lab, you can image like I'm doing a good job, but I'm not like a great washing machine. This in this plant there are these big impellers that just beat the heck out of this polymer and intimately mix it with the washing solution and therefore you can get a much better washing of the polymer. In my lab I can do a good job, but the

manufacturing plant can do a better job.

Q. Does 3M prepare batches for commercial marketing on the bench scale?

A. No.

MR. FINEMAN: Thank you, Dr. DiZio. No further questions at this time.

THE COURT: Thank you, Mr. Fineman.

Mr. Minion.

MR. MINION: Thank you, Your Honor.

BY MR. MINION:

Q. Hi, Dr. DiZio.

A. Hi.

Q. Let's talk a little bit more about your involvement with the R-27149 adhesive. It's my understanding you began working on the R-27149 adhesive around five years ago?

A. That's about correct, yes

Q. And prior to that, you had never developed an adhesive for use in a transdermal product?

A. That's correct. I developed adhesives for the many business divisions in 3M and this would have been my first drug delivery one.

Q. You don't know who actually first

synthesized the R27149 adhesive?

A. I know that representatives of materials resource division made the polymer years ago, the unwashed version.

Q. And so you testified you looked to the DMF. You testified that the R27149 adhesive is washed?

A. The R27149 adhesive is washed and distilled. Yes.

Q. And it's washed until specifications are met?

A. Yes. It is washed until specifications are met.

Q. But you don't know the specification for acetaldehyde in the R27149 adhesive?

A. Well, the washing process, in general, we're washing to get out -- actually the beauty of the way we wash, it's expensive and we pay for it, and the beauty of it is that you wash out things that you know about, which we're checking for and things we didn't know about. So we know we're getting rid of almost any impurity.

Q. Well, let me take a step back. R27149 adhesive is washed?

A. Yes.

Q. All right. Not for a set number of times?

A. The DMF shows three times.

Q. Right. But it's washed until the specifications for the adhesive are met?

A. And when you rely on the process, as we currently do, and you look at the data from the process, it takes three washes.

Q. But you do not know the specification for acetaldehyde in the R-27149 adhesive?

A. The specification for acetaldehyde, I know that, once again, we are ridding the system of impurities. There's -- you know, we indiscriminately rid the system from impurities. And --

Q. That's not my question. I'm asking about the specific specification number for acetaldehyde that's allowed in the manufacturing process to be acceptable.

A. Well, when you look at the data that is on that chart, you'll see that when we do follow this process, which we have to by GMP guidelines and how we've set up the DMF, we will get a percentage of -- well, we'll get a certain PPMs

of acetaldehyde. And it's stated in that chart.

Q. But you don't know the number of PPMs of acetaldehyde that are allowed to be in the product to meet specification?

A. To meet specification toxicological specifications, 3M has people from drug delivery systems, submitted paperwork and experiments that would give them toxicological limit. Now, we, in the plant, we wash this baby until we meet specifications from the monomers which get the acetaldehyde down to levels you see in that test.

Q. Do you know the number for acetaldehyde in the specification?

A. The toxicological limit?

Q. The amount of acetaldehyde that's allowed in the product.

A. The -- well, you know, it's too simplistic to say that. There's different reasons and acetaldehyde is -- if there is a specification, it is a toxicology specification.

So, for instance, if you say what's the specification for water, oh, huge because water is not toxic. And so neither is -- not really is acetaldehyde.

Q. You've never done any testing to determine the acetaldehyde content of the R27149 adhesive?

A. I have never done that. No.

Q. All right. That's because you're not an analytical chemist?

A. Because I'm not part of that team.

Q. So you're not involved with the team that does analytical testing of the R27149 adhesive?

A. I'm not part of that team. Well, I'm part of the -- yes. I'm not part of the analytical team. I'm part of the team from which analytical is also a part.

Q. Understood. You mentioned that, as a result of your work on the R27149 adhesive, you filed a patent application?

A. We followed the -- we are required to follow a DMF and the FDA guidelines, and so we follow the DMF and FDA guidelines.

Q. I'm sorry. I think you misheard my question.

I think you mentioned on your direct examination that, as a result of your work on the washing procedure of the R27149 adhesive, you filed a patent application.

A. That is correct.

Q. Okay. Now, in that patent application, there's no discussion of acetaldehyde.

A. It's an impurity. There's no discussion of it.

Q. Can you put up JTX 017? Actually you should have it in your binder as well, Dr. Dizio.

If you turn to Page 5 of the patent, and you see at Line 6, it discusses what the patent term, what essentially free of any added antioxidant means?

