UNITED STATES OF AMERICA
FEDERAL TRADE COMMISSION
OFFICE OF ADMINISTRATIVE LAW JUDGES

In the Matter of:	)
IMPAX LABORATORIES, INC,	)
a corporation,	) Docket No. 9373
Respondent.	)

October 26, 2017

9:53 a.m.

TRIAL VOLUME 3

PUBLIC RECORD

BEFORE THE HONORABLE D. MICHAEL CHAPPELL

Chief Administrative Law Judge

Federal Trade Commission

600 Pennsylvania Avenue, N.W.

Washington, D.C.

Reported by: Josett F. Whalen, Court Reporter

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FEDERAL TRADE COMMISSION

I N D E X

IN THE MATTER OF IMPAX LABORATORIES, INC.

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OCTOBER 26, 2017

EXHIBITS	FOR ID	IN EVID	IN CAMERA	STRICKEN/REJECTED
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P R O C E E D I N G S

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JUDGE CHAPPELL: Okay. Let me call to order Docket 9373.

Next witness.

MR. LOUGHLIN: Good morning, Your Honor.

Before we call our next witness, could I raise a scheduling issue?

JUDGE CHAPPELL: I was wondering when that would happen.

Go ahead.

MR. LOUGHLIN: Your Honor, unfortunately, we found out that one of our witnesses for tomorrow, Mr. Bryan Reasons, has had a family issue come up and he won't be here tomorrow.

In light of that, we tried to rearrange some witnesses, but we've been unsuccessful in finding anyone who can come tomorrow, and so I think we're going to be done probably my guess is midafternoon with our final witness, unfortunately.

JUDGE CHAPPELL: You mean today or tomorrow?

MR. LOUGHLIN: Tomorrow, Your Honor. Today we're fine. Tomorrow, Mr. Reasons, who was supposed to attend, cannot make it.

JUDGE CHAPPELL: Have you and respondent's

counsel discussed taking witnesses out of order? Because it makes no difference to me when a witness testifies, because, you know, we don't have a jury and we have a record, so that maybe they have someone who could testify they can call.

MR. LOUGHLIN: We -- I'm happy to talk with them about that, Your Honor. I have not heard that that's a possibility at this point.

JUDGE CHAPPELL: He's busting to tell me something. Go ahead.

MR. HASSI: Your Honor, most of our witnesses, I think with the exception of one of our experts, no one is local, and so many of these people are traveling, for example, from California. Mr. Reasons is in New Jersey, but -- and so it's difficult to, on short notice, get someone here, for example, from California to testify. We'll certainly go through our list.

And we have talked about taking people out of order generally -- we've been working together I think, frankly, very well on the schedule, and I apologize for Mr. Reasons' family emergency.

JUDGE CHAPPELL: And I have been assuming that whenever a witness is called and you both examine the witness that even though you might have called the same

witness, that witness is finished.

MR. HASSI: Yes, Your Honor.

MR. LOUGHLIN: Yes, Your Honor.

JUDGE CHAPPELL: I don't know what's going on with Mr. Reasons, but perhaps is he available Monday?

MR. LOUGHLIN: He is available -- no, Your Honor. He's available next Friday. We intend to call him then.

JUDGE CHAPPELL: So tomorrow we would go -- so you've got -- you're expecting Cuca to go a day and a half or do you have someone after Cuca?

MR. LOUGHLIN: We have Mr. Cuca this morning, and we have Dr. Seddon Savage after Mr. Cuca, and then we have Professor Bazerman.

JUDGE CHAPPELL: So you do have those people lined up this week.

MR. LOUGHLIN: Yes.

JUDGE CHAPPELL: So we'll play out the string and see where we end up. All right. Thanks for letting me know.

MR. LOUGHLIN: Thank you, Your Honor.

At this time, Your Honor--

JUDGE CHAPPELL: Wait a minute. I thought that there was more than one. I thought you said a few matters.

MR. LOUGHLIN: No. That was the only issue I wanted to raise.

JUDGE CHAPPELL: Okay. Good. I don't want to encourage them.

MR. LOUGHLIN: Understood, Your Honor.

At this time complaint counsel calls Mr. Roberto Cuca.

And Your Honor, my colleague Maren Schmidt will conduct the examination.

JUDGE CHAPPELL: Okay.

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Whereupon --

ROBERTO CUCA

a witness, called for examination, having been first duly sworn, was examined and testified as follows:

MS. SCHMIDT: Good morning, Your Honor, and may it please the court.

My name is Maren Schmidt on behalf of complaint counsel.

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DIRECT EXAMINATION

BY MS. SCHMIDT:

Q. Good morning, Mr. Cuca.

Would you please introduce yourself to the court by stating your full name.

A. Roberto Cuca.
Q. Mr. Cuca --
JUDGE CHAPPELL: Could I ask you to slow down and speak up.
MS. SCHMIDT: Yes, sir. Yes, Your Honor.
BY MS. SCHMIDT:
Q. Mr. Cuca, we met in Philadelphia back in August of this year when I took your deposition.
How are you doing today, Mr. Cuca?
A. Good.
Q. Great.
Is there anything that may affect your ability to give truthful, complete testimony today?
A. No.
Q. And I will just let you know, if we look at any documents this morning, we will publish them on the screen before you, but there are also paper copies in the binder placed on the table next to you that I may direct you to.
Just to briefly go over your background, Mr. Cuca, I believe you have a master's in business administration?
A. Yes.
Q. And where did you earn your M.B.A.?
A. The University of Pennsylvania.

Q. And when did you graduate?
A. 2004.
Q. And do you hold any financial certifications?
A. Yes.
Q. And what financial certifications do you hold?
A. The chartered financial analyst designation.
Q. And what is a designation as a chartered financial analyst?
A. It's a nonacademic but chartered designation that is granted after a series of three tests establishing competence in financial matters.
JUDGE CHAPPELL: How does that vary from a CPA?
THE WITNESS: A CPA is for auditing, whereas a financial analyst is for analysis of financial statements and companies.
JUDGE CHAPPELL: Is one about as tough as the other to pass?
THE WITNESS: CFAs typically claim that the CFA is harder.
JUDGE CHAPPELL: I would go with that.
BY MS. SCHMIDT:
Q. And Mr. Cuca, when did you obtain your CFA designation?
A. 2010 I believe.

Q. And where are you currently employed?
A. At Trevena, Incorporated.
Q. And what is Trevena's primary business?
A. Pharmaceuticals.
Q. And when did you join Trevena?
A. In 2013.
Q. And what is your position there?
A. I'm the chief financial officer.
Q. And where did you work prior to Trevena?
A. At Endo Pharmaceuticals.
Q. When did you join Endo?
A. In 2010.
Q. Do you recall what month you joined in 2010?
A. I don't.
Q. Okay. Was it -- do you recall it kind of -- time of year at all?
A. I think it was in the fall.
Excuse me. Actually, in the spring.
Q. In the spring. Okay.
And when did you leave Endo?
A. In 2013 in the fall.
Q. And what was your position when you joined Endo in the spring of 2010?
A. I was the vice president of financial planning and analysis.

Q. And how long did you hold that position?
A. For most of the time I was there until the last five or six months.
Q. And in those last few months what was your new position at Endo?
A. I was treasurer and head of business development, finance and tax.
Q. And when you joined -- pardon me.
When you joined Endo as vice president of financial planning and analysis, who did you report to?
A. Alan Levin, the CFO.
Q. And how long did you report to Mr. Levin?
A. The entire time I was there.
Q. And just throughout the day, is financial planning and analysis also referred to or shortened as FP&A?
A. Yes.
Q. And while you were at Endo, what was the function of the financial planning and analysis division?
A. FP&A was in charge of budgeting and forecasting and analyzing the variances between actual results and forecasted results.
Q. And what did budgeting involve at Endo?

A. Setting out the resources that each function in the company would be targeted to spend in a certain period.

Q. And how would you determine what resources were available?

A. We sized the amounts of spend based in part on prior year spends and then forecasted expectations for effort to support new products.

Q. And is there any component of forecasted revenues in your budgeting process?

A. Part of the budget would include an expectation or a forecast of revenues.

Q. And was there a regular timeline for the budgeting process at Endo?

A. Yes.

Q. And what was that?

A. The budgeting process began in the fall of one year and concluded with the presentation of the budget to the board of directors at a January board of directors meeting.

Q. And what would occur when -- after the budget was presented to the board of directors?

A. If the board of directors approved it, that became the budget for that year.

Q. Would the budget be subject to change or was

that firm once approved by the board?

A. The budget wasn't changed once it was set, but new numbers were forecast, and those forecasts were used as new targets for operating goals.

Q. Okay. And I think you also mentioned forecasting.

What is involved -- or what was involved in forecasting at Endo?

A. Forecasting meant that the revenues and spends were updated for actual period spends and revenues and the remaining periods were -- were reforecast.

Q. And did the FP&A group at Endo work with any other divisions to accomplish its forecasting work?

A. Yes. The FP&A group worked with all the divisions to forecast their expenses and then with commercial to forecast revenues.

Q. And what is commercial?

A. Commercial is the part of the company that was responsible for marketing and sales of approved products.

Q. And what kind of assumptions go into forecasting your product sales?

A. I'm sorry. Can you repeat?

Q. Certainly.

What are some of the major assumptions that you

need to make in order to forecast your product sales area at -- Endo's product sales?

A. The two components are price and volume, so you forecast what the demand is for volumes of products and then what the achieved price would be given certain assumptions around rebates and discounts.

Q. And what are some of the primary events that could cause your assumptions to change?

A. If actuals had come in lower suggesting that trends had changed. If the mix of payers had shifted such that more heavily discounted purchasers were purchasing. Anything that would affect price or volume.

Q. And how would the -- your expectations of competition affect your expectations of price or volume?

A. If there was an expectation for increased competition, that could affect certainly volume and potentially price as well.

Q. And in your forecasting I think -- I'm sorry. I believe you just went over price and volume.

Is that what would result in a forecast of revenue?

A. Yes.

Q. And for what purpose would you forecast revenues?

A. To understand what the achieved revenues were likely to be and consequently what the earnings of the company would be.

Q. And then how in turn did that go into your budgeting?

A. In the forecasting, as we got actuals for individual periods and updated the forecasts for the year, we would reforecast the revenues and then potentially adjust spending if needed to achieve a certain bottom-line result.

Q. And for accounting purposes, when are revenues recognized?

A. Pharmaceutical product revenues are recognized when the company sells to the next user, which in the pharmaceutical supply chain for retail products is a wholesale distributor.

Q. So even though you might forecast your revenues for upcoming years, you wouldn't recognize those sales until they had actually been realized?

A. Correct.

Q. Mr. Cuca, do you recall Endo engaging in settlement negotiations with Impax in the spring to early summer of 2010?

JUDGE CHAPPELL: Before you do that, I have a couple questions for the witness.

This process you just described, the job you did at Endo, were you the only person doing that or were there others doing the same job?

THE WITNESS: There were others doing components of the same job.

JUDGE CHAPPELL: How many?

THE WITNESS: In the finance organization and FP&A it was probably ten people, and then revenue forecasting, which was done separately in commercial, probably had six people.

JUDGE CHAPPELL: And all of these people, did they all report to Mr. Levin?

THE WITNESS: The commercial team in commercial did not.

JUDGE CHAPPELL: These processes you just described, did you actually crunch numbers or did someone who reported to you crunch numbers?

THE WITNESS: Both.

JUDGE CHAPPELL: Go ahead.

MS. SCHMIDT: Okay.

BY MS. SCHMIDT:

Q. And just to follow up on Your Honor's questions, Mr. Cuca, out of those number of people

involved in the financial planning and analysis division, how many of those reported to you?

A. Several of them reported directly to me. All of them reported indirectly to me.

JUDGE CHAPPELL: That would be of the ten?

THE WITNESS: Yes.

BY MS. SCHMIDT:

Q. Mr. Cuca, do you recall Endo engaging in settlement negotiations with Impax in the spring to early summer of 2010?

A. Yes.

Q. And did you have a role in those settlement negotiations between Endo and Impax?

A. Yes.

Q. And what was that role?

A. I supported Alan Levin in his discussions with Impax and attended some of the phone calls and meetings.

Q. And Mr. Levin was the CFO?

A. Correct.

Q. And what was Mr. Levin's role in the settlement negotiations with Impax?

A. He would have discussions directly with the counterparty and would advise the rest of the executive committee and the CEO on proposals for

settlement.

Q. So was he the primary negotiator?

A. He was one of them.

Q. One of them. Okay.

And what kind of help did Mr. Levin seek from you?

A. Analysis of proposed settlement terms.

Q. Any particular kind of analysis?

A. Financial analysis.

Q. Okay. And what type of financial analysis did you do for Mr. Levin of the settlement agreement?

A. Analyzing the effect of different proposed settlement packages on the financial performance of the company.

Q. And how could the potential settlement with Impax impact the performance of Endo, the financial performance of Endo?

A. Depending on, for example, when Impax might enter the market and any other provisions around any other terms, the sales of Endo's products could be affected by competition.

Q. And how could the timing of Impax' entry into the market financially affect Endo?

A. When a generic enters a market when there's generic competition, usually the innovator product's

sales decline in volume because of competition.

Q. And does the timing of that entrance have any impact on that analysis?

A. It determines the beginning of the -- the beginning of that effect occurring.

Q. And were there any particular provisions regarding timing that you performed this type of analysis for?

A. There were provisions that defined when Impax could enter the market, and so that would have of affected financial analysis.

JUDGE CHAPPELL: When you refer to "provisions," let's make it clear on the record what you're asking the witness about, whether it's the final agreement or drafts of the agreement, because your last question and his last answer, it's not clear. There might have been a draft that had other provisions. We don't know.

MS. SCHMIDT: Yes, Your Honor.

BY MS. SCHMIDT:

Q. Mr. Cuca, throughout your work supporting Mr. Levin in the settlement with Impax, did all of the agreements include some sort of provision on the generic entry date in which Impax could enter?

A. Yes. I believe so.

Q. Did that date vary between any of the settlements?

Let me rephrase to be more clear.

Did the entry date that was being discussed in any of the settlement drafts exchanged between the parties-- did that generic entry date differ at all?

A. I don't recall if it did.

Q. Beyond the generic entry date, were there any other provisions being or potential provisions being discussed between Endo and Impax that you performed financial analysis of?

A. I performed financial analysis of how the whole -- all the provisions of the agreement would affect Endo.

Q. And beyond analysis of provisions being discussed, did you have any other role in the settlement negotiations with Impax?

A. I think I prepared a draft of one of the provisions.

Q. And which provision was that?

A. That was the -- I think what ended up being named the Endo credit provision.

Q. And what is the Endo credit?

A. The Endo credit, and there was a royalty provision as well, were provisions to reduce the

uncertainty around likely cash flows between the companies.

Q. What do you mean by "cash flows between the companies"?

A. Well, actually, let me correct that. Cash flows to each of the companies.

Q. And how did the Endo credit seek to achieve that objective?

A. The Endo credit established terms based on expectations of Endo product sales and Impax product sales under which there could be a payment from Endo to Impax if those expectations weren't met.

Q. And what were those expectations?

A. They were expectations of growth from the time of the signing of the agreement or the absence of a decline from the signing of the agreement.

JUDGE CHAPPELL: You said you drafted the agreement. Did you call it the Endo agreement yourself from the beginning -- I mean, the Endo credit?

THE WITNESS: Internally we referred to it as a make-whole payment. I think the defined term became the Endo credit at some point.

JUDGE CHAPPELL: Because I think you just said earlier it also could have required a royalty from Impax to Endo; correct?

THE WITNESS: Correct. There was a second provision that was a royalty provision that I -- I don't think I drafted but that worked as kind of the mirror image of the Endo credit.

JUDGE CHAPPELL: And had that happened, it would have been an Impax credit?

THE WITNESS: Essentially.

BY MS. SCHMIDT:

Q. And prior to your work on the --

JUDGE CHAPPELL: Hold on a second.

Did I hear you say you -- when you said you drafted this, you're not talking about the royalty prong, you're talking about the credit based on Endo's sales --

THE WITNESS: Yes, Your Honor.

JUDGE CHAPPELL: -- that may bring a credit back to your company. That's the portion you drafted?

THE WITNESS: I drafted what was called the Endo credit, which would have required a payment from Endo to Impax.

The royalty provision was drafted I think by somebody else, and that would have required a payment from Impax to Endo.

JUDGE CHAPPELL: Well, you think it was someone else. If you didn't draft it, someone did;

right?

THE WITNESS: Yes, sir.

JUDGE CHAPPELL: Okay. In the final form that's in the -- are you familiar with the actual settlement agreement that was signed by the parties?

THE WITNESS: I've seen it. Yes.

JUDGE CHAPPELL: Do you know if your draft is exactly how it occurs, or was it changed after you drafted it?

THE WITNESS: It was definitely changed after the first draft that I prepared, but I was involved in some of the changes, and some of them were proposed by Impax.

JUDGE CHAPPELL: Had you -- did you have experience with other agreements in drafting a term like this one? Had you done this before?

THE WITNESS: Not -- not like this one.

JUDGE CHAPPELL: Did you go to someone for advice or counsel on how to word this thing?

THE WITNESS: No.

JUDGE CHAPPELL: You created it out of whole cloth yourself.

THE WITNESS: Yes, sir.

JUDGE CHAPPELL: Any legal training?

THE WITNESS: Yes.

JUDGE CHAPPELL: You have legal training.

THE WITNESS: Yes.

JUDGE CHAPPELL: Can you tell us about that.

THE WITNESS: Sure.

I graduated from Cornell Law School in 1994 with a J.D. and practiced food and drug regulatory law at a law firm in D.C. for four years and then went to a company, a client of the firm's, called Vira Pharma and worked as a lawyer there for six years doing food and drug regulatory law and transactional law, including collaboration work.

JUDGE CHAPPELL: And so that experience in the legal profession had you run right to an M.B.A. and get into finance.

THE WITNESS: That's correct.

JUDGE CHAPPELL: Yeah. Thank you.

Go ahead.

MS. SCHMIDT: He's smarter than some of us.

BY MS. SCHMIDT:

Q. Mr. Cuca, just to be clear, while at Endo you never worked as an attorney?

A. Correct.

Q. Thank you.

Following up on Your Honor's questions, Mr. Cuca, when you were tasked with and coming up with

this provision, what was your starting point?

A. Can you clarify?

Q. Sure.

What instructions were you given in terms of what you were trying to achieve in drafting this provision?

A. I don't recall the exact instructions.

Q. Did you have any objectives in drafting the provision?

A. So the goal was to reduce the uncertainty around what each of the parties would experience from cash flows, so the goal was to -- if the market changed substantially before the date that the parties agreed that Impax could launch, there would be a way of making Impax whole.

Q. And what do you mean by "making Impax whole"?

A. Helping them achieve cash flows that would have been similar to what they would have achieved had the change in the marketplace not occurred.

Q. And what sort of change in the marketplace were the parties anticipating?

A. I don't know that anyone was anticipating a change in the marketplace, but the provision was designed to insulate against a substantial decrease in sales of the innovator product.

Q. If the parties weren't anticipating any sort of substantial change, why were they bothering to create this provision?

A. In case such a change took place.

Q. Is that a standard practice in patent settlement agreements between brands and generics?

A. I don't know.

Q. But nobody gave you a prior version to look at to include?

A. Correct.

Q. Have you ever heard of one in another brand patent settlement in any other context?

A. I have not.

Q. And -- I'm sorry. I think -- when you're using the term "market," what do you mean by "market"? How are you defining that?

A. The sales for the innovator product.

Q. And that would be Opana ER?

A. Correct.

Q. And what could potentially cause the sales of Opana ER to decrease in a substantial fashion?

A. A supply disruption.

Q. Anything else?

A. A change in the strategy of the company.

Q. And at that time when you were negotiating with

Impax, was Endo considering a change in strategy regarding Opana ER?

A. Endo was working on a different formulation that could have affected the sales of ER.

Q. How so?

A. There was -- Endo was working on what was called CRF, a crush-resistant formulation of Opana, and depending on when that came to market, that could have affected the sales of the non-crush-resistant formulation.

Q. And was that a particular concern that Impax raised?

A. I don't recall if they raised that.

Q. Is there -- did you have any other understanding of why Impax was seeking this provision?

A. I didn't.

Q. And just to make sure I'm clear, Endo was the plaintiff in the action, in the patent action with Impax?

A. Correct.

Q. And Impax was the defendant?

A. Yes.

Q. And why was Endo working with Impax to create a provision in which the plaintiff would be paying the defendant?

JUDGE CHAPPELL: I'm not sure we've heard a foundation for him to tell us about any litigation.

MS. SCHMIDT: Sure. I appreciate the comment, Your Honor. I'll back up.

BY MS. SCHMIDT:

Q. Let me actually go back a little further.

I think you mentioned CRF, crush-resistant formula?

A. Formulation. Yes.

Q. Formulation. Sorry.

And how could the reformulation to a crush-resistant formulation affect the sales of the Opana ER that was on the market when Impax and Endo were negotiating a settlement?

JUDGE CHAPPELL: Excuse me. You're asking him a scientifically based question, aren't you?

I mean, I don't have any -- I haven't heard anything that tells me he knows tamper-resistant from water-resistant or anything else.

MS. SCHMIDT: I'm sorry. I was -- thank you, Your Honor.

JUDGE CHAPPELL: Let's just say that's an improper hypothetical, in my opinion. You know, I want the answers to be something we can all use.

MS. SCHMIDT: Thank you, Your Honor. Let me

definitely strive to be more clear.

BY MS. SCHMIDT:

Q. Mr. Cuca, earlier you mentioned a crush-resistant formulation?

A. Yes.

Q. In your work in financial planning and analysis, did you incorporate -- did you have any reason to analyze Endo's potential introduction of a crush-resistant formulation?

A. There were forecasts, yes, of the sales of a crush-resistant formulation.

Q. And how far in advance would you start making those forecasts?

A. Typically as soon as a development project began.

Q. And was that underway when you joined in the spring of 2010?

A. Yes.

Q. And did Endo anticipate that the introduction of a crush-resistant formulation would have some sort of impact on its current Opana ER formulation sales?

A. I don't recall specifically.

Q. What would Endo's introduction of a crush-resistant formulation -- would that have any impact on the expected sales of Impax' generic

product?

A. I don't know.

Q. At your deposition in August, do you recall testifying that, quote, "If we discontinued selling Opana ER, then their replacement of the market would be less valuable"?

A. That sounds familiar.

Q. Do you agree with that statement still?

A. Yes.

Q. Thank you.

JUDGE CHAPPELL: You realize that was a different question than you asked the man.

MS. SCHMIDT: I'm sorry.

JUDGE CHAPPELL: The one you asked him here is different than the one you asked him in a deposition.

MS. SCHMIDT: Yes, Your Honor. I apologize. I wasn't trying to impeach Mr. Cuca.

JUDGE CHAPPELL: I understand that. I'm just letting you know. To be fair to a witness -- this happens far too often in front of me -- if you're going to bring something out of a deposition, make sure it's the same question you just asked the witness.

MS. SCHMIDT: Thank you, Your Honor.

BY MS. SCHMIDT:

Q. So how --

JUDGE CHAPPELL: You know, in other words, think about yourself sitting in that chair. I don't know if any of you have ever done that, but it's a whole new world. Every trial lawyer should have to be a witness in a case at some point; it will change the way you examine a witness.

MS. SCHMIDT: I believe you. Thank you, Your Honor.

JUDGE CHAPPELL: Go ahead.

MS. SCHMIDT: Thank you.

BY MS. SCHMIDT:

Q. Mr. Cuca, going back to your work on drafting the make-whole provision, what was your starting basis for coming up with a mechanism for the payment?

A. It would have been an expectation -- it would have been a guess or some understanding of what the parties thought would happen if nothing disrupted the ordinary course.

