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Transcript of Jason T. McConville, Ph.D.

Date: August 15, 2024

Case: Intas Pharmaceuticals Ltd. -v- Atossa Therapeutics, Inc. (PTAB)

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WORLDWIDE COURT REPORTING & LITIGATION TECHNOLOGY

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2
3 BEFORE THE PATENT TRIAL AND APPEAL BOARD

4
5 INTAS PHARMACEUTICALS LTD.,

6 Petitioner,

7 v.

8 ATOSSA THERAPEUTICS, INC.,

9 Patent Owner.

10
11 Case PGR2023-00043

12 Patent No. 11,572,334

13
14
15 REMOTE DEPOSITION OF
16 JASON T. MCCONVILLE, PH.D.

17 Thursday, August 15, 2024

18 7:59 a.m. Pacific

19
20 Reported by:

21 Janice M. Kocek, CSR, CLR

22 Job No. 547833

1 The remote deposition of JASON T.
2 MCCONVILLE, PH.D., via Zoom videoconference,
3 reported stenographically by Janice M. Koczek,
4 License No. 084-002871, Certified Shorthand
5 Reporter, Certified LiveNote Reporter, and Notary
6 Public of the State of Illinois, commencing at the
7 hour of 7:59 a.m. Pacific, on Thursday,
8 August 15, 2024.

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I N D E X

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E X H I B I T S

EXHIBIT	DESCRIPTION	PAGE
Exhibit 1003	United States Patent 9,333,190 B2	11
Exhibit 1006	Nature Publishing Group, Article by Ahmad, et al.	91
Exhibit 1007	Journal of Clinical Oncology, Article by Ahmad, et al.	91
Exhibit 1026	"HPMC as Capsule Shell Material: Physicochemical, Pharmaceutical and Biopharmaceutical Properties" - Majee article	15
Exhibit 1027	"A novel hypromellose capsule, with acid resistance properties, permits the targeted delivery of acid-sensitive products to the intestine" - Marzorati article	16

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E X H I B I T S

EXHIBIT	DESCRIPTION	PAGE
Exhibit 1028	"HPMC Capsules: Current Status and Future Prospects" - Al-Tabakha article	18
Exhibit 1029	"Biopharmaceutical Evaluation of Orally and Rectally Administered Hard Hydroxypropyl Methylcellulose Capsules" - Honkanen article	18
Exhibit 1031	United States Patent 9,333,190 B2	11

1 EXHIBIT TECHNICIAN: Thank you to
2 everyone for attending this proceeding
3 remotely, which we anticipate will run
4 smoothly.

5 Please remember to speak slowly
6 and do your best not to talk over one
7 another.

8 Please be aware that we are
9 recording these proceedings for backup
10 purposes.

11 Any off-the-record discussions
12 should be had away from the computer. And
13 please remember to mute your mics for those
14 conversations.

15 Please have your video enabled
16 to help the reporter identify who's
17 speaking. If you are unable to connect
18 with video and are connecting via phone,
19 please identify yourself each time before
20 speaking.

21 We will provide a complimentary
22 unedited recording of this deposition with

1 the purchase of a transcript. I apologize
2 in advance for any technical difficulties.
3 Thank you.

4 (Witness remotely sworn.)

5 MS. KRUMPLITSCH: And we've got
6 Susan Krumplitsch on behalf of Atossa. And
7 with me are my colleagues from DLA Piper,
8 Melissa Harwood and Emma Holland.

9 MR. MENCHACA: Alex Menchaca on
10 behalf of Intas.

11 JASON T. MCCONVILLE, PH.D.,
12 called as a witness herein, having been first duly
13 sworn, was examined and testified as follows:

14 EXAMINATION

15 BY MS. KRUMPLITSCH:

16 Q. Good morning, Dr. McConville.

17 A. Hi.

18 Q. Before we get started since we are
19 doing this over Zoom, I just want to confirm, is
20 there anyone else -- first of all, where are you
21 right now?

22 A. I booked into a hotel in Albuquerque.

1 So it's -- and they've got a little office space
2 in it and just alone on my own.

3 Q. Okay. And do you have any papers with
4 you today?

5 A. Yes, I have a copy of my original
6 declaration and then the responsive declaration
7 that was sent to you.

8 Q. Okay. And the responsive declaration
9 that you have, do you have any notes on that or is
10 it just a clean copy?

11 A. They're both clean copies.

12 Q. Okay. Fantastic.
13 Did you prepare for your deposition
14 today?

15 A. Yes, a little. I looked at my
16 transcript -- sorry, declarations, my transcript
17 as well, and the patent-in-suit also.

18 Q. Did you meet with anyone to prepare for
19 this deposition?

20 A. Alex and I had a brief Zoom meeting. I
21 think it was two days ago. I was teaching
22 yesterday. So schedules, you know.

1 Q. Has school started for you again?

2 A. That's right. I started teaching on
3 Monday, which is why unfortunately we have to have
4 this remotely. So thank you for that.

5 Q. No problem. We appreciate it. I
6 understand how busy everyone's schedule is at this
7 time of the year.

8 So in preparing for your deposition,
9 you met with your lawyer for -- for a bit over
10 Zoom. You reviewed your declarations, your
11 opening declaration and your reply declaration.

12 Did you say that you also reviewed the
13 transcript of your last deposition?

14 A. I -- I took a brief look at it just to
15 prompt myself with, you know, how I had set up
16 preparing the responsive declaration.

17 Q. Okay. And you mentioned that you also
18 reviewed the patents.

19 Did you review the '334 patent that's
20 at issue in this case?

21 A. Yes, that's it.

22 Q. Did you review any other materials?

1 A. Not -- not really, no. I just relied
2 on my declarations.

3 Q. Okay. Did you speak with Dr. Bihovsky
4 yesterday?

5 A. I'm -- I'm not -- no, I -- I didn't. I
6 don't know him.

7 Q. Have you ever spoken with Dr. Bihovsky?

8 A. No.

9 Q. Okay. And you were deposed in this
10 matter I think a few months ago. The same rules
11 apply even though we're doing this over Zoom. So
12 we'll take turns talking.

13 We will be spending a lot of time
14 looking at your expert report. So feel free to
15 use the paper copy in front of you. That might be
16 easier. But it will also be on the screen if you
17 need it.

18 A. Okay. Thank you.

19 (McConville Deposition Exhibit 1031
20 was introduced for identification.)

21 BY MS. KRUMPLITSCH:

22 Q. So let's start with Exhibit 1031, which

1 is the reply expert declaration of Jason
2 McConville, Ph.D.

3 EXHIBIT TECHNICIAN: Stand by.

4 Exhibit should be in the chat
5 and I'm putting it on the screen right now.

6 MS. KRUMPLITSCH: Thank you. Great.

7 And is everyone able to see the
8 exhibit?

9 THE WITNESS: Give me just one
10 second. I'm figuring out where just to put
11 these, to create a little place. I'll open
12 it up as well. I have a separate screen to
13 put the exhibits on also.

14 BY MS. KRUMPLITSCH:

15 Q. Great.

16 A. Okay.

17 Q. Okay. So if you could turn to page --
18 and, again, if it's easier to do in paper copy,
19 whatever is easier for you, Dr. McConville.

20 A. Okay. Thank you.

21 Q. Page 25 of your declaration, which is
22 page 27 of the PDF.

1 A. Okay.

2 Q. And, Dr. McConville, is that your
3 signature?

4 A. It is, yes.

5 Q. Do you recall when you prepared this
6 declaration?

7 A. So I guess it was early last month.

8 Q. How long did you spend preparing your
9 reply declaration?

10 A. Well, I initially went through my
11 transcript, as I said. And I essentially made
12 quite a lot of notes, I think that took me a
13 couple of days to go through that and -- and, you
14 know, outline what I wanted in this declaration.
15 And then from that created a draft essentially,
16 which went back and forth a couple of times.

17 So, you know, altogether it wasn't day
18 after day this happened. So, you know, a couple
19 of weeks or so, three weeks maybe. I can't recall
20 the exact timing of things.

21 Q. Okay. Other than reviewing your
22 deposition transcript from your first deposition,

1 did you review any other materials in preparing
2 this reply report?

3 A. Only would have had a look at exhibits
4 again that may be referenced. I also looked at
5 Dr. Davies' responsive report as well.

6 Q. Are there -- did you review any
7 materials in preparing your reply declaration that
8 are not discussed in your reply declaration?

9 A. No.

10 Q. So you identified in your reply
11 declaration -- I always think these things are
12 easier to do in person.

13 You identified in your reply
14 declaration some new materials. Those are
15 articles by Majee, Marzorati, Al-Tabakha, and
16 Honkanen. I'm sure I butchered all of those
17 names.

18 How did you find each of these
19 exhibits?

20 A. Essentially I think these were linked
21 to just some of the arguments that I was trying to
22 either rebut or clarify. And in some cases I

1 would use possibly Google Scholar and put a date,
2 a search date, as cap on it in those situations.
3 You know, pretty much that's how I find things,
4 yeah.

5 Q. Okay. So for each of these four new
6 exhibits -- references, these are references that
7 you found or were these references that counsel
8 provided to you?

9 A. So I -- if we can have a look at any
10 specific references, I could maybe clarify that.
11 You know, the -- as you said with the names. So
12 it's very difficult to remember exactly what
13 article they were. So, you know, we can have
14 clarifications as we go through if you'd like.

15 Q. Well, let's just do that now.

16 MS. KRUMPLITSCH: Can we pull up
17 Exhibit 1026 if you have that?

18 EXHIBIT TECHNICIAN: Stand by.

19 (McConville Deposition Exhibit 1026
20 was introduced for identification.)

21 MS. KRUMPLITSCH: And this -- that
22 was very fast.

1 BY MS. KRUMPLITSCH:

2 Q. And this is the Majee reference.

3 Dr. McConville, do you recognize
4 Exhibit 1026?

5 A. Yes. Now, let me think about this one.
6 Where this may have -- well, actually in this
7 situation, I'm sorry to say, I think -- you know,
8 I have a -- I have a discussion about HPMC. We
9 talked about this at the last deposition. And I
10 believe I was searching for articles related to
11 the applicability of HPMC to be used overall. So
12 this could have been one that I -- I searched for.

13 But I do know that, you know, on this
14 theme that counsel were looking also for articles
15 in the right time period based on what I had
16 instructed them to look for.

17 MS. KRUMPLITSCH: Okay. And let's
18 take a quick look at Exhibit 1027, if we
19 could pull that one up.

20 EXHIBIT TECHNICIAN: Stand by.

21 (McConville Deposition Exhibit 1027
22 was introduced for identification.)

1 BY MS. KRUMPLITSCH:

2 Q. Dr. McConville, Exhibit 1027 is an
3 article by Marzorati.

4 A. Uh-huh.

5 Q. Do you recognize this exhibit?

6 A. Yes. And I would say the same thing.
7 During that search for HPMC, or hypromellose,
8 capsules. They may have been a bit of overlap
9 between me and counsel. And I'm sorry to say that
10 I thought I'd be able to be specific but lots of
11 articles, you know, pop up in the search. And you
12 have to pick and choose in those situations.

13 Q. Okay. So is it fair to say you can't
14 recall whether or not you or counsel identified
15 Exhibit 1027?

16 A. I mean, I -- so I know that it has the
17 information that I'm looking for. And it's, you
18 know, referenced in my declaration. Specifically
19 I -- you know, I think this sort of argument came
20 first, the response came first. And I knew there
21 was information in the literature about that. And
22 I can't remember specifically whether I had pulled

1 this one out and sent this one or not.

2 MS. KRUMPLITSCH: Okay. Let's take
3 a look at 1028, Exhibit 1028.

4 EXHIBIT TECHNICIAN: Stand by.

5 (McConville Deposition Exhibit 1028
6 was introduced for identification.)

7 BY MS. KRUMPLITSCH:

8 Q. Okay. Dr. McConville, do you recognize
9 Exhibit 1028, which is an article by Al-Tabakha?

10 A. Yes. So I'm trying really hard to
11 think again. So I remember looking at this one
12 even several years ago as well and thinking about
13 manufacture of HPMC capsules.

14 So I don't know whether -- again, same
15 thing, I have to say I don't know whether I pulled
16 this one up recently or not.

17 MS. KRUMPLITSCH: Okay. And then
18 let's look at the last of new exhibits,
19 which is Exhibit 1029.

20 EXHIBIT TECHNICIAN: Stand by.

21 (McConville Deposition Exhibit 1029
22 was introduced for identification.)

1 BY MS. KRUMPLITSCH:

2 Q. Exhibit 1029 is an article by Honkanen.

3 Do you recognize Exhibit 1029,
4 Dr. McConville?

5 A. Sorry. I'm -- yeah, I think I -- I'm
6 pretty sure I pulled this one out because it's a
7 dissertation. And, you know, I know these are
8 lengthy articles, citations sometimes. So, you
9 know, I'm pretty sure I pulled this one out.

10 Q. Is this one that you had found on
11 Google Scholar?

12 A. I believe so, yes. Sometimes I might
13 just do a blanket search using just Google itself
14 as well and that comes up with different hits. Or
15 I've used SciFinder Scholar to -- you know, I
16 don't know where -- whether this -- you end up
17 with 20, 30 tabs at the top of the computer
18 screen. I -- I -- yeah.

19 Q. Okay. Let's go back to your -- your
20 reply declaration, Exhibit 1031. And I'm going to
21 direct you to paragraph 4, which is on the first
22 page of your -- the text of your declaration.

1 And I'll give you a minute to orient
2 yourself and look at paragraph 4.

3 (Witness reviewing document.)

