UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

PFIZER, INC., and UCB PHARMA GMBH, Plaintiffs,	)	CASE NO.
vs.	)	15-00079-GMS
MYLAN PHARMACEUTICALS, INC., Defendant.	)	

VIDEOTAPE DEPOSITION OF
CULLEY C. CARSON, III, M.D.
Atlanta, Georgia
Thursday, August 25, 2016

Reported by:
Judith Leitz Moran, CCR, RPR, RSA
JOB NO.: 111438

CULLEY C. CARSON, III, M.D.

August 25, 2016

9:00 a.m.

Videotape Deposition of CULLEY C. CARSON, M.D., held at Hunton & Williams, 600 Peachtree Street, N.E., Suite 4100, Atlanta, Georgia 30308, before Judith L. Leitz Moran, Registered Professional Reporter, and Certified Court Reporter for the State of Georgia.

CULLEY C. CARSON, III, M.D.

A P P E A R A N C E S:

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BY: ALYSON WOOTEN, ESQUIRE

ALSO PRESENT:
MIKE BROWN, VIDEOGRAPHER

(Pursuant to OCGA 15-14-37 (a) and (b) a written disclosure statement was submitted by the court reporter to all counsel present at the proceeding and is attached hereto.)

CULLEY C. CARSON, III, M.D.

VIDEO TECHNICIAN: This marks the beginning of Video No. 1.

Deposition of Culley Carson, M.D., in the matter Pfizer, Incorporated, et al., versus Mylan Pharmaceuticals, Incorporated.

Today's date, August 25th, 2016. The time on the video monitor 9:01 a.m.

This video deposition taking place at 600 Peachtree Street.

Videographer, Mike Brown contracted by TSG Reporting.

Counsel, please state your name for the record and whom you represent.

MR. OELKE: Yeah, I'm Jeff Oelke from White & Case. I'm appearing on behalf of the Plaintiffs UCB and Pfizer, and with me is my colleague So Yeon Choe.

MS. WOOTEN: Alyson Wooten from Kilpatrick Townsend & Stockton. I'm here on behalf of Defendants and the witness.

VIDEO TECHNICIAN: The court reporter today, Judi Moran of TSG.

Will the court reporter please swear in the witness.

CULLEY C. CARSON, III, M.D.

CULLEY C. CARSON, M.D.,

being first duly sworn, was examined as follows:

THE WITNESS: I do.

EXAMINATION

BY MR. OELKE:

Q Good morning, Dr. Carson.

A Good morning.

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

A Yes, Culley C. Carson, III, M.D.

Q Yes. And what's your address?

A 10387 Holt, Chapel Hill, North Carolina.

Q Have you been deposed before?

A I have.

Q How many times?

A Many.

Q Okay. So you understand the procedure, I'm going to ask you a series of questions today?

A Yes.

Q And you're going to answer those questions subject to your counsel may have objections. But once she imposes those objections, you're expected to answer the question I ask, right?

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A Yes.

Q Okay. And it would help if you wait till I finish my question before you start your answer. That's easier for the court reporter and for the record.

If you need a break, let me know, that's fine. I just ask that you answer the question that's pending before you do so.

A Yes.

Q Okay. The other times you've been deposed, have you ever been deposed as an expert witness before?

A Yes.

Q And how many times?

A As I said, many times. I've been in neurology for more than 30 years. So only once in a patent case, during the others malpractice cases.

Q Okay. And when was that patent case?

A It was about five years ago, I believe. Four or five years ago.

Q And what did that patent case concern?

A It was Sildenafil.

Q And you gave a deposition?

A Yes, I did.

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Q Did you testify at trial?

A Yes, I did.

Q And where was the trial?

A The trial was in Norfolk, Virginia.

Q Now, in that Sildenafil trial, what were your opinions generally?

A The case was about when the idea of Sildenafil for erectile dysfunction had originally begun. And so my opinion was that it was in early -- earlier than what the patent stated.

And there were -- there were some internal -- internal data from or basically communications in Pfizer that showed that they were thinking about ED and -- and Sildenafil prior to the time it was patented for that use.

Q And what parties did you testify on behalf of in that case?

A The -- not Pfizer, the other side.

Q The generics?

A The generic side, yes.

Q Okay. Did you give any opinions on obviousness in that case?

A No.

Q Okay. Prior to this case, had you ever

given any opinions relating to obviousness?

A No.

Q You mentioned in your report that you also have been involved in the case called In re: Testosterone replacement therapy products liability litigation, right?

A Yes.

Q Okay. What was your role in that case?

A The case hasn't actually come to fruition as of yet, but there's a -- there's a major class action suit against testosterone because of cardiac issues.

And -- and basically they subpoenaed virtually all of the people that had any research interest in testosterone clinically and to send all of their information to the -- to the plaintiffs' attorneys, which we've just recently complied with.

Q Okay. So you're -- you're not an expert witness in that case?

A Not yet. I mean, I hope -- I may be, but --

Q Okay.

A -- to date, no.

Q Okay. Now, what is your experience level

with patents?

A Very minimal.

Q Okay. You ever been an inventor on a patent?

A I have two patents of my own.

Q Okay. What do they concern?

A One of them is a tourniquet for bleeding during -- during renal surgery. And another is an instrument to do partial nephrectomy, neither of which have done much other than be patented.

Q Okay. Who's the assignee on those patents?

A I'm not sure what that exactly means.

Q Who's the owner?

A Benad Goldwasser.

Q Who is Benad Goldwasser?

A He's a urologist in Israel.

Q Okay. Is he an inventor on those patents as well?

A He is, yes.

Q Okay. So you have some sort of arrangement with Mr. -- Dr. -- is it Dr. --

A Doctor.

Q -- Goldwasser?

A It is, yes.

Q And what is that arrangement?

A Well, I mean, the patents have never amounted to anything so they just are sort of there. The patents were from the early 19 -- 1990s, I think it was 1991, something like that, and nothing has ever happened with them.

Q Okay. What was your level of involvement in the prosecution of those patents?

A Basically we invented the -- the devices and then at the time I was a faculty member at Duke University and they had some patent attorneys on -- on staff. And so we went to them with the -- the inventions and they basically wrote the patents and that was the end of it.

Q Okay. Were you involved in the communications with -- back and forth with the patent office on those patents?

A We had some meetings, yes, just to kind of define what -- what the -- what the invention actually was.

Q Okay. Now, you said you testified at the trial on Sildenafil, right?

A Yes.

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Q How many other times have you testified at trial?

A Quite a few actually, but none others have been patents, it's always been malpractice cases --

Q Okay.

A -- as expert witness.

Q Okay. Have you ever been a fact witness in -- in any lawsuit?

A No.

Q Okay. Dr. Carson, did you meet with counsel to prepare for this deposition?

A I did.

Q When was that?

A Yesterday.

Q How long did you meet?

A About six hours.

Q Okay. And where was the meeting at?

A At their firm.

Q Okay. You're talking about Kilpatrick Stockton?

A Kilpatrick Stockton, just down the street.

Q Okay. And prior to that meeting, did you

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have meetings with the attorneys at Kilpatrick Stockton?

A One previous.

Q When was that meeting?

A In June, I believe.

Q June of this year?

A Yes.

Q And you were involved in preparing two expert reports in this case?

A Yes.

Q How many hours did you spend on those expert reports?

A Probably all together, close to 40 hours, I would guess.

Q Okay. Now, were you provided documents for those expert reports?

A I was provided some and then I found some on my own.

Q Okay. Which ones did you find on your own?

A Oh, just -- I did a Med-Line search and just found a number of studies on overactive bladder, fesoterodine, tolterodine, a variety of things like that, of that nature.

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Q Do you remember any specific publications that you found?

A The Paul Abrams study from 1998, I think. There are a couple of Steve Kaplan studies. There's studies by -- let me think who else. There are just, I don't know, several others, but those are the -- those are the ones I remember the most vividly.

Q Okay.

MR. OELKE: Let's mark his CV. It's in here?

MS. CHOE: Yeah, I think so.

MR. OELKE: Okay. It's a big exhibit.

I'd like to mark as Carson Exhibit 1 Opening Expert Report of Culley C. Carson, III, M.D., which has attachments.

