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Transcript of Jason T. McConville, Ph.D.

Date: April 12, 2024

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

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Transcript of Jason T. McConville, Ph.D.
Conducted on April 12, 2024

1 (1 to 4)

<p>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 DEPOSITION OF 16 JASON T. MCCONVILLE, PH.D. 17 Friday, April 12, 2024 18 8:56 a.m. CST 19 20 Reported by: 21 Janice M. Koczek, CSR, CLR 22 Job No. 529945</p>	<p>3 1 A P P E A R A N C E S: 2 3 FOR THE PETITIONER: 4 MCANDREWS HELD & MALLOY, LTD. 5 500 West Madison Street, 34th Floor 6 Chicago, Illinois 60661 7 312.775.8000 8 BY: ALEJANDRO MENCHACA, ESQ. 9 amenchaca@mcandrews-ip.com 10 11 FOR THE PATENT OWNER: 12 DLA Piper LLP 13 3203 Hanover Street, Suite 100 14 Palo Alto, California 94304-1123 15 650.833.2440 16 BY: SUSAN KRUMPLITSCH, ESQ. 17 susan.krumplitsch@dlapiper.com 18 701 Fifth Avenue, Suite 6900 19 Seattle, Washington 98104-7029 20 206.839.4815 21 BY: MELISSA M. HARWOOD, PH.D., ESQ. 22 melissa.harwood@dlapiper.com</p>
<p>2 1 The deposition of JASON T. MCCONVILLE, 2 PH.D., reported stenographically by Janice M. 3 Koczek, License No. 084-002871, Certified Shorthand 4 Reporter, Certified LiveNote Reporter, and Notary 5 Public of the state of Illinois, held at 500 West 6 Madison Street, Chicago, Illinois, commencing at 7 the hour of 8:56 a.m. CST, on Friday, April 12, 8 2024. 9 10 * * * 11 12 13 14 15 16 17 18 19 20 21 22</p>	<p>4 1 A P P E A R A N C E S: (Continued) 2 3 ALSO PRESENT: 4 ERIN M. GAFFNEY, Ph.D., 5 DLA Piper, Patent Agent 6 7 STEVEN QUAY, M.D., PH.D., 8 Atossa Therapeutics 9 10 11 12 13 14 15 16 17 18 19 20 21 22</p>

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<p>1 I N D E X</p> <p>2</p> <p>3 JASON T. MCCONVILLE, PH.D. PAGE</p> <p>4 Examination by Ms. Krumplitsch 7</p> <p>5</p> <p>6 E X H I B I T S</p> <p>7 EXHIBIT DESCRIPTION PAGE</p> <p>8 Exhibit 1 Curriculum Vitae of 13</p> <p>9 Jason T. McConville, PH.D.</p> <p>10 Exhibit 2 International Journal of 69</p> <p>11 Pharmaceuticals, Article by</p> <p>12 Berkenfeld, McConville, Lamprecht</p> <p>13 Exhibit 1001 United States Patent 22</p> <p>14 11,572,334 B2</p> <p>15 Exhibit 1003 United States Patent 47</p> <p>16 9,333,190 B2</p> <p>17 Exhibit 1004 WO 2017/070651 A1 64</p> <p>18 Exhibit 1005 WO 2012/050263 A1 91</p> <p>19 Exhibit 1006 Nature Publishing Group, 125</p> <p>20 Article by Ahmad, et al.</p> <p>21 Exhibit 1007 Journal of Clinical Oncology, 136</p> <p>22 Article by Ahmad, et al.</p>	<p>1 (Witness sworn.)</p> <p>2 JASON T. MCCONVILLE, PH.D.,</p> <p>3 called as a witness herein, having been first duly</p> <p>4 sworn, was examined and testified as follows:</p> <p>5 EXAMINATION</p> <p>6 BY MS. KRUMPLITSCH:</p> <p>7 Q. Good morning, Dr. McConville.</p> <p>8 A. Good morning.</p> <p>9 Q. So before this proceeding, you served</p> <p>10 as an expert witness in other PTAB proceedings; is</p> <p>11 that right?</p> <p>12 A. So do you mean with regard to like</p> <p>13 IPR-type cases?</p> <p>14 Q. Yes.</p> <p>15 A. Yeah, just a couple.</p> <p>16 Q. Okay. And were you cross-examined in</p> <p>17 connection with those proceedings?</p> <p>18 A. Once or twice I think, yes.</p> <p>19 Q. And you've also served as an expert in</p> <p>20 district court litigation, correct?</p> <p>21 A. Yes.</p> <p>22 Q. So you understand the ground rules of a</p>
<p>1 E X H I B I T S</p> <p>2 EXHIBIT DESCRIPTION PAGE</p> <p>3 Exhibit 1008 International Journal of 100</p> <p>4 Pharmaceuticals, Article by</p> <p>5 Cole, et al.</p> <p>6 Exhibit 1010 Capsule Technology, 109</p> <p>7 Article by Benameur</p> <p>8 Exhibit 1011 Capsugel, Article by 117</p> <p>9 Stegemann, Bornem</p> <p>10 Exhibit 1012 Handbook of Pharmaceutical 121</p> <p>11 Excipients, Fifth Edition</p> <p>12 Exhibit 1014 Endoxifen Tablets, Zonalta 27</p> <p>13 Exhibit 1020 Expert Declaration of 11</p> <p>14 Jason McConville, Ph.D.</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>	<p>1 deposition?</p> <p>2 A. More or less.</p> <p>3 Q. So we won't talk over each other for</p> <p>4 the beneficial of the court reporter.</p> <p>5 Do you understand that?</p> <p>6 A. Yes.</p> <p>7 Q. And that you need to answer all of my</p> <p>8 questions with a verbal answer.</p> <p>9 A. Yes.</p> <p>10 Q. And I'll assume that you understand my</p> <p>11 questions. If you do not, let me know, just let</p> <p>12 me know and I'll clarify.</p> <p>13 A. Yes, I will do.</p> <p>14 Q. We'll take a break whenever you need</p> <p>15 one. I try to go about an hour at a time. But if</p> <p>16 you need a break at any time, that's fine. I</p> <p>17 would just ask that you answer any pending</p> <p>18 question before we break.</p> <p>19 A. Okay. Thank you.</p> <p>20 Q. And you understand that you're offering</p> <p>21 sworn testimony under oath today, correct?</p> <p>22 A. I do, yes.</p>

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<p>9</p> <p>1 Q. Did you prepare for this deposition</p> <p>2 today?</p> <p>3 A. A little, yes.</p> <p>4 Q. How did you prepare?</p> <p>5 A. I essentially read through my report.</p> <p>6 It was prepared several months ago. So I wanted</p> <p>7 to refresh my memory on that. And looked at some</p> <p>8 of the exhibits also.</p> <p>9 Q. Did you meet with anyone to prepare for</p> <p>10 this deposition?</p> <p>11 A. Yes, I met yesterday with Alex and a</p> <p>12 couple of other attorneys just here in the office</p> <p>13 for a couple of hours.</p> <p>14 Q. A couple of hours?</p> <p>15 A. Yeah.</p> <p>16 Q. So that was just one day?</p> <p>17 A. Yeah, yeah.</p> <p>18 Q. Did you have any phone calls with</p> <p>19 attorneys other than your meeting yesterday?</p> <p>20 A. We had a phone call I think Tuesday. A</p> <p>21 lot of it was to do with logistics.</p> <p>22 Q. And other than meeting with your</p>	<p>11</p> <p>1 Q. And you're being compensated for your</p> <p>2 time testifying today?</p> <p>3 A. Yes.</p> <p>4 Q. How much?</p> <p>5 A. For live testimony it's \$900 an hour.</p> <p>6 Q. So I'm going to hand you what has been</p> <p>7 marked in this proceeding Exhibit 1020, which is</p> <p>8 your declaration.</p> <p>9 A. Oh, okay. Thank you.</p> <p>10 (Deposition Exhibit 1020 was</p> <p>11 introduced for identification.)</p> <p>12 BY MS. KRUMPLITSCH:</p> <p>13 Q. Do you recognize Exhibit 1020?</p> <p>14 A. Yes, it's a copy of my declaration.</p> <p>15 Q. Did you write Exhibit 1020?</p> <p>16 A. Yes.</p> <p>17 Q. How long did you spend writing</p> <p>18 Exhibit 1020?</p> <p>19 A. Well, there was meetings via -- I think</p> <p>20 we used Zoom or Teams. And we discussed relevant</p> <p>21 issues related to the matter at hand. And a draft</p> <p>22 was prepared based on my -- I guess my ideas and</p>
<p>10</p> <p>1 attorneys, reviewing your declaration and some of</p> <p>2 the exhibits, did you do anything else to prepare</p> <p>3 for this deposition?</p> <p>4 A. No.</p> <p>5 Q. Do you recall which exhibits you</p> <p>6 reviewed?</p> <p>7 A. I -- exhibits that are listed in my</p> <p>8 declaration and those really were our focus, yes,</p> <p>9 exactly.</p> <p>10 Q. How long did you spend reviewing those</p> <p>11 exhibits?</p> <p>12 A. Not -- not too long. Just looking over</p> <p>13 how they correlate to my report -- my declaration.</p> <p>14 Sorry.</p> <p>15 Q. Did you review the declaration of</p> <p>16 Dr. Davies?</p> <p>17 A. I did, yes.</p> <p>18 Q. Did you review any other exhibits cited</p> <p>19 by Atossa that are not cited in your declaration?</p> <p>20 A. No.</p> <p>21 Q. Just the Davies declaration?</p> <p>22 A. Just the declaration, yes.</p>	<p>12</p> <p>1 dictation with the attorneys that came back to me.</p> <p>2 And there was several iterations that went back</p> <p>3 and forth where I made corrections, inserted</p> <p>4 information, and -- so I -- I think it took a</p> <p>5 month or so to -- to prepare.</p> <p>6 Q. When did you start working on your</p> <p>7 declaration?</p> <p>8 A. I'm not sure exactly. It was I think</p> <p>9 beginning of the summer last year at some point.</p> <p>10 Q. Summer of 2023?</p> <p>11 A. Somewhere around then, yeah. There was</p> <p>12 a lot going on in the academic calendar at the</p> <p>13 time as well.</p> <p>14 Q. So if you could turn in your</p> <p>15 declaration to paragraph 3 on page 1.</p> <p>16 Are you there?</p> <p>17 A. Yes.</p> <p>18 Q. And do you see the reference to your CV</p> <p>19 attached as Appendix A?</p> <p>20 A. Yes.</p> <p>21 Q. So we did not receive that CV. That's</p> <p>22 okay.</p>

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<p>13</p> <p>1 Is the description of your education</p> <p>2 and professional background in your declaration</p> <p>3 accurate?</p> <p>4 A. Yes. So as I prepared this, this</p> <p>5 covers most of the highlights, if you like, from</p> <p>6 the CV, you know, in a written sense. The CV is</p> <p>7 more of a bullet-point list. So this -- this</p> <p>8 captures most of that.</p> <p>9 Q. Sure.</p> <p>10 MS. KRUMPLITSCH: And I would ask if</p> <p>11 we could mark this as McConville Exhibit 1.</p> <p>12 (McConville Deposition Exhibit 1</p> <p>13 was marked for identification.)</p> <p>14 BY MS. KRUMPLITSCH</p> <p>15 Q. Dr. McConville, the court reporter has</p> <p>16 marked what is Exhibit 1 to your deposition. This</p> <p>17 is a CV -- I'll represent that this is a CV that</p> <p>18 we found online. And it appears to be a CV that</p> <p>19 you submitted in a different IPR proceeding.</p> <p>20 A. Okay. This looks like my CV, yes. I'm</p> <p>21 not sure when this was last updated, this</p> <p>22 particular copy. But I can potentially fill in</p>	<p>15</p> <p>1 UNM.</p> <p>2 Q. Is that a small molecule?</p> <p>3 A. Yes. Most -- most of the research that</p> <p>4 I do is with small molecule drugs.</p> <p>5 Q. So if you could turn to your CV, which</p> <p>6 is Exhibit 1, on page 3, you'll see there's a</p> <p>7 heading, 6, entitled "Current Research Interests."</p> <p>8 Is this maybe a more succinct summary</p> <p>9 of your research interests than what you've just</p> <p>10 described?</p> <p>11 A. Yeah. So there's quite a -- it's a</p> <p>12 broad field, drug delivery and formulation</p> <p>13 science. And so this is a rather broad statement,</p> <p>14 which essentially covers what I just said, yeah.</p> <p>15 Q. Tell me a little bit about your project</p> <p>16 on oral drug delivery.</p> <p>17 A. So at the moment I am looking at 3D</p> <p>18 printed tablets and interaction with various</p> <p>19 excipients, you know, the inactive ingredients, to</p> <p>20 try to deliver drug in -- in various ways from</p> <p>21 immediate release formulations through to more</p> <p>22 sustained release or delayed release as well.</p>
<p>14</p> <p>1 any missing information you might require.</p> <p>2 Q. And so is it accurate to say that this</p> <p>3 CV is accurate but it perhaps was not -- is not up</p> <p>4 to date?</p> <p>5 A. Yes.</p> <p>6 Q. So you are currently an associate</p> <p>7 professor of pharmaceuticals at the University of</p> <p>8 New Mexico?</p> <p>9 A. That's correct.</p> <p>10 Q. In this role do you conduct research in</p> <p>11 pharmaceuticals?</p> <p>12 A. I do, yes.</p> <p>13 Q. And what specific areas of research are</p> <p>14 you currently pursuing?</p> <p>15 A. So I -- I'm doing a lot of formulation</p> <p>16 studies. And I have one project related to</p> <p>17 aerosol drug delivery. Another project related to</p> <p>18 thin film drug delivery. Another project related</p> <p>19 to oral drug delivery, so tablets and that sort of</p> <p>20 thing. And one other project related to -- well,</p> <p>21 it's a pre-cancerous therapy. It's a</p> <p>22 collaborative study with the medical school at</p>	<p>16</p> <p>1 Q. And why do you study the interaction</p> <p>2 between -- let me withdraw that.</p> <p>3 Why do you study the interaction with</p> <p>4 various excipients and the active ingredients?</p> <p>5 A. So the excipients really are the key to</p> <p>6 changing the drug delivery modality within the</p> <p>7 body. Albeit my research is in vitro at the</p> <p>8 moment. But hopefully this translates to an</p> <p>9 in vitro situation. And the excipients are really</p> <p>10 the gatekeepers of drug release, if you like.</p> <p>11 Q. So are you studying -- sorry. Let me</p> <p>12 withdraw that.</p> <p>13 Would different excipients translate to</p> <p>14 different release rates of the drug?</p> <p>15 A. Well, not to give too much away about</p> <p>16 the current research, but I'm trying to effect</p> <p>17 mostly one excipient and change its functionality.</p> <p>18 Q. And to see how that one excipient</p> <p>19 impacts drug release?</p> <p>20 A. Yes.</p> <p>21 Q. Are you currently conducting research</p> <p>22 in the field of synthetic organic chemistry?</p>

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<p>17</p> <p>1 A. No.</p> <p>2 Q. Are you currently conducting research</p> <p>3 in the field of medicinal chemistry?</p> <p>4 A. No.</p> <p>5 Q. Have you ever conducted any research on</p> <p>6 endoxifen?</p> <p>7 A. No.</p> <p>8 Q. Can you tell me the difference between</p> <p>9 a diastereomer and an enantiomer?</p> <p>10 A. Well, I know there are different</p> <p>11 stereoisomers of drugs. And so this would fall</p> <p>12 into that category. And it would really relate to</p> <p>13 a subtle structural differences and -- and how</p> <p>14 that might potentially affect, I guess, things</p> <p>15 such as stability and maybe even efficacy.</p> <p>16 Q. Do you have any laboratory experience</p> <p>17 separating enantiomers?</p> <p>18 A. No.</p> <p>19 Q. Do you have any laboratory experience</p> <p>20 separating diastereomers?</p> <p>21 A. No.</p> <p>22 Q. In your role as an associate professor</p>	<p>19</p> <p>1 Q. And have you ever taught a class in how</p> <p>2 to separate diastereomers?</p> <p>3 A. No.</p> <p>4 Q. Have you ever discussed endoxifen in</p> <p>5 any of the courses that you teach?</p> <p>6 A. Not that I recall.</p> <p>7 Q. In your role as an associate professor</p> <p>8 of pharmaceuticals, do you publish research</p> <p>9 papers?</p> <p>10 A. Yes.</p> <p>11 Q. And is paragraph 12 of your</p> <p>12 declaration, which is on page 4, an accurate</p> <p>13 summary of the number of publications you have to</p> <p>14 your name?</p> <p>15 A. Yes. As I said, there may be one or</p> <p>16 two changes to the CV now. I -- I haven't looked</p> <p>17 at the last publication on here. There's been a</p> <p>18 couple over the last year or so.</p> <p>19 Q. So your CV has a complete list of your</p> <p>20 publications but it might be missing a few from</p> <p>21 the last year or so?</p> <p>22 A. Yeah, one or two, let's say.</p>
<p>18</p> <p>1 of pharmaceuticals, do you teach?</p> <p>2 A. Yes, I teach.</p> <p>3 Q. What courses do you teach?</p> <p>4 A. My courses involve drug -- aspects of</p> <p>5 drug delivery and also pharmacokinetics.</p> <p>6 Q. Paragraph 10 of your declaration, which</p> <p>7 is on page 3, is that an accurate summary of the</p> <p>8 types of classes you teach?</p> <p>9 A. Yes.</p> <p>10 Q. Have you ever taught a synthetic</p> <p>11 organic chemistry class?</p> <p>12 A. No.</p> <p>13 Q. Have you ever taught a medicinal</p> <p>14 chemistry class?</p> <p>15 A. No.</p> <p>16 Q. Have you ever taught a class in how to</p> <p>17 prepare chemically and isomerically pure organic</p> <p>18 compounds?</p> <p>19 A. I have not.</p> <p>20 Q. Have you ever taught a class in how to</p> <p>21 separate enantiomers?</p> <p>22 A. No.</p>	<p>20</p> <p>1 Q. Have you published any research papers</p> <p>2 on endoxifen?</p> <p>3 A. No.</p> <p>4 Q. So turning to paragraph 6 of your</p> <p>5 declaration, which is on page 2, is paragraph 6 an</p> <p>6 accurate description of your Ph.D. thesis?</p> <p>7 A. Yes.</p> <p>8 Q. And your thesis was titled "Pulsed-</p> <p>9 Release Drug Delivery and Development of the Time-</p> <p>10 Delayed Capsule," correct?</p> <p>11 A. Yes. I thought the time-delayed</p> <p>12 capsule would be a big thing at the time.</p> <p>13 Q. Was it?</p> <p>14 A. No.</p> <p>15 Q. How long did you spend on research for</p> <p>16 your dissertation?</p> <p>17 A. Three years, two months.</p> <p>18 Q. Does your thesis include any</p> <p>19 description of drug delivery of endoxifen?</p> <p>20 A. No.</p> <p>21 Q. Why did you research for your thesis</p> <p>22 take three years and two months?</p>

