IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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HERON THERAPEUTICS, INC., :
Plaintiff, :
Civil Action No.:
v. :
22-cv-00985-WCB
FRESENIUS KABI USA, LLC, :
Defendant. :
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DAY 4 - PM

BEFORE JUDGE WILLIAM CURTIS BRYSON

Washington, D.C.

Thursday, June 27, 2024

12:35 p.m.

Reported by: Matthew Goldstein, RMR, CRR

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PGR Petition – USP 12,115,255

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1 C O N T E N T S

2 EXAMINATION OF STEVEN LITTLE, PH.D. PAGE

3

4 By MR. ALY - CROSS 1354

5 By MR. ASHKENAZI - REDIRECT 1443

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1 JUDGE BRYSON: You may resume.
2 BY MR. ASHKENAZI:
3 Q. Before we go to objective indicia,
4 Dr. Little, just for the record --
5 Can we please pull up PDX-4-4 again?
6 And for the record, please read into the
7 record Examples 7 and 8 from CN '845 that you have
8 identified on your Demonstrative PDX-4-4?
9 A. Okay. Sure. Example 7 is 0.115 percent
10 aprepitant, 5.6 percent egg yolk lecithin,
11 5.5 percent soybean oil. It does not have sodium
12 oleate. It has a pH of 8.0. It has .6 percent
13 glycerin and 3.2 percent ethanol.
14 Q. And can you please read into the record
15 Example 8?
16 A. Yes. Example 8 has 0.06 percent
17 aprepitant. .6 percent -- PEG stands for
18 polyethylene glycol -- caprylic glyceride,
19 0.6 percent olive oil. It does not have sodium
20 oleate. 7.2 is the pH. It has 0.5 percent
21 xylitol. And it has 0.6 percent 1, 2-propanediol.
22 Q. Thank you. Now, I'd like to turn our
23 attention to Cinvanti and your opinions about
24 objective indicia of nonobviousness.
25 Can you remind us how the formulation of

1 Cinvanti compared to the formulations described in
2 the asserted claims?
3 A. It meets each of the compositional and
4 stability requirements of the asserted claims.
5 Q. Okay. And you went over that testimony
6 during your direct examination in the infringement
7 portion of the case; correct?
8 A. On Monday, yes.
9 Q. Okay. Dr. Little, is Cinvanti
10 physically stable as required by the asserted
11 claims?
12 A. It is.
13 Q. And you did that analysis, again, on
14 this past Monday?
15 A. Correct.
16 Q. Okay. And can we please turn to
17 JTX-51.1? That's the Cinvanti label. I want to
18 focus your attention on the dosage and
19 administration portion and highlight the first
20 line under the recommended dosage.
21 Can you please read into the record that
22 first sentence?
23 A. Sure. Administer Cinvanti intravenously
24 as an injection over two minutes or an infusion
25 over 30 minutes.

1 Q. Okay. So is Cinvanti administered
2 intravenously?
3 A. Yes.
4 Q. And could we focus our attention on the
5 "Indication and Usage" section of this. So we'll
6 pick up to the top of JTX-51.1.
7 Focusing in under the "Indication and
8 Usage," Dr. Little, what is Cinvanti used to
9 treat?
10 A. Prevention of acute and delayed nausea
11 and vomiting associated with initial and repeat
12 courses of highly emetogenic cancer therapy
13 including high dose cisplatin as a single dose
14 regimen.
15 Delayed nausea and vomiting associated
16 with initial and repeat courses of moderately
17 emetogenic cancer chemotherapy as a single dose
18 regimen.
19 Nausea and vomiting associated with
20 initial and repeat courses of moderately
21 emetogenic cancer chemotherapy as a three-day
22 regimen.
23 Q. And if we could turn to JTX-51.3. Under
24 the "Preparation of Cinvanti for Administration."
25 And, Dr. Little, if we could look at

1 the -- I guess it's the third line/paragraph. Can
2 you please tell us what that's stating starting
3 with "aseptically"?
4 A. Aseptically withdraw 18 milliliters for
5 the 130-milligram dose or 14 milliliters for the
6 100-milligram dose from the vial. Do not dilute.
7 Q. And what type of administration is this
8 referring to for Cinvanti?
9 A. Intravenous administration.
10 Q. And is this the two-minute
11 administration or the 30-minute infusion?
12 A. It looks like it's the two-minute
13 administration.
14 Q. Have you formed an opinion on whether
15 Cinvanti is an embodiment of the asserted claims?
16 A. Yes.
17 Q. And what is that opinion?
18 A. It's my opinion that Cinvanti is an
19 embodiment of the asserted claims.
20 Q. What are the properties of Cinvanti --
21 considering the properties of Cinvanti that we
22 heard from Dr. Roeland, specifically
23 polysorbate 80 free and two-minute IV push
24 associated with?
25 A. It would be associated with the

1 properties of the formulation.
2 Q. And that's the formulation that's -- is
3 that formulation claimed in the patents-in-suit?
4 A. Yes, it is.
5 Q. Can we please pull up JTX-51.24? And
6 I'll focus on Section 16 at the bottom, highlight
7 the second-to-last sentence.
8 How long can Cinvanti remain at room
9 temperature according to the label?
10 A. Room temperature for up to 60 days.
11 Q. And how long could it remain being
12 refrigerated? Sorry, withdrawn.
13 You previously discussed the stability
14 data that's contained in the NDA for Cinvanti;
15 correct?
16 A. Yes.
17 Q. Okay. Can we please pull up JTX-50.1,
18 which is NDA Section 3.2.P.8.1, stability? And
19 could I focus on the page above the table -- the
20 header above the table of contents.
21 Do you see what that says?
22 A. It's Stability Summary and Conclusions.
23 Q. Okay. And what is this document,
24 Dr. Little?
25 A. It's the document that goes through the

1 stability data for Cinvanti in the NDA.
2 Q. Okay. I just want to make sure the
3 record is clear.
4 If we can turn to JTX-50.4 and highlight
5 the first sentence of the last paragraph.
6 How long is Cinvanti stable for?
7 A. It is stable for 12 months at
8 refrigerated conditions.
9 Q. Thank you. What would a POSA attribute
10 the shelf life of Cinvanti at room temperature and
11 refrigerated conditions to?
12 A. It would be the formulation that we've
13 been talking about in the asserted claims.
14 Q. Based on the information that you have,
15 have you formed an opinion on whether there is a
16 nexus between the objective indicia in this case
17 and the patented claims -- the asserted claims of
18 the patents-in-suit?
19 A. I have.
20 Q. And what is that opinion?
21 A. That Cinvanti, as an embodiment of the
22 asserted claims, I believe there is a nexus.
23 Q. Is your opinion based solely on the fact
24 that Cinvanti is an embodiment of the asserted
25 claims?

1 A. It's based on -- it is based on the fact
2 that Cinvanti is an embodiment of the asserted
3 claims, yes.
4 Q. Okay. And have you considered other
5 information other than the fact that -- withdrawn.
6 Have you conducted an analysis to
7 determine -- have you evaluated the other Orange
8 Book listed patents in this case?
9 A. Yes.
10 Q. And, just for the record, I'd like to
11 bring them up shortly one at a time just so we can
12 make sure we're on the same page.
13 MR. ASHKENAZI: Your Honor, this is the
14 small binder that's in front of you.
15 BY MR. ASHKENAZI:
16 Q. If we could pull up JTX-3.
17 Is this one of the patents that are
18 listed in the Orange Book as covering Cinvanti?
19 A. Yes.
20 Q. If we could pull up JTX-5.
21 Is this one of the patents listed in the
22 Orange Book for Cinvanti?
23 A. From my recollection, yes.
24 Q. Okay. I'm going to go through the next
25 bunch of patents and ask you that same question

1 just at the end.
2 Let's look at the JTX-9.
3 Dr. Little, do you see that?
4 A. Yes.
5 Q. Can we go to JTX-11?
6 Do you see that one, Dr. Little?
7 A. I do.
8 Q. JTX-13.
9 And do you see that?
10 A. Yes.
11 Q. JTX-14.
12 And last one JTX-15.
13 Dr. Little, did you see all of those
14 patents?
15 A. Yes.
16 Q. Are those patents listed in the Orange
17 Book as covering Cinvanti?
18 A. Yes.
19 Q. How do those patents affect your
20 analysis in this case, if at all, with respect to
21 objective indicia?
22 A. Yeah, they don't affect my analysis to
23 the degree that it's my opinion that the Cinvanti
24 formulation is stable because of the properties of
25 the asserted claims of the patents-in-suit.

1 Q. And what do these patents that we just
2 referenced, JTX-3, 5, 9, 11, 13, 14, and 15 cover,
3 generally?
4 A. They generally cover aprepitant emulsion
5 formulations.
6 Q. I'd like to turn our attention to
7 specific objective indicia of nonobviousness.
8 Dr. Little, did you consider whether
9 there was any long-felt but unmet need in the art?
10 A. I did. I reviewed reports of
11 Dr. Roeland and reviewed his testimony on that
12 matter.
13 Q. And how does that inform your opinion on
14 whether there was a long-felt but unmet need
15 satisfied by Cinvanti?
16 A. Yeah, it's what I remember reading in
17 the reports. It's my understanding that it's been
18 20 years since the development of the original
19 drug molecule and an IV formulation was necessary.
20 That there was an IV formulation that was
21 fosaprepitant but it had some issues associated
22 with tolerability.
23 So my understanding is that there was a
24 long-felt and unmet need for an IV formulation for
25 an NK-1 receptor antagonist.

1 Q. And do you believe with the information
2 you've seen in this case, have you formed an
3 opinion on whether Cinvanti has satisfied that
4 need?
5 A. Yes, it appears to have satisfied that
6 need.
7 Q. And that's based on what?
8 A. It's based on Dr. Roeland's analysis.
9 Q. Okay. Just so we're clear, the
10 formulation of Cinvanti, including its active
11 ingredient, have shown to be -- well, let me
12 rephrase the question.
13 Dr. Little, in your opinion, have you
14 made a determination on whether the formulation of
15 Cinvanti, including its active ingredients, have
16 been shown to be suitable for the uses shown in
17 the Cinvanti label?
18 A. It does seem to be suitable for the uses
19 shown from what I can see.
20 Q. Dr. Little, have you formed an opinion
21 on whether there was any unexpected properties --
22 any unexpected results for the claimed inventions
23 of the patents-in-suit?
24 A. Yes.
25 Q. And I'm specifically talking about the

1 asserted claims.
2 What is that opinion?
3 A. Yeah, so there were unexpected results
4 because whenever you review the formulations in
5 the prior art, those were found to be nonstable.
6 And whenever you look at the formulations in the
7 patents-in-suit, those were stable.
8 Q. And what formulations are you referring
9 to that were found to be unstable?
10 A. Example 4 and Example 5 which were
11 looking at formulations in CN '845 and Zhou.
12 Q. Okay. And you said those were not
13 stable. What information do you have about those
14 formulations, Examples 4 and 5 of the
15 patents-in-suit?
16 A. Yeah, I showed the Court that earlier.
17 I think if you review the examples, there's a
18 sentence towards the end that says there were
19 crystals that were found by day four.
20 Q. And how does the stability of Cinvanti
21 compare to the stability of Examples 4 and 5?
22 A. They're long-term stable as we saw in
23 the label.
24 Q. Would you refer to Cinvanti as being
25 only stable for seven days?

1 A. No, it's longer. It's stable for longer
2 than seven days.
3 Q. And that stability is both at room
4 temperature and refrigerated temperatures?
5 A. It is.
6 Q. We went over that stability earlier
7 during your direct examination in infringement and
8 a few minutes ago; correct?
9 A. Yes, we did.
10 Q. Have you formed an opinion on whether or
11 not the difference on the stability between
12 Cinvanti in Examples 4 and 5 are a difference of
13 degree or a difference in kind?
14 A. A difference in kind.
15 Q. And why is that?
16 A. Because the Cinvanti formulations are --
17 MR. ALY: Objection, beyond the scope of
18 the report as to difference in kind.
19 MR. ASHKENAZI: Your Honor, he's been
20 referring to the unexpected properties and
21 application of the law of unexpected properties.
22 I don't see how this --
23 JUDGE BRYSON: Yeah, I think this is
24 just a way of articulating the same point.
25 I'll overrule it.