(Deposition Exhibit 1 marked.)

BY MR. OELKE:

Q Can you identify Carson Exhibit 1, please?

A Yes, it's an expert report, the first opening expert report from June of 2016.

Q And that's your signature on the front page?

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A Yes, it is.

Q Okay. When were you first contacted about working in this case?

MS. WOOTEN: Objection, just caution the witness. You may respond to the question, but don't reveal any attorney/client privileged information as part of your response.

THE WITNESS: Okay.

BY MR. OELKE:

Q Well, just -- just for the record, I don't think it's attorney/client, but I agree I don't want you --

MS. WOOTEN: Guess.

BY MR. OELKE:

Q -- to reveal communications with --

A Right.

Q -- Ms. Wooten.

A Sometime in the -- in the spring, like, April or May of 2016.

Q Okay. And your CV is attached as Exhibit 1; is that right?

A Yes.

Q Now, you received your undergraduate degree from Trinity?

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A I did.

Q What was your undergraduate degree in?

A Biology.

Q Okay. Then you received your M.D. in 1971?

A That's correct.

Q What did you do after you received your M.D.?

A I did two years of general surgery at Dartmouth in Hanover, New Hampshire. And then following that, I spent two years in the -- in the Air Force as a flight surgeon. And then following that, did residency at -- at the Mayo Clinic in Rochester, Minnesota.

Q Okay. And you were a urology fellow there?

A Yes.

Q Is that when your -- when you first started specializing in neurology?

A Yes.

Q So you've specialized in neurology since about 1975?

A That's correct.

Q Okay. And at that time in 1975, what was

the treatment standards for urinary incontinence?

A Well, urinary incontinence is a broad spectrum of things. It's -- surgery was one of the things was -- was -- was used in those days for an overactive bladder and urge or urgency, depending on what you want -- how you want to term it, incontinence.

There wasn't much available, although, oxybutynin and Ditropan came out around the time I began my urology training.

Q Okay. You used the term "overactive bladder." Just for the record, what is overactive bladder?

A Basically, overactive bladder is contracting -- is abnormal, uncontrolled contractions of the bladder when patients or people don't want them to contract.

So it produces frequency, produces urgency, produces urge incontinence, urgency incontinence, nocturia, and those things are bothersome to patients.

Q What is nocturia?

A Nocturia is arising at night to pass urine.

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Q Okay. After you were done at the Mayo Clinic, what was your next job?

A I was hired to be on the faculty at Duke University, and I was at Duke University for 15 years.

Q Okay. And you focused on urology at that time?

A Yes.

Q And did you have a subspecialty in urology at that time?

A Most of my entire life of urology has been in men's health areas. So erectile dysfunction, male incontinence, testosterone deficiency, those kinds of things.

Q So when did you -- what was your next job after Duke?

A In -- in 1992-'93, I was -- I was selected to be the head of urology at the University of North Carolina, so I moved down the street to be the chief of urology at the University of North Carolina.

Q Okay. And -- and that's where you're at still?

A Yes.

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Q Okay. And what are your titles at University of North Carolina?

A I stepped down as being the -- the chief and -- and -- but I'm now the Rhodes Distinguished Professor of Urology at the University of North Carolina, Chapel Hill.

Q Okay. And during your time at North Carolina, your function -- your subspecialty has been in men's health?

A Yes.

Q Okay. Sexual dysfunction?

A Sexual dysfunction, incontinence, prostate cancer, prostate diseases.

Q Okay. But your subspecialty has not been overactive bladder, correct?

A Not specifically.

Q Okay. There are other urologists, their specialty is overactive bladder, correct?

A Part of their specialty. I wouldn't say that's all they do.

Q Okay.

A I'm not sure they could make enough money to keep themselves healthy just doing that.

Q Okay. But overactive bladder is not part

of your specialty?

A No. Well, it is to an extent because men with prostate enlargement have overactive bladder associated with it, so I certainly -- I certainly do have -- am involved with that.

Q To the extent it overlaps with sexual dysfunction for men, you are interested in overactive bladder, but your subspecialty is not overactive bladder, right?

A Not that -- not specifically.

Q Okay. Now, do you consult with any pharmaceutical companies?

A I do.

Q And which ones?

A At variable periods of time it depends on the -- the life cycle of a particular product. I've -- I've in the past consulted with Pfizer, with Endo, with Auxilium, with Abbvie used to be Abbott, with GlaxoSmithKline, with Bayer, to name a few. Several other smaller ones as well.

Q Who are you consulting with now?

A Predominantly Abbvie and Endo as well as Boston Scientific, which is not a drug company but it's an industry.

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Q Of those companies, who have you consulted with on the -- in the area of overactive bladder?

A Pfizer for one. I -- I spent some time consulting with the original Ditropan people, I can't even remember the name of the company anymore, that made Ditropan originally, but...

Q The rest of your consulting has been in men's sexual dysfunction?

A Men's health. I mean, it's not just sexual dysfunction.

Q Okay. Overactive bladders, as far as pharmaceutical treatment, is mostly directed to women, right?

A It has in the past, yeah.

Q Okay. What do you think the percentage of the market is for overactive bladder pharmaceutical treatments with respect to male versus female?

A It's probably 70/30.

Q Okay. Do you still see patients?

A Yes.

Q How many patients do you see in a typical month?

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A Let's see, in the neighborhood of 250.

Q And of that number, 250, how many do you see for OAB?

A Pure OAB, probably no more than 15 or 20, something like that. Most of them have other problems such as an enlarged prostate that goes along with their OAB that produces their OAB, associated with their OAB.

Q Okay. Do you prescribe OAB medicines?

A Yes, I do.

Q And of those 250 patients a month, just as an average, how many do you think you prescribed OAB medicine for?

A Probably, again, maybe 10 or 15, something like that.

Q Okay. And what OAB medicines do you prescribe?

A A whole gamut of things. And it -- it's dependent upon what their -- what their insurance company will pay for to be honest.

Generally the insurance companies want you to start with oxybutynin because it's a generic drug and it's inexpensive. And then every insurance company varies as to what they'll do as a

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second line. The one I use most often now is a drug called Myrbetriq or Mirabegron.

Q What kind of mechanism of action does Myrbetriq have?

A Yeah, it's -- it's basically a Beta-3 relaxant, and it has the advantage of relaxing the bladder, although, it's not as potent as some of the anti-muscarinics, but it doesn't have CNS problems and it has very little dry mouth and very little constipation associated with it. So for aging patients, it tends to be the best choice.

But it's usually not covered by insurance. So it's one of those things where you have to start with something else, patients have to fail it and then you move on. So it's kind of -- it's an iterative process.

Q Have you prescribed tolterodine --

A Yes.

Q -- to patients?

A I have.

Q Okay. And are there instances in which you will prescribe tolterodine today to patients?

A Yes. Absolutely, yes.

Q And what are those instances?

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A The instances are when people -- people have failed one anti-muscarinic. And failed means it either doesn't work or they've had onerous side effects that they can't tolerate. Or third thing is that the -- that that's the preferred drug for their particular insurance policy.

Q And when did you start prescribing tolterodine?

A As soon as it was on the market.

Q Okay. Were you involved in clinical trials for tolterodine?

A I was not.

Q Okay. And do you recall that it was approved in March of 1998?

A Yes.

Q When did you start using it?

A You know, I don't really totally remember, but as an academic urologist, I tend to be an early adopter of these new drugs.

So probably within the first three or four months of the time it was approved. I don't remember when I wrote the first prescription particularly, but I'm sure it was early in that period of time.

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Q And before that you had prescribed oxybutynin?

A Yes.

Q Had you described -- had you prescribed other drugs for overactive bladder?

A Yes.

Q What other drugs?

A Flavoxate I used for a while or used in some patients that couldn't tolerate -- couldn't tolerate oxybutynin.

Really that was about the only -- those are about the only reasonable things that were on the market in those days.

Q Okay. Now, at some point trospium became available in the U.S., right?

A Yes.

Q Have you ever prescribed trospium?

A Yes, I have.

Q In what types of patients do you -- have you prescribed trospium for?

A Very similar to the -- to the fesoterodine patients. And those are ones that -- where their insurance company says that that's what you need to use.