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<p style="text-align: right;">21</p> <p>1 A. I'm not sure whether you think that it 2 was a long time or short time. So I'm not quite 3 sure how I should answer that. 4 Q. What were you doing in those three 5 years and two months? 6 A. Bench research. 7 Q. What was your bench research on? 8 A. This pulsed-release drug delivery oral 9 formulation. 10 Q. Were you designing new oral 11 formulations? 12 A. Yes. 13 Q. Is it fair to say that's complex 14 research? 15 A. Well, it -- it depends on the aspect 16 you're looking at. As a whole, it was a unique 17 area of research. Could somebody else have done 18 it? Probably, with the same supervisor. But it 19 was unique the way I did it. So there are 20 complexities involved, of course, down to the 21 individual. But there could have been a different 22 time delayed capsule I suppose that came out from</p>	<p style="text-align: right;">23</p> <p>1 BY MS. KRUMPLITSCH 2 Q. Do you recognize this document? 3 A. Yes. 4 Q. What is it? 5 A. It's the patent-in-suit that I've 6 prepared my declaration with respect to. 7 Q. Is it okay with you if we refer to this 8 as the '334 patent? 9 A. Yes. 10 Q. Before you were approached to serve as 11 an expert in this case, were you aware of the '334 12 patent? 13 A. I'm not sure if I've seen it before 14 this case. Probably not. 15 Q. When were you first approached to work 16 on this case? 17 A. Sometime last year, I think. I can't 18 recall the initial date. I'd have to go in my 19 files and look at when I was first retained and I 20 -- I really don't know. 21 Q. Is it fair to say that it was in the 22 first half of last -- of 2023?</p>
<p style="text-align: right;">22</p> <p>1 somebody else. 2 Q. Did your thesis include any description 3 of the drug delivery of endoxifen? 4 A. No. 5 Q. And turning to paragraph 11 of your 6 declaration, which is on page 3, is this an 7 accurate description of your work with solid oral 8 dosage forms over the course of your career? 9 A. Yes. 10 Q. And is it fair to say if we wanted a 11 more detailed description of your research 12 projects, we could look at your CV? 13 A. Yes. 14 Q. Have you ever worked with a solid oral 15 dosage form of endoxifen? 16 A. Not that I'm aware, no. 17 MS. KRUMPLITSCH: Okay. 18 Dr. McConville, I'm handing you what has 19 previously been marked as Exhibit 1001 in this 20 proceeding. 21 (Deposition Exhibit 1001 was 22 introduced for identification.)</p>	<p style="text-align: right;">24</p> <p>1 A. Somewhere around then I believe, yeah. 2 Q. And who contacted you? 3 A. I think it may have been Ben Mahon, who 4 is an attorney here. 5 Q. Before you were contacted to work on 6 this case, were you aware of the compound 7 endoxifen? 8 A. I think so, yeah. I mean, I hadn't 9 thought about it very much but I think I heard of 10 it and tamoxifen as well. 11 Q. So were you -- let me withdraw. 12 Before you were approached to work on 13 this case, were you aware that endoxifen is a 14 metabolite of tamoxifen? 15 A. I don't know if I'd put that together. 16 Q. So is it fair to say you may have heard 17 of endoxifen before you worked on this case but 18 you can't quite recall? 19 A. Yeah. I can't recall, yeah. 20 Q. Before you were approached to work on 21 this case, were you aware that endoxifen exists as 22 two isomers, the (Z)- and (E)-forms?</p>

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<p>25</p> <p>1 A. I haven't thought about it, no.</p> <p>2 Q. Have you subsequently come to</p> <p>3 appreciate that endoxifen exists as two isomers?</p> <p>4 A. Yes.</p> <p>5 Q. And how did you learn this fact?</p> <p>6 A. By looking at the case material, the --</p> <p>7 the evidence I've relied on, et cetera.</p> <p>8 Q. If you could turn in the '334 patent to</p> <p>9 the claims, which is the very last two pages.</p> <p>10 A. Okay.</p> <p>11 Q. And we're going to focus on Claim 1.</p> <p>12 A. Okay.</p> <p>13 Q. Is it your understanding that the</p> <p>14 molecular structure contained here in Claim 1 is</p> <p>15 endoxifen?</p> <p>16 A. Yes.</p> <p>17 Q. You understand that the wavy line in</p> <p>18 the diagram connected to the attached ethyl group</p> <p>19 represents the two stereoisomers?</p> <p>20 A. The methyl group?</p> <p>21 Q. Let's go back one step.</p> <p>22 Do you see the wavy line in that</p>	<p>27</p> <p>1 follows, (as read): Stereoisomers are compounds</p> <p>2 with the same chemical formula, but a different</p> <p>3 three-dimensional arrangement of atoms.</p> <p>4 Correct?</p> <p>5 A. Yes.</p> <p>6 Q. Do you still agree with that definition</p> <p>7 of stereoisomer?</p> <p>8 A. I do.</p> <p>9 Q. Would a compound and a salt of a</p> <p>10 compound have the same chemical formula?</p> <p>11 A. No.</p> <p>12 Q. Dr. McConville, I'm handing you what</p> <p>13 has previously been marked in this proceeding as</p> <p>14 Exhibit 1014.</p> <p>15 A. Thank you.</p> <p>16 MS. KRUMPLITSCH: I apologize. It is</p> <p>17 in very small print so we're all going to have to</p> <p>18 squint.</p> <p>19 (Deposition Exhibit 1014 was</p> <p>20 introduced for identification.)</p> <p>21 BY MS. KRUMPLITSCH</p> <p>22 Q. Do you recognize Exhibit 1014?</p>
<p>26</p> <p>1 chemical structure?</p> <p>2 A. Yes.</p> <p>3 Q. And what does that represent?</p> <p>4 A. I have -- just as you've said, yeah, I</p> <p>5 believe so, that represents the difference in the</p> <p>6 stereoisomers.</p> <p>7 Q. And you agree that the two</p> <p>8 stereoisomers differ only in the three-dimensional</p> <p>9 arrangement of the ethyl group?</p> <p>10 A. Right.</p> <p>11 Q. And if you could also have your</p> <p>12 declaration out -- we're going to look at both</p> <p>13 documents -- and turn to page 7 of your</p> <p>14 declaration.</p> <p>15 A. Okay.</p> <p>16 Q. And you agree that the two</p> <p>17 stereoisomers (Z)-endoxifen and (E)-endoxifen are</p> <p>18 represented by the structures you present in your</p> <p>19 declaration?</p> <p>20 A. Yes.</p> <p>21 Q. In paragraph 21, which is right above</p> <p>22 that figure, you define the term stereoisomer as</p>	<p>28</p> <p>1 A. Let me see. This isn't one of the</p> <p>2 exhibits I reviewed prior to coming here. So I</p> <p>3 can't recall if I've seen this before and I rely</p> <p>4 on it in my declaration or not. But I -- I didn't</p> <p>5 review this just before the testimony today.</p> <p>6 Q. Okay. And I'll point you to your</p> <p>7 declaration, paragraph 18 on page 6.</p> <p>8 A. Okay.</p> <p>9 Q. I'll give you a second.</p> <p>10 A. Okay. Yeah.</p> <p>11 Q. Do you see that you've cited this</p> <p>12 exhibit in that paragraph?</p> <p>13 A. Sorry. Page 6?</p> <p>14 Q. Yeah. Paragraph 18.</p> <p>15 A. I went to page 18.</p> <p>16 Okay. Yes. I see that now, yeah.</p> <p>17 Okay. Good.</p> <p>18 Q. Okay. So is it your understanding that</p> <p>19 Exhibit 1014 is a drug label for Zonalta?</p> <p>20 A. Yes.</p> <p>21 Q. And this is a drug that is sold by</p> <p>22 Intas Pharmaceuticals?</p>

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<p>29</p> <p>1 A. Okay. Yes.</p> <p>2 Q. And Intas is the same Intas that is the</p> <p>3 petitioner in this case?</p> <p>4 A. It's my understanding, yes.</p> <p>5 Q. Now, Zonalta is an endoxifen citrate</p> <p>6 drug?</p> <p>7 A. Okay.</p> <p>8 Q. Correct?</p> <p>9 A. Yes.</p> <p>10 Q. And if you turn to -- so we're looking</p> <p>11 at the Zonalta drug label on the second page.</p> <p>12 A. Okay.</p> <p>13 Q. The right-hand column.</p> <p>14 A. Yep.</p> <p>15 Q. Midway down, paragraph 7, entitled</p> <p>16 "Description" and there's a chemical structure</p> <p>17 there.</p> <p>18 Do you see that?</p> <p>19 A. Yes.</p> <p>20 Q. And this molecular structure is the</p> <p>21 molecular structure for the endoxifen citrate</p> <p>22 salt, correct?</p>	<p>31</p> <p>1 portion has different atoms but the active moiety</p> <p>2 is exactly the same.</p> <p>3 Q. But my question was not asking you</p> <p>4 about the active moiety. It was asking you about</p> <p>5 the compound as a whole, which would include</p> <p>6 active moiety and anything.</p> <p>7 So with that definition of compound,</p> <p>8 would a compound and a salt of the compound be</p> <p>9 made up of the same atoms?</p> <p>10 MR. MENCHACA: Same objection.</p> <p>11 THE WITNESS: Well, until it</p> <p>12 dissolves, then there are different atoms.</p> <p>13 But once dissolution has occurred, of</p> <p>14 course you've got the same atoms because</p> <p>15 there's the active component released.</p> <p>16 BY MS. KRUMPLITSCH</p> <p>17 Q. So my question was not with regards to</p> <p>18 dissolution.</p> <p>19 Would a compound and a solvate of the</p> <p>20 compound be made up of the same atoms?</p> <p>21 A. Not in the solid sense.</p> <p>22 Q. Turning back to the '334 patent and</p>
<p>30</p> <p>1 A. Yes.</p> <p>2 Q. This is not the molecular structure of</p> <p>3 endoxifen free base, correct?</p> <p>4 A. That's -- that's correct, yes.</p> <p>5 Q. Would a compound and a solvate of a</p> <p>6 compound have the same chemical formula?</p> <p>7 A. No.</p> <p>8 Q. Would a compound and a salt of a</p> <p>9 compound be made up of -- be made up of the same</p> <p>10 atoms?</p> <p>11 A. Well, the active moiety, yes. But the</p> <p>12 salt portion is additional to the active moiety.</p> <p>13 Q. So just to make sure I get an answer to</p> <p>14 that question, would a compound and a salt of the</p> <p>15 compound be made up of the same atoms?</p> <p>16 MR. MENCHACA: Objection. Asked and</p> <p>17 answered.</p> <p>18 THE WITNESS: To an extent, yes.</p> <p>19 BY MS. KRUMPLITSCH</p> <p>20 Q. What do you mean by "to an extent"?</p> <p>21 A. Well, there's the active moiety of the</p> <p>22 drug with a salt portion on it. Now, the salt</p>	<p>32</p> <p>1 looking at those claims again, the molecular</p> <p>2 structure depicted in Claim 1 depicts endoxifen</p> <p>3 that could be a polymorphic endoxifen compound,</p> <p>4 correct?</p> <p>5 A. Yes.</p> <p>6 Q. And the molecular structure depicted in</p> <p>7 Claim 1 depicts endoxifen that could be a</p> <p>8 co-crystal form of endoxifen, correct?</p> <p>9 MR. MENCHACA: Objection.</p> <p>10 Foundation.</p> <p>11 THE WITNESS: This -- this really</p> <p>12 isn't my area of expertise. But as you've</p> <p>13 said, there's -- there's a wavy line there</p> <p>14 and it could be one of -- one of two forms.</p> <p>15 BY MS. KRUMPLITSCH</p> <p>16 Q. The molecular structure depicted in</p> <p>17 Claim 1 does not include any atoms of a salt,</p> <p>18 correct?</p> <p>19 A. It simply shows the active moiety</p> <p>20 portion of a drug.</p> <p>21 Q. What basis are you relying on to</p> <p>22 conclude that the molecular structure in compound</p>

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<p>33</p> <p>1 1 only shows the active moiety?</p> <p>2 A. Well, the patent suggests that's the</p> <p>3 active molecule.</p> <p>4 Q. Where does the patent suggest that?</p> <p>5 A. Right at the beginning it talks about</p> <p>6 endoxifen as being useful for the treatment of</p> <p>7 breast cancer at the start of the patent.</p> <p>8 (Stenographer clarification.)</p> <p>9 THE WITNESS: At the beginning of</p> <p>10 the patent, it talks about the usefulness</p> <p>11 of endoxifen for the treatment of breast</p> <p>12 cancer, et cetera.</p> <p>13 BY MS. KRUMPLITSCH:</p> <p>14 Q. Is it your understanding that the</p> <p>15 molecular structure depicted in Claim 1 is not the</p> <p>16 entire compound?</p> <p>17 A. This -- this is the active compound.</p> <p>18 And, you know, as a formulation scientist and</p> <p>19 anybody in pharmaceuticals would realize that</p> <p>20 oftentimes active compounds are made into salts to</p> <p>21 help with solubility, for example, or stability.</p> <p>22 And this is an active compound depicted. And when</p>	<p>35</p> <p>1 Claim 1 does not include any atoms of a solvate,</p> <p>2 correct?</p> <p>3 A. It would appear that way, yes.</p> <p>4 Q. Now, looking at your declaration, if</p> <p>5 you could turn to page 13, we're going to focus on</p> <p>6 paragraphs 28 and 29.</p> <p>7 Are you there?</p> <p>8 A. Sorry. Did you say 28?</p> <p>9 Q. Yeah, 28 and 29 on page 13.</p> <p>10 A. Yeah.</p> <p>11 Q. So you did not at the time you wrote</p> <p>12 your declaration identify "compound of formula 3</p> <p>13 is (Z)-endoxifen" as a phrase that needed to be</p> <p>14 construed, correct?</p> <p>15 A. I did not -- I assumed, you know, plain</p> <p>16 and ordinary meaning.</p> <p>17 Q. What did you understand the plain and</p> <p>18 ordinary meaning of "compound of formula 3 is</p> <p>19 (Z)-endoxifen" to encompass?</p> <p>20 A. Anything that could yield that active</p> <p>21 molecule as a formulation strategy.</p> <p>22 Q. So this interpretation of the phrase</p>
<p>34</p> <p>1 you have -- if you have a salt form, for example,</p> <p>2 you would still have this active compound</p> <p>3 available in a formulation.</p> <p>4 Q. Is this active compound here in Claim 1</p> <p>5 depicted as a salt form?</p> <p>6 A. It's not depicted as a salt form right</p> <p>7 here.</p> <p>8 Q. Do you --</p> <p>9 A. I mean, it -- but Claim 1 talks about</p> <p>10 an endoxifen composition comprising a compound of</p> <p>11 that formula.</p> <p>12 Q. And why is that important?</p> <p>13 A. Well, because that's the active portion</p> <p>14 of, you know, a free base or it could be the</p> <p>15 active portion of a salt, in my opinion.</p> <p>16 Q. Endoxifen in a salt form has one more</p> <p>17 hydrogen than the free base form, correct?</p> <p>18 A. Well, in the solid sense possibly, yes.</p> <p>19 Q. Possibly?</p> <p>20 A. I guess dependent on the salt. I</p> <p>21 haven't looked at all salt forms.</p> <p>22 Q. The molecular structure depicted in</p>	<p>36</p> <p>1 "compound of formula 3 is (Z)-endoxifen" is not</p> <p>2 reflected anywhere in your declaration, correct?</p> <p>3 A. Sorry. Could you repeat that?</p> <p>4 Q. Your interpretation of this phrase,</p> <p>5 "the compound of formula 3 is (Z)-endoxifen," that</p> <p>6 understanding, which you testified is "anything</p> <p>7 that could yield an active molecule," that is not</p> <p>8 reflected anywhere in your declaration; is it?</p> <p>9 A. That's just what I take as pretty</p> <p>10 obvious to me.</p> <p>11 Q. And that is not reflected anywhere in</p> <p>12 your declaration, correct?</p> <p>13 A. If it's not there, it's a general</p> <p>14 assumption.</p> <p>15 Q. So the phrase "salt form of endoxifen"</p> <p>16 does not appear anywhere in your declaration,</p> <p>17 correct?</p> <p>18 A. I'm not sure. I'd have to look through</p> <p>19 to -- to see if I could find that. But I -- as I</p> <p>20 sit here today, I can't remember whether I</p> <p>21 referred specifically to a salt form anywhere. I</p> <p>22 think I have endoxifen citrate listed somewhere</p>