4 THE WITNESS: Okay. Yes.

5 BY MS. KRUMPLITSCH:

6 Q. So you state here in the third and
7 fourth line that (as read): Nothing in Liu
8 suggests that the API could not have been used in
9 an oral formulation.

10 Do you see that?

11 A. Yes.

12 Q. Actually, let me pause there.

13 In reviewing your reply declaration for
14 this deposition, did you find any errors or any
15 corrections that you'd like to make?

16 A. I mean, not -- not at this point. I
17 mean, there might be one or two typos looking
18 through. But, you know, I'll clarify anything if
19 necessary to you.

20 Q. Okay. So you stand by the opinions as
21 they are presented in your reply deposition?

22 A. I do, yes.

1 Q. So turning back to Liu, you state that
2 nothing in Liu suggests to you that the API could
3 not have been used in an oral formulation.

4 A. Yes.

5 Q. And my question is: When did you
6 review the Liu publication?

7 A. That was during the period of preparing
8 my initial declaration, I believe.

9 Q. Did you go back and review Liu as part
10 of preparing your reply declaration?

11 A. I'm trying to think now whether -- I
12 know we had it out as an exhibit during the
13 deposition. And I think that -- I think that, you
14 know, the point I'm making is that based on what
15 we discussed I have no reason to believe the API
16 couldn't be used in an oral formulation.

17 Q. Okay. And when you say "based on what
18 we discussed," do you mean based on our discussion
19 at our last deposition?

20 A. Yes, yes. And -- and also what I
21 recalled from the Liu publication as well.

22 Q. Okay. Did you review the entire Liu

1 publication?

2 A. Prior to deposition, yes, I did. And
3 I'm trying to think now. Maybe I looked at
4 specific sections related to what we had
5 discussed. So, for example, here we're talking
6 about the recrystallization I believe and, you
7 know, that's really what this paragraph is
8 directed towards.

9 Q. Now, Liu does not describe using the
10 endoxifen that results from the Liu synthetic
11 process as a drug substance, correct?

12 A. Well, I sort of disagree. I mean, the
13 whole point of manufacturing an API is -- as --
14 you know, is ultimately to be used for therapy, a
15 drug substance.

16 Q. Liu does not characterize the endoxifen
17 that's synthesized using the synthetic method
18 described in the publication as an API, correct?

19 A. I mean, a person of ordinary skill
20 knows that it's an API. I don't necessarily think
21 that Liu has to highlight that.

22 Q. So you agree with me that Liu does not

1 describe the endoxifen resulting from the
2 synthetic process described therein as an API?

3 A. There's plenty of other art that
4 teaches that it's an API. So I think Liu assumes
5 everyone would know that. Obviously I can't speak
6 for Liu specifically. But that would be my
7 opinion.

8 Q. So, again, Dr. McConville, with all due
9 respect, I just want to get a clean yes or no.

10 Do you agree that Liu does not describe
11 the endoxifen created as a result of the Liu
12 synthetic process as an API, correct?

13 A. Again, I would say I think it's
14 understood that it's an API. I can't specifically
15 remember whether Liu characterizes it one way or
16 another.

17 Q. And why do you say it is understood to
18 be an API?

19 A. Because it's an active pharmaceutical
20 ingredient and it was known at the time of the Liu
21 publication.

22 Q. Okay. So let's tease that apart a

1 little bit.

2 What was known at the time of the Liu
3 publication?

4 A. That endoxifen was useful for the
5 therapeutic purposes that are described elsewhere.

6 Q. And so that is the basis for your
7 opinion that Liu describes an API?

8 A. I think it was already known as an API,
9 you know, as -- before Liu described his methods.

10 Q. What does Liu -- what is the resulting
11 product produced by Liu?

12 A. Endoxifen.

13 Q. Can you be more specific?

14 A. Yeah, Liu talks about the purification
15 of (Z)-endoxifen.

16 Q. And so it's your testimony that prior
17 to Liu, there were descriptions of 90 percent pure
18 (Z)-endoxifen used as an API?

19 A. Whatever the amount, I think there was
20 descriptions of (Z)-endoxifen being more active.
21 So, you know, with Liu highlighting the
22 purification steps of it, I think that it would

1 have been understood, whatever amount it was in,
2 as it being an API, yes.

3 Q. So is the answer to my question, no,
4 you can't point to a single location that
5 describes a 90 percent (Z)-endoxifen used in a
6 pharmaceutical?

7 A. Well, I mean, I can't specifically find
8 a reference that discusses that. I mean, there's
9 references that discuss the use of endoxifen. It
10 was well known that the (Z)-endoxifen was more
11 active. So obviously a person of ordinary skill
12 would -- would think to use the -- the more active
13 pure form I think.

14 Q. You said you can't point to a
15 publication that describes a 90 percent
16 (Z)-endoxifen.

17 Did you look?

18 A. I mean, I've got several examples in
19 the paper we've got. I mean, for example, Ahmad
20 talks about 90 percent (Z)-endoxifen as well for
21 therapeutic use.

22 Q. Other than Ahmad, any other references

1 come to mind?

2 A. Well, I mean, we can go through, I
3 mean, and look at -- at the other -- there's other
4 -- well, the various Ahmad publications, if you
5 like, describe the use of (Z)-endoxifen.

6 Q. It's your testimony that Ahmad 2010 and
7 Ahmad 2012 describe the use of (Z)-endoxifen?

8 A. Yeah.

9 Q. Would it surprise you to know that
10 Dr. Bihovsky testified yesterday that Ahmad 2010
11 and Ahmad 2012 do not describe a specific ratio of
12 (E)- to (Z)-isomers?

13 A. Well, I -- I do understand that there's
14 no specific ratio described. But I think Ahmad
15 describes the purity as being preferable for use.
16 So greater than 80 percent, greater than 90
17 percent.

18 Q. Okay. So I just want to make sure that
19 I understand your testimony.

20 Ahmad, the patent you're referring to
21 says greater than 80 percent, greater than 90
22 percent, correct?

1 A. Yeah. That's correct, yes.

2 Q. And Ahmad 2010 and Ahmad 2012 do not
3 discuss any purity level of (E)- or (Z)-isomer,
4 correct?

5 A. Not -- not one way or the other.
6 That's -- that's right. We don't know
7 specifically what Ahmad has used. But we do know
8 that the -- the patent prior to that did describe
9 a high purity of (Z)-endoxifen. And Ahmad
10 describes a therapeutically effective amount of
11 (Z)-endoxifen as well -- or endoxifen. Sorry.

12 Q. And to be clear, you're referring to
13 Ahmad 2010 and Ahmad 2012? I just want to make
14 sure that the record is clear.

15 A. In terms of the therapeutic amount,
16 yes.

17 Q. And, again, those two references do not
18 describe whether it is (Z)-endoxifen,
19 (E)-endoxifen, or a mix between the two, correct?

20 A. Yes, but a person of ordinary skill
21 would assume that the (Z)-endoxifen is, you know,
22 more efficacious. And so it would be applicable

1 in the ranges described in the Ahmad 2010 and
2 2012, of course.

3 Q. Okay. Turning back to Liu, Liu does
4 not describe using any endoxifen in a
5 pharmaceutical formulation, correct?

6 A. Well, like I said before, Liu describes
7 the manufacture of an API. And, you know, a
8 person of ordinary skill would assume that the --
9 the use of the API was for therapeutic means. And
10 also a person of ordinary skill would probably
11 look to an oral formulation, too, because this is
12 the most commonly used, you know, dosage form.

13 Q. Dr. McConville, with all due respect,
14 my question was a simple one.

15 Liu does not describe using -- this is
16 the Liu reference itself.

17 Within the Liu reference, is there any
18 description of using endoxifen that results from
19 the Liu synthetic method in a pharmaceutical
20 formulation?

21 MR. MENCHACA: Objection. Asked and
22 answered.

1 THE WITNESS: I mean, I just think
2 that a person of ordinary skill reading Liu
3 would have this in their mind. That's all.

4 Whether Liu explicitly needs to
5 describe a particular dosage form, he's
6 describing the manufacture of an active
7 pharmaceutical ingredient. Of course it's
8 going to be used in a dosage form.

9 BY MS. KRUMPLITSCH:

10 Q. Do you know what residual solvents are
11 present in the endoxifen produced by the Liu
12 synthetic method?

13 A. I -- I don't know what residuals of
14 them there might be.

15 Q. Do you know what impurities are present
16 in the endoxifen produced by the Liu synthetic
17 method?

18 A. I do not know what impurities there
19 are.

20 Q. Wouldn't a person of ordinary skill in
21 the art want to know what residual solvents and
22 impurities are present in considering whether or

1 not the substance could be used in a
2 pharmaceutical formulation?

3 A. Yes, of course they would.

4 Q. Turning to the second half of paragraph
5 4, which is on the next page.

6 I'll give you a second to look at that.

7 A. Okay. I am there.

8 Q. We're on page 2 of your declaration.

9 A. Yes.

10 (Witness reviewing document.)

11 THE WITNESS: Okay. Yes.

12 BY MS. KRUMPLITSCH:

13 Q. Okay. And you'll see here in the
14 second half of paragraph 4 on page 2 you state in
15 the middle that have paragraph (as read): I see
16 no reason that API made by Fauq could not have
17 been used for oral formulations.

18 Do you see that sentence?

19 A. Yes.

20 Q. When did you learn about the Fauq
21 reference?

22 A. This -- this reference may have been

1 one indicated in Dr. Davies' response possibly. I
2 can't recall exactly where that -- where that was
3 from.

4 Q. Do you recall the substance of the Fauq
5 reference?

6 A. Exactly as there. I mean, it talks
7 about the use of endoxifen for preclinical and in
8 vitro analysis.

9 Q. Do you recall what method Fauq used to
10 prepare the endoxifen preparation?

11 A. I think it was a recrystallized method
12 or -- or some other purification method. But I --
13 so there was a purification method involved.

14 Q. When did you review Fauq?

15 A. I really can't recall. I'm sorry.

16 Q. Do you recall whether you reviewed the
17 entire reference?

18 A. Well, I think I did. I can't -- I
19 mean, if we -- if we looked at it again, I might
20 have more of an idea.

21 Q. And, again, you are describing the
22 endoxifen preparation made by Fauq as an API in

1 your reply declaration, correct?

2 A. Yes, exactly. I mean, again, I think
3 the POSA would have that understanding.

4 Q. And did Fauq describe the endoxifen
5 prepared via the synthetic method in Fauq as an
6 API?

7 A. I'm sorry. Could you repeat that?

8 Q. Did Fauq use the phrase "API" in
9 describing the endoxifen that was prepared within
10 that reference?

11 A. I mean, it's an active pharmaceutical
12 ingredient whether he used that explicit phrase or
13 not. So it would be well understood that that's,
14 you know, what -- what was being described.

15 Q. Do you recall how much endoxifen was
16 made using the procedure of Fauq?

17 A. I don't.

18 Q. Well, I can represent to you that it
19 was 200 milligrams of endoxifen.

20 Does that sound familiar?

21 A. Okay.

22 Q. So practically speaking, 200 milligrams

1 of a compound is not enough to be used to create a
2 pharmaceutical formulation, correct?

3 A. 200 milligrams?

4 Q. 200 milligrams.

5 A. I mean, it depends on the -- you know,
6 the effectiveness of a particular dose. But 200
7 milligrams sounds a reasonable amount or -- it
8 depends on the potency of the drug, of course, and
9 you know, its effectiveness.

10 Doing -- are you talking about multiple
11 daily dosing regimen or a single dose or -- or
12 twice daily? I can't -- I don't know what you
13 mean.

14 Q. Is 200 milligrams of endoxifen enough
15 to complete preclinical studies?

16 A. Well, I mean, possibly for some types
17 of preclinical studies.

18 Q. Let me be more clear.

19 Is 200 milligrams sufficient to
20 complete all the preclinical studies that would be
21 needed to create a pharmaceutical formulation?

22 A. Yes.

1 Q. 200 milligrams would be sufficient to
2 create -- to complete all preclinical studies
3 necessarily -- necessary to make formulation?

4 A. Well, that's a different question. I
5 mean, all preclinical studies -- no, I mean, I
6 guess he might do another batch manufacture. I
7 don't see that it's limited by the amount that's
8 in the paper.

9 Q. And, again, do you have a recollection
10 of what methodology Fauq used to create that 200
11 milligrams of endoxifen?

12 A. Well, not exactly. I mean, this --
13 that sort of thing I may have glanced at. But
14 really, it's a chemistry question, again, you
15 know, like...

16 Q. And do you have understanding as to
17 whether it's possible to scale up the process in
18 Fauq to create more than 200 milligrams or is that
19 beyond the expertise that you're an expert in?

20 A. Well, it's my understanding that scale
21 up is -- is just another -- you would have a
22 different type of person of ordinary skill I guess

1 for that amount of approach. But it's my
2 understanding that it's pretty common that these
3 types of synthesis processes can be scaled up, you
4 know, one way or another.

5 Q. But you don't have any specific
6 expertise in the type of process that Fauq used
7 and whether or not that could be scaled up?

8 A. It's a manufacturing technique. So I
9 could imagine it could be scaled up. I don't have
10 any specific expertise in doing so, no.

11 Q. Do you know what impurities are present
12 in the endoxifen produced by the Fauq method?

13 A. I don't.

14 Q. And Fauq does not describe using the
15 resulting endoxifen in any specific formulation,
16 correct?

17 A. I mean, Fauq describes it could be used
18 for animal and tissue studies. So you get an idea
19 that it must have been administered in some way to
20 an animal.