1 THE WITNESS: The Cinvanti formulations,
2 you know, are suitable for long-term stability so
3 that they're able to be utilized, they're able to
4 be commercialized as they fill a need. The
5 formulations that were in the prior art were not.
6 BY MR. ASHKENAZI:
7 Q. Dr. Little, we discussed the aprepitant
8 molecule. I think you said it's been known for
9 over -- well over 20 years; is that your
10 recollection?
11 A. My recollection is around 20 years by
12 the time of the priority date.
13 Q. Okay. And do you recall when Emend was
14 first approved around?
15 A. Oh, that was -- let's see. That was, I
16 think, 2003.
17 Q. Okay. And what were the -- do you
18 recall any discussion about the Merck's efforts to
19 develop an IV aprepitant molecule?
20 A. Yes, I believe Dr. Hale testified to
21 that.
22 Q. And what was the results of Merck's
23 efforts to develop an IV aprepitant product?
24 A. They failed to develop an IV aprepitant
25 product. They had to switch to fosaprepitant in

1 order to develop their Emend IV.
2 Q. Before the priority date, how many
3 intravenous formulations of aprepitant were
4 available on the market?
5 A. Before the priority date, there were no
6 intravenous preparations. There was an oral
7 dosage form, not IV.
8 Q. Before the priority date,
9 September 2014, who, if anyone, was able to
10 develop a stable aprepitant -- intravenous
11 aprepitant formulation?
12 A. Before the priority date, there were no
13 intravenous stable aprepitant formulations.
14 Q. Can you please tell us if you formed an
15 opinion on whether or not there's any copying of
16 the asserted claims that are relevant to this
17 case?
18 A. Yeah, so it's my opinion -- I've said
19 this in my report that when you look at the
20 Fresenius formulation and you compare it -- we did
21 this on Monday -- and you compare it side by side
22 each and every one of the ingredients is present
23 in the exact same amounts.
24 So -- and it's also physically stable,
25 characterized as such, and then reported to the

1 FDA that that was the goal is to reproduce that
2 for the Heron product. So it's my opinion that it
3 is a copy.
4 Q. And were there any alternate
5 formulations that these companies -- well,
6 withdrawn. Let me ask the question again.
7 If you believe Dr. Rabinow that CN '845
8 or Zhou, were stable, could they have -- could
9 Fresenius have used those formulations?
10 A. I mean, if they were stable, they could
11 have developed and used those formulations.
12 Q. Have you seen any effort from Fresenius
13 seeking to modify their formulations to avoid the
14 patents-in-suit?
15 A. I have not seen that, no.
16 Q. Finally, Dr. Little, have you considered
17 whether the claimed inventions were a commercial
18 success?
19 A. I did review the testimony. I was here
20 for testimony for Mr. Tate. So I rely on that.
21 Q. And what do you understand Mr. Tate to
22 have opined on with respect to commercial success?
23 A. That Cinvanti was a commercial success.
24 Q. Based on the totality of information
25 that you have reviewed on -- with respect to

1 obviousness, including objective indicia, have you
2 formed an opinion on whether Dr. Rabinow has shown
3 that the asserted claims are obvious?
4 A. No, it's my opinion he has not shown
5 that they are obvious with everything that I've
6 seen in totality of the evidence.
7 Q. Now, even if we took objective indicia
8 of nonobviousness out, would your opinion be the
9 same?
10 A. It would.
11 Q. And why is that?
12 A. Because for all the reasons that I've
13 said. You just look at the prior art
14 references -- you know, I'm trying to see where
15 you would start. I guess, if you make the
16 assumption that Dr. Rabinow does that you would
17 start with the CN '845 -- you know, you're not
18 there, so you've got to do something.
19 Beyond the assumptions that he makes in
20 order to get to the point where you'd be
21 optimizing it in a particular direction, you
22 have -- right afterwards you have the Zhou
23 reference that optimizes the formulation using the
24 standard stability that they had.
25 And in that situation, it moves in the

1 opposite direction from what you had in CN '845.
2 If you're looking at the claims, it moves in the
3 opposite direction.
4 So I think even without objective
5 indicia, I don't think he's shown that the claims
6 are obvious.
7 Q. Dr. Little --
8 If we could please pull up the
9 transcript from day one, page 306, line 12, to
10 307, line 20.
11 Dr. Little, do you recall hearing
12 Dr. Rabinow's testimony with respect to written
13 description?
14 A. I do remember this, yes.
15 Q. Okay. And if you take a moment, just
16 look at what's on the screen, I believe this is
17 the totality of Dr. Rabinow's testimony on written
18 description; is that correct to your recollection?
19 A. It was short, yes. So this may be all.
20 Q. Okay. And that's specifically
21 pages 306, line 12, to 307, line 20.
22 Did you hear Dr. Rabinow opine that
23 there is no written description support for the
24 asserted claims because the asserted claims have a
25 broader pH range than the examples?

1 A. Yes.
2 Q. And have you formed an opinion on
3 whether that is accurate?
4 A. I don't think it's accurate, no. And I
5 think it's an appropriate analysis, at least as I
6 understand it.
7 Q. Do you believe that there is written
8 description support for the claimed pH range?
9 A. There is.
10 Q. And if we can turn to JTX-1, line 8,
11 please. Sorry, page 8. This is going to be the
12 '229 patent at Column 4, lines 65 to 67.
13 Dr. Little, what is shown here?
14 A. It shows pH ranges. It says: In our
15 embodiment, the composition has a pH of -- and
16 there's a number of ranges there. But you can see
17 in that range, it was disclosed in the
18 specification, 7.5 to 9.
19 Q. With this specific formulation of the
20 asserted claims of the patents-in-suit, did you
21 see a range of pH values that, in fact, did work?
22 A. I'm sorry, could you repeat your
23 question?
24 Q. Sure. With this specific information,
25 did you see a range of pH -- sorry, with this

1 specific formulation of the asserted claims of the
2 patents-in-suit, did you see a range of pH values
3 that did, in fact, work?
4 A. I did. So when we looked at the
5 formulations on Monday on both for Cinvanti and
6 for Fresenius' formulations, this range of pH
7 worked.
8 MR. ASHKENAZI: Your Honor, I have no
9 further questions at this time.
10 JUDGE BRYSON: Very well.
11 Cross-examination.
12 MR. ALY: Yes, Your Honor.
13 Your Honor, we have some binders to
14 distribute. May I approach?
15 JUDGE BRYSON: Of course.
16 You may proceed.
17 MR. ALY: Thank you, Your Honor. And as
18 I do proceed, I wanted to make clear for everybody
19 that I do intend to take the entire time for the
20 remainder of our case on the cross-examination. I
21 have alerted plaintiffs as to the other witnesses
22 that had already been called on rebuttal to tell
23 them the same.
24 Now that we have seen the testimony, I
25 just want to make clear that if anybody is

1 checking their watches, it's not for I'm trying to
2 reserve any rebuttal case.
3 JUDGE BRYSON: Very good.
4 CROSS-EXAMINATION BY COUNSEL FOR THE DEFENDANT
5 BY MR. ALY:
6 Q. Good afternoon, Dr. Little.
7 A. Good afternoon.
8 Q. You understand that the CN '845
9 reference, that's one of the key references in
10 this case; right?
11 A. It's one of the key references I
12 understand in Dr. Rabinow's obviousness analysis.
13 Q. And it's one of the important references
14 that the parties have disputed in this case;
15 right?
16 A. It's been disputed, I agree with that.
17 Q. Do you agree that it's important to get
18 the details right in the CN '845 reference in
19 order to provide opinions about what it discloses?
20 A. I'd say to the degree they affect the
21 opinions, I think that it's important to get
22 details right.
23 Q. And today in court, you were describing
24 Example 7 and 8 and put an asterisk and described
25 why you were doing that asterisk and dilution;

1 correct?
2 A. Yes.
3 Q. Your understanding -- and we'll look at
4 this in a moment, I just want to see if this is
5 your understanding. Your understanding of
6 Examples 7 and 8 from the CN '845 patent is that a
7 stock solution is made and then an aliquot, I
8 think you called it thereafter; is that right?
9 A. Sure, you can call it that.
10 Q. As a formulator, you're well aware of
11 what an injection is as compared to an infusion;
12 correct?
13 A. Yes.
14 Q. An injection is something that is
15 delivered in a relatively short amount of time and
16 an infusion is something that can take longer to
17 deliver.
18 Do you agree with that?
19 A. It can.
20 Q. Do you agree that an injection is
21 something that's given at once?
22 A. Yes, I think you could refer to it that
23 way.
24 Q. And that word "infusion" is used
25 separately to be a slow delivery into the vein;

1 correct?
2 A. It's typically slower than -- in the way
3 you're referring to injection, yes.
4 Q. And for an example, Cinvanti, you were
5 here for testimony and maybe you have an
6 understanding, but let me just ask, there is a
7 distinction that has been made between a
8 two-minute push on the one hand and an infusion on
9 the other.
10 Do you understand that is the case for
11 Cinvanti?
12 A. I think so.
13 Q. And the two-minute push is associated
14 with an injection and the infusion is associated
15 with an infusion.
16 Do you have that understanding?
17 A. I'd have to go back and look at the
18 details of that and whether it was referred to as
19 an injection in that or not, I'm sorry.
20 Q. As you understand Example 7 and 8 from
21 the CN '845 patent, turning attention back to
22 CN '845 --
23 A. Okay.
24 Q. -- do you believe those are disclosing
25 one result of an embodiment? That's what you

1 presented; right?
2 A. What do you mean by "one result of an
3 embodiment"?
4 Q. You presented for Example 7 and 8 --
5 let's look at your demonstrative at this point in
6 time. Let's look at PDX-4-4.
7 And is this your demonstrative on the
8 screen, PDX-4-4?
9 A. It appears to be, yes.
10 Q. In Example 7 you put an asterisk with a
11 footnote; correct?
12 A. Yes.
13 Q. Example 8 you put the name footnote;
14 correct?
15 A. Yes.
16 Q. And the concept that you're showing is
17 that your opinion is Example 7 and 8 only show a
18 diluted product, that's the end product you called
19 it; correct?
20 A. So the values displayed in 7 and 8 are
21 the diluted product, the last step, yes.
22 Q. Are you saying that Example 7 and 8, the
23 result of those examples is a product that is a
24 diluted product; is that your testimony?
25 A. This right here is the diluted -- the

1 concentrations that are diluted, yes.
2 Q. Let's look at DTX-71, the CN '845
3 patent, .13. And if we look at the top, there's
4 paragraph 7.
5 You've reviewed this before, right,
6 Dr. Little?
7 A. Yes.
8 Q. If you read the second sentence, it
9 says: Another object of the present invention is
10 to provide a method for preparing the
11 above-described aprepitant microemulsion for
12 injection.
13 It says that; right?
14 A. Yes.
15 Q. The next sentence says: Still another
16 object of the present invention is to provide a
17 method for preparing the above-described small
18 volume water injection, infusion solution, and
19 lyophilized powder of the aprepitant microemulsion
20 for injection.
21 That's disclosed; correct?
22 A. That's what it says, yeah.
23 Q. There's a distinction between being made
24 between injection, infusion solution, and a
25 lyophilized powder; is that right?

1 A. It says that the objects of the present
2 invention provide methods for those.
3 Q. Let's look now to Example 7, which is on
4 page .17, JTX-71.17, at paragraph 31 through 33.
5 Example 7, of course, is titled
6 "Preparation of the Aprepitant Microemulsion
7 Infusion Solution." You see that; right?
8 A. Yes.
9 Q. And you went to the bottom and you
10 provided -- and I assume you based your opinion
11 about the columns on the last sentence that says:
12 After examining of clarity as qualified, the
13 microemulsion of 115 milligrams aprepitant was
14 added to normal saline for injection and filled in
15 a 100 mL glass vial under nitrogen. And that was
16 done, quote, to obtain the infusion aprepitant
17 microemulsion.
18 Do you see that?
19 A. Yes.
20 Q. The preceding sentence, though, that one
21 says that there was a composition that was made
22 and it describes the composition and it ends in
23 the lines to obtain the aprepitant microemulsion
24 for injection.
25 That's what it says; right?

1 A. Okay. Sure.
2 Q. And that's a different product; right?
3 That's the product that is available for injection
4 before it is diluted and could be available for
5 infusion; correct?
6 A. Well, it's not the one at the end where
7 it was sealed in a glass vial under nitrogen for
8 storage.
9 Q. One is for injection and one is for
10 infusion; right, Dr. Little?
11 A. The first step of this is to make the
12 formulation for injection and then what happens is
13 diluted, that's what's put under nitrogen
14 autoclaved at the end.
15 Q. If, according to CN '845, one were to
16 prepare an injection, they would stop at the step
17 that says here's your injection and be able to
18 administer that; correct?
19 A. I think that's a read-in.
20 Q. I -- you understand that in the art
21 there is a term differentiation between injection
22 and infusion. You already agreed to that; right?
23 A. Well, you're reading in that this was
24 the end and it's not. So what happens is they
25 take that then, they then dilute it; and that's

1 what's put into a vial and terminally sterilized.
2 So that's whenever you're going to take it, it's
3 done, it's ready for storage.
4 Q. But you agree CN '845 said they were set
5 out to do multiple things and in Example 7 are, in
6 fact, showing multiple things; correct?
7 A. I disagree with the implication you're
8 making.
9 Q. And when we look at Example 7, it's
10 referring to the aprepitant microemulsion for
11 injection. At that point in time in the process
12 there is a composition.
13 You agree with that much; right?
14 A. It's not the one that's relevant for
15 analysis here.
16 Q. And the reason it's not relevant for
17 analysis here is because it didn't quite fit in
18 the chart that you were making; right?
19 A. Okay. If you want to make one for the
20 chart, right, you could. It also wouldn't meet
21 the claim elements, that's fine. I'm just trying
22 to show the Court the relevant one which is the
23 one that's going to be ultimately stored under
24 nitrogen, autoclaved, terminally sterilized and
25 stored, which is what's relevant, right.

1 Q. Similarly, for Example 8, do you agree
2 that Example 8 refers back to the process of
3 Example 7? So whatever analysis is applied to
4 Example 7 should apply to Example 8; correct?
5 A. The preparation method was the same as
6 in Example 7.
7 Q. And you asked for a comparison
8 potentially of the injection versus the asserted
9 claims, and we have that. It's DDX-4-1. I will
10 hand out a copy of that demonstrative.
11 MR. ALY: May I approach, Your Honor?
12 JUDGE BRYSON: Yes. Thank you.
13 BY MR. ALY:
14 Q. We're looking up DDX-4-1, and it has
15 Examples 7 and 8, as described and using the
16 numbers in the example; correct?
17 A. I'm sorry, I don't know. Do you want me
18 to go through the example and look for you?
19 Q. We can look at it together, but I'm
20 happy to do that, because this is very important.
21 CN '845 is JTX-71.17.
22 MR. ALY: Let's please go back to that.
23 Paragraph 32.
24 BY MR. ALY:
25 Q. Paragraph 32 lists the components of the

1 composition as CN '845 states them; correct?
2 A. It doesn't -- okay. So with the
3 exception of the -- with the exception of the
4 74 grams of water for injection, and then also
5 without the exception of the additional water
6 that's added in the end in the relevant
7 formulation for analysis here, this is -- it's the
8 beginning, it's just not the total formulation at
9 the end.
10 Q. Okay. And Example 8 is provided here.
11 MR. ALY: Let's go back to the DDX --
12 yes, paragraph 35 on JTX-71.17.
13 BY MR. ALY:
14 Q. It has the components of Example 8 from
15 the CN '845 patent; correct?
16 A. Yeah, I mean, okay. So, again, it's the
17 same thing. You didn't include the 61 gram of
18 water for injection, and you didn't include the
19 amount of water that's added before the
20 formulation is put in the container for storage,
21 but...
22 Q. Other than that, you'll agree the
23 numbers match up, right, Dr. Little?
24 A. Some of the numbers match up.
25 Q. DDX-4-1, let's look at the demonstrative