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<p>37</p> <p>1 within my report.</p> <p>2 Q. And the phrase "solvate form" does not</p> <p>3 appear in your declaration, correct?</p> <p>4 A. Again, same thing. I'd have to read</p> <p>5 through. It wasn't something I was focusing on</p> <p>6 when I was reviewing it.</p> <p>7 Q. So in your declaration at paragraph 18</p> <p>8 on page 6 -- I'll give you a second to get there.</p> <p>9 A. Okay.</p> <p>10 Q. So you identify endoxifen as</p> <p>11 4-hydroxy-N-des-methyl tamoxifen, correct?</p> <p>12 A. Correct.</p> <p>13 Q. At the time you wrote your declaration,</p> <p>14 what did you understand 4-hydroxy-N-des-methyl</p> <p>15 tamoxifen to encompass?</p> <p>16 A. The active portion of the molecule.</p> <p>17 Q. I want to make sure I understand your</p> <p>18 testimony here, Dr. McConville.</p> <p>19 You're saying that the chemical name,</p> <p>20 4-hydroxy-N-des-methyl tamoxifen, only refers to</p> <p>21 the active moiety?</p> <p>22 A. I -- that's what I think, yeah.</p>	<p>39</p> <p>1 4-hydroxy-N-des-methyl tamoxifen.</p> <p>2 Is that what you're talking about?</p> <p>3 Q. If you could go to the third line that</p> <p>4 starts with "the chemical name is."</p> <p>5 A. Oh, yeah, yeah.</p> <p>6 Q. Do you want to read it? Or I can.</p> <p>7 A. I mean, do I have to, really? I see --</p> <p>8 I see what you mean. There's an extended name</p> <p>9 with citrate on the end as the salt, yeah.</p> <p>10 Q. So would you agree with me that Intas</p> <p>11 itself when describing a citrate salt of endoxifen</p> <p>12 uses a different chemical name than</p> <p>13 4-hydroxy-N-des-methyl tamoxifen?</p> <p>14 A. Right. But the active moiety, you</p> <p>15 know, turns out to be the same compound.</p> <p>16 Q. Going back to your description of</p> <p>17 endoxifen as 4-hydroxy-N-des-methyl tamoxifen and</p> <p>18 your testimony that that only refers to active</p> <p>19 moiety, would tamoxifen be included in Claim 1?</p> <p>20 A. Well, I mean, that's -- I'm not so</p> <p>21 sure. I haven't really thought about that as much</p> <p>22 as, you know, the active component being endoxifen</p>
<p>38</p> <p>1 Q. So if you had a salt form, would you</p> <p>2 also call it 4-hydroxy-N-des-methyl tamoxifen?</p> <p>3 A. I mean, if I was referring to the</p> <p>4 active portion of it, I would highlight that. But</p> <p>5 I would state that it's the salt version of the</p> <p>6 form depending on the salt.</p> <p>7 Q. So if you could turn back to the</p> <p>8 Zonalta label, please, which is Exhibit 1014.</p> <p>9 A. Okay.</p> <p>10 Q. And we're going back to -- I apologize</p> <p>11 because it really is in small print -- the</p> <p>12 description with the chemical structure.</p> <p>13 Do you see that on page 2?</p> <p>14 A. Yes.</p> <p>15 Q. What is the chemical name that Intas</p> <p>16 uses to refer to the citrate salt form of</p> <p>17 endoxifen?</p> <p>18 A. Well, they refer to that active</p> <p>19 component of it.</p> <p>20 Q. Dr. McConville, do you see the</p> <p>21 recitation of the chemical name there?</p> <p>22 A. Well, in the first line, yeah,</p>	<p>40</p> <p>1 as a -- as a salt and then the salt cleaving off</p> <p>2 and that being the active portion.</p> <p>3 I hadn't really thought about it in</p> <p>4 terms of the metabolism that could occur to</p> <p>5 tamoxifen to convert it to endoxifen. It's a bit</p> <p>6 more straightforward with a salt form. It's just</p> <p>7 dissolution.</p> <p>8 Q. So can you answer whether or not</p> <p>9 tamoxifen would be included in Claim 1 given your</p> <p>10 interpretation?</p> <p>11 A. As I say, it's something I'd have to</p> <p>12 think about a little more.</p> <p>13 Q. So you can't answer that sitting here</p> <p>14 today?</p> <p>15 A. I -- I wouldn't like to. It would take</p> <p>16 a while for me to really consider my -- it's not</p> <p>17 something I've looked at specifically, no.</p> <p>18 Q. Would you expect endoxifen free base</p> <p>19 and an endoxifen salt to have the same</p> <p>20 pharmacokinetic profile?</p> <p>21 A. Could you repeat that?</p> <p>22 Q. Would you expect endoxifen free base</p>

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<p>41</p> <p>1 and an endoxifen salt to have the same 2 pharmacokinetic profile?</p> <p>3 A. In -- in what sense do you mean?</p> <p>4 Q. Let's take a step back.</p> <p>5 Do you understand when I use the term 6 "pharmacokinetic profile" what I'm referring to?</p> <p>7 A. I mean, there's several aspects of the 8 pharmacokinetic profile to consider. One thing 9 that is very important is the elimination rate of 10 a drug, in which case I would consider that to be 11 the same.</p> <p>12 Q. What other aspects of pharmacokinetic 13 profile are there besides elimination rate?</p> <p>14 A. Absorption rate, for example. That's 15 -- that is something that could vary possibly, 16 depending on the solubility -- well, dissolution, 17 let's say, the ionization state of the molecule in 18 the gut. Where in the gut it's being absorbed. 19 There's many factors that affect absorption. The 20 elimination rate of the drug molecule would be the 21 same.</p> <p>22 Q. So we're still talking -- okay. Thank</p>	<p>43</p> <p>1 elimination might be the same between a free base 2 and a citrate salt; is that correct?</p> <p>3 A. I don't see any reason why it wouldn't 4 be the same.</p> <p>5 Q. +but you also testified, correct, that 6 absorption would be different between the two, 7 correct?</p> <p>8 A. No. It could be. I don't know whether 9 it is. It's something that would need to be 10 tested. You know, normally if you compare one 11 type of, let's say, a salt against a free base, 12 for example, you would use exactly the same 13 formulation to do that comparison. So that -- 14 that would be a study that should really be 15 conducted, I suppose, to compare that absorption 16 rate.</p> <p>17 Q. Did you do any studies comparing the 18 absorption rate between endoxifen free base and 19 endoxifen citrate salt?</p> <p>20 A. No. I'm simply stating the type of 21 study that would be suitable for that sort of 22 analysis.</p>
<p>42</p> <p>1 you.</p> <p>2 For a pharmacokinetic profile, we have 3 absorption, elimination.</p> <p>4 What else, what other pharmacokinetic 5 primers are there?</p> <p>6 A. Well, I mean, those two aspects really 7 dictate the Tmax, the time to maximum 8 concentration, the Cmax, of course, the 9 concentration at which you reach when it gets to 10 the Tmax, and that area under curve.</p> <p>11 Q. Just want to be clear, though. Your 12 testimony is that only absorption and elimination 13 are the -- those are the only two elements of a 14 pharmacokinetic profile?</p> <p>15 A. No, no, there's more things to consider 16 as well. You know, volume and distribution, 17 clearance, and other things related to the 18 molecule.</p> <p>19 But given physiochemical properties of 20 the molecule, some of those pharmacokinetic 21 elements would be the same.</p> <p>22 Q. I believe you testified that</p>	<p>44</p> <p>1 Q. You testified that the absorption rate 2 could vary depending on the solubility, correct?</p> <p>3 A. Well, solubility and dissolution, 4 concentration. You know, there are various things 5 that can affect the absorption. And the window of 6 absorption in the gastrointestinal tract as well, 7 pH.</p> <p>8 Q. Do you have an understanding as to 9 whether the solubility of the salt versus the free 10 base form of endoxifen are -- is the same?</p> <p>11 A. Sorry. Can you repeat that?</p> <p>12 Q. That was a horrible question.</p> <p>13 Is the solubility of the salt form of 14 endoxifen the same as the solubility of the free 15 base form of endoxifen?</p> <p>16 A. I don't know.</p> <p>17 Q. Okay. Do you have any understanding as 18 to whether a POSA would be motivated to make the 19 salt form of a drug?</p> <p>20 A. One of the things that a person of 21 ordinary skill looks at is the solubility of a 22 molecule, as well as potentially the stability of</p>

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<p style="text-align: right;">45</p> <p>1 a molecule. And that might lead them to think</p> <p>2 about making a salt or -- or not.</p> <p>3 Q. So is it fair to say a POSA would want</p> <p>4 to make a drug that has better solubility?</p> <p>5 A. Well, it really depends on whether</p> <p>6 there's an issue with solubility, absorption, the</p> <p>7 bio classification system of the -- that's used</p> <p>8 for a particular drug.</p> <p>9 Let me think. What else?</p> <p>10 Oh, and that stability issue as well.</p> <p>11 You know, that would be taken into account unless</p> <p>12 there's other ways of overcoming it. A person of</p> <p>13 ordinary skill would like to use the easiest route</p> <p>14 possible.</p> <p>15 Q. Why is stability important to a person</p> <p>16 of ordinary skill in the art?</p> <p>17 A. I mean, for example, in the worst-case</p> <p>18 scenario, if a drug isn't stable for, you know,</p> <p>19 more than a few days in its solid form, then</p> <p>20 there's an issue with thinking about making a</p> <p>21 formulation later on for -- for use.</p> <p>22 Q. When you testified that a person of</p>	<p style="text-align: right;">47</p> <p>1 dosage form?</p> <p>2 A. Well, again, there's other factors that</p> <p>3 come into it. The most stable might not</p> <p>4 necessarily be necessary depending on the turnover</p> <p>5 rate of the compound, storage, packaging. You can</p> <p>6 offset stability issues sometimes with packaging.</p> <p>7 MS. KRUMPLITSCH: So, Dr. McConville,</p> <p>8 I'm going to hand you what has been marked as</p> <p>9 Exhibit 1003 in this proceeding.</p> <p>10 (Deposition Exhibit 1003 was</p> <p>11 introduced for identification.)</p> <p>12 BY MS. KRUMPLITSCH</p> <p>13 Q. And do you recognize Exhibit 1003?</p> <p>14 A. Yes.</p> <p>15 Q. And this is a patent by Ahmad, correct?</p> <p>16 A. Yes.</p> <p>17 Q. And it's U.S. Patent No. 9,333,190?</p> <p>18 A. Yes.</p> <p>19 Q. Is it okay with you if I refer to this</p> <p>20 as the Ahmad patent?</p> <p>21 A. Yes.</p> <p>22 Q. When did you last review the Ahmad</p>
<p style="text-align: right;">46</p> <p>1 ordinary skill would like to use the easiest route</p> <p>2 possible with respect to stability, would a POSA</p> <p>3 want to formulate the most stable compound?</p> <p>4 A. Well, it depends on what the most</p> <p>5 appropriate method of delivery might be as well.</p> <p>6 I mean, as a person of ordinary skill, you have a</p> <p>7 new chemical entity, let's say, a drug. You would</p> <p>8 want to think about maybe one of two routes of</p> <p>9 administration to begin with. Intravenous is the</p> <p>10 easiest. Or oral drug delivery, which is the most</p> <p>11 convenient and profitable. And also it's usually</p> <p>12 one of the most stable forms to make.</p> <p>13 So those two things would spring to</p> <p>14 mind immediately. But obviously there are</p> <p>15 different routes of administration. And depending</p> <p>16 on the drug itself, it could be a topical, it</p> <p>17 could be inhaled, or other route.</p> <p>18 Q. So let's just restrict it to oral --</p> <p>19 solid oral dosage forms.</p> <p>20 A. Yeah.</p> <p>21 Q. Would a POSA look to formulate the most</p> <p>22 stable form of that compound in a solid oral</p>	<p style="text-align: right;">48</p> <p>1 patent?</p> <p>2 A. This I think when I was preparing my</p> <p>3 report around that time. It -- it wasn't</p> <p>4 something I brought with me to look at. So it was</p> <p>5 previous.</p> <p>6 Q. Okay. And were you familiar with the</p> <p>7 Ahmad patent before working on this case?</p> <p>8 A. Not that I recall. I don't recall</p> <p>9 coming across this patent.</p> <p>10 Q. How did you learn about the Ahmad</p> <p>11 patent?</p> <p>12 A. It -- it has, you know, obviously</p> <p>13 relevance to this given the date of issuance of</p> <p>14 this patent. It's prior art to the '334 patent.</p> <p>15 Q. Was this patent provided to you or is</p> <p>16 this something that you went out and found on your</p> <p>17 own?</p> <p>18 A. I think I was provided this to look at</p> <p>19 as prior art. I don't -- I mean, I remember</p> <p>20 searching at the time. I think this was provided</p> <p>21 to me at that time.</p> <p>22 Q. Are you familiar with Dr. Ahmad?</p>

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<p>49</p> <p>1 A. Not personally, no. But which you mean 2 the -- the first inventor obviously? 3 Q. That's a good point. Yes, the first 4 inventor. 5 A. Okay. None of them anyway on this 6 particular. I do know some Ahmads but I don't 7 think it's the same. 8 Q. None of the -- do you know any of the 9 named inventors? 10 A. No, not that I am aware. It's possible 11 I've met them. 12 Q. Okay. And so we're going to keep the 13 Ahmad patent and your declaration out. So if you 14 can turn to page 15 of your declaration. 15 A. Okay. 16 Q. And we're going to look at 17 paragraph 33. 18 A. Okay. 19 Q. So you state in paragraph 33 (as read): 20 In sum, Ahmad teaches the use of enteric coated 21 capsules of highly pure (Z)-endoxifen to treat 22 breast cancer and other diseases.</p>	<p>51</p> <p>1 Q. And column 12, lines 14 to 17, Ahmad 2 states (as read): One object of the present 3 invention is to provide (E)-endoxifen or 4 (Z)-endoxifen with at least 80 percent purity, 5 such as at least 90 percent pure or at least 6 95 percent pure... 7 And it goes on. 8 Do you see that? 9 A. Yes. 10 Q. So Ahmad is describing (E)-endoxifen or 11 (Z)-endoxifen at these purity levels? 12 A. Correct, yes. 13 Q. And you pointed out the claims of 14 Ahmad. If you can turn to those, the one claim on 15 the last page. 16 A. Right. 17 Q. You would agree with me that Ahmad is 18 claiming an endoxifen in the form of a citrate 19 salt that is at least 80 percent (Z)-endoxifen? 20 A. Yeah, in part 2, that's right, of 21 Claim 1. 22 Q. And Ahmad is not claiming an 80 percent</p>
<p>50</p> <p>1 Correct? 2 A. Yes. 3 Q. Do you stand by that statement today? 4 A. Yes. 5 Q. Looking at the Ahmad patent, do you 6 agree with me that the only disclosure of 7 90 percent pure endoxifen is at columns 12, lines 8 14 to 17, correct? 9 A. Yes, I believe that's a reference to 10 it. 11 Let me see. Hang on. Give me a 12 moment. 13 I mean, also in Claim 1 it mentions at 14 least 80 percent, which would encompass as well 15 90 percent plus. 16 Q. But, again, my question was: The only 17 disclosure of -- only mention of 90 percent pure 18 endoxifen verbatim is at column 12, lines 14 to 19 17? 20 A. I mean, yes, but obviously as I've 21 said, anything over 80 percent also encompasses 22 90 percent.</p>	<p>52</p> <p>1 pure (Z)-endoxifen free base, correct? 2 A. I -- I see what you mean, yes. But as 3 I mentioned before, upon dissolution you obtain 4 the free base anyway. So to me as a formulation 5 scientist, it doesn't make any difference 6 necessarily to have a salt or -- or not in terms 7 of the active component. 8 Q. So it's your testimony as a POSA that 9 the words of the claim don't matter? 10 A. Oh, of course they do. It's given in a 11 citrate salt. But I'm just reiterating that once 12 the citrate salt is dissolved, you're left with, 13 you know, at least 80 percent (Z)-endoxifen. 14 Q. So is it your testimony as a POSA 15 interpreting the claim of Ahmad that Claim 1 would 16 encompass endoxifen free base? 17 A. In terms of the preparation of the 18 citrate salt, of course. I mean, you can't 19 immediately synthesize the citrate salt. So of 20 course it encompasses the free base as a precursor 21 at least to forming the citrate salt. 22 Q. So your testimony as you sit here today</p>

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<p style="text-align: right;">53</p> <p>1 as a POSA, that Ahmad Claim 1 covers an 80 percent 2 pure endoxifen free base?</p> <p>3 A. As part 1, yes. And then the salt is 4 prepared, yes, in part 2 of the claim. I mean, 5 you can't synthesize the citrate salt immediately. 6 You have to synthesize the free base form of 7 (Z)-endoxifen in this case and then make the salt. 8 So of course the patent as a whole teaches the 9 formation of (Z)-endoxifen as a free base.</p> <p>10 Q. So, Dr. McConville, with all due 11 respect, my question is what is claimed in Ahmad. 12 It's not what the patent teaches.</p> <p>13 And your testimony -- I just want to 14 make sure I understand -- is that Claim 1 claims 15 an endoxifen free base?</p> <p>16 A. Oh, no. I didn't say that. It does 17 encompass a citrate salt. But my -- I'm just 18 describing that of course to get to Claim 1 and 19 have a citrate salt, the patent teaches the 20 formation (Z)-endoxifen pre-base.</p> <p>21 Q. And my question is limited to what's 22 being claimed here. But let's move on.</p>	<p style="text-align: right;">55</p> <p>1 A. So the -- the claim itself, part 1, 2 says synthetic preparation of endoxifen is at 3 least 80 percent (Z)-endoxifen. That -- that's 4 the free base. And then part 2 of that Claim 1 5 said synthetic preparation of endoxifen is in the 6 form of citrate salt. Then obviously the citrate 7 salt is formed. So you end up with a citrate salt 8 of (Z)-endoxifen.</p> <p>9 Q. When you take a free base of endoxifen 10 and add citric acid, isn't it true that you both 11 (Z)- and (E)-endoxifen?</p> <p>12 A. I can't comment on that. That's not my 13 area of expertise.</p> <p>14 Q. Would we put that question to the 15 chemists?</p> <p>16 A. Probably a good idea.</p> <p>17 Q. Ahmad does not provide any working 18 example of the synthetic methods that would work 19 to produce a composition with at least 90 percent 20 endoxifen, correct?</p> <p>21 A. Again, that's more of a chemistry 22 question, for different experts. It tells us that</p>
<p style="text-align: right;">54</p> <p>1 When (Z)-endoxifen citrate dissolves, 2 will it always be a free base?</p> <p>3 A. Once dissolution has occurred, the 4 (Z)-endoxifen is released as -- for absorption, 5 yes. And, you know, depending on where it is in 6 the stomach will depend on its ionization state -- 7 sorry, sorry, gastrointestinal tract, not stomach, 8 because obviously we have an enteric coating.</p> <p>9 Q. Do you agree that the dissolution of 10 (Z)-endoxifen citrate to a free base is dependent 11 on pH?</p> <p>12 A. That's -- that's a factor involved, 13 yes.</p> <p>14 Q. Do you know at what -- above what pH 15 the free base is available?</p> <p>16 A. I'm not sure.</p> <p>17 Q. Dr. McConville, I want to make sure I 18 understand your interpretation of Ahmad. Correct 19 me if I'm wrong here.</p> <p>20 Is it your testimony that Ahmad 21 necessarily encompasses endoxifen free base 22 because it claims an endoxifen citrate salt?</p>	<p style="text-align: right;">56</p> <p>1 greater than 80 percent endoxifen can be produced. 2 It's in the claim.</p> <p>3 Q. Would you have the same answer if I 4 asked whether you agree with the statement that 5 Ahmad does not provide any working examples of a 6 crystallization parameters that would work to 7 produce a composition with at least 90 percent 8 (Z)-endoxifen?</p> <p>9 A. Yeah, I would give you the same answer.</p> <p>10 Q. You'd ask a chemist?</p> <p>11 A. I think that's the best option. I 12 don't want to guess at what's going on here.</p> <p>13 Q. And would you give me the same answer 14 if I asked you to agree with the statement that 15 Ahmad does not include any working example 16 demonstrating that Ahmad ever possessed a 17 composition with at least 90 percent pure 18 (Z)-endoxifen?</p> <p>19 A. I mean, Ahmad describes the preparation 20 of at least 90 percent endoxifen. So I -- this is 21 an issued patent. I have to assume this is 22 correct.</p>