21 You know, I've done this sort of thing
22 in my lab by doing oral gavage methods with

1 rodents, for example. And that would be making a
2 little capsule or so. Or, you know, even, you
3 know, at the minimal, there might be intravenous
4 or an intraperitoneal administration early on.

5 But this is standard process for drugs.
6 At some point a human would have to take it after
7 an animal study, after a preclinical study. And
8 that -- that would lead you to thinking about an
9 oral dosage form usually.

10 Q. So is it fair to say that a person of
11 ordinary skill in the art might consider different
12 types of administrative routes, especially in the
13 animal preclinical studies? You mentioned
14 intraperitoneal, intravenous, oral gavage.

15 But you would agree with me that Fauq
16 does not describe any specific formulation,
17 correct?

18 A. It's just describing the API. And, you
19 know, it would be up to the person of ordinary
20 skill to start thinking about oral formulations,
21 which are the most commonly used.

22 Q. Okay. So in your declaration, you

1 point to Liu that we just talked about and you
2 point to Fauq.

3 Why are you relying on Liu and Fauq
4 rather than Liu and Song?

5 A. Well, I think that -- think that the
6 Song article was flawed, if I remember correctly,
7 in terms of the synthetic pathways. So, you know,
8 at that time I didn't know that, as I'm not a
9 chemist. You know, I couldn't identify that
10 issue.

11 But, you know, Dr. Davies I think
12 correctly pointed out that Song's -- I think the
13 purification step was flawed. I can't remember
14 exactly which part of it was flawed.

15 Although, you know, Song obviously
16 talks about the therapeutic use of (Z)-endoxifen.
17 So, you know, from that respect it was useful
18 because it was obviously known in the art at the
19 time.

20 Q. You would agree with Dr. Davies though
21 and Dr. Bihovsky, who testified yesterday I'll
22 represent to you, that Song made (E)-endoxifen not

1 (Z)-endoxifen?

2 A. Okay. I mean, I really -- I have to
3 agree -- defer to the expertise there really.

4 Q. And staying with paragraph 4 of your
5 reply declaration, you state that (as read):
6 Ali -- another reference -- uses benzene as a
7 solvent.

8 Do you see that sentence? It's at the
9 very top.

10 A. Yeah, yeah, sure.

11 Q. And you -- you write that you (as
12 read): Agree with Dr. Davies that this would
13 render it unsuitable for use in an oral
14 formulation.

15 Correct?

16 A. Well, only -- only so much, you know.
17 Just to clarify what -- what I mean here, if there
18 is residual benzene, which is above the tolerable
19 threshold, then, yeah, of course.

20 So I think that in these cases, that
21 sort of solvent would be switched out in any kind
22 of scaleup or manufacturing process. But the

1 principle is there, that you can purify endoxifen
2 using a solvent system. And I think it's pretty
3 straightforward to sub out benzene, as it has been
4 done in many, many chemical pathways for decades.

5 Q. And, again, Dr. McConville, in this
6 same paragraph you state that you are not an
7 organic chemist and you cannot speak to the
8 synthetic methods described in these papers,
9 correct?

10 A. Yeah, I mean, I can only generally give
11 my opinion. And, you know, generally agree that
12 benzene is not an ideal solvent to use. And it
13 would be worth substituting that out and still
14 maintaining the synthesis method.

15 Q. Is -- sorry. Are you done?

16 A. Yes.

17 Q. Is -- is that because benzene is a
18 Class 1 solvent?

19 A. So by that I guess you mean it's got
20 toxic implications, yeah.

21 Q. Do you know which solvents could be
22 substituted for benzene?

1 A. I don't. I'm not a chemist.

2 Q. Are you familiar with whether
3 1,2-dichloroethane is acceptable for use in an
4 oral formulation?

5 A. I -- I really -- I would have to look
6 at what would be acceptable or not. You know, off
7 the cuff, I wouldn't like to comment.

8 Q. And if we wanted to look that up, where
9 would a person of ordinary skill in the art go to
10 find that information?

11 A. There's likely to be some FDA guidance
12 on -- on that information. And I haven't looked
13 at that.

14 Q. Does the FDA publish a list of Class 1
15 solvents?

16 A. It's likely there's a repository of
17 information related to that, yeah.

18 Q. And would you agree with me that a POSA
19 would understand to avoid the use of Class 1
20 solvents in the synthesis of active pharmaceutical
21 ingredients?

22 A. I -- I would think that that's

1 generally the case. But as I said, from a
2 benchtop system of manufacturing an API, I think
3 that those sort of solvents that are used on the
4 benchtop such as benzene are often substituted
5 out, I mean, to -- to make it applicable for a
6 pharmaceutical product.

7 Q. And just to be clear, you can't tell me
8 how that would be done, the swapping of benzene
9 for another solvent, correct?

10 A. I don't know all the considerations
11 involved. I imagine there's -- part of it is
12 related to the dielectric constant of the solvent,
13 its ability to dissolve and discriminate between
14 different crystal forms, you know, during
15 recrystallization. And that's something a chemist
16 would do routinely I believe.

17 Q. Have you, yourself, done that?

18 A. I've done recrystallization during my
19 bachelor's degree. And we have to go pre-1994 for
20 that. And I --

21 (Simultaneous speaking.)

22

1 BY MS. KRUMPLITSCH:

2 Q. You, yourself, have -- I'm sorry.

3 A. Now I have to reveal my age of course.

4 But, I mean, this is -- this is -- I haven't
5 switched out solvents. We would have been using
6 things like benzene in the lab at that point, just
7 as it was benchtop sorts of experimentation.

8 So I didn't go any further than, you
9 know, using what we were told in the recipe I'm
10 afraid to say.

11 Q. Okay. Let's move on to paragraph 8 of
12 your declaration, which is on page 4.

13 (Witness reviewing document.)

14 THE WITNESS: Okay. I'm there.

15 BY MS. KRUMPLITSCH:

16 Q. Did you have a chance to read paragraph
17 8?

18 A. Yeah. I just glanced over it as we got
19 there, yeah.

20 Q. Great. Excuse me. I'm sorry. Let me
21 take a drink of water.

22 So in paragraph 8 you state -- on page

1 4 you said you thought (as read): It would be
2 routine for a POSA to incorporate (Z)-endoxifen
3 into an enteric formulation and would not have
4 been "highly technical" or "unpredictable."

5 And then you state "I have seen no
6 evidence of such complexities with endoxifen"
7 because in that paragraph you state that
8 "encapsulating formulation is routine."

9 Do you still agree with that opinion?

10 A. Yeah, absolutely.

11 Q. Okay. And you say (as read): I've
12 seen no evidence of any complexities.

13 What did you do to investigate whether
14 or not such complexities existed?

15 A. Well, looking at all the prior art,
16 that nothing appeared. I think I even -- I think
17 I even did a search at the time. And, you know,
18 using SciFinder and Google Scholar. And I didn't
19 see that there was any interactions or any
20 publications related to any interactions with such
21 systems, which often do appear if there is a
22 problem.

1 Q. Uh-huh. And I want to be very precise
2 in my question.

3 When you did your Google -- your
4 searching of the art, did you investigate whether
5 there would be any complexities in formulating a
6 90 percent pure (Z)-endoxifen composition in an
7 enteric-coated capsule?

8 A. Well, I was even broader than that. So
9 any -- any potential issues would have popped up I
10 believe. So I used the search term
11 "(Z)-endoxifen" with "enteric polymers." In fact,
12 I think I put in several different types of
13 enteric polymer during that search. Nothing
14 popped up. And then I went a step further and
15 just looked for endoxifen. Nothing popped up.

16 Q. Did you do any search for 90 percent
17 pure (Z)-endoxifen?

18 A. Well, that would have popped up if I
19 just used the search term "endoxifen" for sure.

20 Q. And it's your testimony that you didn't
21 find anything describing 90 percent (Z)-endoxifen?

22 A. If I didn't find anything describing

1 endoxifen and enteric coatings, then it's
2 impossible really for the 90 percent not to be
3 there, you know.

4 Q. And what time period were you
5 searching? Excuse me, I'm sorry.

6 A. It would have -- I think I put the -- I
7 think I put the date -- wait -- I guess the
8 priority date on there. I can't recall now but I
9 did put a date limit on it.

10 So, you know, I put myself in the
11 mindset of a person of ordinary skill at the time
12 doing a search. And they wouldn't have had any
13 issue. They wouldn't have thought there would
14 have been an issue as far as I'm concerned.

15 Q. And so I just want to make sure I
16 understand your methodology, Dr. McConville.

17 So you're searching for any references
18 that predate the patent. So that would be prior
19 art.

20 And you were looking for "endoxifen"
21 and "enteric coatings"?

22 A. Yeah, that -- that would be the

1 broadest I think.

2 Q. Okay. And it's your testimony that you
3 didn't find anything?

4 A. Yeah.

5 Q. And so in your both opening declaration
6 and your reply declaration, you focus on the
7 reference Cole, correct?

8 A. Yes, yes.

9 Q. And we discussed this at your last
10 deposition that Cole actually describes
11 paracetamol, correct?

12 A. No, Cole describes the use of a model
13 drug. That's right.

14 Q. And just so the record's clear, that
15 model drug is paracetamol?

16 A. It happens to be, yes.

17 Q. Does the active ingredient in
18 paracetamol interconvert to an inactive isomer
19 when exposed to acidic conditions?

20 A. I don't know exactly what the issue is
21 with paracetamol. You know, the -- the idea is
22 that it wouldn't be exposed to an acidic medium

1 that wouldn't be released. Cole is just using
2 this as a marker as far as I'm concerned.

3 Q. And do you know whether the active
4 ingredient in paracetamol interconverts to an
5 inactive isomer when heated?

6 A. Again, I haven't looked at that. You
7 know, Cole is specifically using paracetamol as a
8 marker so we can track where the drug is or being
9 released.

10 Q. Okay. And if you could flip back up to
11 paragraph 7, so the preceding paragraph.

12 I'll give you a second to read that.
13 That is on pages 3 and 4.

14 (Witness reviewing document.)

15 THE WITNESS: Yes, I am there.

16 BY MS. KRUMPLITSCH:

17 Q. Okay. So in paragraph 7 you state that
18 (as read): In the case of an enteric-coated
19 capsule --

20 A. So this is -- it starts.

21 Q. Actually, it's at the top of page 4.

22 A. Oh, okay. Sorry.

1 Q. So paragraph 7 spans 3 and 4.

2 A. Yeah, yeah. Okay. Go ahead.

3 Q. Okay. The top of 4 you state -- and
4 I'm starting on the second line -- (as read): In
5 the case of an enteric-coated capsule, it is the
6 degradation of the enteric coating and capsule
7 that will control the release of the drug, not the
8 nature of the drug itself.

9 Do you see that there?

10 A. Yes.

11 Q. Okay. What is the basis for your
12 understanding that the release profile is solely
13 controlled by the degradation of the enteric
14 coating or capsule rather than the nature of the
15 drug itself?

16 A. Well, just to be specific, it's the
17 delayed release aspect of the formulation, which
18 is controlled by the capsule. So where it is
19 released in the gastrointestinal tract is
20 controlled solely by the capsule.

21 Q. So if you have a highly aqueously
22 soluble material and a highly aqueously insoluble

1 material, those two materials would have the same
2 release profile if you coated them in the same
3 enteric coating?

4 A. They would both be released to the same
5 part of the gastrointestinal tract, yes.

6 Q. So I understand your point is that they
7 both would be released in the -- you know, at the
8 same location in the gastrointestinal tract.

9 But is that -- is it your testimony
10 that that means that they would have the same
11 release profile or is there a difference between
12 release profile and where it's -- the drug is
13 released?

14 A. I -- you know, I -- different active
15 pharmaceutical ingredients do have different rates
16 of dissolution once they are released into a type
17 of medium. So a particular place in the
18 gastrointestinal tract, for example, or even on
19 the benchtop when we -- when we look at the USP
20 method 711, which is described in the '334 patent.

21 You know, you can -- you can see this
22 with the enteric coating not releasing drug in an

1 acidic medium. And then when the pH is increased,
2 the enteric coating dissolves. And that's when
3 this difference in dissolution rate could occur
4 between different APIs. So, yes, that's something
5 to consider.

6 Q. Okay. And do you agree that the rate
7 of release of an API from the formulation impacts
8 the absorption of the API?

9 A. That's one of the things that can, yes.

10 Q. We've been going about an hour but I
11 just have a few more questions on Cole.

12 Is it okay with you, Dr. McConville, if
13 we keep going?

14 A. Yeah.

15 Q. And one question about the enteric
16 coating.

17 Does the coating disappear instantly or
18 gradually?

19 A. Well, that depends on the thickness of
20 the coating I would say. And ultimately I suppose
21 that the idea is that this is very rapid once it
22 gets to the small intestine.

1 There were some tests done to check
2 that the coat is thick enough to prevent release
3 in the acidic media. And literally the 711 -- USP
4 711 dissolution test accounts for this. So the
5 idea is you have the thinness coat possible to
6 prevent drug release.

7 And I think that 10 percent drug
8 release in the acidic -- acidic media is somewhat
9 of a, I guess, bar not to cross. So 10 percent of
10 the drug release in the wrong place if you'd like.
11 So you'd want a thin coat but then dissolves
12 straight away after that two hours in the acidic
13 medium.