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And, you know, I think physicians' prescribing practices are based a lot on what their personal experience is, what the newest thing on the market is, what the marketing of that drug is, but most often what the insurance companies will pay for.

Q Okay. Now, when did Myrbetriq come on the market?

A Oh, probably three, four years ago.

Q Okay. Prior to Myrbetriq's availability, what drugs did you prescribe for elderly patients?

A Again, any -- anything other than oxybutynin because the oxybutynin in elderly patients is really not a very good choice, and the CNS side effects are onerous.

Q Did tolterodine have CNS side effects in -- in instances in which you prescribed it?

A Not so much. I mean, it had some. A headache and -- and that sort of thing, but the confusion issue that you get with oxybutynin was a lot less with -- with tolterodine.

Q Okay. There are certain medications that are on a -- a list that pilots can't use; is that right?

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A Yes.

Q And oxybutynin is on that list, isn't it?

A It is.

Q Tolterodine is not on that list, is it?

A Correct, it is not.

Q The CNS side effects of tolterodine were never judged to be serious enough to be put on that list for -- for pilots, right?

A Part of it's because of the CNS -- CNS issues, part of it's because of the ocular accommodation issues. So those are both significant problems with oxybutynin.

Q And they are not problems for tolterodine?

A That's correct.

Q And other than headache, you've never noticed CNS side effects in patients in which you've prescribed tolterodine?

A You know, patients have all kinds of problems and you never know if it's the medication or it's -- it's the -- just have the problems. But I've had patients that tell me that they have dizziness from any -- from all of the anti-muscarinics and you wonder if it's the drug or

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if they just had dizziness anyway.

So, basically, it's -- it's not something that you can generalize about, I guess, but certainly better than oxybutynin.

Q Did you -- so -- strike that.

You've -- you've consulted with pharmaceutical companies, right?

A Yes, I have.

Q You've been on advisory boards for those pharmaceutical companies?

A I have.

Q And you ever provided advice on the development of drugs for OAB?

A Probably, yes. I don't remember specifically, but it's one of those things where a new drug comes out, they present the data and say what do you think and you say could be better.

Q Do you --

A Is better, but could be better.

Q Okay. Did you ever have any conversations in which you suggested that tolterodine would be a good candidate to make modifications to?

A Not to my knowledge.

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Q Okay. Now, you're familiar with 5-HMT?

A Yes.

Q A metabolite?

A Yes.

Q And it's an active metabolite of tolterodine, right?

A That's correct.

Q Okay. Do you recall ever discussing with any pharmaceutical company representative that 5-HMT would be a good candidate as a lead compound for future drug development?

MS. WOOTEN: Objection, form.

A I don't remember specifically -- having those specific conversations as you're stating them, but I -- but I remember having conversations with some of the marketing people for fesoterodine that -- you know, that was a -- that 5-HMT was a good target.

BY MR. OELKE:

Q Okay. That was after fesoterodine had been developed?

A Yes.

Q Okay.

A I don't recall before. Maybe I did, but

I don't remember.

Q Okay. Do you recall any discussions with other urologists that 5-HMT would be a good candidate for future development prior -- prior to the development of fesoterodine?

A Fesoterodine, yeah. I don't recall. I mean, that's -- that's been a long time ago, so I don't really remember. We have a lot of conversations about a lot of things at meetings and so on, but I don't remember specific conversations, no.

Q And you're not aware of any publications prior to the development of fesoterodine that suggested 5-HMT would be a good candidate for future development?

A No. There are other publications that suggest or show that that 5-HMT is a good agent for bladder relaxation for anti-muscarinic targeting, so, you know. But as far as saying the way that -- the way you said it, no.

Q Those publications you're talking about are describing 5-HMT as a metabolite, right?

A As -- as a metabolite, correct.

Q None of them are discussing 5-HMT as an

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active ingredient?

A Well, they're discussing 5-HMT as an active agent in the -- in the blockade of -- of muscarinic receptors.

Q But only as a metabolite of tolterodine, right?

A Well, as a -- as a particular compound. I mean, you know, whether it's a metabolite or whether it's pure, either way it's -- it's what it's doing to the bladder.

Q Okay. But can you identify any publications prior to the development of fesoterodine that suggested 5-HMT should be administered as an agent?

MS. WOOTEN: Objection, form.

A I can't -- I don't know specifically. I'd have to look back, but I don't remember any specific publications that -- that have that tenor.

BY MR. OELKE:

Q Okay. Now, you said you consulted for Pfizer, right --

A Yes.

Q -- at some point in time?

When was that?

A In the 1990s predominantly.

Q Okay.

A Early -- the early 2000s, but 1990s.

Q And when did your consulting with Pfizer stop?

A I don't even remember, but probably in the mid-2000s, I would guess.

I spoke for them about fesoterodine in the -- in like 2007 to 2009 range, I guess, and that's probably -- that was probably the end of it.

MR. OELKE: I would like to mark Carson Exhibit 2, Consultant Agreement, Healthcare Professional Consultant Agreement.

(Deposition Exhibit 2 marked.)

BY MR. OELKE:

Q Just take a moment to look at Carson Exhibit 2, Dr. Carson.

A (Witness reviews document.)

Q Is Carson Exhibit 2 a consultant agreement between you and Pfizer?

A It surely is, yes.

Q And you executed it in May of 2015?

A I did.

Q Okay.

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A Yeah, basically, this was a -- I gave a talk at -- at the European Association of Urology that was sponsored by Pfizer. I had forgotten about this.

Q Okay. So there was a consulting agreement in place in 2015 between you and Pfizer, right?

A Yes, that's correct.

Q And you didn't include that in your materials for your expert report, right?

A No, I did not.

Q Okay. Is there a reason you left this out?

A I had totally forgotten about it because it was a meeting that -- that I presented some -- some -- to some Middle Eastern urologists. And it was arranged by one of my colleagues in London, and I -- actually, to be honest, I had forgotten that it was sponsored by Pfizer.

Q Okay. Now, do you know Dr. MacDiarmid?

A Yes, very well.

Q Okay. And how do you know him?

A He was a fellow at Duke when I was a faculty member at Duke. And I tried to hire him to

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come to the University of North Carolina which didn't work, and I've known him since that time. We used to work out together actually.

Q Okay. Is Dr. MacDiarmid a specialist -- first of all, is he a urologist?

A He is.

Q And is a subspecialty of his OAB?

A It's female urology.

Q Okay.

A And incontinence. And OAB is a piece of that.

Q Okay. And he sees a lot more patients with respect to OAB than you do, correct?

MS. WOOTEN: Objection, form.

A I don't -- I don't know the answer to that.

BY MR. OELKE:

Q You don't, okay. You don't know who he -- how many patients he sees, for instance?

A I don't.

Q Okay. But you would agree that OAB is certainly more a specialty of Dr. MacDiarmid's than yours, correct?

MS. WOOTEN: Objection, form.

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A Yeah, I mean, that's something he's been interested in for most of his life with the female urology part.

BY MR. OELKE:

Q Okay. Do you respect Dr. MacDiarmid's opinions?

A I do.

Q Okay. Is he a respected urologist?

A He is.

Q How many papers have you published on the topic of overactive bladder?

A Probably not more than two or three.

Q Okay. How many papers have you published total?

A More than 300.

Q Okay. Quite a few, right?

A Yeah.

Q Okay. How many of those papers relate to men's sexual dysfunction?

A I don't even know, but probably a third.

Q Okay. Are there any other areas that most of your writing concerns other than men's sexual dysfunction and OAB?

A Yeah, I mean, incontinence in men --

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Q Okay.

A -- with prostate cancer is another one. Urinary stone disease is another one.

Q Okay.

A Testosterone replacement.

Q Kidney stones?

A Kidney stones.

Q Yeah.

A I mentioned that, yeah.

MR. OELKE: I'd like to mark as Carson Exhibit 3 an article entitled The Pharmacological Treatment of Urinary Incontinence. The first author is Karl Eric Andersson.

(Deposition Exhibit 3 marked.)

BY MR. OELKE:

Q Dr. Carson, have you seen this article before?

A Yes, I have.

Q And who is Karl Eric Andersson?