Q. If nothing would happen to what?

A. If nothing would happen to disrupt the -- the ordinary progress of branded Opana sales and the entry of a generic.

Q. And with that as your starting point, what did

you next look at?

A. What would happen when that disruption occurred or if a disruption occurred.

Q. And how -- what did you include into the provision to address that?

A. An expectation about the relative sales immediately before Impax entered the market and sales earlier in the trajectory of Opana ER's sales.

JUDGE CHAPPELL: When you were working on this provision, sir, did you have any knowledge of your company's plans to introduce a tamper-resistant or crushproof product to compete with Opana ER or replace it?

THE WITNESS: I knew that CRF was under development.

JUDGE CHAPPELL: And were you told in any way, shape, or form to keep that in the back of your mind when you worked on this provision?

THE WITNESS: No. I don't think so.

JUDGE CHAPPELL: Did the knowledge of that, what little you did have, did that affect the way you drafted the provision?

THE WITNESS: No. No. Because it didn't matter what disrupted the revenues, you would draft it the same way.

JUDGE CHAPPELL: Let's try to move this along. What assumptions did you start with when you drafted this?

THE WITNESS: So the provision was intended to capture a loss of value to Impax' launch and its six months of exclusivity post that launch, so I started with what the Opana ER sales could be expected to look like if nothing changed the trajectory of its growth and then tried to understand what the negative impact to Impax would be from a profit perspective if something did disrupt that growth.

JUDGE CHAPPELL: And those were your concerns and assumptions.

THE WITNESS: Correct.

JUDGE CHAPPELL: And you told me earlier that the version you drafted differs from the final version; correct?

THE WITNESS: The first version I drafted differs from the final version. Yes.

JUDGE CHAPPELL: Can you tell me whether or not the final version, the signed agreement, incorporated and covered all of your concerns and assumptions?

THE WITNESS: Yes, it did.

JUDGE CHAPPELL: Did you make any assumption

one way or the other of whether the payment may end up being zero?

THE WITNESS: I didn't make any assumption. I knew that the payment could be zero.

JUDGE CHAPPELL: And that was inartfully worded.

Did you assume there would be a payment when you drafted it?

THE WITNESS: I did not.

JUDGE CHAPPELL: Go ahead.

BY MS. SCHMIDT:

Q. Pardon me. I'm just going to skip here.

Mr. Cuca, what did you mean by Impax' six months of exclusivity?

A. Under the Hatch-Waxman provisions of the Federal Food, Drug and Cosmetic Act, when a Paragraph IV -- so when a generic competitor asserts that patents are -- of the innovator are invalid or inapplicable to their drug product and wins in litigation and becomes the first to enter the market, the FDA is precluded for six months from approving another generic version of the innovator drug, so that's referred to as six months of exclusivity.

Q. And did you include specific metrics or did Endo and Impax ultimately include specific metrics to

capture their expectations of earnings during those six months of exclusivity?

A. In the Endo credit provision?

Q. Yes.

A. Components of the Endo credit provision were intended to reflect that. Yes.

Q. And what were those components?

A. A generic erosion assumption.

A profitability assumption.

A volume assumption preceding the Impax launch.

Q. And would volume be based on a substitution rate?

A. Sorry. I should have been clearer.

Well, a price and volume, so a revenue assumption of the innovator product before the Impax launch.

JUDGE CHAPPELL: I'll give you that one, but that's the last leading question I'll allow.

MS. SCHMIDT: Yes. Thank you, Your Honor.

BY MS. SCHMIDT:

Q. For those six months of exclusivity -- let me rephrase.

And do you recall any ways in which the Endo credit provision changed from your original draft to

the final version?

A. At least one change had to do with measuring revenues before genericization versus measuring units of different strengths of Opana ER before genericization.

Q. And what was the purpose of that change?

A. A version of the provision that was a counterproposal from Impax combined different strengths of Opana ER in a way that didn't allow for the calculation of dollars from that.

Q. And how would that -- how would the inability to calculate the dollars from that have an effect on the payment?

A. You wouldn't be able to use the provision to calculate the payment.

Q. Okay. Earlier Your Honor -- strike that. Let me rephrase.

Earlier you stated that you knew that the potential payment could be zero; is that correct?

A. Correct.

Q. Did you do any analyses to determine what the payment could be?

A. I tested the provision to make sure that it was producing outputs that I thought it was supposed to be producing, and one of them, one of the potential

outcomes and outputs would be a zero payment.

Q. What were some of the other outcomes?

A. Nonzero payments.

Q. Was there a range?

A. It depends on what the peak sales were before the genericization.

Q. And why is that?

A. Because that was one of the inputs into the formula that was captured by the provision.

Q. And how would you go about running these analyses?

A. I would pick a number that seemed like it could be a potential outcome and run it through the formula and make sure it produced a sensible result.

Q. A number for what?

A. A number for all of the inputs, so revenues -- revenues is probably the biggest one.

Q. And what would be the triggering event for Endo to be obligated to pay the Endo credit?

A. The revenues in the period immediately before Impax' launch had to fall below some threshold of the peak revenues between the signing of the agreement and Impax' launch.

JUDGE CHAPPELL: Sir, earlier you were asked the question about -- it included two words --

substitution rate. It was a question I considered leading because it was suggesting an answer. To your credit, you didn't just say yes.

Have you ever heard of the phrase "substitution rate"?

THE WITNESS: That's -- that's not a term that was used in the branded pharmaceutical business.

JUDGE CHAPPELL: It's not a phrase you would use especially.

THE WITNESS: Correct.

JUDGE CHAPPELL: Thank you.

Go ahead.

BY MS. SCHMIDT:

Q. And what sort of tools or programs would you use to run these analyses?

A. Excel.

Q. And did you report your findings to anyone at Endo?

A. So when I'm -- so when you say "analyses," I assume you mean the testing of the provision to make sure it worked. Is that correct?

Q. Yes. Go ahead.

A. That would have been about five minutes of work with maybe one or two sets of numbers that I would have just done to, again, make sure the provision

worked, and once I was satisfied with that, that would have been the end of it.

(Pause in the proceedings.)

JUDGE CHAPPELL: Anything further?

MS. SCHMIDT: Yes, Your Honor.

JUDGE CHAPPELL: Do you need a moment to consult with co-counsel?

MS. SCHMIDT: Yes. I would appreciate --

JUDGE CHAPPELL: I would rather have you do that than waste our time. Go ahead.

MS. SCHMIDT: Thank you, Judge.

(Pause in the proceedings.)

JUDGE CHAPPELL: Go ahead.

MS. SCHMIDT: Thank you, Your Honor.

BY MS. SCHMIDT:

Q. And who did you share this analysis with?

A. No one.

Q. Mr. Cuca, do you recall testifying at your deposition in August, quote, "I would have talked about it with Alan, reviewed it with Alan"?

A. I would have told him that I confirmed that the provision worked, but I wouldn't have brought any results with me or analysis.

Q. Okay. Thank you.

At this point -- and Mr. Cuca, did you continue

to work on the -- on this provision through execution of the agreement with Impax?

A. Yes.

MS. SCHMIDT: At this point I would like to show Mr. Cuca RX 364.

And Ms. Allen, if you would put it up at 001.

Your Honor, this document is admitted as part of JX 002, and it is not subject to Your Honor's in camera ruling.

JUDGE CHAPPELL: Thank you.

MS. SCHMIDT: And Ms. Allen, if you could highlight the top portion prior to Recitals, including the corner. Yes. Thank you.

BY MS. SCHMIDT:

Q. Mr. Cuca, do you recognize this as the settlement and license agreement between Endo and Impax?

A. Yes.

Q. And do you see in the corner that it's marked Execution Version?

A. Yes.

Q. Thank you.

And if I could turn your attention to RX-364.0003.

And if you -- although we will publish this on

the screen, if you prefer, it is in the last tab of your -- or I'm sorry -- the second to last tab of the binder next to you.

Ms. Allen, if you could highlight the definition of Endo Credit at the top.

And Mr. Cuca, do you see where it says, "'Endo Credit' means an amount equal to the product obtained by multiplying (i) the difference between the Trigger Threshold and the Pre-Impax Amount by (ii) the Market Share Profit Value"?

Do you see that?

A. Yes.

Q. And is that consistent with your recollection of the Endo credit?

A. Yes.

Q. Okay. Just as it uses some additional terms in there, I'd like to turn to RX-364.004.

And Ms. Allen, if you could highlight Market Share Profit Factor.

JUDGE CHAPPELL: Let's go back to the previous screen so we don't have to do this again.

You were asked, sir, if this is consistent with your recollection of the Endo credit.

Can you tell me how this final version differs from your original version, since you drafted this?

THE WITNESS: So I was involved with the revisions to it as well.

JUDGE CHAPPELL: And just generally, not per comma or spacing.

THE WITNESS: Sure, sure.

The overall structure is very similar. The changes had to do with pushing a lot of the language into further defined terms and including -- the biggest two changes probably included that the market share profit value, the actual number that was used there, decreased between versions, and the -- I think I mentioned before that there was a version of this that may have been offered as a counterproposal that combined different strengths of Opana ER in ways that didn't produce a dollar value, a sensible dollar value, so that would have been corrected as well.

JUDGE CHAPPELL: And you were asked about the first sentence.

The second sentence that begins with "For the sake of clarity," is that something that was in your draft or is that new?

THE WITNESS: That's -- I don't recall.

JUDGE CHAPPELL: And I think you told me earlier -- and you're looking at it right now -- this addresses the concerns and assumptions you made on your

original draft?

THE WITNESS: Correct.

JUDGE CHAPPELL: All right. Thank you.

Go ahead.

MS. SCHMIDT: Thank you, Your Honor.

BY MS. SCHMIDT:

Q. And turning back to the market share profit factor, which is RX-364-004, Mr. Cuca, do you see it says, "'Market Share Profit Factor' means the factor obtained by multiplying ninety percent (generic substitution rate) by seventy-five percent (the WAC price of unit as measured by FDB Data) by eighty-seven and one-half percent (Impax net profit margin) by fifty percent (half a year, or 180 days), or 0.2953"?

Do you see that?

A. Yes.

Q. And I just want to ask you about these individual components of the market share profit factor.

What is meant or -- to your knowledge, what is meant here by "generic substitution rate"?

A. That -- that is what the branded company would call the erosion rate, so the amount of the preexisting branded revenues that would be replaced by -- or the amount of preexisting branded demand that

would be replaced by generic demand.

Q. Thank you.

And what is the WAC price as -- pardon me. Let me restate -- the WAC price of unit as measured by FDB data?

A. So WAC is wholesale acquisition cost, so that is the published, call it, list price for each one of the individual strengths that was being measured there, individual strengths of Opana.

Q. And what is Impax net profit margin?

A. That is an attempt to measure the net profit that would be achieved by Impax, so including things like their cost to manufacture the generic product and their distribution costs and any G&A or R&D costs.

Q. Okay. And what was the purpose of including the generic substitution rate in the market share profit factor?

A. That was to capture an expectation about the amount of demand, the amount of preexisting demand for the branded product that would be replaced by demand for the generic product.

Q. And what was the purpose of including the WAC price of unit as measured by FDB data?

A. That was intended to capture the typical discount that a generic entrant in the six-month

exclusivity period reduces the price by compared to the branded product.

Q. And what was the purpose of including Impax net profit margin?

A. To calculate the net profit effect rather than the effect on revenues that the -- that this provision was trying to capture.

Q. And what is the overall purpose of the market share profit factor?

A. It is -- it serves as an input into the Endo credit that replicates some expectation of the economics to Impax during the six-month exclusivity period.

Q. Thank you.

And I'm sorry. I forgot to ask about one more of those components.

What was the purpose of including half a year or 180 days?

A. That's to capture the six-month exclusivity period.

Q. Thank you.

JUDGE CHAPPELL: Sir, these definitional terms of the agreement you just discussed, did you have anything to do with drafting these?

THE WITNESS: Yes.

JUDGE CHAPPELL: Thank you.

BY MS. SCHMIDT:

Q. Was the inclusion of -- actually, let me back up.

I believe earlier when asked about some differences between the starting draft and the final draft, one of those I believe you said was a decrease in the market share profit factor -- or I'm sorry. I don't want to put -- to misstate.

Was there a decrease in a number included in the Endo credit provision between the original version and the ultimate version?

A. There was a decrease between one of the intermediary versions, potentially the original version -- I can't remember -- and the final version.

Q. And what was behind that decrease?

A. A version of the provision captured the lost revenues that would -- could have been felt by Impax, and the change -- the proposed -- well, the change that became part of the final provision changed that to capture the lost profit that would have been felt by Impax.

Q. And who proposed that change?

A. I did.

Q. And why did you propose that change?

A. Because to make Impax whole for what they -- what could occur if there was disruption to the supply, we were trying to make them whole at the bottom line, so at their profit line, whereas the prior provision would have made them whole at the revenue line and actually would have advantaged them as compared to what was trying to be achieved.

Q. And how did the switch from revenues to profits impact any potential payment to Impax?

A. All else being equal, it would have reduced the payment.

Q. Thank you.

JUDGE CHAPPELL: Did you say it would have reduced the payment?

THE WITNESS: Yes, Your Honor.

JUDGE CHAPPELL: The payment Impax would have paid you.

THE WITNESS: We would have paid them.

JUDGE CHAPPELL: I'm sorry. Going the other way.

So the amount you pay Impax would have reduced based on this change.

THE WITNESS: Correct. The prior version of the provision captured revenues, and this version of the provision is attempting to capture profit, which

would be a smaller number.

JUDGE CHAPPELL: Well, if I understood you correctly, you said that you were doing it to protect Impax and make them whole, but it sounds like in effect it made them less whole. Am I correct there?

THE WITNESS: It made them more appropriately whole.

JUDGE CHAPPELL: Okay. All right.

So your version -- in your -- your view of things, it accomplished what you wanted in that it was fair.

THE WITNESS: Correct.

JUDGE CHAPPELL: Thank you.

MS. SCHMIDT: Could we look at that market share profit factor one more time, so that was RX-364 at 0004.

And you can just do Market Share Profit Factor. Yes. Thank you.

BY MS. SCHMIDT:

Q. Looking one more time at Impax net profit margin 87.5 percent, is that -- is that the introduction of the profit versus revenue concept?

A. Correct.

Q. And by multiplying by 87.5 percent, would that -- what numerical impact would that have on any

potential payment to Impax?

A. It would have reduced it by 2.5 percent.

Q. 2.5?

A. Excuse me. 12.5 percent.

MS. SCHMIDT: Thank you.

Your Honor, may I have a moment to consult with counsel?

JUDGE CHAPPELL: Please do.

MS. SCHMIDT: Thank you.

(Pause in the proceedings.)

May I begin?

JUDGE CHAPPELL: Go ahead.

BY MS. SCHMIDT:

Q. Mr. Cuca, are you familiar with the term "loss of exclusivity"?

A. Yes.

Q. And what does "loss of exclusivity" mean?

A. It refers to the occurrence to an innovator product of the loss of its right to preclude others from entering the market.

Q. And what are some of the events that can cause loss of exclusivity?

A. Invalidity of a patent, expiration of a patent, the expiration of a regulatory exclusivity period, of which there are a couple of different kinds.

Q. And what relationship does generic competition have to loss of exclusivity?

A. So generic competition would be the -- what actually happens when you lose the exclusivity.

Q. So that would be the market results of the legal loss of --

JUDGE CHAPPELL: Leading. Rephrase.

MS. SCHMIDT: Thank you, Your Honor.

BY MS. SCHMIDT:

Q. What typically happens once exclusivity is lost?

A. So by definition, when you lose exclusivity, there's nobody else on the market, you're exclusively on the market even if there's -- you know, even if your patent has expired and nobody has entered, and that does happen for small products sometimes.

So when you've lost exclusivity, there's another entrant in the market, and so there's increased competition.

Q. And is loss of exclusivity something that the financial planning and analysis group would account for or prepare for?

A. We would prepare scenarios, model scenarios, that would include loss of exclusivity.

Q. Model scenarios of what?

A. Of the financial results of the company.
Q. And what impact does generic competition typically have on a brand's sales from a financial planning and analysis perspective?
A. It typically negatively affects volume.
Q. Does the number of generic competitors have any impact on that?
A. So when there are more generic competitors, there's more competition, and that often more adversely affects volume.
Q. And when you joined Endo in the spring of 2010, do you recall whether Endo was facing potential generic competition for Opana ER?
A. At that time you mean?
Q. Yes.
A. There -- well, there had been ANDAs filed for generic versions of Opana ER, but there was not imminently at that point going to be a generic.
Q. Did your group do any work to analyze a potential impact of any generic entry in 2010?
A. One of the scenarios that was included in the analysis included what -- examined what would be the effect of a generic entry after the expiration of the 30-month stay during the patent litigation that was ongoing between Endo and Impax.

Q. And do you recall what that potential impact was?

A. It would have resulted in a decrease in branded sales.

Q. Do you recall what roughly magnitude decrease in branded sales you were potentially facing?

A. I don't.

Q. Mr. Cuca, are you familiar with the term "profit and loss statement"?

A. Yes.

Q. And what is a profit and loss statement?

A. A profit and loss statement, also sometimes called an income statement, shows the revenues of a company and then all of the expenses that subtract from that to yield a profit or loss at the bottom line.

Q. And did you use profit and loss statements in your work as head of financial planning and analysis?

A. Yes.

Q. How would you use them?

A. We would forecast the different inputs into the profit and loss statement, so changes in revenues, changes in expenses, to determine what the changes to the bottom line-profit or loss could be.

Q. And at Endo was there just one singular profit

and loss statement or did you have profit and loss statements for different products?

A. We -- we analyzed profit and loss statements for different products and across the company as a whole.

Q. And how often would you create profit and loss statements for the individual products?

A. Typically monthly.

Q. Monthly.

A. And more frequently depending on what the demands were for analysis.

Q. And what could cause a more frequent demand than monthly for a profit and loss analysis?

A. Any request from senior management to understand different scenarios or...

MS. SCHMIDT: I'd like to show Mr. Cuca what has been marked as CX 3017. And this document has been admitted as part of JX 002 and is not subject to Your Honor's in camera ruling.

I'd actually like to start at CX 3017-002.

And Ms. Allen, if you could call up the beginning of the e-mail starting in the middle of the page from Hogan, Brian.

BY MS. SCHMIDT:

Q. And Mr. Cuca, do you see where it says from

Brian Hogan, sent May 21, 2010, to Clark Baker, Demir Bingol, Lee Lenkner, MaryJo Magrone, and it's carbon-copied to you, Roberto Cuca, and Darnell Turner, and the subject is Opana ER/IR P&L Scenario Model?

Do you see that?

A. Yes.

Q. And below that, Mr. Hogan writes, "Following up from our meeting today," and then below that he --

JUDGE CHAPPELL: Wait a second.

Why don't you establish whether he got this e-mail or not before you jump into asking him all about that.

MS. SCHMIDT: Thank you, Your Honor.

JUDGE CHAPPELL: There needs to be some connection to this witness.

MS. SCHMIDT: Certainly.

BY MS. SCHMIDT:

Q. Mr. Cuca, do you see that you were carbon-copied on this e-mail?

A. I do.

Q. Do you have any reason to believe you did not receive this e-mail?

A. I don't.

Q. Is this type of P&L -- I know we haven't looked at the whole document yet, but would you typically look

at P&L scenarios in your work as head of financial planning and analysis?

A. Yes.

MS. SCHMIDT: May I proceed, Your Honor?

JUDGE CHAPPELL: Go ahead.

MS. SCHMIDT: Thank you.

BY MS. SCHMIDT:

Q. And in this e-mail Mr. Hogan outlines two P&L scenarios.

Do you see that?

A. Yes.

Q. And what is the Opana ER generic entry date under P&L Scenario 1?

A. It says "Opana ER - generic 7/1," so July 1 I assume.

Q. And under P&L Scenario 2, what is the generic entry for Opana ER?

A. It's similarly July 1.

Q. So under both profit and loss scenarios as of May 28, 2010, Endo was looking at an expected generic entry of July 1; is that right?

A. Under these two scenarios, that was the date that was used.

Q. Okay. And under that first scenario, Mr. Hogan presents --

JUDGE CHAPPELL: You understand you're leading the witness now, don't you? You need to correct that.

MS. SCHMIDT: I'm sorry, Your Honor. Let me fix that.

BY MS. SCHMIDT:

Q. Under P&L Scenario 1, are there any variations in expectations for Endo's performance for Opana ER?

A. It looks like the Opana ER component of these two scenarios is the same.

Q. And are there -- within this scenario of -- within those two scenarios of expected generic entry of July 1, are there any differences in the expectations of erosion?

A. It doesn't look like there are any differences.

Q. Okay. Under P&L Scenario 1, what type of erosion was Endo expecting for Opana ER branded sales?

A. It says "Traditional erosion."

Q. And does traditional -- what does "traditional erosion" mean?

A. I'm sorry. I misunderstood your question before.

In each one of the two scenarios there seem to be three sub erosion scenarios.

Q. And what is the first scenario of erosion?

A. Traditional erosion as determined by forecasting.

Q. Does "traditional erosion" mean anything to you?

A. That it would look like some precedence of generic entry.

Q. Okay. And what is the second traditional -- or I'm sorry.

What is the second erosion possibility?

A. The second erosion scenario is traditional erosion for most segments but that 25 percent access would be maintained at no additional cost.

Q. And does that say "25 percent access through contracts at no additional cost"?

A. Yes.

Q. And what does that mean?

A. That for most of the segments, it looks like probably 75 percent of the segments, that the erosion would be traditional, for the remaining 25 percent of the segments via some aspect of contracting there would be -- there would not be that erosion and there would not be cost for that erosion, for maintaining -- for preventing that erosion.

Q. And what is the third erosion scenario?

A. Traditional erosion for most segments --

sorry -- but maintain 50 percent access through contracts.

Q. And what would be the difference between the first and second scenario that would account for the retention of 50 percent rather than 25 percent of sales?

A. Between the second and third scenarios?

Q. Yes.

A. The difference between them seems to be that there would be a change in the pricing of Opana, so some cost to retain access to the greater portion of contracts.

JUDGE CHAPPELL: I'm looking at this e-mail and I see Scenario 1 and Scenario 2. Where's this third scenario you're talking about? I don't see it on the e-mail.

THE WITNESS: I was similarly confused at first, too.

Under "Opana ER - generic 7/1" you see there's three subbullets?

So those are sub-scenarios within the major scenario.

MS. SCHMIDT: Thank you, Mr. Cuca. You explained it better than I did.

JUDGE CHAPPELL: So Scenario 1 we're told has

three sub-scenarios?

THE WITNESS: Correct.

JUDGE CHAPPELL: And what about Scenario 2? Are there sub-scenarios under Scenario 2?

MS. SCHMIDT: Could you just highlight those.

JUDGE CHAPPELL: She doesn't need to highlight. He's familiar with the e-mail; he got it.

THE WITNESS: Yes. The same sub-scenarios under Scenario 2.

JUDGE CHAPPELL: Does that make sense to you the way this thing is outlined?

THE WITNESS: Unfortunately, yes.

JUDGE CHAPPELL: I understand.

Go ahead.

BY MS. SCHMIDT:

Q. If I might potentially assist, in addition to Opana ER, what other drug are these scenarios assessing?

A. Opana IR.

Q. I'm sorry. Go ahead.

A. Opana ER is the extended release. Opana IR is instant release.

Q. And between P&L Scenario 1 and P&L Scenario 2, what is the difference between the expected generic entry for IR?

A. That there would be no generic for IR in the second scenario.

Q. Are there any other differences between Scenario 1 and Scenario 2?

A. That looks like the only difference.

Q. Thank you, Mr. Cuca.

I'd like to turn to CX 3017-001.

And Ms. Allen, if you could highlight the top e-mail, actually just the e-mail portion and the address and top line of the e-mail. Oh, I'm sorry. You can actually go ahead and include the first paragraph.