14 Q. And is the goal to -- you said dissolve
15 straight away -- but to dissolve as rapidly as
16 possible?

17 A. Yes.

18 Q. Okay. So we're going to look at
19 paragraph 9.

20 So I'll give you a second to look at
21 paragraph 9, which spans 5 and 6.

22 (Witness reviewing document.)

1 THE WITNESS: Okay.

2 BY MS. KRUMPLITSCH:

3 Q. So in this paragraph you are describing
4 how the coatings -- an enteric coating is applied
5 to a capsule after it's been filled with the drug
6 substance; is that right?

7 A. Yes.

8 Q. And I want to ask you a few questions
9 about how the coating actually gets on to the
10 capsule.

11 So is it true that the enteric coating
12 solution is sprayed onto the filled capsules
13 first?

14 A. That's -- that's the general method,
15 yes.

16 Q. And do you know what temperature that
17 spraying occurs at?

18 A. Well, there's a few things that affect
19 the temperature of which it's sprayed on. The
20 hotter you have the spray chamber, the chamber
21 which it's sprayed onto the capsule, the hotter
22 you have it, the quicker it can evaporate.

1 But at the same time, if it evaporates
2 too quickly it spreads. So the temperature's
3 often cooled down a bit so that we want spreading
4 of the liquid containing the polymer over the
5 surface of the capsule. Let me think. So then
6 you incorporate a plasticizer to help that
7 spreading, too.

8 And so I can't give you a definitive
9 answer on the temperature because it also depends
10 on the loading of capsules, the number of capsules
11 you're trying to coat. So if there's a kilogram
12 of capsules as opposed to 10 kilograms of
13 capsules, you know, that changes the temperature
14 at which the coating is applied, too.

15 Q. So is it fair to say that the coating
16 is applied at a heated temperature but what that
17 temperature is varies depending on a number --
18 like how many capsules you're coating?

19 A. Yeah. I mean, in an ideal world you
20 use the lowest temperature setting that you can so
21 that you ensure a good spreading of the polymer
22 over the capsule. Size of the capsule so comes

1 into it as well. And then -- but not so cool that
2 the -- when the capsules come around the chamber
3 again that they're still wet. You want it to have
4 dried off.

5 And it's applied in this sort of --
6 sort of layering approach. You know, a bit
7 sprayed out, it goes around, dries, bit more
8 sprayed on, and goes around this chamber and
9 dries. There's several different coating type of
10 chambers as well that can be used. You don't want
11 the capsules sticking together. It's well known
12 how to do this. It's done for tablets as well,
13 exactly the same process.

14 Q. So after the spraying is -- is applied
15 and then the capsules are dried presumably.

16 Is that what you're describing?

17 A. So after -- after they're completely --
18 after the coating is completely applied, you mean,
19 or --

20 Q. Uh-huh.

21 A. Yes, yes. They would be left in the
22 chamber just to -- either just to air dry and

1 probably the temperature is turned off at that
2 point just to air -- air, yeah, evaporate any
3 residual solvent.

4 Q. Okay. Is the coating temperature --
5 sorry, let me change that.

6 Is the temperature at which the coating
7 is applied, is that an ambient room temperature or
8 -- and I know you can't give me a precise
9 temperature but I'm just trying to figure out is
10 it elevated above ambient room temperature?

11 A. Usually it's a little warmer, yeah.

12 Q. And then when the capsules are dried
13 after the coating has been completely applied, is
14 that drying process, does that take place at
15 ambient room temperature or at an elevated
16 temperature?

17 A. Well, as I said, in some -- some cases
18 you can turn off the heating, the heated air
19 source, and just have air blowing through. And it
20 gradually will cool to ambient temperature. At
21 the end of the process, you are at ambient
22 temperature.

1 Q. So after the capsules have dried, is
2 there a curing step or is that part of the drying
3 progress?

4 A. Well, if it's applied correctly, then
5 there shouldn't really need to be much of a curing
6 step. It is possible you can have a curing step
7 in these processes after applying the coat. But,
8 I mean, if it's working ideally, the -- you know,
9 the sort of layering of the spray on the capsule
10 will be very uniform and not necessarily need a
11 curing step. It depends.

12 Q. Okay. Did you perform any study
13 testing whether exposure to heat would cause
14 isomerization of the endoxifen within the
15 enteric-coated capsule?

16 A. I did not, no.

17 Q. And did you review any literature to
18 determine whether or not this occurs?

19 A. No, I didn't.

20 Q. Just a few more questions to finish off
21 this section.

22 In paragraph 10, take a quick look at

1 that on page 6.

2 (Witness reviewing document.)

3 THE WITNESS: Okay.

4 BY MS. KRUMPLITSCH:

5 Q. In paragraph 10 you reference the '334
6 patent.

7 And my question is: Why did you look
8 to the '334 patent for teachings about whether
9 there would be any interactions between the
10 enteric-coated capsule and the (Z)-endoxifen?

11 A. Well, I didn't use the '334 patent for
12 teachings. The '334 patent simply confirms what
13 was known in the art at the time. It doesn't --
14 it doesn't -- you know, had the '334 had to --
15 have to overcome something that was an issue, I'm
16 sure it would have been pointed out.

17 That's -- that's my point here. The
18 '334 patent doesn't have anything special to say
19 about coating because what was known in the art
20 was -- could be utilized routinely for making a
21 capsule of (Z)-endoxifen in my opinion.

22 Q. You testified earlier that when you

1 tried to search for (Z) or -- sorry. Let me
2 withdraw that.

3 You testified earlier that when you
4 tried to search for references as of the priority
5 date of the '334 patent looking for references
6 that combined endoxifen and enteric coating, you
7 couldn't find any; is that correct?

8 A. Right. Because the standard practices
9 at the time are what essentially -- you know,
10 that's -- that's what came up. And, you know,
11 whoever crafted the '334 patent didn't recognize
12 any issues either.

13 Q. Okay. If you can look quickly at
14 paragraph 12, which is on page 7 and 8.

15 A. Okay. Yep.

16 Q. And we're going to focus on that last
17 sentence of paragraph 12, which is actually on
18 page 8.

19 A. Okay. Sorry.

20 (Witness reviewing document.)

21 THE WITNESS: Okay.

22

1 BY MS. KRUMPLITSCH:

2 Q. Okay. And you state there that you
3 "have not seen any evidence" and you're "not aware
4 of any reason that a positive electrostatic charge
5 on HPMC would have been a concern in relation to
6 the stability of endoxifen, correct?

7 A. Yes.

8 Q. And what did you do to investigate
9 this? You say you have not seen any evidence.
10 Did you look?

11 A. So this issue is really a nonissue
12 because, you know, HPMC by its very -- it's known
13 as a nonionic polymer. And this means literally
14 that it doesn't carry a charge.

15 So I wasn't sure of what Dr. Davies was
16 trying to get at with the assertion that the HPMC
17 capsule carries a positive charge. The only thing
18 I could think about is something which happens,
19 you know, quite frequently in dry powder
20 inhalation where we have a charge induced on a
21 polymer due to, you know, what -- what the
22 environment conditions might be, for example, when

1 the capsule is being filled. What surface is it
2 being filled on.

3 And I mean, this is no different to any
4 other powder or any other capsule-filling process
5 with any powder whatsoever. This issue of
6 charging of the capsule really is very well
7 characterized in the art.

8 So, for example, you wouldn't fill a
9 gelatin or an HPMC capsule in an extremely dry
10 environment because this promotes electrostatic
11 triboelectric charging on polymer surfaces. It's
12 like rubbing a balloon on your sweater and
13 sticking it on the wall. So that's the only thing
14 I can think of.

15 HPMC is a nonionic polymer. It's one
16 of the -- you know, it's probably better use than
17 gelatin in that respect.

18 Q. Okay. I appreciate the explanation.

19 Did you look for any evidence that the
20 positive electrostatic charge on HPMC could impact
21 the stability of the (Z)-isomer?

22 A. No, I -- I didn't specifically. But

1 what I did look for is charges on HPMC capsules.
2 And as I said, comes with what I said, this is a
3 nonionic polymer.

4 MS. KRUMPLITSCH: I think this is a
5 good place for us to take a short break if
6 that's okay with everyone on the call. Say
7 five, ten minutes.

8 Dr. McConville, is that okay
9 with you?

10 THE WITNESS: Yep, no problem.

11 MS. KRUMPLITSCH: Okay. Great. So
12 I'm going to go off video and mute and
13 we'll be back in five, ten minutes.

14 MR. MENCHACA: Let's just say ten
15 minutes.

16 MS. KRUMPLITSCH: Okay. Let's do
17 ten minutes. Thank you.

18 (Whereupon, a recess was taken
19 from 9:11 a.m. to 9:22 a.m.)

20 THE STENOGRAPHER: We're back on the
21 record at 9:22.

22

1 BY MS. KRUMPLITSCH:

2 Q. Dr. McConville, did you speak to your
3 counsel during the break about your testimony?

4 A. No.

5 Q. Could you please -- so we're going to
6 still focus on your reply declaration, Exhibit
7 1031. And can you turn to paragraph 17 that is on
8 page 12? And paragraph 17 spans pages 11 and 12.

9 A. Okay.

10 (Witness reviewing document.)

11 THE WITNESS: Okay.

12 BY MS. KRUMPLITSCH:

13 Q. And I see you have included a footnote
14 here that lists two web pages regarding Capsugel.

15 A. Yes.

16 Q. And you cite these web pages to support
17 your statement that these capsules were
18 commercially available by October 7th, 2016,
19 correct?

20 A. That's right.

21 Q. And what did you do to confirm that
22 these web pages were accurate as of October 7th,

1 2016?

2 A. Well, I think that counsel may have
3 confirmed this -- this time period. I don't know
4 about the web pages themselves but I -- you know,
5 the -- whether they've been updated, probably have
6 been. But those capsules in my understanding were
7 released at that date.

8 Q. So is it fair to say that the web pages
9 that you're citing here in Footnote 1, you don't
10 have any knowledge as to whether or not these web
11 pages would have been available back in 2016?

12 A. Not -- not specifically.

13 Q. Okay. And this section of your report,
14 paragraphs 17 through 24, deals with the
15 combination of Ahmad, the Ahmad patent, and
16 Benameur, correct?

17 A. Yes.

18 Q. And Benameur describes esomeprazole
19 formulated into ECDDT capsule shells, correct?

20 A. Yes.

21 Q. Does esomeprazole isomerize in the
22 presence of acid?

1 A. I know that it has some instability in
2 the presence of acid. I'm not sure about the
3 specific instability. It's probably described in
4 the Benameur reference. But I can't recall
5 exactly.

6 Q. Okay. And if you could turn to
7 paragraph 20.

8 And I'll give you a second to read
9 that.

10 (Witness reviewing document.)

11 THE WITNESS: Yes.

12 BY MS. KRUMPLITSCH:

13 Q. So in paragraph 20 you state in the
14 middle of that paragraph that (as read): The
15 dissolution of the enteric capsule will control
16 the timed-release characteristic of the
17 formulation, not the nature of the active
18 ingredient (e.g., salt compared to free base).

19 Do you see that statement?

20 A. Yes.

21 Q. And then you say (as read): As such, a
22 POSA would expect that the timed release of

1 Benameur's formulations with model drug EMT would
2 be comparable to any other active ingredient,
3 including (Z)-endoxifen.

4 Do you see that?

5 A. Yes.

6 Q. And EMT is the esomeprazole that we
7 were discussing, correct?

8 A. That's correct.

9 Q. Did you review the results of the '334
10 patent that compare the salts and free base
11 pharmacokinetic parameters of endoxifen?

12 A. I had looked at them previously I
13 believe.

14 Q. You don't reference them in this
15 paragraph when you are talking about the release
16 -- the dissolution -- sorry, the release
17 characteristics of the formulation?

18 A. Well, you know, the pharmacokinetic
19 parameters are quite different from release
20 characteristics of a drug.

21 Q. Well, I thought before the break you
22 had mentioned that the release characteristics can

1 impact absorption.

2 A. Yes, I said that that's one aspect.

3 (Simultaneous speaking.)

4 BY MS. KRUMPLITSCH:

5 Q. And absorption is --

6 A. Sorry. I'm just -- I just want to
7 clarify. That's one aspect that can influence
8 absorption. That -- there's quite a few things
9 such as ionization state, for example, and area of
10 the gastrointestinal tract the drug is released,
11 which is probably the most important aspect of
12 drug absorption, the surface area of the
13 gastrointestinal tract.

14 And where these capsules are designed
15 to release drug is right at the key point of drug
16 absorption or any type of absorption, nutritional
17 absorption as well, for the gastrointestinal
18 tract.

19 Q. And you would agree with me that
20 absorption is a pharmacokinetic parameter?

21 A. The rate of absorption.

22 Q. Yes. Thank you for that clarification.

1 So the rate of absorption is a
2 pharmacokinetic parameter, correct?

3 A. Well, it may be a secondary
4 pharmacokinetic parameter.

5 Q. What are the pharmacokinetic
6 parameters?

7 A. I'm sorry, could you repeat that?

8 Q. Yeah. What are the pharmacokinetic --
9 like the pharmacokinetic parameters?

10 A. All of them?

11 Q. Name -- name a few.

12 A. Well, you know, the primary
13 pharmacokinetic parameters then would be Cmax,
14 Tmax, and area under curve.

15 Q. And does absorption factor into any of
16 those pharmacokinetic parameters?

17 A. Not exactly. It influences. It can
18 influence the Tmax and Cmax pretty much. I should
19 -- I should mention the elimination rate constant
20 as being a primary factor which influences the
21 half-life as well.