1 that we prepared.
2 Using the numbers shown in CN '845, you
3 agree that the claimed amount of aprepitant, which
4 is .7, falls within the range .2 and 1.0 of
5 Example 7 and 8 of the CN '845 patent; correct?
6 MR. ASHKENAZI: Objection, Your Honor.
7 This is misleading. He's comparing concentrations
8 and amounts.
9 JUDGE BRYSON: I think the witness is
10 sophisticated enough to respond if he doesn't feel
11 that the question sets out the numbers fairly. So
12 I'll overrule it.
13 BY MR. ALY:
14 Q. Dr. Little, I will clarify the record,
15 because that may be helpful. All of the examples
16 use 100 milliliters total volume and, therefore,
17 approximately 100 grams total volume -- total
18 weight in the examples; correct?
19 A. They use -- you're talking about the
20 examples of the patents-in-suit? Is that what
21 you're asking me, sir?
22 Q. Well, when you were doing the
23 calculation -- you did calculations on all of
24 these components and prepared a demonstrative with
25 all of the components and calculating the dilution

1 into account; correct?
2 A. I used all of the final amounts of
3 everything in the formulation when I did the
4 weight-per-weight percent.
5 Q. And when you -- is it your understanding
6 of the CN '845 that when Example 7 reports
7 .2 grams of aprepitant, because it's in a 100-gram
8 total, that's .2 percent?
9 A. Yes, if it's a 100-gram total and it's
10 .2, then it would be .2 weight-per-weight percent.
11 Q. And so as far as the aprepitant, just
12 looking at Example 7 and 8 of the CN '845 patent,
13 you agree that the claimed .7 falls between the
14 .2 percent aprepitant of Example 7 and the
15 1.0 percent of Example 8; correct?
16 A. Okay. So the thing on the top right
17 should be .7 weight-per-weight percent. So you
18 have a percent under, but I think you meant to put
19 a percent there.
20 Q. Fair.
21 A. So that's a percent. And you're asking
22 me, does .7 fall between .2 and 1. It does.
23 Q. We'll come back to the emulsifier and
24 spend more time there, of course.
25 The oil. I want to confirm that

1 Example 7 and 8 of CN '845 also are the same as or
2 match the claim requirement of 9 to 10 percent
3 soybean oil?
4 A. So, again, not in Example 7 and 8. This
5 is Example 7 and 8 in the CN '845?
6 Q. That's right.
7 A. Okay. So you're not including all the
8 things in this chart. But if you're asking me to
9 only look at what you included in the chart and
10 then assume a 100-gram mass, under that
11 hypothetical, it would be 9.8 percent and
12 10 percent.
13 Q. All right. And what about for the
14 protective agent, do you agree that the claimed
15 5 percent falls between --
16 JUDGE BRYSON: I think there may have
17 been some confusion here. I think Dr. Little
18 might have been reading from the emulsifier line,
19 the 9.8. I think you were asking about the oil
20 line.
21 THE WITNESS: Oh, I'm sorry.
22 JUDGE BRYSON: You skipped over
23 emulsifier.
24 MR. ALY: I did.
25 JUDGE BRYSON: So I think, Dr. Little,

1 the question was with respect to the oil line.
2 And so you can continue.
3 BY MR. ALY:
4 Q. With respect to the oil line and
5 comparing the claimed percentage of 9 to
6 10 percent, do you agree that Example 7 and 8 of
7 the CN '845 match the claimed range?
8 A. Not in the real Example 7 and 8. But if
9 you're going to say, I'm going to not include the
10 water and I'm not going to include the additional
11 information at the end, which I think is relevant,
12 then if I'm only stuck to this and then I assume
13 9.5 grams over 100, that would be 9.5
14 weight-per-weight percent and 10 weight-per-weight
15 percent in Example 8, under your hypothetical.
16 Q. Okay. And in terms of the protective
17 agent, going down to the protective agent line of
18 DDX-4-1, you agree that the claimed 5 percent
19 falls within the 1 percent of Example 7 and
20 8 percent of Example 8; correct?
21 A. Yeah, maybe you could clarify what you
22 mean by "falls between." Is this, like, you're
23 saying if Example 7 was the beginning of a range
24 and Example 8 were the end of a range disclosed in
25 the specification?

1 Q. Well, I will ask the question this way.
2 Do you agree that 5 percent sucrose is
3 between 1 percent and the 8 percent?
4 A. It is.
5 Q. Do you agree that the claimed 2 to
6 6 percent ethanol includes the 5.5 -- includes
7 5.5 percent?
8 A. 5.5 is between 2 and 6.
9 Q. So now the last thing we need to do to
10 make sure there's something for the record to
11 point back at is JTX-71.17, let's go back to that.
12 Paragraph 32.
13 And, Dr. Little --
14 MR. ALY: May I approach, Your Honor,
15 with the --
16 JUDGE BRYSON: Sure.
17 BY MR. ALY:
18 Q. I'm approaching, Dr. Little, with a
19 calculator.
20 Could you please just confirm for the
21 record, Dr. Little, that the sum total of the
22 components identified in paragraph 32 is 100?
23 MR. ASHKENAZI: Objection, Your Honor.
24 He's not showing the full paragraph 32 right now.
25 If you're going to ask him to look at the

1 paragraph, they should show it, or Dr. Little
2 should be able to refer to it in the binder.
3 JUDGE BRYSON: Well, I think Dr. Little
4 has the paragraph 32 up there; doesn't he?
5 MR. ALY: Yes, Your Honor.
6 JUDGE BRYSON: Overruled.
7 THE WITNESS: This is in -- okay. So,
8 look, if you want me to not include the total
9 formulation with the water in it at the end and
10 you only want me to include this beginning portion
11 of it, those numbers in this line, if this is the
12 totality of 32, I could say, because I don't know,
13 but if this is the totality of 32, when you add
14 all the numbers in what you're showing me on the
15 screen, those sum to 100.
16 BY MR. ALY:
17 Q. So if we wanted a weight-weight percent,
18 just let's look at the aprepitant, that would .2
19 divided by 100, which is .2 percent; correct?
20 A. If you assume this is the final
21 formulation, which it's not, that would be true.
22 Q. And what we're showing you is the
23 entirety of paragraph 32, you agree with that.
24 Let's scroll down so that you can see that what
25 you've been looking at is the entirety of

1 paragraph 32.
2 Can you confirm that it's one sentence,
3 it says, The infusion solution of the aprepitant
4 microemulsion for injection is consisting of the
5 following components: .2 grams of aprepitant,
6 9.5 grams of soybean oil, 9.8 grams of egg yolk
7 phospholipid, 5.5 grams of ethanol, 1 gram of
8 glycerin, 74 grams of water for injection?
9 That's what it says; right?
10 A. So that's wrong, though. So this is
11 another mistake. Because when you go down to the
12 bottom --
13 Q. Dr. Little, did I read it correctly?
14 Did I read that sentence correctly?
15 A. So this says infusion solution is these
16 things, but you see at the end, it says the
17 infusion solution includes the additional water
18 that you didn't include.
19 Q. Dr. Little, it says the word "injection"
20 on the first line of 32.
21 Do you see that?
22 A. It says that -- you just read it to me.
23 It says the infusion solution is consisting of,
24 but at the end of the paragraph, it says the
25 infusion solution had the additional water in it.

1 Q. Exactly. Because there's two steps in
2 Example 7, making an injection and then diluting
3 it, if that's desirable; right?
4 A. What I'm trying to point out for you,
5 though, is that this says that the infusion
6 solution is these things, which that's not right.
7 You were saying to me earlier that
8 that's injection solution.
9 Q. It is. Let's look at it together.
10 It says, The infusion solution, as I
11 read it, of the aprepitant microemulsion for
12 injection.
13 So there's an injection component;
14 right?
15 A. I disagree with your interpretation of
16 this example.
17 Q. Do you agree that I read paragraph 32?
18 A. I agree you read the first line of
19 paragraph 32 to me, yes.
20 Q. Okay. And in terms of the examples that
21 are shown in the CN '845 patent, there are also --
22 there is other information about ranges to be
23 considered; correct?
24 A. If you're referring to what I read to
25 the Court earlier, yes.

1 Q. Let's look at those. Paragraph 8 on
2 JTX-71.13.
3 Paragraph 8 identifies in the heading,
4 "technical solutions," ranges of the different
5 components that you testified about; correct?
6 A. These are the broadest ranges of the
7 genuses, yes.
8 Q. And I would like to now look at PDX-4-3.
9 That's your demonstrative about the different
10 examples from CN '845.
11 And you had identified in PDX-4-3 ranges
12 of the CN '845 from the paragraph 8 and explained
13 why -- how they compared to the claims; correct?
14 A. Yeah, the one that would be pointed to
15 the claims are compared to, yes.
16 Q. Sodium oleate is an item that you say is
17 not in CN '845, and of course is in the claims;
18 correct?
19 A. Yes.
20 Q. And the only difference in terms of a
21 formulation component, then, is the emulsifier,
22 which is, in CN '845, in the range .5 to
23 10 percent and in the claims at 14 percent;
24 correct?
25 A. There's that difference, and there's

1 also the fact that the CN '845 is referring --
2 when it says, for instance, .5 to 10 percent, it's
3 not specifically referring to egg yolk lecithin.
4 It's just referring to the entire genus of the
5 emulsifiers.
6 Q. And let's look at the next slide that
7 you prepared, PDX-4-4.
8 And you made the same point that I'd
9 like to ask you about, which is the CN '845
10 doesn't just show that an emulsion can be made
11 with egg yolk lecithin, but also shows egg yolk
12 lecithin along with other examples of emulsifiers
13 also resulted in emulsions; correct?
14 A. I don't know what you mean by "resulted
15 in emulsion," but they made emulsions in
16 Examples 1 through 8.
17 Q. And the oils, different oils were tried
18 and they made -- CN '845 reported an emulsion with
19 all of those different oils; right?
20 A. They went through a process to make an
21 emulsion using those oils.
22 Q. Protective agents. You see there is a
23 variety of protective agents that were
24 demonstrated in the Examples 1 through 8 of
25 CN '845, as well; right?

1 A. They used, yeah, different protective
2 agents.
3 Q. And co-emulsifiers, do you see various
4 co-emulsifiers were also shown in the Examples 1
5 through 8 emulsions that were made?
6 A. They did attempt to make emulsions with
7 those, yes.
8 Q. In addition, in your PDX-4-4, in
9 addition to the type of ingredient, the amount of
10 ingredient was also varied across the range shown
11 in paragraph 8 and also resulted in emulsions in
12 Examples 1 through 8; correct?
13 A. I don't know what you mean by "resulted
14 in emulsions." They did report performing a
15 process on them to make an emulsion.
16 Q. In Example 1, in reporting that they
17 were making a process that resulted in an
18 emulsion, used 3 percent egg yolk lecithin; right?
19 A. They used 3 percent.
20 Q. And in Example 5, they used 10 percent
21 egg yolk lecithin; correct?
22 A. Yes.
23 Q. Looking at oil, Example 1 used
24 30 percent soybean oil; right?
25 A. They did.

1 Q. Example 6, just as another example, used
2 15 percent; correct?
3 A. They did.
4 Q. And protective agent, Example 1 used
5 5 percent glycerin; correct?
6 A. Yes.
7 Q. And Example 2 used 20 percent sucrose;
8 right?
9 A. Yes.
10 Q. For the co-emulsifier, Example 1 used
11 1.5 percent ethanol; right?
12 A. Yes.
13 Q. And Example 6 used 10 percent ethanol;
14 right?
15 A. Yes.
16 Q. And in terms of the variety of emulsions
17 made, CN '845 reported all of Examples 1 through 8
18 are emulsions, as you understand the term;
19 correct?
20 A. That's what they say, that they -- well,
21 they used the phrase "microemulsion," and they
22 define it in the patent as being a correct
23 understanding of microemulsion. These aren't
24 microemulsions, but I think a person of ordinary
25 skill in the art would see it, and say they were

1 trying to make a conventional emulsion.
2 Q. That's what I want to understand.
3 You think a person of ordinary skill in
4 the art, reading CN '845 and although the word
5 "microemulsion" is used, would understand that
6 it's talking about an emulsion?
7 A. They would.
8 Q. In terms of the emulsion of aprepitant,
9 do you agree that CN '845 demonstrated the first
10 time in the world an emulsion of aprepitant?
11 A. What do you mean by "the first time in
12 the world"?
13 Q. Do you know of an earlier reference or
14 report of anyone putting aprepitant in an emulsion
15 and showing that it is, in fact, working?
16 A. What do you mean by "working"?
17 Q. Let me take that part out of it.
18 Do you know of any reported or published
19 result before CN '845 that describes aprepitant in
20 an emulsion?
21 A. I don't think that I remember there
22 being -- the Hingorani reference is
23 contemporaneous to this or after this. So that
24 was an aprepitant emulsion that someone tried, and
25 I think in this case you could say that this was

1 an aprepitant emulsion that -- or several
2 aprepitant emulsions that someone tried.
3 Q. And aprepitant in the prior art was
4 known to have a hydrophobic part and a
5 hydrophilic; correct?
6 A. I think you could identify chemical
7 moieties that are hydrophobic, and you could
8 identify chemical moieties that were hydrophilic.
9 However, that does not mean that that portion of
10 the molecule is hydrophilic. If you have a
11 hydrophilic piece that's surrounded by hydrophobic
12 stuff, that whole thing is hydrophobic. So you
13 have to consider the molecule in context.
14 Q. Do you agree that the aprepitant
15 molecule contains fluorocarbon and phenyl groups,
16 which are hydrophobic?
17 A. It does.
18 Q. Do you agree that aprepitant has amine
19 and amide groups that are known to be hydrophilic?
20 A. They can be.
21 Q. And oxygens that are also hydrophilic?
22 A. Oxygens, in certain circumstances, are
23 not. So it depends on what you mean. But under
24 certain groups, oxygens can represent hydrophilic
25 moieties.