A. Yes. I see those words.

Q. We've got it up here. It should be on your screen as well.

A. Yeah.

Q. The patent says, "As used herein, 'essentially free of any added antioxidant' refers to a transdermal adhesive composition to which no antioxidant has been added for the purpose of preventing a pharmaceutically active compound susceptible to oxidative degradation from forming total drug impurities in excess of two percent within two years at room temperature or two months at 60 degrees Celsius with ambient

humidity. For certain embodiments, preferably less than 0.1 percent, more preferably less than 0.05 percent, most preferably less than 0.01 percent antioxidant is present in the transdermal adhesive composition, which is 'essentially free of any added antioxidant'".

Have I read that correctly?

A. You did.

Q. Now, when it says for certain embodiments preferably less than 0.1 percent of antioxidant is present in the transdermal adhesive. 0.1 percent is a thousand PPM; correct?

A. That's correct.

Q. So a transdermal formulation containing 1,000 PPM antioxidant would satisfy the definition in your patent application as being "essentially free of any added antioxidant"?

A. Now, again, you're asking me about the wording of the patent; right, and this isn't -- I don't know. See, again, I'm not a lawyer and I am a chemist and I scale things up.

I make sure that the customer is well satisfied and the FDA is satisfied. This is a paragraph in the text of a patent and I see

what it says.

And I can tell you that when it comes to the process that I do in 3M for drug delivery systems, I look to get rid of anything and everything from that polymer. I don't look to add anything. It is the spirit of what I do to give clean polymer.

Q. I'm going to ask you some questions now about the extent of your involvement with 3M's Rivastigmine patches. All right.

We talked about your adhesive. I want to talk about 3M's actual patches.

A. Okay.

Q. You're not involved with the formulation of 3M's Rivastigmine patches; right?

A. I am part of the team and, you know, the good part about 3M and I really mean this, is that we trust each other. And we all have different jobs to do.

My job is to give them the cleanest reagent I can possibly give them. Why? Because that simplifies their job.

And I trust that they do their job well. So it's too simplistic to say, no, I'm not

involved in the patch. What is true is that I give them the cleanest reagent I can possibly do and that aids in their job.

Q. You've not been present for the formulation of the adhesive or for the Rivastigmine transdermal patch with its components?

A. No, because, once again, that would cause me not to work on other products in 3M. I trust what my formulators are doing.

Q. And you never actually prepared an active drug in the transdermal formulation?

A. No, it wouldn't be necessary.

Q. Including Rivastigmine?

A. Including Rivastigmine.

Q. And you've never researched whether Rivastigmine is susceptible to oxidative degradation?

A. I have not.

Q. And you never personally reviewed the results of any stability testing on Rivastigmine?

A. I have not. Now, once again, you know, we all work as a team. And if we all overlapped on each other's responsibilities, first off, 3M

would not be a great company.

We have certain responsibilities and we know -- we know what others need and we deliver that. So just because I haven't done that, actually that's a good thing.

Q. I'm trying to establish where you are in the whole scheme of things.

A. I'm an essential part of that team as I'm on many teams on 3M.

Q. But with respect to 3M's Rivastigmine patches, you're not part of the analytical team?

A. I am not an analytical chemist. No.

Q. And you've never seen a certificate of analysis for any of the batches of 3M's Rivastigmine patches?

A. No.

Q. And you've not investigated the acetaldehyde content of 3M's Rivastigmine patches?

A. I have not. I look to rid the system of it.

Q. But you don't recall seeing any data related to acetaldehyde content in 3M's Rivastigmine patches?

A. Say it again, Dan.

Q. You don't recall seeing data related to acetaldehyde content in 3M's Rivastigmine patches?

A. Well, that was one of the examples I just saw here today. That's one of the -- I see data in these hand-outs.

Q. That's for the adhesive. I'm talking for the Rivastigmine patches.

A. Oh, no, I haven't seen that. Again, we're looking to rid the system of impurities.

I think, you know -- you have to. We don't want it. We don't want anything we don't know about.

Q. I asked you about the manufacture of 3M's Rivastigmine patches. You've never actually seen 3M's Rivastigmine patches being manufactured?