A Karl Eric Andersson is probably the expert on overactive bladder in the world. He is -- he is Swedish and he is -- has an M.D. degree, but basically is a pharmacologist.

He spent a lot of time in -- did most of

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his work in Sweden actually. But when he had to retire from Sweden because of age, he actually came to North Carolina and was -- spent some time at Wake Forest, which he subsequently left, and I think he's in Germany right now.

Q Oh, he's not at Wake Forest, okay.

A He's no longer at Wake Forest.

Q Okay. This article is dated 1999?

A Yes.

Q And you understand -- well, just as background, do you understand there's five patents at issue in this case, right?

A Yes.

Q And one of those patents we refer to as the '650 patent?

A Right.

MR. OELKE: Maybe we should mark that rather than just refer to it.

(Deposition Exhibit 4 marked.)

MR. OELKE: Mark this Carson Exhibit 4 U.S. Patent 6,858,650.

THE WITNESS: Thank you.

BY MR. OELKE:

Q Do you recognize Carson 4 as one of the

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five patents-in-suit, U.S. Patent 6,858,650?

A Yes.

Q Okay. And I know you said earlier that -- that patents certainly aren't your specialty, but do you understand there's dates that relate to a patent by which you then determine whether or not the patent is -- meets the standards of patentability?

A Yes. I mean, generally, yes.

Q Okay. And you understand that this patent has a foreign application priority date if you look at the number 30 down in the left-hand column there on the first page. It says, November 16th, 1999. Do you see that?

A I do.

Q Do you understand that that's the date on which this -- the German patent application was filed that underlies this patent?

MS. WOOTEN: Objection, form.

A I see what you're saying, but I didn't -- you know.

BY MR. OELKE:

Q Do you understand --

A I believe you.

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Q Okay. Do you understand November 16th, 1999 is -- is the date by which you should assess the issues with respect to this patent that you've opined on?

A Again, I -- I agree with that, but -- but I'm not --

Q Okay.

A That's not in my area of expertise.

Q Understood. But I'm just making sure you're -- we're working off the same dates. When we talk about dates --

A I gotcha.

Q -- we're working off these dates. So the date for this patent is November 16th, 1999. Do you see that?

A Yes, I do.

Q Okay.

MR. OELKE: Give me the '980.

I'm not going to mark all five patents. I'll just mark one of the other four because they all have the same date.

So this is -- Carson 5 is U.S. Patent 7,384,980.

(Deposition Exhibit 5 marked.)

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BY MR. OELKE:

Q And you see Carson 5 is U.S. Patent 7,384,980?

A Yes.

Q And that's one of the four other patents that are at issue in this case, right?

A Yes.

Q You've reviewed these patents?

A Yes, as much as I can -- I mean, I had reviewed them. Did I understand them? Maybe not.

Q Okay. You're not opining on the -- the claimed subject matter of these patents, right?

A That's correct.

Q Okay. Now, you understand the -- the priority date for this patent and the other three related patents is -- again, if you look at -- at No. 30 down there on the left-hand column of the first page, it says May 12th, 1998.

A Yes.

Q So you understand that the -- the filing date for this patent and -- and the three related patents is May 12th, 1998?

A Yes.

Q So for the patents at issue in this case,

the time frame we're talking about that's relevant is 1998 or 1999, you understand that?

A Correct, yes.

Q Okay. Now, going back to the Andersson publication which is Carson 3. You see that's dated 1999?

A Yes.

Q And you understand this is a summary of -- of -- of the available treatments in 1999?

A Yeah, it's a review article that really expresses the state of the art in 1999.

Q Okay. And there's a table at Page 924 which is PFE08143400. Do you see that?

A Yes, I do.

Q It starts on -- on Page 924 and actually goes on to Page 925.

A Correct.

Q And that table is entitled Drugs used in the treatment of bladder hyperactivity, stress and overflow incontinence.

A Yes.

Q Okay. And there's a -- a large number of -- of compounds that are listed here for bladder hyperactivity, right?

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A Yes.

Q And they're given a -- there's -- there's a key for these different letters that are listed in the columns for these different drugs. Do you see that?

A Yes.

Q One is the Clinical column which has either an A, B or C associated with it. Do you see that?

A I do.

Q And do you understand that A indicates good quality RCT?

A Yes.

Q What's RCT?

A Control trials, randomized control trials.

Q Okay, great.

And Assessment is another column. Do you see that?

A Yes.

Q And under that column, R indicates recommended?

A Yes.

Q Okay. So you see that as of 1999 at

least there were eight different compounds that were listed as recommended for bladder hyperactivity, right?

A Yes, that's correct.

Q If you would just go through those. Propantheline, do you see that's one of the ones that's recommended?

A Yes.

Q Did you ever prescribe propantheline?

A I did, in the olden days.

Q Okay. And what was your experience with propantheline?

A Not very effective and many side effects.

Q Okay. And what about Emepronium, did you ever prescribe Emepronium?

A I did not.

Q Okay. Are you familiar with Emepronium?

A I've read about Emepronium, but I'm not familiar as a -- as a clinically useful agent.

Q Okay. And we already talked about trospium. At some point trospium became available in the United States, right?

A It did.

Q It was available in Europe before that,

though, right?

A Correct.

Q As of 1999 it was already on the market in Europe?

A Right. And it had -- had good clinical trials.

Q Those clinical trials were available as of 1998?

A Correct.

Q Okay. And was the perceived problem with trospium one of bioavailability?

A That was the biggest problem with it, yeah.

Q It had varied bioavailability, right?

A It had varied and really poor bioavailability.

Q So did that mean with trospium you had to modify your dosage depending on the patient?

A Oh, absolutely. I mean, all of the drugs you have to modify the dosage based on the patient, but trospium was even more dramatically such.

Q Okay. And that's because in some patients they got very little effect from the particular dose while in other patients more the

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dose would get to the -- to the desired area?

A Yeah, the responses were extremely variable.

Q Okay. Now, would trospium have been a good candidate to consider as a -- a -- a lead compound by trying to increase its bioavailability?

A I mean, that's -- that would have been a strategy that could have been helpful.

Q Okay. And oxybutynin is on this list as well, right?

A It is, yes.

Q Okay. And that's a drug that a lot of urologists had used starting when?

A 1975 really.

Q Okay. And it was the standard of care until tolterodine became available?

A Correct.

Q Okay. And would oxybutynin have been a good candidate for further development if you could find a way to alleviate the side effects in that compound?

A Yeah, and there were a number of things that a -- a number of people that did exactly that.

Q Right. There were -- there were a number

of research groups in the late 1990s that were researching new OAB drugs, right?

A Correct.

Q And some of those groups were actually trying to modify oxybutynin then, right?

A That's correct.

Q Okay. And that was a reasonable approach to try to develop a new OAB drug in the late '90s, right?

A Absolutely, yes.

Q Okay. Now, Propiverine, do you have any experience with Propiverine?

A No.

Q Okay.

A It was basically withdrawn from the market because of cardiac effects.

Q Okay. How about Terodiline, are you familiar with Terodiline?

A Again, reading, yes, but prescribing, no.

Q Okay. And that drug was withdrawn from the market at some point, right?

A Yes.

Q And that was because of the QT effect associated with Terodiline?

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A QT prolongation, yeah.

Q Okay. What is QT prolongation?

A It's the interval between the Q wave and the T wave in the electrocardiogram. And if it -- if it -- if it's severe enough, it can create what's called torsade de pointes which is basically a lead -- can lead to a fatal arrhythmia.

So it's a -- it's a -- it's a significant issue for drugs. And in fact, there are long lists of drugs that do have QT problems. And the FDA I know looks at the QT interval and has a break point after above which they won't approve a drug.

Q Okay. Now, is QT something that you have to be concerned about with respect to anti-muscarinics generally?

A The ones that are on the market not so much, but the trouble -- one of the problems with -- with this class of drugs is that they're often given to aging patients, and aging patients respond differently to -- to drugs. And -- and so often they have polypharmacies, they have multiple drugs.

So if you stack up a variety of drugs that all have a QT potential, QT prolongation potential, then, yes, if you add more, perhaps that

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can be an issue. So you have to think about it.