22 Q. Uh-huh. So I believe in your last

1 deposition we talked about ADME as absorption,
2 distribution, metabolism, and excretion that
3 describe how the drug moves through the body?

4 A. Yes.

5 Q. And absorption, distribution,
6 metabolism, and excretion all factor into
7 pharmacokinetics, correct?

8 A. I would say it's more of a
9 biopharmaceutics consideration. Of course
10 pharmacokinetics is married to biopharmaceutics.
11 But the actual ADME that you described in those
12 terms is more of a biopharmaceutical consideration
13 than pure pharmacokinetics.

14 But, sure, metabolism can be a single
15 factor or excretion can be a single factor in the
16 elimination of a drug.

17 Q. The next section of your report is
18 beginning on paragraph 25 through -- through 31.
19 And this section is the combination of Ahmad with
20 standard excipients.

21 I'll give you a second to orient
22 yourself there.

1 (Witness reviewing document.)

2 THE WITNESS: Yes. Okay. I'm at
3 that section, yeah, Section 6.

4 BY MS. KRUMPLITSCH:

5 Q. Yes, yes. Did you perform any analysis
6 of the literature to investigate whether any of
7 these excipients were, in fact, compatible with
8 (Z)-endoxifen?

9 A. I mean, other than the HPMC search that
10 I -- excuse me, the HPMC search that I've
11 described earlier, no.

12 Q. So on paragraph 29 on page 18 -- I'll
13 give you a second to read that real quick.

14 (Witness reviewing document.)

15 THE WITNESS: Okay.

16 BY MS. KRUMPLITSCH:

17 Q. So you describe -- you state I think in
18 the third and fourth line that (as read): The
19 HPE -- the Handbook of Pharmaceutical
20 Excipients -- generally lists known
21 incompatibilities.

22 Correct?

1 A. Yes.

2 Q. Okay. Now, would you expect the HPE to
3 list the incompatibilities for a compound that had
4 not previously been formulated?

5 A. It would really depend, you know, on
6 when the edition of the HPE came out and what
7 prior research had been done. Because the HPE is
8 kept up to date with respect to such
9 incompatibilities as they appear.

10 And, you know, it's an important aspect
11 of the handbook to note the types of
12 incompatibilities that can occur in a general
13 sense so that a person of ordinary skill could
14 look at a given API even if it's not listed in the
15 API -- sorry, in the handbook, even if the API is
16 not listed in the handbook, per se. But they
17 would have an idea about the class of compound
18 and, you know, whether there was any
19 incompatibilities potentially there.

20 Q. At a general level of class of
21 compounds, correct?

22 (Stenographer clarification.)

1 MS. KRUMPLITSCH: Class of
2 compounds.

3 THE WITNESS: Yes. So, for example,
4 you know, we section -- it notes here, I
5 guess it's about a third of the way down
6 paragraph 29, (as read): Incompatibilities
7 noting talc is incompatible "with
8 quaternary ammonium compounds."

9 Now, that's a specific
10 particular class of compounds. It doesn't
11 call out any particular API.

12 BY MS. KRUMPLITSCH:

13 Q. What class of compounds does
14 (Z)-endoxifen belong to?

15 A. Yeah. I'm not -- I'm not sure. But
16 I'm -- it's definitely not called out in this
17 respect. You know, tamoxifen is not mentioned.
18 And, you know, there is -- there's no -- nothing
19 surprising in the molecular structure such as a
20 quaternary ammonium group that would cause --
21 which would have cause for concern.

22 So as far as I'm concerned, there

1 doesn't seem to be any issue with (Z)-endoxifen.

2 Q. Did you --

3 A. Or you wouldn't expect -- a POSA
4 wouldn't expect any issues. Sorry.

5 Q. Did you investigate -- one moment. Our
6 laptop just died.

7 Did you investigate the molecular
8 structure of (Z)-endoxifen to determine whether or
9 not there would be any cause for concern?

10 A. I mean, I looked at the structure of
11 it. And I couldn't see anything that jumped out
12 at me as being an issue in terms of
13 incompatibilities with standard ingredients.

14 And then I might just add that a person
15 of ordinary skill has an armory of excipients that
16 they might use, for example, in capsule filling.
17 And so they would test. It would be a routine
18 test to see if there was any incompatibilities
19 that may or may not have been mentioned in the
20 handbook as well.

21 In fact, a person of ordinary skill
22 might be driven to investigate such things as well

1 and, you know, try and highlight that for other
2 researchers. And since nothing was highlighted, I
3 can only assume that -- what has been no issue.

4 Q. So I just want to make sure I
5 understand your testimony. You say nothing was
6 highlighted.

7 You mean nothing was highlighted in the
8 handbook?

9 A. I guess, yes, in the handbook. That
10 would be the main -- you know, the main place a
11 person of ordinary skill would look at various
12 excipients that might be available. That and, you
13 know, other publications.

14 Q. Okay. Let's turn to -- why don't you
15 keep your paper declaration in front of you. And
16 we're going to look at the Ahmad patent and that
17 is Exhibit 10 -- 1003 -- 3? Hold on.

18 A. Okay. I'll -- I'll download this one
19 and look at it on my screen.

20 MS. KRUMPLITSCH: So, 1003, the
21 Ahmad patent.

22 EXHIBIT TECHNICIAN: All right.

1 Stand by.

2 BY MS. KRUMPLITSCH:

3 Q. And we're just going to have that in
4 case we need to refer to it.

5 A. Okay.

6 Q. Dr. McConville, did you review the
7 Ahmad patent before this deposition?

8 A. I haven't specifically looked to the
9 Ahmad patent since our last conversation, I think.

10 Q. Okay. When you say "our last
11 conversation," our last deposition?

12 A. Yeah.

13 Q. Okay.

14 A. Hold on one second. Let me -- because
15 I wanted to get this up to -- oh, there we are,
16 1003.

17 Okay. Got it.

18 Q. Okay. Great. So would you agree with
19 me that Ahmad does not teach a specific example of
20 a -- of a solid oral dosage form of 90 percent
21 (Z)-endoxifen?

22 A. So I think this is the situation

1 whereby Ahmad -- Ahmad describes a solid
2 pharmaceutical composition. I'm looking at
3 Claim 1. And in that case, you know, a person of
4 ordinary skill assumes that this is an oral
5 composition because that's the most commonly used.

6 Q. So other than the language of Claim 1,
7 is there any description of a solid oral dosage
8 form of 90 percent (Z)-endoxifen?

9 And actually, let me withdraw that.
10 Sorry. Let me withdraw that.

11 Claim 1 describes an 80 percent
12 (Z)-endoxifen citrate salt, correct?

13 A. Well, it describes at least an 80
14 percent. You know, I think we discussed this
15 before that that naturally encompasses 90 percent
16 to me. At least 80 percent is a threshold. I
17 think if we refer back, recall correctly, it was
18 column --

19 Q. 12 perhaps.

20 A. -- 12, yes. 12. That's right.

21 To explore the different purity levels.
22 And, you know, it of course mentions 90 percent

1 pure and even goes all the way up to being, you
2 know, 100 percent pure.

3 Q. Right. And we spent a lot of time on
4 this sentence in your previous deposition.

5 A. Yes.

6 Q. And I understand your testimony from
7 that deposition.

8 But can you point to me anywhere within
9 Ahmad where Ahmad made a solid oral dose form of
10 90 percent (Z)-endoxifen?

11 A. Well, I think it's understood that this
12 -- this patent describes various compositions and
13 specifically calls out the solid dosage form, you
14 know, in Claim 1.

15 So, you know, it's my opinion that
16 column 12 starts off with the language "at least
17 80 percent" and, you know, indicates "at least 80
18 percent" means higher also. And that is
19 encompassed in Claim 1.

20 So is there anywhere else? I think
21 that when you read through the patent, it talks
22 about different types of ingredients that are

1 generally used for a solid oral dosage form. So a
2 person of ordinary skill looking at this would
3 easily understand what Ahmad is referring to as a
4 solid pharmaceutical dosage form.

5 Q. And I appreciate that. But my question
6 is -- is a simple one.

7 Anywhere in the patent does Ahmad
8 describe making a formulation of
9 90 percent (Z)-endoxifen in a solid oral dosage
10 form? Actually making the formulation.

11 A. Well, yeah, because it's littered
12 throughout related to the composition of such a
13 solid oral dosage form. You know, I think
14 throughout the description, the body of this
15 patent describes -- it is described, yes.

16 Q. Can you point me to where in the '190
17 patent Ahmad has made a 90 percent (Z)-endoxifen
18 solid oral dosage form?

19 A. Give me a second.

20 Q. Okay.

21 (Witness reviewing document.)

22 THE WITNESS: I mean, column 4, line

1 49, tells us in some embodiments the
2 administering comprises oral. Okay. So it
3 definitely is describing an oral
4 formulation there.

5 Give me -- give me a second.

6 (Witness reviewing document.)

7 BY MS. KRUMPLITSCH:

8 Q. And while you're looking for that, I
9 just want to ask you -- let's pause right there.

10 This passage that you point to at
11 column 4, lines 49 to 53, states (as read): In
12 some embodiments, the administering comprises
13 oral, intravenous, subcutaneous, percutaneous,
14 parenteral, intraperitoneal, rectal, vaginal,
15 and/or topical delivery said composition to said
16 subject.

17 Is it your testimony that that passage
18 describes that Ahmad has made a 90 percent
19 (Z)-endoxifen solid oral dosage form?

20 A. It's my testimony that the Ahmad can
21 envisage that dosage form, as can any person of
22 ordinary skill by looking at this patent as a

1 whole and seeing the compositions that are
2 described.

3 Q. Okay. That's your testimony.

4 Do you have any other passages you'd
5 like to point us to where Ahmad has made a solid
6 oral dosage form of 90 percent (Z)-endoxifen.

7 A. I had to stop for a moment.

8 (Witness reviewing document.)

9 THE WITNESS: Yeah, column 18, lines
10 1 -- can you hear me?

11 BY MS. KRUMPLITSCH:

12 Q. Yes. Sorry. Column 18, line 1?

13 A. Yeah. It starts there (as read):
14 Pharmaceutical preparations that can find use --
15 that find use with the compositions of the present
16 invention include but are not limited to tablets,
17 capsules.

18 Yeah. For the oral mode of
19 administration, preferred forms of endoxifen or
20 even the lipid complex, they describe at length in
21 the patent as well include tablets, capsules,
22 lozenges. I guess powders as well that can be

1 filled into capsules as well. Aqueous solutions
2 as well and suspensions. All can be filled into
3 different oral dosage forms.

4 Let me see.

5 Q. And before you point us to a passage,
6 can I ask you a question about that excerpt that
7 you just pointed us to?

8 A. Yeah.

9 Q. Is it your testimony that that part of
10 the patent at column 18, lines 1 to the end of
11 that paragraph, which is 18, describes Ahmad
12 actually making a solid oral dosage form of (Z) --
13 90 percent (Z)-endoxifen?

14 A. It describes what can be made. I
15 --obviously it doesn't -- that's not an enabling
16 example. We haven't got there yet. But, you
17 know, Ahmad describes that the (Z)-endoxifen can
18 be incorporated into any of those formulations.

19 And a person of ordinary skill would
20 recognize that it's not too complicated to include
21 any particular active pharmaceutical ingredient
22 that doesn't present any significant challenges in

1 formulating into any of those because Ahmad
2 certainly highlights that it can be done.

3 You know, it goes on I guess, line 27
4 talks about the enteric coating of capsules filled
5 with the composition containing endoxifen can be
6 done using the methods known in the art, which is
7 where the person of ordinary skill comes in, of
8 course.

9 Q. And, again, is it your testimony that
10 this passage describing the enteric coating at
11 column 18, the paragraph starts at line 19 through
12 29, describes that Ahmad has actually made an
13 enteric-coated capsule of 90 percent
14 (Z)-endoxifen?

15 A. Again, I would -- I would say a person
16 of ordinary skill would easily be able to pick up
17 and make it. But Ahmad doesn't explicitly
18 describe that there because it's not an enabling
19 example of course.

20 Q. As we're going through the patent, do
21 you have more passages that you'd like to point us
22 to?

1 A. I'm just trying to refresh where I've
2 seen portions that are obviously applicable to
3 that aspect that you, you know, want me to look at
4 here, the oral dosage form. And since I'm only
5 skimming through, it could well be that I miss
6 things. Let me see.

7 (Witness reviewing document.)

8 THE WITNESS: Well, examples 7 and 8
9 talk about the use of different excipients
10 to produce solid particles that contain the
11 active ingredient (Z)-endoxifen.

12 (Simultaneous speaking.)

13 BY MS. KRUMPLITSCH:

14 Q. Uh-huh. And -- excuse me. I'm sorry.

15 A. And so based on the information that's
16 already provided in Ahmad, you know, a person of
17 ordinary skill would see these solid particles can
18 be used to manufacture such solid oral dosage
19 forms.

20 Q. And you'd agree with me that example 7
21 actually describes that a suspension of endoxifen
22 and cholesterol sulfate and soy lecithin was

1 combined and then --

2 A. Yeah, I mean --

3 Q. -- the suspension was filtered and
4 lyophilized, correct?

5 A. Yes, I mean, that's one way of
6 preparing a -- a dry powder with the active
7 ingredient.

8 (Simultaneous speaking.)

9 BY MS. KRUMPLITSCH:

10 Q. And -- I'm sorry.

11 (Stenographer clarification.)