1 Q. And in terms of the drug of the
2 aprepitant, you take no issue with Dr. Rabinow
3 that it would be classified as a Class 3 drug,
4 according to Washington; correct?
5 A. No, I do take issue with that.
6 Q. But you didn't take any issue with it
7 today; did you?
8 A. No, I did. So this is -- here's the
9 distinction. In Washington, there's what's called
10 Class 1. So if I recall correctly, that's like
11 water-soluble things. Under those circumstances,
12 you don't need an emulsion. That fits at the top
13 of the Strickley chart, if Your Honor can recall.
14 There's Class 2, which are oil soluble.
15 Those -- if you want to use them in emulsions,
16 those are your bread-and-butler emulsions. Okay.
17 So if it goes into oil and you really wanted to
18 use an emulsion, that's a candidate for that.
19 Class 3 are molecules that are not
20 soluble in oil or soluble in water. So under that
21 circumstance, you could imagine that it could go
22 with the interface, but that does not mean every
23 molecule that is insoluble in oil and water is
24 going to go to the interface. That doesn't mean
25 that. You would have to have certain properties

1 for that to happen. So there's a distinction.
2 Can you identify a molecule that could
3 be Class 3 in Washington that would go to the
4 interface? Sure. But that does not mean every
5 molecule that's water insoluble or oil insoluble
6 would. We don't know that for aprepitant. It's
7 never disclosed anywhere that that would go to the
8 interface.
9 Q. Let me confirm.
10 MR. ALY: Let's look at JTX-113, please.
11 It's the Washington reference. And we're looking
12 at page 9.
13 BY MR. ALY:
14 Q. These are the three classes that are in
15 Washington; correct?
16 A. That looks familiar to me, yeah.
17 Q. And to make sure that I understand your
18 opinion, you agree that a Class 3 drug that is
19 poorly soluble in both water and oil, you agree
20 with that?
21 A. It says -- it says Class 3 drugs are
22 poorly soluble in both water and oil.
23 Q. Do you agree that aprepitant was known
24 to be in the prior art a drug poorly soluble in
25 both water and oil?

1 A. Sure.
2 Q. The part that you disagree is the next
3 part where for Class 3 drugs, Washington is
4 teaching that they can only be loaded into an
5 emulsion by adsorbing to the droplet interface.
6 Do you see that?
7 A. Uh-huh.
8 Q. And you don't know -- you're saying you
9 don't -- I'm sorry, did you say you agree with
10 that?
11 A. I do.
12 Q. And your testimony is you don't know if
13 that has been demonstrated for aprepitant, in
14 particular.
15 That's what your testimony is; correct?
16 A. My testimony is that this disclosure
17 does not say that any water insoluble/oil
18 insoluble molecule will orient at an interface.
19 This does not say that.
20 Q. So it's some --
21 A. And I'll just finish by saying, there is
22 also no evidence that we have that aprepitant
23 would fall in the category where it would. So
24 here's what I'll do. I'll agree with you that
25 aprepitant, if it's insoluble in oil and insoluble

1 in water, it could potentially go to an interface.
2 It could, but we don't know that.
3 Q. Have you yourself ever used an emulsion
4 approach for a Class 3 drug?
5 A. We might have.
6 Q. And in --
7 A. I would say it's uncommon that you
8 typically do, but you could.
9 Q. Now, the Class 3 drugs you're saying
10 are -- have not been shown -- this statement in
11 Washington about Class 3 drugs has not been shown
12 to result in an emulsion specifically by adsorbing
13 aprepitant to the droplet interface.
14 That's your testimony; correct?
15 A. It's that you're not sure that it would,
16 and if you were to -- if you were to say, okay,
17 maybe it could, at least what we know so far is
18 there's no evidence that it would. We just don't
19 know. There's no data.
20 Q. And even as of today, despite
21 Washington, despite CN, and despite Dr. Rabinow's
22 testimony, you have no other explanation for how
23 the emulsions in this case are physically stable;
24 right?
25 You have not provided any; true?

1 A. I'm sorry, could you repeat that
2 question? You're asking me if they're physically
3 stable?
4 Q. Let me ask the question more directly.
5 A. Okay.
6 Q. You don't have any explanation about why
7 adding lecithin results in increased physical
8 stability in the context of Heron's patents;
9 correct?
10 A. No.
11 Q. You've not provided --
12 A. I don't.
13 MR. ALY: Let's look at JTX-71 again,
14 the CN '845 reference. I'd like to look at
15 page 14, paragraph 16. Paragraph 16 on page 14.
16 JUDGE BRYSON: Are we back to --
17 MR. ALY: The CN '845 reference, again,
18 JTX-71.
19 JUDGE BRYSON: This is the old 71;
20 right?
21 MR. ALY: 71.
22 BY MR. ALY:
23 Q. And are you looking with me at
24 paragraph 16, Dr. Little?
25 A. Yes.

1 Q. Now, the first step that CN disclosed is
2 mixing aprepitant and emulsifier and dissolving in
3 ethanol; right?
4 A. Yeah.
5 Q. That's --
6 A. To the best that we're able to see, yes.
7 Q. Is that a step, mixing a drug in an
8 emulsifier dissolving with ethanol, used with
9 conventional emulsions for drugs that are soluble
10 in oil?
11 A. That are soluble in oil, I don't know.
12 I mean, I guess you could do this if you wanted
13 to.
14 Q. But there would be no need to. Because
15 the drug is already soluble in oil, there would be
16 no need to first dissolve it in ethanol; right?
17 A. Well, I mean, I guess it depends on the
18 degree of oil solubility. I think I would agree
19 that if it's instantly soluble in oil, you could
20 use the oil, but there's degrees of it.
21 So, you know, for instance, sometimes
22 what we do is like a pre-solubilization step. So
23 if you've got something that's a crystal, for
24 instance, maybe the amorphous compound will go in,
25 right. It's disordered in its material state.

1 But if you've got a crystalline compound
2 and you want it to go into the oil, sometimes you
3 do a step where you sort of dissolve it in an
4 ethanol or something like that to get it out of
5 its crystal state, and then it would dissolve in
6 oil.
7 Q. And in this particular situation, CN is
8 teaching to dissolve aprepitant in emulsifier, but
9 if we were using it for the example you just gave,
10 to get it out of its crystal state, then you
11 wouldn't evaporate the ethanol right after that;
12 correct?
13 A. No, it depends on how much ethanol you
14 would want to go into the oil. It would be
15 reasonable to evaporate some of the ethanol,
16 because you might use a lot, you might heat it,
17 and then it goes in fast, right, if you use a lot.
18 So once it's in, then you can cool it down. You
19 know, we do that with coffee and stuff, right. I
20 mean, if you want to dissolve sugar, and if it's
21 hot, it does, and then you can cool it down. It's
22 not like everything crashes out. So it's a
23 kinetic step.
24 Q. And right where it's saying that ethanol
25 is evaporated, there is a sticky residue. That's

1 what CN '845 describes that product in the first
2 step of paragraph 16; correct?
3 A. Yep. Yes.
4 Q. And then that is continued to be heating
5 to dissolve the residue to give a coarse emulsion.
6 That's what they called it, right?
7 A. That's what they say.
8 Q. Now, you did identify the coarse
9 emulsion, but they do distinguish, CN '845 does,
10 between what they've labeled a "coarse emulsion"
11 here and "primary emulsion" later on about four
12 lines down from the bottom.
13 Do you see that?
14 A. Yeah, so later on there is what they
15 call primary emulsion.
16 Q. And if the authors and inventors of the
17 CN '845 reference weren't quite sure what the
18 sticky residue after it was further heated and
19 dissolved, what that was because it was something
20 different than traditionally used in an emulsion,
21 would it be fair to call it a different name, like
22 coarse emulsion?
23 A. Well, first of all, I don't think that
24 this is something that is particularly weird for
25 an emulsion. So I don't know why you're asking me

1 if you can call something a different name.
2 Q. Great. So let me confirm then.
3 You don't think it is particularly
4 unique to combine a drug and an emulsifier in
5 ethanol before it is applied to an emulsion.
6 Is that what you're saying?
7 A. I think, if you wanted to do a step
8 where you're trying to, you know, overcome any
9 kind of kinetic difficulties with dissolution,
10 it's possible that you would start with ethanol,
11 remove the ethanol to some degree, and then put it
12 into an oil.
13 Q. And if one intentionally wanted to make
14 a complex or see if they were making a complex,
15 they would mix drug and emulsifier, dissolve it in
16 ethanol, and evaporate?
17 A. No. No. If you wanted to make a
18 complex -- you know, these complexes will form.
19 And if you've got a complex, I agree that you
20 would put them together in something, right, but
21 just saying that you can put these in ethanol
22 doesn't mean you're trying to make a complex.
23 Q. You agree one way of making a complex is
24 putting drug and emulsifier together in a solvent;
25 correct?

1 A. Sure.
2 Q. The CN '845 reference, you agree,
3 doesn't itself contain stability data over time;
4 right?
5 A. It doesn't talk about stability at all,
6 and it doesn't also contain stability data over
7 time.
8 Q. So maybe you misunderstood Dr. Rabinow's
9 opinion. Do you understand Dr. Rabinow's opinion
10 to be that all of the formulations in CN '845 were
11 already shown to meet the physically stable claim
12 term, as the court has construed it?
13 A. I just remember from his reports and
14 from his testimony that he believes that these
15 would all be stable. To the degree that they meet
16 claim elements, I think -- I'm not saying that
17 he's done the analysis and says that each of the
18 claim elements is in this example. I didn't hear
19 him say that.
20 Q. And that's what I'd like to make clear.
21 So your understanding of Dr. Rabinow's
22 testimony, what you were rebutting is, that
23 CN '845 shows formulations that Dr. Rabinow says
24 could be stable, but not necessarily meeting the
25 claim term "physically stable" as construed?

1 A. Well, my recollection from his reports
2 is he said a person of ordinary skill in the art
3 would understand that they would be stable by the
4 absence of -- the absence of information about its
5 lack of stability would be stable.
6 Q. You understand that there is not an
7 issue of anticipation that's being raised here.
8 In other words, all of the claim terms are in one
9 reference; right?
10 A. At least as far as I'm aware, that I
11 have the ability to know.
12 Q. That you've addressed in responding to
13 the arguments that have been raised, have you
14 addressed an anticipation argument?
15 A. I don't recall responding to an
16 anticipation argument, no.
17 Q. And in terms of the prior art and a
18 POSA's understanding of the CN '845 reference, a
19 person of ordinary skill in the art, if they were
20 working within the parameters of the CN '845,
21 given the breadth of the ranges that are provided,
22 but they were only working within those ranges,
23 you would think that would be obvious; correct?
24 A. Wait a minute, I'm sorry. Could you ask
25 your question again?

1 Q. Yes. Let's go back in paragraph 8,
2 JTX-71.13 at 8.
3 Now, Dr. Little, let's say we're in a
4 room at the priority date and we're looking at
5 CN '845, paragraph 8, and somebody wants to try a
6 formulation or formulations anywhere within these
7 ranges within paragraph 8 of the CN '845
8 reference.
9 You agree those would be obvious;
10 correct?
11 A. Okay. So let me make sure I understand
12 your question. You're saying "obvious" in regard
13 to -- and these are the claim elements? Is that
14 what you're asking me?
15 Q. Comparing to the asserted claims.
16 A. To the asserted claims of the CN '845?
17 Q. Okay. Let's look at the CN '845
18 reference.
19 Do you believe a person of ordinary
20 skill in the art would find it obvious to
21 implement paragraph 8 of CN '845 within anywhere
22 within the ranges that are disclosed in
23 paragraph 8 of CN '845?
24 MR. ASHKENAZI: Objection, Your Honor,
25 beyond the scope. We're not talking about the

1 obviousness of CN '845.
2 JUDGE BRYSON: I think -- I'm a little
3 confused. I think probably -- sustained.
4 But I think I understand where you're
5 going with the question, but somehow the word
6 "obvious" is causing some problems here. Maybe
7 you can walk through this step by step, and we can
8 get to where you intend to go --
9 MR. ALY: I appreciate that.
10 JUDGE BRYSON: -- with the witness.
11 BY MR. ALY:
12 Q. In terms of what a person of ordinary
13 skill in the art would pursue in following
14 paragraph 8 of the CN '845 reference, there are
15 ranges provided by CN '845 itself; correct?
16 A. Yes.
17 Q. And if a person of ordinary skill in the
18 art did exactly everything that was within the
19 ranges, despite their breadth, you would not
20 consider that to be something new or different;
21 right?
22 MR. ASHKENAZI: Objection, Your Honor.
23 Again, this is beyond the scope of Dr. Little's
24 testimony. We're talking about --
25 JUDGE BRYSON: Well, I'm not sure.

1 We'll have to see where this is going, but so far
2 it seems to me pretty innocuous and I don't think
3 it's a problem yet.
4 Overruled.
5 THE WITNESS: Okay. So I want to make
6 sure I understand your question, because I maybe
7 still don't quite understand what you're asking
8 me.
9 You're asking me that if this is
10 disclosed as the percentages that are possible
11 within the context of the CN '845, now considering
12 that I think below, a paragraph or two you have --
13 for instance, like the emulsifiers that could be
14 used are listed.
15 But if you were to be using the
16 concentration of, for instance, that emulsifier
17 that's listed below in this, that would be within
18 the disclosure of the paragraph 8 in the CN '845,
19 at least as I understand it.
20 BY MR. ALY:
21 Q. Let's turn now to the Zhou reference.
22 MR. ALY: Yes, Your Honor.
23 JUDGE BRYSON: I'm a little bit lost
24 here.
25 MR. ALY: Okay.