JUDGE CHAPPELL: Tell us again, who is Brian Hogan?

THE WITNESS: He was a member --

JUDGE CHAPPELL: Maybe not again. Just tell us who is Brian Hogan.

THE WITNESS: He was a member of the FP&A team who worked with the commercial contracting group on issues of uptake via the contracting process.

JUDGE CHAPPELL: Was he on something that might have been called the settlement team regarding this patent litigation?

THE WITNESS: I don't think so.

JUDGE CHAPPELL: Was he a bean counter?

THE WITNESS: He was more the latter.

JUDGE CHAPPELL: And the e-mail you discussed previously to the one that's just been put on the screen, it was also from this same gentleman?

THE WITNESS: Correct.

JUDGE CHAPPELL: Thank you.

BY MS. SCHMIDT:

Q. And I actually just want to look briefly at this e-mail so that we can turn to the attachment, but I just want to make clear, this was from Brian Hogan to you on May 28, 2010 --

A. Yes.

Q. -- is that correct?

And he addresses, "Roberto, Lee and I sent the attached preliminary P&L model to forecasting and contracts for review for the Opana ER/IR scenarios"; is that correct?

A. Yes.

Q. I'd like to turn to that attached preliminary P&L model, which begins at CX 3017-005.

And if we could look at just the top one, Scenario 1.

And Mr. Cuca, if I could just go over some of these terms with you to make sure we understand the model here.

What is Opana ER demand sales?

A. That is the actual end user demand not at the wholesaler or distributor level but at the retail pharmacy level for the product.

Q. So at the actual patient level?

A. Correct.

Q. And what is Opana ER burndown?

A. That would be the amount by which wholesalers and other pipeline participants, distributors, are reducing their holdings in order to offset in this case the expected decrease in demand for the product.

Q. How would they reduce their holdings?

A. By buying less from us -- Endo.

Q. And I'm sorry. I'm not trying to be repetitive, but just to be clear, why would they be buying less from Endo?

A. In expectation of decreased future demand.

Q. What would be driving the expectation of decreased future demand?

A. The erosion in the -- in the ongoing sales for Opana.

JUDGE CHAPPELL: You said, "What would be driving the expectation of decreased future demand?" Just so I'm clear, and I want to make sure the witness is clear, were you actually asking him what would cause

decreased future demand?

MS. SCHMIDT: Yes, Your Honor.

JUDGE CHAPPELL: Is that the way you understood it?

THE WITNESS: Yes.

BY MS. SCHMIDT:

Q. And I'm sorry. I'm not sure if I -- I apologize if I missed it, but I'm not sure if I quite heard.

What would be the driver of the decreased future demand?

A. It would be the -- so with the erosion and the two -- retention scenarios, it would be the entry of a generic version of ER.

Q. Thank you.

And looking at this Scenario 1, is this a typical approach to a profit and loss scenario for a branded drug?

A. It's an approach. Yes.

Q. An approach. Okay.

And is -- under Scenario 1, are there any differences between -- and feel free to look at your paper copy, to flip back and forth, but are there any differences between the assumptions set out here and the assumptions we reviewed in that initial e-mail from

Mr. Hogan?

JUDGE CHAPPELL: If you're going to refer to an initial e-mail and it's not this document, you need to identify the document.

MS. SCHMIDT: Thank you, Your Honor.

The initial e-mail appearing at CX 3017-002 to 003 from Brian Hogan on May 21, 2010.

THE WITNESS: This has the same components as were listed in those scenarios.

BY MS. SCHMIDT:

Q. And just to be clear, in Mr. Hogan's e-mail beginning at CX 3012-002, he notes generic entry 7-1.

Is there a date -- I'm sorry -- a year included there?

A. There's not.

Q. Now, turning to the actual spreadsheet analysis appearing at or beginning at CX 3017-005, what is the date of generic ER expected entry?

A. It says 7-1-10.

Q. So that would be 2010.

A. Yes.

Q. Okay. And just briefly to look at the Opana ER net sales, under -- what would be the expected earnings under steep erosion?

A. The expected earnings?

Q. Oh, I'm sorry.
A. Can you clarify?
Q. You can tell I'm not -- I'm not a financial analyst.
What would be the Opana ER net sales under steep erosion?
A. The Opana ER net sales under steep erosion net of the burndown would be 110,841,133.
Q. And what about under 25 percent retention?
A. 122,000,291.
Q. And under 50 percent retention?
A. 127,929,044.
Q. And looking between 25 percent retention and 50 percent retention, by my math there's only about a five to six-million-dollar difference between Opana ER net sales; is that correct?
A. Yes.
Q. And if you were doubling the amount of your retention, why wouldn't you also be doubling the amount of your Opana ER net sales?
A. Because you were doing it at increased cost.
Q. What's the increased cost?
A. Increased rebates or discounts via contracting.
Q. So that would -- you would be charging a

different price?

A. Correct.

Q. Thank you.

And I just want to look at one more page. The next page of that same spreadsheet is at CX 3017-006.

And actually, Ms. Allen, could you cut the -- cut off the box at the bottom of Scenario 1c.

And do you see at the top of this box it says "Key Assumptions"?

A. Yes.

Q. And the first entry is baseline? Do you see that?

A. Yes.

Q. And what is a baseline?

A. It's the scenario against which the other scenarios are being compared.

Q. Okay. And what are the key assumptions for Opana ER under the baseline scenario?

A. It says "No generic entries until 7-1-11."

Q. And for Scenario 1a, Scenario 1b and Scenario 1c, what is the assumption date for generic entry for Opana ER?

A. It says, "Opana ER has generic entry (at-risk) on 7-1-10."

Q. Okay. You can actually set that aside.

Earlier I think you mentioned management requests for additional analyses?

A. Yes.

Q. What would some of those requests be?

A. For requests -- for analyses of scenarios including different assumptions.

Q. Okay. And who from senior management most frequently made those requests to you?

A. Alan Levin.

Q. And if I could direct your attention to CX 1314.

And again, this is admitted as part of JX 002 and is not subject to Your Honor's in camera ruling.

And this is a single-page document. Ms. Allen, if you could start by emphasizing the bottom e-mail.

And just to be clear, you see from the top where this is from Alan Levin, sent June 1, 2010, to Roberto Cuca, no subject, but importance high? Do you see that?

A. Yes.

Q. And Mr. Levin writes to you: Roberto, can you please -- let me rephrase that -- "Can you tell me please: 1. If we were to assume that Impax launches

Opana ER at risk on July 1, how much would we lose in forgone sales of the branded drug this year?"

Do you see that?

A. Yes.

Q. Would this be a request of the type you were mentioning earlier from senior management for modeling new assumptions?

A. Yes.

Q. Okay. And in number 2, he writes, "What would be the offset at revenues for our authorized generic of Opana ER, assuming we also launched at July 1."

Do you see that?

A. Yes.

Q. And Ms. Allen, if we could now switch to the top e-mail.

And do you see this is a reply from you to Mr. Levin on the same day, June 1, 2010?

A. Yes.

Q. And on Mr. Levin's first question regarding "how much we would lose in forgone sales of the branded drug this year," what was your response?

A. I said, "We would lose $71.2 million in branded ER sales assuming a generic launch on July 1 (using our erosion assumptions)."

Q. And what was your response to Mr. Levin for his

second question of "What would be the offset at revenues for our authorized generic of Opana ER, assuming we also launched at July 1"?

A. "We would gain $25 million in authorized generic sales."

Q. And I don't think we've talked about authorized generic -- what are authorized generic sales?

A. An NDA holder can sell product under its NDA as a generic, and that's sometimes called authorized generic sales.

Q. Is that a practice that Endo used?

A. I don't recall if Endo had sold authorized generics previously.

Q. In order to gain 25 million in authorized generic sales, how would Endo need -- what would Endo need to do to achieve that?

A. To sell an authorized generic.

MS. SCHMIDT: Okay. Thank you, Cuca.

Your Honor, at this time I have no further questions.

JUDGE CHAPPELL: Any cross?

MR. ANTALICS: Yes, Your Honor. Not too lengthy.

(Pause in the proceedings.)

Good morning, Your Honor.

JUDGE CHAPPELL: Go ahead.

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CROSS-EXAMINATION

BY MR. ANTALICS:

Q. Good morning, Mr. Cuca.

A. Good morning.

Q. Michael Antalics with O'Melveny & Myers. We met once before at your deposition. Do you recall that?

A. Yes.

Q. Okay. Mr. Cuca, on direct examination you talked a little bit about forecasts and assumptions and things.

When you create a forecast, does that mean that the forecast will come true?

A. No.

Q. Okay. Are there assumptions that are built into that forecast?

A. Yes. Many.

Q. Okay. And when you put assumptions into a forecast, does that mean that the assumptions will come true?

A. No.

Q. Okay. How many different assumptions do you

put into a forecast?

A. It depends on the forecast, but it can be lots of different ones.

Q. Okay. I think you said that the timing of generic entry was one of the assumptions that you built in some of the forecasts surrounding Impax entry?

A. Correct.

Q. Okay. And did you include an assumption of entry that Impax would enter at the first moment after the statutory 30-month stay?

A. Yes.

Q. Okay. Did you include other assumptions as to other dates when Impax might enter?

A. Yes. In different scenarios, yes.

Q. Okay. Did you -- how many scenarios did you do, if you can recall?

A. I don't, but multiple scenarios.

Q. Okay. So when you were creating these scenarios with different assumptions, did you have any idea at what date Impax would actually enter?

A. No.

Q. Okay. So why would you then create scenarios with varying assumptions?

A. To analyze the full range of potential

outcomes.

Q. During your direct examination, you were shown a number of different forecasts and scenarios. Do you recall that?

A. Yes.

Q. Okay. Were those the only forecasts and scenarios that you created during the time leading up to the signing of the deal with Impax?

A. No.

Q. Okay. There were many others?

A. Yes.

Q. Okay. At the time the settlement agreement with Impax was concluded, did the company book a reserve of any sort for payment under the Endo credit?

A. No.

JUDGE CHAPPELL: Would you be aware -- if the company booked a reserve, is that something you would be aware of?

THE WITNESS: Yes.

JUDGE CHAPPELL: Thank you.

BY MR. ANTALICS:

Q. Why did you not book a reserve at the time the settlement agreement was signed?

A. Under generally accepted accounting principles, which is what would have governed the

booking of that reserve, you wouldn't book that reserve unless the event was probable and the amount of the reserve was estimable, and so we would not have concluded that it was both probable and estimable at that point.

Q. So first it would have to be probable?

A. Correct.

Q. And you would also have to estimate it.

A. Correct.

Q. And did you ever conclude that a payment was required under the Endo credit?

A. Yes.

Q. When was that?

A. After the supply disruption of Opana after which we launched a CRF version and completely pulled the original ER version off the market.

Q. Was that the supply disruption involving Novartis?

A. Correct.

Q. And that was in 2012?

A. Correct.

Q. Okay. Prior to the conclusion and signing of the settlement agreement, did you ever hear anyone at Endo express any view about the likelihood of a payment under the Endo credit?

A. No.

Q. Okay. And did you hear anyone at the time of the settlement agreement, when it was being negotiated, express any view about the potential size of a payment under the Endo credit?

A. No.

Q. Was there any plan, to your knowledge, to pay Impax a large sum of money and in return Impax would delay its intended entry?

A. No.

JUDGE CHAPPELL: Would you be aware of such a plan if there was one at the time?

THE WITNESS: Probably.

MR. ANTALICS: I have nothing further, Your Honor.

JUDGE CHAPPELL: Any redirect based on the cross?

MS. SCHMIDT: Yes, Your Honor.

(Pause in the proceedings.)

May I proceed?

JUDGE CHAPPELL: Go ahead.

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REDIRECT EXAMINATION

BY MS. SCHMIDT:

Q. Mr. Cuca, I think during Mr. Antalics'

examination you mentioned GAAP principles?

A. Yes.

Q. What are GAAP principles?

A. Generally accepted accounting principles.

Q. And what significance do they hold for your work in financial planning and analysis?

A. They govern the standards for presenting and submitting to the SEC actual results on Forms 10-Q and 10-K, and financial planning and analysis, the forecast component of that, attempts to capture what will be actually booked.

Q. How strict are the rules of when things are booked under GAAP principles?

A. Strict.

Q. How so?

A. For example, a liability, you wouldn't book it unless it was both probable and estimable.

Q. And does GAAP have defined meanings for "probable"?

A. I believe it does.

Q. Do you know the definition off the top of your head?

A. I -- I'm not sure of the exact definition, but I think it specifies a probability.

Q. And what about estimable? What does that mean

under GAAP principles?

A. That you can produce an estimate with substantiation that's appropriate for SEC filings.

Q. And when you are going to -- when something is both probable and estimable, what does that mean for the company?

A. So when a liability is probable and estimable, you would book it and publish it in your financials.

Q. What does that mean, to book it?

A. Put it into the accounting system.

Q. Now, when you book it and put it into your financials, can you put a range in there or does it have to be a precise number?

A. It has to be a precise number.

Q. So how precise does it have to be in order to be estimable?

A. You have to be able to create a dollar figure for it.

Q. Okay. And under the Endo credit, what was the triggering event for payment from Endo to Impax?

A. The -- the triggering event was the expiration of the period immediately before Impax' generic launch.

Q. Would the Endo credit payment be both probable and estimable prior to the triggering event?

A. Yes.
Q. How so?
A. When the Novartis supply disruption occurred and we knew that we wouldn't be selling any more Opana ER, we were able to -- we knew what the peak period sales were and were consequently able to estimate -- we also knew that we probably would be selling almost nothing in the final period, so we were able to estimate the difference between the two.
Q. But my question was actually could you have been able to estimate -- would the amount have been estimable prior to that triggering event of knowing when the quarterly peak was?
A. Not prior to knowing when the quarterly peak was but prior to the triggering event to actually pay the credit, so we booked the credit before we were actually obliged to pay it.
Q. So let me back up and be clear because we're using a number of terms here that I think we may not have already gone over today.
And I actually think it might be helpful to turn back to RX-364.
And Ms. Allen, if you could turn to RX-364.0012 and highlight section 4.4.
And if I could just read this, it says,

"Section 4.4. Endo Credit. If the Pre-Impax Amount is less than the Trigger Threshold, then Endo shall pay to Impax the Endo Credit."

Do you recognize this as the Endo credit provision of the settlement and license agreement with Impax?

A. Yes.

Q. Okay. And just to go over those two more terms here, Ms. Allen, if you could turn to --

JUDGE CHAPPELL: Before you do that, I have a question.

You were asked whether the Endo credit payment was both probable and estimable prior to the triggering event and you said yes. You were asked, "How so?" And you referred to the Novartis supply disruption occurring.

That was still prior to a triggering event?

THE WITNESS: So the -- so the Endo credit -- maybe I misunderstood the original question.

I understood that what triggered our obligation to pay the Endo credit is that Impax delivers to us a documentation of all of the inputs into the formula.

JUDGE CHAPPELL: So now you're telling me how you define the triggering event.

THE WITNESS: Yes.

JUDGE CHAPPELL: Would the triggering event also be the status of the market at a point in time specified in the agreement?

THE WITNESS: That would be a component of it. Yes.

JUDGE CHAPPELL: All right.

THE WITNESS: One of the components of the formula is the sales of Opana in the last quarter immediately before Impax' launch. When the Novartis supply disruption took place, we knew that sales in that quarter were likely to be close to zero.

JUDGE CHAPPELL: Once the disruption occurred.

THE WITNESS: Correct.

JUDGE CHAPPELL: Did anyone discuss a possible supply disruption before the agreement was signed, when you were negotiating and talking about this term?

THE WITNESS: Not that I recall.

JUDGE CHAPPELL: And go ahead. What were you telling me about this supply disruption?

THE WITNESS: So Endo would have known that the sales in that final quarter before the Impax launch were likely to be zero or were close enough to zero to estimate the payment, but Impax would not have been able to provide us documentation of what those

sales were in that quarter, so could not have from a legal perspective triggered our obligation to pay yet.

JUDGE CHAPPELL: And if I follow what you just told me, you said Endo would have known the sales in the final quarter were likely to be zero.

And if that were true, there would be zero payment either way; correct?

THE WITNESS: If the sales in the final quarter are zero and the sales in a previous quarter are higher, then there would be a payment for us to them.

JUDGE CHAPPELL: From Endo to Impax.

THE WITNESS: Yes.

And we'd be able to estimate it because in the quarter before the supply disruption we would assume that that was the highest quarter sales. In the final quarter of -- before Impax' launch, we could expect that sales would be zero because we had pulled the product from the market.

And the reason I'm saying likely to be zero is because there could still be product in the pipeline that we hadn't been able to recall that could, you know, end up being a couple dollars in sales, but that would have been immaterial from a GAAP perspective to estimating what the payment was.

JUDGE CHAPPELL: And I think you told us earlier in response to some questioning that you did sit around and brainstorm or talk about possible scenarios that would affect what's called the Endo credit.

THE WITNESS: We didn't talk about what would have prompted our obligation to pay it. We talked about how it was supposed to work and what it was supposed to do.

JUDGE CHAPPELL: All right. Thank you.

Go ahead.

BY MS. SCHMIDT:

Q. Mr. Cuca, when you say "we" talked about it, who are you referring to?

A. The Endo settlement team and specifically probably me and Alan.

Q. So that's an internal discussion?

A. Correct.

Q. So that's not a discussion with Impax.

A. Correct.

Q. If I could turn your direction -- attention to RX-364-005 and actually continuing over to .006, there's a term called Quarterly Peak, and if I could -- Ms. Allen could somehow bring attention to the -- to the definition even though it's over two

pages.

Thank you.

It reads, "'Quarterly Peak' means the highest Prescription Sales of the Endo Product during any calendar quarter period from July 1, 2010 through September 30, 2012, or the last day of the full calendar quarter described in clause (ii) of the defined term Pre-Impax Amount."

Do you see that?

A. Yes.

Q. Do you recall what role the quarterly peak played in the Endo credit?

JUDGE CHAPPELL: Are you asking him about what actually happened?

MS. SCHMIDT: No. I'm actually not --

JUDGE CHAPPELL: Let's be clear if you're asking what they anticipated, what they planned for or what actually happened.

MS. SCHMIDT: Actually a fourth option, which is what role this definition played in the Endo credit provision that was encapsulated in the agreement between Endo and Impax.

THE WITNESS: So it's a component of the defined term "Pre-Impax Amount," which is itself a component of the defined term "Endo Credit."

BY MS. SCHMIDT:

Q. And does "Quarterly Peak" also appear in the market share profit value definition on RX-364-004?

A. Yes.

Q. And what is the quarterly peak capturing?

A. The highest calendar quarter's sales of Opana ER.

Q. And that's between the third quarter of 2010 and the third quarter of 2012?

A. Yes. Including the third quarter of 2010.

Q. And if the payment was triggered, was that in fact based on the difference between the quarterly peak of the highest sales of Opana ER and the Opana ER sales in the fourth quarter of 2012?

A. Yes.

Q. Would it be -- under GAAP standards, would any amount potentially be -- would the amount to be paid under the Endo credit -- would that be estimable prior to the quarterly peak?

A. Potentially, but not likely.

Q. Why do you say --

JUDGE CHAPPELL: I need to know why you are pressing this witness on GAAP standards versus what happened here and why this matters --

MS. SCHMIDT: Yes, Your Honor.

JUDGE CHAPPELL: -- because this has gone on long enough.

MS. SCHMIDT: I'm sorry. I was just addressing what was brought up by Mr. Antalics on cross, which is the concept of being both probable and estimable, and I'm just trying to make -- to understand or establish whether, due to the role of having this peak quarter sales and what that means for the potential payment, whether you could actually have an estimable number to be paid prior to reaching that peak quarter.

JUDGE CHAPPELL: And you expect him to give us this.

MS. SCHMIDT: I'm hoping to.

JUDGE CHAPPELL: Go ahead.

THE WITNESS: So within the period that becomes the quarterly peak period, certainly deeper into that period you might be able to estimate that that is the quarterly peak and what that quarterly peak is, but it could be difficult.

BY MS. SCHMIDT:

Q. And what about prior to that quarterly peak?

A. You could forecast it, but you probably couldn't estimate it for GAAP reporting purposes.

MS. SCHMIDT: Thank you, Mr. Cuca.

I have no further questions.

JUDGE CHAPPELL: Anything further?

MR. ANTALICS: I just have one question, Your Honor.

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RECROSS-EXAMINATION

BY MR. ANTALICS:

Q. Just to clarify, Mr. Cuca, one point, the point in time when Endo first knew that Endo's sales would be zero in the quarter immediately prior to Impax' entry, was that after the Novartis disruption?

A. Correct.

MR. ANTALICS: Okay. Thank you.

JUDGE CHAPPELL: Anything further?

MR. ANTALICS: No, Your Honor.

MS. SCHMIDT: No, Your Honor.

JUDGE CHAPPELL: Thank you. You may stand down.

We're going to take a short break, and when we come back I expect the next witness to be standing by. We'll reconvene at 12:00 noon.

We're in recess.

(Recess)

JUDGE CHAPPELL: Okay. We're back on the record.

Call your next witness.

MR. LOUGHLIN: Thank you, Your Honor.

Complaint counsel calls Dr. Seddon Savage.

And Your Honor, my colleague, Mr. Nicholas Leefer, will conduct the examination.

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Whereupon --

SEDDON SAVAGE, M.D.

a witness, called for examination, having been first duly sworn, was examined and testified as follows:

MR. LEEFER: Good afternoon, Your Honor. Nicholas Leefer here on behalf of the Federal Trade Commission.

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DIRECT EXAMINATION

BY MR. LEEFER:

Q. Dr. Savage, thank you for being here.

Could you please introduce yourself to the court.

A. Yes. My name is Seddon Savage. I am a physician in pain medicine and addiction medicine.

Q. Without getting into the details of your opinion, can you please briefly tell us what you're here to testify about today.

A. I have been asked to testify most specifically

on differences between Opana ER and other long-acting opioids and more generally my understandings about the treatment of pain and the diversity of options available for the treatment of pain, both pharmacologic and nonpharmacologic.

Q. Now, I'd like to ask you a little bit about your professional experiences and education that qualifies you to offer these opinions.

To begin with, could you please describe your current professional positions.

A. I currently am medical director of the Chronic Pain Recovery Center at Silver Hill Hospital in New Canaan, Connecticut.

I'm also an adviser to the Dartmouth Hitchcock Medical Center in New Hampshire on issues of pain and addiction. My advisory role is particularly around developing education for clinicians and the general public as well. It's a fairly broad educational role.

I have a number of professional volunteer roles as well.

Q. Okay. We'll get to those in just a minute.

First, I want to go over your education a little bit.

A. Okay.

Q. Where did you receive your medical degree?

A. I graduated from Dartmouth Medical School, now the Geisel School of Medicine at Dartmouth.

Q. And where did you do your residency?

A. I also did my residency at the Dartmouth Hitchcock Medical Center.

Q. And in what field was your residency?

A. It was in anesthesiology.

Q. After your residency, did you complete any fellowships?

A. I did a one-year pain medicine fellowship.

Q. And where was that?

A. That was also at Dartmouth Hitchcock.

Q. Are you currently licensed to practice medicine?

A. I am licensed in the state of New Hampshire and in the state of Connecticut.

Q. In addition to being licensed in New Hampshire and Connecticut, do you have any board certifications?

A. Yes.

I was board-certified I believe in 1986 by the American Board of Anesthesiology.

I am certified by the American Board of Pain Medicine in pain medicine and by the American Board of Addiction Medicine in addiction medicine.

JUDGE CHAPPELL: Have you taken any courses in

pharmacology?

THE WITNESS: I took courses in pharmacology as a medical student.

JUDGE CHAPPELL: Do you know how many?

THE WITNESS: I -- I do not know how many. I -- probably two courses, yearlong courses.

JUDGE CHAPPELL: Thank you.

