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A P P E A R A N C E S
ON BEHALF OF THE PLAINTIFF, HERON
THERAPEUTICS, INC. :
ISAAC S. ASHKENAZI, ESQUIRE
MARK RUSSELL SPERLING, ESQUIRE
JUSTIN T. FLEISCHACKER, ESQUIRE
CHRISTOPHER HILL, ESQUIRE
STEPHEN KRUSE, ESQUIRE
PAUL HASTINGS LLP
200 Park Avenue
New York, New York 10166
212.230.7892

and

KARTHIK R. KASARANENI, ESQUIRE
2050 M Street, NW
Washington, D.C. 20036
202.551.1901

and

1 A P P E A R A N C E S C O N T I N U E D
2
3 JEREMY A. TIGAN, ESQUIRE
4 MORRIS NICHOLS ARSHT & TUNNELL
5 1201 North Market Street
6 16th Floor
7 Wilmington, Delaware, 19899
8 302.425.3096
9
10 ON BEHALF OF THE DEFENDANT, FRESENIUS KABI
11 USA, LLC:
12 IMRON ALY, ESQUIRE
13 KEVIN NELSON, ESQUIRE
14 HELEN H. JI, ESQUIRE
15 JULIE A. VERNON, ESQUIRE
16 ARENT FOX SCHIFF
17 233 South Wacker Drive
18 Suite 7100
19 Chicago, Illinois 60606
20 312.258.5523
21
22 and
23
24
25

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A P P E A R A N C E S C O N T I N U E D

DANIEL A. TAYLOR, ESQUIRE
SMITH KATZENSTEIN JENKINS, LLP
1000 West Street
Suite 1501
Wilmington, Delaware 19801
302.504.1688

1 JUDGE BRYSON: This is closing arguments
2 in Case No. 22-985, Heron Therapeutics, Inc.,
3 against Fresenius Kabi USA, LLC, District of
4 Delaware.

5 Before we get started, just two quick
6 notes.

7 First, I think I asked the parties to
8 provide redactions to the transcript that they
9 wish to have implemented, and I think those
10 redactions are due fairly soon so that we can have
11 the transcript prepared for -- for posting.

12 The second point is there is a member of
13 the public who has asked permission to
14 participate, not to participate formally but to be
15 present for this hearing; and given that the
16 hearing is in the nature of the public court
17 hearing, the -- well, we have some more people.
18 Let me just make sure they're in there.

19 The -- I want to be sure that if anybody
20 gets into an area in which they think that
21 anything they have to say is something that is
22 sensitive, confidential, and was not -- and did
23 not come out in the first portion of the court
24 proceeding that was public, then they should so
25 advise me, and we can ask the members or member of

1 the public to excuse themselves.

2 I think that's the most efficient way to
3 handle that matter. But be aware that this is all
4 subject to public awareness.

5 Anyway, all right, let's get started.

6 I think each side has been allotted an
7 hour. You can divide the side -- the time. We'll
8 start with Fresenius.

9 But before we get started, I would like
10 to call the roll of who's representing each side.

11 So, first, for the plaintiff.

12 MR. TIGAN: Yes, Your Honor. Good
13 morning. This is Jeremy Tigan with Morris Nichols
14 in Wilmington for Heron.

15 On my screen I see Mr. Ashkenazi, who
16 will be arguing for us, and at least Mr. --

17 JUDGE BRYSON: Mr. Tigan, just a second.
18 I just realized that this isn't yet on record. So
19 let me --

20 MR. TIGAN: Oh, sure.

21 JUDGE BRYSON: Let me do that. I'll fix
22 that.

23 There we go. All right.

24 So would you start again, Mr. Tigan,
25 sorry.

1 MR. TIGAN: Certainly, not a problem,
2 Your Honor.

3 Jeremy Tigan with Morris Nichols in
4 Wilmington for Heron. I am joined by several of
5 my colleagues from Paul Hastings, including Isaac
6 Ashkenazi, who will be arguing for us.

7 I see many boxes on screen, influencing
8 Mr. Fleischacker, and maybe Mr. Ashkenazi can tell
9 me if any other Paul Hastings attorneys are on.

10 MR. ASHKENAZI: Your Honor, we have a
11 number of other Paul Hastings attorneys on, but
12 I'm the only one who will be speaking today.

13 JUDGE BRYSON: Okay. Do you want to run
14 down the roll of who's on your list --

15 MR. ASHKENAZI: Sure.

16 JUDGE BRYSON: -- that are present?

17 MR. ASHKENAZI: Mr. Kasaraneni, Karthik
18 Kasaraneni, Chris Hill, Justin Fleischacker, Mark
19 Russell Sperling, and Stephen Kruse.

20 JUDGE BRYSON: All right. Okay. And
21 that's everybody from your side.

22 And you will be handling the argument
23 entirely, Mr. Ashkenazi?

24 MR. ASHKENAZI: Yes, Your Honor.

25 JUDGE BRYSON: All right.

1 Okay. For the defendant then, who do we
2 have?

3 MR. TAYLOR: Good morning, Your Honor.
4 This is Daniel Taylor from Smith Katzenstein &
5 Jenkins for Fresenius Kabi.

6 And on the call I have with me the
7 co-counsel from ArentFox Schiff, Imron Aly, who I
8 believe will be leading the presentation, Kevin
9 Nelson, Helen Ji, and Julie Vernon.

10 JUDGE BRYSON: Okay. And you're saying
11 Mr. Aly will be leading the presentation. He'll
12 be conducting the entire presentation for
13 Fresenius, I take it?

14 Is that correct, Mr. Taylor?

15 MR. ALY: That's correct, Your Honor.

16 JUDGE BRYSON: Hello, Mr. Aly. You'll
17 be doing the whole thing?

18 MR. ALY: Yes, good morning. Yes.

19 JUDGE BRYSON: Very good. Good morning.

20 Okay. Why don't we do this. Since
21 Fresenius is the party that -- with respect at
22 least to the issue of invalidity, is the party
23 that is seeking to invalidate the patent, let's
24 start with the defendant here.

25 So, Mr. Aly, I will try to restrain

1 myself from asking too many questions and give you
2 an opportunity to make your presentation, I hope,
3 largely uninterrupted. I may not be able to
4 resist interposing a question, but I'll try to
5 give you free reign to present the case the way
6 you'd like.

7 If you want to save time for rebuttal,
8 then you may do so. I will let you know when you
9 get down to a short number of minutes.

10 So go ahead.

11 MR. ALY: Thank you very much,
12 Your Honor.

13 A clarification, which is -- I believe
14 the order had 45 minutes per side. So as I plan
15 and reserve --

16 JUDGE BRYSON: Oh, 45. Okay. Yeah, I
17 had forgotten. I had several hearings this week
18 and I was not sure, but 45, then, it is.

19 MR. ALY: Well, you know us, we'll take
20 the time allotted.

21 JUDGE BRYSON: All right. Well --

22 MR. ALY: No, 45 minutes is perfectly
23 fine, and we're ready to proceed.

24 JUDGE BRYSON: Great.

25 MR. ALY: Thank you.

1 Thank you very much, Your Honor. And
2 may it please the Court.

3 First, we really appreciate, and on
4 behalf of all the sides in the case and the
5 counsel, thank you for Your Honor's schedule and
6 accommodation of us during the trial in D.C. and
7 here for the closing. The convenience of the
8 remote is valuable and having the court reporter
9 do a gentleman's effort and Mr. Albano helping
10 throughout the process has been very, very useful.

11 And in this particular case, our
12 position is the patents are invalid as obvious.
13 CN '845 showed obviousness for all the asserted
14 claims. CN '845 did all the heavy lifting, and a
15 POSA would have refined from there with nothing
16 more than routine optimization.

17 Now, Heron's position results on
18 hindsight. That's what their focus is going to
19 be, and that's common for a patent owner. But
20 here, our position is that it would take hindsight
21 to ignore CN '845 and look some other way.

22 This is not a case where emulsifier is
23 in one reference, oil is in another, the drug is
24 in some third reference, there's a co-emulsifier
25 pulled from an encyclopedia. No. This was

1 preassembled in CN '845.

2 So in my presentation today, I plan to
3 discuss CN '845, motivation to combine, reasonable
4 expectation of success, and secondary
5 considerations, all to show obviousness of all
6 five asserted claims. And I plan to conclude with
7 written description and noninfringement.

8 CN '845, why is that so important?
9 That's JTX71. It's because CN '845 solved a
10 problem which had not yet been solved, and that
11 problem was: How do we put aprepitant itself in
12 an injectable solution?

13 And up until that point, there wasn't an
14 aprepitant solution. And we looked, and heard at
15 trial, Dr. Hale talking about efforts from the
16 mid-1990s to design compounds and what they tried
17 to do at Merck at the design compound level.

18 Well, we don't have a lot of evidence on
19 formulation, even from the mid-1990s, but the
20 point for this trial was that the priority date by
21 that point in time, the world changed.

22 CN '845 issued in 2012. The priority
23 date for the asserted claims is September 2014.
24 And in that window of time, Heron did the routine
25 optimization and obtained the patents that it is

1 asserting here.

2 The CN '845 reference, what did it show?

3 It showed an emulsion as the way to obtain the
4 injectable solution of aprepitant. It showed
5 several ways of making the emulsion, not just one.
6 It showed several different components that could
7 be used within each of the categories. They all
8 worked to make an emulsion.

9 And it showed different ranges for
10 excipient amounts, and they also all made an
11 emulsion. It's undisputed that they were all
12 emulsions in the eight examples.

13 So now, a POSA, who had heretofore
14 thought that aprepitant was hard to formulate --
15 cement dust, brick dust, those are the kinds of
16 phrases that are used. CN '845 showed we can use
17 the emulsion approach to formulate an injectable
18 aprepitant solution. It was done. And the
19 question remained: How stable could it be made?

20 Once it's done, now we're talking about
21 how long can we keep it in an emulsion. And
22 that's why there is a routine optimization,
23 looking at CN '845, whether the question at the
24 state of the art is making an NK-1 antagonist
25 formulation in general or an aprepitant approach

1 in particular, the question is: Why would anyone
2 look anywhere other than CN '845, once that is in
3 the state of the art and a POSA was deemed to know
4 about it?

5 What would the POSA do next? The
6 evidence showed, and Dr. Rabinow explained, the
7 motivation would be to combine that CN '845 with
8 other knowledge, with other information that would
9 explain to a POSA that a POSA would understand
10 from which why that CN '845 emulsion was working
11 and then to optimize based on USP standards, USP 1
12 and USP 729.