1 JUDGE BRYSON: If I may ask you, was the
2 point of your question that it would be -- if a
3 person of skill in the art invented or came up
4 with a formulation that fell within all of the
5 ranges of the components in that paragraph, would
6 you deem that to be a non-inventive or obvious
7 formulation?
8 MR. ALY: That was the intent,
9 Your Honor.
10 JUDGE BRYSON: Plainly true; right?
11 MR. ALY: That's what I was asking the
12 witness to agree.
13 JUDGE BRYSON: Right. All right. Okay.
14 I thought you were going to move on from that, but
15 if that's the point you were raising, okay.
16 MR. ALY: Well, from there, then what I
17 would like to find out is -- Your Honor, to answer
18 the question, from there, I'd like to find out
19 what the POSA would do further.
20 JUDGE BRYSON: Okay. Why don't you go
21 ahead.
22 MR. ALY: Okay.
23 BY MR. ALY:
24 Q. So because you testified that the
25 CN '845 reference did not contain stability data,

1 a person of ordinary skill in the art as of the
2 priority date would be interested in determining
3 stability; correct?
4 A. You could imagine that that would be one
5 of a number of possible things that they would be
6 interested in.
7 Q. And a stability test is considered
8 routine in your field; correct?
9 A. The performance of a stability test is
10 routine.
11 Q. And that's true even if it takes a long
12 time sometimes to wait for the stability test to
13 unfold; correct?
14 A. Correct.
15 Q. There was information in the prior art
16 about stability of formulations like the CN '845
17 formulations; correct?
18 A. What you are referring to, I'm sorry?
19 Q. That's the Zhou article that you
20 testified about, JTX-115.
21 Here, in the Zhou article, you described
22 it as an optimized formulation; correct?
23 A. Well, they described it as an optimal
24 formulation.
25 Q. And they describe it as optimized for

1 something in particular called K sub E; correct?
2 A. The stability parameter that they used
3 was K sub E.
4 Q. Zhou is not about USP -- all of the USP
5 criteria; correct?
6 A. Zhou is not about all the USP criterion,
7 I would agree with that.
8 Q. And as you testified, Zhou does not have
9 PFAT5 information reported; correct?
10 A. It does not.
11 Q. So if a person of ordinary skill in the
12 art takes information about stability from Zhou,
13 they do learn that it has a particle size that
14 meets USP; correct?
15 A. I have to look again, but if I remember
16 correctly, I think that's true. I have to
17 confirm.
18 Q. Let's look. JTX-115.8 at Table 2.
19 And if you see, there's a Table 2 that
20 has -- the first column there is the particle size
21 that's reported; is that right?
22 Let me focus our attention on another
23 table, Table 4 at JTX-115.10, which will have a
24 little bit more comprehensive information. It's
25 2.5, stability analysis, and the Table 4

1 underneath that.
2 You see Table 4 is reporting the
3 optimized recipe, quality, evaluation, results,
4 and stability analysis results, Dr. Little?
5 A. Yes.
6 Q. And the particle size after
7 sterilization is 220 nanometers; correct?
8 A. Yes.
9 Q. Already that meets the USP requirement
10 for particle size; correct?
11 A. Yes, it does. It would be less than
12 500 nanometers.
13 Q. You testified that there is not a
14 description of crystals reported in Zhou, one way
15 or the other; correct?
16 A. Correct.
17 Q. Now, you did explain that the K sub E
18 test is an ultracentrifugation test.
19 A. It's a centrifugation test.
20 Q. And that is a test that spins the
21 compound very, very quickly to separate them, as
22 you described it for the Court; correct?
23 A. It applies a pressure to it. I don't
24 think that it's an ultracentrifuge test. You do
25 centrifuge it.

1 Q. And in terms of the centrifuging of the
2 test that's done, that is done intentionally to
3 try to create a phase separation between the oil
4 and the water; correct?
5 A. No. So, here, you're not trying to
6 completely separate the phases. What you're doing
7 is applying a stress. And even by the way the
8 constant is reported, which is a continuous
9 variable, that you could have high numbers, and
10 you could have low numbers.
11 So what that means is that when you
12 apply that stress, it's possible you'd still have
13 globules at the bottom, some amount so that it
14 doesn't completely -- the light doesn't completely
15 absorb, but some absorbs versus none absorbs. And
16 that's what gives you that numerator continuous
17 variable.
18 So the intent of this is to not crack
19 it. The intent of this is to apply a stress and
20 see what the response of the sample is.
21 Q. And so that's the point, the K sub E
22 information is helpful insofar as it goes but does
23 not confer, in your mind, whether or not there
24 would be crystals under microscopy; correct?
25 A. Yeah, it's a measure of stability that

1 has to do with things like flocculation,
2 coalescence, and things, but it does not report --
3 it does not report or necessarily correlate to
4 crystal formulation.
5 Q. K sub E does provide --
6 JUDGE BRYSON: Doesn't correlate to
7 what?
8 THE WITNESS: Does not necessarily
9 correlate to crystal formulation.
10 JUDGE BRYSON: So crystal formulation.
11 BY MR. ALY:
12 Q. And that's the point, K sub E does help
13 information regarding stability over time;
14 correct?
15 A. It provides one measure of it, yes.
16 Q. And the results for K sub E were
17 positive. In other words, it was stable according
18 to the K sub E measurement that was optimized;
19 right?
20 A. The optimized formulation was -- you
21 could characterize this as approximately as
22 stabling, according to the KE values, as just
23 following sterilization.
24 Q. And if someone in the prior art were to
25 modify the Zhou references, the modifications to

1 those references, you agree one might start with
2 the Zhou reference to do that?
3 A. First of all, you've got to answer a
4 question for me that nobody has been able to
5 answer. Why are we modifying from a formulation
6 that somebody has optimized to be at the
7 stability?
8 Q. Let me ask you the questions.
9 The next question is: Would a person of
10 ordinary skill in the art consider the Zhou
11 report, JTX-115, to be ready for FDA submission?
12 A. To be ready for FDA submission, you'd
13 have to confirm -- you would have to confirm that
14 it meets not just stability criterion, but a
15 number of other criterion that are necessary in
16 order for you to consider a filing of an NDA.
17 Q. And as of JTX-115, this is 2012; right?
18 A. That sounds familiar, but I'd have to
19 check. 115?
20 JUDGE BRYSON: At the very top of the
21 first page is the reference to the date.
22 THE WITNESS: It was published in 2012.
23 BY MR. ALY:
24 Q. All right. And what I want to contrast
25 that with, while we're looking at -- let's go to

1 the first page at the top. I should have done
2 that myself. That's published in 2012.
3 The priority date in this case, of
4 course, is 2014; right?
5 A. The priority date -- is that what you're
6 asking me, is the priority date?
7 Q. That's right.
8 A. Yes, 2014.
9 Q. And now, one of the pieces of
10 information you testified about was Merck's
11 experience in formulating aprepitant and
12 fosaprepitant; correct?
13 A. As I understood it, yes.
14 Q. All of the work that Merck did, spanned
15 approximately 1993 as a start, but ending by 2008
16 when there was a commercial product for
17 fosaprepitant; correct?
18 A. That's my understanding.
19 Q. You have no information about what Merck
20 did after 2008 with aprepitant or fosaprepitant;
21 correct?
22 A. I don't recall seeing information to
23 that effect.
24 Q. No publications that you've discussed
25 about formulating aprepitant and Merck's efforts

1 to formulate aprepitant after 2008.
2 Do you agree?
3 A. At least as far as I can recall. I
4 can't recall that.
5 Q. And even before 2008, you were referring
6 to Dr. Hale's testimony, neither he nor you
7 identify any reference regarding attempts made to
8 formulate aprepitant before 2008; correct?
9 A. As far as a reference, I don't recall
10 that.
11 Q. And in the priority date time frame in
12 2014, the POSA is not starting from scratch,
13 trying to formulate aprepitant for the first time;
14 right?
15 A. Well, it depends on what you mean. I
16 think that somebody would look at all of the prior
17 art, and they would say, you know, what's been
18 tried and what information can I gather from that.
19 So in that regard, they have some information that
20 they could begin to formulate something.
21 Q. And a POSA would know that aprepitant
22 was a drug, as you put it, difficult to formulate;
23 correct?
24 A. I think they would realize that, yes.
25 Q. And you mentioned CN '845 and Zhou and

1 how those were tested and demonstrated in the test
2 in Examples 4 and 5 of the asserted patents; is
3 that right?
4 A. Yes.
5 Q. Let's look at that, if we may. JTX-1,
6 at 15, Example 4.
7 Now, Example 4, to be clear, is
8 information that Heron tested and put into the
9 patent application; correct?
10 A. I think that it represents a formulation
11 that Heron attempted to make here and tested, yes.
12 Q. Well, to be -- let me make sure I
13 understand.
14 The tests that's shown in Example 4,
15 would a POSA have access to the information shown
16 in Example 4 before the priority date for the
17 asserted patents?
18 A. No.
19 Q. Same with Example 5; right?
20 A. Correct.
21 Q. Is it your understanding and do you
22 agree that Example 4 was prepared according to how
23 a POSA would understand and apply the CN '845
24 patent?
25 A. It was -- as a POSA would understand

1 CN '845, it was made according to that, yes.
2 Q. And Example 5 was made according to how
3 a POSA would understand and apply the Zhou
4 reference; correct?
5 A. Yes.
6 Q. The information that you provided that
7 the CN '845 and the Zhou references would not meet
8 the "physically stable" claim term as construed is
9 based on Example 4 and Example 5; correct?
10 A. We know that it wouldn't because of the
11 last sentence in Example 4 and Example 5.
12 Q. And there's nothing in the prior art
13 that you pointed to to support the proposition
14 that there was a failure in stability with an
15 aprepitant emulsion; correct?
16 A. I don't think that there was data
17 showing that there was a failure, but I also don't
18 necessarily think that somebody would look into
19 those references and necessarily see that they're
20 stable.
21 Q. Well, Heron did; right?
22 A. Heron made this formulation and tested
23 it and found that it wasn't.
24 Q. And by "stable" -- and that's what I'd
25 like to make clear.

1 By "stable" you're using the court's
2 claim construction of "physically stable," which
3 requires stability for at least seven days;
4 correct?
5 A. And the multiple tests that the court
6 construed, yes.
7 Q. The time frame for the physically stable
8 test is seven days, correct?
9 A. To my recollection, the construction
10 requires, I think, maybe at least seven days.
11 Q. And in Example 4 and Example 5, those
12 were found to have crystals at four days; correct?
13 A. It says within four days. So it could
14 have become unstable at day one, but they checked
15 at day four.
16 Q. Did you check the records in the lab
17 notebooks to see when the formulations became
18 unstable?
19 A. I did review the lab notebooks. Off the
20 top of my head, I think what they did is they
21 checked within four days.
22 Q. And it's your understanding that within
23 four days means at or after four days; correct?
24 A. Within four days?
25 Q. That's right.

1 A. At or before.
2 Q. At or before four days?
3 A. Yeah.
4 Q. And Example 4, in terms of what's
5 reported here, has gone through and identified a
6 pH, we've talked about the pH, of 7.0. It's at
7 line 38.
8 A. Yes, they were attempting to make the pH
9 7.0.
10 Q. And the purpose of making it at 7.0 was,
11 as you said, to have some example of CN '845, and
12 the CN '845 range was 6 to 8; right?
13 A. The CN '845 example was 6 to 8.
14 Q. And the idea here is that if it's
15 adjusted to 7, there -- is there any example --
16 let me put it the other way.
17 You agree with me, Dr. Little, there is
18 no example that has the same pH with a different
19 emulsifier percentage to see what the effect of
20 that is in the patent; correct?
21 A. I'm sorry, could you please ask your
22 question again?
23 Q. Sure.
24 There is no two examples that have the
25 same pH, but they varied the emulsifier

1 percentages to see the effect; correct?
2 A. I don't think so, no.
3 Q. Similarly, there's no examples in the
4 patent from which there's the same emulsifier
5 percentage at different pHs tested; correct?
6 A. It sounds like maybe you just asked me
7 the same question. Maybe I don't understand the
8 distinction.
9 Q. The distinction is that first I want to
10 hold the pH constant, and the second I want to
11 hold the emulsifier constant.
12 A. Oh, I see.
13 Q. So let me ask the second question again.
14 There's no example in the patents where
15 the emulsifier percentage was the same and the pH
16 was different; correct?
17 A. I don't think so, no.
18 Q. Let's go to the last page of the patent,
19 18, and look at Claim 8.
20 In terms of the Claim 8, there's
21 percentages given of aprepitant of .7
22 weight-weight percent and egg yolk lecithin of 14
23 weight-weight percent; correct?
24 A. The first -- you know, underneath of
25 this first sentence, the first two claim elements

1 are .7 weight-per-weight percent aprepitant and 14
2 weight-per-weight percent egg yolk lecithin.
3 Q. And you have shown no evidence that the
4 aprepitant at .7 weight-weight percent has a
5 special stability or any other property as
6 compared to any other weight-weight percent;
7 correct?
8 You did not do any such comparison,
9 true?
10 A. I didn't do any physical tests in this
11 case.
12 Q. Have you pointed to anyone doing any
13 tests to show that .7 weight-weight percent might
14 have some unique or special characteristic
15 compared to another weight percent?
16 A. I didn't see anybody perform experiments
17 in that regard, if that's what you're asking me.
18 Q. I'm going to skip the egg yolk lecithin
19 for a moment, and I'd like to read the oil line.
20 The oil is 9 to 10 weight-weight
21 percent. You didn't provide any opinion or show
22 any tests that says 9 weight-weight to
23 10 weight-weight percentage of soybean oil works
24 in a unique or special way that does not work for
25 another percentage of soybean oil; correct?

