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 2 - AM

BEFORE JUDGE WILLIAM CURTIS BRYSON

Washington, D.C.

Tuesday, June 25, 2024

8:30 a.m.

Reported by: Matthew Goldstein, RMR, CRR

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PGR Petition – USP 12,115,255

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1 JUDGE BRYSON: Do we have a witness?
2 MR. ALY: Yes.
3 JUDGE BRYSON: There we are.
4 Good morning, Dr. Rabinow.
5 THE WITNESS: Good morning, Your Honor.
6 JUDGE BRYSON: You're still under oath.
7 THE WITNESS: Absolutely.
8 JUDGE BRYSON: Very good. All right.
9 MR. ASHKENAZI: May I begin, Your Honor?
10 JUDGE BRYSON: You may proceed.
11 MR. ASHKENAZI: Thank you.
12 JUDGE BRYSON: Continuing
13 cross-examination.
14 Whereupon,
15 BARRETT RABINOW, PH.D.,
16 being previously duly sworn or affirmed to testify to
17 the truth, the whole truth, and nothing but the truth,
18 was examined and testified as follows:
19 CROSS-EXAMINATION (CONTINUED) BY COUNSEL FOR THE
20 PLAINTIFF
21 BY MR. ASHKENAZI:
22 Q. And, Dr. Rabinow, you still have a
23 number of binders in front of you, if you need any
24 of the documents. If you can't find anything, let
25 me know, and I'll do my best to help you.

1 Dr. Rabinow, you recall explaining
2 yesterday that sodium oleate, if not protected and
3 exposed to the blood, can be hemolytic?
4 A. Yes.
5 Q. And you'll agree with me that CN '845
6 does not refer to oleic acid or sodium oleate;
7 correct?
8 A. Not explicitly.
9 Q. But Zhou, when discussing the optimized
10 formulation, expressly used oleic acid and not
11 sodium oleate; correct?
12 A. Yes.
13 Q. And neither CN '845 nor Zhou have any
14 in vivo testing; correct?
15 A. Correct.
16 MR. ASHKENAZI: Could we please bring up
17 JTX76.1.
18 BY MR. ASHKENAZI:
19 Q. And, Dr. Rabinow, this is the Fell
20 article. And you discussed this during your
21 direct examination yesterday; correct?
22 A. Yes.
23 Q. And you'll agree with me that Fell was
24 published in 2015?
25 A. Yes.

1 Q. So it is not prior art; correct?
2 A. It's a review of prior art, but it
3 itself was after the priority date.
4 Q. Okay. If we could please turn to JTX76
5 at page 4. And if we take a look on the left-hand
6 side, the column that starts under the heading
7 "phospholipid emulsifier," later on it says --
8 there's a paragraph starting, "smaller globule
9 size."
10 Do you see that?
11 A. Yes.
12 Q. And this is the paragraph that you were
13 referring to yesterday?
14 A. Correct.
15 Q. And you focused on the last sentence,
16 which states, In addition to the phospholipid
17 emulsifier, sodium oleate is added as a
18 stabilizing agent and glycerin is added as an
19 osmotic agent.
20 Do you see that?
21 A. Yes.
22 Q. And this is the sentence you were
23 referring to yesterday; correct?
24 A. Yes.
25 Q. And there's no citation in Fell for that

1 sentence; correct?
2 A. Correct.
3 MR. ASHKENAZI: You can take that down.
4 Thank you.
5 BY MR. ASHKENAZI:
6 Q. Dr. Rabinow, you'll agree with me that
7 POSAs were interested in NK-1 receptor antagonists
8 as a class and not just aprepitant; right?
9 A. Yes.
10 Q. And just to be clear, you never worked
11 with aprepitant; right?
12 A. Correct.
13 Q. And fosaprepitant is an NK-1 receptor
14 antagonist; right?
15 A. Yes.
16 Q. And intravenous fosaprepitant was sold
17 under the brand name Emend IV; correct?
18 A. Yes.
19 Q. And Emend IV is not simply an aqueous
20 formulation of aprepitant; correct?
21 A. Correct.
22 Q. Dr. Rabinow, rolapitant is an NK-1
23 receptor antagonist; correct?
24 A. Yes.
25 JUDGE BRYSON: What was that, I'm sorry?

1 MR. ASHKENAZI: I'm sorry, rolapitant.
2 JUDGE BRYSON: Rolapitant.
3 MR. ASHKENAZI: Pitant, I apologize.
4 R-O-L-A-P-I-T-A-N-T.
5 JUDGE BRYSON: Thank you.
6 MR. ASHKENAZI: And I hope I'm
7 pronouncing that correctly.
8 JUDGE BRYSON: That sounds good to me.
9 MR. ASHKENAZI: All right.
10 BY MR. ASHKENAZI:
11 Q. Rolapitant was reported to be safe and
12 effective following Phase 3 FDA clinical trials in
13 May 2014; correct?
14 A. Yes.
15 Q. And netupitant is another NK-1 receptor
16 antagonist; correct?
17 A. Yes.
18 MR. ASHKENAZI: And for the court
19 reporter, it's N-E-T-U-P-I-T-A-N-T.
20 BY MR. ASHKENAZI:
21 Q. And netupitant completed Phase 3
22 clinical trials and was FDA approved by
23 October 2014; correct?
24 A. I believe that's the date.
25 Q. And you would agree with me that you are

1 not aware of any prior art formulations with a
2 difficult molecule like aprepitant that was FDA
3 approved as an emulsion; correct?
4 A. Correct.
5 Q. And you discussed the Strickley review
6 article yesterday; correct?
7 A. Yes.
8 Q. And that was published in 2004?
9 A. Yes.
10 MR. ASHKENAZI: And if we could bring up
11 JTX-105 at page 26. And I want to focus in on
12 Table VIII.
13 BY MR. ASHKENAZI:
14 Q. Dr. Rabinow, you discussed Table VIII
15 during your direct examination yesterday; correct?
16 A. Yes.
17 Q. And to be clear, this is the Strickley
18 reference.
19 And Strickley includes a flowchart
20 titled, "Flow Chart of Suggested Order of
21 Solubilization Approaches for Injectable and Oral
22 Liquid Formulations."
23 Do you see that?
24 A. Yes.
25 Q. And looking at the left-hand side under

1 "Intravenous," if a POSA was seeing instability
2 with an emulsion, they would move on to liposomes;
3 correct?
4 A. Per this chart, yes.
5 Q. And, Dr. Rabinow, you wrote an article
6 in 2004 called, "Nanosuspensions in Drug
7 Delivery"; right?
8 A. Yes.
9 MR. ASHKENAZI: And if we could please
10 pull up JTX-183.
11 BY MR. ASHKENAZI:
12 Q. Dr. Rabinow, is this that article that
13 you published --
14 A. Yes.
15 Q. -- titled -- sorry.
16 A. Sorry, yes, it is.
17 Q. Thank you.
18 And in this article titled,
19 "Nanosuspension in Drug Delivery," you discuss the
20 formulation of compounds that are not soluble in
21 water; correct?
22 A. Yes.
23 Q. You called these compounds -- these
24 water insoluble compounds brickdust candidates;
25 correct?

1 A. I believe I did, yes.
2 Q. And for compounds that are soluble in
3 oil but not water, you said they could be
4 formulated as emulsions; right?
5 A. Yes.
6 Q. And emulsions are considered lipidic
7 systems; right?
8 A. Yes.
9 Q. And you then say that it --
10 JUDGE BRYSON: If I can interrupt.
11 MR. ASHKENAZI: Sorry.
12 JUDGE BRYSON: 183, what line is it?
13 MR. ASHKENAZI: It should be in the
14 binder.
15 JUDGE BRYSON: The big binder?
16 MR. ASHKENAZI: The big binder, yes.
17 JTX.
18 JUDGE BRYSON: JTX.
19 I see it. Yes, I got it. It was
20 hiding. Go ahead.
21 MR. ASHKENAZI: We don't make it easy on
22 you, Your Honor.
23 JUDGE BRYSON: No, you do.
24 I actually compliment the parties on
25 their -- the binders are much more orderly than I

1 ordinarily see. So I have no complaint with the
2 binders.
3 MR. ASHKENAZI: I will not take any
4 credit for that.
5 JUDGE BRYSON: Kudos to the paralegals.
6 BY MR. ASHKENAZI:
7 Q. So, Dr. Rabinow, just to bring us back,
8 I think you just agreed, but emulsions are
9 considered lipidic systems; right?
10 A. Well, they contain both water and oil.
11 They're not just lipidic.
12 Q. I'll rephrase my question.
13 You would consider an emulsion a lipidic
14 system; correct?
15 A. I guess it depends on the context in
16 which you're using it. So I'm not clear.
17 Q. Sure. In the context of your article --
18 and I'll pull up -- if we could go to page 8, you
19 see the -- sorry, page 1.
20 On the left-hand side, you'll see a
21 heading, "What can nanosuspensions help?"
22 And the third line down, you'll see,
23 "although other lipidic systems, such as liposomes
24 and emulsions."
25 A. Yes.

1 Q. So with that in mind, in the context of
2 your article, you'll agree with me that emulsions
3 are considered lipidic systems?
4 A. Correct.
5 Q. Thank you.
6 And then in this article, you go on to
7 say that, "In contrast with lipidic systems,
8 nanosuspensions can be used to successfully
9 formulate compounds that are insoluble in both
10 water and oil"; is that right?
11 A. That's what it says here, yes.
12 Q. And you're stating here that you could
13 use nanosuspensions if you're dealing with a
14 compound that is insoluble in both water and oil;
15 right?
16 A. Yes.
17 Q. And in this article, you never mentioned
18 emulsions could be used for compounds that are
19 insoluble in both water and oil; correct?
20 A. I believe what I said was that if you're
21 dealing with a compound that could not be -- that
22 could not be formulated as an emulsion, then you
23 could consider a nanosuspension. I don't think I
24 ever said here, don't use emulsions for such
25 compounds.

1 Q. In your article, you do not reference
2 that emulsions can be used for compounds that are
3 both -- that are insoluble in both water and oil;
4 correct?
5 A. I don't make that explicit statement.
6 Q. And, in fact, it was your belief at the
7 time you wrote this article that emulsions would
8 not be used to formulate compounds that are
9 insoluble in both water and oil; correct?
10 A. That's probably fair.
11 Q. And just so we're clear, by the time you
12 wrote this article in 2004, the Washington
13 reference, JTX-113, and EP279, JTX-074, existed;
14 correct?
15 A. That's correct.
16 Q. And just so the record is clear,
17 Washington was dated 1996?
18 A. Correct.
19 Q. And EP279 was dated 1991; correct?
20 A. Correct.
21 Q. In its submission to the FDA, Fresenius
22 identified Cinvanti as the reference listed drug;
23 right?
24 A. Yes.
25 JUDGE BRYSON: Let me make sure that I

1 have the --
2 MR. ASHKENAZI: Sorry.
3 JUDGE BRYSON: This article, JTX-183,
4 was published in 2004; is that correct?
5 MR. ASHKENAZI: Yes.
6 JUDGE BRYSON: Okay.
7 BY MR. ASHKENAZI:
8 Q. In its submission to the FDA, Fresenius
9 identified Cinvanti as the reference listed drug;
10 correct?
11 A. Yes.
12 Q. And Fresenius explained to the FDA that
13 the formulation of their ANDA product is the same
14 as Cinvanti; correct?
15 A. Yes.
16 Q. And you're not aware of any evidence
17 that Fresenius considered pursuing a 505(b)(2)
18 filing for their aprepitant product; correct?
19 A. They were filing their drug as a generic
20 of aprepitant.
21 Q. My question is slightly different, but
22 I'll ask it again.
23 You're not aware of any evidence that
24 Fresenius considered pursuing a 505(b)(2) filing
25 for their aprepitant product; correct?

1 A. I'm not -- I thought it was a 505(b)(2),
2 but I could be wrong.
3 Q. Okay. Well, let me ask you this.
4 Are you familiar with 505(b)(2)
5 applications?
6 A. Yes.
7 Q. And are you familiar with a 505(b)(2)
8 application where Fresenius can try to change its
9 formulation compared to the reference listed drug?
10 A. No. If that's what you're asking, no,
11 they did not try to change it.
12 Q. And you realize that a 505(b)(2)
13 application is still a generic drug; right?
14 A. Yes.
15 Q. And just so we're clear, Fresenius did
16 not pursue a 505(b)(2) application; correct?
17 A. Correct.
18 Q. But Fresenius has pursued 505(b)(2)
19 applications in the past; correct?
20 A. I'm sure they have.
21 Q. As of 2014, Fresenius had experience
22 with pharmaceutical emulsions; correct?
23 A. Yes.
24 Q. And you are not aware of Fresenius
25 successfully developing a stable intravenous

1 formulation of aprepitant before September 19th,
2 2014; correct?
3 A. I'm not sure when they developed it. I
4 don't know when the experimental work was actually
5 done.
6 Q. So I just want to make sure we're clear.
7 We're talking about Fresenius now.
8 A. Yes.
9 Q. And are you aware of Fresenius ever
10 attempting to make a successful intravenous
11 aprepitant formulation before September 14th,
12 2014?
13 A. I'm not aware of it, but I'm not -- I
14 don't have access to everything that Fresenius
15 did.
16 Q. You did review Dr. Little's report in
17 this case; correct?
18 A. Yes.
19 Q. Okay. So you are aware that Fresenius
20 did submit a drug application for an injectable
21 fosaprepitant product by August 2014; correct?
22 A. Yes.
23 MR. ASHKENAZI: If we could please pull
24 up the '229 patent, JTX-1. And we're going to go
25 to page 15, which is Example 4.

1 Dr. Rabinow, you discussed Example 4
2 during your direct examination; correct?
3 A. Yes.
4 Q. And you'll agree with me that in
5 Example 4, crystals were observed in the
6 aprepitant emulsion of Example 4 of the
7 patents-in-suit within four days post preparation;
8 correct?
9 A. Yes.
10 Q. Now, the pH range of CN '845 was 6 to 8;
11 right?
12 A. Correct.
13 Q. And Example 4 of the patents-in-suit
14 used a pH of 7.0; correct?
15 A. Yes.
16 MR. ASHKENAZI: And, in fact, if we
17 could please pull that back up, just so we're
18 clear. We're looking at page -- JTX-1 at page 15,
19 which is Column 18, line 39.
20 BY MR. ASHKENAZI:
21 Q. You'll see it says, pH of 7; is that
22 correct?
23 A. Yes.
24 Q. And you'll agree that in Example 2 of
25 paragraph 22 of CN '845, it says that aprepitant

1 emulsion -- that aprepitant emulsion was adjusted
2 to 6.8 -- sorry, we'll pull that up so it's easier
3 for you to see.
4 MR. ASHKENAZI: Can we please pull up
5 JTX-71, which is CN '845. Go to page 15, which is
6 Example 2.
7 BY MR. ASHKENAZI:
8 Q. Dr. Rabinow, do you see that on the
9 screen?
10 A. Yes.
11 Q. And you'll agree with me that the pH of
12 Example 2 is adjusted to 6.8; correct?
13 A. Yes.
14 MR. ASHKENAZI: Now, if we could go to
15 Example 5, which is JTX-71 at page 16.
16 BY MR. ASHKENAZI:
17 Q. You'll agree with me that the aprepitant
18 emulsion contained in Example 5 of CN '845 had the
19 pH adjusted to 6.8; is that correct?
20 A. Yes.
21 MR. ASHKENAZI: And if we could go back
22 to Example 4 of the patent, JTX-1 at page 15.
23 BY MR. ASHKENAZI:
24 Q. Dr. Rabinow, you'll agree with me that
25 the pH that was used in Example 4 of the

1 '229 patent was set out right in the patent
2 specification; correct?
3 A. The relevant question is: What was the
4 pH relevant to the control Heron products? That's
5 the question that should be asked.
6 Q. I just -- I think your testimony is
7 clear, but I want to just make sure that the pH of
8 Example 4 was set out right in the patent
9 specification; correct?
10 A. Yes.
11 Q. And you understand that the examples of
12 the patent specification were created before the
13 patent application was submitted to the patent
14 office; correct?
15 A. Say that again.
16 Q. The examples that are in the patent
17 specification were conducted before the
18 application was actually filed with the patent
19 office; is that correct?
20 A. Example 4 was designed to address
21 questions by the patent examiner.
22 Q. That's your understanding, Dr. Rabinow?
23 A. Yes.
24 Q. And that's the understanding you've been
25 applying to this case; correct?

1 A. Yes.
2 Q. Okay. Can we please -- I want to turn
3 our attention to Example 5 now, which is on JTX-1,
4 page 16. So it's the next page, Dr. Rabinow. And
5 we'll -- it goes between the two pages. So I
6 apologize, it goes from pages 15 to 16.
7 Dr. Rabinow, you'll agree with me that
8 crystals were observed in the aprepitant emulsion
9 of Example 5 of the patents-in-suit within
10 four days post preparation; correct?
11 A. Yes.
12 MR. ASHKENAZI: Now, I'd like to, if we
13 can, keep Example 5 on the screen and also pull up
14 the Zhou reference, which is JTX-115 at page 1.
15 And so if we can, on the left-hand side,
16 we'd like Example 5. So we would need the full
17 example, which spans the next page, if possible.
18 And I'm going to focus in on the abstract of the
19 Zhou reference, JTX-115 at page 1.
20 BY MR. ASHKENAZI:
21 Q. Okay. So, Dr. Rabinow, I'm just going
22 to want to compare the formulation that's in
23 Example 5 of the '229 patent with the optimal
24 formulation in Zhou. Okay? If you need anything
25 more or we could help you, let me know.

1 You'll agree with me that Example 5 of
2 the '229 patent and the Zhou optimal formulation
3 both use 0.25 percent aprepitant; correct?
4 A. Yes.
5 Q. And you'll agree with me that Example 5
6 of the '229 patent and the Zhou optimal
7 formulation both use 2.5 percent egg lecithin;
8 correct?
9 A. Yes.
10 Q. And you'll agree with me that Example 5
11 of the '229 patent and the Zhou optimal
12 formulation both use 15 percent soybean oil;
13 correct?
14 A. Yes.
15 Q. And you'll agree with me that Example 5
16 of the '229 patent and the Zhou optimal
17 formulation both use 0.125 percent oleic acid;
18 correct?
19 A. Yes.
20 MR. ASHKENAZI: We could take that down.
21 Thank you.
22 THE WITNESS: If I could just comment,
23 it was my understanding that Ottoboni represented
24 to the patent office that Example 5 was supposed
25 to be an example of what was in CN.

1 From what you're saying now, yes, it
2 appears to be identical to what was in Zhou, but
3 he told the patent office that this was a
4 comparison to the CN patent. That's what he told
5 them. He didn't mention anything about Zhou.
6 BY MR. ASHKENAZI:
7 Q. And to be clear, Example 5, which we
8 just went through, was clearly in the patent
9 specification, correct, of the '229 patent?
10 A. Yes.
11 Q. Okay. Fresenius Kabi is a company that
12 makes emulsions; correct?
13 A. Yes.
14 Q. And Fresenius has the facilities to test
15 emulsions if they want to; right?
16 A. Yes.
17 Q. And you could have overseen a contract
18 lab to make emulsions; correct?
19 A. Yes.
20 Q. And you haven't offered any testing of
21 CN '845 in this case; correct?
22 A. Correct.
23 MR. ASHKENAZI: Your Honor, I have no
24 more questions at this time.
25 JUDGE BRYSON: Very well.