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<p>57</p> <p>1 Q. Would you point us to where Ahmad 2 describes the preparation of at least 90 percent 3 endoxifen?</p> <p>4 A. Yes, yes, I mean, you had pointed me 5 out to that. I think it's column --</p> <p>6 Q. 12.</p> <p>7 A. -- 12, yes.</p> <p>8 So it describes the objective of the 9 present invention. So -- and then at Claim 1 it 10 describes greater than 80 percent, which 11 encompasses those ranges listed in that column 12.</p> <p>12 Q. Would you agree with me, 13 Dr. McConville, that that passage at column 1, 14 lines 14 to 17, does not include any description 15 of the synthetic methods that Ahmad would have 16 used to generate a 90 percent pure (Z)-endoxifen?</p> <p>17 A. Not specifically, no.</p> <p>18 MS. KRUMPLITSCH: We've been going 19 about an hour. Can we take a short break 20 or do you want to keep going?</p> <p>21 THE WITNESS: That's fine. Take a 22 break.</p>	<p>59</p> <p>1 through to see.</p> <p>2 Q. Is that another one where we would look 3 to a chemist?</p> <p>4 A. I mean, I -- I can't remember all the 5 examples that are in here. But in general we 6 could see if a citrate salt is described, I guess. 7 But if in doubt, it would be better to ask the 8 chemist, yes.</p> <p>9 Q. And I know your expertise is in 10 pharmaceuticals and pharmaceutical formulation. 11 Would you yourself know how to 12 formulate a citrate salt from the free base of 13 endoxifen?</p> <p>14 A. That's -- that's a chemistry issue.</p> <p>15 Q. And do you know in forming a citrate 16 salt from a free base what isomeric purity you 17 would get?</p> <p>18 A. Again, I would have to refer to the 19 chemistry expert on that.</p> <p>20 Q. And then also looking at Claim 1 of 21 Ahmad, I believe you testified that because the 22 claim recites synthetic preparation of endoxifen</p>
<p>58</p> <p>1 THE STENOGRAPHER: We're off the 2 record at 10:02. 3 (Whereupon, a recess was taken 4 from 10:02 a.m. to 10:19 a.m.) 5 THE STENOGRAPHER: We're back on the 6 record at 10:19 a.m. 7 BY MS. KRUMPLITSCH: 8 Q. So Dr. McConville, let's turn back to 9 the Ahmad patent that we were looking at.</p> <p>10 A. Okay.</p> <p>11 Q. And looking at Claim 1 that we were 12 talking about right before the break. And I just 13 want to make sure I understand your testimony. 14 You're looking at Claim 1 and you said, 15 you know, part 1 of Claim 1 is Ahmad making the 16 free base and part 2 is making the citrate salt 17 from that free base; is that correct?</p> <p>18 A. That's how I interpret it, yes.</p> <p>19 Q. Is the synthetic preparation of the 20 citrate salt described anywhere in the Ahmad 21 patent?</p> <p>22 A. I can't recall. I'd have to look</p>	<p>60</p> <p>1 that is at least 80 percent (Z)-endoxifen, it's 2 your testimony that that encompasses 80 percent 3 and above?</p> <p>4 A. Yes.</p> <p>5 Q. All the way to 100 percent?</p> <p>6 A. That's -- that's how I interpret it. 7 At least 80 percent, yes.</p> <p>8 Q. Do you have understanding -- do you 9 have understanding of whether Ahmad teaches how to 10 actually prepare a 90 percent (Z)-endoxifen?</p> <p>11 A. As I said before, it describes that it 12 -- that's one of the objectives. And I assume 13 that it can be prepared just because it's in the 14 claim language.</p> <p>15 Q. Did you do any investigation into the 16 specification of Ahmad to see whether or not the 17 synthetic steps described in the spec would result 18 in a 90 percent (Z)-endoxifen?</p> <p>19 A. Again, that's a very specific chemistry 20 oriented question.</p> <p>21 Q. Do you know if it's possible to produce 22 a 100 percent pure (Z)-endoxifen?</p>

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<p>61</p> <p>1 A. I don't know. I suspect that it's 2 possible. But again, it's a chemistry issue. 3 Q. So is it your testimony that -- let me 4 withdraw that. 5 So the claim of Ahmad is at least 6 80 percent and it's your testimony that that 7 includes 80 percent and above, all the way to 100. 8 A. Yes, that's fair. 9 Q. If the claim said at least 50 percent 10 (Z)-endoxifen, is it your testimony that that 11 would include 50 percent all the way to 100? 12 A. That's a bit more of a stretch. It's 13 more specific at being 80 percent. It's very much 14 closer to 90 and 100 than 50 -- 50 is -- yeah, 15 that's very -- too broad, I think. 16 Q. What -- is there a point in your mind 17 where it's too broad or appropriate? Would it be 18 75 percent? 60 percent? 19 A. I can't comment on that. I see 20 80 percent and I think that's pretty pure. 21 Q. I want to circle back to one other 22 point that you testified about earlier today, the</p>	<p>63</p> <p>1 steps described in Ahmad, correct? 2 A. That's correct. 3 Q. Would you agree with me that different 4 synthetic pathways can result in different 5 impurity profiles? 6 A. It seems reasonable, yes. 7 Q. Did you compare the synthetic pathways 8 disclosed in Ahmad and the synthetic pathway 9 disclosed in the '334 patent? 10 A. I didn't think that that was relevant. 11 Q. Do you have -- do you have any 12 understanding as to whether or not they are the 13 same or different? 14 A. I can't recall. I didn't really go 15 through step by step. And even doing so, I'm not 16 an expert on that. 17 Q. If I represent to you that the 18 synthetic pathways of Ahmad and the '334 are 19 different, would you expect that these two 20 different synthetic pathways would result in 21 different impurity profiles? 22 A. I really don't know. I can't comment</p>
<p>62</p> <p>1 active moiety. 2 Do you remember our discussion about 3 that? 4 A. Yes. 5 Q. Do you have an understanding of whether 6 the active moiety of the endoxifen free base has 7 one less hydrogen than the active moiety of the 8 citrate salt form? 9 A. So you're just talking really about 10 ionization state. And it just -- it's the same 11 molecule. It just depends on the ionization 12 state. 13 Q. Right. And that ionization state 14 requires one additional hydrogen, correct? 15 A. It's either protonated or unprotonated, 16 which is the general term for this ionization. 17 It's a base molecule so it can be protonated. 18 Q. With the hydrogen atom? 19 A. That's what a proton is, a hydrogen 20 atom, yes, missing an electron. 21 Q. Okay. Your declaration does not 22 contain any analysis of the synthetic chemistry</p>	<p>64</p> <p>1 on that. It could be the same profile. I don't 2 know. Just depends on what you end up with. 3 Q. If we wanted to know the answer to that 4 question, would we ask a chemist? 5 A. I think that that would be fair, yes. 6 Q. Doctor, I'm handing you what has been 7 marked as Exhibit 1004. 8 A. Thank you. 9 (Deposition Exhibit 1004 was 10 introduced for identification.) 11 BY MS. KRUMPLITSCH: 12 Q. Do you recognize Exhibit 1004? 13 A. Yes. 14 Q. And this is a patent application that 15 bears Publication No. WO 2017/070651, correct? 16 A. That's correct. 17 Q. And the first inventor is Liu, L-i-u. 18 Do you see that? 19 A. Yes. 20 Q. So for brevity sake, can we refer to 21 this Exhibit 1004 as the Liu application or Liu? 22 A. That's fine.</p>

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<p>65</p> <p>1 Q. Did you review the synthetic pathway 2 described in Liu?</p> <p>3 A. From a thousand feet, yes.</p> <p>4 Q. What does that mean?</p> <p>5 A. Just a broad overview. I was more 6 interested in the claims of this patent.</p> <p>7 Q. Do you have any understanding whether 8 or not the synthetic pathway described in Ahmad is 9 different than the synthetic pathway described in 10 Liu?</p> <p>11 A. They possibly are, yes.</p> <p>12 Q. And would you agree that if these two 13 synthetic pathways are different, this would 14 result in different impurity profiles between 15 Ahmad and Liu?</p> <p>16 A. Again, I'm not sure about that. It 17 depends on what you end up with. So, for example, 18 if both ended up with 100 percent (Z)-endoxifen, 19 then I would say there's no difference.</p> <p>20 Q. Do you know whether or not you could 21 end up with 100 percent (Z)-endoxifen by following 22 the synthetic pathway in Liu?</p>	<p>67</p> <p>1 looking for perhaps the amount of (Z)-endoxifen in 2 there relative to the -- the mass of the material 3 you end up with.</p> <p>4 Q. What else besides the amount of 5 (Z)-endoxifen would you be concerned with if 6 you're looking at the impurity profile?</p> <p>7 A. Yeah, I really don't know. I would 8 refer that to the chemist as well because I 9 suppose, depending on the method of production, 10 there's the potential for, you know, the 11 (E)-endoxifen to be there or solvents or, you 12 know, other parts of material -- chemicals that 13 are used in the process.</p> <p>14 Q. So residual solvents?</p> <p>15 A. Probably, yeah. I mean, that's with 16 all drugs. That's considered to be a -- a 17 standard analysis.</p> <p>18 Q. And would you agree with me that for a 19 pharmaceutical formulation it's important to know 20 the impurity profile of that composition?</p> <p>21 A. Yeah. Specifically for formulation, 22 one would want the drug molecule to comply with</p>
<p>66</p> <p>1 A. I'm not sure. This is a chemist 2 question again.</p> <p>3 Q. And do you know if you would end up 4 with 100 percent (Z)-endoxifen by following the 5 synthetic steps in Ahmad?</p> <p>6 A. Same -- same answer, really. I mean, 7 Ahmad obviously points to it being greater than 8 80 percent pure.</p> <p>9 Q. And the same question with respect to 10 the '334 patent: Do you know if by following the 11 steps laid out in the '334 if you'd end up with 12 100 percent (Z)-endoxifen?</p> <p>13 A. Again, not sure. There's -- there's 14 many references in the '334 patent to previous 15 methods of production as well. So there's a lot 16 to look at there.</p> <p>17 Q. When we talk about the impurity profile 18 -- let me take a step back. 19 What are some of the things that you as 20 a formulation expert are thinking about when you 21 look at the impurity profile of a compound?</p> <p>22 A. I guess in -- in this instance we're</p>	<p>68</p> <p>1 the United States Pharmacopeia standards if the 2 drug is going to be approved by the FDA.</p> <p>3 Q. Are there residual solvents that are 4 not compatible with drug pharmaceutical 5 formulation?</p> <p>6 A. Again, it would depend on the United 7 States Pharmacopeia specification if the drug's 8 for U.S. use.</p> <p>9 Q. So let's say the drug is for U.S. use 10 and we're focused on the U.S. Pharmacopeia. 11 Are the residual solvents not 12 compatible with pharmaceutical drug formulation?</p> <p>13 A. We would have to look at the specific 14 monograph in the USP to determine that.</p> <p>15 Q. Sitting here today, can you tell me any 16 residual solvents that would not be permitted or 17 compatible with drug formulation?</p> <p>18 A. I -- I -- sorry. If I looked at the 19 USP monograph for this, I can't recall what it may 20 have said about residual solvents.</p> <p>21 Q. Is it fair to say that a person of 22 ordinary skill in the art in drug formulation</p>

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<p style="text-align: right;">69</p> <p>1 would consult the USP to evaluate whether or not 2 certain residual solvents are compatible with a 3 pharmaceutical formulation? 4 A. Yes, and possibly other sources as 5 well. I would suspect during the drug approval 6 process there are toxicology studies done. And 7 again, that's somebody else's area. 8 Q. Sure. 9 (McConville Deposition Exhibit 2 10 was marked for identification.) 11 BY MS. KRUMPLITSCH: 12 Q. Dr. McConville, the court reporter has 13 just handed you what's been marked as Exhibit 14 No. 2 to your deposition. 15 A. Yes. 16 Q. I'll give you a second to take a look 17 at it. I can represent to you this was not cited 18 in your declaration. 19 A. Yes. 20 Q. Do you recognize this exhibit? 21 A. Yes. 22 Q. And are you the Jason T. McConville</p>	<p style="text-align: right;">71</p> <p>1 Do you see that? 2 A. Yes. 3 Q. Could you read that sentence out loud, 4 please? 5 A. (As read): From a regulatory 6 perspective, it is essential to know the exact 7 composition of pharmaceutical formulations through 8 -- throughout the entire lifecycle of the product 9 and also exact characterization of residual 10 solvents is essential. 11 Q. And did you believe that sentence to be 12 true when you published this paper in 2020? 13 A. Yes. 14 Q. And do you still believe that to be 15 true? 16 A. Yes. 17 Q. Okay. We're going to turn back to the 18 Ahmad patent. 19 So do you have the Ahmad patent back in 20 front of you? 21 A. Yes. The '190, yes, got it. 22 Q. Could you turn to column 25, Example 4?</p>
<p style="text-align: right;">70</p> <p>1 who's the second author here? 2 A. Yes. 3 Q. Did you co-author this paper? 4 A. Yes. 5 Q. Do you need a moment to look through it 6 or do you remember this paper? 7 A. Well, I guess -- I more or less 8 remember it. If you want to direct me to a 9 specific section. If you want me to read through, 10 I can. It's a hearty paper. 11 Q. No. You are welcome to but I don't 12 think you need to do that for the question I'm 13 going to ask. 14 If you could just read to yourself the 15 introduction on page 1. We don't need to go past 16 page 1. 17 (Witness reviewing document.) 18 THE WITNESS: Okay. 19 BY MS. KRUMPLITSCH: 20 Q. So in the second column, lines -- nine 21 lines down, there's a sentence that starts "from a 22 regulatory perspective."</p>	<p style="text-align: right;">72</p> <p>1 A. Okay. 2 Q. So I'll just give you a second to take 3 a look at Example 4. Let me know when you have 4 had a chance to refresh your memory. 5 (Witness reviewing document.) 6 THE WITNESS: Okay. 7 BY MS. KRUMPLITSCH: 8 Q. Do you understand that Example 4 here 9 is describing adding ethyl acetate to the crude 10 solid product and heating until the solid 11 dissolves? 12 A. I'm not sure what you mean by "crude 13 solid product." 14 Q. Well, let's take a step back. 15 Do you understand that Example 4 16 describes adding ethyl acetate? 17 A. I see that it says (as read): Ethyl 18 acetate (50 mL) was added. 19 Q. And what was it added to? 20 A. I think possibly -- this refers to a 21 gummy residue. 22 Q. Do you have an understanding as to</p>

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<p>73</p> <p>1 whether (E)-endoxifen is more soluble in ethyl 2 acetate than (Z)-endoxifen?</p> <p>3 A. You best ask the chemist about that.</p> <p>4 Q. If I represent to you that 5 (Z)-endoxifen is more stable -- let me withdraw 6 that.</p> <p>7 If I represent to you that 8 (Z)-endoxifen is more soluble in ethyl acetate 9 than (E)-endoxifen, would you agree with me that a 10 crystallization in ethyl acetate would result in a 11 preferential crystallization of the (E)-form?</p> <p>12 A. I better not answer that. It's been a 13 long time since I've done recrystallizations 14 methods.</p> <p>15 Q. So we would consult a chemist to 16 understand the effects of adding ethyl acetate?</p> <p>17 A. I think that would be appropriate.</p> <p>18 Q. At the end of this step, Example 4, do 19 you agree with me that Ahmad does not provide any 20 guidance as to the expected isomeric ratio that 21 would result between the (Z)- and the (E)-forms?</p> <p>22 A. It doesn't state that here, no.</p>	<p>75</p> <p>1 that would, in fact, result in 80 percent purity 2 at least?</p> <p>3 A. I did not, no.</p> <p>4 Q. And, again, would you rely on the 5 chemists to do that analysis of the synthetic 6 steps in Ahmad?</p> <p>7 A. It would definitely be more appropriate 8 than me doing the analysis.</p> <p>9 Q. And do you have an understanding of 10 whether Ahmad provides a working example of 11 obtaining a composition with at least 90 percent 12 (Z)-endoxifen?</p> <p>13 A. Well, as I said in the claims, 14 90 percent is encompassed within that claim. So 15 Ahmad says he can do it. And it's an issued 16 patent. I have no reason to doubt that at this 17 point.</p> <p>18 Q. But you yourself did not go back and 19 look at the synthetic steps described in Ahmad to 20 see whether or not you could actually obtain a 21 90 percent pure (Z)-endoxifen?</p> <p>22 A. That's correct.</p>
<p>74</p> <p>1 Q. And do you -- I suspect I know what the 2 answer is but I'm going to ask.</p> <p>3 Do you agree with me that Ahmad does 4 not provide any method for producing a 5 (Z)-endoxifen enriched filtrate and subsequent 6 crystallization? Correct?</p> <p>7 A. Sorry. Please repeat.</p> <p>8 Q. Do you agree with me that Ahmad does 9 not provide any method for producing a 10 (Z)-endoxifen enriched filtrate and subsequent 11 crystallization. Correct?</p> <p>12 A. Again, I would have to refer to 13 somebody that's got expertise in that area, a 14 chemist.</p> <p>15 Q. Can you answer whether or not Ahmad 16 provides a working example of enriching the 17 mixture in (Z)-endoxifen?</p> <p>18 A. I mean, Ahmad -- Ahmad states that he 19 can get greater than 80 percent -- at least 20 80 percent purity in the claims.</p> <p>21 Q. Did you go back and do any analysis of 22 the synthetic methods provided in Ahmad to see if</p>	<p>76</p> <p>1 Q. Does Ahmad provide any working examples 2 of an enteric coated 90 percent (Z)-endoxifen 3 composition?</p> <p>4 A. So just looking through to confirm 5 whether it's possible -- whether it is -- if you 6 just repeat the question again. Sorry. Yeah.</p> <p>7 Q. Sure. Yeah.</p> <p>8 Does Ahmad provide any working example 9 of an enteric coated 90 percent (Z)-endoxifen 10 composition?</p> <p>11 A. I'm not sure whether the enteric 12 coating is mentioned specifically in this example 13 -- sorry, in this exhibit. I'd have to, you know, 14 go through it a little more thoroughly to refresh 15 my memory on it. But I do know that the prior art 16 does mention enteric coated formulations using 17 (Z)-endoxifen. Not the capsules mentioned here.</p> <p>18 Whether or not enteric coating is 19 described earlier, I think it might be. I would 20 have to look a little bit further in this -- yeah, 21 I mean, column 18 mentions enteric coating of 22 capsules. On line 27, I believe, through 29</p>

