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UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUPIN, LTD. AND LUPIN PHARMACEUTICALS, INC., Petitioners,

VS. POZEN, INC., Patent owner.

Case IPR2015-01773
Patent 8,858,996 B2

ORAL AND VIDEOTAPED DEPOSITION OF
LEON SHARGEL
MAY 25, 2016

ORAL AND VIDEOTAPED DEPOSITION of LEON SHARGEL, a witness produced at the instance of Horizon Pharma, taken in the above-styled and numbered cause on the 25th day of May, 2016, from 9:00 a.m. to 10:02 a.m., before Stacy L. Jordan, a CSR in and for the State of Texas, Registered Professional Reporter and Certified Realtime Reporter, taken in the offices of Wick Phillips, 3131 McKinney Avenue, Suite 100, Dallas, Texas 75204, in accordance with the Federal Rules of Civil Procedure.

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E X H I B I T S

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P R O C E E D I N G S

(May 25, 2016, 9:00 a.m.)

THE VIDEOGRAPHER: This is the videotaped deposition of Dr. Shargel, held in Dallas, Texas. The time is now 9:00 a.m., May 25th, 2016. We are now on record.

At this time, will the counsel please introduce themselves and whom they represent, and the witness will then be sworn in.

MR. RODRIGUEZ: Ricardo Rodriguez from Cooley, LLP, on behalf of Horizon.

MS. KRUMPLITSCH: Susan Krumplitsch, also from Cool- -- Cooley, LLP, also representing Horizon.

MR. HASH: Stephen Hash, from Baker Botts, on behalf of Pozen.

MS. STEVENS: Lauren Stevens from Horizon Pharma.

MS. LaVALLE: Amy LaValle from Wick Phillips on behalf of the Petitioner Coalition for Affordable Drugs.

MR. HARRIS: Jerry Harris from Wick Phillips on behalf of Petitioner Coalition for Affordable Drugs.

LEON SHARGEL,
having been first duly sworn, testified as follows:

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EXAMINATION
BY MR. RODRIGUEZ:
Q. Good morning. Would you please state your name and address for the record.
A. Leon Shargel, at 1535 Caraleigh Mills Court, Raleigh, North Carolina 27603.
Q. Have you previously worked as an expert for any litigation or patent office proceeding?
A. I did one case many years ago, when I was employed by Sandoz, in which there was a patent case in which I was deposed. Sandoz is a generic arm of Novartis, in which case they were being sued -- I don't recall the drug, actually; it was several years ago -- for a particular patent.
Q. Were you deposed as an expert or an employee?
A. I was an employee, but I -- I guess -- I was a vice president of biopharmaceutics. I ran the studies for the company.
Q. Have you done any prior expert work?
A. Yes.
Q. For litigation?
A. I have looked at patents in which I have made my general expert opinion, but these have never really -- they've been settled before going to court.
Q. Can you identify those?

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A. I don't really recall. They were several -- some years ago, but -- I -- I don't recall all the exact -- one was -- I remember was a Cialis-type product --
THE REPORTER: I'm sorry. "Was a"?
THE WITNESS: C-i-a-l-i-s.
A. -- for erectile dysfunction. So that one, of course, I remember a little bit more, perhaps. But there were several others that I don't recall. They were, generally, formulation-associated or biopharmaceutic-associated issues.
Q. (BY MR. RODRIGUEZ) Were you deposed in any of those cases?
A. No.
Q. Did you write expert declarations in any of those cases?
A. On -- a couple of times, I did; and other times, it was mostly oral, by teleconference and discussions of the patent.
Q. Do you recall the law firms that you worked with?
A. One that I worked with was Rakoczy -- I forgot their last name -- in Chicago. There was Steptoe in -- I just remember the first names -- in -- they're in Washington, D.C. And there's a couple other ones.