1 A. Maybe the reason I'm not understanding
2 is when you're saying "work."
3 Q. I apologize.
4 A. I provided an opinion about this overall
5 formulation. If you're asking me did I dissect
6 each one out and try to identify some unique
7 property that 9 and 10 percent soybean oil would
8 endow in the context of a hypothetical
9 formulation, I didn't do that.
10 Q. I'm trying to address something that we
11 call criticality. And do you have an
12 understanding of what that is?
13 A. No.
14 Q. Then I won't use that word. I would
15 like to find out in another word, the 9 to
16 10 percent soybean oil -- let me ask you, if
17 you've shown that if you used 8 or 11 percent
18 soybean oil, something different would happen, you
19 didn't show any such information; correct?
20 A. I didn't think I -- I don't remember
21 anybody ever criticizing that. So I didn't
22 respond to it. All I was asked to do is respond
23 to Dr. Rabinow's opinions. I don't remember that
24 ever being brought up.
25 Q. You do say there are unexpected results

1 to the formulation that weren't attributable to
2 the prior art; correct?
3 A. Yeah, the overall formulation, correct.
4 Q. And let's go to the next claims, 9 and
5 10.
6 Similarly, for Claim 9, you have not
7 shown any evidence that if you use a weight-weight
8 percent sucrose other than 5, a different result
9 will ensue for physical stability; correct?
10 A. I don't think so, no, I didn't. I
11 didn't perform any experiments to that regard or
12 perform an analysis of that.
13 Q. And, finally, for ethanol, there's a
14 range claimed in Claim 10 of 2 to 6 weight
15 percent.
16 You didn't show any test results or any
17 data that if another weight percent was used, that
18 would affect the physical stability of the
19 formulation; correct?
20 A. Yeah, I don't recall that.
21 Q. And in terms of the egg yolk lecithin
22 itself, let's go back to Claim 8 and talk about
23 the egg yolk lecithin.
24 The only test that you're identifying to
25 show some kind of a special result is the 14

1 weight-weight percent egg yolk lecithin, as used
2 in Examples 1, 2, 3, and 6?
3 A. The way I describe this is differently.
4 I think that the overall formulation, based on
5 what I've seen, including the 14 weight-per-weight
6 percent egg yolk lecithin, had those unexpected
7 properties.
8 Q. Is Example 3 one of the examples that
9 uses something Heron developed and was found to be
10 physically stable?
11 A. Let me refresh my memory.
12 Q. Let's look at it together. The bottom
13 of -- let's go to JTX-1.16. On the bottom is
14 Table 7. And it goes on to the top of the next
15 page.
16 Table 7 is showing the stability results
17 for Examples 1, 2, 3, and 6; correct?
18 A. Yes.
19 Q. And the stability result, looking at
20 Example 3 as an example, meets all the criteria
21 for the "physically stable" claim term; true?
22 A. Well, you can see here that the diameter
23 meets 729 -- well, it says later the stability at
24 729 is at two months. So the stability
25 limitations in regard to the size and PFAT5,

1 according to 729, would be met here.
2 Q. Right. And let's look at Example 7, the
3 text above the table on the bottom of Column 20,
4 Example 7.
5 Looking at the bottom rows, do you
6 believe that Example 3 of the patent meets the
7 crystal limitation of the "physically stable"
8 term?
9 Example 3 was included as meeting the
10 crystal formulation test; correct?
11 A. It says, example -- two months of
12 storage, reserved, and then -- okay. Examples 2
13 and 3 were stable at room temperature for three
14 and two months, respectively, and at these time
15 points, aprepitant crystals were observed in the
16 formulations.
17 Q. And let me just make sure I understand.
18 Example 7 is the entirety of the support
19 for the "physically stable" claim term that's
20 being disputed in this case; true?
21 A. Well, so, for instance, like in -- we
22 just looked at Example 4 and 5, and in those cases
23 they mention "physical stability" in those
24 examples. I think this Example 7 was meant to be
25 a summary of the physical stability requirements

1 for the other examples.
2 Q. I just want to make clear.
3 Is Example 3 something that meets or
4 does not meet the "physically stable" claim term,
5 as the court has construed it?
6 A. It would appear it does, because it says
7 it was stable at room temperature for three and
8 two months, respectively. And then -- yeah, so
9 that's what the disclosure is.
10 Q. And let's look at JTX-1.15. In the top
11 right of Column 18 is Table 3.
12 And the middle column is concentration
13 weight-weight percent; correct?
14 A. Yes.
15 Q. For aprepitant, that is .587 percent;
16 correct?
17 A. Yes.
18 Q. That's not .7 weight percent, even with
19 rounding; correct?
20 A. Correct.
21 Q. Emulsifier is 11.7 percent; correct?
22 A. Yes.
23 Q. That's not 14 percent; correct?
24 A. Correct.
25 Q. The oil is 7.83 percent; right?

1 A. Yes.
2 Q. That's not 9 to 10 percent, even with
3 rounding; correct?
4 A. Correct.
5 Q. The protective agent is 20.4 percent;
6 correct?
7 A. Yes.
8 Q. That is not 5 percent; true?
9 A. Correct.
10 Q. In terms of the pH that was used, that
11 is 8.80; right?
12 A. I'd have to look.
13 Q. Let's go back to Table 7 for just a
14 moment. This is JTX-1.16, Table 7. It's spanning
15 to the next page.
16 Can you just please confirm that all of
17 the pHs are between 8.74 and 8.92 for the four
18 examples which are numbered 1, 2, 3, and 6?
19 A. Confirmed.
20 Q. In terms of the pH that was used in
21 Example 44, that was 7.0, you address that; right?
22 A. In Example 44, it was the -- it was pH
23 7.
24 Q. Let's go back to JTX-1.15 at Example 44.
25 And Example 44, it showed that the

1 reason they were making Example 4 is in the first
2 sentence to have an example of a formulation,
3 quote, adjusted to a pH of less than 8.0.
4 Do you see that?
5 A. Yes.
6 Q. So on the one hand, the patent was
7 making a distinction between a pH of less than 8.0
8 and results when the pH was 8.7 to 8.8; correct?
9 A. Well, right, the CN '845 reference says
10 the pH was 6 to 8. So it's making it less than 8
11 to fit within the CN '845.
12 Q. I'm not questioning that right now. I'm
13 just making sure that the point of Example 4, as
14 written in the patent, was to provide an example
15 of something that had a pH adjusted to less than
16 8.0 in contrast to formulations with the pH of
17 more than 8.0.
18 A. That's one of the things that they were
19 trying to do. But I wouldn't say they're trying
20 to do it for the reason you're saying. They're
21 trying to do it because that's what CN '845 is
22 showing it's between 6 and 8.
23 Q. Fair enough. Is there -- in terms of
24 the patent disclosure for lecithin --
25 Let me go to the next document, if I

1 may. I'd like to go to the Liu exhibit, JTX-93.
2 This is the Liu reference that you
3 looked at; right?
4 A. Yes.
5 Q. And in the Liu reference, in terms of
6 the title, it's called "Progress and Research of
7 Injectable Microemulsion"; right?
8 A. Yes.
9 Q. Let's look at JTX-93.11.
10 You identified a Table 1, that we could
11 call up.
12 Table 1, you highlighted for the Court
13 the bottom line "Phospholipids and Phospholipid
14 Derivatives"; correct?
15 A. Yes.
16 Q. There's a list of surfactant types, that
17 does not identify egg yolk phospholipid; correct?
18 A. That doesn't say egg yolk phospholipid
19 there if that's what you're asking me.
20 Q. And your concern was that maybe somebody
21 reading this would think that the phospholipids
22 that are listed would be more in the direction of
23 water in oil emulsion as opposed to oil in water
24 emulsion; right?
25 A. Well, that's what the disclosure says as

1 we saw.
2 Q. But a POSA would have no doubt that in
3 fact egg yolk phospholipids have been in and are
4 used commonly in oil in water emulsions; right?
5 A. They are. It's a completely different
6 system, but they are.
7 Q. And in terms of the emulsions that are
8 used, let's look at one example, JTX-84.
9 The Intralipid compound, that's one you
10 considered in forming your opinions; correct?
11 A. It was.
12 Q. And the point you were making is on
13 page 1, on the part of the description -- that
14 1.2 percent was used in that formulation of egg
15 yolk phospholipids; correct?
16 A. I do know that 1.2 percent egg yolk
17 phospholipid was used in Intralipid.
18 Q. There's no drug in Intralipid, the drug
19 is the oil basically.
20 A. Well, it's not an active pharmaceutical
21 ingredient. It's used for what's called
22 parenteral nutrition or IV nutrition.
23 Q. And if we go down, scroll down to the
24 paragraph underneath the compound, same page where
25 it identifies the components and it says that the

1 major component fatty acids are linoleic and oleic
2 acids; correct?
3 A. I'm sorry, I'm reading above it here to
4 get some context but --
5 Q. We can expand the entire top half,
6 that's not a problem.
7 A. Sorry. I see. You're reading from the
8 part that was underneath of it.
9 Q. Do you agree, sir, that linoleic and
10 oleic acids are components of egg yolk
11 phospholipids?
12 A. Amongst other things, yes.
13 Q. And oleic acid when combined with sodium
14 hydroxide forms sodium oleate; correct?
15 A. You can form sodium oleate by exposing
16 oleic acid by -- by exposing these fatty acids to
17 sodium hydroxide, you can.
18 Q. You didn't identify anything different
19 or unique that would happen if sodium oleate were
20 used as a pH adjuster as compared to sodium
21 hydroxide if that were used as the pH adjuster in
22 the claimed formulation; correct?
23 A. I did.
24 Q. What did -- you described that there
25 might be a difference?

1 A. Yeah, so if you use sodium hydroxide as
2 a pH modifier, one, that's a conventional strong
3 acid or strong base. When you add it, it's going
4 to poof, it's going to dissociate, it's going to
5 do that; right? That's what it's going to do.
6 If you add oleic acid, the oleate is
7 going to be there, it's going to be potentially
8 doing other things. There's the distinction of
9 that.
10 In addition to that, I believe there's
11 going to be concern given the prior art that
12 specifically using oleic acid other than something
13 that's simple like sodium hydroxide that's going
14 to cause tolerability problems or at least that's
15 what I think a person of ordinary skill in the art
16 would consider looking at the prior art.
17 Q. Heron did test with sodium hydroxide,
18 didn't they?
19 A. Heron did test with sodium hydroxide?
20 Q. Are you aware of that?
21 A. In what capacity, I'm sorry?
22 Q. Let's look at DTX-191, one of the lab
23 notebooks. This is in the second binder.
24 A. The second one, you said?
25 Q. Yes, I'm going to page 168 of the

1 document which is the underline 168 on the bottom.
2 It's DTX-191_168. It's also on the screen if you
3 would like to take a look but you can, of course,
4 flip through.
5 And the experiment that's run here is
6 titled "10 milliliters sodium hydroxide (instead
7 of sodium oleate)"; correct?
8 A. Okay.
9 Q. And what they report in the notebook --
10 you can see the claimed amounts for this
11 formulation 612B that are reported in the
12 notebooks specifically 450 milligrams aprepitant,
13 9 grams egg lecithin, 7.2 milliliters ethanol,
14 6 grams soybean oil, 10 milliliters sodium
15 hydroxide, and 32 milliliters water; correct?
16 A. That's what it says here.
17 Q. And did you look at the results to see
18 what happened?
19 A. I did look at the lab notebooks, but I
20 don't remember off the top of my head.
21 Q. Let's turn to page 171. These are some
22 microscopy images to see if there were crystals
23 formed in the formulation that we just looked at
24 titled 6/12B; correct?
25 A. I don't know. I'm sorry. It could be.

1 I see some microscopy images.
2 Q. Let's look at the one on the -- if you
3 see, there's the top right. Let's blow up the
4 text and the image for the top right on page 171
5 of DTX-191.
6 There is an image titled "10X
7 magnification 6/12B." Do you see that?
8 A. Yes.
9 Q. And it says: After 32 days no crystals;
10 correct?
11 A. That's what it says.
12 Q. Now, while we have the notebooks in
13 front of us, let's go to DTX-193. That's the
14 other tab in this same binder. If we would go
15 to -- if we would go to, please, page 43. So it's
16 193_43.
17 A. So we're out of this document now?
18 Q. That's right. We're into Tab DTX-193.
19 And here the title was "Chinese Paper
20 Replicate"; correct?
21 A. I see "Chinese Paper Replicate" written
22 here.
23 Q. And Dr. Han explained that was to
24 replicate the Zhou paper; correct?
25 A. I do know that there was a replication

1 of the prior references. I just -- I'm sorry, I
2 don't remember if this is what this is talking
3 about here. I'm sorry.
4 Q. Well, you didn't show any tests that
5 were done in any notebook on the direct
6 examination; is that fair?
7 A. I did not show notebook tests, but I did
8 show the results in the examples in the patent.
9 Q. And that's what I want to ask about. If
10 this -- if the record will show that this is the
11 example that matches up with Example 5 of the
12 patents, which would rely on Dr. Han's testimony,
13 we'll look beneath the same procedure and see what
14 was the reported pH in the notebook.
15 The pH was 6.5; correct?
16 A. Oh, well, it says after eight passes, so
17 this might be a different part of the process.
18 Q. The only pH reported in the lab notebook
19 is 6.5; correct?
20 A. I see pH 6.5. I just would need to
21 understand a little bit more about the process to
22 say if that's the relevant pH.
23 Q. Is there any other pH reported on this
24 page of the lab notebook which is 193_43?
25 A. On this page I do not see another

1 instance of reporting of a pH.
2 Q. Okay. Let's talk about the terminology.
3 We can move onto the next subject.
4 JUDGE BRYSON: Since you're moving to
5 another subject, I think this would be a good time
6 to take a 15-minute break. So why don't we come
7 back at 2:35.
8 MR. ALY: Thank you. Your Honor.
9 JUDGE BRYSON: Dr. Little, during
10 your -- since you're on cross-examination, during
11 the break, you may talk to anybody about any
12 subject except the subject of your testimony.
13 THE WITNESS: Okay. Understood.
14 JUDGE BRYSON: And to be safe, anything
15 to do with this trial. So baseball, the weather,
16 which is not so great, anything you want but not
17 subject to what we heard this week at trial.
18 THE WITNESS: Understood, Your Honor.
19 JUDGE BRYSON: Thank you. So 2:35.
20 (Recess from the record.)
21 JUDGE BRYSON: You may proceed.
22 MR. ALY: Thank you, Your Honor.
23 BY MR. ALY:
24 Q. Dr. Little, I'd like to talk with you
25 about the terminology of emulsions.

1 Do you agree that a microemulsion is a
2 type of emulsion?
3 A. It could be considered as a category of
4 emulsion.
5 Q. And there's another word that you have
6 introduced that you use called "nanoemulsion";
7 correct?
8 A. Well, so a nanoemulsion is also a term
9 that's used in the field.
10 Q. And a nanoemulsion is a conventional
11 emulsion but with small particle size; correct?
12 A. That's one way to characterize it, yeah.
13 Q. In your nomenclature, to use this new
14 word, nanoemulsion, is what you would use best to
15 describe the claimed inventions; correct?
16 A. I don't know if I remember calling it a
17 nanoemulsion in my direct. I mean, it depends on
18 the categorization of that, I would have to look
19 and see, but it is a conventional emulsion.
20 Q. And it's pretty common in your field,
21 isn't it, Dr. Little, to sometimes use the word
22 "microemulsion" or "nanoemulsion" or "emulsion";
23 right?
24 A. So it is common that you would see
25 somebody make a mistake in referring to something.

