UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE, S.A. and ROCHE PALO ALTO, LLC,

Plaintiffs,

-vs-

DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD.

Defendants.

CIVIL ACTION NUMBER:
11-3962

TRIAL

Clarkson S. Fisher United States Courthouse
402 East State Street
Trenton, New Jersey 08608
June 10, 2015

B E F O R E: THE HONORABLE MARY L. COOPER
UNITED STATES DISTRICT JUDGE

Certified as True and Correct as required by Title 28, U.S.C., Section 753

/S/ Regina A. Berenato-Tell, CCR, CRR, RMR, RPR
/S/ Carol Farrell, CCR, CRR, RMR, CCP, RPR, RSA

United States District Court
Trenton, New Jersey

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I N D E X

(In open court. June 10, 2015, 9:30 a.m.)

THE COURT: Good morning.

ALL: Good morning, your Honor.

THE COURT: On we go.

MR. DITTMANN: For our next witness plaintiffs call Dr. Keith Candiotti.

THE DEPUTY CLERK: Please state and spell your full name for the record. Have a seat.

(Whereupon, KEITH CANDIOTTI, witness for the plaintiffs, sworn.)

THE WITNESS: Thank you. My name is Dr. Keith Allen Candiotti, K-E-I-T-H. Middle name, A-L-L-E-N. Last name C-A-N-D-I-O-T-T-I.

VOIR DIRE EXAMINATION BY MR. DITTMANN:

Q. Dr. Candiotti, I'm going to hand you some exhibits and demonstratives that we'll use today.

A. Thank you.

Q. Good morning, Dr. Candiotti.

A. Good morning.

Q. Could you please bring up PTX-98, which you have in your witness book. And can you tell us what you see here, Dr. Candiotti?

A. This is my current CV as of May 31st, 2015.

Q. And would you please tell us your educational background, starting with college?

A. I attended Washington University in St. Louis, where I majored in biology, psychology, and ancient history. I then went on to medical school at the University of Miami.

Q. And when did you graduate medical school?

A. 1989.

Q. And what did you do after receiving your medical degree?

A. I went on to train in internal medicine, where I completed training for three years, became board certified, and I also then went on to train in anesthesiology, which I completed training and went on to be board certified.

Q. Where do you currently work?

A. I'm still currently at the University of Miami Miller School of Medicine, and I practice at the hospitals within our system, University of Miami Hospital, Jackson Memorial.

Q. What positions do you hold at Jackson Memorial Hospital?

A. I am the executive vice chair of the department of anesthesiology, perioperative medicine and pain management. I'm the -- I'm the vice chair for clinical research. I'm the chief of perioperative medicine, and I hold the rank of a full tenured professor in the department of anesthesia, internal medicine, with secondary appointments in urology, obstetrics and gynecology.

Q. And when did you become chief of the perioperative medicine?

A. Some time in the 1990s, '95 or so.

that were run, even looking at the data from other companies that might be looking to buy each other's drugs or things along those lines.

Q. And have you served as a reviewer for any peer-reviewed publications?

A. Yes. I have been a peer reviewer for quite a few, but New England Journal, Anesthesiology, Anesthesia-Analgesia, those are probably our two top journals. Journal of Clinical Anesthesia. I guess that would be the third, but...

Q. And do you serve on any journal editorial boards?

A. I'm an editor on the Journal of Perianesthesia Nursing and the Journal of Anesthesia and Perioperative Medicine.

MR. DITTMANN: Your Honor, at this time, plaintiffs proffer Dr. Candiotti as an expert in the clinical care of surgical patients, including the management of PONV, and clinical aspects of drug product research and development.

MS. HUTTNER: No objection, your Honor.

THE COURT: Thank you, counsel. Admitted as such.

DIRECT EXAMINATION BY MR. DITTMANN:

Q. Now I'd like to turn to the opinions you are offering in this case. Do you have a slide that summarizes what you're prepared to discuss today?

A. Yes, I do. Thank you.

MR. DITTMANN: Please bring up PDX-402.

BY MR. DITTMANN:

Q. And if you wouldn't mind, Doctor, would you please briefly walk us through what you are prepared to talk about today?

A. So, just briefly, the first point being that a person of ordinary skill in the art would not have been motivated at that time period of 2003 to pursue the development of another 5-HT_3, specifically palonosetron. They probably would have focused more in the area of NK-1 receptor antagonists.

Two, had palonosetron been pursued, a dose of not lower than 2 milligrams for treating emesis would have been chosen based on the prior art that was available.

And, finally, a POSA would have been inclined or would have definitely pursued a volume of, really, 1 to 2 milliliters, but 1 to 5 milliliters and, given the milligram dosing and the volume, would have subsequently pursued or would not have pursued, a POSA at the time, simply because of the milligrams and the volume, a concentration of .05 milligrams per mL.

THE COURT: They would have had a higher concentration?

THE WITNESS: Yes, just by the de facto of having 2 milligrams or more in 1 to 5 ccs. I have a slide later on that. Just straight concentration would have come up much higher than that.