1 Redirect?
2 MR. ALY: Yes, Your Honor.
3 May it please the Court.
4 REDIRECT EXAMINATION BY COUNSEL FOR THE DEFENDANT
5 BY MR. ALY:
6 Q. Good morning, Dr. Rabinow.
7 A. Good morning.
8 Q. I'd like to start where counsel left off
9 with this -- pardon me, regarding Example 5 of the
10 '229 and '794 patents. And you were explaining
11 about what was submitted to the patent office.
12 I'd like to take a look at that.
13 MR. ALY: JTX-2.126. Let's go back a
14 page to JTX-2.125, just to confirm.
15 BY MR. ALY:
16 Q. Is this the declaration from
17 Dr. Ottoboni that we had discussed in direct
18 examination?
19 A. Yes.
20 MR. ALY: And let's go to the next page.
21 BY MR. ALY:
22 Q. And on page JTX-2.126, you see in
23 paragraph 7 --
24 MR. ALY: If we could call that out.
25

1 BY MR. ALY:
2 Q. And Example 7, what were you discussing
3 is what Dr. Ottoboni told the patent office about
4 the tests that were done?
5 A. Dr. Ottoboni said that the examiner had
6 identified Zhou, referring to the Chinese patent
7 CN 102-37-9845 as the primary reference in a
8 rejection.
9 In the nonfinal office action, he says,
10 Zhou describes oil -- referring again to the CN
11 patent, describes oil in water emulsions of
12 aprepitant and provides eight examples describing
13 preparation of aprepitant emulsions.
14 MR. ALY: Let's look at paragraph 9,
15 which spans the pages JTX-2.126 over to 127.
16 BY MR. ALY:
17 Q. And the second sentence where
18 Dr. Ottoboni is reporting to the patent office,
19 what did he tell the patent office were the
20 emulsions prepared according to the invention?
21 A. "Specifically, as summarized in Table 7
22 of the instant specification as filed, the
23 pharmaceutical aprepitant emulsions prepared as
24 described in Examples 1, 2, 3, and 6 were stable
25 at room temperature for at least 2 months. In

1 contrast, the aprepitant emulsions taught by Zhou
2 were not stable."
3 Q. And when the patent application and
4 declaration are referring to this "Zhou" by name,
5 what are they referring to?
6 A. They're referring to the Chinese patent
7 '845.
8 Q. Have you seen any declaration that
9 discusses or addresses what we're calling in the
10 trial the Zhou article?
11 A. No.
12 Q. So to be clear for the record, when
13 Dr. Ottoboni, as you pointed out in paragraph 7,
14 uses the word "Zhou," he's referring to CN '845?
15 A. That is correct.
16 Q. Now, in paragraph 9, two sentences
17 later, what does Dr. Ottoboni represent to the
18 patent office?
19 A. That he's comparing the Heron
20 Examples 1, 2, 3, and 6 to the CN patent examples.
21 Q. And what Dr. Ottoboni writes is, "Two
22 emulsion formulations which comprise the
23 ingredients taught by Zhou were prepared and are
24 described in Examples 4 and 5 of the instant
25 application."

1 How does that compare to what you were
2 testifying about?
3 A. It's identical to what I was saying.
4 Q. What would be the takeaway from a person
5 of ordinary skill in the art reviewing the
6 prosecution history about what was being disclosed
7 and represented?
8 A. That Thomas Ottoboni was comparing
9 Examples 4 and 5 as indicative of the CN '845
10 patent in comparison to the Heron Examples 1, 2,
11 3, and 6.
12 Q. In your review of the prosecution
13 history, did you see Heron ever tell the patent
14 office or the examiner that, in fact, Example 5
15 was representing a test of the Zhou article and
16 not CN '845?
17 A. No.
18 MR. ALY: Let's go to JTX-2.114.
19 BY MR. ALY:
20 Q. For context, 2.113, what we're looking
21 at is an applicant initiated interview summary.
22 Did you review that?
23 A. Yes.
24 MR. ALY: Let's look at the next page.
25

1 BY MR. ALY:
2 Q. And let's look through this document
3 together. If you see --
4 MR. ALY: And we can blow that up.
5 BY MR. ALY:
6 Q. First, the second paragraph is referring
7 to a summary of a discussion that was held. And
8 in the second paragraph -- the third paragraph,
9 Dr. Harlocker, that was the prosecution counsel,
10 wrote, advised that Example 4 in the specification
11 can be compared to the invention of Zhou.
12 What's your understanding of that?
13 A. That's Zhou referring to the CN '845
14 patent Zhou.
15 Q. And it appears the examiner sought
16 clarification regarding the examples.
17 What is your understanding of that
18 discussion?
19 A. He wanted to have an understanding of
20 the differences in -- between Example 4 of the
21 '229 specification versus the examples in the
22 CN '845 patent.
23 MR. ASHKENAZI: Objection, Your Honor.
24 Dr. Rabinow is not an expert in patent
25 prosecution. He's interpreting the prosecution

1 here. And there's no allegation of inequitable
2 conduct in this case.
3 JUDGE BRYSON: Well, given the context,
4 I think, it's -- I think it's reasonable for him
5 to testify about what he understands the language
6 to refer to. So I will allow this. Although,
7 we're getting -- you know, I sense where you're
8 going, and I think that there's probably not a
9 whole lot more that you can get out of this
10 witness.
11 If you have someone who will testify
12 about the way an examiner would treat these
13 references, then that would probably be better
14 than having this witness trying to testify about
15 the meaning of the terms and the way that the
16 examiner was going about trying to elicit
17 information here. But I'll allow it for now.
18 Overruled.
19 MR. ALY: Thank you, Your Honor.
20 JUDGE BRYSON: How much more do you have
21 on this topic?
22 MR. ALY: Three questions.
23 JUDGE BRYSON: Okay.
24 BY MR. ALY:
25 Q. Because let's focus, Dr. Rabinow, not on

1 trying to reinterpret this. Let's just focus
2 on -- you know, Mr. Ashkenazi asked you in
3 cross-examination to compare an example from the
4 patent Example 5 to something that was in the
5 prior art.
6 And what I would like to know is what
7 did Heron tell the patent office about that same
8 comparison. Let's not interpret it. Let's just
9 find out what they said to the patent office. So
10 let's go into this document here.
11 What we have is what the examiner at
12 this paragraph, starting with Dr. Harlocker, the
13 examiner asked some questions.
14 What do you understand about those
15 questions, from the discussion that was being
16 held?
17 A. He was seeking clarification as to the
18 match between what was in CN '845 and what was in
19 the specification of the '229.
20 Q. Let's go two paragraphs down, "The
21 Examiner noted." And there's an explanation here
22 about what the examiner noted regarding Zhou,
23 that's the CN '845 reference, paragraphs 12 and
24 13.
25 And what was the examiner noting here?

1 A. The examiner noted that Zhou appeared to
2 indicate a particle size of 50 to 150 nanometers.
3 Dr. Ottoboni advised that this is a starting point
4 for an injectable composition per USP. And this
5 appears to refer to the size of the lipid droplet
6 in Zhou.
7 Q. Let's go to the next paragraph. That
8 will be the final paragraph of this portion.
9 It's, The Examiner asked if Applicant tried
10 something like Example 4 of the specification
11 using Applicant's method as opposed to Zhou's.
12 What did Heron tell the patent office in
13 this interview?
14 A. He said, Dr. Ottoboni directed the
15 Examiner to Example 5 of the spec, which uses
16 oleic acid instead of oleate and which also uses
17 the lower amount of emulsifier as per Zhou.
18 Example 5 of the spec is prepared using the method
19 Applicant uses for examples according to their
20 claimed invention. The Examiner noted the lower
21 ratio of emulsifier to drug in Examples 4 and 5
22 when compared to the other examples. Per
23 Dr. Ottoboni, this is an important feature of the
24 invention.
25 Q. If this line, Example 5 of the

1 specification, is prepared using the method
2 applicant uses for examples according to their
3 claimed invention, who is Heron taking credit for
4 Example 5?
5 MR. ASHKENAZI: Objection, Your Honor.
6 At this point, he's asking -- well, first of all,
7 leading.
8 JUDGE BRYSON: No, he's asking who.
9 MR. ASHKENAZI: Right. And he's
10 implying --
11 JUDGE BRYSON: He can come up with any
12 answer.
13 MR. ASHKENAZI: He's implying the answer
14 in the question. But I'll withdraw it,
15 Your Honor. That's all right.
16 JUDGE BRYSON: No, I think I'll let this
17 continue at this point. We are getting pretty far
18 away from this particular witness' expertise.
19 He's now reading a patent prosecution history and
20 interpreting it. I'm not sure how far we can go
21 with this witness on that subject, but I'll allow
22 this question.
23 BY MR. ALY:
24 Q. Do you want me to repeat the question,
25 Dr. Rabinow?

1 A. Yes.
2 Q. The question is: Who is Heron saying --
3 who is Heron taking credit for the Example 5 of
4 the specification is prepared using the method
5 applicant uses for examples according to their
6 claimed invention?
7 A. Example 5 is purported to represent the
8 CN '845 patent procedures.
9 Q. And in terms of the -- so let's just go
10 from the prosecution history to the implications
11 of CN '845.
12 MR. ALY: Let's look at JTX-71. Looking
13 at JTX-71.14, Example 1 is in paragraph 19 and
14 spanning to the next page, .15.
15 BY MR. ALY:
16 Q. The focus I'd like to ask about now is
17 the step of pH adjustment where CN -- CN '845 in
18 Example 1 reported the pH was adjusted to 7.2.
19 And you discussed that on direct and cross.
20 What was used to adjust the pH?
21 MR. ASHKENAZI: Objection, Your Honor.
22 We're beyond the scope of the cross-examination.
23 JUDGE BRYSON: Mr. Aly.
24 MR. ALY: It was discussed about what
25 the pH adjusters were for all of the examples in

1 the patent.
2 JUDGE BRYSON: Yeah. Yeah, overruled.
3 I think this is within the scope.
4 MR. ASHKENAZI: Your Honor, just if I
5 may, we didn't ask what was adjusted. We didn't
6 discuss what was used to adjust it. We discussed
7 during the --
8 JUDGE BRYSON: The pH was adjusted.
9 MR. ASHKENAZI: -- what the pH -- that
10 it was adjusted.
11 JUDGE BRYSON: Right.
12 MR. ASHKENAZI: I believe this is going
13 to go into -- I'll withdraw the objection for now,
14 but I do believe this is going into a whole line
15 of questioning that is not -- that was never
16 discussed, which is what was used to adjust the
17 pH.
18 JUDGE BRYSON: Since pH was a subject of
19 the cross-examination, why is what was used to
20 adjust the pH not relevant to the question of the
21 differences in the pH?
22 MR. ASHKENAZI: If there's going to be
23 any new criticisms levied about what pH adjusters
24 should -- what was used to adjust the pH, that
25 would be a problem, because that wasn't raised

1 before.
2 But, again, Your Honor, I'll withdraw
3 the question. We'll see where -- we can see where
4 this goes. I just wanted to make clear what my
5 concerns are.
6 JUDGE BRYSON: I see. All right. Well,
7 let's indeed see where it goes. But I'm skeptical
8 that the nature of the cross-examination does not
9 invite discussion of the whole pH issue beyond
10 simply what specific pHs there were.
11 So you can -- if you have a problem down
12 the line, you can certainly raise it, but my
13 inclination is to think this is an area that's
14 legitimate to be explored on redirect.
15 So go ahead, Mr. Aly.
16 BY MR. ALY:
17 Q. Dr. Rabinow, what did CN '845 report was
18 used for adjusting the pH?
19 A. They didn't indicate the entity of the
20 pH adjuster.
21 Q. What would a POSA do?
22 A. A POSA knows how to adjust pH. He
23 has -- he is knowledgeable about preferred pH
24 adjusters, particularly in the case of emulsions.
25 Q. What do they use in Example 5 of the

1 patents that are asserted to adjust pH?
2 A. They used oleic acid.
3 Q. And in terms of pH adjustment, was the
4 range of the examples towards the alkaline or the
5 basic side -- or the acidic side, in the CN '845
6 reference?
7 A. In the -- I'm sorry, state your question
8 again.
9 Q. Yes. In the CN '845 patent, was the
10 range of pHs in the examples in the basic side or
11 the acidic side?
12 A. In CN '845, for the example -- all the
13 examples?
14 Q. Yes.
15 A. The examples, in terms of pH, ran from
16 6.8 to 8. So they were beyond the alkaline side,
17 primarily.
18 Q. If there was an addition of oleic acid
19 and the goal here is to make a pH that's on the
20 basic side, how would a POSA do that?
21 A. A POSA would -- instead of adding oleic
22 acid, they would simply add the sodium salt or
23 sodium oleate that would achieve a pH adjustment
24 and also get them to the alkaline side.
25 Q. There was a lot of discussion about

1 sodium oleate. And we'll go through the
2 references that Mr. Ashkenazi addressed.
3 My question is: Was it considered a big
4 deal in 2014 for a POSA to use sodium oleate in an
5 emulsion?
6 A. Not at all. I mean, there are prior art
7 references that indicate that it was -- oleate was
8 already used in commercialized emulsions.
9 Q. Let's start with the JTX-112. That's
10 the Wan reference. And looking at the first page,
11 that's the Wan application.
12 What was the publication date?
13 A. February 2011.
14 Q. And we'll go to JTX-112.35. You see on
15 the bottom right there's an Example 7. What is
16 Wan describing in Example 7?
17 What's the title of Example 7?
18 A. Well, "Emulsion Formulation Suitable for
19 Bolus and Slow Infusion Administration."
20 MR. ALY: Let's look at the next page,
21 JTX-112.36. And there's a Table 15 on the lower
22 left.
23 BY MR. ALY:
24 Q. There's a reference to a list of
25 materials that were used.

1 Do you know what compound 1 is within
2 the context of the Wan reference?
3 A. I believe it's rolapitant.
4 Q. And the Wan reference, as far as the
5 description of the approach they did, is that --
6 let's look at that in paragraph 338, above the
7 Table 15, still on the same page.
8 Paragraph 338 of the Wan reference
9 refers to, quote, The emulsion formulations
10 described below have the advantage of enhanced
11 retention of the drug in the hydrophobic core.
12 What does that mean?
13 A. That means that you are -- what they're
14 saying is that you're placing the drug molecule in
15 the oil droplet.
16 Q. And the next line says, "increased
17 droplet size compared to micellar formulation to
18 delay drug transfer/partitioning from the oil
19 droplets to the RBCs."
20 What does that mean?
21 A. That means that you're essentially
22 protecting the red blood cells by using an
23 emulsion, because you're sequestering the drug
24 molecule from the RBCs by placing it in the oil
25 globule of an emulsion as compared to a micellar,

1 and that would delay drug transfer from the oil
2 droplet to the red cells.
3 Q. Let's go where they're referring to the
4 parenteral emulsions a few lines down.
5 Wan reports, "Parenteral emulsions are
6 used to carry poorly water-soluble drugs and
7 typically constitutes small oil droplets in an
8 aqueous solution."
9 How would a POSA understand that?
10 A. He would understand that by saying
11 that -- by understanding that a parenteral
12 emulsion consists of an oil phase that
13 accommodates the poorly water soluble drug in
14 small oil droplets, which are present as a
15 discrete phase distributed throughout a continuous
16 aqueous solution, which is suitable for injection.
17 Q. The next sentence in Wan, paragraph 338,
18 reports, "The preferred emulsifier is selected
19 from those regarded as safe to use for parenteral
20 administration."
21 What does that mean?
22 A. Well, if you're making -- if you're
23 going to use an emulsifier in an injectable, you
24 want it to be safe for injections.
25 Q. And what did they use in Wan and select

1 as the preferred emulsifier?
2 A. Purified egg lecithin is the most
3 preferred, as they indicate.
4 Q. What else did Wan add or consider for
5 the formulation?
6 A. Well, he added oleic acid or sodium
7 oleate.
8 Q. And in this section that we're looking
9 at in paragraph 338 that starts with the phrase,
10 "Parenteral emulsions are used," is it your
11 understanding that's describing the invention or
12 is it describing the state of the art?
13 A. It's state of the art.
14 Q. Why do you say that?
15 A. Because it was understood as of this
16 time that emulsions, which consist of an oil, that
17 the oil could accommodate a poorly water-soluble
18 drug provided that the drug was soluble in oil.
19 And that's what this appears to be saying. It
20 says, "are used to carry poorly water-soluble
21 drugs and typically constitute small oil droplets
22 in an aqueous solution."
23 Q. And as far as the oil phase, let's read
24 that portion. Medium chain -- I believe you
25 pronounced it -- (Myglyol) and long chain

1 triglycerides may also be added.
2 What is that showing?
3 A. That shows that you can add
4 triglycerides of either medium chain length or
5 long chain length.
6 Q. And although the sentence is describing
7 what may also be added, what did Wan actually do?
8 A. He, in fact, used medium chain length
9 oils.
10 Q. And whether they were used alone or in
11 combination, were there any examples in Wan that
12 used a formulation without Miglyol?
13 A. I believe for those that involved egg
14 lecithin, I believe they all used Miglyol.
15 Q. And what was the issue that you were
16 addressing on cross-examination regarding Miglyol
17 in the case that sodium oleate or oleic acid is
18 also used?
19 A. Right. So egg lecithin has a particular
20 chain length, 16 carbons long. It functions as
21 a -- in an optimal way as an emulsifier coating,
22 provided all the molecules are similar so that
23 they can all pack together. If you disrupt the
24 regularity of the packing, you disrupt the
25 efficiency of the membrane coating.