Q Okay. And QT prolongation is actually something that is mentioned in the label for tolterodine, right?

A Yes, it is.

Q And why is that?

A Because of high doses, doses above the recommended doses. In the 8-milligram range there -- there was -- there have been recorded some QT abnormality.

Q And that -- that would be a supratherapeutic dose for tolterodine?

A That's correct.

Q But why would warnings be given -- or strike that.

Why would information be provided about supratherapeutic doses of tolterodine?

MS. WOOTEN: Objection, form.

A A couple of reasons. Some patients think one pill is good, so let's take four and see what happens. So that certainly is a possibility. That's No. 1.

No. 2 thing is, is that if you have, as I mentioned earlier, several drugs that have a

propensity to prolong QT interval and you put them all together in one patient, then perhaps you can -- that will be the one that -- the straw that breaks the camel's back, so to speak.

And the -- the final thing is, is that if a patient is a poor metabolizer of tolterodine, then perhaps they'll have more tolterodine around and perhaps that -- that also in combination with other drugs will -- will predispose them to QT abnormalities.

So it's a concern.

BY MR. OELKE:

Q Okay. Is QT abnormality something that you have taken into account in deciding whether to prescribe tolterodine to patients?

A I don't personally do that, no. But if a patient comes in and tells me that they have cardiac problems, they have preexisting heart disease or heart problems, then I would -- I would take that into account.

Q Okay.

A And there are a number of other drugs I have and feel the same way about.

Q Now, fesoterodine does not have the same

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concern with respect to QT, does it?

A It does not.

MS. WOOTEN: Objection, form.

BY MR. OELKE:

Q And there would have been nothing in 1998 to suggest that a -- a pro drug of 5-HMT would solve any QT issues with tolterodine?

MS. WOOTEN: Objection, form.

A Well, the tolterodine appears to be the drug or the agent that causes the QT abnormality and its metabolite doesn't, and so, you know, I'm not sure when that information was readily available, but certainly that -- that would be an issue.

BY MR. OELKE:

Q When was it -- when did it first become known that tolterodine was the cause of QT and not 5-HMT?

MS. WOOTEN: Objection, form.

A I'm not sure exactly the date.

BY MR. OELKE:

Q It wasn't before 1999, was it?

A It was probably in that range. During the drug development program, I would...

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Q You can't identify any reference or article that indicates that was known in 1999, can you?

A I can't right off the top of my head, no.

Q Okay.

A I'd have to research it.

Q If you'd turn back to Exhibit 1 which is your report. There's an Exhibit 2 to that after your CV.

A Okay.

Q You see this is a list of documents that you considered in preparing this report?

A Yes.

Q Okay. And this includes documents that counsel provided?

A Yes.

Q And it also includes documents that you found in your preparation of these reports?

A Correct.

Q Okay.

MR. OELKE: Are we up to 5?

THE COURT REPORTER: 6.

MR. OELKE: I would like to mark as Carson Exhibit 6, Rebuttal Expert Report of Culley

CULLEY C. CARSON, III, M.D.

C. Carson, III.

(Deposition Exhibit 6 marked.)

BY MR. OELKE:

Q Is Carson 6 your rebuttal report?

A Yes.

Q And that's your signature on the first page?

A It is.

Q And this is in response to Dr. MacDiarmid's report?

A Yes.

Q And again, there's a list of documents considered that's Exhibit 1 -- no, I'm sorry, Exhibit 18.

A Yes.

Q You see that?

A I do.

Q Okay. These two lists of documents considered, are they complete as far as you're aware?

A As far as I'm aware. I mean, I've done some Med-Line searches and things since then, but -- but this is -- at the time of this signature, yes.

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Q Okay. And you're not seeking to add anything additional?

A Not at this time.

Q Okay. Now, you understand there was a previous litigation involving these patents between the Plaintiffs and a group of other generic Defendants?

A Yes.

Q Have you reviewed the decision in that case?

A I've reviewed it, yes.

Q Okay. And you understand that Judge Sleet determined that these patents are not invalid for obviousness on the bases that were set forth by the generic Defendants in that case, right?

A Yes.

Q And you'd agree that the bases for obviousness that were set forth by those Defendants are very similar to the bases that are set forth in -- in your opinion and Dr. Janero's opinion, right?

A Yes.

MS. WOOTEN: Objection to form.

BY MR. OELKE:

Q Okay. Can you identify any differences

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in your opinions than what were set forth by the -- the experts in those cases --

A While --

Q -- in that case, I should say?

A While I reviewed that case, I'm not totally familiar with it and the -- the legal language was a -- was a bit confusing to me, I must say.

Q Do you know who the urologist was that testified on behalf of the generic Defendants in that case?

A I think it was Victor Nitti.

Q He was for the Plaintiffs?

A Oh, he was the plaintiffs, okay. I know -- I know Victor well, so that's...

Q Okay. And Dr. Nitti's now the, I don't know, head of the AUA or something?

A Office of Education, yeah.

Q So he's not --

A Busy.

Q Yeah, he's busy.

If you would look at your opening report going back to Exhibit 1. And turn to Paragraph -- Paragraph 10, I guess. I'm sorry, I'm looking at

the wrong one. I want -- I want to look at your rebuttal report.

A Okay.

Q Go to Paragraph 10 in that report.

A Okay.

Q There's this term the patent lawyers use "person of ordinary skill in the art." Have you heard that term before you worked on this case?

A Yes, I have.

Q Okay. And you opine on the level of ordinary skill in the art at Paragraphs 10 to 12. Do you see that?

A Yes.

Q Okay. And I'll just read what you wrote in Paragraph 10. I -- it says, quote: I have been informed that the person of ordinary skill at the time of invention in this case would have had a Ph.D. in chemistry, medicinal chemistry, pharmacology, or a related field, and at least one year of industrial exposure to drug discovery, drug design, and synthesis. In lieu of an advanced degree, the individual may have additional years of industry experience, including, for example, in drug discovery, drug synthesis, and

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structure-activity work. Do you see that?

A Yes.

Q That's your definition for what a person of ordinary skill would have with respect to these patents in this case?

A Yes.

Q And that person of ordinary skill would not have expertise in urology, right?

A As far as drug development is concerned, no.

Q Okay. And you would not qualify as a person of ordinary skill with respect to these patents under your standards?

A As far as development of a drug, correct.

Q Okay. If you go back to the Andersson article, Carson Exhibit 3 on Page 926, which is PFE01843402.

Do you see the first full paragraph on that page?

A Future Studies, yes.

Q Yeah. It says, quote: Future studies with muscarinic receptor antagonists with a selectivity for M3 receptors, such as darifenacin, vamicamide and zamifenacin, will reveal whether or

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not the principle of selective M3 receptor antagonism offers therapeutic advantages. Do you see that?

A Yes.

Q So at the time of this article, the compound darifenacin was being developed, right?

A It was, yes.

Q And that was a selective M3 inhibitor?

A Yes.

Q And that's on the market today, right?

A It is.

Q And as of the 1998-1999 time frame, there were research groups looking at selective M3 inhibition as a -- a pathway for developing a new OAB drug, right?

A Yes.

MS. WOOTEN: Objection, form.

BY MR. OELKE:

Q Okay. So that would include darifenacin?

A Yes.

Q And then there was also solifenacin, too?

A Correct.

Q Okay. And were there other compounds also being developed in 1998-1999 looking at

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selective M3 inhibition --

A Yes.

Q -- as a basis for developing a drug?

A There were.

Q Okay. And that was a reasonable starting point for persons of skill in the art in the 1998-1999 time frame, right?

MS. WOOTEN: Objection, form.

A Reasonable thought process, yes.

BY MR. OELKE:

Q Okay. If you go back to Exhibit 1. Turn to Page 2, Paragraph 7. It's your compensation. You're being compensated at $1120 per hour, right?

A Yes.

Q How did you arrive at that figure?

A Actually, I came to this process through a company called Scimetex. And they contacted me and asked me if I would be interested in doing this, and they arrived at that number.

Q Okay. So it was a suggested number from them?

A Yes.

Q Okay. You see there a section Summary of This Report?

A Yes. No. 5?

Q Yes.

A Yes.

Q And this summarizes your opinions in this opening report; is that right?

A Yes.