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<p style="text-align: right;">77</p> <p>1 mentions they're known in the art. At this time, 2 of course, enteric coated capsules were routinely 3 used for anything that could be degraded in the 4 stomach by the stomach acid. 5 So since it's mentioned in the patent, 6 I think it's not difficult to think about it. And 7 then of course at the end of Claim 1, mentions 8 that enteric coated tablets, enteric coated 9 capsule as well. 10 But in terms of working example, it's 11 not a difficult leap to get to. 12 Q. So is it your testimony that a person 13 of ordinary skill in the art would know how to 14 enterically coat -- let me withdraw that. 15 Is it your testimony that a person of 16 ordinary skill in the art would be able to make an 17 enteric coated capsule of (Z)-endoxifen without 18 too much experimentation? 19 A. So either an enteric coated capsule or 20 an inherently enteric capsule. I don't think it's 21 too difficult to try that formulation in any way. 22 Q. Okay.</p>	<p style="text-align: right;">79</p> <p>1 "acid-promoted isomerization"? 2 A. I've been made aware of it in this 3 case. I guess it's -- it could be considered a 4 form of degradation. 5 Q. That was my next question. 6 A. Okay. 7 Q. The degradation -- the degradation you 8 describe in paragraph 23, is that different than 9 acid-promoted isomerization? 10 A. Possibly could include it. It's -- 11 from my point of view, any issue with the low pH 12 of the stomach could be avoided. I'm not sure of 13 the exact type of issue associated with the drug 14 molecule. 15 Q. Do you understand that (Z)-endoxifen is 16 prone to isomerize to (E)-endoxifen under acidic 17 conditions? 18 A. Sorry. Was there a question? 19 Q. Do you understand that to be true? 20 A. Yes, I think that that's been made 21 aware to me. And so, great, use an enteric coated 22 system to prevent that because the prior art tells</p>
<p style="text-align: right;">78</p> <p>1 A. It's a very standard test. 2 Q. We'll get back to the enteric coating 3 questions in a bit. 4 If you have your declaration out, let's 5 look at page 8, paragraph 23. I'll give you a 6 second to read that. It's the paragraph we looked 7 at earlier. 8 A. Okay. 9 Q. So I want to focus on that first 10 sentence. You write (as read): Some drugs, 11 including endoxifen, are subject to acid catalyzed 12 degradation in the low pH acidic conditions of the 13 stomach. 14 Correct? 15 A. Yes. 16 Q. What does endoxifen degrade to? 17 A. This is something I think the chemist 18 would be more appropriately commenting on. But 19 any type of degradation from the low pH conditions 20 of the stomach can be easily avoided with 21 protection using an enteric system. 22 Q. And are you familiar with the term</p>	<p style="text-align: right;">80</p> <p>1 us that (Z)-endoxifen is more effective than 2 (E)-endoxifen. And so we don't want the formation 3 of (E)-endoxifen, I suppose. 4 Q. Okay. My question really wasn't about 5 enteric coatings. 6 I just want to make sure you understand 7 and agree with me that (Z)-endoxifen is prone to 8 isomerize to (E)-endoxifen under acidic 9 conditions; yes or no? 10 A. No. The pH of the stomach is very low 11 and it's -- it's very acidic. And so I would say 12 that in that example with such a low pH that that 13 could be the case, yeah. It's more likely to be 14 in such a low pH environment, yes. 15 Q. And do you have understanding at the pH 16 of the stomach, which is what? 17 A. I mean, it can vary from individual to 18 individual. Standard models put it somewhere 1 19 to 3. 20 Q. Let's just choose 2 in the middle 21 there. 22 A. Strange one to choose. But yeah, okay.</p>

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<p>81</p> <p>1 Q. So at the pH in the stomach, would --</p> <p>2 and we're not talking about enteric coating, just</p> <p>3 the (Z)-endoxifen in a low pH, would that result</p> <p>4 in an equilibrium between the (Z)- and the</p> <p>5 (E)-forms?</p> <p>6 A. That's -- that's -- I mean, you're</p> <p>7 going to have to talk to the chemists about that.</p> <p>8 I'm not sure whether equilibrium is the right</p> <p>9 consideration there. So best to talk to the</p> <p>10 chemists.</p> <p>11 Q. Okay. Does Ahmad -- so we're going to</p> <p>12 look at the Ahmad patent -- actually, we are</p> <p>13 looking at the Ahmad patent -- describe anywhere</p> <p>14 the difference in solubility between (Z)- and</p> <p>15 (E)-endoxifen?</p> <p>16 A. I didn't see any specification related</p> <p>17 to the solubilities, no.</p> <p>18 Q. Would a POSA generally expect</p> <p>19 stereoisomers to have similar solubilities?</p> <p>20 A. In -- in all media or any specific</p> <p>21 media?</p> <p>22 Q. Let's start with all media.</p>	<p>83</p> <p>1 Q. Do you agree that it would be</p> <p>2 impossible to predict prior to experimentation the</p> <p>3 exact crystallization conditions that would lead</p> <p>4 to a desired ratio of isomers?</p> <p>5 A. I don't know. There's -- there's some</p> <p>6 predictive tools for many of these sorts of</p> <p>7 processes, I think. So, again, chemists would</p> <p>8 have a better idea than me.</p> <p>9 Q. So if we wanted to have an</p> <p>10 understanding of the challenges in crystallizing</p> <p>11 and recrystallizing, we would talk to a chemist?</p> <p>12 A. They would have more insight than I do,</p> <p>13 yes.</p> <p>14 Q. Do you have an understanding as to</p> <p>15 whether using a different solvent type would</p> <p>16 result in different ratios of stereoisomers?</p> <p>17 A. Again, it's very specific. Chemistry</p> <p>18 question.</p> <p>19 Q. I'm going to ask you a number of these</p> <p>20 just so we have it on the record.</p> <p>21 What about using a different ratio of</p> <p>22 solvents, would that result in a different ratio</p>
<p>82</p> <p>1 A. Obviously they can be separated</p> <p>2 somehow. So I would imagine, you know, that --</p> <p>3 that -- there could be differences, slight</p> <p>4 differences, in solubility that could be exploited</p> <p>5 in extraction techniques such as column</p> <p>6 extraction.</p> <p>7 Q. Do you agree with me that the more</p> <p>8 similar the solubilities are between</p> <p>9 stereoisomers, the more difficult it is to</p> <p>10 separate them using crystallization?</p> <p>11 A. Oh, you better talk to the chemists</p> <p>12 about that one.</p> <p>13 Q. Okay. Do you have an understanding as</p> <p>14 to whether if one wanted to achieve different</p> <p>15 ratios of isomers, one could alter the</p> <p>16 recrystallization conditions?</p> <p>17 A. That's again a very specific chemistry</p> <p>18 oriented question.</p> <p>19 Q. Do you agree with me that there are</p> <p>20 many different crystallization parameters that</p> <p>21 could be altered?</p> <p>22 A. I suppose so.</p>	<p>84</p> <p>1 of stereoisomers?</p> <p>2 A. Better talk to the chemists.</p> <p>3 Q. What about a different maximum</p> <p>4 temperature to promote dissolution?</p> <p>5 A. Temperature would increase the</p> <p>6 solubility -- that's as much as I know -- in</p> <p>7 probably all cases. So better talk to the</p> <p>8 chemists about that.</p> <p>9 Q. How about using a different minimum</p> <p>10 temperature to promote crystallization?</p> <p>11 A. The same answer as last time.</p> <p>12 Q. How about using different</p> <p>13 concentrations of starting materials?</p> <p>14 A. Of course there's a solubility limit</p> <p>15 with solvents and that would affect things, I</p> <p>16 believe. But better ask the chemists.</p> <p>17 Q. And what if you change the rate of</p> <p>18 solvent addition?</p> <p>19 A. I don't know.</p> <p>20 Q. And changing the rate of increasing the</p> <p>21 temperature of the solution?</p> <p>22 A. I don't know.</p>

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<p>85</p> <p>1 Q. Is crystallization impacted by impurity</p> <p>2 profiles?</p> <p>3 A. You know, from my basic understanding,</p> <p>4 different materials within a recrystallization</p> <p>5 system can impact rates of crystallization, types</p> <p>6 of crystal form. But it's a very limited</p> <p>7 understanding I have.</p> <p>8 Q. So for all these we would ask the</p> <p>9 chemists?</p> <p>10 A. I think that that's the best thing,</p> <p>11 yes.</p> <p>12 Q. Is crystallization impacted by residual</p> <p>13 solvents?</p> <p>14 A. I imagine so, yes.</p> <p>15 Q. Do you have an understanding as to</p> <p>16 whether Ahmad describes a crystallization method</p> <p>17 to generate 90 percent (Z)-endoxifen?</p> <p>18 A. As I've said, Ahmad -- the '190 patent?</p> <p>19 Q. Uh-huh.</p> <p>20 A. Yeah, Ahmad does describe that at least</p> <p>21 90 percent (Z)-endoxifen can be achieved, which</p> <p>22 encompasses greater than 90 percent as well.</p>	<p>87</p> <p>1 describes the rate of solvent addition to generate</p> <p>2 90 percent pure (Z)-endoxifen?</p> <p>3 A. I do not.</p> <p>4 Q. Do you have understanding as to whether</p> <p>5 Ahmad describes the concentration of starting</p> <p>6 materials to generate 90 percent pure</p> <p>7 (Z)-endoxifen?</p> <p>8 A. No.</p> <p>9 Q. What about the concentration of</p> <p>10 starting materials to generate --</p> <p>11 (Stenographer clarification.)</p> <p>12 BY MS. KRUMPLITSCH:</p> <p>13 Q. What about the concentration for</p> <p>14 starting materials to generate 80 percent</p> <p>15 (Z)-endoxifen?</p> <p>16 A. No.</p> <p>17 Q. And any understanding as to whether</p> <p>18 Ahmad identifies the crystallization parameters</p> <p>19 required to achieve 80 percent (Z)-endoxifen?</p> <p>20 A. No.</p> <p>21 Q. Does Ahmad disclose the crystallization</p> <p>22 parameters required to achieve 90 percent</p>
<p>86</p> <p>1 Q. But sitting here you can't point to any</p> <p>2 specific crystallization parameters that Ahmad</p> <p>3 disclosed that would result in the greater than</p> <p>4 80 percent?</p> <p>5 A. I better not. It would be guesswork.</p> <p>6 Q. So do you have an understanding as to</p> <p>7 whether Ahmad describes which solvents to use to</p> <p>8 generate this greater than 80 percent?</p> <p>9 A. Not specifically no.</p> <p>10 Q. Do you have understanding of whether or</p> <p>11 not Ahmad describes the ratio of solvents used to</p> <p>12 generate 80 percent?</p> <p>13 A. No.</p> <p>14 Q. What about the ratio of solvents to use</p> <p>15 to generate 90 percent?</p> <p>16 A. Same as before.</p> <p>17 Q. Do you have an understanding as to</p> <p>18 whether Ahmad describes the appropriate</p> <p>19 temperature to generate 90 percent pure</p> <p>20 (Z)-endoxifen?</p> <p>21 A. I do not.</p> <p>22 Q. And how about whether or not Ahmad</p>	<p>88</p> <p>1 (Z)-endoxifen?</p> <p>2 A. Same -- same answer as before. It --</p> <p>3 the claims indicate that at least 80 percent can</p> <p>4 be obtained. So I have no reason to doubt what's</p> <p>5 in the claims.</p> <p>6 Q. And we would look to a chemist to</p> <p>7 actually go through the specification?</p> <p>8 A. Yes.</p> <p>9 Q. And in your work -- your research, your</p> <p>10 -- in your research, do you use -- do you use</p> <p>11 fractional crystallization to separate</p> <p>12 stereoisomers?</p> <p>13 A. I do not.</p> <p>14 Q. If you could turn in your declaration</p> <p>15 to page 14, paragraph 31. I'll give you a second</p> <p>16 to read that paragraph.</p> <p>17 A. 31?</p> <p>18 Q. 31 on page 14.</p> <p>19 A. Okay.</p> <p>20 Q. So in paragraph 31 you state that,</p> <p>21 second-to-last sentence, (as read): Ahmad teaches</p> <p>22 that this purification can be accomplished by</p>

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<p>1 using crystallization or chromatography.</p> <p>2 Do you see that? Third line from the</p> <p>3 bottom of paragraph 31.</p> <p>4 A. Paragraph 31?</p> <p>5 Q. Yes. It's down near the bottom. It's</p> <p>6 second-to-last sentence.</p> <p>7 A. Could you just repeat what you...</p> <p>8 Q. Sure. Do you see in that</p> <p>9 second-to-last sentence you state that (as read):</p> <p>10 Ahmad teaches that this purification can be</p> <p>11 accomplished by using crystallization or</p> <p>12 chromatography?</p> <p>13 A. Oh, there's a -- okay. Yes. Sorry.</p> <p>14 It's just the fact that 61 was on the left there.</p> <p>15 It threw me a little. I was thinking numbering</p> <p>16 went off.</p> <p>17 Right. Yeah. I see that, yes.</p> <p>18 Q. Okay. So we just spent some time</p> <p>19 talking about crystallization and you suggested</p> <p>20 that we would consult with a chemist to understand</p> <p>21 what Ahmad does and does not describe with respect</p> <p>22 to crystallization.</p>	<p>1 a second to read paragraph 56.</p> <p>2 A. Okay.</p> <p>3 (Witness reviewing document.)</p> <p>4 THE WITNESS: Okay.</p> <p>5 BY MS. KRUMPLITSCH:</p> <p>6 Q. So do you see you state kind of in the</p> <p>7 middle of that paragraph (as read): A POSA would</p> <p>8 have been motivated to include the pure form of</p> <p>9 (Z)-endoxifen manufactured using well-known</p> <p>10 methods.</p> <p>11 And then you cite examples -- sorry,</p> <p>12 Exhibits 1004 and 1005.</p> <p>13 A. Yes.</p> <p>14 Q. So 1004 is Liu, the Liu reference that</p> <p>15 we looked at earlier.</p> <p>16 A. Yes.</p> <p>17 Q. And let me give you 1005.</p> <p>18 (Deposition Exhibit 1005 was</p> <p>19 introduced for identification.)</p> <p>20 BY MS. KRUMPLITSCH:</p> <p>21 Q. Dr. McConville, I'm handing you what</p> <p>22 has been marked previously in this proceeding as</p>
<p>1 Do you have an understanding as to</p> <p>2 whether Ahmad identifies the chromatography</p> <p>3 parameters required to identify 90 percent</p> <p>4 (Z)-endoxifen?</p> <p>5 A. Again, that -- that would be the</p> <p>6 chemist to look at that.</p> <p>7 Q. And do you have an understanding as to</p> <p>8 whether or not Ahmad provides a working example of</p> <p>9 purified (Z)- and (E)-endoxifen using</p> <p>10 chromatography?</p> <p>11 A. Same issue.</p> <p>12 Q. Do you recall seeing any chromatography</p> <p>13 data in Ahmad quantifying the isomer purity of</p> <p>14 endoxifen?</p> <p>15 A. Let me see. I didn't think so, no.</p> <p>16 But just checking the figures in there. I don't</p> <p>17 know if there's anything hidden in the text. But</p> <p>18 I don't see any particular figures associated with</p> <p>19 that.</p> <p>20 Q. So now we're going to flip to page 25</p> <p>21 of your declaration, please, and paragraph -- oh,</p> <p>22 sorry. It's page 26, paragraph 56. I'll give you</p>	<p>1 Exhibit 1005.</p> <p>2 A. Thank you. Okay.</p> <p>3 Q. And Exhibit 1005 is International</p> <p>4 Patent Application WO 2012/050263 and the first</p> <p>5 inventor is Song, S-o-n-g.</p> <p>6 Do you agree with that?</p> <p>7 A. Yes.</p> <p>8 Q. Is it okay if I refer to Exhibit 1005</p> <p>9 as Song?</p> <p>10 A. Yes, that's fine.</p> <p>11 Q. Did you review the -- let me withdraw.</p> <p>12 You understand Song provides a</p> <p>13 synthetic -- describes a synthetic pathway?</p> <p>14 A. Yes.</p> <p>15 Q. Did you review that synthetic pathway?</p> <p>16 A. Again, just an overview. Really was</p> <p>17 interested in the claims at the end with what was</p> <p>18 claimed to be produced, yes.</p> <p>19 Q. Okay. Did you compare the synthetic</p> <p>20 pathway in Song to the synthetic pathway described</p> <p>21 in Ahmad?</p> <p>22 A. I did not.</p>