BY MR. LEEFER:

Q. Have you --

A. I certainly have studied pharmacology outside of formal education, however.

Q. I'm sorry. I think we were talking over each other briefly. Could you just complete your last --

JUDGE CHAPPELL: She was trying to add to the answer, but she had already answered my question.

MR. LEEFER: Okay.

JUDGE CHAPPELL: Go ahead.

BY MR. LEEFER:

Q. Have you published in the field of opioid pain treatment?

A. Yes, I have.

Q. Can you give us an estimate of how many papers or books or articles you've published?

A. I've published -- I can't give you the exact number -- between twenty and thirty articles, journal

articles. Most of them relate in some ways -- some way to opioids. They may not be specifically focused on opioid therapy, but they broach the issue.

And I have published several book chapters as well that relate to opioid therapy of pain.

Q. And have you spoken or given presentations on the topic of opioid pain treatment?

A. Yes.

I am a more frequent lecturer than I am a writer. I have lectured well over a hundred times, maybe several hundred -- I'd have to look at my CV -- on issues related to pain, addiction and opioids.

Q. When you were discussing your professional positions, I believe you mentioned that you did a fair amount of educational work. Is that right?

A. That is correct.

Q. Could you explain a little bit more your role as an educator in the field of pain management.

A. Well, currently most of my work is in developing education around issues of pain treatment, opioids and/or addiction for practicing clinicians, physicians, nurses, physician assistants and others.

In the course of my work, however, I also mentor medical students. And up until about five years ago, for ten years I directed a center at

Dartmouth called the Dartmouth Center on Addiction Recovery and Education, DCARE, which specifically was aimed at mentoring and developing student interest and skills and knowledge in that field.

Q. Over the course of your career, have you held any leadership positions in organizations related to pain management?

A. In organizations and also some in relation to agencies as well.

I for the past two years have been cochair of a National Institutes of Health work group aimed at developing research priorities for or around chronic pain for the Federal Pain Research Strategy.

I have chaired at a state level the opioid task force or cochaired it -- I now have a cochair -- for the governor's commission on alcohol and other drugs in New Hampshire.

I served for two years as president of the American Pain Society between 2010 and 2012.

I chaired a number of committees for the American Society of Addiction Medicine.

I was also president of my state medical society.

Q. Thank you, Dr. Savage.

All told, can you approximate the number of

years of experience you have with the use of medication to treat pain?

A. Certainly over thirty years.

Q. Within those thirty years, can you break that down a little bit and explain what you did over the course of that time?

A. Early in my career I directly practiced pain medicine in private practice in an academic pain outpatient clinic at Dartmouth Hitchcock Medical Center. I was director of that in the last I think four or five years of my practice there through 1996.

Then I served as a consultant at the Manchester VA Medical Center on pain medicine, assisting and guiding primary care and other clinicians in their management of patients with pain.

At the same time I was serving as a consultant at the VA, I was director of the -- or there was some overlap with my directing the DCARE center at Dartmouth.

Subsequent to that, about six years ago, I began practice as medical director of the Chronic Pain Recovery Center at Silver Hill.

Q. And during the thirty-plus years of your career, how many of those years involved the use of opioids to treat pain?

A. All of them have involved it --

JUDGE CHAPPELL: Do you mean -- do you mean the use of or prescription of?

MR. LEEFER: Thank you, Your Honor. I should be much more specific. That's an excellent point. I do mean the prescription of it.

THE WITNESS: Oh, the prescription of it.

Certainly through 1996 I regularly prescribed opioids. As a consultant at the VA, I primarily supervised others but would take on occasional patients for transitional periods of time, prescribing for them as we adjusted doses.

And in my current position, I supervise and guide staff clinicians who prescribe opioids either for treatment of addiction or for treatment of pain or a combination of both.

BY MR. LEEFER:

Q. Can you talk a little bit more about your current job as medical director at Silver Spring (sic) Hospital and how you work in the context of prescribing opioids for patients.

A. Well, we are at the Chronic Pain Recovery Center a residential center that treats patients intensively for a minimum of 28 days and sometimes longer than that. We -- our goal -- most of the people

who come into the program have not had adequate or successful management of their pain as outpatients and are struggling in some way either with pain, with co-occurring psychiatric disorders and/or addictive disorders.

Our goal is really to engage them in a recovery plan for both pain and any co-occurring disorders, and to that end, we engage them in a focus on self-management, so an emphasis on nonpharmacologic therapies, noninterventionalist therapies, on exercise physical therapy, medication and use of physical --

(Admonition to slow down.)

So we engage them in physical therapeutic approaches, exercise, meditation, not medication, though we advise on medications, cognitive behavioral therapy, mindfulness, and other approaches to help them gain some awareness of both physical, psychosocial and environmental contributors to their pain and to their distress.

For many of our patients, we aim to taper off of opioids because they haven't been successfully managed with them or they're having challenges related to them, and we are successful in about 60 percent of patients tapering them off without increasing their pain and in fact in most cases --

JUDGE CHAPPELL: Counselor, I expect this to be the end of the open-ended questions. We need to move along in this trial.

MR. LEEFER: Certainly, Your Honor.

JUDGE CHAPPELL: And I'm instructing the witness to listen the questions and answer only the question pending, and if that means yes or no, I want to hear a "yes" or "no."

THE WITNESS: Okay.

JUDGE CHAPPELL: Thank you.

MR. LEEFER: Thank you, Your Honor.

At this point I'd like to tender Dr. Savage as an expert in the fields of pain management and the treatment of pain with opioid medication. She's qualified by reason of her education, training and professional experience.

MR. ANTALICS: No objection, Your Honor.

JUDGE CHAPPELL: Any opinions that meet the proper legal standards and only those opinions will be considered.

MR. LEEFER: Understood, Your Honor.

If you would -- would you prefer in the future that complaint counsel not make a formal tender?

JUDGE CHAPPELL: I prefer not telling complaint counsel how to try their case.

MR. LEEFER: Understood, Your Honor. Thank you.

BY MR. LEEFER:

Q. Now, Dr. Savage, getting to the opinions you're offering in this case, can you give us a brief, high-level summary of your approach to pain management for your patients.

A. Pain is a very complicated experience. It is not straightforward. It's very difficult to describe in a few words an approach. I will try to be brief.

First, we assess the contributors to a person's experience of pain. It is not always completely physiologic.

The physical tissue generation of pain is conducted along the nerves and through the brain and can be modulated at every step along the way, so we look at the physical contributors, the psychosocial contributors, the environmental contributors, and then we draw -- we assess what the patient's goals are both with respect to managing their pain and with respect to function and engagement and quality of life, and then we try and match them to treatments that appropriately address their conditions and their goals.

It's not a matter of choosing a single drug and saying this will cure you.

Q. Thank you, Dr. Savage.

And is there variation between individual patients and the experience of pain?

A. Yes. There's highly variable differences.

Q. Again briefly, could you please tell us your approach to using drugs to treat pain in your patients.

A. Well, drugs will address certain components of the individual's pain. It depends upon whether we're talking about the acute pain setting or the chronic pain setting or somebody with an advanced terminal illness, which medications we might choose.

Q. Let me try and be more specific.

And following up on your note that the use of medication depends, are there different medications that are better for certain patients or certain circumstances?

A. Yes.

Q. In your experience, do individuals often have different responses to different drugs?

A. In my experience -- and I believe the literature supports it -- individuals have highly variable responses to many classes of medications that are used to treat pain, including nonsteroidal anti-inflammatory drugs, anticonvulsant drugs, certain

antidepressants that are used for pain, and to opioids, which are clearly used for treatment of pain.

JUDGE CHAPPELL: You wouldn't include muscle relaxants?

THE WITNESS: I'm sorry?

JUDGE CHAPPELL: You wouldn't include muscle relaxants?

THE WITNESS: Muscle relaxants are interesting medications. We do not generally recommend them for the treatment of chronic pain. They are sometimes helpful in the treatment of acute musculoskeletal pain.

Muscle relaxants are more -- could -- most of them could be classified as -- muscle relaxants some people would like to classify as sedative-hypnotic medications in that many of them act to relax the individual, to relieve stress and anxiety, and therefore allow them to relax their muscles.

There are some subcategories of muscle relaxants that actually do act on the nervous system to cause some muscular relaxation. And then there are certainly potent ones that are used in anesthesia that actually paralyze patients and relax their muscles in that way.

But in general, muscle relaxants are not direct

relievers of pain. If somebody has --

(Admonition to slow down.)

JUDGE CHAPPELL: If somebody has pain?

Continue after you said "If somebody has pain."

THE WITNESS: If somebody has pain?

JUDGE CHAPPELL: It was your sentence. "But in general, muscle relaxants are not direct relievers of pain."

THE WITNESS: That is correct.

JUDGE CHAPPELL: "If somebody has pain" -- it was your statement. That's where she -- she couldn't understand you after that.

THE WITNESS: I'm sorry.

MR. LEEFER: Well, let me --

JUDGE CHAPPELL: Hold on a second.

MR. LEEFER: Sorry.

JUDGE CHAPPELL: If I'm coming to you and I'm in pain, I don't care how it's categorized, I just want the pain to end; correct?

THE WITNESS: That is correct.

BY MR. LEEFER:

Q. Thank you, Dr. Savage.

Let me ask you -- we were talking about differences in the individuals' responses to different drugs. Can you explain why that is?

A. We are all biologically and genetically somewhat different. It depends upon the class of drugs that you're talking about.

With respect to opioids, there are differences in the way different opioids bind to different opioid receptors, and we all express opioid receptors somewhat -- there's variability in the way human beings express opioid receptors, so we may or may not respond the same to a different opioid, so somebody may respond better to oxycodone than to hydromorphone than to morphine.

They may not only experience different levels of analgesia in response to the drug but different side effects. Most people who have taken opioids have experienced different effects with different opioids.

Q. We'll come back to discussing --

A. Okay.

Q. -- these differences in a little bit more detail, but --

JUDGE CHAPPELL: Did this witness submit an expert report in this case?

MR. LEEFER: Yes, she did, Your Honor.

JUDGE CHAPPELL: Are we to the point yet where she's telling us the opinions she formulated in this case?

MR. LEEFER: Yes, she is.

JUDGE CHAPPELL: Good. Thank you.

BY MR. LEEFER:

Q. Now, we had started discussing opioids a little bit, but to back up, can you tell us what type of drug is Opana ER.

A. Opana ER is an extended-release opioid.

Q. And what do you mean when you say "an extended-release opioid"?

A. Well, short-acting or immediate-release opioids are opioids that are taken directly into the body, absorbed and have an immediate onset of effect. It may be somewhat variable for different immediate-release opioids.

Extended-release opioids are opioids that have been pharmacologically formulated or manipulated in a way that provides gradual release of the medication, so they end up being longer acting than they would be as a molecule in their unformulated state, in their immediate-release form.

Q. Within the class of extended-release or long-acting opioids, are there differences between Opana ER and other drugs in that class?

A. Yes. There are numerous differences.

Q. Notwithstanding these differences, is it

possible to switch a patient from one long-acting opioid to another?

A. It's both possible and it's frequently necessary or advisable to switch patients. But we can't do so with a priori predictable effects of what the outcome of the switch will be. Often it requires trial of a number of medications.

JUDGE CHAPPELL: There's an example, Doctor, of a question that required a yes or no answer, yet you went beyond yes or no and gave us a narrative. Please pay attention to the question.

THE WITNESS: I will try to answer yes or no going forward. I'm...

BY MR. LEEFER:

Q. Now, I think that your answer to the last question was that it may be possible to switch a patient from one opioid to another but that you can't do that with a priori knowledge of whether that will work; is that -- am I understanding that correctly?

A. That is correct.

Q. Can you explain what you mean by not having a priori knowledge that the new opioid will work for the patient?

A. Well, as I began to explain earlier, our -- individuals respond differently to different opioids

based on a number of physiologic and pharmacologic processes.

Q. Other than opioids, what are some of the available treatments for pain?

A. Pharmacologic treatments for pain include a number of classes of medications, nonsteroidal anti-inflammatories, acetaminophen, which is a different class of its own, anticonvulsant/anti-seizure medications are often used, antidepressant medications, certain antidepressant medications, tricyclics and certain adrenergic and noradrenergic reuptake inhibitors.

Q. So other than pharmacologic treatments, what are the nonpharmacologic treatments available for pain?

A. Let me mention there are also a number of topical agents that act by different mechanisms pharmacologically.

Other than pharmacologic mechanisms, there are a number of psychobehavioral approaches.

It may be surprising to some people, but meditation is actually turning out to be a neurobiologically active treatment that actually changes conduction of pain and experience of pain.

Cognitive behavioral therapy can be very

helpful. There are a whole group of psychobehavioral therapies.

Physical therapeutic interventions with --

(Admonition to slow down.)

BY MR. LEEFER:

Q. So, Dr. Savage, maybe this will help --

JUDGE CHAPPELL: I believe she was in the middle of an answer, so let's let her finish.

MR. LEEFER: Of course, Your Honor.

BY MR. LEEFER:

Q. Please go ahead.

A. Where was I?

Q. You were -- I believe had started to talk about physical therapeutic treatments.

A. Exercise, specific physical therapy intervention, stretch and manual therapies and others, acupuncture, cold, heat, those physical therapeutic interventions.

Then there are the class of interventions that I think of as interventionalist or procedural interventions, injections, implanted spinal cord stimulators, infusions into the spinal -- in the epidural or spinal space of medications, a number of interventions, sometimes nerve -- interruption of nerves.

And then finally, we've talked about pharmacologic, psychobehavioral, interventionalist and physical therapeutics, so those are the four classes, large classes that I would name.

Q. Okay. Thank you, Dr. Savage.

Understanding that there are these four different classes of pain treatments, when are opioids generally indicated in the treatment of pain?

A. Opioids are generally indicated when other interventions are not effective in treating pain or when opioids present less risk to an individual patient than other therapeutic interventions.

Q. Do you have an opinion on whether or not Opana ER is interchangeable with other treatments for pain?

A. Yes.

Q. Okay. What is that opinion?

A. I believe that Opana ER is not certainly interchangeable with the classes -- with non-opioid interventions. Opioids are not interchangeable with other interventions.

Opana ER as a specific opioid is not reliably interchangeable with other long-acting opioids.

Q. What do you mean when you say that it's not -- that Opana ER is not reliably interchangeable with

other long-acting opioids?

A. That means that while it may provide analgesia to patients who are using another opioid, the level of analgesia that patients experience may be variable and different from that that they experience even when the doses are adjusted to that of other opioids, and the side effect profile that they experience may be different.

Q. Can you predict in advance whether a patient using Opana ER will achieve equivalent results if you switch to another opioid?

A. No.

Q. Now, I'd like to return to the broader category of pharmaceutical treatments for pain, and you mentioned a number of those.

To start with, one of the first ones I believe was nonsteroidal anti-inflammatory drugs; is that right?

A. That's correct.

Q. And for that category of drugs can you just give us one or two examples so we would know what we're talking about?

A. Yes. Those would be drugs such as Naprosyn or ibuprofen.

Q. And for these anti-inflammatory drugs, can you

explain just a couple of the key differences that you see between those drugs and opioids?

A. Nonsteroidal anti-inflammatories are generally indicated for mild to moderate pain. They have some use in severe pain when there's inflammation present, it may be helpful in that category, whereas opioids and Opana are indicated for moderate to severe pain, so greater pain severity.

Nonsteroidal anti-inflammatories, one of the primary mechanisms is a peripheral mechanism interfering with the inflammatory cascade.

Q. So is it fair to say that anti-inflammatory drugs have a different mechanism of action from opioids?

A. That is correct.

Q. I believe another category or another example of a non-opioid medication you provided was acetaminophen.

Again, can you just provide some of the key differences you see between acetaminophen and opioids.

A. Acetaminophen is indicated again for mild to moderate pain. It has a different mechanism of action than opioids. Its mechanism of action is not entirely understood. It appears to have a central mechanism of action, which may relate in part to cannabinoid

receptors.

Q. And you also mentioned antidepressants and anticonvulsants.

How do these drugs differ in important respects from opioids?

A. Anticonvulsants are more often indicated for the treatment of pain that has a neuropathic component that is abnormal conduction of pain signals along either peripheral or central neural pathways. Its mechanism of action is related to changes in ion fluctuations that change transmission of the pain signal along neural pathways, which is different than binding to opioid receptors.

Q. That's helpful. I think we might be venturing a little deeply into the underlying science, which is certainly confusing to me. But generally speaking, you mentioned anticonvulsants were helpful -- more helpful for neuropathic pain.

How does that compare to an opioid, for example?

A. Opioids are the most potent pain-relieving medications we have available. They are effective both for tissue-based pain called nociceptive pain related to injury or inflammation or tissue disruption. They're also effective for neuropathic pain, though

they may need a higher dosing for their efficacy. And they, as I said, are our most potent medications, so they're used for moderate to severe pain.

Anticonvulsants are not as potent in relieving pain, and their efficacy appears to be greater for nerve-related pain.

Q. And what about antidepressants? What are some of the key differences between antidepressants and opioids?

A. Not all antidepressants are analgesic. However, two classes of them, tricyclic antidepressants and SNRI antidepressants, have been shown to be effective for some types of pain.

They act by increasing in the nervous system certain neurotransmitters that inhibit transmission of pain signals. This is independent of their action on depression, so they are not -- many people with chronic pain have co-occurring depression, and treating the depression actually improves pain, but antidepressant medications have an effect on pain independent of their action on depression.

Q. And in your experience, which types of drugs are more potent at relieving pain, antidepressants or opioids?

A. Opioids.

Q. In your opinion --
A. Depending on the context, but I would say opioids overall.
Q. In your opinion, are any of the non-opioid drugs that we've discussed reliably interchangeable with a long-acting opioid like Opana ER?
A. No.
Q. Why not?
A. They have different indications. They have different side effect profiles and toxicity profiles. They have different mechanisms of action.
Q. Now, I'd like to move away from discussing these other categories of drugs and focus on opioids specifically.
A. Uh-huh.
Q. Can you explain the difference between short-acting opioids and long-acting opioids?
A. The primary difference is their duration of action. Short-acting opioids tend to act between three to six hours maximum, whereas long-acting opioids, if they are formulated as extended-release opioids, are available in formulae that last from eight to twelve hours up to seven days in some of the transdermal -- one of the transdermal preparations.
Q. Are you familiar were the term "half-life" as

used in the context of opioids?

A. I am familiar with the term "half-life."

Q. And what does "half-life" mean?

A. Half-life is the amount of time that's required for the plasma level of a drug to be reduced by about -- by 50 percent.

Q. And what will typically have a longer half-life, a short-acting opioid or a long-acting opioid?

A. Typically, a long-acting opioid has a longer half-life.

Q. And generally speaking, how is a longer half-life related to the duration of action for an opioid?

A. Generally, the duration of action is longer with a longer half-life.

May I correct something that I said previously?

Q. Yes. Please.

A. I'd just clarify. It's not really a correction.

But the molecule in a long-acting -- extended-release opioid is not changed, and the half-life of the molecule itself is not changed. The half-life -- the effective half-life is changed

because medication is continuing to go into the body as it is slowly released by the extended-release medication at the same time that the molecule is being cleared, so the effective half-life is longer. The molecule's half-life is unchanged.

Q. I'm sorry. I just want to make sure that I understand this.

Are you saying that the active ingredient doesn't change between a short-acting and a long-acting formulation?

A. That's correct.

I should mention, however, there are two naturally -- three that come to mind, longer-acting opioids with longer half-lifes naturally, methadone, Levo-Dromoran and buprenorphine.

Q. Thank you, Dr. Savage.

Now, even though the -- let me start that question over.

Despite the fact that the opioid molecule is not changed when it's incorporated into an extended-release formulation, how does the extended-release formulation provide more lasting pain relief?

A. Well, I can't speak to the physical chemical properties of all the various formulations that are on

the market, but in general, they provide a physical chemical structure to the tablet or the capsule or the beads, whatever the particular medication is formulated as, that provides gradual release of the molecule into the body for more gradual absorption.

Q. In other words, is it fair to say that an extended-release drug releases the active ingredient more slowly?

A. That is correct.

Q. And in your experience, what are the key clinical advantages of a long-acting or extended-release opioid?

A. Well, there are clinical advantages in specific clinical contexts. They're not always advantageous. If somebody has short-lived, quick-onset pain that goes away fairly quickly, a shorter-acting opioid would be indicated.

Extended-release opioids are indicated for people who have sustained pain usually that goes on longer than 12 to 24 hours or of a chronic nature that requires relief 24 hours a day.

Q. And is there a figure in your expert report that would help to illustrate this concept?

A. There is a figure that -- that approximates short-acting versus long-acting opioid release.

Q. Okay. Let's take a look at that figure. I'd like to show you figure 3 from your report, Dr. Savage. This is CX 5002-35.

And Your Honor, for the record, CX 5002 has been admitted as part of JX 2 and is not subject to an in camera order.

JUDGE CHAPPELL: Okay.

BY MR. LEEFER:

Q. And can you explain to us what this figure is designed to show?

A. Yes. This is designed to show the clinical -- when -- the clinical effects of short versus long-acting opioids.

In addition, there's patient-controlled analgesia as shown on there.

I want to point out that I noted that the colors -- the color coding is wrong. The sustained-release, controlled-release formulation is in yellow; it's not in red. Patient-controlled analgesia is in red.

So I'm not going to talk about patient-controlled analgesia. I don't think it's relevant here.

But if we look at sustained-release medication, if we are trying to relieve pain, we would

like optimally to be between those two parallel black lines, which represent steady-state -- steady blood levels of the medication.

If we go above those blood levels of the medication, the patient is more at risk for side effects, particularly cognitive side effects, sedation, reward, other cognitive side effects.

If we go below, the patient will dip into unrelieved pain, so we'd like ideally to relieve pain to stay at a steady blood level.

Q. And which class of drugs is more likely to achieve that steady blood level, long-acting or short-acting opioids?

A. Well, in clinical settings, long-acting medications are more likely to achieve that.

Theoretically, it is possible to overlap doses of short-acting medications in a way that provides a steady state, but many of them are quicker in onset and fall off, so you're -- you more -- you risk more often having unmasked pain as a result of fallen blood levels or having to have side effects in order to sustain analgesia for a prolonged period of time.

So, generally speaking, for patients with sustained pain, long-acting or extended-release opioids will provide more stable analgesia.

Q. Towards the top of this figure there's an entry that indicates "CNS Side Effects."

Can you tell us what that means?

A. Central nervous system side effects.

Q. And what are CNS side effects?

A. Sedation, fatigue, cognitive blurring. Reward is one, euphoria or reward.

Q. Is a patient more or less likely to experience those side effects with a short-acting opioid or a long-acting opioid?

A. Well, it depends upon their tolerance. It depends upon how they're using the medication.

In general, quick onset is associated with greater side effects, so used as prescribed, long-acting or sustained-release medications will have less peaks, therefore less side effects, less values -- valleys, therefore less breakthrough pain and/or, if there is physiologic dependence on the medication, less experience of intermittent withdrawal.

Q. Now, in your opinion, do you consider long-acting opioids like Opana ER to be interchangeable with short-acting opioids or not interchangeable?

A. They're not routinely or reliably interchangeable.

Q. Thank you, Doctor.

Now, we spent some time talking about differences with non-opioid medication and we've talked a little bit about differences with short-acting opioids.

I'd like to now spend some time focusing on differences between long-acting opioids. Okay?

A. Okay.

Q. At a high level, how does Opana ER differ from other long-acting opioids?

A. Well, first, it's a different opioid molecule from other long-acting opioids, most other long-acting opioids. There are generic Opana ERs -- I'm sorry -- oxymorphone, sustained-release oxymorphone.

But it's a different molecule from many of the other long-acting opioids; therefore, we can expect that individuals may experience different levels of analgesia, adjusted for dose, different side effect profiles, and different tolerance depending upon what they've been using and different potential for interactions with other medications.