12 MS. KRUMPLITSCH: Yep. Sorry.

13 THE WITNESS: Yeah, I said that's
14 one way of preparing a powder that could be
15 used with the active ingredient.

16 BY MS. KRUMPLITSCH:

17 Q. And example 8 is a suspension of
18 endoxifen in soy lecithin that is, again, mixed
19 with a sucrose solution and lyophilized, correct,
20 Dr. McConville?

21 A. For use in a solid oral dosage form.

22 Q. And do examples 7 and 8 recite the

1 isomeric ratio that endoxifen used?

2 A. No, no. That's described elsewhere in
3 the patent. For example, column 12 and then
4 Claim 1.

5 Q. Does Ahmad teach any precautions need
6 to be taken during formulation of an endoxifen
7 solid oral dosage form?

8 A. You know, in this case I might have to
9 go through with that in mind and look at that
10 aspect of things. I can't say that I have noted
11 any special precaution with that couple of
12 examples so far.

13 Q. So let me be more specific with my
14 questions and maybe that will help you.

15 Does Ahmad teach any precaution needs
16 to be taken during formulating endoxifen with
17 regards to controlling pH?

18 A. Now, I don't want to mix my references
19 up. I think there is a concern that a very low pH
20 is a potential issue. I'm not sure whether it's
21 in the Ahmad reference here or not.

22 Q. Does Ahmad teach any precautions to be

1 taken during formulating endoxifen with respect to
2 controlling temperature?

3 A. I'd have to look through and -- just to
4 confirm that. I can't recall at this point.

5 Q. And does Ahmad teach any precautions to
6 be taken during formulating endoxifen with respect
7 to minimizing interactions with coatings and the
8 (Z)-endoxifen?

9 A. I don't recall that, no.

10 Q. And that same question with respect to
11 minimizing interactions with excipients and
12 (Z)-endoxifen.

13 A. I don't recall that there is
14 precautions related to that, no.

15 Q. So let's keep that Ahmad patent up.

16 Can you go back to column 12? And you
17 pointed us to lines 14 to 18 that describes that
18 one object of the present invention is to provide
19 (E)-endoxifen or (Z)-endoxifen with the various
20 levels of impurity that we just discussed. And I
21 want to focus on the following sentence.

22 I'll give you a second to orient

1 yourself.

2 (Witness reviewing document.)

3 THE WITNESS: Okay.

4 BY MS. KRUMPLITSCH:

5 Q. So the sentence at column 12, line 18
6 to 19, states that (as read): Another object of
7 the present invention is to provide solubilized
8 endoxifen in, e.g., aqueous acid.

9 Do you see that?

10 A. Yes.

11 Q. Why would a POSA reading -- I'm sorry.
12 Let me withdraw that.

13 And then examples 5 and 6, if we're
14 looking at the examples, 5 and 6 are in column 26,
15 those describe creating an endoxifen solution of
16 endoxifen in a glacial acetic acid, correct?

17 A. Let me just check that. Hang on.

18 Q. Sure.

19 A. Examples 5 and 6, you say?

20 Q. Yeah, at column 26.

21 (Witness reviewing document.)

22 THE WITNESS: Okay.

1 BY MS. KRUMPLITSCH:

2 Q. So taken together, we've got examples 5
3 and 6 and this statement at column 12 saying an
4 object of the present invention is to provide
5 solubilized endoxifen in aqueous acid.

6 Why would a POSA reading these examples
7 in this passage want to create an enteric-coated
8 formulation?

9 A. I -- so there's quite a difference in
10 acidity that I think you're referring to. When I
11 look at examples 5 and 6, for example, the pH is
12 approximately 5 -- well, it's over 5. So, you
13 know, that's chalk and cheese in terms of
14 hydronium ion concentration.

15 So if you want -- if you're worried
16 about acid degradation in the stomach, you're
17 looking at a pH of 1 here. This is, you know,
18 millions of times more concentrated in terms of
19 the hydronium ion than a pH of 5. Remember, it's
20 a large scale.

21 Q. And so as a POSA reading this, is it --
22 tell me if this is a fair characterization.

1 That the Ahmad is suggesting that
2 endoxifen needs to be protected from the strong
3 acid of the stomach but can be mixed with a weaker
4 acid and that's actually preferable?

5 A. Well, without, you know, knowing too
6 much about the chemistry of the degradation, you
7 know, I would assume that it's the strong acid we
8 have to worry about here just because of the
9 nature of the reducing potential of a strong acid
10 compared to such a weak acid at pH 5. I mean,
11 it's closer to neutral than it is to being a
12 strong acid. I mean, it's nearly 6, you know,
13 nearly a pH of 6 really. Very weak acidity.

14 Q. Is it your testimony that a pH 5 is the
15 same as a pH of 6?

16 A. 5.75 and 5.56 round up to pH of 6. I
17 mean, I don't know how the pH was calculated.
18 Several different ways of calculating that. You
19 can measure it with a pH probe even. But it's --
20 pH of 6 or 5.56 or 5.75 is certainly closer to
21 neutral than a pH of 1.

22 Q. What is -- what about the citric acid

1 used when making the citric salt, would that
2 qualify as a weak acid?

3 A. Yes.

4 Q. And I'll point you back to column 12 in
5 the specification.

6 So around line 34 it says (as read):
7 In certain preferred embodiments, the pH of a
8 composition containing endoxifen according to the
9 present invention are between 4 and 8.

10 A. Sorry. I'm just going back to column
11 12. Oh, yes, I see.

12 Q. Yeah, yep. You see that?

13 A. I see, yeah. I mean, preferably above
14 5 it's suggesting, which is quite in line with
15 what we saw with those enabling examples.

16 Q. But you agree with me that it says the
17 pH range -- in a preferred embodiment the pH is
18 between 4 and 8, correct?

19 A. Yes. And if I recall correctly, the --
20 well, I think the pKa of citric acid is, you know,
21 going to sit around 4 or so. I mean -- sorry.
22 The measured pH, let's say, of citric acid in

1 solution depending on the concentration, of
2 course.

3 Q. Uh-huh.

4 A. Will sit around there. But it's a
5 buffer system. You can adjust the pH above 4
6 quite easily with citric acid and sodium citrate
7 for example.

8 Q. I just want to -- is it fair to say
9 that a POSA reading the Ahmad patent would
10 understand that you could mix (Z)- or
11 (E)-endoxifen with a weaker acid from pH 4 on up?

12 A. I think a person of ordinary skill as a
13 formulation scientist would look at this and
14 realize there that the endoxifen -- (Z)-endoxifen
15 should not really go below a pH of 4. I think
16 that that's a valid concern.

17 And, you know, that the -- the -- the
18 fact that the patent describes the use of an
19 enteric coat sort of confirms this, underscores
20 that. The examples that are listed have a higher
21 pH than 5 as well. So, you know, 4 seems to be
22 some sort of number that below 4 could be a higher

1 concern, yeah.

2 And I don't know why exactly without
3 digging deep into this. And, you know, maybe a
4 chemist might be able to answer that. But, you
5 know, at the end of the day, a formulation
6 scientist would understand that aspect.

7 Q. Okay. Okay. I want to turn now --
8 it's going to get a little confusing on our
9 screens. We're going to look at Ahmad 2010 and
10 Ahmad 2012, which those are Exhibits 1006 and
11 1007. So maybe we can start with 1006.

12 (McConville Deposition Exhibit 1006
13 and Exhibit 1007 were introduced for
14 identification.)

15 BY MS. KRUMPLITSCH:

16 Q. And, Dr. McConville, I just want to
17 make sure I understand your opinion with respect
18 to ground 6, which is the combination of Ahmad,
19 the patent, Ahmad 2010 and Ahmad 2012.

20 And tell me if I get this wrong. But
21 it's your opinion that the combination of those
22 three render obvious both the dosage and the pK

1 ranges.

2 Is that a fair summation of your
3 opinions?

4 A. Yeah, more or less, I think so.

5 Q. And you agree with me, don't you, that
6 Ahmad 2010, which is Exhibit 1006, and Ahmad 2012,
7 which is Exhibit 1007, neither of those references
8 disclose the ratio of (E)- to (Z)-isomers in the
9 endoxifen preparations that are used, correct?

10 A. Well, that is correct. But, you know,
11 again, I would say a person of ordinary skill
12 knowing that (Z)-endoxifen has higher activity
13 would think about that in a formulation.

14 Q. And if you use the less potent
15 (E)-isomer of endoxifen, you would expect to need
16 a higher dosage, correct?

17 A. That I -- you might expect that.

18 Q. And if the dosage of the endoxifen
19 composition is at the upper end of the claimed
20 range, wouldn't it be important to understand what
21 the isomeric ratio of the composition is?

22 A. I'm sorry. Could you repeat that?

1 Q. If you're giving a dose of endoxifen
2 composition at a -- the higher end of, let's say,
3 200 milligrams, wouldn't it be important to
4 understand what the isomeric ratio of the
5 composition is, whether it's more (Z) or more (E)?

6 A. I -- I don't know about that.

7 Q. Do you agree or disagree that the
8 isomeric ratio of the endoxifen would affect the
9 dosage needed to achieve claimed pharmacokinetic
10 effect?

11 A. No.

12 Q. Just so I understand, it's your
13 understanding that the isomeric ratio of (Z) to
14 (E) would have no impact on the dosage needed to
15 achieve a particular pharmacokinetic value?

16 A. That's right.

17 Q. Why do you say that?

18 A. I -- I don't understand how a
19 difference in (Z) or (E) can affect the
20 pharmacokinetic measurements of (Z)- or
21 (E)-endoxifen. I don't see that there would be a
22 difference.

1 Q. So the fact that -- I'm just trying to
2 understand.

3 The fact that (Z) is a more active
4 isomer, if you had a composition that was 100
5 percent (Z) compared to a composition that was 100
6 percent (E), you'd expect those compositions to
7 have the same pK values?

8 A. I -- I might, yes.

9 Q. So the activity of the isomer has no
10 impact on the pK values?

11 A. I don't see why it would.

12 Q. Could the solubility be different for
13 the (Z)- and (E)-isomers?

14 A. I haven't seen any information to
15 suggest that. And I can't think why it would be
16 really significantly different. I -- I -- I don't
17 think that there would be much of a difference in
18 vivo that would affect the pharmacokinetics.

19 Q. Did you do any analysis of whether or
20 not the pharmacokinetics would differ between (E)
21 and (Z)?

22 A. No, I didn't do any studies to look at

1 those different pharmacokinetics. I -- I wouldn't
2 think that there would be a difference in
3 pharmacokinetics between the two isomers.

4 Q. So it's your understanding that an
5 80 percent (Z)-endoxifen would have the same
6 pharmacokinetic parameters as a 90 percent
7 (Z)-endoxifen?

8 A. I mean, you are talking about the
9 purity here, not the concentrations, right? So --
10 so just to -- I mean, I just want to clarify this.

11 When -- when you say 90 percent
12 (Z)-endoxifen, do you mean that the other 10
13 percent is (E)-endoxifen?

14 Q. Yes.

15 A. Okay. And so when you say 80 percent
16 (Z)-endoxifen, you're assuming 20 percent
17 (E)-endoxifen?

18 Q. Yes. I'm talking about the isomeric
19 purity.

20 A. Okay. In that case we have in both
21 cases 100 percent endoxifen, whether it be (Z) or
22 (E) .

1 Is that what you mean?

2 Q. Hold on.

3 Yes.

4 A. Okay. I don't think there would be a
5 difference in pharmacokinetics.

6 Q. So we have been going about an hour.

7 Could we take a five-minute break?

8 A. Yeah.

9 THE STENOGRAPHER: We are off the
10 record at 10:16.

11 (Whereupon, a recess was taken
12 from 10:16 a.m. to 10:23 a.m.)

13 THE STENOGRAPHER: We are back on
14 the record at 10:23.

15 BY MS. KRUMPLITSCH:

16 Q. Dr. McConville, can you look at
17 paragraph 36 of your reply declaration? It's on
18 page 22.

19 A. Okay.

20 Q. And here you're saying that a
21 90 percent endoxifen capsule would not have the
22 exact same pK values as an (E)/(Z)-endoxifen

1 citrate tablet. And the difference in
2 pharmacokinetics can be attributed to the
3 difference in dosage form, tablet versus capsule.

4 Is that an accurate statement of what
5 you opined?

6 A. Yeah. That's accurate, yes.

7 Q. Okay. So following on the -- what we
8 were discussing right before we took a break, if
9 you have a 90 percent -- sorry, a 90 percent (Z)
10 enteric-coated capsule and an 80 percent (Z)
11 enteric capsule, you'd expect them to have the
12 same pharmacokinetic values because the difference
13 between the 80 and the 90 percent purity would not
14 impact pharmacokinetics?

15 A. Yes, if the only difference is that
16 purity but it is 100 percent (Z)-endoxifen --
17 sorry, 100 percent endoxifen in both cases --

18 Q. Uh-huh.

19 A. -- I don't expect to see a difference.

20 Q. Okay. And that same question.

21 If you have a 90 percent (Z)-endoxifen
22 enteric capsule and an 80 percent (Z)-endoxifen

1 citrate enteric capsule -- so, again, that -- the
2 enteric capsule is the same -- would you expect a
3 difference in pharmacokinetic values?

4 A. And, sorry. Just I got a little lost
5 there.

6 Q. Yeah. Sorry.

7 A. Just to make sure we're -- so we have a
8 90 percent (Z)-endoxifen base-containing capsule
9 and a 90 percent (Z)-endoxifen citrate -- sorry.

10 You mean an 80 percent?

11 Q. Yes, yes. So -- so both of these are
12 going to be -- let's take it one step at a time.

13 Both are in the same enteric capsule.
14 One is a 90 percent (Z)-endoxifen and the other is
15 an 80 percent (Z)-endoxifen.