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There's Simmons & Simmons, out of London, whom I've never met, actually. We've done everything by teleconference.
Q. Are you working as an expert for or in connection with Wick Phillips for any matter other than this one?
A. No.
Q. How did you get in contact with Wick Phillips?
A. I was contacted, actually, by lawyers for Conley Rose and -- in which case I initially got involved in several of these patents, including the '907 patent.
Q. How did they identify you?
A. Actually, I --
MS. LaVALLE: Objection, form.
A. I -- I got a call.
Q. (BY MR. RODRIGUEZ) Do you know where they got your -- your name?
A. No, I didn't.
Q. Do you know now how they got your name?
A. I'm not clear how they got my name.
Q. Can you give me an overview of your clinical trial experience?
A. In -- in terms of what context?
Q. Any context.

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A. Well, in -- I would have to start very early. In 1969, when I completed my degree, I started at Sterling Winthrop. Then I was involved in drug metabolism in the areas of looking at blood levels of drugs involved in some clinical trials. So that goes back many years ago.
At Forest Labs, I also was in charge of running mainly generic company -- or generic products dealing with bioequivalence and looking at pharmacokinetics absorption studies. We looked at a few new drug applications, what we called 505(b)(2)s, which are old drugs in new carrier systems, new drug products.
In my last job, I was vice president of Sandoz in biopharmaceutics and re- -- responsible for other generic clinical studies, leading to generic approval.
Q. Have you been involved in clinical trials for new drugs?
A. On occasion, where there is a drug interaction, absorption/pharmacokinetic issue, blood level related to pharmacodynamic effect.
Q. What has been the nature of your involvement in clinical trials?
A. Again, it's in the area of pharmacokinetics and biopharmaceutical aspects of the drug.

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Q. Can you be more specific?
A. Biopharmaceutics deals with how the drug gets out of a tablet or a capsule into the body, and we're looking at absorption of the drug from said tablet into the body. And then we would give different doses and you look at how -- the doses and the amount of drug coming in. So if you have 10 milligrams, how much drug comes in the body. A 10 -- if you have a 20-milligram, how much does that -- and you build up a dosage regimen response for the new drug.
Q. Can you identify the drugs?
A. I worked on many of them, particularly in the generic areas, from Claritin to -- actually, you have Naproxen, diclofenac. I have to re-think of many of these. I'm sorry. I don't have all of the drugs that -- we usually worked on -- we had 20 different products a year or more.
Q. Any others you can think of?
A. Metaxalone was one, which is Skelaxin. Xanax, another one. Several -- those are called benzodiazepines, things similar to Valium, because I -- I worked on several different ones of those series, but I don't recall all of the drugs.
Q. And these are all generic forms of the drugs that you've mentioned?

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A. No. In some cases, they were branded. At Forest Labs, which is now part of Actavis, they had both a brand and generic side. So we had several on the brand side that we did blood-level work and -- and such. As I mentioned, pharmacokinetics.
Q. For the branded side, which are the ones that you can remember?
A. I'm trying to think. No, I don't recall. There was one for Alzheimer's, but I don't recall the name of the drug.
Q. Was it with Forest?
A. Forest Labs, which is now bought out by Actavis.
Q. Was that Namenda?
A. They bought that after the fact. They were -- Forest Labs had an interest in the Alzheimer's drugs, and they licensed out Namenda, but I didn't work on that particular product.
Q. For the branded Alzheimer's drug where you did do work in a clinical trial, what was your involvement?
A. The involvement was look at blood levels and pharmacokinetics and how the drugs are absorbed and the relationship with the blood level to a clinical end point.
Q. For the clinical trials in which you have been involved, has your role ever included the identification of the patients who are to be studied?

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A. May I ask: What do you mean by "identification"?
Q. Determining whether or not a particular patient should be part of the study.
A. When a study is put together, a protocol is written, which is sort of the operating idea of the study, and you include what is called "inclusion" and "exclusion factors" so that if you're looking for a particular set of patients -- you may not want smokers; you may not want women of childbearing age, or you may include women if they're on birth control or something of this sort. So there is criteria for inclusion or exclusion of subjects, depending upon the study.
Q. Can you describe for me your experience in identifying the inclusion or exclusion criteria?
A. I have audited the generic studies and reviewed the case report forms, which is the people who have been in a study, and looked to see whether they met the inclusion and exclusion criteria.
Q. Other than the auditing, do you have any experience in identifying the inclusion or exclusion criteria?
A. Your -- your term "identifying," I -- I would look at it as recruitment. Is that what you mean? When you recruit, you advertise or you look for a patient in a study and you put in the characteristics that they must be this way or that way within an age group. We don't identify as an identifier. I'm not sure of your question.