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<p>93</p> <p>1 Q. And did you compare the synthetic 2 pathway in Song to the synthetic pathway described 3 in the '334 patent?</p> <p>4 A. I did not.</p> <p>5 Q. Do you have understanding as to whether 6 Song teaches the use of ethyl acetate for 7 fractional crystallization?</p> <p>8 A. I can't recall that.</p> <p>9 Q. Do you recall whether Song 10 characterized the results of -- characterized the 11 resulting endoxifen product using NMR?</p> <p>12 A. Yes. I'm aware of that, yes.</p> <p>13 Q. Did you review the NMR data?</p> <p>14 A. Not thoroughly, no.</p> <p>15 Q. And did you compare the NMR data in 16 Song to NMR data in other references?</p> <p>17 A. Well, only after I read Dr. Davies' -- 18 Dr. Davies' or Davis' report, Davies.</p> <p>19 Q. So after you read Dr. Davies' report, 20 did you then compare the NMR data in Song to the 21 NMR data in other references?</p> <p>22 A. Just with respect to what Davies had</p>	<p>95</p> <p>1 see any reference to solid oral dosage forms, for 2 example?</p> <p>3 A. Well, as I've -- as I've said, I think 4 from a person of ordinary skill in the art 5 presented with a compound, it's the go-to thing, 6 really, the solid oral dosage form.</p> <p>7 I'm not sure whether Song mentions it 8 specifically. But, you know, with any patent 9 that's producing a therapeutic compound, that's 10 one thing on the table, I think. Now, it's not 11 necessarily a formulation patent, per se, though.</p> <p>12 Q. Looking at the Liu application, which 13 is Exhibit 1004.</p> <p>14 A. Okay. Yeah. Sorry.</p> <p>15 Q. You agree with me that the claims of 16 the Liu application are directed to processes for 17 preparing (Z)-endoxifen?</p> <p>18 A. In general, yes.</p> <p>19 Q. And there are no claims to a 20 pharmaceutical formulation?</p> <p>21 A. Well, not explicitly stating that, so 22 correct. I -- again, I would suggest that</p>
<p>94</p> <p>1 written. And he indicates that Song had some 2 errors in the NMR interpretation. And so as a 3 result obviously, you know, Song is not to be 4 relied upon in my opinion because I agree with 5 Dr. Davies in that respect.</p> <p>6 I think, though, that the '334 patent 7 also cites Song as an other publication somewhere. 8 So they made the same mistake as I did, I suppose.</p> <p>9 Q. Would you also agree with me that Song 10 does not teach an endoxifen composition to be used 11 in a pharmaceutical formulation?</p> <p>12 A. Say that again, please.</p> <p>13 Q. Song does not teach endoxifen 14 composition to be used in pharmaceutical 15 formulations, correct?</p> <p>16 A. Well, sort of disagree with that. I 17 think that in the background art obviously it 18 describes breast cancer. I can't think of any 19 other way to administer endoxifen to treat a 20 condition other than with a pharmaceutical 21 formulation.</p> <p>22 Q. When you were reviewing Song, did you</p>	<p>96</p> <p>1 obviously it's an active compound and the -- in 2 the background of the patent, obviously there was 3 a description of what this could be used to treat. 4 And from that point of view, obviously an active 5 compound does form part of a pharmaceutical 6 formulation. Doesn't explicitly state what that 7 formulation is.</p> <p>8 Q. Okay. And if we wanted to understand 9 whether or not the reagents used by Liu are 10 different or the same as that used in the '334 11 patent, would we ask the chemists?</p> <p>12 A. You mean in terms of the synthesis of 13 the molecule?</p> <p>14 Q. Yes.</p> <p>15 A. Yeah, I think that's fair.</p> <p>16 Q. And if we wanted to understand whether 17 the use of different reagents would result in a 18 different impurity profile between Liu and the 19 '334 patent, would we ask -- rely on a chemist?</p> <p>20 A. Yes.</p> <p>21 MS. KRUMPLITSCH: I think we've been 22 going another hour. Do you want to take</p>

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<p>97</p> <p>1 another short break?</p> <p>2 MR. MENCHACA: Sure.</p> <p>3 THE STENOGRAPHER: We're off the</p> <p>4 record at 11:12.</p> <p>5 (Whereupon, a recess was taken</p> <p>6 from 11:12 a.m. to 11:36 a.m.)</p> <p>7 THE STENOGRAPHER: We're back on the</p> <p>8 record at 11:36.</p> <p>9 BY MS. KRUMPLITSCH:</p> <p>10 Q. Dr. McConville, when we broke, we were</p> <p>11 talking about the Song reference.</p> <p>12 A. Yes.</p> <p>13 Q. And you mentioned that you agreed with</p> <p>14 Dr. Davies that Song misinterpreted the NMR data.</p> <p>15 A. I'm -- I'm -- you know, he's an expert</p> <p>16 in that field. And so I -- I believe that he's</p> <p>17 right in pointing out those disparities, yeah.</p> <p>18 Q. And then do you also recall testifying</p> <p>19 before the break that the '334 patent made the</p> <p>20 same mistake in relying on Song?</p> <p>21 A. I believed so. I thought I saw</p> <p>22 somewhere in there that there was a reference to</p>	<p>99</p> <p>1 A. Well, I mean, I can't comment on -- on</p> <p>2 that. I mean, I don't know to what extent Song</p> <p>3 thought they were making (Z)-endoxifen or not.</p> <p>4 It's really to you a chemist, you know. Endoxifen</p> <p>5 is a term used for (Z) and (E) in my opinion.</p> <p>6 Q. Okay.</p> <p>7 A. Sometimes interchangeably.</p> <p>8 Q. I also want to circle back to something</p> <p>9 you said earlier. We talked a lot about the</p> <p>10 claims of Ahmad -- the claim, sorry, the single</p> <p>11 claim. And we spent some time going through the</p> <p>12 synthetic pathways that are described in Ahmad.</p> <p>13 A. Well --</p> <p>14 Q. And you said that you would rely on a</p> <p>15 chemist to really go through those in detail,</p> <p>16 correct?</p> <p>17 A. Yes.</p> <p>18 Q. And you also made the statement that</p> <p>19 you assume that the specification teaches you how</p> <p>20 to make the claimed invention, correct?</p> <p>21 A. I have no reason to doubt that Ahmad --</p> <p>22 Ahmad -- Ahmad's claim is valid.</p>
<p>98</p> <p>1 Song. But, you know, I could be mistaken on that.</p> <p>2 I thought I had seen it somewhere.</p> <p>3 Q. Well, let me point to you the '334</p> <p>4 patent, column 18.</p> <p>5 A. Okay.</p> <p>6 Q. And it's column 18, starts at line --</p> <p>7 the paragraph that starts at line 23 that starts</p> <p>8 with "several methods."</p> <p>9 A. Yes.</p> <p>10 Q. And you'll see that Song is referred --</p> <p>11 I'll let you read that paragraph, but Song is the</p> <p>12 very last reference in that paragraph. So take a</p> <p>13 second and read that paragraph.</p> <p>14 A. Yes, yes. No, that's -- that's exactly</p> <p>15 where I recall seeing it.</p> <p>16 Q. So do you agree with me here that the</p> <p>17 '334 patent is citing Song as describing a method</p> <p>18 for the synthetic preparation of endoxifen?</p> <p>19 A. Yes.</p> <p>20 Q. And the '334 patent is not citing Song</p> <p>21 for methods of purifying (Z)-endoxifen.</p> <p>22 Do you agree with that?</p>	<p>100</p> <p>1 Q. And you're relying on the presumption</p> <p>2 that Ahmad is an issued patent?</p> <p>3 A. Yes.</p> <p>4 Q. And did you do any of your own</p> <p>5 investigation to see whether or not Ahmad actually</p> <p>6 does enable a POSA to make the claimed invention?</p> <p>7 A. That's really chemist's field.</p> <p>8 Q. Okay, Dr. McConville, I'm handing you</p> <p>9 what has previously been marked as Exhibit 1008 in</p> <p>10 this proceeding.</p> <p>11 (Deposition Exhibit 1008 was</p> <p>12 introduced for identification.)</p> <p>13 BY MS. KRUMPLITSCH:</p> <p>14 Q. I'll give you a chance to look at that.</p> <p>15 A. Yes. Okay.</p> <p>16 Q. Is it okay with you if we refer to</p> <p>17 Exhibit 1008 as the Cole reference?</p> <p>18 A. Yes.</p> <p>19 Q. And do you agree with me that Cole</p> <p>20 describes enteric coating of capsules containing</p> <p>21 paracetamol?</p> <p>22 A. Yes.</p>

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<p>101</p> <p>1 Q. Do you have an understanding of the</p> <p>2 solubility of paracetamol?</p> <p>3 A. I can't recall what it is. It's</p> <p>4 possibly mentioned in here somewhere. It's</p> <p>5 something I have looked at in the past. But I</p> <p>6 can't remember what the solubility of paracetamol,</p> <p>7 acetaminophen, is.</p> <p>8 Q. Do you have an understanding of whether</p> <p>9 or not paracetamol is highly soluble as compared</p> <p>10 to endoxifen?</p> <p>11 A. I haven't got the numbers in front of</p> <p>12 me. I wouldn't like to say.</p> <p>13 Q. But a POSA could look up those numbers,</p> <p>14 the solubility of each compound, correct?</p> <p>15 A. They – they could. But I mean in</p> <p>16 general this paper is about stopping drug release</p> <p>17 in the stomach, at least. You know, and doesn't</p> <p>18 really matter what the solubility of the drug is.</p> <p>19 It could be any solubility whatsoever. It's just</p> <p>20 not being released in the stomach area.</p> <p>21 Q. Okay. Cole does not describe using an</p> <p>22 enterically coated capsule to control other delay</p>	<p>103</p> <p>1 have been very routine to take endoxifen as made</p> <p>2 by Ahmad and formulate it in a -- in an enteric</p> <p>3 capsule.</p> <p>4 Do you stand by that statement?</p> <p>5 A. It's not necessarily referring to</p> <p>6 Ahmad, my statement. But any method of</p> <p>7 synthesizing endoxifen and incorporating it into</p> <p>8 an enteric capsule would be reasonable, I believe.</p> <p>9 Q. So when you are formulating a compound,</p> <p>10 can you choose any enteric coating?</p> <p>11 A. Depending on, for example, where you</p> <p>12 would like the drug to release, you'd have a</p> <p>13 choice of different enteric coatings. The Cole</p> <p>14 article, for example, indicates the use of</p> <p>15 Eudragit, a polymethacrylate copolymer. There are</p> <p>16 other choices for enteric coating that you could</p> <p>17 use. So there's options out there for enteric.</p> <p>18 It's not limited to anything in particular.</p> <p>19 Q. Okay. When designing a formulation or</p> <p>20 dosage form, can you take a compound and choose</p> <p>21 any capsule formulation?</p> <p>22 A. Sure. Again, there's lots of different</p>
<p>102</p> <p>1 disintegration and absorption of endoxifen</p> <p>2 compositions, correct?</p> <p>3 A. Could you repeat?</p> <p>4 Q. Yep. Cole does not describe using an</p> <p>5 enterically coated capsule to control or delay</p> <p>6 disintegration and absorption of endoxifen in the</p> <p>7 GI tract?</p> <p>8 A. Cole describes the use of paracetamol,</p> <p>9 which it could have been any drug that Cole</p> <p>10 describes, really, as far as I'm concerned in</p> <p>11 terms of where it's released. So yes, I agree</p> <p>12 that endoxifen is not referred to in Cole's</p> <p>13 article. But a standard drug like paracetamol is</p> <p>14 well known as a model drug for market purposes</p> <p>15 possibly.</p> <p>16 Q. Cole does not describe whether an</p> <p>17 enteric coated endoxifen capsule would provide a</p> <p>18 sustained action over a longer period of time,</p> <p>19 correct?</p> <p>20 A. That's correct, yes.</p> <p>21 Q. And so in your declaration at</p> <p>22 paragraph 71 on page 31 you state that it would</p>	<p>104</p> <p>1 options for capsules you can choose from. So...</p> <p>2 Q. What are some of those options?</p> <p>3 A. Gelatin, HPMC, enteric polymers</p> <p>4 themselves, insoluble polymers as well, time</p> <p>5 delayed.</p> <p>6 Q. What factors would you consider in</p> <p>7 determining what type of capsule you would use?</p> <p>8 A. That's a very broad answer, I'm afraid</p> <p>9 to tell you. But you might look at cost, you</p> <p>10 might look -- first -- first, let's just say if</p> <p>11 you want to protect it from the stomach, the first</p> <p>12 port of call would probably be the Eudragit</p> <p>13 polymethacrylate copolymers. They're commonly</p> <p>14 used, easy to get ahold of. There's articles</p> <p>15 indicating their use. So that would be the first</p> <p>16 thing you'd probably try.</p> <p>17 Q. When making an enteric capsule</p> <p>18 formulation, would a POSA consider interactions</p> <p>19 between the enteric material and residual</p> <p>20 solvents?</p> <p>21 A. So this -- just to clarify, this is for</p> <p>22 human use or?</p>

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<p>105</p> <p>1 Q. Yes, for human use.</p> <p>2 A. Well, one would hope the endoxifen, for</p> <p>3 example, if that's the drug you're using is -- is</p> <p>4 -- passes the muster in terms of the Pharmacopeia</p> <p>5 standards. And so then, no, a POSA would assume</p> <p>6 that we're in good shape with that drug.</p> <p>7 Q. So assuming the residual solvents that</p> <p>8 are present are safe for human dosing I guess, so</p> <p>9 assuming we pass that hurdle, would you then</p> <p>10 consider interactions between the enteric material</p> <p>11 and the residual solvents?</p> <p>12 A. I think I just answered that, that</p> <p>13 everything should be fine at that point with the</p> <p>14 drug itself and I don't think residual solvents</p> <p>15 would come into this.</p> <p>16 Q. When making an enteric capsule</p> <p>17 formulation, would a POSA consider interactions</p> <p>18 between the enteric material and impurities?</p> <p>19 A. I mean, it depends on I guess testing</p> <p>20 results that one might see. If everything seems</p> <p>21 to release correctly and the analytical data comes</p> <p>22 back fine from the in vitro testing initially, I</p>	<p>107</p> <p>1 It shouldn't -- shouldn't be an issue</p> <p>2 once dissolution occurs, electrostatic charging, I</p> <p>3 wouldn't suspect.</p> <p>4 Q. Would -- when making an enteric capsule</p> <p>5 formulation, would a POSA consider interactions</p> <p>6 between the enteric material and an unstable drug?</p> <p>7 A. So the drug itself is unstable?</p> <p>8 Q. Correct.</p> <p>9 A. What -- so I'm not sure -- I guess if</p> <p>10 the enteric coating -- I mean, if it's an enteric</p> <p>11 coating, this is what we're talking about, this is</p> <p>12 removed from the drug itself. So there's a</p> <p>13 barrier in the way with whatever the capsule is</p> <p>14 made of. The capsule is coated -- we're talking</p> <p>15 about a capsule still, right?</p> <p>16 Q. Yes.</p> <p>17 A. We're not talking about a tablet, are</p> <p>18 we?</p> <p>19 Q. Enteric capsule formulation.</p> <p>20 A. Okay. There's -- there's something</p> <p>21 between the drug and the enteric coating. So I'm</p> <p>22 not sure it's too much of an issue.</p>
<p>106</p> <p>1 suppose there's not -- nothing to worry about.</p> <p>2 But if there's some unknown reason why</p> <p>3 concentrations might be lower, for example, and</p> <p>4 then it's a fair game to look at the drug</p> <p>5 composition and make sure that there's no</p> <p>6 interactions from anything that may be there. But</p> <p>7 as I said, if it conforms to monograph</p> <p>8 specifications that is -- it shouldn't be a</p> <p>9 consideration.</p> <p>10 Q. When making an enteric capsule</p> <p>11 formulation, would a POSA consider interactions</p> <p>12 between the enteric material and a charged</p> <p>13 compound?</p> <p>14 A. Do you mean electrostatically charged</p> <p>15 or -- how do you mean?</p> <p>16 Q. Electrostatically charged, let's start</p> <p>17 with that.</p> <p>18 A. Mainly for aerosol formulations.</p> <p>19 Q. That's when --</p> <p>20 A. Sorry. You did specify enteric. So</p> <p>21 yeah, I guess you wouldn't use enteric for an</p> <p>22 aerosol formulation. That would be a bit silly.</p>	<p>108</p> <p>1 Q. So we talked about some of the factors</p> <p>2 a POSA would consider when choosing an enteric</p> <p>3 coating. You mentioned cost. Maybe availability.</p> <p>4 A. Uh-huh.</p> <p>5 Q. Are there other factors that might come</p> <p>6 into play?</p> <p>7 A. Well, the key factor that one would</p> <p>8 think about is where we want this to start</p> <p>9 dissolving in the gastrointestinal tract.</p> <p>10 Q. Any other factors besides those three</p> <p>11 that you can think of?</p> <p>12 A. Nothing springs to mind right now. But</p> <p>13 I'm sure there may be other factors.</p> <p>14 Q. Do you know if HPMC carries a charge?</p> <p>15 A. What type of charge do you mean?</p> <p>16 Q. An electrostatic charge.</p> <p>17 A. It can, yes.</p> <p>18 Q. And do you know whether enteric</p> <p>19 materials generally carry a charge?</p> <p>20 A. So HPMC is not an enteric material.</p> <p>21 Q. Right. Sorry. It's a separate</p> <p>22 question.</p>

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<p>109</p> <p>1 A. So the question is do enteric materials 2 carry an electrostatic charge or -- there's -- 3 okay. 4 Q. Yes. 5 A. They can. 6 MS. KRUMPLITSCH: Let's put that 7 exhibit away. 8 I'm handing you what has been marked as 9 Exhibit 1010 in this proceeding. 10 (Deposition Exhibit 1010 was 11 introduced for identification.) 12 BY MS. KRUMPLITSCH: 13 Q. Are you familiar with Exhibit 1010? 14 A. Yes. 15 Q. Is this one of the documents you 16 reviewed in preparing for this deposition? 17 A. Again, this is something I looked at 18 prior. Didn't look at it recently, no. 19 Q. And is it fair to say -- do you need a 20 minute to look through Exhibit 1010 again? 21 A. I can skim through it, yeah, sure. 22 (Witness reviewing document.)</p>	<p>111</p> <p>1 procedure that's used for enteric formulations 2 irrespective of the drug used. And in this case 3 the brand name Nexium is used in their test 4 analysis. 5 But, you know, as pointed out in the 6 concluding statement just before the references in 7 the Benameur paper it indicates (as read): The 8 capsules trials are underway to further evaluate 9 the technology's range and application, including 10 normal biopharmaceutical products, vaccines, and 11 oral peptide products from preclinical to Phase 12 III. 13 So it just shows a broad range of 14 things that can be put into the capsule. And in 15 this example they're showing a small molecule drug 16 that they obviously showed that it could be used 17 for macro molecules and really anything that could 18 be subject to an issue with the acidity of the 19 stomach. 20 Q. I am going to break this down. 21 So esomeprazole is Nexium, correct? 22 A. Yeah.</p>
<p>110</p> <p>1 THE WITNESS: Okay. 2 BY MS. KRUMPLITSCH: 3 Q. So first of all, is it okay with you if 4 I refer to Exhibit 1010 as Benameur? 5 A. Yes. 6 Q. So Benameur describes enteric capsule 7 drug delivery tested in esomeprazole, correct? 8 A. So -- 9 Q. And I can point you to page 3. 10 A. Okay. 11 Q. Okay. "The Human Biostudy Results," do 12 you see that heading right there? 13 A. Yeah. 14 Q. So do you agree with me that Benameur 15 is testing esomeprazole with these enteric capsule 16 drug delivery system? 17 A. Yes. 18 Q. And Benameur does not describe using 19 enteric capsule drug delivery technology to 20 control or delay disintegration and absorption of 21 endoxifen in the GI tract, correct? 22 A. Again, it's a standard testing</p>	<p>112</p> <p>1 Q. And esomeprazole is known to be 2 sensitive to acidity in the stomach? 3 A. I believe so, yes. 4 Q. And do you know if Nexium or 5 esomeprazole is positively or negatively charged? 6 A. In what conditions? 7 Q. As it is formulated in this enteric 8 capsule drug delivery technology. 9 A. Yeah. I'm -- I'm not sure. So the 10 esomeprazole -- let me -- if I can just take a 11 look through, if that's okay, for a second. 12 (Witness reviewing document.) 13 THE WITNESS: So I'm not sure in 14 this case because I think they refer to 15 Nexium quite a lot. And my issue is that 16 I'm not sure which type, whether it's OTC 17 form -- 18 (Stenographer clarification.) 19 THE WITNESS: -- over-the-counter, 20 OTC, or whether it's prescription form. So 21 I can't tell just by looking at it as we 22 sit here. Yeah, sorry. I just can't glean</p>