THE COURT: Okay.

BY MR. DITTMANN:

Q. And we see reference on the slide a POSA, or a person of ordinary skill in the art. Do you have a slide setting forth the definition of a POSA you applied --

A. Yes, sir.

Q. -- in reaching your opinions?

A. Yes.

MR. DITTMANN: Please bring up PDX-403.

BY MR. DITTMANN:

Q. Is this the definition you applied?

A. This is. I actually took this from Dr. Amidon, which I thought was quite relevant. And, basically, I feel I fit into this because I am very active in the development of pharmaceutical products.

THE COURT: Whatever you are, you're not a person of ordinary skill.

THE WITNESS: Oh.

THE COURT: You're a higher skill in your field.

THE WITNESS: Thank you, your Honor.

THE COURT: But anyway, we're looking for a definition of what a person of ordinary skill in whatever the art is that we're trying to focus on here.

Go right ahead.

THE WITNESS: I should continue with this slide?

THE COURT: Yes.

THE WITNESS: Okay. I possess a degree in medicine, and I have experience in designing, developing, evaluating, and testing pharmaceutical formulations. I possess an M.D. with many more years than one or two years of experience.

BY MR. DITTMANN:

Q. Dr. Candiotti, did you review the patents-at-issue in this case?

A. I did.

MR. DITTMANN: Could you please bring up PDX-404.

BY MR. DITTMANN:

Q. And can you explain what we see on the slide, Dr. Candiotti?

A. So, this is the '219 patent, and I'm referring to Claim 1 here. The part that would concern me for my background is simply the topic that this is a pharmaceutical single-use agent to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting. It would be in a 5-mL sterile solution with an amount of .25 milligrams by weight.

Q. And do you understand there are three other patents at issue in this case?

A. Yes, sir.

Q. Can we bring up PDX-405?

THE COURT: Before we get there, I think, Mr. Dittmann, I interrupted when Dr. Candiotti was saying what his definition of person of ordinary skill in the art is, and we

saw the slide on the screen, but the slides are demonstratives, and he didn't get a chance to say how he would define the person of ordinary skill in the art for purposes of these four patents.

So, I'd suggest you go back and get his testimony on that, because the slide is just a demonstrative.

MR. DITTMANN: Sure.

BY MR. DITTMANN:

Q. Dr. Candiotti, you discussed the definition of a POSA we see on PDX-403, correct?

A. Yes.

Q. And you understand this is a definition that was offered by Dr. Amidon in connection with his expert reports, correct?

A. I do.

Q. And do you agree with this definition?

A. I do agree with it.

THE COURT: And what is, it for the record? Just read it out from the slide.

MR. DITTMANN: Oh, for the record, the definition of a person of ordinary skill in the art is "Someone who is actively involved in the development of pharmaceutical products which involves collaborative teamwork among persons with relevant experience. This person would have a degree in chemistry, pharmaceutical chemistry, pharmacy, medicine, clinical pharmacology, or another pharmaceutical

science-related field and experience in designing, developing, evaluating, and/or testing pharmaceutical formulations with a B.S. or master's degree in, and two to three years experience, or a Ph.D. or M.D. degree and one to two years of experience."

Thank you, your Honor.

THE COURT: Do you subscribe to that, sir?

THE WITNESS: I do.

THE COURT: Okay. Go on.

MR. DITTMANN: Thank you.

Can we go back to PDX-405, please.

BY MR. DITTMANN:

Q. And can you explain what we see here with respect to the other patents-in-suit besides the '219 patent, Doctor?

A. So, the other three patents, basically, refer again to a pharmaceutical agent for reducing emesis and reducing the likelihood of emesis at a concentration of .05 milligrams per mL of palonosetron.

Q. And, again, these are the portions of the claims on which you focus your testimony today, correct?

A. Yes, sir. I'm clinically oriented, and that's what I focused on.

MR. DITTMANN: Could we please bring up PDX-402 again?

BY MR. DITTMANN:

Q. And I would like to start, Doctor, with your first

opinion listed here on the slide, that a POSA would not have been motivated in 2003 to pursue palonosetron.

Do you have a slide discussing the types of classes of drugs that were used to treat PONV in the 2003 time period at issue in this case?

A. Yes, I do.

MR. DITTMANN: Can we please bring up PDX-406.

BY MR. DITTMANN:

Q. And can you please explain what we see here on the slide?

A. So, I believe something similar was presented to the Court the other day. This is simply just showing the classes of medications that we use to either prevent or treat: Phenothiazines, butyrophenones, dopamine antagonists, steroids, antihistamines, 5-HT_3 receptor antagonists, which of relevance are the drugs ondansetron, granisetron and dolasetron. These three drugs were on the market at that time and available for use.

Q. And we see here that ondansetron was introduced in 1991. At this time when the first setron was introduced, how was this class of drugs perceived by the medical community?

A. They were quite welcome. Nausea and vomiting, emesis, was a problem, both a significant problem for chemotherapy patients and post-operative patients. Whether the drugs were -- had superior efficacy or not depends on how you look at it, but for sure they had better side effects.