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Q. Yeah, maybe we're just not using the -- the same terminology. Somebody has to write out what the inclusion criteria is; is that correct?
A. Yes. That's done by a medical committee.
Q. And somebody has to write out what the exclusion criteria is; is that correct?
A. By the same committee.
Q. And have you ever been involved in that?
A. Yes.
Q. Can you describe your involvement?
A. In putting together -- let's -- let's take a straightforward study. We can pick on a generic product that we want to look at. And in this case, the criteria, which is often given by FDA, that the study must be -- be done in normal, healthy patients or subjects. And we may add they may be between a certain age group. So 18 through 55 years of age, who are otherwise healthy by standard clinical tests and things of that sort. So we -- we put that. If they are

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smokers, use drugs -- we do a drug test on these subjects as they come in -- they're excluded. So we -- we put together inclusion criteria and we put together exclusion criteria.

Q. And the inclusion and exclusion criteria is determined at the outset of the study; is that correct?

A. Every protocol is put together as clear as possible, including an informed-consent form, and goes to an institutional review board for that particular hospital or clinic in which the study is going to be done. The institutional review board is an ethics committee, and they will review the inclusion/exclusion as well as all the other observations that would be done on the subjects in the protocol.

Q. Approximately how many medical -- medical committees have you been on that have identified the inclusion and exclusion criteria?

A. In terms of being on an IRB, which it's called, the institutional review board, I was on the institutional review board for the National Institute of Drug Abuse in Baltimore. I was involved at Massachusetts College of Pharmacy on the IRB. In the other cases, I am involved in putting the protocol together, so I am putting the protocol -- which will be then submitted to the IRB. So in one case, I'm on the

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board for certain products; in the other case, I'm -- I'm the person who's involved in submitting the protocol.

Q. And approximately how many products?

A. Hundreds.

Q. What is the methodology by which the inclusion and exclusion criteria is determined?

A. The first part of any study is to have a hypothesis and -- so the scientific method. So what are you trying to prove? And in this case, in the generic, you're trying to prove that the generic product is what we call a "bioequivalent" to the brand-name products. So that is our hypothesis. It is either equivalent or it is not equivalent.

Then we have to have some methodology in terms of determining that, in terms of subjects, in terms of the healthy subjects. Are we going to use patients that have a disease entity? Are we going to use women? Are we going to use -- I did, for example, an estrogen patch that was, obviously, going to be done in women, and it was done in postmenopausal women. So in that particular case, they were normal, healthy -- you wouldn't want to say a postmenopausal woman is unhealthy, but we wanted to put criteria to be sure that she otherwise had no other particular problems, such as

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Parkinson's or Alzheimer's or any of these other kinds of things. So we would -- it's a criteria. According to hypothesis, is the estrogen patch equivalent to, say, Estraderm, which might be the brand name.

Q. Now, in addition to determining inclusion and exclusion criteria, there is also a determination made of what factors or criteria will be tracked in a study; is that correct?

A. That is part of the hypothesis, yes.

Q. And how is that determined?

A. The determination is always: What is the objective of the study?

And once you have a clear-cut idea of what the objective is, then you can have other objectives. For example, again, going back to my bioequivalents, is the product bio- -- we'll pick on Estraderm, since I used that as an example -- is the estrogen patch made by Sandoz equivalent to Estraderm? That would be our hypothesis.

We may look at other factors, such: Does the patch on the skin irritate the skin, as an adhesive? Does the patch fall off from the skin or does it stay on for seven days? Say it's a seven-day patch. So input on that. Do women who have this complain of headaches or anything else?

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So we would put other observations. But our main hypothesis still remains: Is the drug bioequivalent? That's the first hypothesis. But we're also going to look at safety, adverse events, and other issues that may occur.