Q And in the second sentence there you say: Based on this understanding -- that's referring to your explanation of the state of the art, that's -- that's referred to in the first sentence.

A Uh-huh.

Q Based on this understanding, it is my opinion that one of ordinary skill in the art would have selected 5-HMT for further development and that the benefits of a modified 5-HMT molecule would have been -- would have -- would have been recognizable from the recognized problems of tolterodine therapy. Right?

A Yes.

Q Now, as of the 1998-1999 time frame, there were a number of groups that were looking to develop a new OAB drug, right?

A That's correct.

Q And we've talked about some of those

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groups today?

A Right.

Q Other than the inventors of the patents-in-suit, can you identify anyone else that was using 5-HMT -- that selected 5-HMT for further development?

A Well, the inventors, Scarf basically said in his -- in his deposition, that he had that idea and that physicians were stimulating him or encouraging him to try to develop a 5-HMT agent.

Q Right. Other than -- other than the inventors, though, can you identify anyone else that was developing a drug based off of 5-HMT?

A No, but I'm not privy to the -- the discussions at some of the drug companies. And I'm sure that they had discussions about that very issue, but I don't know. I don't know that.

Q Okay. And you can't identify any publications that suggest 5-HMT should be selected for further development as an agent itself to be administered to patients?

A No, I think --

MS. WOOTEN: Objection, form.

A I think I already said that, but I agree

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with that.

BY MR. OELKE:

Q Okay. And in fact, as of 1998-1999, 5-HMT had never been administered orally to patients, had it?

A Well, 5-HMT by itself doesn't absorb very well, so oral administration of 5-HMT by itself probably wouldn't be a -- a reasonable alternative.

Q Well, you say it would not be absorbed. But no one actually knows that, right? No one's ever tried to see if 5-HMT would be absorbed, have they?

A No. As far as I know, they have not.

Q Right. And, in fact, you're aware that there are experts in this case that have opined that they think 5-HMT would be well absorbed orally?

A I've seen that in the -- in the depositions, but I -- but I don't know that -- there's no publication that has looked at that and said yes or no.

Q Right. It's -- it's an unknown issue --

A Unknown.

Q -- as of 1998, right?

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A Correct.

Q It's an unknown issue as of 1999 whether 5-HMT would be well absorbed orally, right?

A Correct.

Q It's unknown as of 2016 whether or not 5-HMT would be well-absorbed orally, right?

A That's -- as far as I know, it's unknown.

Q Now, you're not opining that all -- well, strike that.

You're opining that 5-HMT would have been selected for further development?

A Yes.

Q But you're not opining on what that further development would be, correct?

A Which direction it would go?

Q Right.

A No, but that -- that it would be -- that would be a very good agent for decreasing overactive bladder and -- and with tolerable side effects.

Q But you're not giving an opinion on whether it should be a pro drug or whether you should make a modification to 5-HMT or whether you should try to come up with a formulation of 5-HMT,

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that's not your area?

A No, that's correct.

Q And you're not giving an opinion on the ultimate issue of whether the claim subject matter of the patents-in-suit would have been obvious, right?

MS. WOOTEN: Objection, form.

A No. Correct.

BY MR. OELKE:

Q That's something for someone that's of skill in the art as to these patents, right?

A That is --

MS. WOOTEN: Objection, form.

A -- chemist, pharmacologist, industry individual.

BY MR. OELKE:

Q Okay. You mentioned you -- you had prescribed Flavoxate?

A Yes.

Q What is Flavoxate?

A It's kind of a mixed drug that has some effect on the bladder, probably as a result of excretion into the urine, but it's not very good. In fact, it's not good at all.

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But -- but in the days before the options we had in 2016 or in 2000 -- early 2000s, there weren't many other options. So if somebody could not tolerate oxybutynin, you were stuck with some things that didn't work very well.

Q It's not indicated for OAB, right?

A Well, it's indicated. It's probably not in the package insert, but people use it for that.

Q You know, I'm just -- what is the -- what's the actual indication for it, do you know?

A Basically burning on urination is what we use it for in -- in -- in urology.

Q Okay.

MR. OELKE: Why don't we take a break.

VIDEO TECHNICIAN: Marks the end of Video 1. Off the record. The time is 10:12.

(Recess taken.)

VIDEO TECHNICIAN: Marks the beginning of Video 2. Deposition of Culley Carson, M.D. Back on the record. The time 10:25.

BY MR. OELKE:

Q Dr. Carson, tolterodine metabolizes into 5-HMT in patients, right?

A Yes, it does.

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Q And there's different groups of patients that fall into the categories of poor metabolizers and extensive metabolizers?

A Yes.

Q And for extensive metabolizers, those patients are getting the -- their effect from 5-HMT, correct?

A They're getting more. Yeah, not a hundred percent but more.

Q Okay. They're getting a majority of their effect from 5-HMT, right?

A Probably the majority, yes.

Q And poor metabolizers are getting their effect more from tolterodine, right?

A That's correct.

Q And tolterodine and 5-HMT both are effective in the treatment of overactive bladder, right?

MS. WOOTEN: Objection, form.

A They are.

BY MR. OELKE:

Q Okay. And their net activity for extensive metabolizers and poor metabolizers have been determined to be similar, right?

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A Yeah, there haven't been any really great head-to-head studies, so it's a little hard to know exactly.

But -- but -- and -- and it's known that -- that tolterodine is more likely to be bound to protein, so it's less available to the receptors than 5-HMT.

So there is more activity from 5-HMT pound for pound than -- than probably tolterodine. But those things haven't been teased out in a clinical trial.

Q And the studies -- the clinical studies on tolterodine did determine, though, that -- that patients that were poor metabolizers were getting the same net effect as patients that were extensive metabolizers, right?

MS. WOOTEN: Objection, form.

A Again, not extensively studied with large numbers, but that was the -- that was the -- the conclusion of the studies that looked at it.

BY MR. OELKE:

Q And you were aware of those studies when you were prescribing tolterodine to patients?

A Yes.

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Q Do you ever try to determine whether or not a patient is a poor metabolizer before prescribing the drug to them?

A That's really something that's not generally tested for.

Q Right. And there's a lot of drugs that act through the CYP2D6 pathway, right?

A Yes.

Q And for patients that take drugs that act through the CYP2D6 pathway, some of them are poor metabolizers, right?

A Yeah, about -- in Caucasians, around 7-8 percent.

Q Right. So for the 92 to 93 percent that are extensive metabolizers, those patients -- the -- well, strike that.

The -- you suggested that 5-HMT would be a good starting point, right?

A Yes.

Q As -- as a -- a compound to research further?

A Yes.

Q Is that due to the effects in poor metabolizers only?

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A Oh, no, I think that's one subset. Certainly be better in poor metabolizers.

Also, be better in the patients that are taking other CYP2D6 drugs that are competing for the same binding spot, so that's another set of -- of individuals.

Also, I think that as I mentioned the -- the -- the binding of -- of the drugs -- protein binding of the drugs also makes it more -- a better target.

And then the final thing is the -- is the CNS issues. You know, I think there's -- there's definitely a CNS difference.

Q But you have not seen a problem in CNS effects in the patients that you have prescribed tolterodine to?

A I have not.

Q Okay.

MR. OELKE: Let's mark this.

(Deposition Exhibit 7 marked.)

MR. OELKE: Let's mark as Carson Exhibit 7 a label for Detrol with the Bates range PFE01843539 to 3545.

THE WITNESS: Thanks.

CULLEY C. CARSON, III, M.D.

BY MR. OELKE:

Q So is it your view that fesoterodine provides a benefit over tolterodine based on less CNS side effects?

A Yes.

Q And is that a reason for you to prescribe fesoterodine rather than tolterodine to patients?

A Especially in aging patients, yes.

Q Okay. And you're aware that there are studies on prescribing -- I'm sorry, there are studies on the treatment of elderly patients using fesoterodine, right?

A Yes.

Q And in those studies, fesoterodine was judged to be a -- a good treatment for those patients, right?

A Yes.

Q Okay. And are you aware of any other OAB drugs where it has been studied -- where the efficacy of that drug has been studied in elderly patients?

MS. WOOTEN: Objection, form.