1 In the context of adding oleate, oleate,
2 as we've seen in my cross, was shown to have the
3 effect of causing hemolysis. And the reason for
4 that is that it was inadequately sequestered in
5 the emulsifier envelope of the emulsions that Wan
6 was making. And the reason for that is because of
7 the addition of middle chain oils that disrupted
8 the regularity of packing of the egg yolk
9 phospholipid.
10 So despite the fact that they state that
11 they used egg yolk phospholipid, it's true they
12 did, but they also used Miglyol, which would have
13 interfered with its function to adequately isolate
14 the oil globules and to sequester the sodium
15 oleate, thereby allowing it to attack the red
16 cells.
17 JUDGE BRYSON: And what is the mechanism
18 by which the mid-length -- what did you refer to
19 them -- middle chain oils have the effect of
20 disrupting the packet?
21 THE WITNESS: So envision, if you will,
22 soldiers on parade. If you want to give a nice
23 presentation to the president of the country, they
24 all have the same height. Now imagine you have
25 some soldiers which are 6-foot 8 interspersed with

1 some that are 4-foot 11. All right? It doesn't
2 look nice. They don't pack well. You don't have
3 everyone having the same shoulder length, that
4 kind of thing.
5 It's similar to regularity of packing.
6 That's what you're trying to -- you're almost
7 making a crystalline coat. You're not actually
8 having a crystal that precipitates at a solution,
9 but people refer to crystallinity of the
10 emulsifier coat which is hard and almost nearly
11 impenetrable. And to the extent that they all
12 have the same length, they all fit together well,
13 then they can do their function more
14 expeditiously.
15 JUDGE BRYSON: So the -- again, middle
16 chain, is that what you referred to for the oils?
17 THE WITNESS: That is correct.
18 JUDGE BRYSON: The middle chain oils
19 interspersed in cells among the other molecules.
20 THE WITNESS: Exactly. Why --
21 JUDGE BRYSON: And that -- it leads to,
22 for a lack of a better term, leakage.
23 THE WITNESS: Yes. So the middle chain
24 oils have a length of 8 carbon, something like
25 that, and because they're lipophilic, they're

1 going to naturally associate with the fatty chains
2 of the egg yolk lecithin.
3 JUDGE BRYSON: Right.
4 THE WITNESS: But the egg yolk lecithin
5 has fatty chains that are 16 carbons long because
6 they consist of oleic acid. So now you have,
7 essentially, ropes of 8 carbons long, attempting
8 to interpolate with ropes that are 16 carbons
9 long. So you can imagine that there's not -- that
10 you're going to be disrupting the regularity of
11 the packing.
12 JUDGE BRYSON: Okay. Thank you.
13 BY MR. ALY:
14 Q. And, Dr. Rabinow, what is the
15 significance, if any, of egg yolk lecithin having
16 oleic acid in it?
17 A. The egg yolk lecithin acts as a
18 stabilizer for the emulsifier coating, and it
19 confers additional stability on the oil globules.
20 Q. And does egg yolk lecithin have as one
21 of its constituents oleic acid?
22 A. Yes.
23 Q. In terms of the formulation reported by
24 Wan and the approach shown in paragraph 338, let's
25 look at the last sentence, "Glycerin may be used

1 as a tonicity adjustor and ethanol may be used as
2 a co-solvent/solubilizer for the lecithin and
3 drug."
4 What is that showing to a POSA?
5 A. That shows to a POSA that Wan almost is
6 prior art for what was being done in CN, in the
7 sense that glycerin was used both in Wan and
8 subsequently in CN as a tonicity adjuster, and
9 ethanol was used as a cosolvent for the lecithin
10 and drug compound.
11 Q. How does the disclosure in Wan,
12 paragraph 338, regarding the state of the art for
13 emulsions for poorly soluble drugs compare to the
14 opinions that you were giving in court yesterday?
15 A. Wan mentions that he -- well, Wan
16 mentions that he's considering applications to
17 NK-1 antagonists, number one. He is talking about
18 long chain soybean oil triglycerides, as well as
19 egg yolk lecithin emulsions that could be used to
20 formulate successful injectables for that.
21 He's mentioning glycerin here as an
22 osmotic agent that can also be used. And he's
23 also mentioning the use of ethanol, specifically
24 as a solvent for lecithin and the drug compound,
25 similar to what CN used.

1 Q. When we were referring to Wan, you had
2 discussed the hemolysis portion, but did Wan also
3 contain stability information for the formulation?
4 A. Wan reported stability information for
5 many, not all, of his formulations.
6 MR. ALY: Let's look at JTX-112.40,
7 paragraph 371.
8 BY MR. ALY:
9 Q. In Wan, there is a discussion in the
10 first sentence, "Microfluidization processing thus
11 provided physically stable emulsion formulations."
12 Was that including formulations with and
13 without sodium oleate?
14 A. I believe so.
15 Q. And in terms of the Wan reference, did
16 they further analyze the stability of several
17 formulations, including those with sodium oleate
18 and without sodium oleate?
19 A. Yes.
20 Q. Now, as far as the droplet size, what
21 was reported for the droplet size that could be
22 achieved by that process in paragraph 371?
23 A. It says, The present invention relates
24 to emulsion formulations of Formula I having
25 droplets with median diameters of about

1 500 nanometers or less and a D90 of about 600 or
2 less.
3 Q. And separately from that, there is
4 conclusions about hemolysis on the bottom of
5 paragraph 371 that Wan is also reporting, to be
6 fair, "non-hemolytic results were reproducibly
7 achieved using phospholipid based emulsion
8 formulations for both bolus and slow infusion
9 administration."
10 What is that teaching?
11 A. That teaches you that you can use
12 phospholipid based emulsions without incurring the
13 adverse events of hemolysis.
14 Q. Now, did Wan do any patient tests in
15 humans for whether or not there was hemolysis in a
16 clinical setting?
17 A. No.
18 Q. What did Wan do?
19 A. He used rodents and looked at their
20 urine and essentially quantified --
21 JUDGE BRYSON: I'm sorry, he used what
22 did you say?
23 THE WITNESS: Rodents.
24 JUDGE BRYSON: Rodents. I see. All
25 right.

1 THE WITNESS: And he quantified,
2 essentially, the intensity of red coloration as
3 indicative of hemoglobin that was present in the
4 urine.
5 BY MR. ALY:
6 Q. Now, in terms of the patents that are in
7 this case, the '229 patent and '794 patent, in
8 those specifications, is there any testing --
9 JUDGE BRYSON: If I could interrupt. I
10 take it that the presence of hemoglobin in the
11 urine at a high level would be indicative of
12 hemolysis?
13 THE WITNESS: Exactly. Precisely, yeah.
14 BY MR. ALY:
15 Q. And in terms of the asserted patents,
16 the '229 patent and '794 patent, do those patent
17 specifications show any testing of hemolysis?
18 A. No.
19 Q. One way or the other?
20 A. No.
21 Q. Do they do any rodent tests for
22 hemolysis in the asserted patent specifications?
23 A. No.
24 Q. Do the claims have any limitation or
25 restriction about hemolysis happening or not

1 happening?
2 A. No.
3 Q. In terms of the use of sodium oleate,
4 what was clinically understood about whether it
5 was safe for use in an emulsion formulation?
6 A. It was understood to be safe because it
7 was a constituent of commercialized emulsions,
8 numerous emulsions, as of that date.
9 Q. Let's look at JTX-88, which is the Jumaa
10 reference that you mentioned.
11 On the top, let's make sure, what is the
12 Jumaa reference?
13 A. The Jumaa reference is a publication
14 that appeared in 2000 in the European Journal of
15 Pharmaceutical Sciences, entitled, "Lipid
16 emulsions as a novel system to reduce the
17 hemolytic activity of lytic agents: mechanism of
18 the protective effect."
19 Q. All right. And let's do -- and what was
20 the date of publication or the year?
21 A. 2000.
22 Q. Let's look at page JTX-88.2. On the
23 bottom right is a "Results" section.
24 And what -- on the bottom, the Jumaa
25 article reports, Concentrations from .03 to

1 .05 percent are generally used in commercial
2 parenteral emulsions.
3 What are they talking about is generally
4 used in commercial parenteral emulsions?
5 A. Sodium oleate.
6 Q. In the next sentence, because people --
7 I'm sorry, in the next sentence, Jumaa reports
8 that it could be predicted that these preparations
9 will also lead to complete hemolysis, as the
10 sodium oleate concentrations are 10 times higher
11 than other tests.
12 What is that saying to a POSA?
13 A. That's saying that if you have -- if you
14 put sodium oleate in an aqueous solution, it is
15 observed to be hemolytic. And the concentrations
16 that are used of sodium oleate in commercial
17 parenteral emulsions are ten times higher than the
18 ones that are observed to be hemolytic in strictly
19 aqueous solutions.
20 Q. And for emulsions, the next sentence
21 says, "Surprisingly, a different behavior was
22 observed in emulsions."
23 What does that mean?
24 A. That means that emulsions appear to be
25 protective and prevent the lytic effect of oleate

1 upon red cells.
2 Q. How does what Jumaa is reporting
3 regarding the use of sodium oleate in commercial
4 formulations to your opinions?
5 A. It supports it. It's essentially saying
6 even though you have sodium oleate, which is
7 observed to break apart red cells in just an
8 aqueous solution, if you now consider an emulsion,
9 you no longer observe hemolysis. There seems to
10 be a protective effect conferred.
11 Q. And you were discussing with the Court
12 how that lays out in terms of different types of
13 components.
14 MR. ALY: Let's look at page JTX-88.5,
15 Figure 5. And we'll need the key underneath
16 Figure 5, Mr. Haw.
17 BY MR. ALY:
18 Q. Dr. Rabinow, in Figure 5, Jumaa is
19 describing -- well, what is he describing, using
20 the code words here, I think there's Ery, M, and
21 OD?
22 A. Right. So he is -- he has a cartoon
23 here where he is showing various scenarios. He's
24 showing an A that you have a scenario just the
25 lytic agent, that's the oleate, freely available

1 in an aqueous solution, freely available to attack
2 an erythrocyte, leading to hemolysis.
3 In the next one, he's showing that if
4 you add a micelle, it's going to compete with the
5 erythrocyte for the available oleate and
6 sequester, essentially, the oleate into the
7 micelle, and thus the erythrocyte would have been
8 spared and remains intact.
9 And to the extent that you -- if you
10 have excess amount of lytic agent, again, and you
11 exceed the capacity of the micelle to sequester
12 it, well, then it is available to attack the
13 erythrocyte. But then, again, if you add a lipid
14 emulsion in D, that has a high amount of oil
15 phase, resulting again in a decrease of the free
16 amount of lytic agent and, consequently, reduced
17 hemolysis.
18 Q. For the record, what is an erythrocyte?
19 A. It's a red cell.
20 Q. What is a micelle?
21 A. A micelle is a regular array of
22 surfactants, in this case lecithin, that form
23 globules in solution.
24 Q. And the oil droplet, how does that
25 compare to what we've been discussing in this

1 case?
2 A. It is equivalent to an emulsion
3 particle.
4 JUDGE BRYSON: An emulsion?
5 THE WITNESS: An emulsion particle.
6 JUDGE BRYSON: Particle.
7 MR. ALY: Let's go to JTX-88.1, the last
8 piece of the Jumaa reference.
9 JUDGE BRYSON: Is what's going on here
10 simply that the addition of the oil droplet
11 increases the capacity for the absorption of the
12 lytic agent?
13 THE WITNESS: Yes.
14 JUDGE BRYSON: All right.
15 BY MR. ALY:
16 Q. And why is the emulsion -- according to
17 the Jumaa and your understanding, why would a POSA
18 consider an emulsion appropriate for using sodium
19 oleate in as many commercial products as use that
20 combination?
21 A. You're asking why sodium oleate is used
22 in commercial lipid emulsions?
23 Q. I'm asking why would a POSA -- would a
24 POSA consider it acceptable to use sodium oleate
25 in an emulsion composition?

1 A. Yes.
2 Q. And let's look at the -- does Jumaa also
3 explain why that might be happening, that the
4 emulsion could have that?
5 A. Yes. Yeah, he offers the explanation
6 that the --
7 Q. And let's take a look at that in the
8 abstract. If we could look at the
9 next-to-the-last -- I think it's the
10 third-to-the-last sentence. This is on JTX-88.1.
11 In the abstract, it's referring to the
12 sentence, "As an explanation for these effects it
13 is proposed that the lytic agent is either
14 incorporated into the lipophilic core or
15 intercalates between the emulsifier molecules at
16 the interface."
17 What does that mean?
18 A. That means that the oleate associates
19 with emulsifier molecules at the interface of the
20 oil globule and water or goes into the bulk oil
21 phase itself. There's a -- essentially what
22 they're saying is that if you have an emulsion, it
23 acts as a reservoir to absorb the lytic agents and
24 keep it sequestered in that system, so as to
25 reduce the free concentration of oleate and

1 thereby protect the red cells.
2 Q. And what would a POSA's understanding be
3 for intercalate? What does that mean?
4 A. Associate with. It's like putting your
5 fingers together like this (indicating),
6 intercalate.
7 MR. ALY: The record will reflect the
8 witness is merging his fingers together in between
9 one another.
10 BY MR. ALY:
11 Q. Okay. Let's go to another reference and
12 another topic.
13 The discussion during cross-examination
14 was about terminology at some points,
15 microemulsion, emulsion. And one of the
16 references that was raised was Von Corswant,
17 JTX-110.
18 What is the Von Corswant reference?
19 MR. ASHKENAZI: Objection, Your Honor.
20 We did not discuss the Von Corswant reference at
21 all during cross-examination.
22 JUDGE BRYSON: No, but you did get into
23 the whole question of microemulsions and
24 emulsions. I think this is fair redirect.
25 Go ahead.

1 MR. ALY: And I'd also like -- okay.
2 JUDGE BRYSON: Assuming that this has
3 something to do with microemulsions and emulsions?
4 MR. ALY: Yes, Your Honor.
5 But I simply would also add for the
6 record that the deposition portions they played,
7 one of them on page 330 of the transcript, was
8 about the same reference. So that's why I wanted
9 to make that addition.
10 Thank you, Your Honor.
11 BY MR. ALY:
12 Q. JTX-110, what is the publication date of
13 the Von Corswant application?
14 A. July 2001.
15 Q. And in terms of the discussion on
16 microemulsion, let's look at JTX-110.3.
17 MR. ALY: I'm going to look at the
18 paragraph, bottom left, paragraph 11. And as much
19 as of the right half as we can, please, Mr. Haw.
20 BY MR. ALY:
21 Q. And during the cross-examination, the
22 discussion was about the classical definition of
23 "microemulsion."
24 What did you mean by that?
25 A. The classical definition of a

1 "microemulsion" is as stated here, that it is
2 thermodynamically stable and translucent as
3 opposed to the emulsions that we have been talking
4 about that look like milk.
5 Q. And in terms of the usage of the terms
6 "microemulsion" and "emulsion," what did
7 Von Corswant report he found, referring to the
8 EP258 application?
9 A. He found a preparation called an
10 oil-in-water microemulsion. However, he commented
11 that in that reference, the microemulsification is
12 achieved by using mechanical energy input; that
13 is, the droplet size reduction via
14 microfluidization.
15 And he comments that that -- therefore,
16 it's not a microemulsion because you're pumping
17 energy into the system. And it is also not a
18 single optically isotropic, which means you can
19 see through it, and thermodynamically stable
20 liquid solution.
21 Q. As of the state of the art, how was the
22 classical definition and the actual usage
23 compared?
24 A. At the time that the microemulsions came
25 on the scene, there were purists who would adhere

1 rigidly to the classical definition. There were
2 also many others who tried to use it, and they
3 were -- tend to overlap it and recognize that
4 there wasn't a clear distinction between the two.
5 And they recognized that there could be
6 times when -- and they referred to microemulsions
7 as emulsions and back and forth. So it was less
8 clear for another group of persons of ordinary
9 skill, if you will.
10 Q. And let's look at the references that we
11 were discussing regarding aprepitant.
12 What did CN '845 label the approach that
13 they were using?
14 A. They called it a microemulsion.
15 JUDGE BRYSON: Is it fair to say in this
16 context that there is a non-breaking continuum
17 between the microemulsion and the emulsion, such
18 that there is no point at which there is a clear
19 definition between the one and the other?
20 THE WITNESS: That's a very good
21 question. Certainly there are examples which are
22 clearly a microemulsion, and there are clear
23 examples which are clearly an emulsion. However,
24 there are also intermediate forms that appear to
25 resemble and have features of both, which are

1 neither. They're more fluid. So that's a very
2 interesting question, actually.
3 JUDGE BRYSON: All right. Thank you.
4 BY MR. ALY:
5 Q. And in terms of that formulation
6 approach with the same lead author in the Zhou
7 article, what did the Zhou article -- what word
8 did they use to describe the composition?
9 A. They called what they made emulsions.
10 Q. In terms of procedures throughout the
11 two and the components that were used, how did
12 they compare to one another as between CN '845 and
13 Zhou?
14 A. They were identical. They both used
15 high pressure homogenization.
16 Q. Let's change to another subject, and
17 that is the subject that was raised yesterday
18 about the Washington reference and what its
19 teachings included. It's JTX-113.
20 This is the Washington reference;
21 correct?
22 A. Yes.
23 MR. ALY: Let's go to 113.9. And there
24 is a Table 1 that we should look at on the left
25 side, please.

1 BY MR. ALY:
2 Q. Counsel in cross-examination identified
3 emopamil but didn't show this table.
4 What category of drug, what type, did
5 Washington classify emopamil?
6 A. He classified it as a Type 2A.
7 Q. What is a Type 2 article within the
8 Washington description?
9 A. A Type 2 article is a drug which is
10 soluble in lipid by itself. So it's soluble in
11 oil.
12 Q. What is the significance of emopamil
13 being a Class 2 drug versus aprepitant being a
14 Class 3 drug?
15 A. So it's a lot easier to put emopamil
16 into a conventional emulsion, if you will, which
17 most people would recognize as being able to
18 solubilize a lipid soluble drug that would go
19 into -- completely into the oil core.
20 And, furthermore, to be able to do that
21 with a 1.2 percent, a relatively small amount of
22 emulsifier, because that's the conventional amount
23 of emulsifier that's used to make standard soybean
24 oil egg phosphatide emulsions.
25 Aprepitant, on the other hand, is a

1 Class 3 drug, which means it's soluble neither in
2 oil nor in water. And for that reason, as
3 Washington goes on to state, you need a lot more
4 emulsifier to be able to accommodate that, both
5 particularly to be able to increase the surface
6 area of the interface between the oil and the
7 water to be able to accommodate the drug, because
8 that's the only place where the drug can reside.
9 It can't reside in the bulk phases. So it must
10 reside in the interface. So you need more
11 emulsifier to create more interface.
12 Q. Let's transition to the last subject and
13 my last line of questions is to JTX-183. That was
14 discussed on cross-examination. That's your
15 article.
16 What was the title of your 2004 article,
17 JTX-183?
18 A. "Nanosuspensions in Drug Delivery."
19 Q. Why were you writing about
20 nanosuspensions?
21 A. We were developing nanosuspensions as a
22 drug delivery platform for our pharmaceutical
23 partners. We were trying to focus on that and to
24 indicate where you might consider using it,
25 mindful of the fact that the Pharma was developing

1 a lot of water insoluble drugs at the time.
2 Q. Let's look to the next page. There's a
3 Figure 1. This is JTX-183.2, top half.
4 And counsel had asked during
5 cross-examination if you ever addressed emulsions
6 in your article. Did you?
7 A. Yes.
8 Q. In Figure 1, there's a text underneath
9 Figure 1, with a legend. And it reports, quote,
10 If there is adequate solubility in lipidic systems
11 the micelles, emulsions and so on are tried.
12 What did you mean by that?
13 A. You -- if you had an adequate degree of
14 solubility in oils for the drug of interest, then
15 you would try this class of formulation approaches
16 involving micelles, emulsions, et cetera.
17 Q. How does that comport with your opinions
18 in this case?
19 A. It agrees completely. I have said that
20 if there is a simpler approach that can be used,
21 by all means do it. My article does not say,
22 don't use emulsions for difficult molecules. It
23 says, if emulsions do not work, then you try
24 nanosuspensions.
25 Q. And what information did a person of

1 ordinary skill in the art have in 2014
2 specifically about aprepitant that would affect
3 their analysis --
4 A. Well, by 2014, they had the CN '845
5 patent that said, yes, you can use an oil-in-water
6 emulsion to formulate aprepitant. So clearly they
7 went well beyond what I was aware of in 2004. I
8 just didn't have visibility to what would happen
9 ten years hence when I wrote this article.
10 MR. ALY: No further questions,
11 Your Honor.
12 JUDGE BRYSON: Very well.
13 There has been a pretty long range in
14 redirect. So if you have specific areas,
15 Mr. Ashkenazi, that you would like to recross on,
16 I will allow it.
17 MR. ASHKENAZI: Just some questions,
18 Your Honor.
19 JUDGE BRYSON: Very well.
20 MR. ASHKENAZI: I hesitate to say a few
21 again.
22 JUDGE BRYSON: Oh, yes, avoiding the
23 word "few." Very well.
24
25

1 RECROSS-EXAMINATION BY COUNSEL FOR THE PLAINTIFF
2 BY MR. ASHKENAZI:
3 Q. Dr. Rabinow, the Zhou article was an
4 optimized formulation following the Zhou CN '845
5 patent; correct?
6 A. I guess I don't understand some of
7 the -- there's a number of concepts that I don't
8 understand. Okay. It was opti- -- Zhou had an
9 optimized formulation, but it was optimized per
10 his criteria, which was centrifugal equilibrium.
11 So that part is correct.
12 I don't know when he did his work that
13 resulted in the Zhou article versus what was done
14 in CN '845. I know that one appeared to come
15 after the other, but I don't know when the work
16 was actually done.
17 Q. You'll agree with me that the Zhou
18 article is a formulation that's within CN '845;
19 correct?
20 A. Yes.
21 MR. ASHKENAZI: If we could please pull
22 up JTX-112.
23 BY MR. ASHKENAZI:
24 Q. This is the Wan reference that you
25 discussed.

