UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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ALCON RESEARCH, LTD.,

Plaintiff, Civil Action No.

v. 16-129(LPS)(SRF)

WATSON LABORATORIES, INC.,

Defendant.

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VIDEOTAPED DEPOSITION
OF
MAUREEN DONOVAN, PH.D.
New York, New York
Friday, August 24, 2018

Reported by:
ANNETTE ARLEQUIN, CCR, RPR, CRR, CLR
JOB NO. 145678

M. Donovan, Ph.D.

And, again, nearly every product in the armamentarium of all drug products could have something done to it that would make somebody happier with it.

Q. In the course of your work in this case, did you consider what options were available to the person of ordinary skill in the art in 2009 who wanted to improve the Nevanac product?

A. Yes. I looked at, you know, what was known about ophthalmic formulations in 2009 and preceding that, or at least refreshed my memory regarding the specific date 2009 and what was already being done in the art; investigated regarding ophthalmic delivery; and, you know, looked at a little bit of information in specific about Nevanac.

Q. And in your view, what options would the person of ordinary skill have considered in 2009 if they wanted to improve the Nevanac product?

A. Can you specify what improvement the --

Q. Well, you said that, if I understood

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you correctly, that the person of ordinary skill would have thought there was room for improvement in the Nevanac product like there is room for improvement in many products.

A. Um-hmm.

Q. Fair?

A. Right. Yes.

Q. And the question I have is: Looking at the Nevanac product and thinking there may be ways to improve this product, what sorts of options would the person of ordinary skill have thought of as ways it could be improved, formulation steps that could be taken to improve it?

A. Right. But I mean, each of those formulations steps is directed at improving an aspect --

Q. Okay.

A. -- or maybe a group of aspects or something. So I think I need a little bit more definition in the question of what aspect would you like me to focus on.

Q. I'm asking you about -- let's ask this: What aspects do you think the person of

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ordinary skill would have focused on in order to improve Nevanac?

MR. JAGOE: Objection to form.

A. So you're asking me to identify what I -- if I -- as a POSA, if I were to look at Nevanac and be asked to improve Nevanac, what approach would I use?

Q. Yes. Or what options of approaches would be available to you?

A. Well, there is a myriad of options, some of them already available in the commercial space and some of them that were research-based.

So if my goal as a POSA was to bring another commercial product into the marketplace in a reasonable time period, there are many of the -- especially the things that were in the research realm that probably wouldn't be seriously considered.

Q. And why is that?

A. Well, they are just -- the understanding of how they work is probably underdeveloped, and the actual basic research effort to understand whether they apply to Nevanac would take a longer period of research

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and development time. And there would be other approaches that, again, were well-known in the art that could be brought forward that would get an additional product or an improved product into the marketplace in a faster way without having to do an excessive -- or not an excessive, but even just a battery of more R&D regarding a more unique formulation.

So to go back to the question I think you asked, I'll identify it, so we were talking about maybe it would make sense to try to identify formulations that could be administered less than three times a day. That would be one potential improvement to the Nevanac product that a person of ordinary skill that is a formulator would be able to identify and would understand that there were known methods to bring forward to do that.

Q. Okay. And let's back up for one second.

You drew a distinction in your answer between the commercial space and what I think you called the research area or the research space.

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Q. Okay.

Okay. And based on that, what is the answer to the question?

A. Well, Figure 2 actually is a graphical depiction of how someone calculates the AUC and demonstrates the area under the curve.

The bioavailability of a -- and we'll do this -- might as well stay -- well, the bioavailability of a drug product is a measure or a description of the amount of drug that the body was exposed to following administration of that formulation or dosage form.

Okay. So the initial comparator is an intravenous or interarterial administration typically because you don't have absorption effects. You don't have other dosage form effects.

So that is your baseline that you compare against is what were the distribution parameters when you gave something intravenously. And then when you added a formulation, delivery system, whatever, to that, how much drug, what time course and so forth as

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a comparison, you either -- either you understand that all of the drug you gave, the body was exposed to the same amount of drug and gave the same area under the curve, or it was not exposed to the same amount of drug, or it was exposed in a different time frame, which you may tease out of your data or whatever.

So the bioavailability is a description relative to a well-understood control of what you're willing to represent as 100 percent. It may not be 100 percent. And that's where relative bioavailability -- in my report, I chose to include that because whatever your reference is, whatever you're using as 100 percent, what's your fractional comparison to that is the, is the bioavailability.

But if you're using blood as a measure, for example, the built-in assumption to that is that blood represents the rest of the body, which it may or may not.