A You know, all of the -- all of the agents have parts of their studies in patients over the

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age of 65 which are elderly patients, so I think they're all studied for that. The FDA wants that information basically.

BY MR. OELKE:

Q It includes patients over the age of 65, but -- but a study that's specifically focused on patients over the age of 65, that was done for fesoterodine, right?

A That's correct. But a lot of those studies for the aging patients are post hoc analyses of subgroups of the patients in the studies.

Q Okay.

A So they're not designed specifically for elderly patients.

Q Are you aware of any post hoc analyses for drugs other than fesoterodine in the elderly?

A I'm not aware, but I'm --

MS. WOOTEN: Objection, form.

A They're -- I'm -- I would imagine that they're out there. I can't -- I can't quote you any at this time.

BY MR. OELKE:

Q Okay. We'll look at some of those

studies later.

Can you just look at the label that we just marked which is Exhibit 7.

A Yes.

Q You see this is the label for immediate release Detrol?

A Yes.

Q And if you look at the last page, it's dated March 1998?

A Yes.

Q If you look at the second page, which is PFE01843540.

A Okay.

Q There's a section there that says Variability in Metabolism in the second column. Do you see that?

A Yes.

Q It says, A subset (about 7 percent) of the population is devoid of cytochrome P450 2D6. Do you see that?

A Yes.

Q And is that consistent with your understanding, about 7 percent of the population is -- is poor metabolizers?

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A Yes. I mean, I think you have to subcategorize that a little bit. That's basically the Caucasian populations, less in Asians.

Q Okay. And it's also less in African-Americans, right?

A That's correct.

Q And less in Mexican Americans?

A Yeah, but I mean, Mexican Americans are a large variety of people. But in native -- native peoples, yes.

Q I was just looking at your report, that's where I got that --

A Oh, okay.

Q -- Mexican Americans. It says 3 to 6 percent of Mexican Americans.

A Right, right.

Q Okay. In any event, this section in the -- in the label, it says, Variability in Metabolism. It's talking about the poor metabolizers when it talks about that subset, right?

A Yes.

Q And that 7 percent subset is, as you say, for Caucasians, right?

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A Correct.

Q So it's actually a lower number for the overall population, correct?

A Yeah, if you --

Q Okay.

A -- include others.

Q It says, The identi -- the next sentence says: The identified pathway metabolism for these individuals, referred to as "poor metabolizers," is dealkylation via cytochrome P450 3A4 to N-dealkylated tolterodine. Do you see that?

A Yes.

Q The remainder of the population is referred to as extensive metabolizers. Right?

A Yes, uh-huh.

Q Now, this section talks about this variability between these two groups, the -- the extensive metabolizers and the poor metabolizers, right?

A Yes.

Q And at the end of that paragraph, it -- the last sentence says: Since tolterodine in the 5-hydroxymethyl metabolite have similar anti-muscarinic effects, the net activity of Detrol

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Tablets is expected to be similar in extensive and poor metabolizers. Do you see that?

A I do.

Q And so, according to the label for Detrol anyway, the net effect of this drug in extensive metabolizers and poor metabolizers was the same, right?

MS. WOOTEN: Objection, form.

A That's basically what they're saying, but as I say, there were no specific studies to document that, so I guess we don't totally know that. But that's -- that's the -- the FDA agreed with that as part of the package insert.

BY MR. OELKE:

Q Right. The FDA agreed with that conclusion, right?

A Yes, they did.

Q Okay. And if you look on the next page, PFE01843541, there's a section there entitled Drug-Drug Interactions. Do you see that?

A I do.

Q And it's talking about fluoxetine. Do you see fluoxetine?

A I do.

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Q Do you know what fluoxetine is?

A Yeah, it's an antidepressant, SSRI antidepressant.

Q Okay. And it's also a 2D6 -- it also works the 2D6 pathway, right?

A It's metabolized by 2D6 pathway, yes.

Q Okay. And so Pfizer did studies -- or the pharmacy at Upjohn at this time?

A Right.

Q Did studies on whether or not fluoxetine as a 2D6 inhibitor would have an effect on Detrol, right?

A Yes.

Q And in that paragraph, it states they did this in a study to assess the effect of fluoxetine on the pharmacokinetics of tolterodine and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine in extensive metabolizers. Right?

A Yes.

Q And then goes on to say -- I'm sorry -- resulting in a 4.8-fold increase in tolterodine AUC. And that's area under the curve, right?

A Correct.

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Q Okay. It goes on to say, there was a 52 percent decrease in Cmax and a 20 percent decrease in AUC of the 5-hydroxymethyl metabolite, right?

A Yes.

Q So concluded, fluoxetine thus alters the pharmacokinetics in patients who would otherwise be extensive metabolizers of tolterodine to resemble the pharmacokinetic profile in poor metabolizers. Right?

A Yes.

Q So if a patient is an extensive metabolizer, is prescribed tolterodine, is already on a CYP2D6 drug like fluoxetine, it's going to cause that patient to act like a poor metabolizer of tolterodine according to this?

A It does, yep. Yes.

Q But their conclusion is, No dose adjustment is required when Detrol and fluoxetine are co-administered, right?

A Yes.

Q And that's because the net activity for extensive metabolizers and poor metabolizers of tolterodine was judged to be the same by this

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label, right?

A Yes.

MS. WOOTEN: Objection, form.

A That's -- the FDA says, right, the label says.

BY MR. OELKE:

Q So there are other drugs that act through the CYP2D6 pathway where the -- the drug prior to metabolism doesn't act in the same way as the metabolite, right?

A Yes. I mean, there's a huge list of drugs that are metabolized by 2D6.

Q Right. And so, tolterodine is really in a different category than those drugs that don't, you know, prior to metabolism act on as a therapeutic, right?

MS. WOOTEN: Objection, form.

A Some of them have acting metabolites and some don't. And it depends on the drug.

BY MR. OELKE:

Q Right, right.

But in this case, Detrol or tolterodine acts in extensive metabolizers and poor metabolizers to give the same net activity, right?

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A Yes.

MS. WOOTEN: Objection, form.

A That's the information that we have, yes.

BY MR. OELKE:

Q Okay. And if you look at the adverse events reported for tolterodine which is on Page PFE01843544.

This table will list adverse events for patients that are either on placebo or on -- on the Detrol, right?

A Yes.

Q And it's 2 milligrams b.i.d. for Detrol, right?

A That's -- yeah, that's what they're using in this.

Q And that's -- that's taking 2 milligrams twice a day?

A Correct.

Q Okay. And that was the highest approved dose for tolterodine, right?

A For the -- for the immediate release, yes.

Q And even today for the immediate release, the highest approved dose is 4 milligrams, right?

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A Correct.

Q And for the extended -- for the long-acting version of Detrol, Detrol LA, the highest dose is 4 milligrams --

A 4 milligrams.

Q -- a day, right?

A That's correct.

Q Okay. So this table lists all the adverse events that were reported where that percentage is greater than 1 percent, right?

A Correct.

Q So any adverse event that's less than 1 percent isn't even recorded here, right?

A That's correct.

Q Okay. And that's consistent with how these are typically reported in a label, right?

MS. WOOTEN: Objection, form.

A Virtually all drugs are the same, yep.

BY MR. OELKE:

Q Okay. So the -- there are a number of different side effects listed here and many of them are not CNS side effects, right?

A Correct.

Q CNS is central nervous system, right?

A That's correct.

Q So which adverse events that are reported here relate to the central nervous system?

A Well, they have categorized central and peripheral nervous system, but also, if you include psychiatric which is central nervous system, nervous system somnolence I think are also central nervous system adverse events.

Q Okay. So for central/peripheral nervous there's paresthesia and vertigo/dizziness, right?

A Yes.

Q What is paresthesia?

A Paresthesia is like tingling.

Q And for paresthesia, the reported percentage of incidence for tolterodine is 1.1 percent?

A Yes.

Q And that's compared to 0.6 percent for placebo, right?

A Correct.

Q And for vertigo/dizziness, the -- the percentage for Detrol is 8.6 percent?

A That's correct.

Q But for placebo, it's even higher, it's

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9.1 percent?

A Correct.

Q And you mention the psychiatric adverse events. The two listed there are nervousness, do you see that?