13 There's no dispute in this case that the
14 USP is important, that a POSA would have pursued
15 it for stability. All of the experts and both of
16 the named inventors said that a POSA would look at
17 the USP.

18 And that's what sets forth the physical
19 stability claim limitations, and they're entirely
20 consistent with the term "physically stable," as
21 used in Claims 9 and 10 of the '794 patent.

22 The reasons to --

23 JUDGE BRYSON: Now, let me interrupt for
24 just a moment, Mr. Aly.

25 Fresenius argues that, in fact, CN '845

1 was not stable. And so if you would address that
2 question.

3 MR. ALY: Yes, Your Honor.

4 Fresenius' position is that CN '845 has
5 some stability information in it, but it is not
6 showing USP stability. So the thing to be done is
7 to test for USP stability and optimize for that
8 parameter. What I mean by some --

9 JUDGE BRYSON: So your -- your response
10 to their argument is that the substance with the
11 composition in CN '845 was stable at least under
12 the standard that was being assessed in CN '845,
13 but not necessarily USP?

14 MR. ALY: Yes, Your Honor.

15 JUDGE BRYSON: All right.

16 MR. ALY: That's right.

17 JUDGE BRYSON: So is the standard -- was
18 it K subE that the Chinese patent was -- or
19 publication was directed to?

20 MR. ALY: Yes, Your Honor, it was. And
21 to be more precise, CN '845 was the patent
22 application that had the -- it didn't have the K
23 subE or other stability testing. It did still
24 have positive stability information in the form of
25 sterilization tests that had been done, heating

1 the product to a high temperature, and showing an
2 emulsion will remain. That is not KE or USP.

3 JUDGE BRYSON: When did the K subE
4 standard come in? Was that in Zhou?

5 MR. ALY: That was in the Zhou article
6 later in --

7 JUDGE BRYSON: Oh, okay.

8 MR. ALY: -- later in 2012.

9 JUDGE BRYSON: Not in '845 patent?

10 MR. ALY: Correct.

11 JUDGE BRYSON: Okay.

12 MR. ALY: And Zhou, though, the same
13 lead inventor in Zhou, that's JTX115, did the
14 stability study and, yes, did look at several more
15 variables over time and temperature conditions and
16 showed that it maintained that K subE measurement.

17 But, again, this is more helpful,
18 favorable information in the right direction,
19 giving optimism and a reasonable expectation of
20 success. It's not quite still USP standards. And
21 that's why everybody would have now said, as
22 Dr. Rabinow explained, a POSA would have next
23 pursued USP optimization. That's the thing that
24 had not been done yet, and that's the thing that
25 would have been entirely obvious.

1 When doing the routine optimization,
2 taking that K subE standard -- and this is where
3 in the Heron submissions that had been made to
4 date, they mix and match, sometimes saying, Well,
5 if KE was already there, why would somebody need
6 to do something more, and using the word
7 "stability-oriented information."

8 And that's correct, it is
9 stability-oriented information, but not the USP
10 that everybody had agreed at trial would be the
11 next step to pursue.

12 When pursuing K subE, what -- and going
13 from K subE to the USP 1 and USP 729 standard,
14 what would a POSA focus upon? He or she would
15 focus upon lecithin amount, which is what
16 Dr. Rabinow testified about.

17 And this wasn't really disputed that the
18 POSA could look at lecithin amount for the purpose
19 of routine optimization. And Dr. Rabinow gave
20 three reasons for why the POSA would have focused
21 on lecithin. Not based on hindsight, but looking
22 at the prior art and showing what CN '845 taught a
23 POSA.

24 The first of those three was CN '845
25 itself. It used high lecithin levels, up to

1 10 percent with ratios of up to 49 to 1 in the
2 examples. And there are more -- those high
3 emulsion levels had a reason because prior art
4 used 1 to 2 percent in their lecithin, if the goal
5 was to make an emulsion.

6 So something else was going on, and a
7 POSA would have looked to CN '845 and looked at
8 the procedure within CN '845 and recognized that
9 there is a step. The first step is not just
10 dumping everything into a formulation, but
11 actually to put the drug, aprepitant, and egg yolk
12 lecithin, the emulsifier, together in ethanol and
13 then evaporating the ethanol.

14 And Dr. Rabinow explained, again
15 un rebutted, that that would be a way to form a
16 complex between those two components.

17 The second reason Dr. Rabinow emphasized
18 for why a POSA would focus on lecithin levels is
19 the Washington reference, JTX113. Here, the
20 Washington reference described that for Class III
21 compounds, and these are compounds like aprepitant
22 that are neither soluble in water or in oil, that
23 those could be soluble at the interface between
24 the two phases, the oil and the water.

25 And that is what the explanation

1 somebody would recognize, a POSA would see, once
2 CN '845 is available that Washington explained the
3 mechanism for why it worked.

4 But Washington went on. It went on to
5 say that increasing the surface area would help to
6 further increase and solubilize the drug, and a
7 POSA would, therefore, take from Washington the
8 motivation and direction to increase lecithin
9 levels specifically for stability.

10 And the third focus point that
11 Dr. Rabinow explained were other POSA knowledge
12 regarding complexation. And the complexation
13 references here were just to show examples that a
14 POSA would have been aware of, as Dr. Rabinow
15 explained, where egg yolk lecithin in particular
16 had been used to form complexes with drugs.

17 And those complexes, these are basically
18 interactions between the egg yolk lecithin and a
19 drug, helped to stabilize the formulations in the
20 prior art examples, as well.

21 Each of these three reasons points in
22 the direction of higher emulsifier levels for
23 higher stability. That set the expectation, and
24 that expectation was reasonable.

25 Heron's response to all --

1 JUDGE BRYSON: Just briefly, if I could
2 interrupt.

3 What is the best authority that you have
4 in the form of exhibits or otherwise for the third
5 proposition?

6 MR. ALY: Yeah, for the third
7 proposition, it's the testimony of Dr. Rabinow.
8 And in his testimony, he's referring to three
9 exhibits. The three exhibits are the Yue
10 reference, Agarwal, and EP825.

11 JUDGE BRYSON: Now, when you say "Yue,"
12 is that -- did I misunderstand you? Are you
13 talking about the Liu reference, L-I-U, or a
14 different reference?

15 MR. ALY: Sorry, different reference.
16 Y-U-E.

17 JUDGE BRYSON: Y-U-E. Oh, okay. Good,
18 I got it. All right.

19 MR. ALY: And for the record, those
20 are -- Yue is JTX114; Agarwal, JTX67, and EP279
21 reference was -- by Bombardelli is JTX74.

22 And from there --

23 JUDGE BRYSON: Okay.

24 MR. ALY: Thank you.

25 From there, what is Heron's response to

1 these motivations and the reasonable expectation
2 of success? It is simply that we could not
3 predict for sure with absolute certainty --

4 JUDGE BRYSON: Let me interrupt once
5 again.

6 Those three references do not include
7 aprepitant; right? They're not aprepitant
8 related, they just are talking about other
9 complexing with lecithin; right?

10 MR. ALY: That is correct, Your Honor.
11 Yes.

12 JUDGE BRYSON: Okay. All right. Go
13 ahead.

14 MR. ALY: And so the question that
15 Dr. Rabinow was addressing on those points and why
16 he was talking about those examples is to answer
17 the concern or, you know, maybe caution: Was
18 CN '845 the first to come up with complexation or
19 in coming out of this argument using just a new
20 approach, Dr. Rabinow?

21 And it's the commonality of the approach
22 of complexation that Dr. Rabinow was addressing,
23 and those were not about aprepitant in particular.
24 CN '845 was the first to do this approach. But it
25 was to show that that approach was established and

1 known, and at that point it was not disputed.

2 And Heron's response is that it's not
3 absolutely certain. Their expert Dr. Little
4 explained that increasing lecithin does not always
5 guarantee increased stability and that there is
6 some upper limit. Both are true. But neither
7 address the reasonable expectation of success.

8 A reasonable expectation of success, of
9 course, must be reasonable, not absolute. And
10 here, there was every reason to conclude that the
11 reasonable expectation of success for achieving a
12 stable formulation that meets USP 1 and USP 729
13 and, therefore, also meets the construed term
14 "physically stable."

15 What were those reasons in particular?
16 I explained earlier the CN '845 reference reported
17 terminal sterilization, that's favorable
18 information, with lecithin levels at 10 percent.

19 Zhou, JTX115, did the stability study
20 and as we pointed out with KE, but, again, gave
21 that positive confidence, both directions, to show
22 that increasing lecithin would likely meet USP
23 standards.

24 And in response, again, Dr. Little does
25 not say there's no reason to conclude that would

1 not happen. He's just saying it may not happen
2 always. That was the testimony.

3 This is a good place to discuss the Liu
4 reference that Your Honor mentioned. That's
5 L-I-U. That's JTX93. And that fits in as far as
6 the routine optimization and combination about how
7 much emulsifier could a POSA have used.

8 To answer that question, Dr. Rabinow
9 first looked at CN '845 and said, 10 percent is
10 not an upper limit. A POSA would naturally try
11 values above the 10 percent within routine
12 optimization.

13 And Dr. Rabinow also looked to the Liu
14 reference and explained that a POSA would look to
15 a reference to find out -- for several reasons,
16 but two among them would be that Liu was about
17 microemulsions, which Liu itself said were part of
18 emulsions.

19 And at that point in time, this 2014
20 time frame, the word "microemulsion," the word
21 "emulsion," they were used in overlapping ways,
22 not always technically precise, reflecting a
23 continuum between the two as related terms.

24 And Liu also was used for a different
25 reason that Dr. Rabinow explained, which is if a

1 POSA wanted to know what information there was for
2 safety of increasing lecithin, is 10 percent
3 really a cap?

4 Liu showed that actually up to
5 30 percent phospholipid had been used.
6 Phospholipids, in particular, were called out, as
7 the testimony showed, as natural products that
8 were, therefore, known to be safe.

9 For those reasons, Dr. Rabinow explained
10 the 5 to 30 percent of the Liu reference gave a
11 working range for testing the emulsifier level.

12 Here, in response, Dr. Little explained
13 that Liu is about a microemulsion. But,
14 unfortunately, Heron's briefing doesn't address
15 the fact that microemulsions were part of
16 emulsions, they were overlapping terms, and that
17 Von Corswant explained that that's how they were
18 used. So people were looking at each of them in
19 parallel.