1 A. Yes.
2 Q. And if we could turn to page 36. So
3 it's JTX-112 at 36. I want to focus on Table --
4 well, before we do that, let me just ask a quick
5 question.
6 You referred to Miglyol; right?
7 A. Yes.
8 Q. And how did you refer -- what did you
9 say Miglyol is?
10 A. It's a middle chain, middleweight chain
11 triglyceride.
12 Q. And you're saying that that interacts --
13 that that is dispersed within the phospholipids?
14 A. I said that it interferes with the
15 phospholipid membrane.
16 Q. Okay. So it's on the membrane?
17 A. The phospholipid sits on the interface
18 between the oil globule and the water.
19 Q. Okay.
20 A. Directly underneath the lecithin
21 membrane, you have your bulk oil. So there is
22 going to be interaction and intercalation between
23 the fatty acids of the Miglyol with the fatty
24 acids of the emulsifier at that point.
25 Q. So if we could just be clear, if we

1 could look at Table 15, please. This is of the
2 Wan -- this is on JTX-112, page 36.
3 We'll see Miglyol here is characterized
4 as a solubilizer; correct?
5 A. That's what it says.
6 Q. And I'll -- just for the record, I
7 didn't read the whole thing in. Miglyol is
8 described as MCT with a function
9 solubilizer/hydrophobic component; correct?
10 A. Yes.
11 Q. And so is soybean oil listed as a
12 solubilizer and hydrophobic component; correct?
13 A. Yes.
14 Q. And over here, the lecithin is listed as
15 an emulsifier; correct?
16 A. Yes.
17 Q. Now, you'll agree with me that Jumaa
18 discussed emulsions; correct?
19 A. Yes.
20 Q. And you'll agree with me that Jumaa
21 determined that sodium oleate at 0.3 percent in an
22 emulsion caused a hemolytic effect; right?
23 A. Jumaa was using a different system. He
24 was not using egg yolk lecithin. He was using soy
25 lecithin, which is a different entity. And he was

1 also using a very low level of emulsifier. Jumaa
2 goes on to say that if you want to reduce further
3 the amount of hemolysis, increase the level of
4 emulsifier, which is what Zhou and CN did.
5 Q. Dr. Rabinow, just so we're clear, in
6 Jumaa, sodium oleate at 0.3 percent caused
7 hemolytic effect; correct?
8 A. With soybean lecithin.
9 Q. And that was a system called S75, was
10 the S lecithin used -- sorry, withdrawn.
11 A. Soy lecithin.
12 Q. S75 was the soy lecithin that was used
13 in that article; correct?
14 A. Yes.
15 Q. And the emulsions in Jumaa did not use
16 Miglyol that we saw in Wan; correct?
17 A. Okay. The soy lecithin has double bonds
18 in their fatty acid chains. Egg lecithin does
19 not. What does that mean? That means that the
20 egg lecithin fatty acid chains pack more easily
21 and in a more regular manner to thus effect a more
22 effective membrane.
23 Soy lecithin has got double bonds in it,
24 which means that this disturbs the regularity of
25 packing of the fatty acid tails. So the net

1 effect is the same as if you were to add Miglyol.
2 Miglyol disturbs the egg lecithin
3 packing, because the chain length is different.
4 Whereas, soy lecithin does not have as effective
5 an emulsifier coating because its chains are
6 unsaturated, and that means that they can't fit
7 together well, right.
8 They don't go together as well as my
9 fingers. It's like trying to bend the fingers of
10 one hand and trying to interlock them with the
11 fingers of another hand.
12 Q. Dr. Rabinow, just so we're clear,
13 though, the emulsions in Jumaa did not contain
14 Miglyol; correct?
15 A. They did not contain Miglyol.
16 Q. And at your deposition, I had asked you,
17 do you know how S75, the phospholipid used in
18 Jumaa --
19 JUDGE BRYSON: We have an objection.
20 MR. ALY: The deposition is being used
21 for substance and not impeachment.
22 MR. ASHKENAZI: Your Honor --
23 JUDGE BRYSON: Let's find out what --
24 well, first of all, if you're going to introduce
25 the deposition or question him about the

1 deposition, let's do it -- according to oil, let's
2 go through the process of asking him if he was
3 deposed and so forth, if that's where you're
4 going.
5 MR. ASHKENAZI: I'm not going to -- this
6 was actually a question I was going to ask him, if
7 he recalls that I asked him this question and how
8 he responded. I wasn't going to introduce any
9 deposition testimony right now.
10 JUDGE BRYSON: Okay. Okay. Well, let's
11 see where this goes.
12 For now, overruled.
13 MR. ASHKENAZI: Again, Your Honor, just
14 to be clear, we did have a deposition in this
15 case. At that point we had spent seven hours
16 going over things. I don't want to have to lay
17 that same groundwork. So if Dr. Rabinow recalls
18 the deposition, that would allow us to move
19 forward.
20 JUDGE BRYSON: Right. Yes, but if what
21 you're going to do is impeach or attempt to use it
22 for substantive purposes, then we need to know.
23 MR. ASHKENAZI: Absolutely. I would
24 just like to also point out that to the extent
25 that a witness doesn't recall, that under 803, I

1 believe it's 4 --
2 JUDGE BRYSON: It -- well, maybe you
3 mean 801(d)(1)(a); is that right?
4 MR. ASHKENAZI: You could also use 804
5 which is -- this is a prior sworn testimony that
6 he gave under oath at the deposition.
7 JUDGE BRYSON: Well, he's present, and
8 he's not unavailable.
9 MR. ASHKENAZI: To the extent that he
10 doesn't recall anymore, Your Honor, under 803, it
11 would be an unavailable. But we don't have to go
12 there. Let's step back. I'm not going to fight
13 with Your Honor on the Rules of Evidence because
14 I'm sure you --
15 JUDGE BRYSON: Well, if you have a
16 point, feel free to fight. I --
17 MR. ASHKENAZI: Okay. But I don't think
18 we need to go there right now, but --
19 JUDGE BRYSON: Why don't we see where we
20 go.
21 MR. ASHKENAZI: Yeah.
22 JUDGE BRYSON: I'll overrule the
23 objection for now, but if you do get to a point in
24 which you want to impeach or use the deposition
25 for substantive reasons then --

1 MR. ASHKENAZI: We'll have this
2 conversation.
3 JUDGE BRYSON: -- let's have this
4 conversation.
5 MR. ASHKENAZI: Absolutely.
6 BY MR. ASHKENAZI:
7 Q. Dr. Rabinow, at your deposition, I had
8 asked you if you know how S75 compared to egg yolk
9 phospholipid.
10 Do you recall that?
11 A. I believe I do.
12 Q. And at that time, you said you did not
13 know how the S75 used in Jumaa compared to egg
14 yolk phospholipid; is that right?
15 A. I believe that's correct.
16 Q. Okay.
17 MR. ASHKENAZI: That was all I...
18 BY MR. ASHKENAZI:
19 Q. One more question, I believe.
20 You were discussing microemulsions
21 during your redirect. Can you recall a particular
22 formulation from your direct or cross or redirect
23 that was a formulation that was neither an
24 emulsion or a microemulsion, but in the middle?
25 A. I went to Stockholm to confer with

1 surface scientists who developed a whole range of
2 very interesting surface stabilized drug delivery
3 types of things; micelles, emulsions, cubosomes, a
4 whole bunch of things.
5 Okay. I spent two weeks there. I was
6 exposed to things that I, doing this before, had
7 not experienced before, and some of those involved
8 intermediate forms between micelles and emulsions.
9 Q. Dr. Rabinow, have you discussed in this
10 case, pointed to a single prior art formulation
11 that was neither an emulsion or a microemulsion,
12 but in the middle?
13 A. So I think between Liu, Karavas, and
14 Von Corswant, they were talking about an
15 intermediate form. They were talking about an
16 intermediate particle that was between the two.
17 Q. Just to be clear, it's your assertion
18 that there's a specific formulation in Liu -- what
19 were the three references you just mentioned now,
20 I apologize?
21 A. Liu, Karavas, Von Corswant, potentially
22 even Hingorani, but I think it's -- within those
23 four, there was a mention of another entity that
24 was more fluid.
25 Q. Dr. Rabinow, during your direct -- at

1 any point have you pointed us to a specific
2 formulation in any of the documents in the prior
3 art that was something that was in the middle
4 between an emulsion and a microemulsion?
5 A. Well, the question didn't come up until
6 afterwards. So I guess I'm not sure I understand
7 what you want me to say.
8 Q. Sitting here today, you have not
9 provided us with a specific -- any single
10 formulation that was in the middle between an
11 emulsion and a microemulsion; correct?
12 A. Well, I thought I tried to tell you that
13 among the references that I referred to, it
14 referred to this entity, although I didn't
15 specifically discuss it verbally.
16 Q. What specific formulation in this case
17 is in between an emulsion and a microemulsion,
18 according to you?
19 A. I -- it wasn't -- I didn't discuss one
20 that was directly involved in this case. I merely
21 addressed a question about theoretically is there
22 a continuum between the two, or are they discrete
23 entities. That's what I addressed.
24 Q. So you haven't pointed us to a single
25 formulation anywhere in the prior art --

1 A. If -- okay. If you want me to look for
2 it, I can do that now. Is that what you want me
3 to do?
4 Q. No, I apologize. I want to make sure
5 the record is clear that you haven't pointed us to
6 a single formulation that is neither an emulsion
7 or a microemulsion, but in the middle?
8 A. Well, I didn't think I had to until now.
9 Q. Okay.
10 MR. ASHKENAZI: No further questions.
11 JUDGE BRYSON: All right. Mr. Aly, do
12 you have any re-redirect?
13 MR. ALY: Nothing further, Your Honor.
14 JUDGE BRYSON: Very well. Good.
15 Now, I think -- are you planning to
16 potentially recall this witness?
17 MR. ALY: Yes, Your Honor.
18 JUDGE BRYSON: Okay. Dr. Rabinow, thank
19 you for your testimony. You are excused for now,
20 but don't jump on an airplane and leave, because
21 we'll need you later in the case.
22 THE WITNESS: Thank you, Your Honor.
23 JUDGE BRYSON: All right. Next witness.
24 MR. ALY: Your Honor, we'll now move to
25 some depositions to present in court.

1 JUDGE BRYSON: Very well. What are the
2 lengths for the depositions? How many, first of
3 all?
4 MR. ALY: There are two depositions, and
5 they're approximately an hour each.
6 JUDGE BRYSON: Ooh. Okay. Well, let's
7 take our morning break now. And then we'll come
8 back, and we'll do the long march through the
9 depositions.
10 MR. ALY: Thank you.
11 JUDGE BRYSON: Let's come back at --
12 let's make it 10:10.
13 (Recess from the record.)
14 JUDGE BRYSON: We have depositions.
15 MR. ALY: Your Honor, I'd like to
16 introduce Julie Vernon to the Court, for purpose
17 of reading introductions to the deposition.
18 JUDGE BRYSON: Very well.
19 Ms. Vernon.
20 MS. VERNON: Good morning, Your Honor.
21 I'm Julie Vernon for defendants. The parties
22 present the deposition testimony of Dr. Hannah Han
23 taken on October 19th, 2023. Dr. Han is one of
24 the named inventors on the two asserted patents
25 and testified in her individual capacity.

1 41 minutes and 19 seconds is allotted to
2 defendant, and 25 minutes and 17 seconds is
3 allotted to plaintiff.
4 JUDGE BRYSON: Very well.
5 Whereupon,
6 HANNAH HAN, PH.D.,
7 being first duly sworn or affirmed to testify to the
8 truth, the whole truth, and nothing but the truth, was
9 examined and testified by videotaped deposition as
10 follows:
11 DIRECT EXAMINATION BY COUNSEL FOR THE DEFENDANT
12 BY MR. NELSON:
13 Q. Can you please state your full name and
14 address for the record?
15 A. Hannah Han. [--- Redacted
16 ---]
17 Q. And who is Tom Ottoboni?
18 A. Tom Ottoboni was my direct boss.
19 Q. I want to talk a little bit about the
20 work that you did while you were at Heron.
21 What was your role in the development of
22 the aprepitant emulsion product?
23 A. I was a scientist formulating through
24 trial-and-error experiments to formulate a
25 aprepitant emulsion.

1 Q. Okay. So you did nothing out of the
2 ordinary from what you would normally do as a
3 formulation scientist; is that fair?
4 A. I did through trial-and-error
5 experiments a lot of observation, a lot of
6 considering to develop this Cinvanti emulsion.
7 Q. When you started at Heron, was that in
8 about 2013? Is that about right?
9 A. I started in early 2013.
10 Q. And had you done before that any other
11 formulation development work?
12 A. Are you asking had I done any
13 formulation development work before my time at
14 Heron?
15 Q. Yes.
16 A. My Ph.D. is developing formulations.
17 Q. When did you first start on the
18 aprepitant project, approximately?
19 A. Approximately early 2014.
20 Q. Who assigned you that work?
21 A. I do not recall exactly who. It would
22 have been either Tom Ottoboni or my direct
23 supervisor at the time, Laura Lerner.
24 Q. Was the project currently underway when
25 you started on it, or were you part of the

1 beginning of the project?
2 A. I was part of the beginning of
3 formulating the aprepitant emulsion.
4 Q. Do you know who came up with the initial
5 formulation for aprepitant that you worked on?
6 A. I do not recall.
7 Q. Did you come up with the initial
8 formulation?
9 A. I do not know which initial formulation
10 that you're referring to.
11 Q. Whatever initial formulation either you
12 were given or started with.
13 A. Are you asking who came up with the
14 initial formulation?
15 Q. Yes.
16 A. As far as I understand and recall, it
17 was from a patent.
18 Q. Do you recall the patent generally?
19 A. I do not recall the patent.
20 Q. Was it an English language patent or a
21 foreign language patent? Do you recall that?
22 A. I do not recall.
23 Q. What was your first task that you were
24 given for the aprepitant project?
25 A. I do not recall.

1 Q. Your Ph.D. is in chemical engineering;
2 is that right?
3 A. That's correct.
4 Q. Who was involved in the aprepitant
5 project when you began working on it at Heron?
6 A. Tom Ottoboni and my direct supervisor at
7 the time, Laura Lerner, that I can recall.
8 Q. Did either Dr. Ottoboni or Dr. Lerner
9 tell you that they wanted to prepare an emulsion
10 aprepitant intravenous product?
11 A. The general understanding was to develop
12 an aprepitant emulsion for intravenous use.
13 Q. Was this your first time making an
14 emulsion formulation?
15 A. That's correct.
16 Q. And did you participate in the various
17 stability evaluations of the formulations that you
18 made?
19 A. I participated in some of the stability
20 studies.
21 Q. Was that your first time testing and
22 evaluating the stability of emulsion formulations?
23 A. That's correct.
24 Q. How did you go about educating yourself
25 on how to make an emulsion formulation?

1 A. I recall looking to review articles to
2 help me understand emulsion stability.
3 Q. Anything else?
4 A. I do not recall anything else.
5 Q. And then how did you educate yourself on
6 testing the stability of emulsion formulation?
7 A. I looked into the USP, how FDA had
8 been -- had been testing emulsion products for
9 other products.
10 Q. Do you have an understanding of what the
11 USP is?
12 A. In the context of what I use the USP for
13 developing Cinvanti emulsion, I used it to see
14 what has been done for injectable emulsions.
15 Q. Why did you select the USP to educate
16 yourself on stability aspects of emulsions?
17 A. The USP -- as to my understanding, USP
18 is followed.
19 Q. Followed by who?
20 A. Followed by -- followed by FDA-approved
21 products to determine characteristics.
22 Q. So the scientists making those
23 FDA-approved products follow the USP in developing
24 and testing their products.
25 Is that an accurate characterization?

1 A. My understanding for the USP is that for
2 FDA-approved drug products, those are the tests
3 required.
4 Q. After the aprepitant emulsion
5 application was filed with FDA, did you have any
6 more involvement in the project?
7 A. I had more involvement. I helped
8 manufacturing scale up the emulsion formulation,
9 the contract manufacturing organizations.
10 Q. Any other involvement with aprepitant?
11 A. I also helped if there's any
12 manufacturing deviations.
13 Q. Do you know of any benefits of the Heron
14 aprepitant emulsion IV product over any other
15 product that's available on the market?
16 A. I do know that Cinvanti emulsion has
17 advantage over Emend for injection, in that
18 Cinvanti emulsion does not contain polysorbate 80,
19 which can cause hypersensitivity reactions in
20 patients.
21 Q. Any other advantages or benefits?
22 A. Cinvanti can also be administered by IV
23 push versus Emend for injection, which needs to be
24 administered by IV infusion.
25 Q. I have marked a document as Han

1 Exhibit 2, a document that bears Bates numbers --
2 and Bates numbers are the -- there's some printed
3 numbers at the very bottom of the document, you'll
4 see. And it says, HERON_0054723 to 790.
5 Do you see this document?
6 A. I do.
7 Q. And do you know what this document is?
8 A. This is a HTX-019 formulation
9 development report.
10 Q. And did you write this formulation
11 development report?
12 A. I wrote most of it.
13 Q. And it reflects the development work
14 that you did on the project; is that right?
15 A. It does not contain everything that I
16 did. It's only selected -- selection of what I
17 had done.
18 Q. Was it your team's goal to develop a
19 product that did not contain polysorbate 80?
20 A. Our goal was to develop an emulsion
21 system that contains safe excipients for patients,
22 including not containing polysorbate 80.
23 Q. And it says there, the second sentence
24 says, "Ethanol is added in a preparation of the
25 oil phase to aid aprepitant and lecithin

1 dissolutions, as well as to reduce the viscosity
2 for processing."
3 Do you see that?
4 A. I see that.
5 Q. At the time you were working on the
6 emulsion product, it was known that ethanol could
7 reduce the viscosity of emulsions; correct?
8 A. When I was developing the emulsion, I
9 had found out that ethanol helps to reduce the
10 viscosity for processing.
11 Q. When you first used ethanol, did you
12 have an expectation that it would reduce the
13 viscosity of the emulsion?
14 A. I had found that ethanol helps reduce
15 viscosity for processing through development work.
16 Q. My question was: When you first used
17 it, did you have an expectation that it would
18 assist in reducing the viscosity of the emulsion?
19 A. I do not recall.
20 Q. Did you have an expectation that it
21 would aid in dissolution of any other product in
22 the emulsion?
23 A. Ethanol is a cosolvent. So I do have an
24 expectation that it will help dissolve aprepitant.
25 Q. Let's turn to the fourth page, which is

1 Bates No. 54726, please.
2 A. Yes.
3 Q. And I want to focus on that Table 2 for
4 these questions.
5 Now, you can see on the left there, it
6 says, "Egg lecithin, lipoid E80."
7 Do you see that?
8 A. I see that.
9 Q. And the function that's listed there is
10 as an emulsifier.
11 Do you see that?
12 A. I see that.
13 Q. And you would agree with me that egg
14 lecithin was known as an emulsifier when you
15 started on your project; is that right?
16 A. I agree.
17 Q. And "soybean oil" is the next field.
18 Do you see that?
19 A. I see that.
20 Q. And that's listed as a function as a
21 solubilizer; is that right?
22 A. It's listed as solubilizer.
23 Q. But it was known at the time that you
24 started your development work as a solubilizer --
25 it was functioning as a solubilizer in emulsion

1 formulations; correct?
2 A. Soybean oil may help dissolve
3 aprepitant.
4 Q. Soybean oil is a well-known component of
5 an oil-in-water emulsion; correct?
6 A. That's correct.
7 Q. Ethanol, we talked about its function as
8 a cosolvent earlier; is that right?
9 A. Yes, ethanol is listed as a cosolvent.
10 Q. And that's a known function of ethanol
11 in emulsion formulations; correct?
12 A. I cannot speak for other emulsions.
13 Q. Well, it says there that ethanol is a
14 cosolvent, and it lists the USP as a reference
15 quality standard.
16 Do you see that?
17 A. I see that.
18 Q. Would the USP reflect that ethanol -- a
19 function of ethanol is as a cosolvent?
20 A. Ethanol can be a cosolvent for
21 formulation work.
22 Q. Now, at the time you did your
23 development work, aprepitant was known to be
24 relatively insoluble in water; is that correct?
25 A. That's correct.