A. No, they are in California. I have other jobs to do.

Q. And you've never seen a document describing how 3M formulates its Rivastigmine patches?

A. I know that the formulation is -- because of what I'm giving them is probably fairly

simple. But, no, I would -- that would be formulated in the coating plant.

Q. So you don't know the components of 3M's Rivastigmine patches?

A. I know what I supply and I know that because I supply an exceptionally clean adhesive and that I only give them the polymer, they can minimize the reagents that they put in there.

Q. You supplied polymer in the past; right?

A. I supplied polymer to drug delivery systems, yes, and to other business units.

Q. All right. But if 3M in the future were to manufacture Rivastigmine patches on behalf of Par pharmaceuticals, you do not know what adhesive 3M would use in that formulation?

A. What adhesive 3M would use?

Q. Correct.

A. That's an interesting question. I mean, that's like saying if you had to start all over again, what would you do?

I think if I had to start all over again and drug delivery had to start all over again, we'd do the same thing. So almost like you're from drug delivery saying, Hey, Jim, let's

make an adhesive for a patch. We have a history with a certain adhesive and we know it works.

So my guess is we would pick the same group. Right?

Q. But you don't know; right?

A. But you don't know, either. I mean, who would know?

It's like saying, Hey, make a patch. Well, with this -- if they -- if we're going to use the adhesive that we developed for this drug, we're going to use the adhesive I developed. Yes.

Q. Okay. But if 3M were to manufacture a Rivastigmine transdermal formulation incorporating the R27149 adhesive, you do not have an understanding of how that adhesive would be prepared?

A. I have the adhesive being prepared. Again, and we have a DMF and that DMF details how to do it.

We are going to follow that because that's what we've told the FDA again it's -- and it's good for the customer and I'm very proud. 3M is very proud of this adhesive. This is good

for the customer. This adhesive is exceptionally clean.

It is a minimalist. When you make a medical product, you don't want to add stuff. You want to have the minimum that you possibly can have.

It's just generally a good idea. But it costs money to do it and that's why people like 3M, because we spend the money to do that.

Q. If 3M were to manufacture Rivastigmine transdermal formulation incorporating the R27149 adhesive, you do not have an understanding of how that R27149 adhesive would be prepared in the future?

A. I -- okay. So it's almost like you're saying, Hey, anything can happen. But anything can't happen. This is business.

In business, you've spent the money to scale a product. You paid people like me and my team to do an exceptional job for the customer. It would be unlikely that you would not go there.

It would -- it would be almost impossible. But so I think we would use the

adhesive scaled for this purpose.

MR. MINION: No more questions, Your Honor.

THE COURT: All right. Any redirect, Mr. Fineman?

MR. FINEMAN: No redirect at this time, Your Honor. We have no objection to reopening the courtroom.

THE COURT: Okay. Well, let's if somebody -- if I can ask Ms. Lester to go back and -- in any event, Dr. Dizio, you may step down.

THE WITNESS: Thank you. Judge, the book?

THE COURT: Leave the book there.

THE WITNESS: Okay.

THE COURT: They'll take care of it.

All right. What's next?

MR. FINEMAN: Your Honor, at this time, Par will be playing certain video deposition designations. Although I think we may still have a couple small issues.

THE COURT: All right. Well, start playing them.

MR. FINEMAN: Thank you, Your Honor.

MR. SILVER: I think we may be able to address them on the front end, if we can. Mr. Loh is here.

THE COURT: All right. I'm charging the time to you all.

So, go ahead.

MR. LOH: Just briefly, Your Honor, the substance of the testimony that you're about to see comes from an inventor and two, 30(b)(6) witnesses, one Novartis, one LTS.

It's not clear from opposing counsel what they intend to use the testimony for. They indicated it's both for infringement and validity. Based on the substance, we believe it's probably more related to validity.

And, as Your Honor knows from the pretrial order in this case, those issues are written description, definiteness and enablement. Each of these inquiries is one that is assessed from the objective standpoint of the person of ordinary skill in the art. And it's from his perspective looking at the '031 patent and the disclosures therein.

The testimony that you're going to see is about what the inventors, Novartis and LTS did and believed before the '031 patent was even filed by the Patent Office. So, for that reason, we'd submit that the deposition testimony that you're about to see is, in fact, irrelevant to the validity issues in this case.

Additionally, to the extent that they're going to transform this fact testimony into opinion testimony relating to the person of ordinary skill in the art used, we don't think there's a foundation for that. And so we think this testimony is also improper opinion testimony and there's no foundation to offer this particular testimony as that of the person of ordinary skill.