20 JUDGE BRYSON: You said --

21 MR. ALY: CN '845 itself --

22 JUDGE BRYSON: If I could interrupt for
23 a second.

24 MR. ALY: I'm sorry.

25 JUDGE BRYSON: No, it's Zoom. You're

1 not hearing when I start talking if you're
2 talking. So it's not your fault. It's the fault
3 of Zoom.

4 The whole question of which a
5 considerable chunk of the briefing is addressed to
6 of whether microemulsions of this sort, or
7 whatever you want to call them, the items that
8 were discussed in Liu, are different not just in
9 degree but in kind from the emulsions that are
10 discussed in other references and the emulsions
11 that are applicable here.

12 The argument that Alcon is making is
13 that you really can't extrapolate from anything
14 said in Liu because you're talking about something
15 that is different in kind.

16 And I understand that certainly at a
17 certain point in time, and perhaps even to some
18 extent today, the microemulsion -- there's some
19 perhaps lack of agreement in the field as to the
20 scope of what constitute -- the scope of what is
21 an emulsion incorporating or not incorporating
22 microemulsions.

23 But I'd like you to address that
24 question. It does seem to me to be a fairly
25 important question with respect to the

1 applicability of Liu.

2 MR. ALY: Of course, Your Honor.

3 Three things that I'd like to respond
4 to.

5 Point number 1, that it is related art
6 to the same field, which is formulating emulsions.
7 And under Dr. Rabinow's analysis, the emulsions as
8 a category included various sorts which were not
9 differences in kind, not different animals
10 altogether, but they're subsets which have a
11 continuum, was the word that he had used at trial,
12 to show that there isn't a bright line when
13 something is a microemulsion versus an emulsion.

14 And that's important here because in the
15 vocabulary, as Dr. Little acknowledged, people
16 would call these formulations microemulsions
17 because they used a microfluidizer and had
18 microscopic level particles.

19 And so there's always overlap between
20 the formulations, not only because of the
21 similarity in how they were used, the formulation
22 components, approaches to making emulsions, but
23 also because of the vocabulary. That's point
24 number 1.

25 Point number 2 that I'd like to

1 emphasize is that as far as the safety teachings,
2 so if -- even if one were to assume that it's a
3 different kind of formulation altogether, which is
4 not our position, but even under our assumption,
5 Heron has not responded to the point that if a
6 POSA wanted to look at what levels were safe,
7 where would they look?

8 And this could be in something of a
9 manual, a Remington's-type manual, which is
10 something formulators might look to. That would
11 be a general reference. And that would say, Here,
12 people have used up to 30 percent lecithin, and
13 that's safe.

14 In this case, though, Dr. Rabinow
15 explained, We have something far more precise. We
16 have, within the emulsions world, the
17 microemulsion reference that is showing up to
18 30 percent lecithin would be safe. So even if
19 it's used for the safety reason, that would be
20 useful.

21 And the third point I'd like to make is
22 that it is, at the minimum, analogous art because
23 it's showing that we're talking about items
24 directed to the same problem. We're talking about
25 two references that are directed to making

1 emulsions. An emulsion is the combination of two
2 phases, that it's basic, oil and water.

3 And so when you have those two
4 combinations of oil and water, the distinction
5 Dr. Little has made is some are going to be more
6 stable than others. And that's the distinction
7 that has been made so far.

8 But that, again, is a matter of degree
9 and not something that is a matter of kind, and
10 there's no evidence that showed that suddenly
11 there's a flip switched and here's something that
12 happens in this formulation and does not apply at
13 all to another formulation.

14 And for those three reasons, Your Honor,
15 the Liu reference is applicable, and Dr. Rabinow's
16 analysis is appropriate.

17 I would also add that even without Liu,
18 the analysis remains the same. Dr. Rabinow
19 explained that CN on its own had up to 10 percent
20 emulsifier already showing the emulsifier worked
21 with stability and complexation.

22 And then asked the question just when
23 CN '845 was being discussed about whether the
24 levels were enough for USP stability and how high
25 a POSA would go just by looking at CN '845,

1 recognizing the small differences between
2 10 percent and moving up from there, 11, 12, 13,
3 14, 15 percent.

4 So this is not a matter of where
5 night-and-day difference between what had been
6 used and what had been applied for that reason, as
7 well, just looking at CN '845.

8 JUDGE BRYSON: Okay.

9 MR. ALY: Next, as far as routine
10 optimization is concerned for why would it be
11 routine optimization to address this problem, the
12 routineness of the approach is not disputed.
13 Dr. Little conceded at trial that stability
14 testing is routine even if it takes a long time to
15 get results. The approach is routine, something
16 within the POSA's wheelhouse.

17 For optimizing, Dr. Rabinow explained
18 that would be a POSA's bread-and-butter job to
19 look at variables, assess them, test them, and
20 obtain results for a standard. And here, it's not
21 just shooting in the dark.

22 Here, we know, and the POSA would have
23 known, that actually optimizing for lecithin would
24 be a result effective variable, because -- a POSA
25 knew that from looking at CN, of course.

1 But, more importantly, Khan itself
2 expressly explained that there would be a result
3 effective variable because the egg yolk lecithin
4 in a formulation was known to be very important,
5 most important formulation component in an
6 emulsion for stability in particular. That's the
7 Khan reference, JTX91.

8 And when a POSA then, therefore, is
9 looking at the prior art and optimizing,
10 Dr. Rabinow explained that they would set the
11 parameters, run the tests, and then come up with
12 the results.

13 And in response, Heron showed no
14 criticality for any particular component or
15 number, and there's nothing that Heron showed or
16 Dr. Little explained would be known as a redline
17 or too much lecithin from the prior art.

18 And what instead happened here is that
19 Heron says, If you look at their real-world
20 evidence, it showed they did something dramatic
21 and different. But what was that?

22 It was optimizing the prior art,
23 starting with CN '845, in particular, and
24 optimizing for USP. It's not following something
25 new or coming up with an invention. It's calling

1 the prior art and implementing it.

2 So that 14 percent, which is a claim
3 term, is something a POSA would have arrived at
4 from the routine optimization specifically for USP
5 optimization, and that is the critical issue in
6 the case for which Heron did not show criticality
7 for that number.

8 Now, Your Honor, I'd like to move to two
9 components and then move to secondary
10 considerations. There are two components, sucrose
11 and sodium oleate, which are in dispute.

12 Sucrose, we were surprised to see that
13 it was disputed. It had never been called out
14 before or at trial. But the short answer is
15 sucrose was in CN '845, in the list and in the
16 patent disclosure, as one of equivalent options
17 and tested by Heron to show that it made no
18 difference which sugar was used.

19 Sodium oleate, more dispute about this
20 was at trial. We know there's --

21 JUDGE BRYSON: What function does the
22 sucrose serve, as best we know in this
23 formulation?

24 MR. ALY: It's a tonicity agent. And
25 Dr. Rabinow explained it helps the osmolality of

1 the drug.

2 JUDGE BRYSON: Osmolality. And --

3 MR. ALY: Osmolality.

4 JUDGE BRYSON: And that's it; right? Is
5 it osmolarity or osmolality? It doesn't sound --

6 MR. ALY: Osmolality. But people tell
7 me they're very related. It's with the two Ls.

8 JUDGE BRYSON: Oh, I know they're
9 related, but for purpose of getting it right, I
10 want to make sure that I get the right consonant.

11 It's osmolality; right?

12 All right. That's what --

13 MR. ALY: Osmolality, that's right.

14 JUDGE BRYSON: That's what I understood.
15 Okay.

16 Keep going then.

17 MR. ALY: Yes. Sodium oleate, there is
18 dispute about this component. And we know that
19 there is a pH adjuster that is used in CN -- it
20 says that in CN '845, but a particular one was not
21 named.

22 So what Dr. Rabinow explained is that
23 sodium oleate would be obvious in view of the
24 CN '845 disclosure. It may not be the only
25 choice, but obvious choice. Why? Because Zhou

1 was -- the Zhou reference, switching to the Zhou
2 reference, added oleic acid and had a basic pH of
3 7.3.

4 So as Dr. Rabinow explained, instead of
5 a POSA using the oleic acid and then adding sodium
6 hydroxide to raise the pH, it would be -- the
7 direct approach would be to use sodium oleate.
8 They're conjugate bases, the oleic acid, the
9 sodium oleate. Sodium oleate is a salt form of
10 oleic acid. So it's basically inherently formed
11 whenever there's anything with sodium that is
12 added. And the --

13 JUDGE BRYSON: If you have a pH over 7,
14 then you're going to be converting the oleic acid
15 into an oleic just automatically?

16 MR. ALY: Automatically and inherently.

17 JUDGE BRYSON: Yeah.

18 MR. ALY: Yes. Yes.

19 JUDGE BRYSON: All right.

20 MR. ALY: And another reason Dr. Rabinow
21 explained to use sodium oleate is it's already in
22 egg yolk phospholipid. So if you're going to use
23 it, why add something different, foreign, when
24 it's already a natural component, you're just
25 shifting the values of it.

1 Finally, sodium oleate commonly used in
2 emulsions, looked at Wan, Fell, and Jumaa. Those
3 are JTX112, JTX76, and JTX88, in that order. And
4 the key point for Heron's briefing is that they
5 contest whether sodium oleate would have been
6 safe. But Jumaa, JTX88, made clear that sodium
7 oleate was very safe in the emulsion context with
8 egg yolk phospholipids. And that is why they were
9 so commonly used.

10 JUDGE BRYSON: Could you give me
11 those --

12 MR. ALY: Dr. Little, in response at
13 trial --

14 JUDGE BRYSON: I'm sorry, could you give
15 me those exhibit numbers again? I want to make
16 sure that I have them right. The three exhibit
17 numbers you recited.

18 MR. ALY: Yes. Wan, JTX112; Fell,
19 JTX76.

20 JUDGE BRYSON: Right.

21 MR. ALY: And Jumaa, JTX88.

22 JUDGE BRYSON: Right. Okay. Thank you.

23 MR. ALY: And the point I was simply
24 making is that Dr. Little and any of Heron's
25 experts at trial didn't mention Jumaa. It was a

1 totally un rebutted analysis that Dr. Rabinow
2 provided, showing sodium oleate's safety
3 specifically in emulsions.

4 Now moving to secondary considerations,
5 Your Honor.

6 First, there's an assertion of a
7 long-felt need, but there's a confusion as to what
8 that need is. And I'll be listening carefully
9 today, as well, because there's a back-and-forth
10 between hypersensitivity and injection site
11 reactions, injection site adverse events, what are
12 those differences and what was the trial evidence.