1 Q. Okay. So you took aprepitant and tried
2 to dissolve it in different types and amounts of
3 emulsifiers; is that right?
4 A. It is more complicated than that.
5 Q. Okay. Well, what more did you do
6 besides that?
7 A. I found out that aprepitant cannot
8 dissolve just in lecithin by itself, and then I
9 had to determine what is -- tried to find out what
10 is the solubility of aprepitant in lecithin. To
11 do that, I had to put two different components in
12 there. Many different experiments were done to
13 find out that lecithin is key in helping
14 solubilizing aprepitant.
15 Q. Let's turn to page 11, which is
16 Bates 54733, please. And I'm looking at that
17 Section 2.2.2.
18 Do you see that section?
19 A. I see that.
20 Q. It says there, "The initial formulation
21 process of the oil-in-water emulsion containing
22 aprepitant was adapted from patent CN 102379845
23 (Zhou, et al., 2022)."
24 Do you see that?
25 A. I see that it was adapted from the

1 patent.
2 Q. From what you wrote here about the
3 initial formulation process, does that seem
4 consistent that you started with an initial
5 formulation from patent CN 102379845?
6 A. This is what's written on here.
7 Q. And for the record, Exhibit 3 is a
8 document bearing Bates Nos. HERON_0035072 to 81.
9 Let's turn back to Exhibit 2, that
10 formulation development report. And if we look
11 below the preparation procedure, you list there
12 that 24 hours later aprepitant crystals were
13 visible under polarized light at 100X
14 magnification.
15 Do you see that?
16 A. According to data, aprepitant crystals
17 were visible under polarized light at 100X
18 magnification, yes.
19 Q. Did you perform that magnification
20 experiment or evaluation?
21 A. I did.
22 Q. Why did you choose to use 100X
23 magnification?
24 A. So that was chosen to see if aprepitant
25 crystals is present or not.

1 Q. Have you ever heard of or used 10X
2 magnification to observe crystals?
3 A. On a microscope, there is objective on
4 the bottom, and the lens on the top. The lens on
5 the top is 10X, and then the objective is 4X or
6 10X. In here, I used the lens, which is 10X, and
7 the objective, which is 10X equal. If you count
8 them together, that's 100X magnification.
9 Q. So in doing that, you're able to
10 increase magnification at least ten times as
11 compared to a 10X magnification by itself;
12 correct?
13 A. 100X is ten times more than 10X, that's
14 correct.
15 Q. If you turn to page 12, which is
16 Bates 54734, please. And at the top, there's a
17 discussion about the decision that was made to
18 reduce the particle size using a microfluidizer to
19 improve the formulation.
20 Do you see that?
21 A. A microfluidizer was to be incorporated
22 into the process to reduce the particle size
23 further.
24 Q. Was it your first time using a
25 microfluidizer?

1 A. It was my first time using a
2 microfluidizer.
3 Q. Let's look at 2.2.3 on this page,
4 please. And here you're discussing aprepitant
5 solubility in the oil phase.
6 Do you see that?
7 A. I see that.
8 Q. And from this, at the end of the day,
9 you identified the correct ratio of lecithin and
10 soybean oil to aprepitant that would solubilize
11 the aprepitant sufficiently for an emulsion
12 formulation; is that right?
13 A. This is one of many, many experiments
14 that were done to determine the correct
15 composition of an emulsion to make it stable.
16 Q. Yes, but I'd like to just talk about
17 this one, and I'm correct that at the end of the
18 day, from this experiment, you were able to
19 identify the correct ratio of lecithin and soybean
20 oil to the aprepitant that would solubilize the
21 aprepitant sufficiently for an emulsion
22 formulation; right?
23 A. That's not correct.
24 Q. So that's not the result that's
25 described here in this report?

1 A. The results described in this particular
2 experiment is one of many that's used to determine
3 the optimum composition of the emulsion.
4 Q. Let's turn to page 17, which is
5 Bates 54739, please. And I want to focus on that
6 first full paragraph at the top of the page. In
7 particular, the statement that starts, "However"
8 in the middle of the paragraph, and I'll read it.
9 It says, "However, when ethanol was not
10 present (Sample C), aprepitant was insoluble."
11 Do you see that?
12 A. I see that.
13 Q. And then it goes on to say, "In
14 contrast, when egg lecithin was absent (Sample D),
15 aprepitant was partially insoluble."
16 Do you see that?
17 A. I see that.
18 Q. So is it fair to say that it was your
19 conclusion that ethanol and egg lecithin are the
20 most important components for solubilizing
21 aprepitant?
22 A. Egg lecithin and ethanol composition in
23 the emulsion is one of many important factors to
24 make a stable aprepitant emulsion.
25 Q. So it's fair to say that ethanol and egg

1 lecithin are the most important components for
2 solubilizing the aprepitant; correct?
3 A. Compared to soybean oil, egg lecithin
4 and ethanol are most important for solubilizing
5 aprepitant.
6 Q. And if you can't get -- if you can't
7 solubilize the aprepitant, you're not going to be
8 able to make an injectable emulsion; correct?
9 A. If you do not solubilize aprepitant, you
10 won't be able to make a stable oil in water
11 emulsion for aprepitant emulsion.
12 Q. The next paragraph below where we were
13 just reading on page 18 at HERON_54740, the one
14 that starts, "Under polarized light," do you see
15 that?
16 A. I see that.
17 Q. And you state, "Under polarized light
18 microscopy, interesting structures were observed
19 in emulsions containing egg lecithin (Figure 5)."
20 You go on to say, "They appeared to be
21 entrapped crystals with droplet size of
22 approximately 15 microns."
23 Do you see that?
24 A. I see that.
25 Q. And did I read that accurately?

1 A. You did.
2 Q. You go on to say, "Initially, it was
3 hypothesized that these structures contained
4 entrapped aprepitant crystals"; correct?
5 A. Correct.
6 Q. And then you say, "However, by
7 aprepitant HPLC assay, the aprepitant
8 concentration remained the same before and after
9 filtration of the emulsions through a 0.45-micron
10 nylon filters (the entrapped crystals were no
11 longer present by microscopy)."
12 Do you see that?
13 A. I see that.
14 Q. HPLC. What is HPLC?
15 A. High performance liquid chromatography.
16 Q. And what is HPLC used for?
17 A. It's used for -- in this case, for
18 characterizing the amount of aprepitant.
19 Q. Am I correct that what you were
20 initially observing and what you thought were
21 aprepitant crystals under a microscope were
22 actually not aprepitant crystals; is that correct?
23 A. The particular structures that I had
24 observed under the microscope were different than
25 what aprepitant crystals look like.

1 Q. So you originally hypothesized these
2 crystals were aprepitant crystals, but they were
3 actually lecithin crystals; right?
4 A. That's correct.
5 Q. And that's because there wasn't enough
6 ethanol to dissolve the lecithin; is that right?
7 A. I do not know why there were
8 birefringent structures that were observed in the
9 formulation, but those birefringent structures
10 were not aprepitant crystals.
11 Q. And that was determined by using HPLC;
12 right?
13 A. That was determined by doing a
14 filtration study determining the amount of
15 aprepitant that was in the filtrate and before
16 filtration.
17 Q. And just so I'm clear, the original
18 crystals that were entrapped in the droplet that
19 you thought were aprepitant crystals, that was
20 based on an observation done by microscopy;
21 correct?
22 A. That was done by microscopy.
23 Q. You had to do the HPLC to learn that,
24 no, they weren't aprepitant crystals, those
25 instead were lecithin crystals; right?

1 A. When I look under polarized light
2 microscopy, crystals that I see I expected them to
3 be aprepitant. However, in this case, the
4 crystals that I saw were in droplets that had very
5 different structure than aprepitant crystal
6 structure, and that is why I did a filtration
7 study and HPLC assay to determine what it was.
8 Q. But, again, you didn't -- you weren't
9 able to make the determination of what those
10 crystals were until you did the HPLC; correct?
11 A. I found, after doing HPLC work, that
12 those structures, those very interesting cellular
13 structures that I had never seen before that looks
14 very different from aprepitant crystals, were, in
15 fact, not aprepitant crystals.
16 Q. You didn't write in this report on
17 page 54740 that these crystals were observed to be
18 different than aprepitant crystals; right?
19 A. I wrote, "Interesting structures were
20 observed in the emulsions."
21 If I see aprepitant crystals, I wouldn't
22 have said it's interesting structures.
23 Q. You didn't say they were different
24 structurally than aprepitant. You didn't write
25 that here; correct?

1 A. I wrote, "interesting structures." And
2 on Figure 5, I wrote, "entrapped crystal
3 structures."
4 Q. Sticking with Han Exhibit 2, if we could
5 turn to page 20 of that document, which is
6 HERON_54742, please.
7 A. Okay.
8 Q. And I want to focus -- under that
9 Table 8, the paragraph there, you wrote here, "Of
10 primary interest was lipoid E80 using the
11 preparation of parenteral nutrition emulsions."
12 Do you see that?
13 A. I see that.
14 Q. What does "parenteral" mean?
15 A. "Parenteral" means injected into the
16 body.
17 Q. Would that include intravenous
18 emulsions?
19 A. That includes intravenous emulsions.
20 Q. We can agree that lipoid E80 was
21 previously used in emulsion formulations that were
22 used parenterally; correct?
23 A. Correct.
24 Q. Okay. And that was before you used it
25 in your formulation; right?

1 A. As far as I know, there were other
2 emulsions that used lipoid E80.
3 Q. The next page, page 21, that's
4 HERON_54743, down at the bottom, Section 2.2.6,
5 "The selection of oil."
6 Do you see that section?
7 A. I see that.
8 Q. And that first sentence there says,
9 "Soybean oil is the primary candidate for the oil
10 component because it is the principal oil used in
11 parenteral nutrition emulsions."
12 Do you see that?
13 A. I see that.
14 Q. Okay. And, again, you're indicating
15 here that soybean oil had been previously used
16 before your work in parenterally administered
17 emulsions; isn't that right?
18 A. That's correct.
19 Q. Why did you target a pH of 8 for the
20 formulations?
21 A. For parenteral injections, the pH should
22 be between 5 to 9, and pH 8 is slightly below 9
23 for safe dosing in humans.
24 Q. Dr. Han, I'm providing to you what was
25 marked as Han Exhibit 4, a document with Bates No.

1 HERON_0032697 to 33075.
2 Can you identify this document for me?
3 A. This is one of my lab notebooks at
4 Heron.
5 Q. And it's laboratory notebook 1255; is
6 that right?
7 A. That's correct.
8 Q. Is the laboratory notebook page 156, is
9 that the procedure that's described in Exhibit 2
10 for formulation 7/3?
11 A. According to the dates, it is the
12 procedure for formulation 7/3.
13 Q. And the Exhibit 4, page -- laboratory
14 notebook page 156, that was an experiment you
15 conducted on July 3rd, 2014; is that right?
16 A. That's correct.
17 Q. And the amount of the various components
18 of the formulation that's reflected in Exhibit 4,
19 laboratory notebook page 156, that's the same as
20 the amounts that are reflected for the preparation
21 procedure formulation 7/3 in Example -- or in --
22 I'm sorry, in Exhibit 2; correct?
23 A. I'll have to check on that.
24 Q. Sure. Please do.
25 A. They have the same formulation

1 composition.
2 Q. For the 7/3 formulation, you found no
3 crystals were observed after 67 days; is that
4 correct?
5 A. Where do you get that number from?
6 Q. Well, let's look at the laboratory
7 notebook, Exhibit 4, and look at page HERON_32928,
8 which is lab notebook page 157.
9 A. Okay.
10 Q. And you observed no crystals after
11 67 days; is that right?
12 A. That's one of the observations.
13 Q. And at the bottom of that page, there's
14 a notation about PFAT5 results.
15 Do you see that?
16 A. I see that.
17 Q. And Han Exhibit 5 is a document bearing
18 Bates HERON_0003912 to 3968.
19 Do you recognize this document?
20 A. This was one of the documents submitted
21 for Cinvanti NDA.
22 Q. And the next section, The Selection of
23 Osmolarity and pH Modifiers, did you write this
24 paragraph, as well?
25 A. I did.

1 Q. And you wrote, "Sodium oleate was added
2 to raise the pH of the emulsion from approximately
3 5.5 to approximately 8.4, which was shown to be an
4 important determinant of emulsion stability."
5 Do you see that?
6 A. I see that.
7 Q. Was it your expectation that when you
8 used sodium oleate, it would raise the pH in the
9 formulation?
10 A. I anticipated it to increase the pH of
11 the emulsion.
12 Q. And then did you also anticipate that by
13 raising the pH, you would improve the emulsion
14 stability?
15 A. Raising the pH to approximately 8.4,
16 along with many other factors, are important for
17 emulsion stability.
18 Q. Han Exhibit 6 is a document bearing
19 Bates No. HERON_0034346 to 49.
20 So this is an e-mail from Francis Wong
21 to you, dated March 25th, 2014; correct?
22 A. That's what's written there.
23 Q. Do you recall generally Mr. Wong being
24 asked to translate something in connection with
25 your work on the aprepitant emulsion project?

1 A. I recall that he was asked to translate
2 something from Chinese to English.
3 Q. Who is Francis Wong?
4 A. He was a colleague at Heron.
5 Q. Based on the fact that there's the same
6 patent number, the same listed first inventor, the
7 same general weight percentage of all the same
8 emulsion ingredients, and the same preferred
9 weight percentage of all those same ingredients
10 between the two documents, in addition to all of
11 the example ingredients in Exhibit 6 and in
12 Exhibit 3, it's reasonable to say that this is a
13 document that Mr. Wong translated for you.
14 You would agree with that?
15 A. I believe this was a document that
16 Mr. Wong translated.
17 Q. But can you verify for me that Exhibit 7
18 is a -- an excerpt from your laboratory
19 notebook 1255?
20 A. It is a portion of my notebook 1255.
21 Q. And looking at laboratory notebook 1255,
22 page 186 of the notebook, which is HERON_33032.
23 A. Yes.
24 Q. It says at the top, "Duplicate Chinese
25 Patent."

1 You wrote that; correct?
2 A. That's correct.
3 Q. And if it's reasonable that Exhibit 3 is
4 the same basic document that Mr. Wong was
5 translating for you, as we've discussed before, is
6 it reasonable then to say that Exhibit 3 was the
7 Chinese patent that you're duplicating in your
8 laboratory notebook 1255 at page 186?
9 A. I believe that the Chinese patent does
10 refer to my lab notebook 1255, page 186, the Zhou
11 patent in Exhibit 3.
12 Q. And you agree with me, looking at
13 Mr. Wong's summary of the Zhou CN '845 patent, you
14 didn't follow any of these examples, these eight
15 examples, when you did your reproduction; correct?
16 A. I did not use 500 milligrams, like in
17 the examples. I used 450 milligrams of
18 aprepitant. The other compositions I'll have to
19 look further.
20 Q. Okay. Well, let's -- so there's not a
21 single example out of these eight that have
22 450 milligrams of aprepitant, 6.67 grams of egg
23 lecithin -- let's stop there -- correct? None of
24 them have that; right?
25 A. That's correct.

1 Q. Okay. And none of them that have those
2 two components in those amounts and also have
3 7.2 milliliters of ethanol; correct?
4 A. That's correct.
5 Q. And none of them that have those three
6 components in those amounts and also have 6 grams
7 of soybean oil; right?
8 A. That's correct.
9 Q. And none of them that have those four
10 components and those amounts and also have
11 3.36 grams of sucrose; right?
12 A. That's correct.
13 Q. And none of them have all of those
14 components in those amounts and 50.5 milliliters
15 of water; right?
16 A. Correct.
17 Q. Okay. So you didn't follow any of the
18 examples in the Zhou CN '845 patent; correct?
19 A. It looks like the composition were not
20 followed from the examples.
21 Q. How did you decide what components and
22 how much of each component to use when you're
23 saying you're duplicating the Chinese patent?
24 A. I do not recall.
25 Q. Well, did you just pick components and

1 amounts of those components randomly from your
2 review of the Zhou patent?
3 A. I recall that I picked components with
4 the best success in terms of making a stable
5 emulsion for the Zhou patent.
6 Q. Well, you weren't able to do that; were
7 you?
8 A. It says here that within four days post
9 preparation at room temperature, crystals were
10 observed by microscopy.
11 THE COURT REPORTER: Sorry, crystals
12 were observed?
13 THE WITNESS: By microscopy.
14 BY MR. NELSON:
15 Q. You had only been making emulsion
16 formulations for about three to four months at
17 this point in time; right?
18 A. I started in early 2014, and at this
19 time it was July 25th, 2014.
20 Q. So three, four months; is that fair?
21 A. It may have been long -- it may have
22 been three, four months, or it may have been
23 longer than that.
24 Q. No more than seven months; right?
25 A. No more than seven months.