That's the basis for our objection.

THE COURT: All right. Well, I'm going to overrule your objections, not because I think you're misstating the law, but because I'm going to charge the time of playing this to Par. If it turns out to be irrelevant, tough. Then, it's just irrelevant.

MR. LOH: Understood. Thank you,

Your Honor.

MR. FINEMAN: Your Honor, I think there is an issue with one counter designation in the third deposition, the Ogorka deposition while we're --

THE COURT: Why don't we play the first two deposition and then I'll hear you on the third one.

MR. FINEMAN: I was going to say I'm going to try to work it out with Mr. Silver while we're playing it.

THE COURT: All right. Even better.

(Beginning of videotape deposition excerpt:)

Q. Can you state your name for the record?

A. Harry Tiemessen.

Q. But you're aware that antioxidants act as reactive oxygen scavengers?

MR. MINION: Objection to form.

THE WITNESS: I think I heard of that, yes.

Q. Dr. Tiemessen, you've been handed what's been marked as Tiemessen Exhibit Number 20, Bates labeled N0257460 through N0257466; is that

correct?

A. That's correct.

Q. And this is United States Patent Number 6,316,023; is that right?

A. That's right.

Q. Are you familiar with this document?

A. Yes.

Q. And are you listed as an inventor on this patent?

A. That's correct.

Q. If I could direct you to Column 4 of the patent, which is N0257462.

A. Which column?

Q. Column 4.

A. Four, okay.

Q. Line 14, it states, "The applicant has found that an effective stabilizing effect is surprisingly achieved when the antioxidant is selected from tocopherol, esters thereof, e.g., tocopherol acetate, ascorbyl palmitate acetic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate, preferably alpha tocopherol or ascorbyl palmitate."

Did I read that correctly?

A. You read that correctly.

Q. And so there's a listing here of antioxidants; is that correct?

A. That's correct.

Q. And as those compounds are antioxidants, a pharmaceutical formulator would understand that those compounds can be added to a formulation to stabilize that formulation; is that correct?

MR. MINION: Objection to form.

THE WITNESS: These antioxidants, they can be used in a certain set of circumstances for certain compounds, certain formulations to -- to stabilize and to reduce the level of oxidation.

Q. And a --

A. But it's not -- not that you take just one and put them in and it works. That is not the case. It can even be worse if you add an antioxidant. So this is high level of fine-tuning that's required on that.

Q. Did Sandoz or Novartis ever test any antioxidants listed here for use in the rivastigmine transdermal system other than alpha tocopherol and ascorbyl palmitate?

A. Not that I'm aware of.

Q. We talked just a bit a few minutes ago -- well, you said that Novartis never assessed acetic acid, butylhydroxytoulene, butylhydroxyanisole, propyl gallate. How do you know that those antioxidants would have a stabilizing effect on rivastigmine?

MR. MINION: I object as outside the scope of the 30(b)(6) notice.

(Witness peruses the exhibit.)

MR. MINION: And to form.

THE WITNESS: I think it have to be investigated.

Q. So you're not aware -- I'm sorry. You're not aware of any if the antioxidants in that list other than alpha tocopherol, would have a stabilizing effect on rivastigmine in a rivastigmine transdermal system?

MR. MINION: Objection to form. Outside the scope of the 30(b)(6) notice.

THE WITNESS: I have not seen these data.

(End of testimony)

Q. What's your current job title there?

A. I'm heading the project management department in LTS.

Q. And when did you start in that position? Sorry.

A. I started with LTS in November 1997. The Exelon patch was the first project which I took responsibility for when I started at LTS.

Q. You don't have any independent knowledge of the testing aside from the documents?

A. I was not at LTS at this time, so I just know what I know from reading the documents.

Q. Let's start with that. So after they confirmed that they believed the degradation was oxidative in nature, what was the next step?

A. After they had identified the structure of the two degradation products and the possible pathways, they started to look into ways on how to reduce the amount of degradation.

Q. In what ways did they evaluate?

A. Based upon the information I'm aware of, since they know it was oxidative degradation based upon the data, they tested antioxidants in order to find out whether that would have an impact on the formation of the degradation

products.