13 The trial evidence was that in some
14 articles polysorbate 80 is associated with
15 hypersensitivity, the systemic allergic reaction.
16 Both Dr. Roeland and Dr. Markman addressed that.
17 But that's distinct from a localized injection
18 site adverse event, something that's happening
19 where the needle is going into the skin.

20 And there's not evidence and data about
21 a hypersensitivity problem or difference. The
22 evidence and data that Dr. Roeland relied upon was
23 not about hypersensitivity, even though that is
24 the thing associated with polysorbate 80,
25 according to Heron.

1 Instead, what Dr. Roeland testified
2 about was a difference in warning label as to the
3 injection site adverse events, and much of the
4 briefing is about injection site adverse events.
5 That isn't linked to polysorbate 80.

6 And in any event, those injection site
7 adverse events are 1 to 3 percent reported for the
8 drug, and there's nothing that showed that there
9 was a long-felt need or a clamoring to eliminate
10 those injection-site reactions.

11 One evidence that they did point to,
12 Heron did in their briefing, is a Mayo Clinic
13 example that switched from the injection of
14 Emend IV to the oral aprepitant. But it seemed to
15 me, reviewing the briefing and the article, that
16 that's a common sense approach that you're going
17 to have more injection-site reactions when you
18 give an injection as opposed to giving something
19 orally.

20 It wasn't the combination of different
21 injection versions of aprepitant. It was just
22 saying that when you have an oral version and it
23 worked as well for some patients, why go through
24 the injection that introduces potential
25 injection-site adverse reactions? That's the Mayo

1 Clinic study that Heron referenced.

2 But either way, on long-felt need --

3 JUDGE BRYSON: So is there any evidence
4 as to what the cause of the injection-site
5 reactions might have been?

6 MR. ALY: No, there was not evidence
7 provided at trial, and Dr. Roeland did not explain
8 what he thought was causing the injection-site
9 adverse events either. There is definitely a
10 pallor of polysorbate 80 is doing something
11 problematic, but that's -- the evidence was about
12 hypersensitivity and allergic reactions --

13 JUDGE BRYSON: Okay.

14 MR. ALY: -- not injection site.

15 And, ultimately, when it comes to
16 long-felt need, whatever we assume or whatever the
17 allegations are that are made as far as assertions
18 regarding a long-felt need, CN '845 addressed
19 them.

20 If it's because of polysorbate 80,
21 that's addressed by CN '845. If it's because
22 of -- because CN '845 had formulations without
23 polysorbate 80 and preferred formulations without
24 polysorbate 80.

25 If there's some other issue about time

1 or administration, CN '845 addressed those as
2 well. And, ultimately, there could not be a
3 long-felt need between when CN '845 issued, which
4 is the pertinent question, in 2012 and when the
5 patent was -- the priority date for the patent is
6 in September 2014.

7 And Dr. Markman just concluded it simply
8 this way. There's not a long-felt need because
9 any of the side effects that were shown, be they
10 hypersensitivity or injection site, were medically
11 manageable.

12 But all else being equal, if there was a
13 formulation that didn't have polysorbate 80 in it,
14 it's just one more reason to pursue the CN '845
15 formulation. Not the only reason, but certainly
16 one more reason to pursue it.

17 Second commercial -- secondary
18 consideration is failure of others. Here, the
19 focus is on Merck's work from the 1990s. And it's
20 from Dr. Hale primarily, who is not a
21 formulator -- the Court found is not a formulator
22 in the Daubert setting.

23 Dr. Little was given an opportunity to
24 tie things together and explain how a formulator
25 would have interpreted materials, but Dr. Little

1 did not do that.

2 So the trial evidence that we have is
3 1990s era work regarding medicinal chemistry, how
4 to make different kinds of chemical compounds, and
5 no evidence of formulation work that Merck did,
6 tried, or published.

7 And even assuming there had been
8 formulation work or evidence, it does not apply to
9 the state of the art by 2012, when CN '845 and
10 Zhou were published. And so, too, was Hingorani
11 published. Hingorani was another reference that
12 did an emulsion approach. It's JTX21.

13 For those reasons, we don't see and
14 there was no evidence of any failure. Everybody
15 who tried to make these emulsions did.

16 Unexpected results is the next secondary
17 consideration for this. As a threshold matter,
18 Heron did not have any evidence about an
19 expectation in the first place from which to
20 conclude that any test result they did would have
21 been unexpected.

22 And we called that out in our opening
23 brief, but Heron still didn't provide any -- a
24 prior art expectation that somebody would have had
25 to show that there was an unexpected result.

1 Instead, what we have is just test
2 results. And there's a question as to those test
3 results, whether they were even compared to the
4 closest prior art and accurately replicated prior
5 art, because there was no apples-to-apples
6 comparison in terms of pH.

7 We have the CN '845 example, which is
8 Example 4, but that used the pH of 7. Whereas,
9 all of the other working examples, the first
10 stable formulations in the patents, showed pH of
11 around 8.8.

12 We have Example 5 --

13 JUDGE BRYSON: I missed -- you broke up
14 there. Could you go back to the point at which
15 you said the other examples, and then give me what
16 the pHs were for those?

17 MR. ALY: Yes, the other examples in the
18 patent were -- shown in Example 7 of the patent
19 were between 8.7 and 8.9.

20 JUDGE BRYSON: Okay. Okay. Thank you.

21 MR. ALY: And there's also Example 5 of
22 the patents, which we now know was a comparison to
23 the Zhou article test. But there, again, they did
24 not report in the patent what the pH was. And
25 Dr. Rabinow's opinion was simply they did not

1 report it, so a comparison could not be made.

2 In Dr. Little's testimony at trial, we
3 showed the lab notebook for that test that had a
4 pH of 6.5 for the Example 5 formulation.

5 So, ultimately, the unexpected results
6 evidence does not compare to the closest prior
7 art. Next, if we look at the evidence, even at
8 face value and what Heron is saying, unexpected
9 results shows that increasing emulsifier increased
10 stability. That's what Dr. Rabinow and the
11 evidence showed would have been expected.

12 And, ultimately, all of these
13 differences were of degree. One was more stable
14 than another. So there is no evidence of
15 unexpected results that should affect obviousness.

16 Copying, we saw -- it's called a white
17 flag at this point in the response brief. So I'll
18 move onto commercial success. Commercial success
19 is where there is confidential information, but I
20 won't go into it. I will just refer to what Heron
21 did not redact, which is that strategic pricing
22 here controlled the sales of the product and not
23 any other advantages.

24 And there's no evidence that anyone
25 bought Cinvanti for reasons having to do with side

1 effects or two-minute administration. In fact,
2 it's all about the cost. Emend IV is still on the
3 market, and the two are in tandem working to this
4 day to address problems. And it's the strategic
5 pricing that is why buyers make decisions for one
6 versus the other in a particular amount of time.

7 The conclusion on obviousness is that
8 when we weigh the strong case of obviousness,
9 including the CN '845, Zhou, and Liu and
10 Washington references, in view of all the
11 secondary considerations, Claims 9, 10, and 21 of
12 the '229 patent are obvious. And Claims 9 and 10
13 of the '794 would have been obvious, as well.

14 To point out, Claim 21 of the
15 '229 patent is a method of using the formulation
16 to treat CINV, but that is not in dispute that if
17 the formulation is obvious, the method for
18 administering it for that purpose --

19 JUDGE BRYSON: I just want to alert you
20 that you're down to seven and a half minutes. You
21 can either conclude now and save your time, or if
22 you want to talk about infringement, you can do
23 so.

24 MR. ALY: Yeah, my goal is to reserve
25 about five minutes for the rebuttal.

1 JUDGE BRYSON: Okay.

2 MR. ALY: So the conclusion on
3 obviousness that I want to emphasize is that --
4 what happened here? What was the big project that
5 occurred?

6 Heron put up to its real-world example a
7 new formulator who she testified, Dr. Han, was the
8 first time working on an emulsion and applied
9 CN '845 and did tests to show that adding
10 emulsifier increased stability. That's what the
11 evidence showed. Even for Heron's argument that
12 we should look to what the inventors did as
13 real-world evidence supports obviousness.

14 Briefly on written description and
15 noninfringement. On written description, the
16 claims include the full range of 7.5 to 9.0, even
17 though the patent specification distinguished pHs
18 less than 8 in Example 4. And the physically
19 stable formulations were all 8.74 to 8.92. So
20 there's no showing of a possession of 7.5 to 8.
21 That's the argument.

22 Noninfringement is simply -- there's one
23 element of the '794 patent physically stable, and
24 that element is microscopy, for which there needed
25 to be a microscopic test showing no visible

1 particles. Heron didn't test Fresenius Kabi's
2 product, even though it could have done so and it
3 was looking at a microscope after one week.

4 So they used their own tests instead and
5 relied on inherency to do so. Same formulation
6 means the same properties. And here in this case,
7 inherency would be true whether the magnification
8 is 4X to 10X or if it's 40X to 100X.

9 The point is, since Dr. Little relied on
10 and Heron relies on the similarity of the
11 formulations itself to imply what the properties
12 would be for the formulation, that makes the
13 "physically stable" term an inherent property of
14 the claimed formulation and not something
15 additional or more.

16 Heron points to other tests that they
17 relied on at trial, but those used naked-eye
18 observations, not microscopy. And Dr. Little
19 himself said that you couldn't use the naked-eye
20 observations to look for aprepitant crystals.

21 In conclusion, starting where -- ending
22 where I started, we thank Your Honor and all
23 involved for the time and ask for entry of
24 findings that all the asserted claims are invalid
25 and lack written description and are obvious, and

1 that the claims of the '794 patent are not
2 infringed.

3 I reserve the rest of my time. Thank
4 you, Your Honor.

5 JUDGE BRYSON: Thank you.

6 Mr. Ashkenazi, you have 45 minutes.

7 MR. ASHKENAZI: Your Honor, if I could
8 have 30 seconds just to switch here. One second.

9 JUDGE BRYSON: Sure.

10 MR. ASHKENAZI: Thank you, Your Honor.

11 JUDGE BRYSON: Yeah.

12 MR. ASHKENAZI: Can you hear me fine?

13 JUDGE BRYSON: Yeah, I can hear you
14 perfectly.

15 MR. ASHKENAZI: Great.

16 Apologies, one second, Your Honor. I'm
17 just getting the audio up on my side.

18 JUDGE BRYSON: Okay.

19 MR. ASHKENAZI: Very good.

20 Good morning, Your Honor, and may it
21 please the Court. Isaac Ashkenazi of
22 Paul Hastings for plaintiff, Heron Therapeutics,
23 Inc.