Q. Sorry, Doctor. What are the practical implications of these differences between Opana ER and other long-acting opioids?

A. Well, that's just one difference, so there are

many differences, but as I said, it means that people may respond differently to Opana ER than they do to oxy- -- sustained-release oxycodone or morphine or hydromorphone.

JUDGE CHAPPELL: Excuse me. I think I've heard you say twice "may respond differently."

It's not your opinion that they will respond differently; is that correct? But that they may respond differently?

THE WITNESS: I can't predict that prospectively whether they will or they may.

JUDGE CHAPPELL: Well, I've heard you say "may" more than once.

THE WITNESS: They may. I can't predict how any particular patient will respond to an opioid that I'm going to prescribe them. They may respond very similarly to oxycodone as they do to oxymorphone as they do to hydromorphone, or they may experience them very differently.

We can get some information on that based on their history of past responses, so we'll always take a history and ask, you know, did you tolerate this particular medication, did you have nausea or vomiting or itching or other side effects, in particular, sedation, or other side effects with different opioids,

so it's important to take a history of what people have used in the past in order to begin to predict what they're going to tolerate best.

But as I said in my report and as the literature supports, many patients need to try two, three or four different opioids before they arrive at one that's both effective for them with minimal side effects.

JUDGE CHAPPELL: And since your opinion -- you're an expert, you're limited to an opinion, which is speculation, you're going to say may respond rather than will respond differently because your testimony is not based -- is not to be here as a fact witness.

THE WITNESS: I'm sorry. Say that again, please.

JUDGE CHAPPELL: You're an expert witness; am I correct?

THE WITNESS: I am an expert witness.

JUDGE CHAPPELL: You understand that's not the same as a fact witness. I saw something, I did something, you understand the difference.

THE WITNESS: I do not understand the difference between an expert and a fact witness. I'm sorry.

JUDGE CHAPPELL: Interesting. Okay. A fact

witness is someone who observed an event. I saw the collision at the intersection.

THE WITNESS: Uh-huh.

JUDGE CHAPPELL: An expert is someone who comes in later and says, I'm calculating that this occurred because of, fill in the blank, weren't there, didn't see it.

Do you understand the difference?

THE WITNESS: I do.

JUDGE CHAPPELL: Thank you.

Go ahead.

MR. LEEFER: Thank you, Your Honor.

THE WITNESS: Thank you.

BY MR. LEEFER:

Q. In your view, Dr. Savage, is it important to have a variety of opioids as options for treatment of pain?

A. It's very useful to have a variety of opioids for the treatment of pain.

Q. Why --

A. It's --

Q. -- why is that?

A. Because, as I've said, people respond very differently to different opioids. And it's not only because -- I mentioned the differences in the

molecules and our responses based on our own particular biology and genetic makeup may be very different, but there are differences between many of the opioid formulations in the interval of administration, whether it's 12 hours or 24 hours or three days or a week of administration.

There are differences in the way we metabolize these opioids. That's another inter-individual variation that's very important to how we respond to opioids.

There are differences in the -- some of the molecular actions, whether they act on mu opioid receptors or some of our opioids have some kappa activity as well, and I don't want to get too deeply into this, but there are differences between some of the long-acting opioids in the way they may affect neuropathic or -- or visceral pain.

Also, some of the long-acting opioids have second mechanisms of actions which aren't opioid-related, so that we have methadone, which is a long-acting opioid that seems to act on what are called NMDA receptors and may have different effects because of the interaction there, tapentadol, which may have a noradrenergic effect --

(Admonition to slow down.)

BY MR. LEEFER:

Q. Dr. Savage, please speak a little bit more slowly, and let's try to break your answers up a little bit. I'll try to ask better questions, and if you can keep your answers sort of more short and focused, I think that will help everybody.

JUDGE CHAPPELL: This is your witness. If you want the transcript to reflect what your witness says, it's your responsibility to slow down your witness.

MR. LEEFER: Yes, Your Honor, I understand. And as I said, I'll try to ask better questions and --

THE WITNESS: I apologize. I'm speaking at about half the speed I would normally speak. I will try and slow down further.

BY MR. LEEFER:

Q. Let's shoot for a quarter.

Now, I want to get back to the answer you were in the process of giving, Dr. Savage, and it was a long answer, but is it fair to summarize that as saying it's useful to have different tools to address different circumstances?

A. Yes.

Q. Now, I'd like to focus on some of the differences specifically between Opana ER and other long-acting opioids, and the first one of those that

you identified was the fact that Opana ER incorporates the molecule oxymorphone. Is that right?

A. That is correct.

Q. And generally speaking, is it easier to switch a patient that is doing well on Opana ER to a different opioid molecule, for example, oxycodone, or to switch them to a generic version of oxymorphone?

A. The outcomes of switching a patient to a generic version of oxymorphone would be more predictable than switching them to oxycodone.

Q. Why would the outcomes be more predictable?

A. Because it's the same molecule.

Q. And what's the significance of the opioid molecule being the same as opposed to different?

A. We would expect that it would have the same effect on the individual's opioid receptors and the -- no differences in potential drug interactions or different side effects. We would expect them to be the same in terms of the molecule itself.

Q. Thank you.

And another difference I believe you mentioned was that different opioids may be metabolized differently.

How is oxymorphone metabolized by the body?

A. It's -- it's metabolized in the liver. It's

metabolized, which -- what's called glucuronidated. It's -- it does not require a system that many drugs require, which is called the cytochrome P450 system, which is a system that many opioids, not all, but many of them do require, and it's known to have variability so that people may have even more unpredictable effects from use of those opioids if they have a -- either a deficit or an increase of certain enzymes, whether if they are rapid metabolizers or slow metabolizers of drugs that use that system.

Oxymorphone doesn't require that system.

Q. Let's go into in just a little bit more detail about what you called the CYP450 system. Can you explain what that is?

A. It is a system of enzymes that -- there are multiple different CYP450 enzymes that break down molecules, drug molecules, into metabolites.

Q. Do most opioids use the CYP450 metabolic pathway?

A. Many of them do. Probably most of them do. I can think of three that do not.

Q. Are there other drugs other than opioids that use the same metabolic pathway?

A. Yes. Many drugs use those metabolic pathways.

Q. What are the possible complications that exist

if a patient taking an opioid that uses this metabolic pathway is also on another drug using the same pathway?

A. You may need to adjust the dose of the opioid that you're using. And particularly, if a drug is introduced that inhibits an enzyme that is metabolizing a drug, you might find a patient with a higher level of the opioid in their body because it's not being broken down as rapidly.

Q. What's the practical implication of a patient having a higher blood level of the opioid?

A. They may develop more side effects, particularly sedation. It's conceivable that they could have an overdose as a result of that.

Q. And conversely, is it possible that this sort of interaction between drugs could result in lower blood levels of an opioid?

A. Yes. And that does occur as well.

Q. And what are the practical implications of experiencing a lower blood level of an opioid?

A. They may experience a recrudescence of pain. If they're physiologically dependent, they can experience withdrawal.

Q. Can you give us any real-world examples from your experience in which you've seen these sorts of

effects with the CYP450 metabolic pathway?

A. I can.

I would say that we are only in the last two to three years becoming more aware in medicine of these types of interactions. We've known about them for many years, but now that we're beginning to be able to test people for certain drug interactions and/or for the propensity -- for metabolic differences, I think our awareness of them is being heightened.

So looking back on my career, I know that many patients I've followed on opioids have occasionally had unexpected changes. Their pain suddenly is much worse with no change in medication. Tolerance sometimes occurs over time, but a sudden change is unusual.

Some people have suddenly had increased opioid effects for reasons that are unclear. Looking back, I wonder whether some of those may have been due to our introducing other drugs.

More recently, we had a patient, who was followed by our team, who had been on methadone for a period of time and out of the blue, on a stable dose of methadone, became very sedated and sleepy on the medication. We looked at many of the different variables, what could have been associated with that,

and it was our conclusion that it was likely an antidepressant that inhibited one of the important methadone breakdown enzymes that caused an increase in the methadone level.

Q. So was it the medical judgment of your team that the unexpected sedation of this patient resulted from an interaction with the CYP450 pathway?

A. That is correct.

Q. And are there examples of these sorts of CYP450 interactions in the medical literature as well?

A. Yes, there are. I cited some in my rebuttal report I believe.

Q. Could you just provide one example that you're familiar with.

A. One of the articles talked about an individual who had been on oxycodone and was then put on a -- I believe it was an antifungal agent and had -- which it can inhibit breakdown of oxycodone, and it had an increased medication effect as a result.

Q. What do you mean by "increased medication effect"?

A. Became sedated on the medication.

Q. And just to make sure I'm clear on this, this sort of sedation is undesirable for a patient?

A. Yes. In most circumstances. If you're trying

to nap, it may not be, but I'm trying to --

Q. So now, going back to differences between -- other differences between Opana ER and other opioids, generally speaking, how does the half-life of the molecule oxymorphone compare to other opioids?

A. The half-life of the molecule is somewhat longer for even for the immediate -- well, the molecule itself is somewhat longer than typical immediate-release opioids. I believe it's about seven hours as opposed to three --

THE REPORTER: I'm sorry. Can you say that again, please.

THE WITNESS: It is approximately seven hours, my understanding is, as compared to three to four hours for oxycodone, hydrocodone, morphine and others.

BY MR. LEEFER:

Q. And what is the practical significance of the relatively long half-life of oxymorphone compared to other opioids?

A. We would expect it to have a longer duration of action.

Q. In preparing your report, Dr. Savage, did you review any documents from Endo Pharmaceuticals that described the significance of oxymorphone's relatively long half-life?

A. Yes.
Q. And did you cite some of those documents in your report?
A. I did.
Q. Okay. I'd like to take a look at one of those documents now.
And can we please pull up CX 3158.
And Your Honor, for the record, CX 3158 was admitted into evidence as part of JX 2 and is not subject to an in camera order.
And actually, let's go to the second page of this document rather than the cover e-mail.
A. Oh.
Q. I believe this is the first tab in your binder, Dr. Savage.
A. I'm sorry. What was your question?
Q. I haven't asked a question yet --
A. Oh, okay.
Q. -- which I will now do.
Do you recognize this document as one that you reviewed in the preparation of your report?
A. Yes.
Q. And turning to page 6 of this document, that's CX 3158-006, Dr. Savage, can you please identify the portion that discusses the advantages of Opana ER's

longer half-life?

A. I'm looking at it.

(Document review.)

Q. Can you identify the portion of this document that identifies the advantages of Opana ER's longer half-life?

A. Oh, I'm sorry. That was a question.

Yes. I'm -- I'm -- can I identify it?

Q. Please do, Dr. Savage.

A. Yes.

I believe under Clinical Evidence Endo has listed at least two qualities that it believed were clinical benefits.

Q. And what is the first of those qualities that it believed was a clinical benefit?

A. It states "True 12 hour dosing."

Q. Now, here --

A. And --

Q. Sorry.

(Counsel and witness speaking at the same time and cautioned by court reporter.)

MR. LEEFER: My apologies.

BY MR. LEEFER:

Q. In about the middle of this page here, this says: Lower daily average consumption with Opana ER as

compared with -- to OxyContin.

What does "lower daily average consumption" mean to you?

A. My understanding of the way they're using it here -- I haven't looked at the study that informed that statement -- is they are saying because it has true twelve-hour dosing, the inference is that patients --

JUDGE CHAPPELL: Excuse me, Doctor. You started your answer with "My understanding." I want you to limit your answers to what you know, not your understanding.

BY MR. LEEFER:

Q. Dr. Savage, do you know what the term "lower daily average consumption" means?

A. In fact, I do not because they don't state whether it is milligrams consumed or number of tablets consumed.

Q. In your clinical experience, Dr. Savage, are there patients that are able to take -- excuse me. Let me rephrase the question.

In your clinical experience, Dr. Savage, are most patients taking Opana ER able to use it on a twelve-hour dosing schedule?

A. Yes.

Q. And in your clinical experience, have you encountered patients taking OxyContin that take it more frequently than every twelve hours?

A. Yes.

Q. Those patients taking OxyContin more often than every twelve hours, do they end up using more tablets or fewer tablets than a patient taking the drug every twelve hours?

A. They would use more tablets.

Q. In your experience, if a patient is taking more tablets per day, does that usually result in higher or lower cost for the patient?

A. It would depend upon their insurance. I -- the cost of the medication, depending upon the relative cost of the two different medications, would be more if they're taking more tablets.

Q. I'd like to go back just briefly to the CYP450 pathway that we were discussing earlier, and you've mentioned a few examples from -- well, one example from your experience and one example from the medical literature.

I'd like to ask you, in your experience, how common are these sorts of CYP450 interactions?

A. I imagine that they occur quite frequently at subtle levels that don't become clinically apparent.

One study I reviewed recently suggested that up to 30 percent of people taking an opioid that is metabolized by the CYP P430 -- 450 pathway are also taking a second medication that is either an inhibitor or an inducer of enzymes in that pathway or also metabolized by the pathway so that there's a risk of an interaction between the two drugs.

JUDGE CHAPPELL: You started your answer with "I imagine that they occur quite frequently at subtle levels that don't become clinically apparent."

THE WITNESS: That is correct.

JUDGE CHAPPELL: Is that the same thing as saying you don't know because you're not going to be told about it?

THE WITNESS: This is an evolving area of understanding --

JUDGE CHAPPELL: But my question was a yes or no.

THE WITNESS: I'm sorry?

JUDGE CHAPPELL: Your own words, are you saying you're not going to be aware of it because they occur quite frequently at subtle levels that don't become clinically apparent?

THE WITNESS: That is correct.

JUDGE CHAPPELL: Thank you.

THE WITNESS: That is my opinion.

BY MR. LEEFER:

Q. And is it your opinion, Dr. Savage, that in some cases these interactions occur at unsubtle levels that are clinically apparent?

A. Yes.

Q. And the study that you were just discussing, does that study suggest that up to 30 percent of patients may be at risk for these sort of CYP450 drug interactions?

A. Yes.

Q. Thank you, Dr. Savage.

I'd like to now talk about --

JUDGE CHAPPELL: The leading of your expert ends now, Counselor.

MR. LEEFER: Understood, Your Honor.

JUDGE CHAPPELL: I allow it when you're placing the witness at the beginning and we've got to hear about all the background, but we are into this to the point now where I will not allow you to lead your own expert. She can either answer what her opinions are or she cannot, on her own.

MR. LEEFER: Okay. Thank you, Your Honor.

BY MR. LEEFER:

Q. Dr. Savage, I'd like to talk a little bit now

about some of the other available long-acting opioids.

Can you list a few of those other long-acting opioids that you've discussed in your report.

A. Morphine is available in an extended-release form, several extended-release forms.

Oxycodone is available in extended-release forms.

Hydromorphone is available in extended-release forms.

Hydrocodone is available in extended-release.

Fentanyl.

Q. And we'll discuss --

A. Tapentadol.

Q. We'll discuss some of these in more detail, but for now I just want -- is there a portion of your report that compares the characteristics of all these different opioids in one place?

A. There is.

Q. I'd like to show you a portion of your report. This is CX 5002-106. This is Appendix C to your report.

Dr. Savage, can you tell us what this table is designed to show.

A. Oh. Yes. Thank you very much for enlarging it.

That table is a comparison of some extended-release formulations of various molecules, types, in comparison according to a number of different features of the medications.

Q. I'm sorry, Dr. Savage. Can you point the microphone a little bit more back towards you so that you're easier to hear.

Thank you.

And where does the information that's in this table come from?

A. I elected to use information from the prescribing -- the official prescribing information for each of the formulations.

There is a couple of areas where it is supplemented by information from the scientific literature where I couldn't find the information in the FDA prescribing area.

Q. Now, I'd like to zoom in on a portion of this table and specifically the top two lines and the first five columns or so.

A. Uh-huh.

Q. Dr. Savage, can you tell us what the active ingredient of Opana ER is as indicated in your table.

A. It's oxymorphone.

Q. And how does that compare to the active

ingredient of the second line here, which is OxyContin?

A. It's oxycodone.

Q. And what is the significance of the two drugs having different active ingredients?

A. Could you repeat the question. I didn't hear the end of it.

Q. Certainly.

What is the practical significance of the two drugs having different active ingredients?

A. The significance is that different patients may respond differently to the medications.

Q. Now, let's zoom in on a different part of this table.

JUDGE CHAPPELL: When a patient walks in, would you have any basis or reason to prescribe one of these over the other, the two you've just described, in the beginning?

THE WITNESS: In the very beginning if a patient walks in?

JUDGE CHAPPELL: Right.

THE WITNESS: I would take a history of which if they've had either one or the other and how they responded to it to see if I could know a priori which might be preferred by the patient or might be more

satisfactory to the patient.

If they had no history of using it, first of all, we would start with -- generally with an immediate-release form to see how they tolerated it before going to a longer-acting medication, so we'd see how they respond to the molecule before -- to the sustained-release preparation.

There -- it would depend upon the type of pain that they had. There is some evolving suggestion that oxycodone may in fact --

JUDGE CHAPPELL: I'm not talking about something that's evolving. I asked you a specific question.

A patient walks in with a pain. Would you have any reason to prescribe one or the other --

THE WITNESS: Yes.

JUDGE CHAPPELL: -- any difference?

Assuming they don't have what you call your a priori information. Your a priori facts aren't there. Somebody walks in with a back pain. Any reason why you would prescribe one of these drugs over the other or not?

THE WITNESS: For back pain, that's a very specific type of pain. Yes. I would -- there are a couple of differences that I would consider.

Do they -- if they told me that they take all their medications at breakfast and at dinnertime, I probably wouldn't use oxymorphone because you're supposed to take oxymorphone an hour before meals or two hours after meals.

If they said they take it first thing in the morning, an hour before breakfast, and they take it after exercising, before dinner, then that would be fine.

There are different formulations, so there are a number of clinical characteristics to consider.

If I thought the patient was at risk for using it with alcohol, I probably would advise them not to use it with alcohol, but if I had some reason --

JUDGE CHAPPELL: That would be either one, though, wouldn't it?

THE WITNESS: What?

JUDGE CHAPPELL: That would be either of these drugs. You don't want to take alcohol with either of these --

THE WITNESS: No, you definitely do not want to take alcohol, but the reality is that occasionally you're concerned that a patient might use it with alcohol, in which case you wouldn't want to use a drug that had a black box warning against using it with

alcohol.

I'm trying to think of other reasons -- oh, just I couldn't predict which was -- which would be the more satisfactory molecule for them, that is correct, other than those two features that I mentioned.

JUDGE CHAPPELL: I'm not sure you answered my question.

Would you prescribe either of those drugs at the point you got to at the end of your answer, when you couldn't predict?

THE WITNESS: Would I prescribe -- I'm sorry.

JUDGE CHAPPELL: Either of the two drugs you were just discussing.

THE WITNESS: Yes.

JUDGE CHAPPELL: You would prescribe either of them; correct? If you couldn't have your predictions you talked about.

THE WITNESS: I could prescribe either of them.

JUDGE CHAPPELL: Thank you.

Go ahead.

BY MR. LEEFER:

Q. Dr. Savage, despite the fact that you could prescribe either drug in an initial consultation, are

there factors that you would consider in deciding which one to use?

JUDGE CHAPPELL: We've already heard a number of those. I don't want to hear them repeated.

You can ask her to give you any factors she didn't just tell us in response to my question.

BY MR. LEEFER:

Q. Are there additional factors beyond those you discussed, like the alcohol black box warning or the mealtime restrictions, that you would consider?

A. I might consider whether the patient was going to be using any strong inducers of the P450 system or strong inhibitors of the P450 system, in which case there would be -- I would be more inclined to use the oxymorphone, which I know wouldn't interfere, those inhibitors or inducers would not interfere with the medication.

Q. Thank you, Dr. Savage.

Going back to this chart here, can we zoom in again on the first two lines and I think the columns Metabolic Pathway through T1/2.

And in this chart, Dr. Savage, what does "T1/2" mean?

A. That's a half-life.

Q. And how does the half-life of Opana ER compare

to the half-life of OxyContin?

A. It's longer than the half-life of OxyContin.

Q. How much longer is it?

A. Repeat the question, please.

Q. How much longer is the half-life of Opana ER as compared to OxyContin?

A. It's at least double the half-life. One is 4.5; the other is 9 to 11 hours.

Q. Based on this difference in half-life, which drug would you expect to have a longer duration of action?

A. I would expect oxymorphone to have a longer duration of action.

Q. And looking at the column for metabolic path, can you describe the differences between the metabolic path for Opana ER as compared to OxyContin?

A. Yes. Again, as I mentioned, oxymorphone primary metabolic pathway for degradation is through glucuronidation, which is not part of the CYP P450 pathway, whereas oxycodone has a black box warning about using CYP P450 -- the particular enzyme is 3A4 -- inducers or inhibitors.

Q. You've used the term "black box warning" a couple times now. Can you just define that for us.

A. The black box warning -- the FDA puts important

safety information that they want to be sure gains the attention of prescribers in black boxes at the beginning of the prescribing information.

Q. And to you as a doctor, what's the significance of a black box warning related to the CYP P450 pathway for OxyContin?

A. It would steer me towards not using a drug with that type of black box warning in a patient for whom there was another option for treatment. It's not an absolute contraindication, but I would consider it very strongly.

Q. Now, Dr. Savage, rather than going through every line of this appendix, I'd just like to ask you, in general, does this identify distinguishing characteristics for the opioids that are discussed in your report?

A. Yes.

Q. Let's take a look at another figure in your report. I'd like to direct your attention to figure 4, which is page CX 5002-045.

And Dr. Savage, could you please explain what this table is designed to show.

A. This is designed to show the key differences between OxyContin and Opana ER.

Q. We've already discussed a number of these

differences, and I don't want to belabor those, but can you explain what the significance of possible kappa activity at therapeutic doses is?

A. Well, this is evolving possibility -- well, we know -- what we know is that OxyContin at typical therapeutic doses binds to kappa as well as mu receptors. Most of the opioids we're talking about are primary mu active opioids. OxyContin also binds to kappa receptors.

There is some emerging evidence, not conclusive, that that may lead it to have different effectiveness, possibly more effectiveness in treating visceral pain and some speculate in treating neuropathic pain, but there's less evidence for that.

Q. What is visceral pain, Dr. Savage?

A. Visceral pain is pain related to internal organs, so pancreatic pain or bowel-related pain or other internal organ-related pain.

Q. And also listed in this table is abuse-deterrent formulation. Can you explain what that means?

A. "Abuse-deterrent formulation" can mean a variety of different things, but it discourages misuse of the medication. The FDA will grant specific labeling around abuse deterrence --

THE REPORTER: I'm sorry. You're going to have to say that again.

The FDA will grant specific labeling around abuse deterrence --

THE WITNESS: Abuse deterrence --

THE REPORTER: The FDA will grant specific labeling around --

THE WITNESS: Abuse deterrence. Leave it at that. That's fine.

And OxyContin is required by the FDA to meet certain abuse-deterrent qualities.

BY MR. LEEFER:

Q. Does Opana ER or oxymorphone ER carry any abuse-deterrent qualities?

A. It does not carry FDA credentials as abuse-deterrent.

Opana ER, as you know, was recently taken off the market. They had made an effort to make a crush-resistant version of it, but it was not granted crush-resistant certification by the FDA.

Q. And Dr. Savage, is this a factor that you would consider in prescribing medications to your patients?

A. On occasion, I think the -- the -- the effectiveness of abuse deterrence is controversial. I

think many clinicians will -- in patients who they are not a hundred percent confident are using medications as prescribed will elect abuse-deterrent medications.

Q. Dr. Savage, I'd like to direct your attention to figure 6 next in your report, and that is at CX 5002-049.

And again, could you please explain what this table is designed to show.

A. This is designed to show the differences between Exalgo and Opana ER. The one difference it doesn't show is that it's a different molecule. It's hydromorphone versus oxymorphone.