Q. Which antioxidants did they test?

A. Based upon the data I had access to, they tested tocopherol, ascorbyl palmitate, and the combination of both.

Q. So you're not aware of any other antioxidants?

A. I'm not.

Q. Why did the working group believe that these antioxidants would reduce the amount of degradation?

MR. MINION: Objection to form.

THE WITNESS: I think there was no -- I would use another word. I think there was no belief. They were just making trials in order to find out whether antioxidant would be able to reduce the level of degradation which was observed.

Q. What were the results of the testing of the tocopherol and the ascorbyl palmitate?

A. Astonishingly and unexpectedly, it turned out that the vitamin E was having the best impact on the formation of the degradation products.

Q. So you're saying it was astonishing that

an antioxidant would prevent oxidation?

A. It's astonishingly because you can't predict which kind -- whether an antioxidant -- it's not predictable. You may be successful. You may not be successful. And it's not predictable which kind of antioxidant is working.

Q. So it's not predictable that an antioxidant stops oxidation?

MR. MINION: Objection to form.

A. It's not predictable that any kind of antioxidant is stopping any kind of oxidation.

Q. So you're saying it's entirely unpredictable that you have no way of knowing whether or not an antioxidant could stop oxidation?

MR. MINION: Objection to the form. Outside the scope of the 30(b)(6) notice.

THE WITNESS: That's not what I'm saying, what I'm saying is it's unpredictable in respect to a specific API -- specific formulation which antioxidant is going to work. You can't predict. You have to run a series of experiments in order to find out whether at all and which one is doing the job.

Q. To reduce the degradation of rivastigmine, you'd have to select an antioxidant that was effective with respect to rivastigmine; right?

MR. MINION: Objection to form.

THE WITNESS: That's not correct. What I'm saying it must be effective for the API in combination of the formulation, the API is composed in.

Q. So you're saying that not every antioxidant would be effective with respect to rivastigmine in a transdermal system; right?

MR. MINION: Objection to form. Outside the scope of the 30(b)(6) witness.

THE WITNESS: What I'm saying, it's not predictable which antioxidant would work and would result in reduction of the amount of degradation products observed.

(End of testimony).

MR. FINEMAN: Your Honor, I believe we worked everything out. We need a couple of minutes for technical purposes.

THE COURT: All right.

MR. FINEMAN: In the meantime, it will give me an opportunity to clear up my under

seal document issue. I consulted with Mr. McCann while we were talking about the video clips as well, so the record is clear, Your Honor, it is JTX 65, JTX 177, and JTX 200 that should be placed under seal. And of those three, JTX 177 is the DMF that we would coordinate with Novartis to make sure Your Honor has a copy.

THE COURT: All right. Then those three documents are under seal.

MR. FINEMAN: Thank you, Your Honor.

THE COURT: All right. So are you working on getting this next video ready?

MR. FINEMAN: Yes, I think it should only be a minute.

THE COURT: By the way, the last deposition witness who I assume is Mr. Theobald, does he have a first name?

MR. FINEMAN: I believe it's Frank, Your Honor.

THE COURT: All right:

(Deposition testimony).

THE WITNESS: My name is Joerg Ogorka. I'm living in Germany. The street name is Im Steinbrunnen -- sorry, 19/3, 79585 Steinen

in Germany.

Q. Would you consider adding an antioxidant to prevent oxidation to be a common-sense solution?

A. You're talking in general terms or do you talk about the Exelon patch?

Q. Let's talk about in general terms first.

A. In general terms, considering to prevent or slow down oxidation by means of an antioxidant is something which you may consider. What is uncertain, though, is how to prevent. There are -- depending on what the situation is, you may exclude oxygen, for example. You cannot predict which antioxidant will be effective. That is very much compound-specific and chemistry related to the compound and also how the antioxidant works. There is some chemical interaction that is not predictable.

So it's not something -- it's not an obvious solution you can offer right away. There requires a lot of experimentation to identify the right antioxidant and even more experimentation to establish the adequate level of this.

Q. As a general matter, though, adding an

antioxidant to prevent or minimize oxidation would be something that would be common sense to attempt; is that right?

MR. MINION: Objection to form.

THE WITNESS: There are many ways to address instability and degradation. So --

Q. I want to be clear. I'm talking about oxidation. So not --

A. I'm talking also there -- I guess you may want to look into other ways, for example, excluding oxygen, as an option. If you know any -- any excipient could do any oxidation, might exclude this one.