24 If it's okay with the Court, I'm going
25 to spend a few minutes on infringement at the end

1 of my presentation and really focus on invalidity.
2 Because Fresenius really hasn't disputed
3 infringement at trial or in post-trial briefing
4 or, as we heard today, nor is there really any
5 basis for a noninfringement finding.

6 And, Your Honor, I know you said you'll
7 let the parties go through their presentation, but
8 I would really encourage -- any questions
9 Your Honor may have, I'm more than happy to
10 answer.

11 JUDGE BRYSON: All right.

12 MR. ASHKENAZI: So focusing on
13 obviousness, I'd like to go over some of the big
14 picture details and then -- big picture points and
15 then get into some of the details.

16 The fundamental problem with Fresenius'
17 obviousness analysis is that it's infected every
18 step of the way with impermissible hindsight. And
19 simply put, Fresenius has not satisfied its burden
20 in proving by clear and convincing evidence that
21 the asserted claims are obvious.

22 At the end of the day, no matter what
23 we've heard from Fresenius today, there is no
24 denying certain objective facts. There was a need
25 for an IV NK-1 receptor antagonist with minimal

1 side effects, fewer side effects than Emend IV,
2 that aprepitant with its properties akin to cement
3 dust and its propensity to form crystals is an
4 extremely difficult molecule to formulate as an IV
5 for use in humans, and that Merck had to move to a
6 pro-drug approach and create fosaprepitant because
7 it could not make an IV for use in humans.

8 In fact, no one was able to accomplish
9 this before Heron. And Fresenius has not pointed
10 to a single prior art emulsion that had greater
11 than 10 percent egg lecithin. And that's key,
12 because we hear about this conjecture from
13 Dr. Rabinow, but not a single reference had above
14 10 percent egg lecithin in an emulsion.

15 Zhou, which came after CN '845, had
16 optimized down to 2.5 percent lecithin. And I
17 want to be clear, because there was a question,
18 Your Honor, CN '845 does not contain any stability
19 test data at all.

20 Zhou, which comes afterwards, does
21 optimize for K subE, as Your Honor pointed out.
22 And that optimization gave 2.5 percent egg
23 lecithin as the optimal formulation, in
24 conjunction with other ingredients, which we'll
25 get to.

1 Simply put, when it comes down to it,
2 Your Honor, Cinvanti was and remains the first and
3 only IV aprepitant emulsion on the market.

4 Now, facing all of this, Fresenius' only
5 option was to look backwards at the prior art with
6 hindsight and to inject new concepts where they
7 just don't exist to come up with some obvious
8 combination.

9 But the idea that a POSA would share any
10 of these untested hypotheses just can't be
11 reconciled with the evidence, like complexation,
12 which isn't even mentioned in CN '845. And it
13 can't be reconciled, that concept. A POSA
14 wouldn't assume any complexation looking at the
15 examples of CN '845 or Zhou. And we'll get into
16 that.

17 Or the relationship of emulsifier amount
18 to interface size and stability that Fresenius
19 asserts, they say that's in Washington, which was
20 published in 1996, but that's simply not stated
21 there. And we'll try to go through that, as well.

22 But I think the most head-scratching
23 thing, Your Honor, is they go to a completely
24 different formulation system, microemulsions. And
25 I want to be clear, this is not a terminology

1 question, whether sometimes people use the term
2 "microemulsions" instead of "emulsions." These
3 are entirely different and distinct formulation
4 systems.

5 JUDGE BRYSON: That's an important
6 question, and one that I would like to hear more
7 from you and, ultimately, from Mr. Aly, as well,
8 as to the distinction between the categories of
9 emulsions and microemulsions, whether they are
10 simply overlapping degrees -- differences as
11 opposed to differences in kind.

12 So if you could help me on that, that
13 would be useful.

14 MR. ASHKENAZI: Sure. So let's start
15 off with just the concept of a microemulsion.

16 A microemulsion is a thermodynamically
17 stable system. Emulsions are not. There is no
18 continuum here, Your Honor. You can't have
19 something that's maybe thermodynamically stable or
20 possibly. These are just completely separately
21 distinct things.

22 One just sort of snaps together. That's
23 the microemulsions. They sort of come together,
24 and they're stable by themselves. And they use
25 very different and distinct components and ratios

1 and amounts of those components. And we'll get --
2 I can get into that in a little bit more detail,
3 Your Honor.

4 Conventional emulsions are not. And
5 that's these oil-in-water, as Fresenius puts it,
6 or conventional emulsions or the standard
7 emulsions that everybody looks at are not --
8 they're nowhere near the same level of detail with
9 microemulsions -- sorry, the level of complexity.

10 Let's get into that for just a little
11 bit more specific, Your Honor. There's no
12 evidence that there's any -- been any
13 microemulsion approved by the priority date.

14 Second, there's no evidence that anybody
15 in the art would ever look to a microemulsion
16 literature to say, Let me apply that to emulsions.
17 It's just simply not present.

18 When we look at Liu, Liu itself says
19 that these are very distinct systems that have
20 their own properties. For example, Your Honor,
21 I'm just going to pull up one point.

22 If we look at Liu, that's JTX93, at
23 page 11, maybe if we could pull that up -- sorry,
24 10, if we can pull that up on the screen.

25 The first -- sorry, if we could go to

1 the top of the screen.

2 JUDGE BRYSON: I've got it.

3 MR. ASHKENAZI: Yeah. So it's the first
4 line under 1.1 at the top, the second line -- the
5 first line, the second sentence.

6 Liu, when talking about the
7 microemulsions here, says, Firstly, the oil phase
8 must have adequately high solubility for the drug.

9 And this is just one point, and
10 Dr. Little went chapter and verse through this
11 reference. But aprepitant is not soluble in oil.
12 This has nothing to do with the emulsions of
13 CN '845, Zhou, or anything like that.

14 If we could take that down.

15 Your Honor, let's also take a couple of
16 points here. If microemulsions were so common and
17 ubiquitous and the knowledge that you could use
18 very high amounts of emulsifier would be known to
19 a POSA, CN '845 clearly set the range of
20 emulsifier from 0.5 to 10.

21 Also, if we're going to look at the
22 microemulsions, we look at the distinction or the
23 components that are used. And I mentioned this a
24 little earlier, and I think I misspoke when I said
25 the complexity.

1 Microemulsions use very different
2 emulsifiers. They even use blends of emulsifiers.
3 If we could go back to JTX93 at page 11.

4 So this is Liu, Your Honor. If we look
5 at that table, that table is the list of
6 emulsifiers that typically use surfactants for
7 injectable microemulsions. And if we look at all
8 these different types of emulsifiers, they
9 don't -- we'll note one thing. They mention
10 phospholipids, but they don't reference egg yolk
11 lecithin.

12 Again, here, the point being is that
13 this is a completely different type of system.
14 It's completely different variables that you would
15 consider here.

16 I want to be clear, we asked
17 Dr. Rabinow, did he give us a single example of
18 a -- this -- some emulsion that somewhere in the
19 continuum between a conventional emulsion and a
20 microemulsion, and he couldn't identify one. And
21 that's because it doesn't make any sense.

22 We can take that down.

23 It doesn't make any sense, because one
24 is thermodynamically stable, the other one is not.
25 One snaps together and uses different formulation

1 components, and the other one doesn't. And they
2 haven't identified any single piece of prior art
3 that says, Oh, there is a continuum.

4 Rather, they're focused on terminology
5 of Fresenius. Sometimes people make the mistake
6 that a microemulsion -- they call conventional
7 emulsions or oil -- conventional oil-in-water
8 emulsions microemulsions.

9 Making a mistake doesn't mean a POSA now
10 is just going to ignore science and go to and take
11 from one reference something that nobody has ever
12 done before.

13 And, again, I want to emphasize that.
14 Not a single person -- not a single piece of
15 evidence has been shown that somebody used
16 microemulsion art to inform the formulation and
17 development of an emulsion, the conventional
18 emulsions that we see in CN '845 and Zhou.

19 With that, Your Honor, I'd like to --
20 unless you have any further questions, I'd move
21 back to my presentation.

22 JUDGE BRYSON: That's fine.

23 MR. ASHKENAZI: Now, knowing all of
24 these problems, Your Honor, the problems with
25 Washington, with Liu, with general CN '845,

1 Fresenius tries to shift the burden, and we heard
2 it a little bit today, for Heron to prove
3 criticality of the ranges, but they have to prove
4 obviousness by clear and convincing evidence.
5 That's the burden on Fresenius.

6 They have to prove that there was a
7 motivation to combine and a reasonable expectation
8 of success. That's not Heron's burden. But,
9 regardless, we did prove criticality. Criticality
10 is shown through the Examples 4 and 5 of the
11 patents-in-suit, which are the prior art for
12 CN '845 and Zhou.

13 And this is a difference in kind, not
14 degree. A difference of a formulation that's not
15 stable, period, could not be given to humans and
16 formulations that are claimed inventions. And,
17 Your Honor, that's not even addressing all of the
18 other objective indicia, which we'll get to a
19 little later.

20 I want to, if I can, take a step back
21 for a moment and talk about the state of the art
22 in 2014. There was a need for an IV NK-1
23 antagonist with minimal side effects. Now,
24 Fresenius says a POSA trying to solve this problem
25 would have gone straight to aprepitant and

1 straight to emulsions instead of any other NK-1
2 receptor antagonist or formulation approach, but
3 we saw by the priority date that Merck and others
4 had failed with aprepitant and moved onto other
5 NK-1 receptor antagonists.

6 Even Dr. Rabinow agreed, and if we could
7 pull up 395, 6 to 9, that the POSA was
8 interested -- POSAs were interested in NK-1
9 receptor antagonists as a class, not just
10 aprepitant.

11 And if we could pull up 127, 17 to 24.

12 Dr. Rabinow also said that, in response
13 to my question -- in response to the question that
14 was asked of him at the time during direct, What
15 would you like to see is development of an -- he
16 responded, What you would like to see is
17 development of an injectable that did not contain
18 polysorbate 80 of fosaprepitant IV formulation.

19 That's Emend IV. That's recognition
20 that a POSA would be looking to make something
21 with fosaprepitant that did not contain
22 polysorbate 80, not be focusing exclusively on
23 aprepitant.

24 And there's very good reasons why a POSA
25 would look elsewhere. Aprepitant, which is a

1 limitation of the asserted claims, is poorly
2 soluble in both oil and water.