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<p>113</p> <p>1 it by looking at that right now.</p> <p>2 BY MS. KRUMPLITSCH:</p> <p>3 Q. Okay. If you look at the -- if you</p> <p>4 look at the first sentence of introduction -- I'll</p> <p>5 give you a second.</p> <p>6 Do you have a second to read that first</p> <p>7 sentence?</p> <p>8 A. Oh, yeah. Sorry. I was waiting on</p> <p>9 you.</p> <p>10 Q. Ready for lunch soon.</p> <p>11 So you agree with me that Benameur is</p> <p>12 describing this enteric capsule drug delivery</p> <p>13 technology that provides full enteric protection</p> <p>14 and rapid release in the upper GI tract?</p> <p>15 A. Yes.</p> <p>16 Q. And Benameur does not describe using</p> <p>17 this enteric capsule drug delivery technology to</p> <p>18 control or delay disintegration and absorption of</p> <p>19 endoxifen compositions in the GI tract?</p> <p>20 A. I mean, it talks about drug delivery.</p> <p>21 It would infer that -- you know, that first</p> <p>22 sentence there talks about full enteric protection</p>	<p>115</p> <p>1 A. And when you refer to sustained action,</p> <p>2 you're talking about the pharmacodynamics, the</p> <p>3 efficacy of the drug over time for an extended</p> <p>4 period --</p> <p>5 Q. Yes, for endoxifen.</p> <p>6 A. -- following absorption?</p> <p>7 Oh, endoxifen?</p> <p>8 Q. Yes, endoxifen.</p> <p>9 A. So it talks -- so this paper with the</p> <p>10 example of Nexium does show -- and I'm looking</p> <p>11 just above the summary section on page 3.</p> <p>12 Q. I'm there.</p> <p>13 A. It shows overall bioavailability was</p> <p>14 increased with a Cmax and AUC increased by</p> <p>15 56 percent and 32 percent for the example drug</p> <p>16 shown. And so for that example drug, one might</p> <p>17 think that the increase in Cmax could potentially</p> <p>18 lead to an increased effectiveness, especially</p> <p>19 with the increased AUC shown as well.</p> <p>20 And from that you might think other</p> <p>21 drugs could perhaps follow suit if they're</p> <p>22 protected substantially from the gastric acid.</p>
<p>114</p> <p>1 and rapid release in the upper gastrointestinal</p> <p>2 tract, small intestine. It doesn't go into any</p> <p>3 particular example of drug at that point.</p> <p>4 Q. And Benameur does not describe whether</p> <p>5 or not an enteric capsule drug delivery technology</p> <p>6 -- sorry. Let me withdraw that.</p> <p>7 If you formulated endoxifen using this</p> <p>8 enteric capsule drug delivery technology, Benameur</p> <p>9 does not describe whether that would provide a</p> <p>10 sustained action over a longer period of time,</p> <p>11 correct?</p> <p>12 A. Just reviewing the results a bit, if</p> <p>13 you don't mind.</p> <p>14 Q. No problem.</p> <p>15 (Witness reviewing document.)</p> <p>16 THE WITNESS: So can you repeat your</p> <p>17 question again? Sorry.</p> <p>18 BY MS. KRUMPLITSCH:</p> <p>19 Q. Benameur does not teach that the use of</p> <p>20 this enteric capsule drug delivery technology</p> <p>21 would provide a sustained action over a longer</p> <p>22 period of time for endoxifen?</p>	<p>116</p> <p>1 Q. You would need to test that for</p> <p>2 endoxifen, though, correct?</p> <p>3 A. For -- for any other drug you would</p> <p>4 look at the pharmacokinetics, of course.</p> <p>5 MS. KRUMPLITSCH: Can we go off the</p> <p>6 record for a second?</p> <p>7 THE STENOGRAPHER: We're off the</p> <p>8 record at 12:09.</p> <p>9 (Whereupon, a lunch recess was taken</p> <p>10 from 12:09 p.m. to 1:06 p.m.)</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>

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<p>117</p> <p>1 AFTERNOON SESSION</p> <p>2 THE STENOGRAPHER: The time is</p> <p>3 1:06 p.m.</p> <p>4 JASON T. MCCONVILLE, PH.D.,</p> <p>5 having been previously duly sworn was examined and</p> <p>6 testified further as follows:</p> <p>7 RESUMED EXAMINATION</p> <p>8 BY MS. KRUMPLITSCH:</p> <p>9 Q. Dr. McConville, I'm going to hand you</p> <p>10 what has previously been marked as Exhibit 1011.</p> <p>11 A. Thank you.</p> <p>12 (Deposition Exhibit 1011 was</p> <p>13 introduced for identification.)</p> <p>14 BY MS. KRUMPLITSCH:</p> <p>15 Q. And is it okay with you if I refer to</p> <p>16 Exhibit 1011 as Stegemann?</p> <p>17 A. Yes.</p> <p>18 Q. I'll give you a second to look at that.</p> <p>19 (Witness reviewing document.)</p> <p>20 THE WITNESS: Okay.</p> <p>21 BY MS. KRUMPLITSCH:</p> <p>22 Q. And Stegemann describes hard gelatin</p>	<p>119</p> <p>1 gelatin capsule is enterically coated or not for</p> <p>2 immediate release?</p> <p>3 A. They could be, yes.</p> <p>4 Q. And Stegemann does not describe using</p> <p>5 any excipient in an enterically coated capsule</p> <p>6 with respect to endoxifen compositions, correct?</p> <p>7 A. Stegemann lays the foundation for use</p> <p>8 of any drug in capsules such as represented in</p> <p>9 Table 4.</p> <p>10 Q. And Stegemann does not describe whether</p> <p>11 any particular excipient would impact the</p> <p>12 stability of a 90 percent pure (Z)-endoxifen</p> <p>13 composition?</p> <p>14 A. Stegemann really outlines excipient</p> <p>15 choices that can be used in combination for any</p> <p>16 drug. It doesn't -- doesn't specify any drug in</p> <p>17 particular with respect to that table.</p> <p>18 Q. And is it your -- let me withdraw that.</p> <p>19 Would a POSA -- how would a POSA decide</p> <p>20 which excipients to use in an endoxifen</p> <p>21 composition?</p> <p>22 A. I suppose one of the first things to</p>
<p>118</p> <p>1 capsules, correct?</p> <p>2 A. Yes.</p> <p>3 Q. And you cite to Stegemann, Table 4, on</p> <p>4 page 8 -- 7. It says page 7 of 23, but it's</p> <p>5 page 8 of the document.</p> <p>6 A. Okay. Yeah.</p> <p>7 Q. If you want to follow along, it's in</p> <p>8 your declaration at page 22.</p> <p>9 A. Got it.</p> <p>10 Q. And these are -- this Table 4 is a list</p> <p>11 of excipients used in the formulations of</p> <p>12 immediate release hard gelatin capsules?</p> <p>13 A. Yes, that's correct.</p> <p>14 Q. And Stegemann does not describe using</p> <p>15 any excipient in an enterically coated capsule,</p> <p>16 correct?</p> <p>17 A. Yeah, if the capsule is coated, one of</p> <p>18 the -- the capsule could be comprised of gelatin</p> <p>19 -- hard gelatin in exactly the same way, just on</p> <p>20 the outside of the capsule has a coating.</p> <p>21 Q. So is it your testimony that the</p> <p>22 excipients could be the same whether the hard</p>	<p>120</p> <p>1 think about is -- well, there's a few moving parts</p> <p>2 with this. But one of the things to think about</p> <p>3 is powder flowability, whether the drug itself can</p> <p>4 flow properly or not.</p> <p>5 In a -- in an automated process to make</p> <p>6 many capsules, you want a nice powder flowability.</p> <p>7 However, on a research scale you can sort of</p> <p>8 bypass that by dispensing a known amount in each</p> <p>9 capsule rather than relying on powder flow.</p> <p>10 That's one thing.</p> <p>11 Other things might be related to the</p> <p>12 dose you want to put in a capsule of a given size.</p> <p>13 So along with powder flow you possibly choose a</p> <p>14 diluent that was suitable. Those are the first</p> <p>15 sort of considerations, I think.</p> <p>16 Q. Would you give any consideration to any</p> <p>17 potential interactions between the (Z)-endoxifen</p> <p>18 and any of the excipients?</p> <p>19 A. For -- for any drug you would consider</p> <p>20 if there was any potential interaction, yes.</p> <p>21 Q. I'm going to hand you what has been</p> <p>22 marked previously as Exhibit 1012.</p>

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<p>121</p> <p>1 A. Thank you. 2 (Deposition Exhibit 1012 was 3 introduced for identification.) 4 BY MS. KRUMPLITSCH: 5 Q. Dr. McConville, is it okay with you if 6 I refer to Exhibit 1012 as the HPE? 7 A. Yes. 8 Q. Now, you included this exhibit with 9 your declaration. 10 And this exhibit is just an index, 11 correct? 12 A. Yes, but the index is used with the 13 book as a whole. 14 Q. So is it your intention to incorporate 15 the teachings of the entire book or just the 16 index? 17 A. I mean, the index represents a specific 18 citation within the book itself. So I don't see 19 any problem with including the entire book from 20 this point of view. Obviously we don't have that 21 with us. But a particular excipient is listed. 22 There's more details than just the listing, of</p>	<p>123</p> <p>1 obviously the 2006 edition. I can't remember off 2 the top of my head. There's editions – pretty 3 much every revision, there's additional excipients 4 added, so it's big. 5 Q. So a big -- a big book? 6 A. Yes. 7 Q. Did you review the entirety of that for 8 this proceeding? 9 A. No. I've looked at a lot of the book 10 over several years. For this proceeding I did not 11 look at the entirety of the book. I wanted to 12 point out that, you know, one could easily look in 13 the index and find a particular category of 14 excipient would be useful, you know, for an 15 intended use such as capsules or -- or whatnot. 16 Q. Okay. Do you know whether the HPE 17 describes using any particular excipient with an 18 endoxifen composition? 19 A. Like all -- like the previous exhibits, 20 it's a general guide for excipient use for a wide 21 array of drugs. In some instances the excipients, 22 the monographs listed will indicate certain drugs</p>
<p>122</p> <p>1 course. 2 Q. And you cite the HPE. And in your 3 declaration it's paragraphs 50 and 51 if you want 4 to look at that. 5 You cite this as an index that provides 6 a list of excipients by category, directing those 7 in the art to information about how to use that 8 excipient for its intended purpose, right? 9 A. Yes, as a quick reference somebody can 10 look through the index at a particular use. For 11 example, I guess the third page you can look under 12 where it says disinfectants. And it lists a whole 13 slew of different excipients used as 14 disinfectants. And then obviously you can hone in 15 on a particular excipient by going to the exact 16 page within the excipient handbook -- handbook and 17 pharmaceutical excipients. 18 Q. Dr. McConville, are you aware -- did 19 you review the entire -- let me withdraw that. 20 How many pages or how big is this 21 handbook? Couple hundred? 22 A. That's a very good question. This is</p>	<p>124</p> <p>1 and whether or not the excipient is suitable for 2 use with that particular drug. I can't comment on 3 whether endoxifen is listed anywhere in the 4 handbook because it's a big volume. 5 Q. So, for example, looking at this index, 6 and I'm at page 5 of 8, if you wanted an 7 emulsifying agent you could look in this index 8 under emulsifying agents and there are -- I'm not 9 going to count them but there are a long list of 10 emulsifying agents, correct? 11 A. Yes. 12 Q. And one skilled in the art would have 13 to go through and identify which emulsifying agent 14 had the correct properties for what they were 15 trying to formulate; is that right? 16 A. Maybe not the entire list. A person of 17 ordinary skill in the art may have an idea which 18 excipient might be suitable for their particular 19 application and so might have a shorter list than 20 the entirety to -- to focus on. 21 Q. Okay. Let's -- I'm going to hand you 22 what has been marked as Exhibit 1006 in this</p>

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<p>1 proceeding.</p> <p>2 A. Thank you.</p> <p>3 (Deposition Exhibit 1006 was</p> <p>4 introduced for identification.)</p> <p>5 BY MS. KRUMPLITSCH:</p> <p>6 Q. And if it's okay with you,</p> <p>7 Dr. McConville, can I refer to Exhibit 1006 as</p> <p>8 Ahmad 2010?</p> <p>9 A. Yes.</p> <p>10 Q. Do you need a minute to review Ahmad</p> <p>11 2010?</p> <p>12 A. I'll just -- I'm just reminding myself</p> <p>13 as to what I have used it for.</p> <p>14 Q. Sure.</p> <p>15 A. If you don't mind.</p> <p>16 (Witness reviewing document.)</p> <p>17 THE WITNESS: Okay.</p> <p>18 BY MS. KRUMPLITSCH:</p> <p>19 Q. And your discussion of Ahmad 2010 is --</p> <p>20 it's on page 16. So it's on page 16 of your</p> <p>21 declaration.</p> <p>22 A. Okay.</p>	<p>125</p> <p>127</p> <p>1 chemist for, if they have any other information</p> <p>2 related to the endoxifen citrate that was used in</p> <p>3 the study.</p> <p>4 Q. A POSA would understand that the PK</p> <p>5 parameters of an endoxifen citrate composition</p> <p>6 would vary depending on the ratio of (Z)- to</p> <p>7 (E)-isomers in the composition, correct?</p> <p>8 A. You have to repeat that again.</p> <p>9 Q. Well, let me just ask: Would the PK</p> <p>10 parameters of an endoxifen citrate vary depending</p> <p>11 on the ratio of (Z)- to (E)-isomers in the</p> <p>12 composition?</p> <p>13 A. The pharmacokinetics?</p> <p>14 Q. Yes.</p> <p>15 A. I'm not sure that they would vary.</p> <p>16 Q. Did you do any investigation to</p> <p>17 understand whether or not they would?</p> <p>18 A. I can't think of a reason why there</p> <p>19 would be much variability in pharmacokinetics for</p> <p>20 (Z) or (E) since just that endoxifen is measured</p> <p>21 in this article. It -- that's the compound which</p> <p>22 is analyzed by -- I think they used some sort of</p>
<p>126</p> <p>1 Q. So Ahmad 2010 describes a safety study</p> <p>2 comparing endoxifen citrate to tamoxifen, correct?</p> <p>3 A. Yes.</p> <p>4 Q. Ahmad 2010 does not describe the level</p> <p>5 of purity of the endoxifen citrate that was</p> <p>6 administered, correct?</p> <p>7 A. So this is -- if you wouldn't mind just</p> <p>8 repeating that again.</p> <p>9 Q. Sure. Ahmad 2010 does not describe the</p> <p>10 level of purity of the endoxifen citrate that was</p> <p>11 administered, correct?</p> <p>12 A. It just refers to as endoxifen citrate.</p> <p>13 So that's as far as it goes, yeah.</p> <p>14 Q. And so we don't know the ratio of (Z)-</p> <p>15 to (E)-isomers of endoxifen citrate that was</p> <p>16 administered?</p> <p>17 A. Not precisely, no.</p> <p>18 Q. Were you able to confirm or study or</p> <p>19 understand the ratio of (Z)- to (E)-isomers that</p> <p>20 were administrated -- was administered in Ahmad</p> <p>21 2010?</p> <p>22 A. It's possibly something to refer to the</p>	<p>128</p> <p>1 HPLC method.</p> <p>2 If I can just -- yes, so</p> <p>3 chromatographic method to analyze endoxifen. So</p> <p>4 we -- as established, we don't know the difference</p> <p>5 in (Z) or (E), whether there even would be one in</p> <p>6 terms of pharmacokinetics. But this is measuring</p> <p>7 for endoxifen as a whole.</p> <p>8 Q. And to be precise, it's measuring</p> <p>9 endoxifen citrate, correct?</p> <p>10 A. It's a pharmacokinetic analysis. So</p> <p>11 it's not measuring the citrate salt. This is</p> <p>12 blood samples of endoxifen in the body.</p> <p>13 Q. But you'd agree with me that what was</p> <p>14 administered to the patient was endoxifen citrate?</p> <p>15 A. Correct, yes.</p> <p>16 Q. And so I just want to make sure I</p> <p>17 understand your testimony, that you believe the</p> <p>18 pharmacokinetic properties of endoxifen and</p> <p>19 endoxifen citrate would be the same?</p> <p>20 Actually, let me withdraw that.</p> <p>21 You believe that the pharmacokinetics</p> <p>22 of endoxifen free base and endoxifen citrate would</p>