But, yes, using antioxidant is one of the means one could consider once you have established the mechanism and know it's oxidation, which is not obvious right away. It requires a lot of experimentation, structure elucidation and chemical know-how to understand is this an oxidative pathway that led to the degradation perhaps or is this anything else.

Q. Which antioxidants are you aware of that LTS or Sandoz tested in the Exelon patch?

A. I'm aware of tocopherol and ascorbyl

palmitate.

Q. Would you agree that they had been used in pharmaceutical formulations prior to 1995?

A. As I said, I don't know other examples. I just think it has been known before, yeah; but I don't have examples.

But what was not known, maybe if I just add this, is that the tocopherol did a much better job as antioxidant than the ascorbyl palmitate. That was clearly unobvious. Because if you would have guessed prior, you would have thought it might be the other way around.

Q. You're saying that it's unobvious that an antioxidant would stop oxidation?

A. No, it was unobvious to see how good the effect was, in terms of effectiveness. You could see that the effectiveness of this tocopherol was much better than the one of ascorbyl palmitate. And the effectiveness meaning the level of resulting degradation products out of Exelon over time, this was unpredictable. That required the experiments to be made to then establish this.

Q. So it was unpredictable that tocopherol reduced the amount of oxidation?

A. First of all, it's unpredictable whether or not it would reduce the amount of degradation products from Exelon. This is unpredictable as you can see as it was unpredictable that the ascorbyl palmitate was not a good antioxidant. That's why I say it is unpredictable which one would work. That's why a series of different options were tried. And the clear differentiation of tocopherol being superior to others, that was unpredictable.

Q. So you're saying that it was unpredictable that when you tested tocopherol and ascorbyl palmitate, tocopherol worked better than ascorbyl palmitate?

A. As an antioxidant, yes.

Q. You've just been handed a document marked as Exhibit 1. And if you look at the bottom right corner, it's bearing Bates number LTS 0055040 through LTS 0055063. This document appears to be a fax and attachment from yourself to Paul Gargiulo. The subject is ENA TDS market formulation development report. Did I read that correctly?

THE WITNESS: You have

Q. So you're saying now while your company is in litigation asserting patents that require an antioxidant, that all of a sudden it has to be a suitable antioxidant; is that right?

A. I don't think that you say all of a sudden it has to be. I mean, it has been there all the time, as you see when you look at the data of the document. You see the huge difference of the unsuitability -- the suitability of tocopherol and the unsuitability of ascorbyl palmitate, these data are there. It's not a new statement from my perspective. It's just -- as we discussed this, is clearly showing that the data speak for themselves, so to speak, that you cannot just take any antioxidant and then have solved the problem.

Q. Is ascorbyl palmitate a suitable antioxidant for rivastigmine?

A. Ascorbyl palmitate looks like not to be suitable for the purpose.

Q. So not an antioxidant that you would test would necessarily be suitable for rivastigmine; right?

A. That is true, what you're saying, not any

antioxidant you would select or test would give you a suitable antioxidant for Exelon patch.

Q. But knowing that the Exelon patch was subject to oxidation, here you could assume that the addition of antioxidants would reduce that degradation?

MR. MINION: Objection to form.

A. That was a driving rationale for testing there.

Q. But then the testing would determine whether or not the antioxidant actually worked; is that right?

A. The testing would show which one is the one, and what is the effect of this antioxidant in terms of, in terms of reducing the speed of oxidation, yeah.

Q. And would you agree that it was reasonable to assume that tocopherol or ascorbyl palmitate may reduce the degradation --

MR. MINION: Objection to form.

Q. -- in the transdermal patch?

MR. MINION: Objection to form.

THE WITNESS: That was -- that was the hypothesis that some of these antioxidants

that we tested would work, and of course any hope that you put into your work saying hopefully one of these candidates I'm putting in there will in the end prove.

MR. BROWN: So, Your Honor, we're finished with the deposition clips. Our next witness will be Dr. Graham Buckton. We think, given the time, it's probably appropriate to start tomorrow morning.

THE COURT: All right. Well, so I'm just going to charge you three minutes and anymore minutes I have to use up today.

MR. BROWN: Three minutes is fine, Your Honor.

THE COURT: So we're done. So I can see that, subject to any adjustments, if there are any, you're very close to both having used three and a half hours. You'll get the exact time tomorrow morning.

Just in terms of -- so, we have Dr. Buckton. We have some other expert whose resume I haven't seen for your side and then we have Dr. Klibanov. And that's kind of what we're expecting for tomorrow; right?