3 As Dr. Hale explained, and this is at
4 901:17 to 902:5, the physical characteristics of
5 aprepitant made it very difficult to work with.
6 Mr. Aly referred to this, and so did Dr. Hale, as
7 cement dust, because it's largely insoluble.

8 And if we pull up 903, 8 to 22, we see
9 here that Dr. Hale also explained how aprepitant
10 really favored a crystalline structure. And he
11 describes this as individual molecules readily
12 efficiently pile onto each other to form these
13 crystals. And he goes on to say, stacking each
14 other in an ordered lattice.

15 JUDGE BRYSON: Isn't that really the
16 critical problem to be solved here, was how to get
17 aprepitant into solution?

18 You mentioned a moment ago that there
19 were -- that there was a broader range of inquiry
20 into how to solve the general problem of an emetic
21 or an NK-1 antagonist. But with respect to the
22 particular issue -- this issue comes up a lot in
23 obviousness cases, is how broadly to characterize
24 the problem.

25 But if we characterize the problem here

1 as what is it that is necessary to put aprepitant
2 into solution, then that, it seems to me, confines
3 the range so you're not worried about other NK-1
4 inhibitors.

5 Why is it that we should not
6 characterize the problem to be solved as how to
7 put aprepitant into solution? I guess that's the
8 best way to put my question.

9 MR. ASHKENAZI: So I guess I have two
10 points on that, Your Honor.

11 First, that's using hindsight. It's
12 using the inventor's own work and the inventor's
13 patented invention, the claims, to work backwards
14 to say, Well, what's the simplest way to solve the
15 problem.

16 There's no dispute, we just saw
17 Dr. Rabinow agreed, that the goal, the motivation
18 for a POSA, was to make an IV NK-1 receptor
19 antagonist with minimal side effects.

20 To say that I'm just going to go
21 straight to work with aprepitant, something that
22 has been, number one, extremely difficult to work
23 with and for over 20 years, nobody has made an IV,
24 and say, I'm going to focus on that instead of
25 easier solutions, that's working through

1 hindsight.

2 And that's very similar to what happened
3 in the --

4 JUDGE BRYSON: I know of federal circuit
5 cases that have addressed this kind of problem. I
6 think of the Barr Pharmaceuticals case, the
7 Bayer -- Bayer case, the Fulton -- In Re Fulton
8 case, all of which are addressing problems of what
9 is the scope of the -- how do we characterize the
10 scope of the problem.

11 And each of them has said, You don't
12 simply say, well, how in the world would one go
13 about address -- given all the possible ways of
14 approaching a solution to how to cure a particular
15 illness, you look at what the prior art has shown
16 you as pathways and ask, what are the barriers
17 between the prior art and the solution.

18 And if that's the right approach, then
19 the question is: How obvious is it to go from
20 what the prior art has proposed a solution to
21 actually having a solution. That isn't typically
22 characterized as hindsight, but rather looking at
23 the focus of what the prior art has suggested.

24 So that's the issue that -- one of the
25 issues that concerns me here, is how to

1 characterize the problem to be solved.

2 MR. ASHKENAZI: Well, Your Honor, what
3 we do see in the prior art is people working on a
4 number of different issues. We see people in the
5 prior art, for example, Fresenius cites the
6 Karavas reference, but you'll see they're only
7 talking about fosaprepitant there. Dr. Rabinow
8 agrees that a POSA would be working on
9 fosaprepitant.

10 So to say I'm going to be exclusively
11 focused on aprepitant, or I'll go one step
12 further, Your Honor, just aprepitant emulsions,
13 because they've identified two references, that's
14 saying a POSA, out of the sea of information
15 that's available to them, would be narrowly
16 focused on CN '845 and Zhou, instead of all the
17 other options.

18 For example, in Hingorani they tried
19 other steps other than emulsion techniques to try
20 to get an aprepitant emulsion -- to try to get an
21 IV aprepitant.

22 Again, the problem here is there's two
23 parts. Number one, are we going to focus on just
24 aprepitant knowing that there's things like
25 fosaprepitant out there that are much more -- have

1 much better properties that don't readily
2 crystallize, that aren't going to have this
3 problem in the -- you know, when they're put into
4 an IV.

5 And, number two, why am I going straight
6 to an emulsion approach? And to say that a POSA
7 is going to focus on -- just because there's two
8 references out there, CN '845 and Zhou, and say
9 let's just go straight to that, when there are
10 other references showing people trying other
11 things.

12 Or recognizing that there have been
13 failure after failure of someone trying to get an
14 IV aprepitant out there is to say, I'm just going
15 to go and narrowly focus on what the inventors
16 did.

17 JUDGE BRYSON: Okay.

18 MR. ASHKENAZI: Your Honor, I would say
19 this issue was addressed in the Insight case,
20 where the problem to be solved and the recognition
21 of the properties of the molecule, just like here,
22 a very difficult molecule to work with, lended
23 itself to looking at the broader question.
24 Because there's no motivation for the POSA to
25 ignore those properties, the difficulty of working

1 with aprepitant.

2 And, Your Honor, we cited that in our
3 briefs.

4 JUDGE BRYSON: Right. Yes, I saw that.

5 MR. ASHKENAZI: With respect to the
6 other formulation approaches, if we can, I just
7 want to focus on the fact that, as I mentioned,
8 Hingorani did address cosolvents and surfactants.

9 And if we look at Strickley and
10 Kamantz -- let's look at Strickley, JTX105.25.

11 To be clear, and to go back to the
12 point, emulsions were not commonly used. In fact,
13 there was only two FDA-approved emulsions. And as
14 we see here, Strickley references that at this --
15 you know, this formulation strategy is rarely used
16 for a commercial product.

17 I want to be clear, we're taking a very
18 complex molecule, aprepitant, that has very
19 difficult to work with properties, and we're
20 talking about a complex system.

21 Fresenius tries to paint the picture
22 that emulsions are easy to work with, they're so
23 simple, they're so straightforward, but they're
24 not, actually. And here, we see Strickley
25 recognizing they're rarely used in commercial

1 products.

2 And if we could go to JTX105, that's
3 Strickley at page 26, please.

4 If we could focus on that left-hand
5 side, Your Honor, this is the table that you heard
6 Dr. Little and Dr. Rabinow discuss. We see that
7 these oil-in-water emulsions, not microemulsions,
8 but oil-in-water emulsions is listed as the
9 second-to-last.

10 Dr. Little referred to this as, you
11 know, the order in which you're going to approach
12 an IV development, and you go from the simpler to
13 the more complex, with oil-in-water emulsions
14 being the more complex, the second-to-most
15 complex.

16 And even Dr. Rabinow testified when he
17 was talking about -- sorry, go ahead.

18 JUDGE BRYSON: Getting back to the
19 discussion a moment ago, do you agree that Merck,
20 during its work on this problem, did identify
21 solubilizing aprepitant as a method of approaching
22 the problem, even though that was not something
23 that they ultimately succeeded in doing?

24 MR. ASHKENAZI: Yeah, so solubilizing
25 is -- yes, Your Honor, Dr. Hale explained that

1 they tried to find ways in order to increase the
2 solubility of aprepitant to get it into an IV.
3 And Dr. Hale gave the explanation of him actually
4 making a salt of aprepitant.

5 We're not talking about emulsions.
6 We're talking about making a salt of aprepitant.
7 And he got it into solution, but then it soonly
8 [sic] crystal -- it shortly after crystallized
9 out. And the purpose --

10 JUDGE BRYSON: But they identified the
11 problem, in part at least, as being how to
12 solubilize aprepitant.

13 MR. ASHKENAZI: Your Honor, again,
14 solubilizing aprepitant doesn't lead to emulsions.
15 But, also, that's one of the --

16 JUDGE BRYSON: That's a different
17 question. But thinking about the scope of the
18 problem, there was at least something in the prior
19 art that indicated that one approach to the
20 problem was solubilizing aprepitant. So in that
21 sense, it's not pure hindsight; right?

22 MR. ASHKENAZI: Except they failed to do
23 that, and they said they had to move onto
24 fosaprep- -- to make a pro-drug approach with
25 fosaprepitant. The question is: Does a POSA

1 ignore all of this information, all of these
2 difficulties instead of working with, for example,
3 fosaprepitant or making an IV that doesn't contain
4 polysorbate 80, Your Honor.

5 JUDGE BRYSON: All right. You can go
6 ahead.

7 MR. ASHKENAZI: And, Your Honor, they
8 did publish on that failure, and that was
9 discussed, among other things, in the Hargreaves
10 reference.

11 But I want to -- if we can shift our
12 attention now. Your Honor, let's just assume a
13 POSA is working with aprepitant. And let's just
14 assume a POSA is working on an emulsion, which,
15 again, I showed you is a truly difficult complex
16 system.

17 To start, Fresenius hasn't convincingly
18 explained why a POSA, looking at aprepitant
19 emulsions, would be fixated on CN '845 as their
20 starting point.

21 They say a POSA would have focused on
22 CN '845 in 2014, because it had been a game
23 changer for showing that you had to increase
24 emulsifier towards 10 percent to be stable. But
25 Dr. Rabinow asserted everything in CN '845 was

1 stable, even though it included formulations with
2 as little as 0.5 percent emulsifier.

3 We also discussed at length at trial,
4 Your Honor, and in the briefing, the Zhou
5 reference, which comes after CN '845. Those
6 authors optimized their previous work, and
7 Fresenius pays lip service to it. They talk about
8 it as if it provides information on KE, but then
9 they ignore all the information that's contained
10 in there.

11 If we could please pull up PDX5-1.

12 And this is -- on the top, Your Honor,
13 is JTX115, which is the Zhou reference. And at
14 the bottom, Your Honor, is JTX71 at page 13, which
15 is CN '845 and the portion that Fresenius focuses
16 on.

17 And what we can see here is in the top
18 reference, this is the abstract of Zhou. They
19 talk about the optimal formulation of aprepitant
20 emulsion was, and it gives specific ingredients,
21 aprepitant, 0.25 percent; soybean oil, 15 percent;
22 egg yolk lecithin, E80, at 2.5 percent; and oleic
23 acid was 0.125.

24 Your Honor, it's not saying anything
25 about high amounts of emulsifier. It doesn't talk

1 about things approaching 10 in Zhou. It's
2 focusing on optimizing down, bringing the number
3 down to 2.5 percent. And they tested their range
4 of 2 to 4, after doing some prescreening and
5 initial work they described in Section 2.1.