1 Because it's micro and nano, you will have
2 somebody say a micron-sized emulsion is a
3 microemulsion. Sometimes you'll say that and then
4 you can say, What do you mean? Do you mean it's a
5 micron-size emulsion or do you mean you're
6 referring to the classification of emulsions that
7 are thermodynamically stable that just may be
8 so -- not so fortuitously were at one point in
9 time called microemulsions.
10 Q. And just to wrap up on that, the patent
11 office prosecution history, you reviewed that,
12 nobody called attention to any difference between
13 a microemulsion or emulsion or nanoemulsion; true?
14 A. I think there was an understanding
15 amongst everybody that they were talking about
16 conventional emulsions.
17 Q. Even though the CN '845 patent reference
18 was discussed; correct?
19 A. It was, but as I said in that
20 circumstance, there's a definition of the type of
21 emulsions they're using that a person of ordinary
22 skill in the art would understand is -- I mean,
23 it's just mistaken.
24 Q. And finally, the Zhou reference --
25 finally on that point, the Zhou reference does use

1 the word "emulsion"; correct?
2 A. It then uses the word "emulsion," yes.
3 Q. I wrote a note here and I'd like to
4 figure out what you were addressing.
5 You said there was something that was
6 impossible during direct examination, and my note
7 says that it would be impossible for the mass of
8 lecithin to be greater than the mass of oil. Is
9 that what you said?
10 A. Well, what I mean is that if under the
11 circumstance where you've got a droplet and your
12 drug and your lecithin are on the surface of that
13 droplet, that's where they are, and you say, okay,
14 well -- I mean, we're talking about masses now.
15 So unless the density of the thing at
16 the surface was dramatically higher than the
17 density of the bulk, which would not be the case
18 here -- we're talking about common densities,
19 things floating around in water -- then there's no
20 way for the surface of an object to be more volume
21 than the entire object. It's the surface of the
22 object for a reason. It's a part of that object.
23 Q. To be clear, when you have more
24 emulsifier available in a formulation, there is
25 more -- an emulsion is something where everything

1 is moving around, there's more emulsifier
2 available to be at the interface; correct?
3 A. I don't understand what you mean. If
4 it's all packed at the surface. What do you mean
5 it's available?
6 Q. Let me ask a different question.
7 An emulsifier within the context of the
8 CN '845 reference. Let's start there. Do you
9 have an opinion that the emulsifier in that
10 reference is, in fact, emulsifying, mixing oil in
11 water. Do you agree with that?
12 A. Well, I mean, it doesn't say, but at
13 least some of it is going to be.
14 Q. And do you agree that increasing
15 emulsifier levels increases surface area?
16 A. It might. So if you're under the
17 circumstance where you add an emulsifier and that
18 allows you to maintain smaller droplet sizes, now
19 you have maintained a higher surface area. But
20 it's not like you have a particular surface area
21 and then you add emulsifier and all of a sudden
22 your surface area increases. It's just that the
23 emulsifier potentially permits you to maintain the
24 size of emulsion that you made when you originally
25 made it.

1 Q. Do I understand you correctly,
2 increasing the emulsifier in a system will reduce
3 the globule size; is that true?
4 A. It will allow you to make a globule size
5 potentially that is smaller than before. However,
6 it's important to recognize -- and I said this
7 before -- it is not necessarily the case that when
8 you increase emulsifier concentration that always
9 happens.
10 Remember, if you add an emulsifier and
11 it is other places and causing things to
12 flocculate and coalesce, you add an emulsifier and
13 you decrease your surface area.
14 Q. And throughout your review of materials
15 and the opportunity to present on direct
16 examination, you've not provided any one example
17 where somebody used too much lecithin and resulted
18 in flocculation with an aprepitant emulsion;
19 correct?
20 A. Well, so now -- I mean, if you're
21 talking about the references that have aprepitant
22 emulsions, we have a much smaller number of those.
23 And many of them were not talking about stability
24 at all.
25 In the one we have with Zhou that's

1 talking about stability, they optimized it to a
2 particular amount. So that's what we know.
3 Q. The references that you now say one
4 might look to -- the drugs that you say that one
5 might look to to improve their formulations, you
6 mentioned rolapitant, netupitant, and
7 fosaprepitant; correct?
8 A. You would at least consider those, yes.
9 Q. And the reason one would consider those
10 is to address the need you identified of an NK-1
11 antagonist IV solution; correct?
12 A. That would have reduced or minimal
13 tolerability issues, yeah.
14 Q. For rolapitant, as of the priority date,
15 there was no FDA approval for that product, but it
16 was under Phase 3 studies.
17 That's your testimony; correct?
18 A. Yeah, my understanding is that it had
19 passed Phase 3 studies but it was not approved.
20 Q. The rolapitant already had an IV
21 formulation; correct?
22 A. I'd have to refresh my memory on that.
23 But -- I'd have to refresh my memory on that.
24 Q. You didn't base your opinion on whether
25 or not rolapitant already had an IV formulation?

1 A. No, I just think that, first of all, a
2 person of ordinary skill in the art would consider
3 it. That was something that I was critical of
4 that I felt like could be an obvious analysis that
5 wasn't considered.
6 The degree of the formulations that were
7 in existence, one could look at those and they
8 could see whether or not, you know, perhaps you
9 could improve upon those formulations. But I did
10 consider it; right? It's just that my critique
11 here is that those weren't even considered in the
12 obviousness analysis of Dr. Rabinow.
13 Q. Netupitant, similarly, that was not FDA
14 approved but was in an IV solution already;
15 correct?
16 A. It was not FDA approved. It was
17 available for a person of ordinary skill in the
18 art to consider it.
19 Q. In terms of fosaprepitant, that was also
20 already in an IV formulation; correct?
21 A. It was. As I understand from
22 Dr. Roeland, there was a need to make some
23 improvements in it which a person of ordinary
24 skill in the art could have undertaken.
25 Q. But as of 2014, you'll agree that there

1 was an opportunity or a motivation to change a
2 formulation of either aprepitant or fosaprepitant
3 without polysorbate 80 in it; correct?
4 A. That's something you could consider.
5 Q. A POSA would want to do that; right?
6 A. You would -- I think that's one thing
7 you could do. You could try to remove the
8 polysorbate 80 and you could try to reformulate.
9 You would need to look at replacing the function
10 that it served and you would need to produce a
11 formulation that was tolerable.
12 You also could potentially try to do
13 something with formulation to mediate the effects
14 of polysorbate 80, but each of those things are
15 things that a person of ordinary skill in the art
16 could consider.
17 Q. And as far as from a formulator's point
18 of view, when you were giving the testimony, you
19 did not identify any formulation of rolapitant
20 much less any publications for somebody for why
21 they would consider a rolapitant formulation
22 improvement and not an aprepitant formulation
23 improvement; correct?
24 A. I just said given the properties of
25 aprepitant that one would certainly be motivated

1 to look at other possibilities, and I felt like
2 those were not considered. That was my point I
3 was making.
4 Q. Same for netupitant; right?
5 A. Yes.
6 Q. But your opinion about why someone
7 should consider them is because there are other
8 NK-1 antagonists, not because there was any
9 publications or motivation or teaching to change
10 the existing formulations for rolapitant and
11 netupitant; correct?
12 A. I'm sorry, I don't understand your
13 question.
14 Q. Let me put it a different way.
15 For rolapitant and netupitant, there
16 were existing formulations and you didn't identify
17 any reason to change those existing formulations;
18 correct?
19 A. I -- as far as I went into my analysis
20 is, is that those were also available. In fact,
21 they had already passed Phase 3 testing. Those
22 would be something that one would consider. They
23 weren't FDA approved. Perhaps that one would have
24 been FDA approved, but they would have -- you
25 would have been able to review them, you would

1 have been able to see if that's something that you
2 would want to pursue. My critique was that that
3 wasn't done in the obviousness analysis.
4 Q. But for aprepitant, of course, there
5 were publications that said there were reasons to
6 change the prior art formulation and the CN '845
7 reference explained additional reasons to change
8 the formulation; right, expressly?
9 A. How does CN '845 -- maybe you can
10 explain that to me. How does CN '845 tell you to
11 change the formulation? There's no stability
12 data. There's no preference for a given
13 formulation.
14 Q. Let's look at the CN '845 one more time.
15 This is JTX-71 at 13.13. Objects of the
16 invention, paragraph 7 on the top.
17 I'd like to just confirm with you that
18 CN '845 in describing the objects of invention
19 identifies disadvantages to prior art aprepitant
20 formulations; correct?
21 A. Oral formulations. So all this is
22 saying is that -- what I've been saying is that
23 there was a need for an IV formulation.
24 Q. And, in fact, they're also identifying
25 fosaprepitant in the CNA 845 reference and give

1 reasons why one would want to change fosaprepitant
2 also; correct?
3 Let's look at paragraph 17.
4 In JTX-71.14 at paragraph 17, you see a
5 section, Beneficial Effects.
6 Here in the last line, CN '845 is
7 expressly saying, "The cost of the aprepitant
8 microemulsion for injection is reduced greatly
9 when compared to a fosaprepitant dimeglumine
10 injection, and has very good practicality and can
11 bring about better economic and social benefits."
12 They're reporting that; correct?
13 A. They're saying -- that's what they're
14 saying here.
15 Q. And those are advantages of an
16 aprepitant formulation, if one were to pursue it;
17 correct?
18 A. They could be. I don't think that
19 they're far enough along in the development to
20 know how much it would cost to actually go through
21 the development effort to do this, but at this
22 stage that's what they're saying.
23 Q. But you understand that fosaprepitant,
24 because it's a prodrug and requires additional
25 synthesis steps, is indeed more complicated and

1 more expensive than just using aprepitant?
2 A. From a synthesis standpoint, yes. But
3 if you have to deal with a lot of formulation
4 problems, now you've got to invest a whole bunch
5 of money in to doing that. So it depends on the
6 time frame.
7 Q. But as far as the issue of identifying a
8 compound for which to improve the formulation, can
9 we agree CN is saying aprepitant would be a good
10 compound to improve the formulation?
11 A. They are saying that the cost of it
12 would be greatly reduced because -- I agree with
13 you, because of the synthesis step.
14 JUDGE BRYSON: The synthesis being
15 getting to the prodrug?
16 THE WITNESS: Getting to the prodrug,
17 yes, Your Honor.
18 BY MR. ALY:
19 Q. Now, in terms of the prior art -- we'll
20 move to our next question.
21 You have identified opinions on
22 unexpected results going to the stability of the
23 claimed formulation as compared to the stability
24 of prior art; correct?
25 A. Yes.

1 Q. But a person of ordinary skill in the
2 art, before doing any testing, would not have any
3 expectation one way or the other regarding the
4 stability of the CN '845 formulations; right?
5 A. Before you do the test, if you look at
6 CN '845, there's no information on stability. So
7 you wouldn't have the ability to look at that and
8 say, I think it's going to be stable.
9 Q. So a POSA couldn't look at it and say it
10 was going to be unstable either, for the same
11 reason; correct?
12 A. I think that they might have some
13 concerns on some of them, but I don't think that
14 they would know, given that only information.
15 Q. Next, on Claim 21, that's a method claim
16 from the '229 patent that's being asserted.
17 You understand that; right?
18 Let's look at --
19 A. I believe there is a method.
20 Q. JTX-1.18. It's the last claim.
21 A. Yes.
22 Q. That method of administration, you agree
23 that a person of ordinary skill in the art would
24 understand aprepitant in an emulsion would have a
25 reasonable expectation of success to treat nausea

1 and vomiting; correct?
2 A. From my understanding -- from my
3 understanding, aprepitant, if it was put into a
4 stable formulation for intravenous use, could be
5 used to treat nausea and vomiting.
6 Q. And a POSA would know that in the prior
7 art; correct?
8 A. I think that they would know that if you
9 could -- if you could make a stable IP formulation
10 and it would have reduced tolerability -- or
11 increased tolerability, the drug itself has the
12 ability to treat nausea and vomiting.
13 Q. Next question. The CN and Zhou
14 references, you call those failures because they
15 did not result in a commercial product by the
16 inventors and authors of those references;
17 correct?
18 A. Yeah, I think what I said is that we see
19 an attempt to make them and then we see an attempt
20 to even optimize them and then you don't see
21 anything after that, yes.
22 Q. You have not provided any evidence nor
23 are you aware of what actually the inventors of CN
24 or the authors of Zhou did after their
25 publications; correct?

1 A. No.
2 Q. Correct, you agree with me?
3 A. I did not present to you information
4 postdate CN '845 and Zhou about actions undertook
5 by those inventors.
6 Q. For the long-felt unmet need opinion
7 that you offered, you didn't consider or mention
8 the CN '845 or Zhou references; correct?
9 A. No, for long-felt unmet need, I'm
10 primarily relying upon Dr. Roeland.
11 Q. You have an opinion on copying that you
12 offered; correct?
13 A. Yes.
14 Q. Let's look at JTX-43.
15 This is one of the documents you
16 identified during your infringement testimony from
17 Fresenius Kabi's ANDA submission; correct?
18 Section 5313.
19 A. Okay.
20 Q. And the next page, 2, page 2, 43.2.
21 Let's look at the text on the top half of the
22 page.
23 You understand and you testified on
24 direct during your infringement testimony, there
25 are requirements, including what is numbered here,

1 for an ANDA submission; correct?
2 A. I'd say that if you're going to do this
3 kind of ANDA submission, there are these kind of
4 requirements, yes.
5 Q. And the requirement that's listed first,
6 No. 1, is The Test and Reference Listed Drug
7 formulations are qualitatively (Q1) and
8 quantitatively (Q2) the same; correct?
9 A. Yes.
10 Q. That means they should have the same
11 formulation components for a regulatory reason if
12 a person wants to submit an ANDA and get approval
13 as a generic; correct?
14 A. Well, so you are able to submit to the
15 FDA a formulation that does not have every single
16 excipient the same. So you're able to change the
17 excipient, and you're able to demonstrate to the
18 FDA that that's acceptable. You are allowed to do
19 that.
20 Here, what they're doing is they're
21 taking the path of saying, We are going to
22 represent to you, FDA, that we're qualitatively
23 and quantitatively the same. And they're using
24 that as a basis to get waivers on the product.
25 Q. There's regulatory permission to

1 opportunity -- a regulatory opportunity to use the
2 ANDA pathway with the same formulation to get
3 regulatory approval?
4 A. Yes, you have the opportunity to make
5 everything the same. You have that opportunity.
6 Q. And next page then, JTX-43.3, the first
7 row on formulation, if one is submitting the ANDA
8 to meet the regulatory requirement of Q1/Q2, then
9 it's showing that Fresenius Kabi's drug
10 formulation is the same as that of the RLD under
11 the Q1/Q2 equivalence analysis; correct?
12 A. Yes, if you choose to go this route to
13 make each of the things the same, that's true.
14 Q. And the RLD, for the record, is
15 reference listed drug; correct?
16 A. Yes.
17 Q. Okay. Now, as we wrap up, Dr. Little, I
18 want to make clear, it's been a few days of trial,
19 but let's focus on what this case is about.
20 This case is not about the invention of
21 aprepitant; correct?
22 A. The molecule, no.
23 Q. This case is not about the invention of
24 fosaprepitant; right?
25 A. The invention -- the claims are not

1 about the invention of fosaprepitant, no.
2 Q. And the problem to be solved that a
3 person of ordinary skill in the art, as of the
4 priority date, is to develop an NK-1 injectable
5 formulation; correct?
6 A. Yeah, with good tolerability, yes.
7 Q. And you would consider the goal that a
8 POSA would have to provide a stable aprepitant
9 formulation for IV administration; true?
10 A. That's not -- as a POSA standing at the
11 priority date, that's not true. And if you go
12 into the patent, if you're looking at the patent
13 and you're looking at ultimately the problems
14 they're working on inside -- in the context and
15 the specification, that's -- they're using
16 emulsion techniques for aprepitant.
17 Q. And the CN '845 reference showed in a
18 published document how to make an emulsion with
19 aprepitant, in particular, in 2012; correct?
20 A. I thought you asked me this question
21 already before. I mean, they did disclose various
22 formulations where they were at least attempting
23 to make emulsions. It's just you don't have any
24 information about whether they worked or not or
25 the stability or anything like that.