Q. Again, I think we've discussed the difference between or the significance of different opioid molecules, but I want to ask you what this entry for potential H-3-G neuroexcitatory effects means.

A. Both hydromorphone and morphine have a glucuronide -- 3-glucuronide molecule which has demonstrated -- H-3-G is hydromorphone-3-glucuronide, and it has been shown to have neuroexcitatory effects. That means it can cause irritability, hyperreflexia, in patients, particularly those using high doses of hydromorphone or particularly in those with renal failure who aren't excreting this molecule.

Morphine similarly has neuroexcitatory --

(Admonition to slow down.)

BY MR. LEEFER:

Q. Dr. Savage, I'll -- we can get to morphine later. Let's stick for now --

A. There was a reason that I mentioned that.

JUDGE CHAPPELL: Hold on a second. Don't interrupt each other. One at a time.

MR. LEEFER: I'm sorry, Your Honor.

BY MR. LEEFER:

Q. Okay, Dr. Savage. Could you explain why you mentioned morphine effects in this context.

A. Because seizures have been documented with morphine that has similar neuroexcitatory effects, and though I have not read of seizures with hydromorphone, it raises a concern.

Q. Would you consider these sorts of effects in deciding whether or not to prescribe Exalgo or morphine to a patient?

A. Yes.

Q. Now, this table also indicates that all doses are contraindicated in opioid-naive patients.

Can you please explain what that means.

A. Well, current recommendations of the Centers for Disease Control are that we start all opioids -- we start no sustained-release opioids in

opioid-naive patients. That is, when patients have not demonstrated a tolerance to moderate doses of opioids, it's recommended that we start with immediate-release doses.

However, there are some opioids that are formulated with very, very low doses so that they can be started in patients, safely clinically started in patients who are opioid-naive.

Exalgo hydromorphone is not formulated in a low enough dose to make it safe to begin with the extended-release.

Q. Is oxymorphone ER formulated in a low enough dose that it could be prescribed to opioid-naive patients?

A. Yes. FDA prescribing recommendations permit the lowest dose to be used in opioid-naive patients.

Q. Now let's take a look at another figure, figure 9 from your report, Dr. Savage. This is at CX 5002-054.

And Dr. Savage, which drug is this designed to distinguish from Opana ER?

A. Duragesic, which is fentanyl, an extended-release fentanyl preparation.

Q. What's the significance here of the transdermal administration?

A. Fentanyl is prepared -- is available only in transdermal or in the short-acting form, transmucosal form. It's not available in oral form.

So it may be preferred by some patients over the oral preparations, including Opana ER, in patients who have difficulty swallowing or absorbing oral medications.

Q. Are there situations in which a patient would prefer Opana ER over Duragesic?

A. Yes.

When you're using a transdermal preparation such as fentanyl, it's not advised to sit in a hot bath, to raise your body temperature through very vigorous exercise, or otherwise expose the patch to intermittent heat, because you will get a bolus dose of it. It increases the absorption of the medication.

So for individuals who want to engage in those activities, a transdermal would not be preferred. An oral medication would be preferred.

Q. In your experience, Dr. Savage, do some patients that are in pain rely on the use of hot baths or other application of heat to relieve their pain?

A. Yeah. It's very common for individuals with musculoskeletal pain.

Q. And what is the significance of the 72-hour

dosing that you've identified in this table?

A. Again, it's a different interval of administration. As a matter of convenience, many people would elect to have a medication that they only need to attend to every 72 hours.

I wanted to point out on your last slide with Exalgo that that's a 24-hour preparation as opposed to a 12-hour preparation --

JUDGE CHAPPELL: That comes under the heading of a question you weren't asked, ma'am. Stick to the question that's pending.

BY MR. LEEFER:

Q. Dr. Savage, are there some patients that prefer to take medication more often than every 72 hours?

A. Yes.

Q. Why would a patient ever want to take medicine more often?

A. I think it gives patients often a better sense of control that they're able to do something active to manage their pain.

There may be times that they don't need the medication and they may want to leave out a dose, and if they are on a 72-hour dose, that isn't an option to lower the medication.

Q. Rather than going through every single figure in your report, I'd just like to ask, have you -- rather, do each of the figures in this section of your report identify differences between a particular drug and Opana ER?

A. Yes.

Q. And what is the information in these tables, or where does this information come from?

A. As I said before, the information comes primarily from the prescribing information approved by the FDA for distribution with the medications.

Q. Are there any other sources for the information in these tables?

A. Yes. It's supplemented in a couple of places I believe with information from the scientific literature.

Q. Now, we've spent a fair amount of time discussing the numerous differences between Opana ER and other long-acting opioids.

In your opinion, is Opana ER superior to these other opioids?

A. I can't say that any opioid is superior to any other opioid, so no.

Q. In the context of treating an individual patient, are opioids superior to other opioids?

A. In the treatment -- in the clinical setting, for individual patients with specific types of pain in specific contexts, almost always there is a medication or medications that are better than other medications, so in that sense, there are superior choices for individuals in particular contexts. Yes.

Q. Dr. Savage, once you've identified the medication that is best for an individual patient, do you prefer to keep them on that medication or switch to a different one?

A. Once a patient has found a medication that's satisfactory for them, we would prefer to keep them on the medication.

Unless there's a reason they no longer need the medication certainly.

Q. Okay. We'll come back to that momentarily, but now I want to ask you a little bit about Impax' expert, Dr. Michna.

Have you read Dr. Michna's expert report?

A. Yes.

Q. Do you agree with Dr. Michna's opinion that the differences that you've identified between opioids are not clinically relevant?

A. No.

Q. Why do you disagree?

A. Because I think the differences between the various opioids have real clinical impacts on patients both in terms of pain, side effects and their quality of life and their lifestyles.

Q. Can you give an example of a real effect that these differences might have on a patient?

A. There are numerous examples.

Somebody may have nausea and vomiting on one medication and not tolerate it well.

Some patients may prefer to take their medication twice a day than every three days.

They may need to take an antidepressant or erythromycin for infection and experience fluctuations in a particular opioid that they wouldn't experience on another opioid.

Those are several examples. I could give more if you --

Q. That's fine for now. Thank you, Dr. Savage.

Dr. Savage, are you familiar with a REMS program for long-acting opioids?

A. Yes, I am.

Q. And what is a REMS program?

A. Well, a REMS program is a Risk Evaluation and Mitigation Strategy that FDA sometimes requires for individual drugs. In the case of opioids, it required

it for the class of extended-release and long-acting opioids.

Q. Are you aware that Impax' expert, Dr. Michna, cites to the existence of this common REMS program for long-acting opioids to support his opinion that there are not significant differences between them?

A. Yes.

Q. Do you agree with Dr. Michna's reliance on the existence of a common REMS program?

A. I agree with Dr. Michna that all opioids have certain risks of overdose and misuse or addiction, which is the purpose of the REMS program, but I do not agree that that means that all opioids are the same or all extended-release opioids are the same. They share that similar feature.

Q. Has the FDA published any information about education that prescribers of opioids should undergo in connection with a common REMS program?

A. Yes.

One element of their Risk Evaluation and Mitigation Strategy is a requirement that the pharmaceutical companies make available education to physicians on best practices in prescribing opioids. They developed a blueprint to guide the development of that education.

Q. This education blueprint, is this something that you considered in preparing your expert report?

A. It is.

Q. I'd like to take a look at that now. Can we please bring up CX 3355.

And Your Honor, for the record, CX 3355 has been admitted as part of JX 2 and is not subject to an in camera order.

Dr. Savage, is this the REMS blueprint that you were just discussing a moment ago?

A. It's the introduction to the blueprint. I guess, yeah, that's the cover page of it that I'm looking at.

Q. And what is the purpose of this blueprint?

A. This is to provide guidance to the development of education on best practices around the use of extended-release and long opi- -- long-acting opioid analgesics.

Q. Are you familiar with the REMS blueprint from your work in the field of pain management?

A. Yes, I am.

Q. And can you just explain briefly how it's used.

A. Well, there are a number of organizations that provide what's called REMS education, and it's

encouraged that all physicians who use extended-release or long-acting opioids be familiar or have taken the education. It's not required, but it's widely available and encouraged.

And the blueprint informs that education.

Q. Did you have any role in preparing the REMS blueprint?

A. Not directly. The blueprint is very similar. We brought together -- the American Pain Society brought together, with a variety of other organizations, experts and representatives from very diverse organizations, from AMA and American Nursing Association and others, to discuss what should be the elements of best practices in the prescribing of extended-release and long-acting opioid analgesics, and I was involved in chairing that meeting and facilitating it.

We developed a document that was not identical to this but very similar and sent to the FDA.

JUDGE CHAPPELL: The question was: "Did you have any role in preparing the REMS blueprint?" That's a yes or no.

THE WITNESS: Not directly. No.

BY MR. LEEFER:

Q. Did the document that came out of the meeting

that you chaired, which you were discussing just a moment ago -- was that similar to the REMS blueprint that the FDA ultimately --

A. It was similar, not identical by any means.

Q. Understood. Thank you.

And I'd like to direct your attention to the bottom of page 6. This is CX 3355-006.

And specifically under the subheading Roman numeral vi.

Now, this is kind of a long sentence, but Dr. Savage, can you just summarize for us what this is trying to convey.

A. Essentially this section says that prescribers should be knowledgeable about the specific characteristics of individual extended-release or long-acting opioid analgesics that they prescribe.

Q. And do you agree with that?

A. I do.

Q. -- statement?

Why?

A. For all the reasons we've been discussing because it -- the differences have a real impact on the clinical effects and the quality of life that patients experience when using these medications.

Q. I'd like to now direct your attention to

page 10, so CX 3355-010.

And Dr. Savage, can you explain what the table that begins on this page is designed to show.

A. I believe -- I'm only looking at one page, and I know it's 10 or 15 pages, but I believe that this is a section that talks about the specific characteristics of different extended-release opioids.

Q. Dr. Savage, in your opinion, are the different characteristics reflected in the table beginning on page 10 clinically significant to the prescription of opioids for the treatment of pain?

A. Yes.

Q. I'd like to take a look specifically at page 13, CX 3355-013.

JUDGE CHAPPELL: How much more time do you think you'll need with this witness?

MR. LEEFER: Your Honor, I am well over halfway done. I do still have two sections to get through. I would estimate 20 to 30 more minutes, but in the interest of full disclosure, I am not always accurate in estimating time.

JUDGE CHAPPELL: We're going to take our lunch break.

MR. LEEFER: Thank you, Your Honor.

JUDGE CHAPPELL: We'll reconvene at 2:45.

We're in recess.

(Whereupon, at 1:44 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(2:48 p.m.)

JUDGE CHAPPELL: Okay. We're back on the record.

Next question.

MR. LOUGHLIN: Your Honor, can I raise one question or one issue before we begin?

JUDGE CHAPPELL: Go ahead.

MR. LOUGHLIN: Your Honor, unfortunately, the witness we had scheduled after Dr. Savage, Professor Bazerman, is not able to be here until tomorrow morning.

Based on Mr. Leefer's belief in terms of his timing and I've spoken with Mr. Antalics, it does not look to me, Your Honor, like we will get to 5:30 today with Dr. Savage. I think -- my guess is, based on their estimates, we're going to be about an hour short.

JUDGE CHAPPELL: What have we learned this week, Counsel?

MR. LOUGHLIN: Your Honor, I apologize. But as I mentioned, we are dependent upon the availability of the fact witnesses from -- that are not in our control. We would have loved to have all the fact witnesses lined up and here. We haven't been able to

do that, Your Honor.

JUDGE CHAPPELL: What do you mean, fact witness? Bazerman is not a fact witness.

MR. LOUGHLIN: No. I understand that, Your Honor. But we would have preferred to have all the fact witnesses. We were not able to do that, and so we've tried to schedule expert witnesses in their place, and the expert witnesses have schedules, and Professor Bazerman was not available until Friday.

JUDGE CHAPPELL: As we all do, which is why I don't like to not have a witness available here when we're available for court.

There's nothing we can do about it. What's next?

MR. LOUGHLIN: Thank you, Your Honor.

MR. LEEFER: Thank you, Your Honor. May I proceed?

JUDGE CHAPPELL: Go ahead.

BY MR. LEEFER:

Q. Dr. Savage, before the lunch break, we were discussing the material in the FDA REMS blueprint. Do you remember that?

A. I do.

Q. And I'd like to direct your attention to a particular page in the blueprint, and this is

CX 3355-012, and then that continues onto -013.

Can you please pull those up.

And Dr. Savage, the product shown here at the bottom of page 12 is Dolophine.

Which opioid is that?

A. Dolophine is methadone.

Q. And is methadone an opioid that you're familiar with in your --

A. Yes.

Q. On page 13, under Product-Specific Safety Concerns, this says "QTc prolongation."

What does that mean?

A. On an electrocardiogram the QC -- QTc -- the QT interval is the area of electrical activity that roughly corresponds to ventricular activity, the pumping of the heart.

Q. And why is QTc prolongation here under Product-Specific Safety Concerns for methadone?

A. Because when that interval is prolonged, it puts individuals at risk for cardiac arrhythmias, such as torsades de pointes syndrome, which can be a lethal arrhythmia.

Q. Dr. Savage, is a safety concern like QTc prolongation a factor you would consider in deciding whether or not to prescribe methadone?

A. It is.

JUDGE CHAPPELL: Hold on a second.

Mr. Loughlin, have you issued subpoenas to these witnesses?

MR. LOUGHLIN: We did issue subpoenas, Your Honor.

JUDGE CHAPPELL: Have you released anyone from subpoena?

MR. LOUGHLIN: No, Your Honor.

JUDGE CHAPPELL: Then they should be here.

MR. LOUGHLIN: Understood, Your Honor. We are working with them to try to get them here on a schedule that is -- that works for them and works for us.

JUDGE CHAPPELL: Subpoena doesn't leave wiggle room unless you give wiggle room, sir. You know what a subpoena is; right? You know how it works?

MR. LOUGHLIN: I do know how it works, Your Honor.

JUDGE CHAPPELL: You don't need to give them wiggle room. When you issue a subpoena, they shall be here.

MR. LOUGHLIN: Well, Your Honor, we're working with counsel to try to make that happen, but we don't have the power to send deputies to drag them to court.

JUDGE CHAPPELL: You bring it to me, and I'll get you a deputy involved. There are ways to enforce subpoenas. If you don't believe it, look at the rules. I'm not saying you have a deputy, but there will be a deputy -- there will be a marshal involved if someone doesn't honor a subpoena. You know that; correct?

MR. LOUGHLIN: Your Honor, yes, and that's wonderful to hear. We would like nothing more than to have witnesses lined up. We have not been able to make that happen, but we will try harder.

JUDGE CHAPPELL: Thank you.

BY MR. LEEFER:

Q. Dr. Savage, in your opinion, is a factor like QTc prolongation associated with methadone clinically significant in deciding which opioid to prescribe?

A. Yes. And there are clear guidelines about not prescribing methadone for patients with a QTc interval that is over a certain duration.

Q. Does oxymorphone have a similar safety concern associated with QTc prolongation?

A. To my knowledge, it does not.

Q. Okay. You can set that aside, Dr. Savage.

Now, the information that we were looking at in the FDA REMS blueprint, is that similar to the

differences between opioids that you discuss in your expert report?

A. It is.

Q. Dr. Savage, are you aware that Impax' expert, Dr. Michna, cites to the common indication for long-acting opioids in support of his position that they are all essentially the same?

A. I'm aware of that, yes.

Q. Do you agree with Dr. Michna's reliance on the common indication for long-acting opioids?

A. I agree that they for the most part -- there are at least one or two exceptions, but they do have a common FDA indication. That doesn't mean they have identical effects and side effects.

Q. Why don't you believe that the common indication for long-acting opioids means that they're all essentially the same?

A. For all the reasons that I described in my report and that the FDA includes in their blueprint documenting that there are differences between all these opioids, and the FDA recommends that it's incumbent on us to understand those differences and to accommodate them.

Q. To sum up these differences, what is your opinion, Dr. Savage, about the degree of

interchangeability of Opana ER with the other available long-acting opioids?

A. I don't believe that we can predict that they will be reliably interchangeable with one another in a particular patient. They are sometimes interchangeable and often not, but we cannot know that prospectively. Therefore, I believe that they're not reliably predictably interchangeable.

Q. Thank you, Doctor.

Earlier, before lunch, you testified that notwithstanding the significant differences between opioids, it's sometimes possible to switch a patient from one to another. Do you remember that?

A. Yes.

Q. Are there any complexities involved in switching a patient from one long-acting opioid to another?

A. Sometimes there are; sometimes there are not.

Q. And can you identify what some of those complexities are?

A. Well, again, we can't predict whether the new opioid to which one is switching is going to be well-tolerated and adequate for analgesia for the individual.

We can't predict the relative dose that will be

the same for an individual. We have guidelines about what dose of oxycodone equals what dose of oxymorphone, what dose of morphine equals what dose of hydromorphone, but it's very approximate and it's based on experimental conditions.

So there is a risk of having somebody, when you switch them all at once, to have them on too low a dose where they will have an experience of pain until you've caught up with the dosing or to have them on too high a dose, which usually will just amount to somebody being sedated or having side effects and you back off but can result in overdose, and overdoses have been reported.

Q. Let's start with the risk of over- or underdosing the patient.

Why is that a risk when you switch from one opioid to another?

A. Because we can't predict an individual's response to the new opioid based on their response to the opioid that they're on with any accuracy.

Q. Are all opioids equally potent at relieving pain?

A. No. Milligram for milligram, different opioids have different potency.

What we generally do in trying to calculate

equivalents, there are what are called opioid analgesic equivalency charts, and we will calculate what are called morphine equivalents for each opioid.

So if somebody is on oxymorphone, we would calculate the morphine equivalents of oxymorphone they're on, and if we wanted to switch them to oxycodone, we'd calculate what that would be. That would give us the relatively equivalent dose, but because the individual is not tolerant to the new opioid, we will generally cut that back by half or two-thirds, three-quarters, something along those lines.

Q. When you say that --

JUDGE CHAPPELL: I'm sorry. I just want to verify something.

Are you saying then it's your opinion that patients never switch, never change opioids once they're on one opioid?

THE WITNESS: No. I'm sorry if I stated that. No.

Opioid rotation is a very important clinical tool that we use when there's a clear reason that somebody needs to change from one opioid to another.

JUDGE CHAPPELL: What would be a clear reason?

THE WITNESS: I'm sorry?

JUDGE CHAPPELL: You said "when there's a clear reason." What's a clear reason?

THE WITNESS: If somebody is becoming tolerant to one opioid and they're having to increase and increase and increase their dose, often by rotating them to a different opioid, they will achieve pain relief on a much lower dose of that opioid.

If somebody has persistent nausea or itching or other side effects, we might change them to a different opioid.

If they're on methadone and their QTc interval, as we talked about, the potential for cardiac arrhythmias, if we see that going up, we may want to rotate them to a different opioid.

JUDGE CHAPPELL: What if their insurance changes and they no longer can get the opioid you prescribed?

THE WITNESS: If -- if -- it depends in that case. If somebody is doing really well and they've tried other opioids and they don't respond well, we might seek to get authorization for the opioid even if it's not one that's commonly approved by the insurance company. If the insurance company denies that, we'll do our best with whatever opioids are available.

The challenge sometimes is you end up doing

polypharmacy to try and treat side effects of opioids, you know, putting somebody on an antinausea drug if they're nauseated. Or sometimes if somebody is sedated on a medication, you'll see people adding an amphetamine to treat that.

And in general, I would prefer in my practice to keep it as simple as possible and have the best clinical match for the patient.

JUDGE CHAPPELL: So if I understood your answer, you prefer not to switch a patient who is on a certain opioid, but it happens often.

THE WITNESS: Yes, it happens -- I don't know what "often" is, but it happens clinically that we elect to switch patients.

And sometimes, as I said, it's simple. If they're on a low dose of an opioid, they can switch easily to something else. They may or may not tolerate it as well and we'll try something else.

But if they're on a high dose and sometimes people are on two or three different opioids, it's a bit more complicated then.

I don't want to overstate the risk, but I have spent literally hours writing out regimens for people to help switch them over safely and easily to a new drug.

JUDGE CHAPPELL: So did I hear you say a number of people are on two or three different opioids?

THE WITNESS: Yes. Sometimes people will be on two or three different opioids. I have seen that not infrequently. I would not generally do it.

JUDGE CHAPPELL: And one of those might be Opana ER or its equivalent and one of them might be what?

THE WITNESS: A short-acting opioid. I have seen people on a fentanyl patch and long-acting oxycodone or oxymorphone and then a short-acting drug.

There --

JUDGE CHAPPELL: So like an opioid cocktail.

THE WITNESS: What?

JUDGE CHAPPELL: An opioid cocktail.

THE WITNESS: It's an opioid cocktail.

I'm not saying I'd recommend that. I'm saying that patients will come to us on those.

And the rationale, if I may -- would you -- the reason that people will sometimes do that is because of the fact that different opioids are different and they seem to bind somewhat differently to different mu opioid subreceptors, and so there is a theory -- and there are number of articles on this --

suggesting that adding different opioids to each other gives you improved analgesia.

The problem with that is then you become tolerant to several opioids and it's difficult, if you start losing your -- the effectiveness of the medication, to find an opioid that works, so I personally in my practice would prefer people to be on a single or at most two opioids.

MR. LEEFER: Thank you, Your Honor.

BY MR. LEEFER:

Q. And Dr. Savage, I want to return to something you were mentioning just a little bit earlier.

I think you mentioned that there are opioid equivalent charts that allow you to calculate equivalent dosages of different opioids. Is that right?

A. That is correct.

Q. When you switch a patient from one opioid to another, can you just cut the dose by the percentage indicated by the opioid equivalent charts?

A. No. It's more complicated than that.

The equivalency charts will give you kind of an average equivalency across the population, and they're based on very limited studies, but they'll give you some idea of the relative strength.

Then if the person is tolerant to the first drug, you don't expect them to be tolerant to the next drug, so you have to cut that dose back even further.

And then that doesn't take into account the individual's responsiveness to either of the opioids.

JUDGE CHAPPELL: Are you saying that using these charts is something that the AMA requires, let's say, a general practitioner out here in the suburb who's seeing 15-20 patients a day, kids are screaming in the waiting room, climbing all over everybody, that that doctor is looking at charts before he prescribes -- he or she prescribes opioids to every patient?

THE WITNESS: If he or she is rotating the patient from one opioid to another, they either have the equivalencies in their head if they do it quite often or they do look at the chart or they just go blind. And that's why, you know, I would say unless there's a clinical indication and you do a lot of this, you have to have -- you have to exert great care in opioid rotations.

There are people who get profoundly sedated because of overprescribing. There are people who are in withdrawal because they've been underprescribed, too. It's -- it is -- for high-dose opioids, it can be

complicated.

Again, I don't want to overstate it. If you're taking two Percocet a day and you want to switch to a couple of hydrocodone, that's not going to be a complicated switch. It may or may not work as well for you. But when we have people on complex regimens and they're taking a number of other medications, it has to be done thoughtfully and with great care.

JUDGE CHAPPELL: Okay. Again, is there an AMA requirement or any law or regulation you're aware of that requires a doctor to review these charts and apply them before prescribing a different opioid?

THE WITNESS: I'm thinking.

No.

JUDGE CHAPPELL: Thank you.

THE WITNESS: May I say one caveat, though. The FDA --

JUDGE CHAPPELL: Well, I guess so since you're saying it. Go ahead.

THE WITNESS: The FDA in the REMS blueprint suggests that you know the relative potencies of the different medications. They do not provide a chart, but to know the relative potencies, you need to be looking at --

JUDGE CHAPPELL: So if I follow you, that's a

suggestion in the FDA REMS blueprint; correct?

THE WITNESS: Correct.

JUDGE CHAPPELL: Not a requirement by law or regulation as you know about.