6 By contrast, if we look at CN '845, it
7 gives a broad range. For example, the emulsifier
8 range is 0.5 to 10 percent. And, again,
9 Dr. Rabinow said that everything in CN -- all the
10 examples in CN '845 were stable, and they used as
11 little as .5 percent.

12 Now, Your Honor, we do not agree that
13 they were stable, and we've pointed out that
14 they're not stable. There's no evidence that they
15 were stable. And Dr. Rabinow admits, in fact,
16 that there's no testing data. I want to be clear
17 on that.

18 If we could pull up 318, 9 to 11.

19 Dr. Rabinow agreed that CN '845 does not
20 contain any test data. He said, not explicitly.

21 If we could take that down.

22 That's where turning to Example 4 of the
23 patents-in-suit gets interesting, Your Honor.

24 That is where Heron tried to make an emulsion from
25 CN '845, and they used 9.95 percent emulsifier.

1 And they found that it formed crystal within
2 four days. And the pH that they tested was right
3 in the range of 6 to 8, which is what's identified
4 in CN '845.

5 So what does all this suggest,
6 Your Honor, that a POSA would not have expected
7 that CN '845 was stable. It had no stability
8 data. And if a POSA would have made and tested
9 it, they would have seen it's not stable.

10 If we could please pull up PDX5-1 for a
11 few minutes.

12 And, again, I want to look at the range
13 that's in -- these are very broad ranges of --

14 JUDGE BRYSON: Example 4 was taken
15 effectively directly from the high range of
16 CN '845?

17 MR. ASHKENAZI: So CN '845 is not a
18 replicate of any example of CN '845, but rather it
19 uses the high range 9.95, so right below
20 10 percent.

21 JUDGE BRYSON: And was that taken as a
22 way of demonstrating that the range shown -- the
23 top of the range shown in '845 was unworkable?

24 MR. ASHKENAZI: I would say that,
25 Your Honor, with using all the other --

1 JUDGE BRYSON: And that was based on
2 looking at '845?

3 MR. ASHKENAZI: That was based on the
4 inventors' own work, Your Honor. The inventors
5 took what they had, the information that they had,
6 the knowledge that they built up, and they made
7 Example 4.

8 And with that Example 4 -- and Dr. Han
9 actually testified to this, that she used her best
10 efforts to see what would work, to get something
11 that would work, which included using at the high
12 end of the range of emulsifier, Your Honor.

13 JUDGE BRYSON: I'm just wondering if
14 there was any indication that the effectively
15 10 percent used in Example 4 was intended to
16 demonstrate that CN '845 didn't work?

17 MR. ASHKENAZI: Well, that is what it
18 shows, Your Honor. Whether that's the --

19 JUDGE BRYSON: In other words, was
20 that -- were they aware of the CN '845 and they
21 were saying, Okay, this just doesn't work, and
22 here's why?

23 MR. ASHKENAZI: Yes, Your Honor. They
24 were aware of CN '845. Yes, Your Honor.

25 JUDGE BRYSON: Okay.

1 MR. ASHKENAZI: And if we look at the
2 range here at the bottom, this is, again, CN '845,
3 JTX71, at page 13.

4 The portion that Fresenius focused on,
5 this is an extremely broad genus, Your Honor, with
6 aprepitant, but then just classes of drugs and
7 huge ranges of these. It just says emulsifier,
8 0.5 to 10 percent. Co-emulsifier, 1 to
9 10 percent.

10 A POSA would have to make all of these
11 choices -- a number of choices to get to the
12 asserted claims, Your Honor.

13 JUDGE BRYSON: All right.

14 MR. ASHKENAZI: If we could now turn
15 to -- if we could take that down.

16 Fresenius talks about routine
17 optimization. It's not credible to think that a
18 POSA would have made all these choices from within
19 CN '845, all these departures from CN '845 that
20 we're going to talk about, for example, going
21 above the 10 percent limit of egg lecithin, using
22 sodium oleate, which is not even referenced at all
23 in CN '845.

24 And as the Federal Circuit found in
25 Moderna, the unpredictable interactivity of these

1 various components really does render the claim
2 obvious -- nonobvious.

3 JUDGE BRYSON: And what was the case you
4 cited, I missed it?

5 MR. ASHKENAZI: Yes, Moderna versus
6 Arbutus.

7 JUDGE BRYSON: Moderna, yes. Okay,
8 fine. Okay.

9 MR. ASHKENAZI: Thank you.

10 JUDGE BRYSON: Go ahead.

11 MR. ASHKENAZI: We heard Mr. Aly talk
12 about USP. It's not really credible to say that
13 USP is going to motivate a POSA to select any
14 ingredient or to select specific amounts of
15 ingredients or to focus on certain directions or
16 to pick 14 percent egg lecithin or sodium oleate.

17 The USP is really just a standard that
18 needs to be met. It doesn't give any guidance
19 whatsoever on which particular ingredients to use,
20 what to change, or how to change it.

21 And let's be clear, Fresenius' argument
22 is that the prior art was not stable and that you
23 need to optimize to get stability. That's really
24 important because that means the prior art did not
25 actually have anything that worked. Nothing that

1 could be given to a human. Nothing that could
2 be -- that would be stable for a sufficient time
3 period. And we see that in Examples 4 and 5.

4 Instead, they have to try to get there.
5 There could be no -- I just want to jump to this,
6 because it was a point that Mr. Aly made. How
7 could you have reasonable expectation of success
8 if what you're basing it off of was a failure, it
9 didn't work?

10 Now, Fresenius --

11 JUDGE BRYSON: Didn't it work; did it
12 not? Part of it established that you could
13 solubilize aprepitant?

14 MR. ASHKENAZI: Your Honor, the
15 question --

16 JUDGE BRYSON: So what's missing is the
17 stability; right?

18 MR. ASHKENAZI: Well, yeah, but --

19 JUDGE BRYSON: In your view, that's
20 missing the whole ball game, I understand, but it
21 is -- it worked to the extent that it solved one
22 part of the problem; right?

23 MR. ASHKENAZI: No, I don't believe it
24 solved any part of the problem. The problem --
25 and maybe this goes back to where Your Honor was

1 going to earlier. The problem is not, how do I
2 solubilize aprepitant. Even Dr. Hale said that I
3 could get it soluble, it just crashes out. How do
4 I get something that could be an IV product,
5 that's the key.

6 JUDGE BRYSON: Well, the first stage is
7 to get it solubilized; right? As I understood,
8 the prior art had failed to solubilize, period.
9 It's just cement dust to begin with and cement
10 dust to end with. But this is, as Mr. Aly
11 characterized it, and I think this is a fair
12 statement of his argument, that the breakthrough
13 was to solubilize aprepitant. And then --

14 MR. ASHKENAZI: So, Your Honor --

15 JUDGE BRYSON: His argument is that
16 after that, routine optimization is what is
17 necessary to establish the increased stability up
18 to the point that you have something that
19 satisfies USP?

20 MR. ASHKENAZI: Your Honor, I don't
21 believe that that's the proper way of approaching
22 it. Because it's not just, can I get this
23 solubilized, can I get it solubilized for a short
24 period of time. That wasn't the issue. Dr. Hale
25 said that he did that 15 years earlier.

1 The question is: Can I get something
2 that's going to maintain its solubility? It's not
3 about -- you know, they tried to say that CN '845
4 provided -- you know, gave a way to tell you that
5 you could get it solubilized. Hingorani, for
6 example, shows that 1 percent is going to
7 solubilize. There's nothing to tell you that
8 going -- there's nothing to tell you going higher
9 is going to matter or is going to help.

10 But much more importantly, Your Honor,
11 if the question is just about solubilizing, that
12 would be one thing. It's not. It's about how to
13 maintain the stability over time. That is the
14 creek -- sorry, I can't hear you, Your Honor.

15 JUDGE BRYSON: I understand your
16 distinction. I just am trying to parse out what
17 portions of the multiphase problem were addressed
18 by 49 -- '845 and which portions weren't. And I
19 understand the argument you're making.

20 MR. ASHKENAZI: Okay. I'll say,
21 Your Honor, if the whole point is to get it
22 solubilized and to look at what the properties
23 are, then we can look at Zhou for a moment.

24 Zhou says they optimized. They took a
25 range of different ingredients, right, because all

1 of these are interdependent. If we look at Zhou,
2 they looked at multiple different ingredients and
3 different ranges for the ingredients, because they
4 all matter.

5 And they look at Zhou, and Zhou says,
6 Okay, I'm going to determine that from my previous
7 work, I'm going to focus on, you know, what -- I'm
8 going to try to see what would be the best optimal
9 formulation. And they optimize at 2.5 percent.
10 So if we're going to optimize, why are we going
11 any bit higher, Your Honor?

12 JUDGE BRYSON: Okay.

13 MR. ASHKENAZI: Now, I want to touch on
14 complexation for a moment.

15 JUDGE BRYSON: Sure.

16 MR. ASHKENAZI: Fresenius says that a
17 POSA, looking at CN '845, is going to say that it
18 complexes, but let's be clear. They can't
19 reconcile that aprepitant is -- that they would
20 look at this, and a POSA would realize that
21 aprepitant complexes with the phospholipid egg
22 yolk lecithin.

23 First thing, CN '845 mentions nothing at
24 all about complexation, not a single word.

25 Second, when we look at Example 6, that

1 had 0.5 percent -- this is Example 6 of CN '845.
2 It had 0.5 percent emulsifier. Dr. Rabinow agreed
3 that that doesn't sufficiently complex. Or when
4 we look all the other examples in CN '845 -- if we
5 could go to PDX4-4.

6 We'll see here, Your Honor, that a
7 number of the other examples in CN '845 don't even
8 use egg yolk lecithin. They have poloxamer for
9 Example 2. Example 3 has polysorbate. Example 8
10 has PEG, and I'm not going to try to pronounce it.

11 But the point is, is that to say that
12 CN '845 -- to say that CN '845 is focused on
13 talking about complexation can't be reconciled
14 with what CN '845 is. It doesn't rec- -- it can't
15 be reconciled with the amounts that are used in
16 CN '845, and it can't be reconciled with the
17 ranges and the described examples of the
18 emulsifiers.

19 Probably most importantly, Your Honor,
20 is that to say that CN '845 is teaching you
21 complexation, they've already given you a range
22 for complexation then, 0 to 10, which we don't
23 agree with because, again, there's nothing
24 referenced in here.

25 Your Honor did ask about the other three

1 references. That's EP279, Yue, and Agarwal. I
2 just want to be clear. Those were not IV -- those
3 were not complexes for IV products, for IV
4 application. They're related to different drugs.