16 I think I understand your testimony to
17 say that those two would have the same
18 pharmacokinetics, right?

19 A. I think so, yes.

20 Q. Okay. And then if we have both in the
21 -- I hate to use my hands here -- both in the same
22 enteric capsule, one is a 90 percent (Z)-endoxifen

1 and the other is an 80 percent endoxifen citrate,
2 would you expect the pharmacokinetic values to be
3 the same?

4 A. I think it would have to be measured.
5 I don't know for sure. It could be.

6 Q. And is it your testimony that if two
7 compounds have different solubility, this would
8 not change the pK parameters or would a difference
9 in solubility change the pK parameters?

10 A. That, I think -- I -- I -- well, I
11 don't -- I don't know for sure. This is something
12 that would have to be tested. Rather the
13 dissolution rate is more important than the
14 solubility. And -- well, the concentrations on
15 either side of the absorbing membrane are
16 important, too.

17 So the rate of absorption of the drug
18 (Z)-endoxifen, whether it's from a citrate or
19 whether it's from a free base, is -- is dependent
20 on concentrations.

21 Q. Can solubility impact the dissolution
22 rate?

1 A. It can, yes. Just -- just to add, that
2 generally the solubility of a salt is higher than
3 that of a free base or free acid drug.

4 Q. Can you turn to paragraph 39 on page
5 23?

6 A. Okay. I'm there.

7 Q. Okay. And is it your opinion that a
8 POSA would -- so tamoxifen -- sorry. Let me
9 withdraw that.

10 Is it your opinion that a POSA would
11 have known the target pharmacokinetics of a
12 90 percent pure (Z)-endoxifen because the
13 pharmacokinetics of tamoxifen were already known?

14 A. I think this -- this is a -- somewhat a
15 starting point for a person of ordinary skill. It
16 was known to be -- tamoxifen was metabolized into
17 endoxifen. And so given that that was known, it
18 may give a person of ordinary skill an idea about
19 the dosing required. And then obviously in Ahmad
20 the -- both those references, he describes a
21 suitable dose using endoxifen.

22 Q. And do you have understanding of what

1 endoxifen composition was provided in Ahmad 2010
2 and 2012?

3 A. Let me just go back and look at that if
4 you don't mind.

5 (Witness reviewing document.)

6 THE WITNESS: So it's my
7 understanding that the 2010 publication
8 with Ahmad describes the use of an
9 enteric-coated tablet.

10 Let me just pull up the 2012
11 just to confirm. So that's 1007.

12 Here it describes oral dose.
13 And I can't see exactly what specific oral
14 dose that is.

15 BY MS. KRUMPLITSCH:

16 Q. And there's no specific disclosure of
17 the (E) to (Z) ratio in Ahmad 2010 and 2012,
18 correct?

19 A. There is a no specific disclosure of
20 that, no.

21 Q. But as I understand your testimony,
22 it's almost irrelevant what the (E) to (Z) ratio

1 is on the resulting pharmacokinetics; is that
2 right?

3 A. I think so, yes.

4 Q. And going back to the tamoxifen
5 discussion of paragraph 39.

6 Did you look at any literature
7 comparing the pharmacokinetics of tamoxifen with
8 endoxifen?

9 A. I think that the only review I looked
10 at was really related in this Ahmad 2010
11 publication where there's a 20 milligram dose of
12 tamoxifen administered.

13 Q. Okay.

14 A. So we have pharmacokinetic parameters
15 described there.

16 Q. In paragraph 40 -- I'll give you a
17 second to read 40 through 42 on page 24.

18 (Witness reviewing document.)

19 THE WITNESS: Okay.

20 BY MS. KRUMPLITSCH:

21 Q. Are you ready to go or did you want to
22 take --

1 A. Yes.

2 Q. Okay.

3 A. No, no. I looked at it. I was saying
4 okay. Sorry. Should be more specific.

5 Q. Okay. No problem.

6 So in paragraph 40 you state that to
7 the -- it's the last sentence (as read): To the
8 extent patent owner is arguing that the synthetic
9 method taught in the '334 patent leads to improved
10 pharmacokinetics over other synthetic methods, the
11 claims are not limited to that method.

12 Do you see that?

13 A. Yes.

14 Q. Do you agree that residual solvent
15 content could affect pharmacokinetics as a general
16 proposition?

17 A. Not -- no, I don't think that the
18 extent of any residual solvent in formulation
19 that's been approved by an institutional review
20 board for a pharmacokinetic study in humans would
21 have any impact on the pharmacokinetics.

22 Q. And that's just coming from your

1 general knowledge of a person of ordinary skill in
2 the art?

3 A. I think that if a dosage form
4 containing a drug of any type meets pharmacopoeia
5 standards for -- which means it would be suitable
6 for human use and -- and an institutional review
7 board agrees that certain standards are met, I
8 don't think there would be enough residual solvent
9 to cause any concern.

10 Q. Okay.

11 A. Sorry. Let me just add, the only
12 difference is if you actually deliberately add
13 solvent to make, you know, something like a liquid
14 dosage form or pre-dissolve the drug. Then of
15 course you have a different starting point.

16 Q. Is it fair to say that if there were
17 sufficient residual solvents, that might impact
18 pharmacokinetics?

19 Is that what you're saying?

20 A. No, it's not what I'm saying. I'm
21 saying if you had a different dosage form you
22 might affect pharmacokinetics. But if you're

1 comparing a tablet against a tablet -- I mean, are
2 we talking about two different (Z)-endoxifen
3 sources here now? I'm a little confused to what
4 the comparison is really.

5 Q. Okay. So I guess, you know, at the
6 most basic level, I'm trying to ask if you have a
7 tablet with a certain amount of residual solvent
8 and one that doesn't have that same residual
9 solvent, whether the difference between the two
10 could result in a difference in pharmacokinetics.

11 A. I don't think it would be suitable for
12 dosing if there was, you know, any -- enough to
13 have any effect. I don't think there would be
14 approval from an IRB perspective or to do a human
15 study.

16 You'd have to have so much. There
17 wouldn't really be a residual solvent. I think
18 the definition of residual means it's not going to
19 do anything.

20 Q. Okay. I understand your testimony
21 there.

22 And then with respect to the presence

1 of chemical impurities, so you have a tablet that
2 has -- you know, the same dose -- same like
3 enteric-coated tablet, one has a certain amount of
4 chemical impurities, the other one has a different
5 impurity profile.

6 Could that difference in impurity
7 profiles impact pharmacokinetics?

8 A. You're just talking about the purity of
9 the drug, correct?

10 Q. Right. I suppose if you had a higher
11 level of chemical impurity, you'd have a lower
12 purity of the drug. But different -- let's just
13 say same purity, different chemical impurities.

14 A. And when you say different chemical
15 impurities, do you specific -- I mean, trying to
16 be specific here.

17 Q. Uh-huh.

18 A. Because my testimony has been about
19 (Z)- and (E)-endoxifen not really affecting
20 pharmacokinetics at all. So when you talk about
21 impurities, you're not meaning there's more
22 (E)-endoxifen in one (Z)-endoxifen formulation are

1 you or --

2 Q. No. Say we've got tablets that --
3 okay. So enteric coated tablets in both
4 scenarios. Both have the same isomeric purity but
5 they have different impurity profiles.

6 A. I can't say. I mean, it's very
7 difficult. I don't know what the impurities might
8 be. And, you know, it's a difficult hypothetical
9 for me to answer. Sorry.

10 Q. I appreciate that.

11 Do you agree or disagree that
12 (Z)-endoxifen can isomerize to a mixture of (Z)-
13 and (E)-isomers in the presence of acid?

14 A. It's more of a chemistry question. But
15 that that's a general understanding in strong
16 acids, that can occur.

17 Q. And do you have any knowledge as to
18 whether that can happen in a weak acid -- weaker
19 acid?

20 A. When I look at the Ahmad publication we
21 -- we looked at earlier, the patent, it's my
22 understanding that weaker acids don't pose much of

1 a problem.

2 Q. Okay. And you're basing that on the
3 Ahmad patent, just to be clear?

4 A. Yeah. I don't have any other in-depth
5 chemical knowledge of the stability.

6 Q. Okay. And do you agree or disagree
7 that (Z)-endoxifen can isomerize to a mixture of
8 (E)- and (Z)-isomers in the presence of heat?

9 A. I mean, possibly at very high
10 temperatures. I -- again, I wouldn't -- I haven't
11 investigated the thermal stability of
12 (Z)-endoxifen. I -- it is possible. I know high
13 temperatures can, you know, induce quite a few
14 reactions.

15 Q. Would a POSA consider the stability of
16 the API during synthesis?

17 A. I think a synthesis person would
18 consider stability of the final product, yeah.

19 Q. And would a POSA consider the stability
20 of the API during formulation?

21 A. Yes.

22 Q. And would you agree or disagree that a

1 POSA would want to avoid isomerization of the
2 (Z)-endoxifen to a mixture of (Z)- and (E)-isomers
3 during synthesis?

4 A. That, I'm not sure of during synthesis.
5 As long as there's a purification step, you know.
6 I suppose, you know, you want maximum yield if
7 you're trying for (Z)-endoxifen. But I suppose
8 you would want to avoid isomerization during
9 synthesis to get a maximum yield at the end. But
10 as long as there's a purification step, I think it
11 should take care of too many issues.

12 Q. And would you agree that a POSA would
13 want to avoid isomerization of (Z)-endoxifen to a
14 mixture of (Z)- and (E)-isomers during
15 purification?

16 A. Yes, I suppose so.

17 Q. And would you also agree that a POSA
18 would want to avoid isomerization of (Z)-endoxifen
19 to a mixture of (Z)- and (E)-isomers during
20 formulation?

21 A. If their goal was to use (Z)-endoxifen,
22 yes.

1 Q. And did you look for any guidance in
2 the prior art regarding how to prevent
3 isomerization of (Z)-endoxifen during synthesis?

4 A. No, that would have been more of a
5 chemical expert.

6 Q. Did you look for any guidance in the
7 prior art regarding how to prevent isomerization
8 of (Z)-endoxifen during formulation?

9 A. You know, a person of ordinary skill
10 would perhaps have considered that issue with the
11 acidity. You know, and obviously steps are taken
12 by using an enteric coat for formulation to
13 protect against stomach acid. So that's a check
14 there. And, you know, things like the coating
15 process that I mentioned that may have some --
16 some heat.

17 Again, routine testing of the -- the
18 finished product to make sure that the potency of
19 the finished product is -- has the desired amount
20 of (Z)-endoxifen. I think those sorts of
21 stability questions are commonly raised during
22 formulation and storage. And it's a simple matter

1 of routine testing to ensure the product quality.

2 I think it's done across the board for all drugs.

3 Q. So I understand your testimony that

4 this is routine testing to test for the

5 isomerization. But the question is a little bit

6 more nuanced than that.

7 And it is whether or not you found any

8 guidance in the art about conditions to avoid, to

9 prevent isomerization.

10 A. Well, you know, not -- not specifically

11 about the isomerization issue with (E)-endoxifen

12 -- (Z) or (E)-endoxifen issues. More guidance of

13 testing the formulations at the end.

14 I mean, at the very basic level,

15 there's a simple test in the United States

16 Pharmacopeia that requires content uniformity

17 testing. This is done for all formulations. And

18 prior to any type of clinical study for sure,

19 even. And then it's done on batch-to-batch

20 testing of products that are available for

21 purchase or approved products.

22 But this requires -- if the test is for

1 (Z)-endoxifen, it would require that there is a
2 certain level of (Z)-endoxifen that is acceptable.
3 There would be a -- you know, typically a standard
4 deviation that was allowable around a mean
5 concentration for a particular active therapeutic
6 compound. And so it's very, very routine.

7 Of course, if -- if a formulator makes
8 a formulation and it falls below a threshold, they
9 would, of course, look at what was done and try to
10 avoid particular issues. So humidity, heat.
11 These are all common things for all types of
12 formulations.

13 Q. And I just want to make sure I
14 understand.

15 So I understand the necessity to do
16 stability testing, especially, you know, after a
17 drug product has been sitting, you know, for three
18 months or six months or even after it's
19 manufactured. So I understand that this type of
20 testing would be done and that some of like the
21 pharmacopeia that you mentioned and the guidances.

22 But did you find any guidances in the

1 prior art specifically regarding how to prevent
2 isomerization from (Z) to (E)?

3 A. I think isomerization is nothing new
4 for this compound. I think it's a general
5 stability question. And, you know, the -- there's
6 guidance on checking for stability. The
7 simplified -- the simple test of drug content
8 uniformity takes care of the issue of
9 isomerization as well.

10 Q. Okay. And then sitting here today, you
11 cannot identify any reference that provided this
12 knowledge about what conditions to avoid during
13 formulation to avoid this isomerization problem,
14 correct?

15 A. Everybody's frozen. Okay. You're
16 back. It was frozen for a second there I think.
17 We're okay.

18 Q. Do you want me to -- should we read
19 back that last question?

20 A. Okay. It's having a little instability
21 but I think it's okay now.

22 I was just saying on my last -- my last

1 sentence, unless it froze, that I think
2 isomerization falls into the category of general
3 stability. It's another consideration a person of
4 ordinary skill would generally have.

5 MS. KRUMPLITSCH: Okay. I think
6 with that, and maybe with the instability
7 issues with respect to our connections
8 here, let's go off the record.