A Yes.

Q And for -- for Detrol that's 1.1 percent?

A That's correct.

Q Compared to 0.6 percent for placebo?

A Correct.

Q And for somnolence it's 3.3 percent?

A I think it's 3.0 percent.

Q Right. Compared to 1.7 percent for placebo?

A Yes.

Q And what's somnolence?

A Somnolence is sleepiness.

Q Okay. So these are the -- the four reported CNS side effects for -- for Detrol on the label, right?

MS. WOOTEN: Objection, form.

A Yes. I don't think -- let me just look to be sure that none of the others are -- could be --

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BY MR. OELKE:

Q Okay.

A -- central nervous system, but I don't think -- and I looked at this before and I don't remember seeing any other culprits.

No, that -- that's basically -- those are the ones. I mean, fatigue could be, but they're the same, so...

Q So the -- the four that are reported here that you identify, would you consider any of those to be side effects to be concerned about based on these numbers?

A Probably the somnolence, I mean, it's almost doubled. The somnolence of placebo -- or of Detrol versus placebo, but still a small number, 3 percent.

Q Have you ever had patients that told you that it created somnolence to them when they were on tolterodine?

A Yes, but it's hard to know that that was the exact culprit because many of those patients are on polypharmacy. So is it that one that causes somnolence or is it something else they're taking?

Q Does fesoterodine have a better side

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effect profile for CNS side effects than this for tolterodine?

MS. WOOTEN: Objection, form.

A It does. But the head-to-head studies show pretty much the same CNS side effects for tolterodine and fesoterodine. There are little tweaks, you know, between the two, but they're not statistically significant.

BY MR. OELKE:

Q The -- the main side effect reported for tolterodine was dry mouth, right?

A Uh-huh, that's correct.

Q Okay. Now, this label came out in March of 1998. How quickly did Detrol become the -- a drug that was commonly used by urologists?

A It's hard to recall exactly, but my memory of it was very quickly because this alternative was far better than oxybutynin, so -- as far as side effects were concerned, and the efficacies were the same.

So I think urologists who tend to be pretty much up on what's happening with the overactive bladder community of patients adopted Detrol pretty quickly.

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Q Now, you say Detrol had the same efficacy as -- as Ditropan. Was that -- was that ever established in any head-to-head studies?

A Yeah, there are head-to-head studies of that. There's a study by Paul Abrams --

Q Right.

A -- that looked at head-to-head.

Q And was -- was Detrol determined to be -- have the same therapeutic efficacy as oxybutynin by those?

A In frequency, yes. In urgence -- urgent incontinence, actually, oxybutynin was a bit better.

Q Right.

A But the side effects were far better with -- with Detrol.

Q Right. So for patients that were extensive metabolizers who were not on other CYP2D6 drugs, there would have been no reason to look to 5-HMT as a -- as a starting point for those patients, right?

MS. WOOTEN: Objection, form.

A No, I think there are reasons. I think the CNS issue is a -- is a reason even though, you

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know, that -- that's a small number of people that complain of CNS issues.

And the other thing is the -- the protein binding of -- of tolterodine versus 5-HMT. So the bioavailability is different.

So I think there are -- I think there are still reasons.

BY MR. OELKE:

Q But the CNS and extensive metabolizers would be attributable to the 5-HMT, right, not to tolterodine?

MS. WOOTEN: Objection, form.

A I don't know that you can say that. The 5-HMT clears the central nervous system more rapidly than tolterodine because of the P-gp system.

BY MR. OELKE:

Q That wasn't known in 1998, right?

A Well, the P-gp system was known.

Q Right.

A I mean, it's been studied for 50 years, but it wasn't known that that was a clearance issue in 1998 that I know of. And it wasn't -- at least there's nothing in the literature about it.

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Q Right. In fact, it was determined that 5-8 -- I'm sorry, that tolterodine was a P-gp --

A Substrate.

Q -- substrate? Thank you. Acted through a P-gp substrate mechanism, right?

A Yes.

Q In the late 2000s, right?

A Yes.

Q Okay. Prior to that, there was no knowledge that tolterodine could cause CNS effects because of P-gp, right?

A Yeah.

MS. WOOTEN: Objection, form.

A That wasn't -- hadn't been studied at that stage.

BY MR. OELKE:

Q Okay. And if you look at this label, there's nothing in this label that would indicate that any of these CNS side effects were attributable to tolterodine rather than 5-HMT, right?

A It's -- it's not --

MS. WOOTEN: Objection, form.

A -- not determined. It's not...

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BY MR. OELKE:

Q And was that ever teased out for tolterodine?

A As far as whether it was 5-HMT or the tolterodine that was causing the -- the issues?

Q Let -- let me ask the question. You're right, let me get it on the record.

A Okay, please.

Q For tolterodine, was it ever determined whether CNS side effects were attributable to 5-HMT or to tolterodine?

A No.

Q And there's nothing in the Detrol label that would indicate which of these side effects are attributable to 5-HMT and which are attributable to tolterodine, right?

A There are not.

Q Okay.

MR. OELKE: I would like to mark as an article entitled Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of a detrusor hyperreflexia by H. Madersbacher and others.

(Deposition Exhibit 8 marked.)

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THE WITNESS: Thank you.

BY MR. OELKE:

Q Have you seen this article before?

A I have seen it, yes. It's one of the few papers that actually looked at urodynamic changes. Most of the -- most of the studies are patient reported outcomes.

Q Right. And this is a -- a study that considered trospium versus oxybutynin, right?

A Yes.

Q And the -- the doses that were studied were for trospium chloride was two times -- 20 milligrams twice a day; is that right?

A That's correct.

Q And for oxybutynin, it was 5 milligrams three times a day?

A Correct.

Q And why were those two different dosages studied against each other?

A Oxybutynin and 5 t.i.d. was the established dose in that -- in those -- in those days, so that was kind of a standard clinical dose.

The 20 milligrams of -- of trospium was chosen, I -- I assume and I don't know why because

this was before it was approved, at least in the U.S.

I assume that was the -- the dose that they were targeting for -- for a clinical use.

Q You understand that those are the -- the highest approved doses for those drugs?

A Yes.

Q So this is a study of the highest approved doses of trospium versus oxybutynin?

A Yes, correct.

Q And is that an appropriate study to compare the highest dose of two drugs?

A Absolutely.

Q Okay. And the conclusion was that trospium chloride and oxybutynin judged in terms of objective urodynamic parameters are of substantially equal value as parasympathetic antagonists. Do you see that?

A Yes.

Q However, assessment of tolerance in terms of adverse drug effects showed that the trospium chloride had certain advantages, right?

A Yes.

Q Those advantages were largely because of

dry mouth?

A Dry mouth, correct.

Q Okay.

A Had other side effects, but dry mouth was the predominant one.

Q Okay. Now, does urodynamic parameters, just generally, how are those studied?

A I mean, urodynamics is basically a study of bladder function and it's done in a variety different ways.

Usually with a catheter in the bladder and the -- and pressure sensors and -- and nerve sensors and the bladder is filled and emptied and the response of the bladder to that filling and emptying is -- is recorded. So that's basically the -- kind of what urodynamics is.

And so it evaluates contraction of the bladder in both normal and abnormal.

It also -- it also registers the tone of the bladder, meaning the underlying contractility or compliance of the bladder.

So that -- that's kind of the most scientific way of seeing what a drug effect on the bladder are.

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Q Okay. But you said most of these studies instead focus on diary entries by the patients, right?

A Correct.

Q Why are there more studies in diary entries versus urodynamics?

A No. 1, they're easier.

No. 2 thing is that the FDA is very interested in patient-reported outcomes.

No. 3 thing, at the end of the day if the drug is safe, it's really what the patient perceives as the effect that's the most important effect.

Q Okay. Now, the -- if you look on Page 75 which is PFE01844309.

It shows there two paragraphs from the bottom in the right-hand column: Withdrawal from the trial occurred more frequently in patients taking oxybutynin (No. 7, 16 percent) than in those taking trospium chloride (No. 3, 6 percent.) Do you see that?

A Yes.

Q Furthermore, the Oxy patients withdrew earlier (after an average of 7.1 days) than the