MR. BROWN: Correct, that I believe, is the rest of the case, Your Honor.

MR. KALLAS: Your Honor, they're bringing Dr. Buckton on two issues, noninfringement and I assume they're bringing him back after the experts you haven't seen the CV of after that, to do the 112 issues. Then we'll have Dr. Klibanov.

THE COURT: Can't we do the noninfringement all at once?

MR. KALLAS: Well, we can if he separate them. If you recall from the pretrial order, their infringement case has blurred with their 112 case. And we're at a loss. It's a moving target and we're at a loss as what is 112.

THE COURT: I ruled at the pretrial they have to finish infringement before they can start on --

MR. KALLAS: The Pretrial Order specifically says infringement should finish and then you start invalidity. That's our preference.

I know I don't want to inconvenience the witness. He's going to be here.

THE COURT: No. No. I'm not too worried. He gets paid well for his inconvenience.

Is that what you're planning on doing, Mr. Martin -- sorry, Mr. Brown?

MR. BROWN: We were planning to bring him one time and have him take the stand and testify. I think that's the normal course of things. We're happy to do it however the court wants us to do it.

MR. KALLAS: Your Honor, our problem is, as we said at the pretrial conference, they're blurring the issues. You then said you would allow Dr. Klibanov to handle it, whatever they came forward with.

But unless we know what's infringement and 112.

THE COURT: So, Mr. Brown seems to be agreeable. So Dr. Buckton, if he's the first witness tomorrow, will testify on noninfringement. They can cross-examine on noninfringement. You can rest your noninfringement case and then you can proceed with your invalidity case and call whichever one

you want.

And you can call them, you know. You can rest and start over again with him or you can call your other expert. Right?

MR. BROWN: That's fine, Your Honor.

THE COURT: All right. So, as a practical matter, do we think this is going to take another seven hours tomorrow?

MR. KALLAS: They're all his witnesses except for Dr. Klibanov, you know.

THE COURT: You say they're all his witnesses. He has two. You have one; right?

MR. KALLAS: Well, put it this way, he has the majority of -- I misspoke, Your Honor. He has the majority of witnesses.

Depending on how much they do with 112 is how much Dr. Klibanov will have to respond. I can't imagine Dr. Klibanov's more than 45 minutes. But, again, I don't know what their actual plan is.

THE COURT: All right. Is there anything else you want to me to address tonight or tomorrow morning? Well, I guess you can't tell me what you want me to address tomorrow

morning.

Is there anything you want me to address tonight?

MR. FINEMAN: I'd just like to hand up Dr. Michniak-Kohn's CV.

THE COURT: Oh, okay. Thank you.

All right. Did I give you back the other two that you had handed up earlier or, I mean, I looked at them and I'll give them back, so we don't have extra copies floating around. I will look at Dr. Michniak-Kohn's overnight.

Anything else before -- so, do you want me to come out tomorrow morning sometime before we actually start to see whether you have any problems or --

MR. BROWN: I think that's probably a good idea like today, Your Honor.

THE COURT: Well, and did you have a little trouble getting in the courthouse this morning?

MR. FINEMAN: Pretty smooth, Your Honor.

THE COURT: Oh, do we --

(Following a discussion held off the

record:)

THE COURT: Okay. So I think -- all right. Well, so I'll plan to sort of just come out and see what's happening with you all at 8:00 tomorrow. We'll start at 8:30.

And if we need to discuss things between 8:00 and 8:30, that's on my time, not yours. Okay?

MR. BROWN: Thank you, Your Honor list.

THE COURT: All right. So I'll see you tomorrow, then.

THE CLERK: All rise.

(Court was recessed at 5:02 p.m.)

State of Delaware)
)
New Castle County)

CERTIFICATE OF REPORTER

I, Heather M. Triozzi, Certified Professional Reporter, Registered Professional Reporter and Notary Public in the State of Delaware, do hereby certify that the foregoing record, Pages 1 to 346 inclusive, is a true and accurate transcription of the above-captioned proceeding on the 1st day of May, 2014, in Wilmington.

IN WITNESS WHEREOF, this 1st day of May, 2014, at Wilmington.

/s/Heather M. Triozzi, CSR, RPR
Heather M. Triozzi, CSR, RPR
Cert. No: 184-PS
Exp: Permanent

DATED: May 1, 2014

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