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<p>129</p> <p>1 be the same?</p> <p>2 A. The pharmacokinetic properties, yes.</p> <p>3 Q. A POSA would understand that the</p> <p>4 (Z)-form of endoxifen is more active, correct?</p> <p>5 A. Yes.</p> <p>6 Q. So is it your understanding that -- let</p> <p>7 me withdraw that.</p> <p>8 Would the bioavailability of</p> <p>9 (Z)-endoxifen citrate vary depending on the ratio</p> <p>10 of (Z)- to (E)-isomers?</p> <p>11 A. I don't see why it would.</p> <p>12 Q. So is there any correlation in your</p> <p>13 mind between the higher active (Z)-form and</p> <p>14 bioavailability?</p> <p>15 A. Not to my understanding. Just that,</p> <p>16 you know, pharmacokinetics is the -- to put it</p> <p>17 bluntly, is the study of concentrations of a</p> <p>18 molecule in the body. And pharmacodynamics is the</p> <p>19 study on the activity in the body. So they're</p> <p>20 distinct.</p> <p>21 Q. So is it your -- would a POSA</p> <p>22 understand that the pharmacodynamics of</p>	<p>131</p> <p>1 parameters as a pharmaceutical composition</p> <p>2 administering an endoxifen free base?</p> <p>3 A. If it was exactly the same</p> <p>4 pharmaceutical composition, I would expect to see</p> <p>5 the same pharmacokinetic behavior.</p> <p>6 Q. And if it's not the same pharmaceutical</p> <p>7 formulation, you would expect a different</p> <p>8 pharmacokinetic behavior?</p> <p>9 A. Not necessarily.</p> <p>10 Q. But it could be?</p> <p>11 A. You would have to test them. It could</p> <p>12 be. It might not be.</p> <p>13 Q. So you couldn't assume one way or</p> <p>14 another that it would be the same or not the same?</p> <p>15 You'd have to test it?</p> <p>16 A. Normally -- so, for example, if there's</p> <p>17 a generic version of a product, any -- any drug,</p> <p>18 let's say, paracetamol, for example, there would</p> <p>19 have to be bioequivalence demonstrated. And so</p> <p>20 the generic formulation should have some</p> <p>21 similarity to the brand formulation potentially.</p> <p>22 From batch to batch variability for a brand</p>
<p>130</p> <p>1 (Z)-endoxifen citrate would vary depending on the</p> <p>2 ratio of (Z) to (E)?</p> <p>3 A. That's a possibility. It doesn't tell</p> <p>4 us anything about the bioavailability or</p> <p>5 pharmacokinetics, of course. It's distinct. It's</p> <p>6 different.</p> <p>7 Q. Okay. So I just want to make sure that</p> <p>8 I understand your testimony here.</p> <p>9 Is it your testimony that a POSA would</p> <p>10 understand that the pharmacokinetic properties of</p> <p>11 an endoxifen citrate composition and an endoxifen</p> <p>12 free base would be identical?</p> <p>13 A. The only thing that could be changed is</p> <p>14 potentially the rate of absorption due to the</p> <p>15 formulation. But the molecule itself, endoxifen,</p> <p>16 whether it's liberated from a citrate salt or it's</p> <p>17 from the free base, would behave the same</p> <p>18 pharmacokinetically.</p> <p>19 Q. Right. But that wasn't my question.</p> <p>20 So if you're administering a</p> <p>21 pharmaceutical composition comprised of endoxifen</p> <p>22 citrate, would you expect to have the same PK</p>	<p>132</p> <p>1 product, they'd have to test using exactly the</p> <p>2 same composition formulation, otherwise the</p> <p>3 pharmacokinetic parameters would be different.</p> <p>4 So if I had a capsule containing</p> <p>5 paracetamol and it was coated in some way in one</p> <p>6 batch and then the next batch produced the</p> <p>7 following day had a slightly thicker coating on</p> <p>8 it, then that would affect the absorption</p> <p>9 potentially of the drug. So there wouldn't be</p> <p>10 bioequivalency there. So we have to be careful</p> <p>11 when we're testing things to have the same</p> <p>12 pharmaceutical product for comparison.</p> <p>13 Q. Have you conducted any tests comparing</p> <p>14 the absorption rate of endoxifen citrate as</p> <p>15 compared to an endoxifen free base?</p> <p>16 A. No.</p> <p>17 Q. Would a POSA need to perform that</p> <p>18 comparison, comparative study, to draw the</p> <p>19 conclusion that you're drawing, that they'd be</p> <p>20 identical?</p> <p>21 A. What -- what would be identical?</p> <p>22 Q. That the absorption rates would be</p>

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<p>1 identical.</p> <p>2 A. So once the citrate's dissolved, it's</p> <p>3 available for absorption in much the same way the</p> <p>4 non-salted form is. And so, yeah, I would agree</p> <p>5 that it -- the best thing would be to test those.</p> <p>6 But in terms of pharmacokinetic parameters,</p> <p>7 following absorption, which is pretty much reliant</p> <p>8 on the formulation itself, pharmacokinetics should</p> <p>9 be exactly the same.</p> <p>10 Q. So the area under the curve would be</p> <p>11 exactly the same?</p> <p>12 A. Given dose equivalency, I would suspect</p> <p>13 so.</p> <p>14 Q. Would the area under the curve be the</p> <p>15 same for an endoxifen citrate composition with a</p> <p>16 different portion of (Z) to (E)?</p> <p>17 A. I don't think so, no.</p> <p>18 Q. So as you change the proportion of (Z)-</p> <p>19 to (E)-isomer in your endoxifen citrate</p> <p>20 composition, the area under the curve would</p> <p>21 change?</p> <p>22 A. I don't think so. For example, in the</p>	<p>133</p> <p>1 administered to the patients, correct?</p> <p>2 A. Yes.</p> <p>3 Q. And this paper does not distinguish</p> <p>4 between the (Z) and the (E), so we don't know the</p> <p>5 level of purity that was administered to these</p> <p>6 patients, correct?</p> <p>7 A. Well, we know that a certain bar was</p> <p>8 met in terms of it being safe enough to administer</p> <p>9 to patients. So not sure what you mean by purity.</p> <p>10 I'm guessing you mean (Z) to (E) ratio. And I</p> <p>11 think they're distinct things. So I think from a</p> <p>12 purity point of view to give to an individual, it</p> <p>13 relies on meeting a monograph, which this has met.</p> <p>14 Q. But -- thank you for that</p> <p>15 clarification. So let's talk about isomeric</p> <p>16 purities, so a certain percentage of (Z) to (E).</p> <p>17 A. Yeah.</p> <p>18 Q. And Ahmad 2010 doesn't tell us what</p> <p>19 that isomeric -- of the endoxifen citrate that was</p> <p>20 given to the patients; is that correct?</p> <p>21 A. That is correct, yes. I mean, it tells</p> <p>22 us a range of endoxifen, not knowing the (Z) or</p>
<p>134</p> <p>1 paper we're looking at, the Ahmad 2010, the</p> <p>2 analysis is for endoxifen. It doesn't</p> <p>3 discriminate between the (Z) or the (E). So the</p> <p>4 only -- the only thing I can think of is that</p> <p>5 endoxifen behaves as endoxifen, whether it's</p> <p>6 (Z) or (E).</p> <p>7 Q. Did you look at any other studies to</p> <p>8 confirm that the (Z)- and (E)-forms behaved the</p> <p>9 same?</p> <p>10 A. I didn't look at any other studies to</p> <p>11 look at that. This is not something that I've</p> <p>12 ever seen, that you would look at different</p> <p>13 pharmacokinetics behavior of a different isomer.</p> <p>14 I'm not aware of any. I know you can have</p> <p>15 different forms of many drugs. But I'm not aware</p> <p>16 of any reported differences in pharmacokinetic</p> <p>17 parameters as such, but widely varying</p> <p>18 pharmacodynamics for different types of drugs, of</p> <p>19 course, and toxicities profiles.</p> <p>20 Q. So I think you've pointed out a few</p> <p>21 times that this Ahmad 2010 paper just refers to</p> <p>22 endoxifen and the fact that endoxifen citrate was</p>	<p>135</p> <p>1 (E) ratios, and it describes it as being an</p> <p>2 effective amount for therapeutic use.</p> <p>3 Q. When you say range, you mean a dosing</p> <p>4 range?</p> <p>5 A. There are different doses, yeah, given</p> <p>6 in Table 1, 0.5 to 4. Sorry. And, you know, the</p> <p>7 form of the gram, for example, gives us a Cmax of</p> <p>8 15.1-nanograms per mL and an AUC of 801 nanogram</p> <p>9 hours per mL and that is a therapeutically</p> <p>10 effective amount according to Ahmad.</p> <p>11 MS. KRUMPLITSCH: I'm going to give you</p> <p>12 what has been marked 1007 in this proceeding.</p> <p>13 (Deposition Exhibit 1007 was</p> <p>14 introduced for identification.)</p> <p>15 BY MS. KRUMPLITSCH:</p> <p>16 Q. Dr. McConville, is it okay with you if</p> <p>17 I refer to Exhibit 1007 as Ahmad 2012?</p> <p>18 A. Yes.</p> <p>19 Q. I'll give you a second to look at that.</p> <p>20 (Witness reviewing document.)</p> <p>21 THE WITNESS: Okay.</p> <p>22</p>

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<p>137</p> <p>1 BY MS. KRUMPLITSCH:</p> <p>2 Q. So one question: If we're talking</p> <p>3 about the effective amount of a drug, would that</p> <p>4 be its pharmacodynamics?</p> <p>5 A. There's a dose/response relationship.</p> <p>6 And so the pharmacokinetics should refer to be</p> <p>7 proportional to a pharmacodynamic response</p> <p>8 ideally. Not the case for all drugs. But in this</p> <p>9 case I think there is a good dose/response</p> <p>10 relationship from what I've seen.</p> <p>11 Q. What did you look at to establish that?</p> <p>12 A. Well, I -- this particular article</p> <p>13 describes multiple daily doses being efficient for</p> <p>14 -- being sufficient for effective therapy. So</p> <p>15 whatever they are administering here at the steady</p> <p>16 state is an effective therapy. Sorry. Between 4</p> <p>17 and 8 specifically, 4 and 8-milligrams exposure.</p> <p>18 Q. And so the record is clear, you are</p> <p>19 looking at Ahmad 2012?</p> <p>20 A. Yes.</p> <p>21 Q. I want to take a step back.</p> <p>22 So we agree that the (Z)-isomer is more</p>	<p>139</p> <p>1 Q. Okay. And so the effective dose for</p> <p>2 whatever composition was administered in Ahmad may</p> <p>3 not be the same effective dose if the ratio of (Z)</p> <p>4 to (E) were different.</p> <p>5 Is that fair to say?</p> <p>6 A. Could you repeat that, please?</p> <p>7 Q. Maybe. Okay. So we don't know what</p> <p>8 the effective dose is -- sorry. Let me withdraw</p> <p>9 that.</p> <p>10 We don't know the ratio of (Z) to (E)</p> <p>11 in Ahmad 2012, correct?</p> <p>12 A. That's correct.</p> <p>13 Q. So we cannot say that the dose that was</p> <p>14 administered in Ahmad 2012 is the effective dose</p> <p>15 for any composition of endoxifen.</p> <p>16 You can't generalize that, right, you</p> <p>17 would need to know the ratio of (Z) to (E)?</p> <p>18 A. I mean, if it is all (Z), this is the</p> <p>19 effective dose. If it has a different ratio of</p> <p>20 (Z) to (E), it's an effective dose. I mean, it's</p> <p>21 an effective dose. I -- I can't tell -- it</p> <p>22 doesn't specify here what (Z) to (E) is. But it's</p>
<p>138</p> <p>1 active, right?</p> <p>2 A. Yeah.</p> <p>3 Q. So if you formulate an endoxifen</p> <p>4 citrate with 50/50 (Z) to (E), you would expect</p> <p>5 that to be less effective than an endoxifen</p> <p>6 citrate with 80/20 (Z) to (E), right?</p> <p>7 A. Well, it depends on the therapeutic</p> <p>8 endpoint that you are looking for. So I don't</p> <p>9 know. 50/50 might be suitable. 80/20 might be</p> <p>10 suitable. It's really difficult to say what</p> <p>11 threshold is effective necessarily. Clearly in</p> <p>12 the art it was recognized that (Z) is the goal to</p> <p>13 have an effective therapy.</p> <p>14 Q. And we've established that at least in</p> <p>15 Ahmad 2010, we don't know what the ratio of (Z) to</p> <p>16 (E) was, right?</p> <p>17 A. Yes.</p> <p>18 Q. And Ahmad 2012 we don't know what the</p> <p>19 ratio of (Z) to (E) is, correct?</p> <p>20 A. Yes.</p> <p>21 Q. We do know the ratio or we don't?</p> <p>22 A. No, you're correct.</p>	<p>140</p> <p>1 an effective dose.</p> <p>2 Q. Right. And if you were comparing the</p> <p>3 results in Ahmad to another endoxifen citrate</p> <p>4 composition that had a different ratio of (Z) to</p> <p>5 (E), it's possible that you would have a different</p> <p>6 effective dose, correct?</p> <p>7 A. I mean, I think this is -- I think this</p> <p>8 is the same Ahmad, the 190-pound. I think so</p> <p>9 because -- anyway, the point is that prior to 2012</p> <p>10 Ahmad and Ahmad -- which I think is the same one,</p> <p>11 not 100 percent -- anyway, an Ahmad described (Z)</p> <p>12 as being effective stereoisomer of endoxifen.</p> <p>13 And so putting those two things</p> <p>14 together, one could assume that given a pure -- a</p> <p>15 pure (Z)-form, or purer (Z)-form, the ratio being</p> <p>16 leaning to (Z) for this, would be an effective</p> <p>17 dose. Whatever they've used is effective dose.</p> <p>18 And you know, there's previous description of</p> <p>19 greater than 90 percent of (Z) being a target for</p> <p>20 synthesis.</p> <p>21 Q. When you say there is a greater than</p> <p>22 90 percent target for synthesis, you're referring</p>

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<p>141</p> <p>1 to that statement in the Ahmad patent that said</p> <p>2 one object was to achieve 90 percent purity of</p> <p>3 (Z)?</p> <p>4 A. Yes. That's right, yes.</p> <p>5 Q. But you don't have any indication in</p> <p>6 the actual composition that was administered in</p> <p>7 Ahmad 2012 as to what the purity level is -- or</p> <p>8 was, correct?</p> <p>9 A. It doesn't explicitly state it. That's</p> <p>10 right, in terms of (Z) to (E). You know, just</p> <p>11 getting back to the purity thing, obviously the</p> <p>12 endoxifen is safe for human use.</p> <p>13 Q. Right. When I say purity, I'm</p> <p>14 referring to isomeric purity here.</p> <p>15 A. Yes.</p> <p>16 Q. And do you agree with me that Ahmad</p> <p>17 2012 describes the administration of endoxifen</p> <p>18 citrate composition similar or the same as Ahmad</p> <p>19 2010?</p> <p>20 A. It's a little -- it's a little short on</p> <p>21 details. I can't be sure that that's necessarily</p> <p>22 the case. It just says endoxifen.</p>	<p>143</p> <p>1 cite this paper in the label? If it does, then</p> <p>2 that's fine. I don't know if it's just my -- my</p> <p>3 -- the small print but I do not see that it</p> <p>4 necessarily cites this article.</p> <p>5 Q. It might be a combination of the small</p> <p>6 print and just what's in the label itself. The</p> <p>7 label itself is also not dated so that doesn't</p> <p>8 help us much there.</p> <p>9 So you give no import to the fact that</p> <p>10 the table -- these two tables have identical data?</p> <p>11 A. I mean, on face value they have the</p> <p>12 same numbers, of course. So, you know, just if</p> <p>13 one is endoxifen citrate and one is not endoxifen</p> <p>14 citrate, it's just endoxifen, then, I mean, that</p> <p>15 would be outstandingly good for my analysis of the</p> <p>16 pharmacokinetic parameters that one might expect</p> <p>17 comparing the salt to the non-salt.</p> <p>18 I mean, if one is citrate and the other</p> <p>19 is citrate, that's okay, too, because obviously I</p> <p>20 have my opinion about the pharmacokinetics</p> <p>21 associated with both.</p> <p>22 Q. Would an endoxifen salt have the same</p>
<p>142</p> <p>1 Q. If you -- I'm going to ask you to</p> <p>2 compare two things. See if this helps shed some</p> <p>3 light on this question.</p> <p>4 If you could -- so we're going to look</p> <p>5 at that table in Ahmad 2012. And if you could</p> <p>6 compare that to the Zonalta label that we looked</p> <p>7 at earlier, that tiny print. And on the back of</p> <p>8 that you'll see a table with some pharmacokinetic</p> <p>9 parameters. It's that bottom table there.</p> <p>10 A. Yes.</p> <p>11 Q. And if you compare the numbers, they</p> <p>12 look to be identical?</p> <p>13 A. Well, they do. But as I've stated,</p> <p>14 pharmacokinetics shouldn't be an issue with either</p> <p>15 the citrate or the endoxifen without a citrate.</p> <p>16 These values are based on the measurements of</p> <p>17 endoxifen, not endoxifen citrate.</p> <p>18 Q. So you would expect each one of these</p> <p>19 parameters to be absolutely identical even to the</p> <p>20 level of standard deviation between endoxifen and</p> <p>21 endoxifen citrate?</p> <p>22 A. It doesn't say that this -- does it</p>	<p>144</p> <p>1 solubility as an endoxifen free base?</p> <p>2 A. I haven't looked at those numbers. I</p> <p>3 don't know.</p> <p>4 Q. Does solubility impact</p> <p>5 pharmacokinetics?</p> <p>6 A. With respect to the rate of absorption,</p> <p>7 yes. But once absorption has occurred, then</p> <p>8 pharmacokinetic parameters are governed by</p> <p>9 elimination processes, which are the same.</p> <p>10 MS. KRUMPLITSCH: I think we can go</p> <p>11 off the record.</p> <p>12 THE STENOGRAPHER: Off the record at</p> <p>13 1:52 p.m.</p> <p>14 (Whereupon, a recess was taken</p> <p>15 from 1:52 p.m. to 2:00 p.m.)</p> <p>16 THE STENOGRAPHER: It's 2:00 p.m.</p> <p>17 MS. KRUMPLITSCH: Thank you,</p> <p>18 Dr. McConville. We have no further</p> <p>19 questions.</p> <p>20 THE WITNESS: Thank you.</p> <p>21 MR. MENCHACA: No questions.</p> <p>22 THE STENOGRAPHER: We are concluded</p>


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<p style="text-align: right;">145</p> <p>1 at 2:00 o'clock p.m. 2 (Time concluded: 2:00 p.m.) 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22</p>	<p style="text-align: right;">147</p> <p>1 marriage, I am not employed by or an attorney to 2 any of the parties to this action, and that I am 3 in no way interested, financially or otherwise, in 4 the outcome of this matter. 5 6 7 IN WITNESS WHEREOF, I have hereunto 8 set my hand and this 16th day of 9 April, 2024. 10 11  12 13 My commission expires: 14 12/18/24 15 NOTARY PUBLIC IN AND FOR THE 16 STATE OF ILLINOIS 17 18 19 20 21 22</p>
<p style="text-align: right;">146</p> <p>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, Intas Pharmaceuticals, Inc., was represented 14 by counsel at the deposition. 15 I further certify that the deposition 16 of Jason T. McConville, Ph.D., occurred at the 17 offices of McAndrews, Held & Malloy, Ltd., at 18 500 West Madison Street, Chicago, Illinois, on the 19 12th day of April, 2024, commencing at 8:56 a.m. 20 CST to 2:00 p.m. CST. 21 I further certify that I am not related 22 to any of the parties to this action by blood or</p>	

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