1 Q. Now, do you really think with between
2 three and seven months of experience making an
3 emulsion formulation, you were in the best
4 position to decide what components and how much of
5 those components would likely give a stable
6 emulsion formulation?
7 A. Those months of development work,
8 between four to seven months, was spent on
9 developing and understanding a stable aprepitant
10 emulsion. So at that point, I had a good
11 understanding of what it takes to make a stable
12 aprepitant emulsion.
13 Q. But you weren't able to make one from
14 how you duplicated Zhou; correct?
15 A. The compositions in the Zhou patent
16 resulted in an unstable emulsion.
17 Q. We can agree that there are broader
18 ranges in Zhou than the specific amounts of the
19 different ingredients that you used; correct?
20 A. The Zhou patent ranges were very broad.
21 So we cannot replicate all the ranges that were in
22 the patent.
23 Q. But, again, you have no idea if you
24 would have chosen different amounts in that same
25 range whether you would have achieved a stable

1 emulsion; correct?
2 A. I do not know this now, but that was
3 many, many years ago. I chose a composition that
4 had the best success for it to be stable for the
5 Zhou patent.
6 Q. I'll read it back to you.
7 You made the determination that the Zhou
8 patent was unable to provide stable emulsions
9 based on one formulation that you made that you
10 deemed was within the scope of the broad Zhou
11 teachings; is that right?
12 A. We chose a composition to replicate the
13 Chinese patent based on trying to be -- to find
14 the most stable formulation based on the
15 composition that was disclosed, and that resulted
16 in an unstable emulsion from the Chinese patent.
17 Q. If you were trying to make a stable
18 emulsion from the Zhou patent and you didn't
19 succeed, did not succeed, you made an unstable
20 one, why didn't you try adjusting the variables
21 provided in Zhou to then see if you could make a
22 stable emulsion?
23 A. I do not recall.
24 Q. If you look at your lab notebook,
25 page 186. You wrote at the top, Duplicate the

1 Chinese patent.
2 What does duplicate mean to you?
3 A. It means to replicate something.
4 Q. But you didn't copy any specific
5 formulation from Zhou; correct?
6 A. I didn't copy any specific examples from
7 Zhou.
8 Q. That's the problem I'm having, is I
9 don't see this specific procedure anywhere in
10 Zhou. So I think you can agree with me that this
11 specific procedure, while many of the steps are
12 disclosed either specifically or broadly, this
13 specific procedure that's described here in your
14 lab notebook, I don't find anywhere in Zhou.
15 You can agree with me on that; correct?
16 A. I would have to take time to look
17 through this patent, but under Section 16 of the
18 patent -- we had read through this earlier. We
19 had read through this earlier.
20 Mixing aprepitant emulsifier, dissolving
21 ethanol, that's the same as Step 1 and 2, and what
22 I've done on page 186 in my notebook.
23 (Unintelligible) -- and evaporated to give a thick
24 residue or a thick emulsion as translated by
25 Francis Wong in Exhibit 6 is on Step 3 of my

1 notebook.
2 Add appropriate amount of ethanol to
3 dissolve it, keeping the temperature at 60, and
4 stir until obtain a clear oil phase. That's on
5 Step 4 of my notebook.
6 Dissolving a protected agent in water
7 for injection, heated to 60 degrees to obtain an
8 aqueous phase. That's on Step 5 of my notebook.
9 Stirring at a high speed and mashing, at
10 the same time adding appropriate amount of water
11 for injection, adjusting the pH to 6 to 8 to
12 obtain a primary emulsion. That's on Step 6 of my
13 notebook -- Step 6 and 7 of my notebook.
14 And then adding the prime emulsion to a
15 high pressure homogenizer, homogenizing for
16 several times. That's on Step 6, which is
17 supposed to be Step 8, of my notebook.
18 Q. And paragraph 16 doesn't provide a
19 number of passes in a microfluidizer or the KPSI
20 or cooling using ice cubes or ice water, as you
21 have; correct?
22 A. It does not provide the number of passes
23 through there.
24 Q. And it doesn't provide the cooling with
25 ice cubes or ice water; correct?

1 A. That's correct.
2 Q. And it doesn't state to adjust with 1 --
3 .1 normal hgl -- or .1 normal NaOH; correct?
4 A. It does not mention what is added to
5 adjust the pH.
6 Q. The Zhou patent, if you look at -- you
7 can look at Exhibit 3, either paragraph -- well,
8 we'll look at paragraph 8 -- look at paragraph 9.
9 It says the amount of the co-emulsifier
10 can be between 7 percent and 13 percent in a
11 preferred embodiment; is that right?
12 THE COURT REPORTER: I'm sorry, Counsel,
13 could you repeat?
14 MR. NELSON: I'm sorry, yeah.
15 BY MR. NELSON:
16 Q. The amount of co-emulsifier can be
17 between 7 and 13 percent in a preferred
18 embodiment; is that right?
19 A. That's what's written there.
20 Q. And you used about, it looks like from
21 your notebook, about 8 and a half percent; is that
22 right?
23 A. That's correct.
24 Q. So did you try to see if using more of
25 the co-emulsifier would help in delaying crystal

1 formation?
2 A. I did not.
3 Q. Zhou allows for more ethanol than you
4 used; correct?
5 A. The general composition preparation
6 method says it's 1 to 10 percent of the
7 co-emulsifier.
8 Q. You don't know what those crystals are
9 specifically; do you?
10 A. Those are aprepitant crystals.
11 Q. I believe Mr. Ashkenazi just handed you
12 what is Han Exhibit 8, which bears Bates
13 No. HERON_0000019.
14 Do you have that document in front of
15 you?
16 A. I do.
17 Q. And this is U.S. Patent No. 9,808,465.
18 Is this one of the patents that you are
19 a named inventor on?
20 A. My name is on there, yes.
21 Q. If you could, please, turn to -- it's
22 Bates page 33, HERON_33. It's going to be
23 Column 18 of the patent in Example 4. And --
24 A. Okay.
25 Q. If you could confirm for me that

1 Example 4 in the '465 patent, which is Exhibit 8,
2 is that the same procedure that you have in your
3 lab notebook 1255 that's Exhibit 4 and Exhibit 6
4 at page 186 of that lab notebook?
5 A. Yes, Example 4 from the patent refers to
6 the experiment that was done on July 24th on
7 page 186.
8 Q. In your experiment, you said you
9 adjusted the pH to 8.0.
10 Do you see that?
11 A. I see that.
12 Q. You testified earlier, in response to my
13 question, that you followed the procedure in
14 paragraph 16, correct, from the Zhou patent?
15 A. As close as I could.
16 Q. And you can look at paragraph 16 of
17 Exhibit 3.
18 Again, there is no teaching in there to
19 adjust the pH once and then adjust it again a full
20 pH unit down; correct?
21 A. It does not say on there.
22 Q. Okay. And if we look back at the
23 '465 patent, Exhibit 8, Example 4. If you look
24 sort of near the middle of the paragraph, it's
25 line 35. It says, "The pH of this crude emulsion

1 was adjusted to 7.0."
2 Do you see that?
3 A. I see that.
4 Q. What did you use to adjust the pH to
5 7.0?
6 A. According to my notebook, it's 0.1
7 normal sodium hydroxide.
8 Q. Where is the step in your notebook where
9 you made that adjustment?
10 A. So the steps that's written on there are
11 the procedure that I was to follow to adjust the
12 pH. And then the step -- and then in writing by
13 hand is what actually happened. But looking at
14 this today, it says, at 1 mL pH goes to 9, adjust
15 to pH 8 with 0.1 normal HCL. After
16 homogenization, the pH went to 7.
17 Reading this today, I do not recall what
18 exactly happened because it's been so long ago,
19 like ten years ago. But the patent was written
20 much sooner after this experiment, and whatever is
21 in the patent is accurate.
22 Q. Well, we don't know from the patent
23 how -- what you used to adjust the pH from 8 to 7;
24 correct? It doesn't tell us?
25 A. It does not say what was used to adjust

1 the pH to 7.0.
2 Q. But the Zhou patent, as we talked about,
3 doesn't have two pH adjustments; right? There is
4 no teaching of using two pH adjustments?
5 A. It does not state that, but nor is it
6 stated in Example 4.
7 Q. Well, you did -- it does make two pH
8 adjustments; right? You adjusted the pH to 8, and
9 then you adjusted it again to pH 7; right?
10 A. Again, I do not recall exactly what
11 happened when I made this formulation about
12 ten years ago.
13 Q. This is a laboratory notebook 1263,
14 bears Bates No. HERON_0033076.
15 Do you recognize this document?
16 A. This is my notebook.
17 Q. So I'd like to mark the second portion
18 of that -- yeah, the second portion of that as
19 Exhibit 9-A, if you're in agreement with that,
20 Counsel. It's just the second part of the lab
21 notebook.
22 Starting on lab notebook page 16, you
23 have an objective, "Patent Writing."
24 Is that what that says?
25 A. That's what it says.

1 Q. And if we could go to the next page.
2 For the record, that's HERON_33118, page 17 of lab
3 notebook 1263.
4 And this is a formulation and procedure
5 that was performed on 8/29; is that correct?
6 A. That's correct.
7 Q. And here it says, "Chinese paper
8 replicate."
9 Do you see that?
10 A. I see that.
11 Q. And Exhibit 11 bears Bates
12 Nos. HERON_003511 to 14.
13 Do you recognize this document?
14 A. I do not recall this document.
15 Q. Is this document an article by first
16 author Zhou?
17 A. That's correct.
18 Q. If you would for me, please look at page
19 HERON_35113, section designated as 2.4 on that
20 page.
21 A. Okay. I'm there.
22 Q. And take a look at that formulation and
23 procedure described there.
24 Is this the formulation procedure that
25 you used in your laboratory notebook 1263 at

1 page 17?
2 A. It appears to be the same formulation.
3 Q. The next page, which is HERON_3511 and
4 2.5, at the top there, it says, "Observe the
5 stability of emulsion after sterilization and
6 3-month storage after sterilization prepared
7 according to Item 2.4 method."
8 Do you see that?
9 A. I see that.
10 Q. Okay. So they observed the stability of
11 the product that was made according to that
12 2.4 method; right?
13 A. It says they observed the stability of
14 emulsion after sterilization at three-month
15 storage.
16 Q. And the product was stable after
17 three-month storage; correct?
18 A. I cannot tell by reading this whether
19 the product was stable or not.
20 Q. Is that because you can't read the
21 information, it's illegible, or you're not able to
22 make the determination?
23 A. Table 4 cannot be seen clearly, and
24 nowhere does it say that it looked for aprepitant
25 crystals in the emulsion.

1 Q. Now, the procedure 2.4 of the Zhou
2 article, Exhibit 11, what is the pH of that
3 product?
4 A. 7.31 plus or minus 0.30.
5 Q. And where are you reading that?
6 A. It says, pH and one content label amount
7 percent before and after preparation
8 sterilization.
9 Q. Now, the pH of your formulation that you
10 used, that's a pH of 6.5; correct?
11 A. I followed the instructions of 2.4 from
12 the Chinese paper, and the resulting pH that I had
13 measured was approximately 6.5.
14 Q. What did you do to adjust the pH?
15 Because the procedure in the Zhou paper that you
16 followed had a pH that was at least a whole half a
17 pH unit higher than what you did; correct?
18 A. The Zhou paper -- the Zhou -- this
19 Chinese paper did not ask to adjust the pH. So I
20 did not adjust the pH after formulating the
21 emulsion.
22 Q. Now, when you followed the Zhou patent,
23 you did a second pH adjustment even though it
24 didn't say so.
25 Here, where you had a different pH than

1 the Zhou paper, you didn't bother to do a further
2 pH adjustment to match the pH; correct?
3 A. The Zhou patent asked to adjust the pH.
4 The Zhou paper did not ask to adjust the pH, and
5 that's why I did not adjust the pH. If I had
6 adjusted the pH outside of this paper, then I
7 would have done something different.
8 Q. So if there's any discrepancy between
9 your lab notebook and the patent, the lab notebook
10 is probably more accurate; right?
11 A. Again, looking at my lab notebook -- can
12 we look at the lab notebook so we can --
13 Q. Yes, absolutely.
14 A. So this one.
15 Q. Absolutely. So that is -- if it helps,
16 it's Exhibit -- Exhibit 6 is the excerpt, if
17 that's easier to use the smaller document.
18 Exhibit 4 is the larger one.
19 A. Okay. To answer your question, in the
20 Zhou patent, they asked the pH be between 6.0 to
21 8.0 and they adjusted the pH in the steps and
22 that's why I took specific step to adjust the pH.
23 However, in the Zhou paper, there is no step to
24 adjust the pH, and that's why I did not adjust the
25 pH.

1 Q. But in the Zhou patent, you had already
2 obtained a pH of 8.0. You didn't have to make a
3 second adjustment. You were already in that range
4 of 6.0 to 8.0; correct?
5 A. Then I don't remember exactly what
6 happened.
7 Q. But you'd agree with me that --
8 MR. ASHKENAZI: She didn't finish her
9 answer, please.
10 MR. NELSON: I apologize, I thought she
11 was done. My bad.
12 BY MR. NELSON:
13 Q. Go ahead, please.
14 A. Again, I don't recall exactly what
15 happened on July 24th, but what's written on the
16 patent would have been accurate -- is accurate.
17 Q. Now, with the Zhou paper, which is
18 Exhibit 11, you chose to follow the specific
19 procedure in 2.4; correct?
20 A. I followed it as close as I could.
21 Q. And even though you purported to follow
22 this specific example, 2.4, you had a different
23 pH, as we discussed; correct?
24 A. Again, different pH measurements may
25 have been -- different pH measurements meters may

1 have been used. At the time of August 29, 2014, I
2 did not have a pH meter. I used a pH paper, and
3 that's why it was approximately 6.5. It may have
4 been 7, it may have been 7.5.
5 Q. But this is your patent. You understand
6 that; correct?
7 A. I invented this patent along with Tom.
8 Q. And this is a formulation that you came
9 up with, this stable emulsion formulation as
10 described here in Claim 1; is that right?
11 A. We came up with this formulation
12 together.
13 Q. Well, you don't know from looking at
14 this that each one of those pH adjusters is going
15 to work to make a stable emulsion aprepitant
16 formulation; correct?
17 A. The aprepitant emulsion is very complex.
18 It has many components, needs specific ratios. So
19 changing the pH modifier may or may not make it
20 into a stable emulsion.
21 Q. So you would have to do the experiment
22 with each one of those pH modifiers listed there
23 in different amounts to determine which ones and
24 at what amounts that will result in a stable
25 formulation and which ones won't; correct?

1 A. I only know for the aprepitant emulsion
2 that we developed, I tried sodium hydroxide and
3 sodium oleate. I did not write this section of
4 the patent, so -- and I'm not a patent attorney.
5 So I cannot speak more on this.
6 Q. Let's look at Bates page HERON_29 at
7 Column 10 of Exhibit 6 -- or 8, please.
8 Exhibit 8, the '465 patent.
9 If we look at line 20 -- do you see
10 where I'm indicating there, line 20?
11 A. Yes.
12 Q. It says here, Prior to combining the oil
13 phase with the aqueous phase, the oil phase will
14 have an oil to aprepitant ratio of about 13 to 1.
15 Do you see that?
16 A. I see that.
17 Q. It says, Use of this ratio was
18 surprisingly found to produce when mixed with the
19 water phase, an emulsion which is more stable as
20 compared to an emulsion in which the oil phase
21 contains an oil to aprepitant ratio of less than
22 about 12 to 1 or 11 to 1 and/or greater than about
23 15 to 1, 20 to 1, or 30 to 1.
24 Do you see that?
25 A. I see that.

1 Q. Now, my question is not going to be
2 whether or not you wrote that. My question is:
3 Is that your contribution to this patent? Did you
4 come up with this what's called a surprising
5 result?
6 A. The emulsion is very complex. The ratio
7 of lecithin to aprepitant, oil to aprepitant,
8 sodium oleate used, everything is important to
9 make a stable emulsion. And Tom and I -- Tom and
10 I came up with this together through a lot of
11 trial-and-error experiments.
12 So to pick out and say is this my
13 particular contribution, "this" being the only
14 particular important thing here, is not accurate.
15 There's many other important aspects in this
16 invention.
17 Q. The testing that's listed in the next
18 paragraph that starts at line 57, those were all
19 known tests for measuring -- making the various
20 measurements listed there when you filed your
21 patent; right?
22 A. The testing that's shown here for USP
23 Chapter 729 is for lipid injectable emulsions, and
24 that was published information.
25 Q. And you mentioned USP 729. If we look

1 at the first couple of lines of Column 2, it says,
2 "Emulsion formulations must be physically stable.
3 The droplet size limits defined in USP 7290 apply
4 throughout the assigned shelf life."
5 Do you see that?
6 A. I see that.
7 Q. And was that something that was known
8 before you filed your patent?
9 A. That was known to achieve a stable
10 formulation that you have to meet the USP
11 Chapter 729 limits.
12 Q. Yes, I understand that.
13 My question is, though, you don't know
14 of any reason why someone would want to make a
15 pharmaceutical emulsion that is not physically
16 stable?
17 A. I do not know of any reasons.
18 Q. And if an aprepitant emulsion was
19 crystallizing, one way to stop that crystallizing
20 and maintain stability is to increase the amount
21 of emulsifier; is that right?
22 A. There are many reasons why aprepitant
23 from aprepitant emulsion could be crystallizing
24 out. So depending on the situation that it's in,
25 then different steps will be taken.

1 Q. And one of those steps could be to
2 increase the amount of the emulsifier; correct?
3 A. In making the aprepitant emulsion, the
4 amount of lecithin that's required is very
5 important, as well as many other factors, to help
6 with reducing the time the aprepitant is out of
7 solution.
8 Q. And I've marked and posted for your
9 review Exhibit -- Han Exhibit 14, I believe it is,
10 which is a document bearing Bates
11 Nos. HERON_195354.
12 A. I do not recognize this document.
13 Q. Let me just ask you just a couple of
14 questions. This is an article from 2013 of
15 August; is that right?
16 A. It was published in 2013, August.
17 Q. If you could turn to the second page of
18 the article, it says, "Cosolvency and surfactant
19 solubilization."
20 Do you see that?
21 A. I see that.
22 Q. And it says, Formulation of insoluble
23 drugs using cosolvents is also one of the oldest
24 and widely used technologies for formulation of
25 insoluble drugs, especially for a liquid

1 formulation intended for oral and intravenous
2 administration.
3 Do you see that?
4 A. I see that.
5 Q. I understand that's what they stated.
6 You have no reason to disagree with that
7 statement; correct?
8 A. I do not disagree.
9 MS. VERNON: Your Honor, defendants move
10 into evidence the following exhibits: DTX-23,
11 DTX --
12 JUDGE BRYSON: Just a second.
13 MR. ALBANO: I got it.
14 JUDGE BRYSON: All right. Go ahead.
15 MS. VERNON: DTX-23, DTX-80, DTX-190,
16 DTX-191, DTX-192, DTX-194, DTX-199, DTX-202,
17 DTX-262, DTX-283, JTX-3, and JTX-102.
18 MR. ASHKENAZI: No objections,
19 Your Honor.
20 JUDGE BRYSON: Very well. They'll be
21 admitted.
22 (Exhibits DTX-23, DTX-80, DTX-190,
23 DTX-191, DTX-192, DTX-194, DTX-199, DTX-202,
24 DTX-262, DTX-283, JTX-3, and JTX-102 were offered
25 and admitted.)