The other drugs were not well tolerated, and sometimes patients were almost more miserable from the drugs than they were from the nausea and vomiting. And these drugs were very welcome. They were extensively used, and I think made a big difference to patients.

Q. So, that moving forward now about a decade later to the 2003 time period, how did the available setrons compare with one another in terms of their efficacy and safety concerning PONV?

A. I would say that the vast majority of the literature that I'm aware of felt that the drugs were, basically, interchangeable. The three 5-HT_3s, some minor differences in dosing perhaps and cost at the time, but they really weren't different from each other.

They were safe, as understood in 2003, and were used almost interchangeably. You'd find different hospitals with different 5-HT_3s for no particular reason. They would just have one or the other.

Q. Now, in the 2003 time period, what was being done to try to help improve the treatment of PONV?

A. So, since we had -- so the key to treating a patient -- and this was even recognized many years before this -- is multimodal therapy, and what that really means is attacking the different receptors to get a combined effect to help treat or prevent a patient from getting sick.

So, we already had drugs to address these related different receptors, whether it be the histamine or the serotonin receptors, and, as I said, these three drugs were basically interchangeable.

So, around that time period, including myself, people started looking towards new drugs and new targets, and the most or the best candidate at that time was the NK-1 receptor, which is a receptor for something called substance P. And we were trying to develop NK-1 receptor antagonists as part of the armamentarium to develop drugs to help protect patients as well as treat them.

MR. DITTMANN: Can we please bring up PTX-100?

THE COURT: As part of your arsenal, right?

THE WITNESS: Yes, ma'am, if you will.

THE COURT: Is that what you mean? Okay.

BY MR. DITTMANN:

Q. Doctor, can you please tell us if you recognize this document?

A. I do.

Q. What is it?

A. This is a paper by Dr. Geszetesi that was the first -- I believe was the first trial for an NK-1 receptor antagonist designated by its number CPP 122721.

This was -- this paper is from 2000, as I recall, and, as I said, this was a major effort to try and develop the

NK-1s and bring them into clinical use.

Q. And do you recognize any of the authors of this article?

A. I personally know three of them.

Q. And can you explain who they are and how you know them?

A. I know Dr. Scuderi, Dr. White and Dr. D'Angelo. These were all people doing research in the area of post-operative nausea and vomiting, and it became kind of a circle, if you will. You know the people who deal in the field that you deal in.

Q. Do you know what their reputation was in the PONV field in this time period of 2000 to 2003?

A. Yeah, they were viewed as good researchers, good clinicians, well known.

Q. And could you briefly summarize what this article generally discusses?

A. It shows the efficacy of this particular NK-1 receptor antagonist. As I recall, this drug didn't happen to make it to market, but -- for other reasons; but it showed good efficacy in, I believe, the 200-milligram range or so, as I recall. Basically, showed promise for these types of drugs in this class.

Q. If we can look over on the right column around midway down, yes, there's a sentence that starts, "Given the limited." Do you see that?

I'll read it for the record. It states, "Given the

limited efficacy and well known side effects associated with the available antiemetic drugs, the search for more efficacious compounds without side effects has continued."

Do you see that, Doctor?

A. Yes, sir.

Q. What would a POSA understand this sentence to be saying?

A. So, they're really talking about two different things in this sentence.

First of all, when they say given the limited efficacy and well known side effects, they're talking about two things. The efficacy of the 5-HT_3 receptor antagonists, as I read it, who really didn't have a lot of side effects; but they're also describing the problem with the side effects of the more classic agents, if you will, droperidol and things like that.

Furthermore, they make the point that while there are -- there were a fair number of drugs available at the time, people were still getting sick. So, we had -- we did better, but we needed to do better. And the goal was to develop additional drugs to make a more comprehensive therapy for patients by combining agents.

So, this being a whole new receptor, you could add it to the list of receptors you were able to address.

THE COURT: And the NK-1 receptor had been identified as playing a role in nausea and vomiting of patients?

THE WITNESS: Yes, and approximately -- substance P

is quite old, it was known, I mean, for a long time, and we knew what was involved probably in the 1990s.

BY MR. DITTMANN:

Q. And approximately --

THE COURT: Now, just a second.

There's a sentence right before what you have highlighted there and -- from 2000, this article, it says, well, even ondansetron has recently been reported with side effects.

THE WITNESS: Every drug has side effects, but it was unusual. As a matter of fact, that's why they even mentioned it. You know, nobody mentioned that droperidol causes side effects because it was so common. This was less common.

Ondansetron can cause allergic reactions, it can cause EKG changes, as can the other drugs of the class; but, generally, speaking it is extremely well tolerated. If you compare it to what we had, way better, but no drug is flawless. There's no question.

THE COURT: Okay. So, that's how you interpret that sentence.

THE WITNESS: Yes, ma'am.

BY MR. DITTMANN:

Q. And turning to your Honor's question about NK-1s, if we can look at the next paragraph and blow that up, please. You see here the second sentence states, "It has been suggested

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