1 Q. And your testimony and understanding is
2 that USP 1, USP 729, that's something that a
3 Bachelor's of Science person would have knowledge
4 of; correct?
5 A. I think a Bachelor of Science in
6 pharmaceutics would understand the USP standards,
7 yes.
8 MR. ALY: Thank you very much, Your
9 Honor.
10 JUDGE BRYSON: Thank you.
11 Let me ask just one question, picking up
12 on the polysorbate 80 question that was asked.
13 What is, to your knowledge -- and I think we may
14 have had evidence of this, but I need to be
15 reminded. I guess it's a two-part question.
16 Number 1 is, what function does the
17 polysorbate 80 play that could not be, to your
18 knowledge, performed by any number of other
19 surfactants? Is there something special about
20 polysorbate 80 that couldn't -- that would prevent
21 it being replaced readily?
22 THE WITNESS: Yeah, so here's what I'd
23 say. Generally, now, polysorbate 80 is a compound
24 that's used in pharmaceutical formulations.
25 JUDGE BRYSON: Right. I understand

1 that.
2 THE WITNESS: And it has functions. It
3 has proposed functions.
4 JUDGE BRYSON: Right.
5 THE WITNESS: There are other -- if you
6 get to handle the pharmaceutical excipients, you
7 can find others that would have that function.
8 So, theoretically, as long as it was that clean,
9 you would be able to use another excipient that
10 represented it had a function. But my only
11 concern with answering the question is simply
12 that, that what you're asking me about, I think,
13 is the fosaprepitant formulation.
14 JUDGE BRYSON: Yes.
15 THE WITNESS: So could you replace it in
16 that one? That would require an analysis of the
17 fosaprepitant formulation, and I didn't do that.
18 JUDGE BRYSON: Right. I guess let me
19 ask the question in a negative way. Is there
20 anything that would suggest to you that
21 substituting another surfactant for polysorbate 80
22 would pose difficulties, either side effects or
23 functional difficulties with the particular
24 formulation, setting aside the regulatory issues
25 that we create, which I understand?

1 THE WITNESS: Right. Based on basic
2 function, I think it would be reasonable to say
3 that a person of ordinary skill in the art could
4 begin to explore alternatives to it.
5 JUDGE BRYSON: Okay.
6 THE WITNESS: And then it could solve
7 the problem. I think that's probably the best
8 that I can answer your question.
9 JUDGE BRYSON: That's fine. Thank you.
10 Very well.
11 MR. ALY: May I have one follow-up?
12 JUDGE BRYSON: You have about a minute.
13 So you can follow up.
14 BY MR. ALY:
15 Q. The Zhou -- this is in case nobody has
16 said it. The Zhou reference does not have
17 polysorbate 80 in the formulation; correct?
18 A. I would have to go back and look. I'm
19 sorry, I don't remember.
20 MR. ALY: Thank you, Your Honor.
21 JUDGE BRYSON: Thank you.
22 Cross-examination -- pardon me,
23 redirect.
24
25

1 REDIRECT EXAMINATION BY COUNSEL FOR THE PLAINTIFF
2 BY MR. ASHKENAZI:
3 Q. Dr. Little, just to be clear, if a POSA
4 started with aprepitant and wanted to make an IV
5 form and even wanted an emulsion, like Dr. Rabinow
6 says, did Dr. Rabinow show that the asserted
7 claims are obvious over the art?
8 A. No.
9 MR. ASHKENAZI: Now, if we could pull up
10 JTX-71. Go to page 13. That's the '845 patent.
11 BY MR. ASHKENAZI:
12 Q. And do you recall you were asked some
13 questions on --
14 MR. ASHKENAZI: Sorry, I think it's the
15 next page, paragraph 17.
16 BY MR. ASHKENAZI:
17 Q. Do you recall you were asked some
18 questions about this paragraph, Dr. Little?
19 A. Yes.
20 Q. And counsel pointed out that an IV
21 aprepitant emulsion would, quote, bring about
22 better economic and social benefits, close quote;
23 right?
24 A. Yes, that's what it says.
25 Q. Okay. What is the only IV aprepitant

1 that succeeded for treatment of emesis?
2 A. The only one that was aprepitant that
3 was approved for treating emesis was Cinvanti.
4 Q. And is it your opinion that it had
5 brought about benefits?
6 A. Yes, from what I've seen.
7 MR. ASHKENAZI: Your Honor, no
8 further -- I just want to make one other point,
9 Your Honor. So it's not for redirect, but it's
10 something that occurred between your discussion
11 with opposing counsel.
12 So for the record, so Heron's position
13 is clear, whether a species within a genus would
14 or would not be obvious is its own separate
15 analysis. And it hasn't been alleged by Fresenius
16 with respect to CN '845. We would, therefore, do
17 not agree that Fresenius has established that any
18 particular species would be obvious over a genus.
19 JUDGE BRYSON: And does this go back to
20 the exchange dealing with whether -- and this was
21 a hypothetical question, I think, whether if you
22 had a drug that had components that fell all
23 within the same ranges --
24 MR. ASHKENAZI: Yes.
25 JUDGE BRYSON: -- that that would not be

1 obvious, would or wouldn't be obvious.
2 MR. ASHKENAZI: Yes.
3 JUDGE BRYSON: Normally, I think -- I
4 can imagine an exception if you had a very large
5 species, but I would think normally -- and you can
6 disagree with this proposition, and I -- when we
7 went through that exchange and I was thinking of
8 the exception case, maybe the Edge case even.
9 But normally, I would think if you
10 have -- and I recall those were fairly tight
11 ranges. If you have fairly tight ranges and
12 somebody comes into the patent office and says, I
13 have something, I'm not going to show you
14 criticality, but I will show you that I have a
15 drug which doesn't span the entire range but it
16 falls within all those ranges, the examiners are
17 going to throw them out.
18 MR. ASHKENAZI: So to --
19 JUDGE BRYSON: With those conditions on
20 the proposition that I was discussing, would you
21 disagree with that proposition?
22 MR. ASHKENAZI: So I would say a couple
23 of things on that, Your Honor. First, this is way
24 far afield of what --
25 JUDGE BRYSON: It is, but I think it's a

1 fair point for you to raise, and I just wanted to
2 see exactly where we are.
3 MR. ASHKENAZI: I also think that if
4 we're looking at the ranges of CN '845
5 paragraph 8, which is the broad ranges of
6 excipients, broad ranges, in that case a species
7 within that broad range can show can be
8 nonobvious.
9 JUDGE BRYSON: But wouldn't it have to
10 be to able to show criticality? In other words,
11 if I just came in and said, I claim something that
12 falls halfway between every one of these ranges,
13 and I'm not going to tell you that it's any better
14 than what was there before the prior art. It
15 cannot even be critical, so to speak, to this --
16 to any patentability; would it not?
17 MR. ASHKENAZI: Your Honor, I think -- I
18 would tend to agree, but what I will say is I do
19 know there are exceptions and I haven't
20 technically researched all of those for this
21 situation, but I think I agree with what you're
22 saying.
23 JUDGE BRYSON: Okay. Very well.
24 Dr. Little, thank you for your
25 testimony, and you are excused.

1 THE WITNESS: Thank you. Nice to meet
2 you, Your Honor.
3 JUDGE BRYSON: Okay.
4 MR. ASHKENAZI: Can I submit some
5 exhibits, Your Honor?
6 JUDGE BRYSON: Of course.
7 And in the event that Mr. Aly has any
8 exhibits, he can do the same.
9 MR. ASHKENAZI: JTX-1, JTX-7, JTX-21,
10 JTX-50, JTX-51, JTX-67, JTX-71, JTX-74, JTX-93,
11 JTX-105, JTX-112, JTX-114, JTX-115, and then a
12 couple more, JTX-3, JTX-5, JTX-9, JTX-11, JTX-13,
13 JTX-14, and JTX-15.
14 JUDGE BRYSON: All right.
15 MR. ALBANO: Okay.
16 MR. ALY: No objection, Your Honor.
17 JUDGE BRYSON: Let me see, did you get
18 all of those?
19 MR. ALBANO: Yeah.
20 JUDGE BRYSON: Okay.
21 MR. ALY: To add to those from
22 defendants, JTX-113, JTX-84, DTX-191 --
23 MR. ALBANO: Sorry, one second. Okay.
24 MR. ALY: -- DTX-193, JTX-43.
25 JUDGE BRYSON: Okay. Did you get the

1 DTXs and the JTXs?
2 MR. ALBANO: Yes.
3 MR. ASHKENAZI: No objections,
4 Your Honor.
5 JUDGE BRYSON: No objections to either
6 one?
7 MR. ALY: Yes, Your Honor.
8 JUDGE BRYSON: They'll all be admitted.
9 (Exhibit Nos. JTX-1, JTX-7, JTX-21,
10 JTX-50, JTX-51, JTX-67, JTX-71, JTX-74, JTX-93,
11 JTX-105, JTX-112, JTX-114, JTX-115, and then a
12 couple more, JTX-3, JTX-5, JTX-9, JTX-11, JTX-13,
13 JTX-14, and JTX-15, JTX-113, JTX-84, DTX-191,
14 DTX-193, and JTX-43 were offered and admitted.)
15 MR. ASHKENAZI: Your Honor, I have one
16 other point.
17 JUDGE BRYSON: Yes.
18 MR. ASHKENAZI: I believe my colleague,
19 Mr. Hill, can address just a correction of two
20 exhibits that the parties have discussed.
21 JUDGE BRYSON: Okay.
22 MR. HILL: It's three exhibits,
23 Your Honor. So the parties, including the exhibit
24 wranglers, have conferred, and we inadvertently
25 did not move to admit PTX-33. So we would to move

1 to admit PTX-33. And JTX-39 and DTX-263 were
2 moved to be admitted, but we'd like to withdraw
3 those.
4 JUDGE BRYSON: They're withdrawn.
5 (Exhibit Nos. JTX-39 and DTX-263 were
6 withdrawn.)
7 MR. ALBANO: I'm sorry, can you say the
8 withdrawn again? 39?
9 MR. HILL: JTX-39.
10 MR. ALBANO: Okay.
11 MR. HILL: And DTX-263.
12 MR. ALBANO: Okay.
13 JUDGE BRYSON: Okay. And no objection
14 from either party?
15 MR. ALY: No objection, Your Honor.
16 JUDGE BRYSON: It will be done.
17 All right.
18 (Exhibit No. PTX-33 was offered and
19 admitted.)
20 MR. ALY: We have one -- I just wanted
21 to raise the parties had discussed one other
22 issue, and that is, personally identifiable
23 information in deposition transcripts that were
24 played in court. And we just wanted to raise with
25 Your Honor that we have conferred, and we can just

1 work with the reporting transcript to take out
2 individual's home addresses --
3 JUDGE BRYSON: Yes.
4 MR. ALY: -- by stipulation.
5 JUDGE BRYSON: You know, when they were
6 being read, I had exactly the same reaction, and
7 that's fine with me.
8 And I'm sure that Mr. Goldstein will be
9 able to do that.
10 MR. ASHKENAZI: Your Honor, I have one
11 further point --
12 JUDGE BRYSON: Yes.
13 MR. ASHKENAZI: -- which is really more
14 of a question for you, which is now moving into
15 post-trial briefing --
16 JUDGE BRYSON: Well, is that your last
17 witness?
18 MR. ASHKENAZI: That is my last witness,
19 Your Honor.
20 JUDGE BRYSON: Okay.
21 MR. ASHKENAZI: We close our rebuttal
22 case.
23 JUDGE BRYSON: Well, yeah, and I have a
24 few housekeeping matters to discuss as well. But
25 you're first, your question.

1 MR. ASHKENAZI: Well, I think our
2 question would be, Your Honor, is if there's a
3 specific time in which you believe closing
4 arguments would be helpful to you. Backing out of
5 that, when you would like briefing completed, the
6 parties can then confer on a schedule.
7 We didn't want to presume when
8 Your Honor would want something done or at what
9 point in time.
10 JUDGE BRYSON: There's no problem with
11 presumptions. I would like -- well, my own
12 schedule for the next several weeks is pretty
13 cluttered. I have two trials in July. So I don't
14 know how much I'm going to be able to squeeze in
15 during July.
16 What I would propose, and this goes to
17 my principal housekeeping issue, is that -- you
18 know, I think we can probably do this off the
19 record, actually, and allow Mr. Goldstein to take
20 a break here.
21 (Off the record at 3:07 p.m.)
22
23
24
25

1 DISTRICT OF COLUMBIA)
2
3 I, Matthew Goldstein, RMR, CRR, Notary
4 Public within and for the District of Columbia, do
5 hereby certify:
6
7 That I reported the proceedings in the
8 within entitled matter, and that the within
9 transcript is a true record of said proceedings.
10
11 I further certify that I am not related to
12 any of the parties to the action by blood or
13 marriage, and that I am in no way interested in the
14 outcome of this matter.
15
16 IN WITNESS WHEREOF, I have hereunto set my
17 hand this 27th day of June, 2024.
18
19
20 Matthew Goldstein, RMR, CRR
21
22
23
24
25

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