Q. The issues that you're interested in looking at as the study goes forward, how are those tracked?

A. Well, we can start at the beginning of the study, in which case -- if we go back to my estrogen patch example, there would be -- this was done in Florida, with a contract research organization. And they would advertise for women in terms of who would meet the minimum criteria, being otherwise healthy, being postmenopausal, and -- and within an age group specified.

Now, they got that information from the protocol. This is -- and -- and the protocol hadn't been approved. So advertising is done first. There will be women who will come in and will be initially recruited if they meet the criteria. If they're alcoholic or a drug problem or such, they will, obviously, be refused in the study.

At that point in time, they will enter the clinic at a specified day or time, receive the appropriate treatment. They will be housed, usually, at

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least for 24 hours, and blood samples will be taken; the protocol will be followed. There will be a physician, nurses, phlebotomists, quality-assurance people.
Q. How does that procedure work in the case of a -- of a drug that is taken orally?
A. The same procedure, except you don't put it on the skin; you swallow the drug.
Q. Are they housed, as well, the patients?
A. Yes.
Q. Would it be atypical not to house the patients?
A. I don't quite understand the question. If you don't have the patients, you wouldn't have the study, which, apparently -- maybe I'm reading your question wrong.
Q. Are there studies where the patients are not housed, where they are provided with the drug and then they just go home?
A. That --
MS. LaVALLE: Objection, form.
A. That, again, depends upon the hypothesis of the study. If your hypothesis is going to be a longer-time treatment, it may be necessary to give instructions and then the patients understand that they carry a diary; they're responsible for self-medication.

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And there are some controls about counting the number of pills they've taken at any specific time, and they may be calling in. There will be something in the protocol to track them, even though they are ambulatory and on their own.
Q. (BY MR. RODRIGUEZ) Okay. And you've answered part of this with your response right now, but can you identify for me the steps that are taken to make sure that each patient receives the right amount of drug at the right time?
MS. LaVALLE: Objection, form.
A. Again, it depends upon the study that we're doing. If we're doing an in-house study, a nurse or a nurse-practitioner will administer the drug. It could be some specialized medical assistant to administer the drugs that the person is taking at a specified time under specified conditions.
Q. (BY MR. RODRIGUEZ) You mentioned before that a couple of common exclusion criteria are drugs and alcohol. How is that monitored to make sure that, initially, they may not have been involved with either of those, but later, during the study, they might?
A. Well, you have it open-ended in terms of study. Again, we have to go back to what is the study hypothesis, and is this going to be an -- in-house

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patients or is this going to be patients that are brought in and then sent out, after certain training, to be on their own. So we would have to determine what we have, as far as a protocol, and what is our objectives.
Q. What are the possibilities?
A. Possibilities for what, sir?
Q. For tracking that.
A. I'll come back to the hypothesis of the question -- I mean, of the study. If we have an in-house study, we have it monitored very well.
Q. And if it's not?
A. The subjects are monitored. They initially have a training period, and then they will be monitored during the period of time -- over a period of time.
Q. How would they be monitored?
A. They may come in to the clinic each day. They will be called. There will be a pill count at -- at a certain time to see what they have not taken. It can be done a number of different ways.
Q. What records are kept?
A. They keep all records of all contact, all e-mails, all phone calls, all measurements of bodily functions, such as blood pressures and whatever else is needed.
Q. What records are kept with respect to the

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exclusion criteria?
A. When the patients are initially recruited, they're first checked whether they meet the recruit- -- exclusion criteria. And if they don't meet it, they're rejected from the study.
Q. And thereafter?
A. This is -- what we try to do is track the patients. If they're not in-house, they're -- and I assume -- well, I never assume, but is that what you're asking --
Q. Yes.
A. -- if they're --
Q. Not in-house.
A. -- not in-house?
So if they're not in-house, we'll have to track by phone calls, by having them come in periodically. They may have to be -- certain testing done periodically, in which case you can do a drug test.
Q. And there are records kept of all of these testings?
A. It's mandatory.
Q. You mentioned a diary before. How does a diary -- diary work in connection with one of these studies?
A. It will go back to what -- what -- the kind of

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