1 MS. VERNON: And at this time we have
2 another witness to present by deposition.
3 JUDGE BRYSON: Okay. And how long is
4 this deposition?
5 MS. VERNON: About an hour, as well.
6 JUDGE BRYSON: Okay.
7 MR. ALBANO: Could you repeat the times
8 for the first deposition for me?
9 MS. VERNON: 41 minutes and 19 seconds
10 is allocated to the defendant, and 25 minutes and
11 17 seconds is allotted to plaintiff.
12 MR. ALBANO: Thank you.
13 JUDGE BRYSON: Okay. And how about on
14 this deposition, do you have those times?
15 MR. ALY: I do. 33 minutes and
16 28 seconds is allotted to defendant.
17 MR. ALBANO: I'm sorry, I need a second.
18 All right.
19 MS. VERNON: All right. For Dr. Thomas
20 Ottoboni's deposition, 33 minutes and 28 seconds
21 is allotted to defendant, and 23 minutes and
22 20 seconds is allotted to plaintiff.
23 MR. ALBANO: Okay. Thank you.
24 JUDGE BRYSON: Very well.
25 Let me go off the record just a moment

1 and consult with the court reporter.
2 (Discussion off the record)
3 JUDGE BRYSON: Okay. You may proceed.
4 MS. VERNON: Thank you.
5 JUDGE BRYSON: Back on the record.
6 MS. VERNON: The parties present the
7 deposition testimony of Dr. Thomas Ottoboni, taken
8 on October 26th, 2023. Dr. Ottoboni is one of the
9 named inventors on the two asserted patents. He
10 is the former chief scientific officer and senior
11 vice president of plaintiff, Heron.
12 He testified in his individual capacity
13 and on behalf of Heron as a 30(b)(6) corporate
14 designee on topics relating to the research and
15 development of the claimed formulations, use and
16 indications of the claimed formulations, and the
17 preparation, filing and communications with FDA
18 regarding the NDA for Cinvanti.
19 JUDGE BRYSON: Very well.
20 Whereupon,
21 THOMAS OTTOBONI, PH.D.,
22 being first duly sworn or affirmed to testify to the
23 truth, the whole truth, and nothing but the truth, was
24 examined and testified by videotaped deposition as
25 follows:

1 DIRECT EXAMINATION BY COUNSEL FOR THE DEFENDANT
2 BY MR. NELSON:
3 Q. Can you please state your name and
4 address for the record?
5 A. Thomas Ottoboni. [--- Redacted
6 ---]
7 Q. You're an employee of Heron
8 Therapeutics; is that right?
9 A. I am an employee of Heron Therapeutics.
10 Q. Do you understand that you are here and
11 have been designated to testify on a series of
12 topics on behalf of Heron?
13 A. I do understand that, yes.
14 MR. ASHKENAZI: And, Counsel, these are
15 all subject to the parties' objections and the
16 specific scope that we had identified in advance
17 of the deposition.
18 BY MR. NELSON:
19 Q. So just to make sure the record is
20 clear, I want to make sure we got this.
21 So it looks like it's Topics 1 through
22 7, 9 through 10, 16, 20 through 23, 33, 36, 37, 39
23 and 40; is that correct?
24 A. That appears correct, yes.
25 Q. So, Dr. Ottoboni, we've placed before

1 you at least electronically a document that's been
2 marked as Exhibit 3, and it bears Bates Nos.
3 HERON_0000307 through 10.
4 Can you identify this document for me,
5 please?
6 A. This is my CV.
7 Q. Do you have a more recent version, or is
8 this the most recent version of your CV?
9 A. This is probably the most recent
10 version. I have not updated it since I've been
11 employed throughout this period.
12 Q. And did you prepare this CV?
13 A. I -- I did. It may have been -- I did
14 actually, yes.
15 Q. It's an accurate summary of your
16 education and professional employment experience;
17 is that right?
18 A. I have to review it just quickly here.
19 It is an accurate representation at the
20 time it was prepared.
21 Q. You obtained your Ph.D. in organic
22 chemistry in 1986; is that right?
23 A. I obtained my Ph.D. in 1986, correct, in
24 organic chemistry.
25 Q. Now, you have a list of patents and

1 patent applications that follow under your
2 professional certification.
3 Do you see that?
4 A. I see those.
5 Q. And there are two patents on sustained
6 release emulsions that are on there, one patent
7 that ends in 171 and the one that ends in 153.
8 Do you see those?
9 A. I do see those.
10 Q. Now, if you can turn to your employment
11 history, which is on page HERON_309. And I want
12 to exclude your work at Heron for a moment and
13 focus on your other employment.
14 Aside from the InSite work that you did,
15 did you do any other formulation work at any other
16 positions that involved intravenous products?
17 A. POINT Biomedical.
18 Q. Were those intravenous products at POINT
19 Biomedical -- and I don't need to know the product
20 itself, but were any of them emulsion
21 formulations?
22 A. The products were colloidal systems at
23 POINT Biomedical.
24 Q. What does that mean, "colloidal"?
25 A. They were basically microspheres

1 generated by an emulsion process, but they were
2 polymeric microspheres in the end that were
3 injected intravenously.
4 Q. Now, when did you start at Heron
5 Therapeutics?
6 A. I started at Heron Therapeutics, I
7 believe, as an employee in 2012.
8 Q. What are your current responsibilities
9 at Heron?
10 A. I am the chief scientific officer and
11 senior vice president. I am responsible for
12 pharmaceutical development, which includes
13 analytical, technologies, quality control,
14 translational sciences which -- and translational
15 sciences, which encompass nonclinical, as well as
16 clinical pharmacology.
17 Q. When did the aprepitant formulation
18 project begin at Heron?
19 A. I don't recall an exact date, but,
20 again, very early in my tenure there. It was --
21 yeah, in -- very early in my tenure, the first few
22 years I was there.
23 Q. When you started at Heron, was it your
24 responsibility to identify new drugs for
25 development?

1 A. I -- I provided suggestions that were
2 discussed in a more team environment for new
3 drugs.
4 Q. And I want to focus on the research and
5 development portion of the aprepitant product
6 right now.
7 Who was involved in that project from a
8 research and development standpoint?
9 A. It was -- again, we were a very small
10 company, very small organization at that point.
11 Hannah and myself were involved in the
12 formulation. I had a technician helping me early
13 on, as well as a couple of analytical chemists who
14 were doing just the analyses of the results of
15 Hannah and my work.
16 Q. Now, when you were early on instructing
17 Lee Ann Schillinger to perform some work on your
18 behalf, was that the first time that you had sat
19 down to formulate a -- an intravenous emulsion
20 product?
21 A. We had -- we had -- I had directed
22 Lee Ann to initially start with an extended
23 release formulation and that evolved into
24 potentially using an IV formulation.
25 Q. Was that extended release formulation

1 going to be an oral formulation, or was it going
2 to be administered via a different route?
3 A. It was intended to be a subcutaneous
4 product, administered product.
5 Q. And why was it decided to shift from the
6 subcutaneous formulation that you discussed to an
7 intravenous emulsion?
8 A. During the very initial development of
9 that subcutaneous formulation, we conducted animal
10 studies to understand the release profile
11 pharmacokinetics of aprepitant in this formulation
12 and used fosaprepitant as a -- as a standard, if
13 you will, to calibrate what those release profiles
14 look like, what they -- what levels we should be
15 achieving in the bloodstream.
16 When we did those animal studies, we had
17 a very profound adverse event in the dogs, and
18 that led us to try to understand a little bit
19 better the IV formulation.
20 Q. Did you identify the root cause of that
21 adverse event?
22 A. It was due to Emend IV.
23 Q. And what do you mean, "It was due to
24 Emend IV"?
25 A. It was -- well, at the moment -- within

1 minutes of administering Emend IV, the dogs had an
2 anaphylactic reaction.
3 Q. And did you determine what the basis or
4 the cause of that reaction was?
5 A. We didn't understand what the cause of
6 the reaction was at the time.
7 Q. So then why did you decide to shift to
8 an emulsion-based formulation versus any other
9 different kind of formulation?
10 A. Well, we actually investigated a number
11 of formulations prior to attempting to formulate
12 with an emulsion, a number of IV formulation
13 approaches.
14 Q. What are those approaches that you
15 recall?
16 A. They were cosolvents, surfactants.
17 Those are the two major ones I recall.
18 Q. And were you able to formulate products
19 with those other approaches?
20 A. We -- the initial experiments were not
21 successful.
22 Q. Was it your decision to then shift to an
23 emulsion approach?
24 A. I suggested an emulsion would be a
25 potential approach to delivering aprepitant by

1 intravenous injection.
2 Q. Now, you'd agree with me that any
3 pharmaceutical product that's intended to be
4 administered to a patient should be stable for
5 some period of time.
6 We can agree on that?
7 A. Pharmaceutical projects -- products, you
8 know, certainly must be stable through the --
9 through the duration of administration.
10 Q. Did you do anything to educate yourself
11 on how to evaluate the stability of an emulsion
12 intravenous product before you endeavored in this
13 project?
14 A. Not before we started, but during the
15 project certainly.
16 Q. What were some of the things that you
17 and your team looked at for figuring out how to
18 evaluate the stability of emulsion formulations?
19 A. In developing pharmaceutical products,
20 we rely on the U.S. Pharmacopeia. It has
21 parameters required for stability, for acceptable
22 pharmaceutical stability. It gives us those
23 metrics.
24 Q. And U.S. Pharmacopeia, is that also
25 known as the USP?

1 A. It is.
2 Q. And those are standards that are well
3 known and used in the industry; is that correct?
4 A. Someone developing a product would go to
5 the Pharmacopeia very early on to understand the
6 requirements.
7 Q. And they would attempt to formulate
8 their product such that it met those standards
9 generally; is that right?
10 A. We certainly look to the Pharmacopeia to
11 provide guidance on the -- the elements of
12 stability.
13 Q. Have you heard of the term 505(b)(2)?
14 A. I am aware of that. I'm familiar with
15 that term, yes.
16 Q. What is your understanding of 505(b)(2)
17 with respect to a regulatory filing?
18 A. In a 505(b)(2), one relies partially
19 on -- it's typically an established marketed drug,
20 and one relies to some degree on the label, the
21 package insert label of that drug when it comes
22 time to approval.
23 Q. And the Cinvanti aprepitant product that
24 Heron markets, that's a -- that was filed as a
25 505(b)(2); is that right?

1 A. It was filed as a 505(b)(2).
2 Q. Do you know what the product that was
3 referenced for that 505(b)(2) is?
4 A. I believe -- I believe it was
5 fosaprepitant, as well as oral aprepitant.
6 Q. Can you identify this document for me,
7 sir?
8 A. It is the 9,561,229 patent for emulsion
9 formulations of aprepitant.
10 Q. And you are a named inventor on this
11 patent; is that right?
12 A. I am a named inventor on this patent.
13 Q. What is your contribution to this
14 patent?
15 A. Hannah and I developed the technology
16 incorporated in this patent.
17 Q. And the application number for this
18 application -- for the '229 patent -- sorry, the
19 application number for the '229 patent is listed
20 as 15/083,071.
21 Do you see that?
22 A. I see that.
23 Q. And counsel has just handed to you the
24 document that we've had marked as Ottoboni
25 Exhibit 5, a document bearing Bates Nos. HERON_178

1 to 372.
2 Do you have that document in front of
3 you, sir?
4 A. I have this document, yes.
5 Q. And are you familiar with this document?
6 A. Parts of it. I am familiar with parts
7 of it.
8 Q. And what do you understand this document
9 to be?
10 A. It appears to be the application forms
11 submitted with the specification and the first
12 claims of an application, though it has some
13 further elements during prosecution.
14 Q. So at the time you filed your
15 application, aprepitant was already known for
16 being used in the prevention of acute and delayed
17 nausea and vomiting associated with initial and
18 repeat courses of highly emetogenic cancer
19 chemotherapy; is that right?
20 A. Aprepitant had been approved for the
21 presentation of acute and delayed nausea and
22 vomiting associated with initial and repeat
23 courses of highly emetogenic chemotherapy.
24 Q. So you didn't come up or invent with
25 the -- this use of aprepitant with patients,

1 that's right?
2 A. I did not invent this use of aprepitant
3 with -- for chemotherapy-induced nausea and
4 vomiting.
5 Q. In your career, have you formulated any
6 products that were poorly soluble into emulsion
7 formulations?
8 A. I believe I did, but I don't recall
9 specifics right now.
10 Q. In that paragraph, it talks about
11 crystals are considered visible when they're
12 viewed at magnification of 4X to 10X.
13 Do you see that?
14 A. Yes, I see that.
15 Q. Is that part of the USP criteria for
16 determining stability?
17 A. It is not part of USP 729.
18 Q. And do you recognize the portion of this
19 document that starts at page 258 as being an
20 office action from the examiner?
21 A. Yes, this is an office action from the
22 examiner.
23 Q. The office action here has a
24 notification date of June 3rd, 2016; is that
25 right?

1 A. Correct. That is June -- yeah, it says
2 June 3rd.
3 Q. Please turn to HERON_263, which is
4 page 5 of the examiner's discussion.
5 So focusing on paragraph 29 of
6 HERON_263, and it says the -- Claims 1 and 11 are
7 rejected under 35 USC 103(a) as being unpatentable
8 over Zhou, et al., CN 102379845 published
9 March 21st, 2012, cited on IDS in view of Bromer,
10 et al. (U.S. 2007/0011777 A-1).
11 Do you see that?
12 A. I see that.
13 Q. And you recognize that number that is
14 associated with the Zhou, et al., as the same Zhou
15 patent application we've been seeing so far
16 throughout this prosecution; is that right?
17 A. Yes.
18 Q. Now, paragraph 31, the examiner lists
19 the injectable pharmaceutical emulsion of your
20 application.
21 Do you see that?
22 A. I see that paragraph, yes, 31, yes.
23 Q. Well, let's look through it. What are D
24 through H that are listed there?
25 A. They are weight percents of components.

1 Q. D, the function of the aprepitant,
2 that's the active ingredient; right?
3 A. Aprepitant is the active ingredient.
4 Q. And the egg yolk lecithin, that's the
5 emulsifier; is that right?
6 A. Egg yolk lecithin is considered an
7 emulsifier.
8 Q. Now, sodium oleate, it's listed there,
9 is to adjust pH.
10 Do you see that?
11 A. It does say that, yes.
12 Q. Is that accurate?
13 A. That is one of the functions of sodium
14 oleate.
15 Q. Turn to page HERON_266, please.
16 A. Okay. I'm on page 266.
17 Q. And I want to look at paragraph 42 of
18 page 8 of the examiner's statement.
19 It says here, "The only ingredient
20 recited in the instant claims with a range that
21 does not at least touch the range taught by Zhou,
22 et al., is that of the emulsifier."
23 Do you see that?
24 A. I see that.
25 Q. My question is: There is an overlap

1 between the 0.4 to 1 weight percent of aprepitant,
2 as described per your claims, and the 0.5 percent
3 to 2.0 weight percent aprepitant, that's described
4 as being disclosed in Zhou; correct?
5 A. The numbers -- the numbers -- just on
6 the face of it, the numbers -- I'm sorry, I lost
7 the -- I lost the composition referred to here
8 now. Our composition, I'm sorry.
9 Q. That's in paragraph 31.
10 A. Paragraph 31. And the examiner here
11 states that our aprepitant ratio is .4 to 1. And
12 it states in paragraph 33 that the composition is
13 .5 to 2 weight percent.
14 Q. So there is an overlap in those two
15 surfactant numbers; right?
16 A. The numerical values appear to overlap.
17 Q. And the same with the oil, the numerical
18 values between the 9 to 10 weight percent for your
19 claims and the 5 to 30 weight percent of the oil
20 in Zhou, there is an overlap there; correct?
21 A. The 9 to 10 is within the numerical
22 range of 5 to 30.
23 Q. And if you look at paragraph 32, at the
24 end there is a 2 to 6 weight percent of ethanol.
25 And that overlaps with paragraph 33(l), which has

1 a co-emulsifier of ethanol between 1 to 10 weight
2 percent.
3 Those two overlap; right?
4 A. The numerical values of, yeah, 2 to 6
5 overlap with the range of -- fall within the range
6 of 1 to 10 for ethanol.
7 Q. Could you please turn to HERON_282,
8 please.
9 A. On page 282.
10 Q. This is a notification from the patent
11 office, U.S. Patent Office, dated August 31st,
12 2016; is that right?
13 A. It is dated, yeah, August 31, 2016.
14 Q. And if you could turn to the next page,
15 please, 283. This is an applicant initiated
16 interview summary.
17 Do you see that?
18 A. I see that.
19 Q. And you are listed as one of the
20 individuals who participated in this interview; is
21 that right?
22 A. I am listed as such, yes.
23 Q. Do you recall attending this interview?
24 A. I vaguely recall the interview. I don't
25 recall the meeting itself.

1 Q. If you could please turn to page 285.
2 A. I'm on 285.
3 Q. The third paragraph that starts,
4 "Dr. Harlocker," do you see that?
5 A. I see that.
6 Q. Is Dr. Harlocker your attorney?
7 A. Dr. Harlocker was a patent agent
8 employed by our patent counsel -- by our patent
9 firm -- or IP prosecution firm, rather.
10 Q. It says, "Dr. Harlocker advised that
11 Example 4 in the specification can be compared to
12 the invention of Zhou."
13 Do you see that?
14 A. I do.
15 Q. And then it goes on to say, "The
16 examiner sought clarification regarding the
17 process described in Example 4 of the
18 specification versus the examples of Zhou."
19 Do you see that?
20 A. I see that sentence, yes.
21 Q. Did you provide the patent examiner with
22 a -- any comparison of the process described in
23 your Example 4 of the patent specification versus
24 the examples of Zhou?
25 A. From -- from this document, I see that

1 the examiner had specific questions regarding some
2 of the steps in our example, and we tried to
3 answer the examiner's questions.
4 Q. It goes on to state, The examiner
5 suggested that Dr. Ottoboni provide a declaration
6 to explain any differences in the procedure of
7 Example 4 versus the process used in Zhou (e.g.,
8 Zhou Exhibit 1 uses the term, quote, coarse
9 emulsion, close quote, but does not have two
10 phases at that point, Zhou Example 1 appears to
11 dissolve the, quote, sticky residue with soybean
12 oil and ethanol before heating, but Example 4 of
13 the spec appears to require heating to dissolve
14 the material).
15 Do you see what I read there?
16 A. Yeah, the second -- the third paragraph.
17 Q. First of all, did you understand the
18 examiner to be discussing the Zhou patent
19 application that we've been discussing thus far
20 today?
21 A. I believe that the examiner was -- was
22 referring to the Zhou application.
23 Q. So we are still in Exhibit 5. And if
24 you could turn to page HERON_294, please.
25 A. Page -- I'm on page 294.

1 Q. This portion of the document is titled,
2 "Amendment Under 37 CFR Section 1.111."
3 Do you see that?
4 A. I see that.
5 Q. So this is a response to the office
6 action that we were just looking at.
7 Is that your understanding?
8 A. That would be my understanding.
9 Q. Let's turn on page 2 of this portion,
10 which is HERON_295.
11 And these remarks, did you participate
12 in drafting these remarks?
13 A. I don't recall, honestly.
14 Q. Please turn to HERON_296, which is the
15 third page of these remarks.
16 A. 296. I'm on 296.
17 Q. Now, "The examiner noted that Zhou does
18 not teach the use of sodium oleate as a pH
19 modifier."
20 Do you see that?
21 A. I see that.
22 Q. Now, the examiner also noted that, "Zhou
23 does not recite any particular agent as preferred
24 for adjusting the pH and, therefore, any suitable
25 compounds may be used."

1 Do you see that?
2 A. I see that it says, "because Zhou does
3 not recite any particular agent as preferred for
4 adjusting the pH, and therefore any suitable may
5 be used."
6 Q. Okay. So a formulator that wanted to
7 adjust the pH of an aprepitant emulsion would have
8 to test different compounds that are known to be
9 used for pH adjustment; is that fair?
10 A. I know that we evaluated compounds for
11 the adjustment of the question during our
12 development program.
13 Q. And you selected those compounds because
14 they were known to be used for adjusting pH in
15 compositions; correct?
16 A. We selected compounds that would result
17 in an adjustment to the pH.
18 Q. Well, in order to determine whether Zhou
19 taught a stable formulation, you had to actually
20 perform at least one experiment following Zhou; is
21 that right?
22 A. We performed a number of experiments
23 with aprepitant -- emulsifier aprepitant and other
24 components in the range of Zhou and found that
25 those were not stable.