9 If we could do ten minutes, 15
10 minutes -- 15 minutes. I just want to kind
11 of look back and make sure that we've
12 covered everything we need to cover and
13 then we can wrap up if that's okay with
14 everyone.

15 THE WITNESS: Okay.

16 MS. KRUMPLITSCH: So let's come back
17 at 4 or 5 past the hour.

18 THE STENOGRAPHER: We're off the
19 record at 10:51.

20 (Whereupon, a recess was taken
21 from 10:51 a.m. to 11:08 a.m.)

22 THE STENOGRAPHER: We are back on

1 the record at 11:08 a.m.

2 BY MS. KRUMPLITSCH:

3 Q. Dr. McConville, do you agree that a
4 citrate salt and free base of endoxifen have
5 different solubilities?

6 A. I would assume so, yes.

7 Q. Did you try to investigate this?

8 A. I can't recall whether at some point I
9 tried to look those up. It's possible prior to my
10 first declaration that I might have tried to look
11 it up and drawn a blank.

12 Q. Could you predict the rate of
13 absorption of each of these -- the citrate salt
14 and the free base of endoxifen?

15 A. I mean, I -- I didn't make any effort
16 to do that. I -- I suppose there are some --
17 there is some software modeling that could be used
18 to do that, to give some sort of prediction. But
19 ultimately it's -- it's something to -- you know,
20 to test.

21 Q. The software modeling, would that -- so
22 I'm trying to understand the state of the art as

1 of 2017 or 2018.

2 Would that software modeling be
3 available then?

4 A. I think so, yeah. But it's no
5 substitute for testing at all. And in fact, with
6 search systems, there's usually a disclaimer to
7 indicate that one must perform a test to confirm
8 results.

9 MS. KRUMPLITSCH: I'm going to go
10 off the record for two seconds. Everyone
11 stay there. I'll be right back.

12 (Whereupon, a discussion was had
13 off the record at 1:10 p.m.)

14 MS. KRUMPLITSCH: Dr. McConville,
15 thank you very much for your time. We
16 don't have any further questions.

17 THE WITNESS: Thank you.

18 MR. MENCHACA: I have questions.

19 EXAMINATION

20 BY MR. MENCHACA:

21 Q. Dr. McConville, please turn to page 22
22 of your reply report, Exhibit 1031, paragraph 36.

1 And I'm going to focus on the bottom two sentences
2 of that paragraph.

3 The first -- or the bottom two
4 sentences read (as read): Rather, I opined that
5 the pharmacokinetic limitations in the '334 patent
6 are the inherent and natural result of dosing a
7 patient with a 90 percent (Z)-endoxifen capsule as
8 taught in Ahmad. In other words, the '334 patent
9 simply claims the results of dosing a patient with
10 90 percent (Z)-endoxifen capsules, which was known
11 in the art.

12 Did I read that accurately?

13 A. Yes.

14 Q. I'd like you to turn to paragraph 39 --
15 I'm sorry, paragraph 38 on page 23. I'm going to
16 start with the first sentence.

17 And it reads (as read): This is simply
18 the natural result of dosing a patient with 90
19 percent (Z)-endoxifen in an enteric-coated capsule
20 - and a POSA would have expected the same or very
21 similar results dosing a patient with the
22 90 percent pure (Z)-endoxifen enteric capsules

1 taught in Ahmad.

2 Did I read that accurately?

3 A. Yes.

4 Q. The first word of that sentence is
5 "this."

6 By that word "this," are you referring
7 to the pharmacokinetic characteristics that appear
8 as claim limitations in some of the claims of the
9 '334 patent?

10 A. Yes, those -- those limitations seem to
11 be inherent to me.

12 Q. Yes. Earlier counsel asked you a
13 question regarding your opinion as to the
14 disclosure in the prior art of the pharmacokinetic
15 limitations, something along the lines of what
16 your opinion was as to how the prior art disclosed
17 those pharmacokinetic limitations.

18 Do you recall that testimony at all?

19 A. I think so. Right. Yeah.

20 Q. Can you -- can you go ahead and explain
21 to us what is your opinion regarding how the prior
22 art discloses the pharmacokinetic limitations that

1 appear in some of the claims of the '334 patent?

2 A. Okay. So let me -- I think we have the
3 -- did we send over the '334 patent early on? I
4 can't recall if it was one of the exhibits
5 presented to me. I don't think it was the '334
6 patent. I don't think it was an exhibit sent over
7 to me. So I don't have it to hand.

8 But if I recall correctly from the '334
9 patent, there is a dosing limitation, which is
10 quite broad. And that dosing is reflected in
11 other claims that talk about the Cmax and area
12 under curve as limitations.

13 And in fact, I think it refers to
14 pharmacokinetics related to a particular dose. So
15 for every 4 milligrams of endoxifen administered,
16 there is a subsequent pharmacokinetic range either
17 put on the Cmax or area under curve for two of the
18 claims.

19 Q. Having reviewed paragraphs 36 and 38 of
20 your report, can you explain to us your opinion as
21 to how the prior art discloses the pharmacokinetic
22 limitations that appear in some of the claims of

1 the '334 patent?

2 A. Yes. So the '334 patent describes the
3 use of neat (Z)-endoxifen to provide
4 pharmacokinetic range with an area under curve as
5 well as Cmax. So the prior art also discloses the
6 same range of (Z)-endoxifen administered and the
7 ranges fall within the claim ranges, too.

8 Q. From your answer I understood you to
9 reference some of the information in paragraph 37
10 wherein you indicate that the '334 patent teaches
11 the use of neat (Z)-endoxifen and the
12 pharmacokinetic tests were simply measuring the
13 administration of that neat (Z)-endoxifen.

14 Is that what you're saying?

15 A. Yes, that's exactly right.

16 Q. Separately on a different issue,
17 counsel asked you a number of questions regarding
18 the pharmacokinetics of (E) and (Z) mixtures of
19 endoxifen.

20 My understanding of that testimony was
21 that it's your opinion that the pharmacokinetics
22 of (E) and (Z) mixtures is the same regardless of

1 percentage of each isomer.

2 Is that -- was that your testimony?

3 A. Yes, that's my testimony.

4 Q. What are the pharmacokinetic
5 characteristics you are referencing?

6 A. That would be particularly Cmax and
7 area under curve.

8 MR. MENCHACA: I have no further
9 questions.

10 MS. KRUMPLITSCH: I do.

11 FURTHER EXAMINATION

12 BY MS. KRUMPLITSCH:

13 Q. Dr. McConville, you state in paragraph
14 38, as counsel just read into the record, that (as
15 read): A POSA would have expected the same or
16 very similar results dosing a patient with a
17 90 percent pure (Z)-endoxifen enteric capsules
18 taught in Ahmad.

19 I asked you earlier at the deposition
20 where in Ahmad there is a description of dosing a
21 patient with a 90 percent pure (Z)-endoxifen
22 enteric capsule.

1 And you were not able to identify that
2 for me, correct?

3 A. So which -- so are you -- let me just
4 get this straight on which Ahmad reference we're
5 talking about. The 2010 --

6 (Simultaneous speaking.)

7 BY MS. KRUMPLITSCH:

8 Q. I don't mean to interrupt. I'm talking
9 about the Ahmad patent.

10 A. Oh, okay. Sorry. Well, as I pointed
11 out, the Ahmad patent specifically describes this
12 oral dosage form with an enteric coating.

13 Q. Right. And, again, I understand that
14 you were able to point to words in the
15 specification that reference an oral dosage form
16 and that reference an enteric coating.

17 I'm asking if you can identify anyplace
18 in Ahmad where a patient, a human being, was dosed
19 with a 90 percent (Z)-endoxifen enteric capsule.

20 A. My -- it's my understanding that Ahmad
21 describes that type of dose. There is no data in
22 there which reflects that type of dose exactly.

1 Q. And I understand your testimony when
2 counsel was pointing to you paragraph 37 of your
3 expert report where you are discussing --
4 actually, do you need to look at paragraph 37 for
5 a second?

6 A. I have it right here.

7 Q. Okay. And you said that the prior art
8 -- let's see if I can pull up your testimony real
9 quick.

10 That prior art references fall under
11 the same pK ranges that are claimed in the '334
12 patent.

13 Is that your testimony?

14 A. Yes.

15 Q. Some prior art references fall outside
16 of that, those pK ranges, correct?

17 A. Which -- which ones are you referring
18 to?

19 Q. Well, let me ask you: Is it your
20 testimony that all of the prior art that you have
21 cited in this case that discloses pK ranges, all
22 of those pK ranges are within the pK ranges cited

1 within the '334 patent?

2 A. Well, it's my testimony that at least
3 some of the prior art falls within those ranges
4 and the pharmacokinetic parameters reflected
5 within the same ranges as claimed by the patent,
6 the prior art.

7 Q. Okay. So you agree with me that some
8 of the prior art references you've discussed fall
9 outside of those ranges?

10 A. Well, I'd have to dig into that. But I
11 think in general the prior art describes this
12 scalable or linear pharmacokinetic relationship.
13 And when you look at the dose ranges in the
14 patent, which are very broad, they encompass that
15 scaling range, especially since the patent
16 describes this very broad range as being
17 applicable to each 4 milligrams of drug.

18 Q. So sitting here today, you can't tell
19 me whether all of the prior art references fall
20 within that pK range or just some of them do?

21 A. At least some of them do. I'd have to
22 look more specifically.

1 Q. And we could easily check that, right?
2 We could look at the ranges that are cited in the
3 prior art and compare them to the patent?

4 A. Yeah, I mean, specifically when we look
5 at the endoxifen 4 milligrams, which is, you know,
6 claimed within the patent, that falls smack bang
7 within the range claimed.

8 So, you know, the patent describes this
9 4 milligrams of endoxifen and, you know, the prior
10 art shows us ranges that fall within that scale.
11 So if we think about per 4 milligram, that's
12 probably the easiest place to start.

13 Q. So, again, it would be real easy to
14 look at the prior art and the pharmacokinetic
15 ranges that are reported and compare those to the
16 patent, correct?

17 A. So the patent is very clear about it
18 being per 4 milligram in the claims.

19 Q. And why is it relevant?

20 A. Because we have data in the prior art
21 which talks about 4 milligrams of endoxifen
22 dosing.

1 Q. And which prior art are you referring
2 to?

3 A. I guess I'm looking at Exhibit 1006,
4 which is the Ahmad publication from 2010. And
5 there's a table. Table 1 indicates the endoxifen
6 ranges doses. You know, we can just look at the
7 4 milligram dose and look at Cmax and area under
8 curve.

9 Q. And if we looked at Ahmad 2012, you
10 would agree with me that Ahmad 2012 reports
11 different pharmacokinetic data for a 4 milligram
12 endoxifen citrate dose, correct?

13 A. The Ahmad 2012 is a multiple dosing
14 paper.

15 Q. So that wasn't my question,
16 Dr. McConville.

17 The pharmacokinetics reported in Ahmad
18 2012 are different than the pharmacokinetics
19 reported in Ahmad 2010, correct?

20 A. Hang on a second here. So, you know,
21 this is after multiple dosing. So of course
22 they're going to be different. You're going to

1 have different Cmax and different area under
2 curve. That means multiple dosing. These are
3 average steady-state parameters in the 2012
4 publication. The patent doesn't talk about steady
5 state in the claims.

6 Q. And that is a distinction you're
7 drawing between the two?

8 A. Well, I mean, one would expect there to
9 be differences. I mean, you know, to reach steady
10 state, you'd have to have multiple dosing. And so
11 when you compare single pK dose against a single
12 pK dose, that's very different to comparing a
13 single pK dose -- sorry, sorry, a single
14 pharmacokinetic peak against a multiple dosing
15 regimen. Those are different things.

16 MS. KRUMPLITSCH: Let's go off the
17 record for two minutes so I can clean this
18 up. And then I think we'll be done.

19 (Whereupon, a discussion was had
20 off the record at 1:28 p.m.)

21 MS. KRUMPLITSCH: We have no further
22 questions.

1 THE WITNESS: Thank you.

2 MR. MENCHACA: I have no further
3 questions.

4 THE STENOGRAPHER: We are off the
5 record at 11:28 a.m.

6 (Time concluded: 11:28 a.m.)

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1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

2 I, Janice M. Kocek, Certified Shorthand
3 Reporter, Certified LiveNote Reporter, and
4 Notary Public within and for the State of Illinois,
5 do hereby certify:

6 That JASON T. MCCONVILLE, PH.D., the
7 witness whose deposition is hereinbefore set
8 forth, was duly sworn by me before the
9 commencement of such deposition and that such
10 deposition was taken before me and is a true
11 record of the testimony given by such witness.

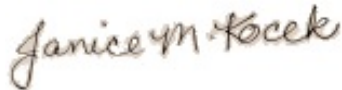
12 I further certify that the adverse
13 party, PETITIONER, was represented
14 by counsel at the deposition.

15 I further certify that the deposition
16 of JASON T. MCCONVILLE, PH.D., occurred via Zoom
17 videoconference, on the 15th day of August, 2024,
18 commencing at 7:59 a.m. Pacific to 11:28 a.m.
19 Pacific.

20 I further certify that I am not related
21 to any of the parties to this action by blood or
22 marriage, I am not employed by or an attorney to

1 any of the parties to this action, and that I am
2 in no way interested, financially or otherwise, in
3 the outcome of this matter.

4
5
6 IN WITNESS WHEREOF, I have hereunto
7 set my hand and this 20th day of
8 August, 2024.

9
10 
11 _____

12 My commission expires:

13 12/18/24

14 NOTARY PUBLIC IN AND FOR THE
15 STATE OF ILLINOIS
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