THE WITNESS: No. There may be states that require it. I'm not familiar with all the state laws. Many states are implementing legislation regarding how to use opioids.

BY MR. LEEFER:

Q. Dr. Savage, in your capacity as an educator of others in the use of opioids, do you instruct people switching patients from one opioid to another to use these dosage equivalency charts?

JUDGE CHAPPELL: When you say "people," do you mean prescribing doctors who are licensed?

MR. LEEFER: I do mean prescribing doctors. My apologies, Your Honor.

THE WITNESS: I do, with the caveat that I usually provide three different methods for rotating.

BY MR. LEEFER:

Q. Thank you, Dr. Savage.

Now, getting back to the various risks that may arise when rotating from one opioid to another, is there a risk that new side effects may develop with the use of a new opioid?

A. Yes.

Q. Given the various complexities and potential risks of opioid rotation, how do you mitigate against those risks when you switch a patient from one opioid to another?

A. Well, there's several ways. Sometimes we suggest that rather than giving the full dose of the new medication and stopping the old medications, that you give maybe a quarter of the new medication and go down about a quarter of the calculated dose of the old medications, and so see how somebody responds to the new medication and gradual- -- it's called gradually rolling them over.

Another method is to give no more than the recommended starting dose of the new medication as long-acting because we believe, based on studies, that people will tolerate that new dose and then provide only short-acting medications on top of it and ask the person to hold that short-acting dose, don't take it, if you're sedated or having other major side effects.

Q. Is it always complicated and difficult to switch a patient from one opioid to another?

A. No.

Q. What's a circumstance in which it would be relatively straightforward?

A. Well, the example I gave before, if somebody is taking two tablets of a short-acting opioid and they're having itching or nausea and it persists and you want to try a different opioid, then switching them to something else.

If you're in the ER and somebody gets side effects on one drug, often the very next dose would be a different opioid. That's quite straightforward.

Q. Even in those relatively straightforward situations, do the risks of new side effects or unsatisfactory analgesia still exist?

A. Yes.

Q. In your experience, can switching a patient from one opioid to another result in additional costs for the patient?

A. Generally, when somebody is being rotated, particularly from a complicated regimen that requires increased care and monitoring, we'll recommend that prescribers see them more regularly or at least have their office contact the patient more regularly.

And for example, often we'll see people once a month who are using opioids. You may need to see them on a weekly basis or more and talk to them more frequently than that. It's highly individualized. It depends upon the drugs and -- but that can increase

healthcare costs certainly.

Q. I believe you touched on this earlier, but given these complexities and risks, would you typically rotate a patient from one opioid to another absent a clinical need to do so?

A. No.

Q. And Dr. Savage, if you had a patient that is doing well on a long-acting opioid like Opana ER, would you prefer to keep them on that drug or switch them to a new opioid?

A. If they're tolerating it well and it's meeting their needs, I'd prefer to keep them on the drug that they're using.

Q. Now, Dr. Savage, in your experience, would a minor increase in price for an opioid that one of your patients is taking cause you to switch that patient to a different opioid?

A. It would depend upon the patient and what the increase in price meant to them. Most of our patients are insured and don't experience minor fluctuations in price directly.

So generally speaking, no; in some cases, yes.

Q. And generally speaking, are you aware of the prices of long-acting opioids?

A. No.

Q. So would you be aware if the price of a long-acting opioid increased or decreased?

A. No. Not -- not unless I were in a healthcare system where they regularly informed us of those issues, which I'm not.

Q. Now, why wouldn't minor changes in prices change your prescribing habits?

A. First, because I'm generally not aware of the minor changes in price.

Second, because the -- my clinical -- my concerns here are for the clinical well-being of the patient, and those would take priority over more abstract financial concerns.

Q. Understanding that you don't generally know the price of opioids exactly, do you know anything about relative prices of opioids?

JUDGE CHAPPELL: I thought she said "no" a few moments ago. That was a pretty broad question you asked her.

MR. LEEFER: Let me try and rephrase that, Your Honor.

BY MR. LEEFER:

Q. Do you know any general information about the prices of opioids?

A. Fairly limited. My understanding is that

short-acting opioids most often are less expensive than sustained-release opioids. Methadone is a very, very inexpensive long-acting opioid.

Q. In your experience, which tend to be cheaper, generic versions of opioids or brand name versions?

A. Generic versions. That's the only thing I know.

Q. Could cost information of that sort shape prescribing decisions that you make?

A. For an uninsured patient who is -- has limited financial means, certainly those would be considerations.

JUDGE CHAPPELL: But I thought you told us you're unaware of those things, so evidently you don't think it's important enough to know this; correct?

THE WITNESS: If a patient brought to my attention that they had no insurance that paid for their drugs and they were concerned about their finances, I would incorporate that into my clinical decision-making.

JUDGE CHAPPELL: So that's purely hypothetical?

THE WITNESS: And excuse me.

JUDGE CHAPPELL: If a patient brought it to you?

THE WITNESS: If a patient brought it to my attention, which has happened, then I would consider the cost.

It's not that I don't care enough to notice. I don't have ready access to the information of the actual price of drugs.

JUDGE CHAPPELL: Frankly, your care is not an issue, ma'am. I'm just looking at what I see to be inconsistent, trying to have a complete record here in this trial, so whether you care or not is not an issue.

THE WITNESS: Well, you said that, you don't care enough to know -- I'm sorry. I thought that's what you said.

JUDGE CHAPPELL: It might have been inartfully worded, but I'm trying to prevent inconsistencies in our record. That's my job.

THE WITNESS: Thank you.

JUDGE CHAPPELL: We're getting at the truth here whether anybody likes it or not.

Go ahead.

MR. LEEFER: Your Honor, maybe this is my fault. I can try and clarify.

I believe Dr. Savage was drawing a distinction between knowing the specific price of an opioid and

knowing sort of generally that generics are cheaper than brand name drugs, and so she -- I believe she testified that she knows that general information but not the specific prices of drugs.

MR. ANTALICS: At some point I think I'd preferred the witness to answer the questions rather than the lawyer describe what he'd like her to say.

JUDGE CHAPPELL: He's --

MR. ANTALICS: Leading, Your Honor.

JUDGE CHAPPELL: -- in an indirect way saying you're leading and suggesting an answer and coaching the witness.

MR. LEEFER: My apologies, Your Honor. I will rephrase my questions.

BY MR. LEEFER:

Q. Dr. Savage, if a patient does not raise the cost of opioid medication with you as a concern, is it something you independently consider when prescribing drugs?

A. Not in the -- no.

Q. Dr. Savage, when you prescribe opioids, what are your primary considerations in deciding which drug to give to a patient?

A. My primary considerations are matching the patient to a medication that's clinically effective for

them with the least amount of side effects and one that meets convenience issues such as interval of dosing and matches their pain needs.

JUDGE CHAPPELL: Have you ever testified as an expert witness in a trial before?

THE WITNESS: Yes.

JUDGE CHAPPELL: Often?

THE WITNESS: No.

JUDGE CHAPPELL: Because if you do, you'll understand none of this is personal, ma'am.

THE WITNESS: I'll understand what?

JUDGE CHAPPELL: None of this is personal.

THE WITNESS: Thank you.

JUDGE CHAPPELL: It's about getting to the truth.

THE WITNESS: Thank you very much, Your Honor.

BY MR. LEEFER:

Q. Dr. Savage, if you have a patient that is doing well on a long-acting opioid like Opana ER, would you switch them to a different opioid based on a minor change in price?

A. I probably would not be aware of the minor change in price, and I wouldn't switch them without knowing that. It depends upon what you mean by "minor" and how the patient experience -- if I did become aware

of it, how the -- it impacted the patient and how they experienced that fluctuation in price.

Q. If you didn't become aware of it, would it play any role in your prescribing decisions?

A. I want to be sure I understand your question. If I were not aware of the change in price, would it influence my prescribing decision.

Q. Yes, that was my question.

A. No, it would not influence my prescribing decision.

JUDGE CHAPPELL: How could it? To state the obvious.

MR. LEEFER: That's a fair point, Your Honor.

JUDGE CHAPPELL: I'm glad you didn't slip up on that one.

BY MR. LEEFER:

Q. Generally, Dr. Savage, in your thirty-plus years of prescribing opioids, have you been aware of minor changes in price in opioids?

A. I have not been.

MR. LEEFER: Thank you, Dr. Savage.

I have no further questions at this time.

JUDGE CHAPPELL: Will there be any cross?

MR. ANTALICS: Right, Your Honor.

JUDGE CHAPPELL: Go ahead.

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CROSS-EXAMINATION

BY MR. ANTALICS:

Q. Good afternoon, Dr. Savage. Good to see you.

A. Good afternoon, Mr. Antalics. Good to see you.

Q. I'd like to start, Dr. Savage -- I'm not going to show you very many documents, but I would just like to show you one to begin. It's -- it's a chapter from a book that I believe you authored.

If you could turn to the first document.

Okay. This is the name of the book; correct? Principles of Addiction Medicine?

A. (Witness nodding.)

Q. Okay. And if you could turn a few pages in to where it says "Opioid Therapy of Pain." It's on page -- I think it's 1500.

JUDGE CHAPPELL: By the way, can the witness just look at the screen if she'd prefer?

MR. ANTALICS. Yes, you may if you like. That might be easier actually.

JUDGE CHAPPELL: Just so we're clear, I know you don't make a living at this, from what you told me earlier. If you find that what you see on the screen is too limiting, look at the book.

THE WITNESS: Okay. I may need to do that, unless it gets magnified again, but we'll see.

MR. ANTALICS: I think you'll recognize the parts that we're looking at.

MR. LEEFER: Sorry. Your Honor, I object. This document doesn't appear to be marked as an exhibit or a demonstrative.

MR. ANTALICS: No, it's not an exhibit or a demonstrative. It's one of the materials Dr. Savage relied upon. I'm just going to ask her a couple questions about it.

JUDGE CHAPPELL: About one of her books?

MR. ANTALICS: Yes. One of the materials she relied on in preparing her report.

JUDGE CHAPPELL: That's fair game. It doesn't need to be an exhibit. Depending on -- we'll see how this develops.

BY MR. ANTALICS:

Q. Okay. The chapter is called Opioid Therapy of Pain.

You were the primary author for that chapter?

A. Correct.

Q. Okay. Now, if you could turn to page 1508, and we'll spend our time just on that page, 1508. It has a chart with a number of opioids on it.

Do you recognize that chart?

A. I do.

Q. Okay. And on the top half of the page where it says "Mu Agonists" --

A. Correct.

Q. -- do you see that?

Going down to halfway down?

Now, all of the --

THE REPORTER: I'm sorry. She keeps nodding.

(Discussion off the record.)

BY MR. ANTALICS:

Q. On the top half, top left corner, it says "Table 97-3." Immediately under that it says "Opioid." And immediately under that it says "Mu Agonists," a category of opioids.

A. Correct.

Q. Okay. Now, all of the drugs listed in that top category, those are all mu opioids; is that correct?

A. That is correct.

Q. Okay. And all of the drugs on that page are still considered opioids, though, although they're not all mu opioids, mu agonists.

A. As far as I can see the page, they are all mu opioid agonists.

Some have dual mechanisms of analgesia, and some may have a little kappa activity, but they're mostly mu agonists.

(Counsel and witness speaking at the same time and cautioned by court reporter.)

JUDGE CHAPPELL: And also, it's your record, but if you're going to be asking a lot about this page, are you going to make it a demonstrative exhibit, or are you going to cover everything in dialogue?

MR. ANTALICS: Well, if you'd like, Your Honor, I could offer it now. I don't believe there will be an objection since she relied on it.

JUDGE CHAPPELL: I'm not going to tell you what to do. I'm just saying it's your job --

MR. ANTALICS: I was going to offer it, Your Honor, but --

JUDGE CHAPPELL: If you're cross-examining a witness, it's on you to make sure --

MR. ANTALICS: I was --

JUDGE CHAPPELL: Now you're talking while I do.

If you want the record to be understandable, it's up to you to decide how to do that. But if you're going to be talking about page-whatever and the record has no page-whatever even as a demonstrative, it may be hard to follow.

Again, I don't know. You might have one question and we're moving on. I don't know what you're doing.

MR. ANTALICS: I intend to offer it, Your Honor.

JUDGE CHAPPELL: As a demonstrative?

Take a moment, talk to opposing counsel --

BY MR. ANTALICS: Yes, I'd like to --

JUDGE CHAPPELL: Take a moment. Talk to opposing counsel. See if you have an agreement.

(Pause in the proceedings.)

MR. ANTALICS: Your Honor, we'd like to offer this as a demonstrative exhibit, I believe without objection, but it will be listed as RX D-1.

Do we have one of those yet? I don't think so.

JUDGE CHAPPELL: And just for better reference, that is what page of what book?

MR. ANTALICS: The book is titled -- it is page 1508 of the book called The ASAM Principles of Addiction Medicine, Fifth Edition.

JUDGE CHAPPELL: Any objection to this as a demonstrative?

MR. LEEFER: No objection to it as a demonstrative, Your Honor.

JUDGE CHAPPELL: So admitted.

(RX Exhibit Number D-1 was admitted into evidence.)

BY MR. ANTALICS:

Q. Okay. Once again, you wrote this chapter?

A. I did.

Q. Okay. Now, could we go down the list of the mu agonists, and could you tell us which of these, to your knowledge, has a generic drug available associated with that molecule.

Let's start with morphine.

A. Okay. Morphine -- a generic extended-release?

Q. An extended-release generic.

A. Is that what you're asking?

Morphine, oxycodone, oxymorphone, hydrocodone, hydromorphone, fentanyl, tapentadol, in Europe codeine but not in this country, and methadone is long-acting, but it's not extended-release.

Q. Okay. Thank you.

What I'd like to do now is direct your attention down to the bottom of the page, the first full paragraph starting with "Though most mu agonists."

Can we get that on the screen.

Okay. And the paragraph on the third line down, it says, "Though most mu agonists are

interchangeable if attention is paid to relative potencies and onset and duration of action, individuals may respond differently to different opioids in terms of both analgesia and side effects."

Do you still agree with that sentence, Doctor?

A. I do.

Q. Okay. Thank you.

Now, when you talk about relative potencies and onset and duration of action in the first part of that sentence, you mean you may have to adjust the dose of the alternative to get the same analgesic effect; correct?

A. Yes.

Q. Thank you.

And it's also possible, as we see in the second half of the sentence, that you would have to give the patient some additional medication if there are side effects in the alternative.

A. That was not what I intended. I don't mention giving people additional medications.

Q. Okay.

A. I intended what's actually written -- may I read it?

JUDGE CHAPPELL: Just so we're clear, when you're saying, That's not what I intended, you're

talking about what's printed on this page? Or testimony previous today?

THE WITNESS: He said that in the second half -- my understanding of what you just said, if I'm remembering it correctly, is that in the second half of that sentence I intended to say you may need to give medications for side effects and --

BY MR. ANTALICS:

Q. Let me rephrase it for you. Okay?

In the second part of the sentence, where you say "individuals may respond differently to different opioids in terms of both analgesia and side effects," now, with respect to the analgesia, that's a matter of altering the dose; is that correct?

A. No. No. As I go on to say, it may be in part owing to variability in mu opioid receptor expression.

Q. Right.

A. That's that concept of mu opioid polymorphism that I mentioned earlier, that we all express our mu receptors differently and therefore may respond differently to different opioid medications, which match differently with those opioid subreceptors.

Q. So they may have side effects; is --

A. Not only side effects but differences in response.

Q. Okay.

A. So --

JUDGE CHAPPELL: Wait, wait a second. The question was "they may have side effects," so is your answer --

THE REPORTER: Wait. Can we do -- wait. I didn't get any of that because she started talking before you were done.

JUDGE CHAPPELL: My question was -- you have to wait till I finish -- he asked a question and you said "not only." Is your answer yes, but also?

THE WITNESS: Correct. Thank you.

JUDGE CHAPPELL: Thank you.

BY MR. ANTALICS:

Q. So if the patient has side effects, is it possible that you may be able to treat those side effects with some additional medication?

A. Yes.

Q. Thank you.

Okay. Now, in certain parts of the world, morphine has been the standard of care; is that correct?

A. That is correct.

Q. Okay. And they use principally morphine, almost exclusively morphine.

A. In certain parts of the world, that's the only opioid available.
Q. Okay. It's cheap. Correct?
A. Pure morphine, yes.
Q. Okay.
A. Not extended-release. Yes.
JUDGE CHAPPELL: I guess depending on the village you're in, it may not be relatively cheap.
MR. ANTALICS: That could be. You're correct.
JUDGE CHAPPELL: Where a dollar is a million dollars to us.
BY MR. ANTALICS:
Q. Now, morphine is still frequently used in the United States; correct?
A. Yes.
Q. Okay. And in outpatient settings, outpatient settings, based on your clinical practice and your experience, the most commonly prescribed opioids are oxycodone, hydrocodone and morphine; correct?
A. I believe when I said that --
Q. Is that correct?
A. In my experience -- yes, it is correct.
Q. Thank you.
JUDGE CHAPPELL: Are you finished with the book and that page now?

MR. ANTALICS: Yes.

THE WITNESS: Oh, okay.

BY MR. ANTALICS:

Q. You can -- and in emergency rooms and in acute care inpatient settings, in your experience, in your region, hydromorphone, fentanyl and morphine are the most commonly used; correct?

A. That's correct.

Q. Okay. But medical practices are very regionalized, in your view; correct?

A. Correct.

Q. Okay. Practice in one hospital is very different from practice in another hospital; correct?

A. Correct.

Q. And that's because medical practices are shaped by many different things; correct?

A. Correct.

Q. And one of those things is knowledge of the literature; correct?

A. Yes.

Q. And another is experience with patients and their own observations; correct?

A. Correct.

Q. And the practices of their colleagues and mentors also shapes their views; correct?

A. That is correct.
Q. Okay. And the marketing of different companies for their drugs also forms an awareness of products; correct?
A. Yes.
Q. Okay. And it's the relative balance of all those influences that can change from region to region; correct?
A. Correct.
Q. Okay. And from hospital to hospital; correct?
A. Correct.
Q. And from physician to physician; correct?
A. Correct.
Q. All right. So medical practice with respect to the selection of opioids, whether it's a full mu agonist opioid or a partial opioid, is different across the spectrum depending on where you are; correct?
A. The initial selection is what we're talking about; correct?
Q. Correct.
Okay. Now, I believe you said opioid therapy is always individualized. Correct?
A. Ideally it is.
Q. Okay. But you can't say that any particular

group of people need morphine or oxymorphone, because it's always an individual thing; correct?

A. Correct.

Q. Now, if a patient is opioid-naive, meaning they've never taken an opioid before, but they need one now, doctors usually start with what they're familiar with; correct?

A. Correct.

Or with a patient -- oh, they're opioid-naive. Yes. Correct.

Q. And that could be oxycodone; correct?

A. Could be.

Q. Could be hydrocodone; correct?

A. Could be.

Q. Could be oxymorphone; correct?

A. Yes.

Q. Or any number of different opioids; correct?

A. Yes.

Q. Okay. Now, sometimes it takes two or three times to get them to the right opioid, as I think you said; correct?

A. Yes.

Q. Okay. And maybe somewhere in the middle, somewhere in the middle, could be down to 30, could be 70 percent, somewhere in the middle, the doctors get

the right one on the first try; correct?

A. Correct.

Q. Okay. So even though they're starting with different opioids, they're getting the right try half the time, somewhere in that range.

A. I don't know if it's half the time.

Q. But just -- I understand you're not being precise.

A. Yeah. Sometimes they get it right.

Q. Okay.

A. Some --

JUDGE CHAPPELL: When you say they're getting it right, you mean the prescribing doctor?

MR. ANTALICS: The prescribing doctor prescribes an opioid and it successfully treats the patient.

Is that -- that's the way we use that term?

THE WITNESS: Yes. Sometimes the first opioid is well-tolerated without side effects; sometimes it's not.

BY MR. ANTALICS:

Q. Okay. You agree with Dr. Michna that clinically no opioid is ipso facto superior to any other opioid; correct?

A. Correct.

Q. And across broad populations of individuals, you're not aware of any evidence that one opioid is superior to other opioids; correct?

A. That is as written in my report. Correct.

Q. Okay. There's no one best opioid across populations of people --

A. Correct.

Q. -- correct?

A. I agree with you.

Q. Okay.

A. Yes.

Q. For example, there's no one opioid that's better for men than for women; correct?

A. Correct.

Q. Okay. And there are no medical conditions, to your knowledge, which produce pain for which oxymorphone ER is the only opioid choice; correct?

A. Correct.

Q. And you agree with Dr. Michna that no single opioid is superior in the abstract and that most patients can successfully be switched from one opioid to another; correct?

Most patients.

A. Can be switched from one opioid to some other opioid, but --

Q. Okay. With that -- with that change, is that correct?

A. I would say yes.

Q. Okay. For example, based on a study you've seen, you believe that most patients on oxymorphone -- and by that I mean more than 50 percent -- could successfully be switched to oxycodone; correct?

A. I don't know that to be true. I -- weighing my own personal experience, I can't give you a number. I know you asked me that before. I can't give you a number with any certainty that one can switch from that particular drug to another drug.

There was a study I reviewed that looked at people successfully switching from oxycodone to oxymorphone, from oxymorphone to oxycodone, but what it didn't do was look at what they -- across the board, the average analgesia was similar, and across the board, as they said in the study, all the typical opioid side effects were experienced in about the amount that you'd experience them.

But what they didn't do is look at which individuals preferred one drug versus preferring another drug, so it's difficult to say that they could satisfactorily switch as individuals.

JUDGE CHAPPELL: Did you get an answer?

MR. ANTALICS: I'm not sure, Your Honor.
THE WITNESS: I can't say --
BY MR. ANTALICS:
Q. But it's your belief -- I think it's your belief that you can't say if 90 percent could successfully be switched; correct?
A. I can't say if 30, 40, 50, 60, 70, 80, 90 percent could successfully switch.
Q. Did you once before tell me --
JUDGE CHAPPELL: Wait, wait, wait. She was still talking.
THE WITNESS: I believe that I said, after being pressed to give some kind of an answer, probably. I believe that's what I said.
So probably 50 percent, but I don't say that with certainty that I am correct.
BY MR. ANTALICS:
Q. Okay.
A. I have to see the study.
Q. Okay. In your own personal experience, though, you have switched patients from oxymorphone to other opioids; correct?
A. Yes.
Q. Okay. And in fact, you've never seen a situation where somebody had been on oxymorphone ER and

you wanted to rotate them off and you were unable to; correct?

A. That's correct.

Q. Now, the medical profession does not have the ability to identify the differences in people in advance to match them with the best possible opioid for them; is that correct?

A. Not yet. It's correct.

Q. Okay. It's anticipated that somewhere in the future they might do that, but we can't do that now; correct?

A. Correct.

Q. Okay. Now, you talked a little bit earlier about the CYP450 system. Do you recall that?

A. I do.

Q. And I think you said oxymorphone is not metabolized in the liver via CYP450?

A. It is metabolized in the liver, but it doesn't utilize the CYP450 system --

Q. Right.

A. -- to my knowledge.

JUDGE CHAPPELL: Hold it, hold it, hold it. You stop talking. Let her finish.

MR. ANTALICS: Okay. I apologize.

Go ahead.

JUDGE CHAPPELL: We didn't hear the last thing you said. You said it is not --

THE WITNESS: It is metabolized in the liver, but it is not -- does not utilize the CYP P450 system.

BY MR. ANTALICS:

Q. Okay. And it's because it doesn't utilize the CYP450 system that you don't have to worry about certain drug interactions; correct?

JUDGE CHAPPELL: Wait a minute, wait a minute.

To me that question is vague because you say "it doesn't utilize." What is "it"?

MR. ANTALICS: It -- oxymorphone. I'm sorry, Your Honor.

JUDGE CHAPPELL: Let's be clear.