1 Q. Let's turn to page HERON_302, please.
2 A. I'm on 302.
3 Q. And what is this portion of the document
4 that we're looking at?
5 A. It says, Declaration Under 37 CFR,
6 paragraph 1.132.
7 Q. And this is a declaration you submitted;
8 is that correct?
9 A. It was a declaration by me.
10 Q. And is that your signature next to the
11 date of August 31st, 2016, on page 305?
12 A. That is my signature.
13 Q. Now, you say in paragraph 10 of your
14 declaration, "The examiner asked about possible
15 differences between the preparation method
16 described by Zhou, specifically Example 1 in Zhou,
17 and the preparation method described in Example 4
18 of the instant application."
19 Do you see that?
20 A. Yes, I see that.
21 Q. In response to your understanding of
22 what the examiner asked about, did Heron reproduce
23 Example 1 of Zhou?
24 A. I do not believe we reproduced Example 1
25 of Zhou.

1 Q. Why when the examiner was asking about a
2 comparison with Example 1, did Heron decide to not
3 reproduce Example 1 of Zhou?
4 A. The examiner had specific questions
5 regarding the method of preparation, and we
6 addressed those in this declaration.
7 Q. Why did Heron decide not to reproduce
8 Example 1 of Zhou?
9 A. The examiner didn't request that we
10 repeat that example. He had specific questions
11 regarding Example 1 -- she, I'm sorry.
12 Q. If we could go back to your declaration
13 now on page 304 where we were at.
14 A. Yes, I'm there.
15 Q. And that next sentence from where we
16 were looking starts, "I have carefully read."
17 Do you see that?
18 A. "I have carefully read Example 2."
19 Yes, I see that.
20 Q. And you state there that, "the phrase
21 'soybean oil' was added to the coarse emulsion
22 represents an inaccuracy in translation with
23 respect to the word 'emulsion' because up to this
24 point it is clear that no emulsion (mixture of oil
25 phase and aqueous phase) exists."

1 Do you see that?
2 A. I do see that.
3 Q. But how would you know if you're
4 following Zhou properly and getting the right
5 mercurial if Zhou got a coarse emulsion and you
6 got a thick residue and you can't explain what the
7 difference between those two are?
8 A. Hannah would have followed the procedure
9 in Zhou and would have gotten at the end of
10 this -- these steps described here something -- a
11 product -- an end product that was the same as
12 what Zhou had gotten.
13 Q. And we agree that your declaration
14 doesn't list all the similarities and differences
15 between Example 4 of your application and
16 Example 1 of Zhou; correct?
17 A. The patent examiner had very specific
18 questions that she wanted to address in our
19 discussion and followed up with this declaration,
20 not every aspect of it.
21 Q. The next page, HERON_340, paragraph 25.
22 A. Paragraph 25.
23 Q. Do you see there is a description of the
24 reference called Wan, et al.
25 Do you see that?

1 A. Yes, I see that.
2 Q. And it says here that the Wan reference
3 teaches intravenous formulations of neurokinin-1
4 (NK-1) antagonists.
5 Do you see that?
6 A. Yes, I see that.
7 Q. Do you recognize aprepitant as an NK-1
8 antagonist?
9 A. Yes, aprepitant is an NK-1 antagonist.
10 Q. It mentions lipoid E80.
11 Do you see that?
12 A. Yes, I see that.
13 Q. Do you know what that is?
14 A. That is the egg lecithin -- or lecithin
15 derived from egg yolk.
16 Q. That is the same emulsifier Heron uses
17 in its Cinvanti product; correct?
18 A. It is. We use lipoid E80 in our
19 Cinvanti product.
20 Okay. I have Exhibit 6 with me.
21 Q. And for the record, Exhibit 6 is
22 HERON_611 to 639. You can see at HERON_636, you
23 can compare that it's the same application number
24 listed in the declaration as Exhibit 5 at
25 HERON_302. You can use either document.

1 I'm providing you the smaller, shorter
2 version, if it's easier, because we're going to
3 compare to some other documents. So please feel
4 free to use either one, but you can confirm for me
5 that the declaration at Example -- or Exhibit 6 is
6 the same as the declaration at Exhibit 5 at
7 HERON_302?
8 A. Yes, it's dated the same.
9 Q. And I've had marked as Exhibit 7 a
10 document bearing Bates HERON_34346 to 34349.
11 Can you tell me what this document is,
12 sir?
13 A. The first page appears to be an e-mail
14 from Francis Wong to Han Han and Laura Lerner.
15 Q. At the very bottom of the first page,
16 it's the original message is an e-mail from you to
17 Laura Lerner and Han Han; correct?
18 A. That's correct.
19 Q. And that's dated March 22nd, 2014?
20 A. Yes, it's dated March 22nd, 2014.
21 Q. Were you sending a link or a file that
22 was the Zhou patent, Chinese patent application,
23 to Ms. Lerner and Dr. Han?
24 A. As I recall, yes.
25 Q. So you have in front of you Ottoboni

1 Exhibit 8, which is -- bears Bates
2 Nos. HERON_0188566 to 570.
3 This is an e-mail from July of 2014, and
4 this is you providing the translation from
5 Mr. Wong to Mr. Sullivan via Dr. Han; is that
6 correct?
7 A. Dr. Han appears to have sent me the
8 batch formula, as well as the patent translation
9 document, which I then, looks like, sent --
10 there's an e-mail then from me to Robert Sullivan.
11 Q. So Ottoboni Exhibit 9, which is in front
12 of you and up on the screen, bears Bates
13 Nos. HERON_003-5072 to 81.
14 Do you recognize this document, sir?
15 A. It appears to be a translation of the --
16 well, it's the Zhou patent. I'd have to look at
17 the numbers, but I believe it's the Zhou patent,
18 yes.
19 Q. Okay. And then the first named inventor
20 there is Zhou on this application publication;
21 correct?
22 A. Yeah, Zhou Wei, yes.
23 Q. And the publication number, the CN ends
24 in '845, we saw that during the prosecution
25 history that we were looking at; is that right?

1 A. I believe this is the same number.
2 Q. And the publication date, March 21st,
3 2012.
4 Do you see that?
5 A. I see that.
6 Q. And Exhibit 10, Ottoboni Exhibit 10,
7 bears Production Nos. HERON_0032697 to 33075.
8 A. It is an A.P. Pharma notebook.
9 Q. It is notebook 1255; correct?
10 A. I'm sorry, yes, 1255.
11 Q. And who was this notebook issued to?
12 A. On page 2, it says, assigned to Han Han.
13 Q. On this project, did Dr. Han take her
14 direction directly from you or from Dr. Lerner or
15 both?
16 A. Dr. Han and I collaborated and spoke
17 frequently regarding the project.
18 Q. Did you discuss where in the ranges you
19 would choose to use the different various
20 components?
21 A. We collaborated throughout the
22 development program, and we discussed things on a
23 daily basis. I don't remember a specific
24 conversation.
25 Q. But there is no specific embodiment that

1 was duplicated; is that correct?
2 A. The examples were not duplicated.
3 Q. And no other non-example that has these
4 specific amounts of the components and percentages
5 of them, that's not disclosed anywhere in Zhou;
6 correct?
7 A. The specific amounts used here are not
8 literally disclosed in Zhou.
9 Q. Why did Dr. Han choose these specific
10 amounts of the components and percentages of those
11 amounts?
12 A. At this stage of development, Dr. Han
13 had significant experience in testing and
14 evaluating multiple, many, many aprepitant
15 emulsions, and these were likely selected -- I
16 can't speak for her, but these fall within the
17 range -- let me back up a little bit and take that
18 back.
19 These appear to me to be values that she
20 felt would provide the best chance for success for
21 this particular form -- for a formulation that
22 fell within the ranges provided by Zhou.
23 Q. How is "success" defined?
24 A. Stable, that the formulation didn't have
25 crystals less than one week after preparation and

1 that it would have met the criteria of USP 729.
2 Q. Why did you choose the one week for
3 evaluating whether crystals appeared?
4 A. If under two sets of stability
5 conditions, 25 or 5, if a formulation isn't stable
6 for one week, it becomes almost impossible to
7 commercialize.
8 Q. Now, Dr. Han's work here in the
9 laboratory notebook in Exhibit 10, she was not to
10 obtain a product that had -- that did not exhibit
11 crystals later than a week; correct?
12 A. It says within four days post
13 preparation at room temperature crystals were
14 observed by microscopy.
15 Q. And you don't recall any other
16 experiments adjusting the Zhou amounts from what
17 Dr. Ottoboni did here on laboratory notebook
18 page 186 but still being within the ranges
19 disclosed by Zhou; correct?
20 A. I can't recall if she -- I'm not aware
21 of that or can't recall that she specifically
22 deliberately adjusted the ranges. I do know that
23 we conducted many, many experiments, some of which
24 may have fallen within the ranges. And, again,
25 everything we -- many years worth of work we came

1 up with a composition that -- or a range of
2 compositions that provided a stable formulation.
3 Q. You can see from Step 7, and then it
4 says Step 6 after that, I don't know if that's a
5 typo, but that's where I'm focusing on.
6 Do you see those two steps?
7 A. I see the last two steps in that
8 sequence.
9 Q. Yes. Thank you.
10 A. Okay.
11 Q. It looks like the pH was adjusted from 9
12 to 8 using the one normal -- it says used one
13 normal HCL; is that right?
14 A. Using .1 normal HCL.
15 Q. So is that a different pH adjustment
16 than was done than what's listed in Step 7?
17 A. If I were running this experiment, I
18 would attempt to adjust first -- raise -- it looks
19 like raise the pH with sodium hydroxide and then
20 measure it and then continue to adjust it until I
21 achieved the right pH. It's not unusual to have
22 to move sort of back and forth within pH. So I
23 view that as a single pH adjustment.
24 Q. Do you know why the pH went from 8 to 7?
25 A. I do not know why. It's not unusual for

1 the pH to kind of settle in a little bit.
2 Q. An entire pH unit?
3 A. It depends on the precision of the
4 measurement used. If it was, for example, pH
5 paper with a reading of one pH unit per color, it
6 would have been -- the 8 and 7 may have been
7 almost the same or the same. So it doesn't
8 specify the methodology.
9 Q. This is Exhibit 11.
10 A. I have notebook 1263.
11 Q. And for the record, Exhibit 11 bears
12 Bates HERON_33076 to 33619. And you identified
13 this laboratory notebook by its number.
14 Who was this laboratory notebook issued
15 to?
16 A. Page 2 indicates -- yeah, it's assigned
17 to Dr. Han Han.
18 Q. What's the date issue for this
19 laboratory notebook?
20 A. The date issue is 7 August 2014.
21 Q. And if you could turn to page -- Bates
22 page 33121, it's laboratory notebook page 17.
23 A. Okay. I'm on page 17 of the notebook.
24 Q. And the objective here is microfluidizer
25 829.

1 Do you see that?
2 A. I do see that.
3 Q. And the laboratory notebook page is
4 dated August 29, 2014.
5 Do you see that?
6 A. 8/29/14, yes.
7 Q. And it says, Chinese paper replicate.
8 Do you see that?
9 A. I see that.
10 Q. Now, it's your understanding that this
11 is an experiment based not on the Zhou patent, but
12 on an article publication.
13 Is that your understanding?
14 A. That is my understanding of this
15 particular one, yes.
16 Q. And Exhibit 12 is Document Production
17 No. HERON_0035111.
18 Do you recognize this document, sir?
19 A. It is a paper by Zhou with the title,
20 "Preparation of Aprepitant Emulsions for
21 Intravenous Injection." I've seen this before.
22 Q. And is this the Chinese paper that's
23 referenced in Dr. Han's laboratory notebook 1263
24 at page 17?
25 A. I believe so.

1 Q. Is this -- well, let me ask.
2 If you can turn, please, to HERON_35113
3 at Section 2.4.
4 A. Okay. I'm there.
5 Q. Is this the disclosure from the Zhou
6 article that Dr. Han followed in her laboratory
7 notebook 1263?
8 A. It appears to be, except in the notebook
9 it's in milligrams and in the paper it's in
10 percentages. I'm trying to quickly do the
11 conversion, but in my head, I believe it does
12 match, yes.
13 Q. Why did Dr. Han follow this specific
14 disclosure in Ottoboni Exhibit 12 Zhou article
15 instead of following sort of more of the general
16 disclosures and picking an amount like she did
17 with the Zhou patent?
18 A. In this particular one, Zhou -- in this
19 paper, Zhou described this as prescription
20 optimized and, therefore, we assume this to be the
21 best formulation of the ones that were prepared.
22 Q. And Zhou determined that this optimized
23 formulation was stable for three months; correct?
24 A. Zhou conducted several tests, and those
25 tests are presented in the paper. Yet, there's no

1 acceptance criteria, or I wouldn't know if
2 anything is stable because I don't know what
3 the -- I don't know all these tests and what was
4 -- what the acceptance criteria would have been
5 for those tests.
6 Q. Okay. But Zhou does conclude from their
7 stability tests that the formulation was stable
8 for three months after, correct?
9 A. They don't claim it's stable. They say
10 they observed the stability and the results show
11 no obvious changes in the appearance and still
12 show milky white, no layering and demulsifying
13 phenomenon.
14 Q. Now, going back to Exhibit 11, the Han
15 notebook at page HERON_33121. Let me know when
16 you're there.
17 A. 33121, which would be notebook page 17.
18 Okay.
19 Q. And is this laboratory notebook page
20 experiment at Exhibit 11, is that Example 5 of
21 Exhibit 4 of the '229 patent?
22 A. The elements of it correlate, yes.
23 Q. What are some of the factors that you
24 know of that would impact aprepitant emulsion
25 stability?

1 A. Essentially every component has a role
2 in the stability of the formulation.
3 Q. And Exhibit 14, Ottoboni Exhibit 14,
4 bears Bates Nos. HERON_0000373 to 726. And
5 Ottoboni Exhibit 15, which is before you and up on
6 the screen, bears Production Nos. HERON_0054723 to
7 54790.
8 Are you familiar with this document,
9 sir?
10 A. It's a formulation development report
11 prepared by Hannah Han.
12 Q. And was it the goal of Heron to create a
13 product that did not have polysorbate 80?
14 A. The goal of the project was to
15 develop -- was to develop a formulation of
16 aprepitant, and that evolved into -- it started
17 out in very broad terms and then evolved into an
18 IV formulation of aprepitant.
19 Q. Was one of the goals of the project to
20 formulate a product -- withdrawn.
21 Was one of the goals of the project to
22 develop a formulation that did not have
23 polysorbate 80?
24 A. No, it was -- the goal of the -- the
25 goal of the project was to develop a product that

1 we hoped would be safer than Emend for injection
2 when administered to people.
3 Q. Turn back one page for me, if you would,
4 please, to 54733.
5 A. Okay.
6 Q. And it says there, 2.2.2, initial
7 formulation process.
8 Do you see that?
9 A. I see that.
10 Q. And there's a reference there to patent
11 CN 102379845 Zhou, et al., 2012.
12 Do you see that?
13 A. Yes, I see that.
14 Q. Was that the initial formulation process
15 that Heron used at the onset of its product
16 development for aprepitant?
17 A. The words here say that, and I will take
18 it that Hannah wrote that correctly.
19 Q. Do you agree with that conclusion based
20 on the work that Heron has done?
21 A. This is a very early experiment, and
22 I -- what we learned, and if you read through this
23 entire report, the components all interact
24 together. And this is an isolated experiment, and
25 it's an over -- it is a simplification of the fact

1 that everything kind of interplays together. We
2 can -- they are contributors. I will say that egg
3 lecithin and ethanol are contributors to the
4 solubility.
5 Q. And Heron was interested in using lipoid
6 E80 as the emulsifier because it was used in
7 preparation of parenteral nutrition emulsions; is
8 that right?
9 A. Lipoid E80 had a history of use in a
10 number of pharmaceutical emulsions.
11 Q. Turn to 54743, please.
12 A. Is that on page 21 of the report?
13 Q. Yes.
14 A. Okay.
15 Q. And I'm in "The selection of oil"
16 section at the bottom, 2.2.6.
17 A. Okay.
18 Q. And here, Heron identified soybean oil
19 as a primary candidate for the oil component
20 because it is the principle oil used in parenteral
21 nutrition emulsions.
22 Do you see that?
23 A. I see that sentence.
24 Q. So it was known that soybean oil had a
25 previous use in emulsion formulations; is that

1 right?
2 A. Soybean oil was -- has been used in
3 emulsion formulations, yeah.
4 Q. And Heron wasn't the first company to
5 use sodium oleate as a pH adjuster; correct?
6 A. Sodium oleate is -- was present in one
7 other pharmaceutical formulation that I'm aware
8 of.
9 Q. Turn to Heron 54768, please, which is
10 page 46.
11 A. Page 46 of the report. Okay. I'm on
12 page 46.
13 Q. And if you look at Figure 11, it says,
14 "Stability of emulsion containing various amounts
15 of ethanol after processing at room temperature."
16 Do you see that?
17 A. Yes, I see that Figure 11.
18 Q. And all of those formulations listed
19 there are stable for more than 20 days; correct?
20 A. Correct. The graph shows that the
21 lowest one is above 20 on the Y axis.
22 Q. If you could pull back up Exhibit 10,
23 which is the big lab notebook 1255. And I'd like
24 to go to page HERON_32927.
25 Let me know when you get there.

1 A. Page 32927.
2 Q. Would you agree with me that the
3 formulation in Exhibit 10, laboratory notebook
4 1255 at HERON_32927, is the formulation that is in
5 Ottoboni Exhibit 15 at page 42?
6 A. The weights of the components match up.
7 Q. I've had marked as Exhibit 16 the
8 document in front of you and on the screen bearing
9 Bates HERON_0032399 to 32696.
10 What is this document, sir?
11 A. A lab notebook.
12 Q. And is this Dr. Han's lab notebook?
13 A. It was assigned to Dr. Han.
14 Q. And it's lab notebook 1249; is that
15 right?
16 A. Notebook 1249.
17 Q. So laboratory notebook page 110, and
18 this says, "Making aprepitant emulsions."
19 Do you see that?
20 A. I see it in the objective. It says,
21 "Making aprepitant emulsion."
22 Q. And I will represent to you I was not
23 able to find aprepitant emulsion work in this
24 laboratory notebook prior to this page dated
25 2/10/14.

1 Is it your recollection that this was
2 the first formulation work that Dr. Han had done
3 on aprepitant emulsion formulations?
4 A. After reviewing the notebooks, this is
5 the first one I could find, as well.
6 MS. VERNON: Your Honor, defendants move
7 into the record the following exhibits: DTX-172,
8 DTX-193, DTX-201, DTX-259, DTX-316, JTX-1, JTX-2,
9 and JTX-4.
10 MR. ASHKENAZI: No objections,
11 Your Honor.
12 JUDGE BRYSON: Very well. They will be
13 admitted.
14 (Exhibits DTX-172, DTX-193, DTX-201,
15 DTX-259, DTX-316, JTX-1, JTX-2, and JTX-4 were
16 offered and admitted.)
17 JUDGE BRYSON: And, also, we're up to
18 the time for our lunch break.
19 What do you anticipate will be your
20 order of proceeding in the afternoon?
21 MR. ALY: Your Honor, we'll have a live
22 witness next and then another video after that and
23 a final live witness.
24 JUDGE BRYSON: Good. Okay.
25 Let's take until 1:05.

1 (Recess from the record.)
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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 transcript
9 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 marriage,
13 and that I am in no way interested in the outcome of
14 this matter.
15
16 IN WITNESS WHEREOF, I have hereunto set my
17 hand this 25th day of June, 2024.
18
19
20 Matthew Goldstein, RMR, CRR
21
22
23
24
25

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