So there's always assumptions on what your sampling matrix means regarding the rest of the systems exposure.

Q. Okay. So let's go back to page 52.

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(Witness complies.)

Q. You say, "Although AUC is generally an indicator of bioavailability, formulations with different bioavailabilities can achieve the same efficacy results in clinical endpoint studies higher bioavailability may not produce any additional benefit."

Do you see that?

A. I see that.

Q. Can you explain to me how it is that higher bioavailability may not produce any additional benefit?

A. Well, because for the actual clinical results, and for a drug that has a receptor, a known receptor or a know ligand in the body where you're targeting the drug to go to have an effect, the standard or the understanding in pharmacology is that the dose response relationship is not linear and it doesn't go on forever. So that is you increase the dose, you don't necessarily get a proportional increase in response.

And at some point in dosing or exposure concentration to the receptor that you

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don't have any more receptors to accept the drug, it can't have any more response regardless of how much more drug is in the system. And so you can have more drug in the system, it -- that more drug doesn't elicit more response.

Q. I see.

You say, "That appears to be the case for Nevanac and in Ilevro since these formulations have nearly the same effectiveness in clinical studies even when both are administered once a day."

Is what you're saying there is that Ilevro has higher bioavailability than Nevanac, but it doesn't produce any additional clinical benefit?

Am I understanding that correctly?

A. That's not what I intended to communicate when I wrote this.

Q. What did you intend?

A. Well, the intention was, it's in the description in the paragraph about some of the clinical data that I was reviewing and that clinical data has -- some of the charts have information about concentration in various

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A. No, I didn't.

Q. And since 1991, am I correct that you haven't worked as an employee for any pharmaceutical company?

A. No, I haven't.

Q. And have you ever the developed an ophthalmic suspension?

A. I've worked on formulations in my laboratory that could have or, you know, even were applied in an experimental sense as -- I think they were suspensions. I don't even -- the issue at hand that I'm thinking of was something that was a multi-component formulation that we were looking at. I don't remember whether all of the components were in suspension or whether one was in solution. But we've certainly looked at formulations that could have been used ophthalmically. I don't recall since I've been at Iowa actually personally being the principal investigator at least of a formulation development activity where we've actually tested anything even in an animal model for ophthalmic use.

Q. Would it be fair to say, then, that

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you've never worked on an ophthalmic suspension formulation that had been administered to a human, at least to your knowledge?

A. So "worked on" is -- that I've never developed a formulation for an ophthalmic suspension that was administered to a human?

Q. Correct. That's the question.

A. Yes, that's true.

Q. And have you ever developed an FDA-approved product of any kind?

A. No. My work is not focused on trying to develop FDA-approved products.

Q. Now your CV is at the end of your opening report, but you may not need it for this question.

Am I correct over the years you've published a number of articles and abstracts in professional scientific journals; is that correct?

A. Yes.

Q. Would it be fair to say that you have published many articles related to the nasal administration of drugs?

A. Yes, I think it's fair to say.

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Q. How many articles have you published that are focused on ophthalmic administration?

A. That's probably one article out of what I've published.

Q. And can you identify for me which article that is?

A. It's the first article on the publication list and it's -- the pages are not numbered on Exhibit A, but it's page 2 of Exhibit A.

Q. And it's the Miller & Donovan --

A. Yes.

Q. -- effect of poloxamer gels article --

A. Yes.

Q. -- from International Journal of Pharmaceutics in 1982?

A. Yes.

Q. And was that about ophthalmic suspensions?

A. The test agent we were using in that formulation, the drug was in solution I believe in those products.

MR. PERLMAN: Okay. Should we take a

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short break?

MR. JAGOE: Sounds good.

THE VIDEOGRAPHER: The time is 9:12 a.m. We are off the record.

(Recess is taken.)

THE VIDEOGRAPHER: The time is 9:24 a.m. We are on the record.

BY MR. PERLMAN:

Q. Doctor, before the break, we had spoken about how in an ophthalmic suspension, some of the API is dissolved in solution and the rest is in the form of undissolved particles in the suspension.

Do you recall that?

A. Yes.

Q. And am I correct that in order for the undissolved particles to be absorbed and used by the eye, they have to first dissolve into the solution?

A. That's the general understanding of things unless they're really small and there is another biological mechanism that's actually taking them into the body.

Q. As a general matter?

INDEX OF EXHIBITS(Cont'd.)

ERRATA SHEET

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Signature of Deponent

SUBSCRIBED AND SWORN BEFORE ME

THIS ____ DAY OF _____, 2018.

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(Notary Public) MY COMMISSION EXPIRES:_____