MR. ANTALICS: I'll try.

JUDGE CHAPPELL: Clear questions lead to clear answers.

MR. ANTALICS: Got it.

BY MR. ANTALICS:

Q. Because oxymorphone is not metabolized via the CYP450 system, oxymorphone doesn't have -- when you use that, you don't have to worry about certain types of drug interactions; correct?

A. That is correct.

Q. Okay. But morphine is an alternative opioid

that also is not metabolized via the CYP450 system; correct?

A. That's correct. And --

Q. So --

A. -- hydromorphone as well.

Q. I'm sorry. Which one?

A. And hydromorphone as well.

Q. Okay. So both of those you wouldn't have to worry about the drug interactions either, would you?

A. That's correct.

Q. Okay. And with respect to the other opioids that are metabolized via the CYP450 system, they can still be used with that interaction with proper care and attention to dosing; correct?

A. They can be.

Q. Okay.

A. Some of them carry black box warnings not to, but they can be, yes, as long as you adjust dose.

JUDGE CHAPPELL: Hang on a second.

Just so -- for people that may read the record that don't live with drugs every day --

THE WITNESS: Uh-huh.

JUDGE CHAPPELL: -- would you be able to tell us right now the brand name of one of these opioids and then the generic name? For example, hydromorphone.

THE WITNESS: Exalgo.
JUDGE CHAPPELL: Hydromorphone, what is that?
THE WITNESS: Dilaudid is the short-acting version.
JUDGE CHAPPELL: And what is one that someone would refer to as Percocet?
THE WITNESS: Percocet is oxycodone.
JUDGE CHAPPELL: Vicodin?
THE WITNESS: Hydrocodone.
JUDGE CHAPPELL: Are there any others that are common?
THE WITNESS: Sorry. That's true. You know, I wouldn't expect people to know that.
JUDGE CHAPPELL: Tramadol?
THE WITNESS: Tramadol is tramadol. It's Ultram, is the long-acting version of it I think.
JUDGE CHAPPELL: And Opana ER I think we've learned is what the generic is called, but the brand name is no longer there.
THE WITNESS: Correct.
JUDGE CHAPPELL: But a doctor writes Opana ER and a pharmacist prescribes the generic.
THE WITNESS: Oxymorphone.
JUDGE CHAPPELL: Which is oxymorphone.
THE WITNESS: That's correct.

JUDGE CHAPPELL: That's Opana ER.

I think those are the common ones. Thank you.

THE WITNESS: Yep. Sorry for not making it clear before.

JUDGE CHAPPELL: It wasn't just you. We've been here a few days and nobody had done that.

THE WITNESS: Yeah.

BY MR. ANTALICS:

Q. Now, in your report, one of your reports anyway, you made the point that oxymorphone has an injectable form and the -- also the tablet form, and that gave it an advantage for people that were in the hospital and then leaving the hospital; correct?

A. Yes.

Q. Okay. But you agree that often people are changed from whatever the injectable form is in a hospital to an entirely different molecule upon release; correct?

A. That's correct.

Q. Okay. The most common opioid in a postoperative setting is oxycodone; correct?

In your view.

A. I'm not certain of that. That's my impression.

JUDGE CHAPPELL: I want to make sure the

record is clear on part of your previous question.

MR. ANTALICS: Okay.

JUDGE CHAPPELL: You asked her about someone in a hospital gets an injectable form and then an entirely different molecule upon release.

What I want to make clear is, are we talking about an injectable form being drug A and a different molecule upon release being drug B, or is it -- is there a drug that has an injectable form and a take-home capsule or pill form that's the same drug?

I want to make sure you understood his question and we understand her answer.

THE WITNESS: I did understand --

MR. ANTALICS: I was going to get into that a little bit more, Your Honor, but --

JUDGE CHAPPELL: Well, that question has already been asked, so I'd like for that to be clear.

MR. ANTALICS: Yeah. No. Certainly.

THE WITNESS: Would you like clarification?

JUDGE CHAPPELL: Yes.

THE WITNESS: I was tempted to clarify, but I don't want to talk too much.

So in general, yes, it's common practice to provide an IV drug, whatever the favored drug is or what works for that patient in the hospital, and

then -- it might be morphine, it might be fentanyl, it might be hydromorphone, and then often practice is to discharge people home on Vicodin or Percocet, oxycodone or hydrocodone, so there is a change in molecule.

All I said -- and it's not a point that --

JUDGE CHAPPELL: Well, no. Back up. When you said "a change in molecule," though, do you mean a change in drug?

THE WITNESS: Molecule I mean -- yes, a change in -- it's a change from IV of one molecule to oral of another -- a different molecule.

JUDGE CHAPPELL: But there are opioids that are both injectable and tablet form?

THE WITNESS: That is correct.

JUDGE CHAPPELL: All right.

THE WITNESS: So -- so theoretically --

JUDGE CHAPPELL: And in that example where the same opioid is injectable or tablet, those two, same drug, would be a different molecule?

THE WITNESS: No. They're the same molecule.

JUDGE CHAPPELL: That's what I --

THE WITNESS: So IV morphine and if somebody chose to give you PO or oral morphine tablets, that could be done. More often people are switched.

My only point in my report is that you reduce one more uncertainty when you have somebody on the same molecule in the hospital that you discharge them on.

JUDGE CHAPPELL: When you say "same molecule," I just -- I'm not trying to beat a dead horse -- maybe it's been done already -- but when you say "not the same molecule," you mean a different medicine, a different opioid?

THE WITNESS: Well, the reason I use the term "molecule" -- I'm sorry -- is because -- because there are different brands of drugs and --

JUDGE CHAPPELL: Right. That's how we have the various patents. I understand that.

THE WITNESS: Yeah.

JUDGE CHAPPELL: But if you were going to say, I'm on IV heroin -- or heroin, jeez -- morphine --

THE WITNESS: Morphine.

JUDGE CHAPPELL: -- and -- I'm hoping there's not a tablet form of heroin -- I'm on IV morphine and I go home and the doctor says, Everything else makes him vomit, give him tablet-form morphine, if that happened to me, I've got an IV morphine, I go home and I've got a bag of morphine tablets.

THE WITNESS: Yes.

JUDGE CHAPPELL: Is that the same molecule or a different molecule?

THE WITNESS: That's the same molecule.

JUDGE CHAPPELL: All right.

THE WITNESS: That's what I mean by "the same molecule."

JUDGE CHAPPELL: At least I finally understand it.

THE WITNESS: And the reason that would be preferred -- it's not often done, but it's just a theoretical consideration -- is that I know that you tolerate morphine because you had it injected in you. I know that you'll get good relief with no side effects if you did in the hospital, so I give you the oral.

And the point about the oxymorphone is it is available as an IV formulation, not widely used, but it is available, so you could switch it to an oral form when you leave the hospital and know that the person will tolerate it.

But it isn't routine practice, so it's a minor point, but it's just another difference that it's available in both forms.

JUDGE CHAPPELL: I'm just going to throw this out here. I think that's the first time we've heard

that there is an injectable form of Opana ER, don't know who makes it, don't know who sells it, don't know anything else. Maybe some witness will know.

MR. ANTALICS: I think Dr. Savage --

THE WITNESS: It's not under that brand name. Is it?

BY MR. ANTALICS:

Q. Did you just say --

(Counsel and witness speaking at the same time and cautioned by court reporter.)

BY MR. ANTALICS:

Q. Did you just say the injectable form of oxymorphone is not commonly used --

A. I don't know -- oh.

JUDGE CHAPPELL: Well, let's start it this way.

Is there an injectable form of Opana ER?

THE WITNESS: It's my understanding that there is an injectable form of Opana ER.

JUDGE CHAPPELL: But that's all you know about it?

THE WITNESS: It's not widely used, to my knowledge, at least in the systems that I work in.

BY MR. ANTALICS:

Q. Okay. Okay.

Okay. I'd like to speak briefly with you about formularies.

Now, I think you acknowledged that you know very little about formularies having different tiers and copays; correct?

A. That is correct.

Q. You don't have much experience dealing with insurance companies; correct?

A. That is correct.

Q. You're a consultant in your practice area, and it's the staff positions who are the ones that deal with the insurance companies and write the prescriptions; correct?

A. That is correct.

Q. Okay.

A. It's only part of the reason that I'm not as familiar. It also is the practice context.

Q. But you do understand that formularies encourage clinicians and patients to work out a therapeutic plan that is the least costly for the patient in terms of copays; correct?

MR. LEEFER: Your Honor, I'm going to object for a lack of foundation.

JUDGE CHAPPELL: Response?

MR. ANTALICS: Well, in both Dr. Savage's

initial expert report and in her rebuttal report she deals with formularies. She has probably five or six long paragraphs dealing with formularies. She also testified about formularies and pricing on direct examination. I think I'm entitled to examine the extent of her understanding and knowledge if she's expressing opinions about them.

MR. LEEFER: May I respond, Your Honor?

JUDGE CHAPPELL: Hold on. The judge is pondering.

Go ahead.

MR. LEEFER: I believe Mr. Antalics just asked Dr. Savage to confirm that she has --

JUDGE CHAPPELL: Hold on. Before you say that, let me ask the witness.

Did you hear and understand the question?

THE WITNESS: I did not understand the question. I was going to ask you to repeat it.

JUDGE CHAPPELL: Okay. Well, let's do this. Why don't you rephrase and let's see if we're still going here.

MR. ANTALICS: Okay.

BY MR. ANTALICS:

Q. Formularies encourage clinicians and patients to choose the least costly drug for the patient in

terms of copays; correct?

MR. LEEFER: Your Honor, I have the same objection. Mr. Antalics elicited from the witness that she has very little knowledge of formularies. Now I believe he's asking what formularies encourage clinicians and patients to do.

MR. ANTALICS: Your Honor? Could I respond briefly, Your Honor?

JUDGE CHAPPELL: Go ahead.

MR. ANTALICS: I think the language that I used was almost precisely what Dr. Savage used in her deposition, so I'm not sure why we're asking whether she can --

JUDGE CHAPPELL: What we have here is an expert witness under cross-exam being tested for depth of knowledge and understanding. Overruled.

THE WITNESS: Would you ask the question again. I'm sorry. I was looking at my report, and I have barely a paragraph. You said I have five long paragraphs. I'm sorry. I was trying to find what I had written.

BY MR. ANTALICS:

Q. Formularies encourage --

JUDGE CHAPPELL: By the way, if you're referring to something in her report, tell her where it

is so we can save a little time.

MR. ANTALICS: Okay.

JUDGE CHAPPELL: If you are.

MR. ANTALICS: I am.

BY MR. ANTALICS:

Q. It's in your report at paragraphs 176 through 179, the initial report, deals with formularies. And in her rebuttal report, paragraphs 31 through 34 deal with formularies and insurance coverage.

A. I'm sorry. I only see one paragraph, and it's really just the first part of it that deals with formularies.

And I don't know what I'm -- I've been requested to only respond to questions that are asked me, so I'd prefer not to give unwelcome commentary.

177?

Q. 176 through 17- -- oh, it may have been in the uncorrected version. You have a whole section on insurance, pricing effects on long-acting opioids.

(Pause in the proceedings.)

JUDGE CHAPPELL: Well, I didn't mean to throw a wrench in the works, but if you asked the witness about something in her report and she wanted to look at it and find it, we would have to wait for her to do that anyway.

MR. ANTALICS: No. That's quite all right, Your Honor.

BY MR. ANTALICS:

Q. You mention -- Dr. Savage, in paragraph 32, you mention formularies.

You also mention formularies in paragraph 33 of your rebuttal report.

A. Okay. Oh, rebuttal. I'm sorry. I thought you said in my original report.

Q. And you also mention it in paragraph 34 of your rebuttal report.

A. Okay.

So in my report, I don't believe I discuss formularies; is that correct?

I don't see anything in there.

The rebuttal report?

(Document review.)

Q. Could I also direct your attention -- I won't read it out loud right now, but could I direct your attention to page 114 in your deposition, lines 16 through 23.

And if you'd like, I can -- well, let me just -- can I read it to refresh her recollection, Your Honor?

JUDGE CHAPPELL: Go ahead.

BY MR. ANTALICS:

Q. "QUESTION: Do you understand what the concept of having different tiers with different copays is for?

"ANSWER: My understanding is that it encourages clinicians to start -- and patients to work on a therapeutic plan that is the least costly for the patient in terms of copays, and so the preferred drugs would be put on the most available tier."

Do you recall saying that?

A. I do recall saying that.

Is that all I said there?

Q. That was your complete answer to that question.

A. Okay. That's fine.

Q. Is that accurate?

A. That's accurate.

MR. ANTALICS: Okay. That's the only thing I was trying to get at, Your Honor.

THE WITNESS: I thought you said I addressed it in my report, and I don't find anything in my report.

BY MR. ANTALICS:

Q. And you understand that the insurance companies put drugs on the most available formulary tier in -- that are, in the opinion of the insurance

company, adequate to provide the relief that's contemplated; correct?

MR. LEEFER: Sorry, Your Honor. I object. It seems like Mr. Antalics is asking Dr. Savage to testify what's in the mind of insurance companies, and I object on lack of foundation.

MR. ANTALICS: I think I asked her understanding.

JUDGE CHAPPELL: And we all know that the judge doesn't want to hear anybody's understanding, he wants to hear what people know.

Rephrase.

MR. ANTALICS: Okay.

JUDGE CHAPPELL: I will allow the question in essentially that form without asking about understanding because she works with medications and she's talked about prices, so I'm going to allow it.

Overruled.

THE WITNESS: Okay.

BY MR. ANTALICS:

Q. Do you know whether insurance companies attempt to put drugs on the tier -- on the first tier that are, in the opinion of the -- that are -- let me strike that.

Do you know that insurance companies put drugs

on the most available formulary tier that are intended to be adequate to provide the relief contemplated?

A. I don't know the criteria that insurance companies use to determine how many or what drugs they put in a tier. My understanding is that they --

JUDGE CHAPPELL: Hold on, hold on. We don't want to hear your understanding.

THE WITNESS: Oh, okay. Thank you. I don't know.

BY MR. ANTALICS:

Q. You don't know.

A. I don't know how insurance companies make their decisions --

Q. Okay.

A. -- regarding tiering.

Q. Okay.

JUDGE CHAPPELL: She testified -- if you're thinking that the door was opened on direct, she testified a lot about patients and prices and all that, but it was very general.

MR. ANTALICS: I'm moving on, Your Honor.

BY MR. ANTALICS:

Q. You talked on direct a little bit about the nonsteroidal anti-inflammatory drugs and also acetaminophen; correct?

A. Correct.
Q. Now, you agree that when you walk down the aisle in a drugstore you can find aspirin right next to ibuprofen, Advil; correct?
A. Correct.
Q. And those drugs are right next to Tylenol, which is acetaminophen; correct?
A. Correct.
Q. And those drugs are right next to Naprosyn, which is Aleve; correct?
A. Correct.
Q. Okay. Now, each of those four relieves mild to moderate pain; correct?
A. Correct.
Q. But they each do it differently; correct?
A. They have different mechanisms of action.
Q. Okay. Acetaminophen acts at the level of the spinal cord to block pain transmission; correct?
A. Correct.
Q. And the other --
A. We think. We think. It's not certain, but we think, yes.
Q. And the other three, ibuprofen, Naprosyn and aspirin, they act closer to the site of the injury; correct?

A. That's their major mechanism. Yes.
Q. But even those three act differently from one another in terms of where they interact to meet the pain; correct?
A. That is correct.
Q. Okay. And they also have differences in how often you should take them; correct?
A. Correct.
Q. Aleve, for example, says it can be taken every twelve hours; correct?
A. Correct.
Q. Ibuprofen every four to six hours; correct?
A. I believe so.
Q. And aspirin every four hours?
A. I believe so.
Q. Okay. And they each have different toxicity profiles; correct?
A. Correct.
Q. And they all act differently in different individuals; correct?
A. Correct.
Q. Okay. And that's because people are biogenetically slightly different in the way our bodies' pathways lead to pain; correct?
A. Yes.

Q. Okay. So the bottom line is, just like opioids, some people respond to one of the four better than others; correct?

A. Correct. Some people respond better to one than to others.

Q. Now, despite that, all four of those products have on their labels that they can be used for headaches; correct?

A. Yes.

Q. And they can -- all four say they can be used for toothaches; correct?

A. I -- I haven't looked at labels recently, but I would believe you if you tell me that is true. Yes.

Q. Okay.

A. They're certainly used for those --

Q. Let me list -- give you a list of other indications, and you tell me if you think I missed any.

A. Okay.

Q. They can each be used for muscle aches, each be used for back pain, the common cold, minor pain of arthritis, menstrual cramps, and all four say they reduce fever; correct?

A. Tylenol doesn't reduce -- yes.

Q. Okay.

A. Sorry. Yes.
Q. Okay. So all four of them are out there right next to each other in the aisle, and they're competing for people who have headaches; correct? Even though they do it differently.
A. Yes.
Q. Okay. And for all of those indications; correct?
They do it differently, but they're competing for the same patients.
A. I want to make sure -- what I started to say is Tylenol doesn't reduce inflammation, and I think I erroneously said "yes" when you listed inflammation in that list, so I wanted to make sure that I corrected that.
Q. Okay. I don't think I mentioned inflammation.
A. Okay. That's what I was thinking. Thank you.
JUDGE CHAPPELL: Fever. It was fever he mentioned.
THE WITNESS: Fever -- what?
JUDGE CHAPPELL: Fever.
BY MR. ANTALICS:
Q. Okay. So they're out there, those companies that produce those products, they're competing for the same consumers; correct?

A. Yes.
Q. Okay. And in the same fashion the makers of the opioids, even though they do things differently, are competing generally for the same consumers; correct?
A. I believe so.
Q. Okay. Now, you're familiar with Endo's crush-resistant formulation of oxymorphone?
A. Yes.
Q. You're aware that it's off the market now; correct?
A. Yes.
Q. Impax, though, still has its generic version of oxymorphone ER on the market; correct?
A. Correct.
Q. Now, for the patients that had been on the crush-resistant formulation that was just taken off the market, those patients have had to go either to Impax' generic version of oxymorphone ER or to another opioid; correct?
A. Correct.
Q. Okay.
A. If they continued on opioids.
Q. Right.
So in your view, there's been a benefit to

patients who like oxymorphone because Impax' generic oxymorphone ER is still on the market; correct?

A. I didn't hear the first part of your statement. Could you repeat it, please.

Q. In your view, there has been a benefit to patients who like oxymorphone ER because Impax' generic oxymorphone ER is still on the market; correct?

A. Yes.

Q. Okay. If a physician wanted to rotate a patient to another opioid rather than going to Impax' generic, the physician might try a trial rotation to any of the opioids listed in that chart that we looked at earlier; correct?

A. Depending upon the individual's prior experiences and comorbidities and other issues that might impact the decision, but yes.

Q. Okay. And if Impax' generic version of oxymorphone ER was for some reason taken off the market, you would expect that the physicians would rotate their patients to the other opioids; correct?

A. As long as they still needed an opioid, correct.

Q. But that, in your view, would increase risk of some discomfort or side effects potentially; correct?

A. Potentially, yes.
Q. Okay. It might create some anxiety; correct?
A. Yes.
Q. Okay. So you would expect in that instance, if Impax' version of oxymorphone ER was taken off the market, that there would be negative effects for some patients; correct?
A. Correct.
Q. Oxymorphone came on the market just several years ago; correct?
A. Yes.
Q. You were able to treat patients before it came on the market, though; correct?
A. Yes.
Q. Okay. But for some patients today you think it's been an especially good medication; is that right?
A. Yes.
Q. Okay. And it's a benefit to those patients, and you would prefer to have it as an option in the market; correct?
A. I believe having diversity in our choice of opioids improves patient care and outcomes.
Q. So --
A. Yes.

Q. -- is the answer yes? Okay.
A. Sorry.
Q. And you'd be concerned if Impax' generic oxymorphone ER was not on the market; correct?
A. Define "concerned."
I -- I think I answered your question that it would create some anxiety and at least transient negative changes for some patients.
Q. Okay. And because it's a benefit then for some patients, there's a benefit to having it on the market.
A. I believe so.
MR. ANTALICS: Okay. I have nothing further, Your Honor.
JUDGE CHAPPELL: Redirect?
MR. LEEFER: Your Honor, I think I have a couple things I want to ask about. May I have a moment to confer with co-counsel?
JUDGE CHAPPELL: Go ahead.
(Pause in the proceedings.)
Are you through consulting?
MR. LEEFER: Yes, Your Honor. I will just have a few questions.
JUDGE CHAPPELL: Go ahead.
MR. LEEFER: Thank you.

- - - - -

REDIRECT EXAMINATION

BY MR. LEEFER:

Q. Dr. Savage, do you remember Mr. Antalics asking you whether it was possible to treat opioid side effects with additional medications?

A. Yes.

Q. In your view, is it desirable to treat opioid-related side effects with additional medications?

A. No.

Q. Why not?

A. It's preferable to find an opioid that has lesser side effects that don't require treatment. Anytime we add a new medication in, we have risks of additive side effects, toxicities.

Simple is better. When you can accomplish the same thing with one medication, it's preferable not to begin adding. That can go on and on.

We see this -- oh -- frequently when patients come in with a medication that causes a side effect and another medication is given to treat the side effect of that, and then they get another side effect because they have some side effect of that. And when possible, I believe it's best to take care of the symptoms with

as few side effects as possible and as few medications as possible.

Q. Thank you.

A. In most cases.

Q. I believe you were also asked about small villages that might only have access to a single opioid like morphine. Do you remember that?

A. Yep.

Q. And if you were in a small village like that, would you try to make due as best you could with that single opioid?

A. Yes.

And we did that before we had many different kinds of opioids, but we've been able to improve patient care I believe from having a diversity of options.

Q. And in the United States, in your experience with thirty years treating pain with opioids, is it better to have more options to treat patients?

A. More opioids from which to select, not necessarily more opioids out there in the world, but more opioids from which to select.

Q. Thank you. I appreciate that clarification.

A. Yes.

Q. Now, Mr. Antalics also asked you if you had

ever had a patient who was unable to rotate from oxymorphone to a different opioid. Do you remember that?

A. Correct.

Q. Have you ever had a situation where a patient tried to rotate to another opioid but then had to rotate back to Opana ER or oxymorphone?

A. Yes. Well, patients who have started to rotate, and then they preferred the original drug, yes, I've certainly had that happen.

And we haven't necessarily tried every opioid, but they say, This is fine, I'm going back to the one I was on before.

And also related, had patients who couldn't tolerate opioids. They just didn't use them, except in the extreme situation of when the pain was so severe. But for chronic pain, I've had people who just say, No, I'm not going to use an opioid.

Q. And so for those patients that tried to rotate from Opana ER and then came back, was that because that was the opioid that worked best for them?

A. Yes.

MR. LEEFER: Thank you, Doctor. I have no further questions.

JUDGE CHAPPELL: Anything further?

MR. ANTALICS: Nothing further, Your Honor.

JUDGE CHAPPELL: Thank you, ma'am. You're excused.

THE WITNESS: Thank you.

JUDGE CHAPPELL: Anything further today?

MR. LOUGHLIN: Not from us, Your Honor.

MR. HASSI: No, Your Honor.

JUDGE CHAPPELL: The witness will be here at 9:45 in the morning?

MR. LOUGHLIN: Yes, Your Honor.

JUDGE CHAPPELL: Until then we're in recess.

(Whereupon, the foregoing hearing was adjourned at 4:15 p.m.)

CERTIFICATE OF REPORTER

I, JOSETT F. WHALEN, do hereby certify that the foregoing proceedings were taken by me in stenotype and thereafter reduced to typewriting under my supervision; that I am neither counsel for, related to, nor employed by any of the parties to the action in which these proceedings were taken; and further, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of the action.

s/Josett F. Whalen
JOSETT F. WHALEN
Court Reporter