5 And each one of them just used a ratio
6 of 3 -- of a little bit less than 3 -- about 3 to
7 1 of emulsifier to the drug. Nothing near what
8 we're talking about here, which is a 20 to 1 ratio
9 and using high amounts of emulsifier way above
10 10 percent.

11 I would like to talk about Washington
12 for a moment, Your Honor, because a lot has been
13 said about what Washington teaches, but I want to
14 actually just take a moment to look at what it
15 actually says.

16 If we could look at JTX113.9.

17 So this is the portion of Washington
18 that Fresenius is focused on. The actual teaching
19 from Washington is that it's often necessary to
20 post load emulsions with Class III drugs in order
21 to have a large surface area available for
22 loading.

23 All it says is that you add the drug to
24 an emulsion after the emulsion is formed instead
25 of before the emulsion has formed for loading the

1 drug. It doesn't say anything about increasing
2 emulsifier amounts, about getting higher surface
3 area, or about relation to stability, nothing.

4 And let's be clear, Your Honor.

5 Washington was published in 1996. This is while
6 Merck was still working in the field, before
7 CN '845, before Zhou, before Hingorani, before all
8 the other prior art references. Nobody took
9 Washington and said, Oh, I need to get a much
10 higher surfactant -- much higher emulsifier
11 amount.

12 There's actually no evidence that anyone
13 looked at Washington or would even suggest that
14 Washington says use higher emulsifier to increase
15 stability, as Fresenius has consistently asserted.

16 If we could turn, Your Honor -- I do
17 want to focus on for a minute the Khan reference,
18 because we heard a little bit about that, how Khan
19 explained how emulsifier is really important.

20 That's JTX91. If we can go to page 5,
21 please.

22 Your Honor, this is the paragraph from
23 Khan that Fresenius is focused on. And they focus
24 on the first sentence saying, The amount of
25 emulsifier agent is one of the most important

1 factors having an influence on the emulsion.

2 What they quickly gloss over is the fact
3 that later on what we see is that emulsifier --
4 that the emulsifier concentration window is tight.
5 And afterwards you quickly -- emulsion stability
6 quickly declines. And at high emulsifier
7 concentrations, emulsion instability occurs
8 because of rapid coalescence.

9 Now, what we discussed with Dr. Rabinow
10 and what this reference is pointing to, that high
11 amount of emulsifier concentration, in that
12 reference that's being discussed, Gonglun and
13 Daniel, which I believe is JTX79, was 0.5 percent
14 emulsifier in that emulsion. Not 5 percent, not
15 10 percent, 0.5 percent.

16 The point being is that increasing
17 emulsifier is not just simply, Oh, I go as high as
18 I -- just keep going higher and higher until I
19 achieve stability. No, what it's saying is that
20 increasing emulsifier can lead to instability and
21 that be very careful going higher. And, in fact,
22 Dr. Little explained that you generally -- when
23 using ingredients like this, you want to use as
24 low as possible.

25 If we could turn our attention to --

1 Your Honor, I did want to mention with respect to
2 Liu a couple of things. There's no dispute that
3 Dr. Rabinow agreed that the aprepitant emulsions
4 that are in this case, CN '845, are not
5 microemulsions. He actually -- he testified to
6 that. There is no question that CN '845 is -- the
7 specific emulsions that are being tested in there
8 are not microemulsions, or Zhou.

9 And, Your Honor, if we can, if we can go
10 to 161:3 to 162:4 -- 24.

11 I'll just -- I'll state it, Your Honor.
12 If we look at that portion, Dr. Rabinow said,
13 We're not -- we're obviously not forming a
14 microemulsion, we're forming an emulsion. That's
15 a distinction he drew.

16 And I will say, Your Honor, that when we
17 look at the references, for example, Von Corswant
18 explicitly draws a distinct difference between
19 emulsions and microemulsions. And I mentioned
20 this a little bit earlier, but maybe if we can go
21 to PDX5-3.

22 So PDX5-3, this is Von Corswant on the
23 left side. And you see here they're not talking
24 about a continue- --

25 JUDGE BRYSON: The Von Corswant exhibit

1 number?

2 MR. ASHKENAZI: Yeah, sure, JTX --

3 JUDGE BRYSON: Oh, JTX110?

4 MR. ASHKENAZI: Yes. And I'm
5 specifically at page 3, Your Honor. And the
6 portion of the testimony that I have on the
7 right-hand side is 341:1 to 23.

8 And what we're seeing here is that, for
9 example, Von Corswant and everybody else, they
10 know there's a distinction between emulsions and
11 microemulsions. And they don't talk about them as
12 a continuum. They actually talk about them as
13 distinctive and different. Only Dr. Rabinow was
14 the one who said that there's a continuum, but
15 provided no support whatsoever.

16 Again, we're not talking about whether
17 there's a broader, you know, title emulsion, and
18 maybe some people talk about conventional
19 oil-in-water emulsions and microemulsions. We're
20 talking about the systems themselves.

21 If we could take that down, please.

22 And, Your Honor, I do want to mention
23 this one thing because you heard --

24 JUDGE BRYSON: Now, you have -- you're
25 down to about a little over four minutes. So --

1 MR. ASHKENAZI: Okay. A couple of
2 points quickly, Your Honor.

3 With respect to safety, safety has
4 nothing to do with thermodynamic stability.
5 Knowing that you could give a micro- -- knowing
6 that microemulsions may have up to 30 percent --
7 by the way, again, no FDA-approved microemulsions
8 that we were discussing from the prior art --
9 doesn't tell you anything about them confer --
10 about how that's going to deal with stability.

11 And, in fact, we discussed this, we
12 referenced this at pages -- in our brief, and it's
13 Dr. Rabinow's testimony 341:24 to 342:11.

14 Your Honor, with respect to sodium
15 oleate, I just want to make a quick point.
16 There's no dispute that Wan -- the authors of Wan
17 found that sodium oleate caused hemolysis in
18 emulsion. That was their conclusion.

19 Dr. Rabinow disagrees with their
20 conclusion. He has some hypotheses, but they
21 haven't shown that a POSA would ignore the
22 authors' conclusions.

23 And let's be clear. Jumaa actually
24 showed that for their systems, a certain amount of
25 sodium oleate does cause a problem.

1 The point is sodium oleate is a known
2 issue. Why use sodium oleate as a pH modifier,
3 Your Honor? There's no evidence to say a POSA
4 would choose that over something else, when the
5 goal is to make something with minimal side
6 effects.

7 Your Honor, when it comes to unexpected
8 properties, I just want to make a couple of quick
9 points. Again, we don't believe we need to show
10 criticality. They haven't met their burden of
11 proving obviousness by clear and convincing
12 evidence before even addressing objective indicia.

13 But I will say that with respect to
14 Example 5, Example 5 is a re-creation, and
15 Dr. Rabinow agreed, of Zhou. There is no pH
16 modification step at all in Zhou. They took the
17 ingredients, they put it together, and they tested
18 it.

19 And Dr. Han explained that, Well, look
20 there could be differences in the pH meter that
21 was specifically used at the time. But it doesn't
22 matter. Fresenius hasn't shown or provided any
23 basis to say that the formulations were stable.
24 And, in fact, their whole argument is, Well,
25 they're not stable. So I need to increase the

1 stability, I need to go higher, I need to increase
2 the lecithin amount.

3 Your Honor, I will also -- with respect
4 to the other objective indicia, I think our brief
5 is clear.

6 For infringement, I do want to be clear,
7 because we didn't hear Mr. Aly discuss it.
8 Fresenius does conduct a more stringent test for
9 proving crystal content. Besides the fact that
10 their specification clearly -- they seek approval
11 for a product that's going to have zero crystals,
12 their test, which uses this ultracentrifugation
13 test, shows that they concentrate a thousand times
14 the volume to get it down and to look through
15 the -- and to evaluate the crystal content.

16 There is no dispute in this case, no one
17 has provided any testimony or any evidence to
18 contradict Dr. Little's assertion that is a more
19 stringent test. And, Your Honor, as we know, the
20 case law is clear, and you actually addressed this
21 during summary judgment, you do not -- there is no
22 requirement to use the actual test, but rather
23 something that could be used to show that that
24 test criteria would be satisfied.

25 And with respect to written description,

1 Your Honor, I do want to, if we can, please pull
2 up PDX5- -- sorry, if we could please put up
3 JTX1.18, and that's Claim 8 of the patent, and
4 JTX1.8, Column 4, line 65 to 67.

5 JUDGE BRYSON: Why don't you just tell
6 me what's in those. I can't --

7 MR. ASHKENAZI: Yeah. Your Honor, it's
8 a simple visual to cite. To assert that the
9 specification didn't have the claimed range of the
10 pH is preposterous. We see right there at the
11 bottom, which is a portion of the specification,
12 they explicitly state the claim range.

13 And, Your Honor, I want to be clear,
14 because Fresenius tried to misconstrue what we
15 were showing. We're not using Fresenius'
16 specification or Heron's specification to say, Oh,
17 we could prove written description.

18 No, we're just saying that their
19 assertion that these lower pH ranges would not
20 work is preposterous, and it can't be reconciled
21 with their own obviousness assertion that a POSA
22 believes that the alkali range would -- that
23 anything that's in the alkali range would work for
24 an emulsion.

25 JUDGE BRYSON: Okay.

1 MR. ASHKENAZI: Your Honor, I think that
2 reached my time there.

3 JUDGE BRYSON: Yes, you have.

4 I do have one follow-up question with
5 the sodium oleate causing problems, but sodium
6 oleate is in the patent. Why --

7 MR. ASHKENAZI: Yes, Your Honor. Yes.

8 JUDGE BRYSON: Why is that not as
9 problematic if it's in the patent?

10 MR. ASHKENAZI: Well, the point is,
11 Your Honor, what a POSA would believe at the time.
12 Is a POSA going to choose sodium oleate? And
13 we're not asserting sodium oleate always causes
14 problems.

15 What we are saying is a POSA, back in
16 2014, would they have chosen to use sodium oleate,
17 when it's not contained in CN '845. The point is
18 that sodium oleate can in certain instances and
19 certain formulations --

20 JUDGE BRYSON: It's referenced in Zhou;
21 correct?

22 MR. ASHKENAZI: I'm sorry?

23 JUDGE BRYSON: Sodium oleate, if I
24 recall correctly, is referenced in Zhou; correct?

25 MR. ASHKENAZI: Only oleic acid,

1 Your Honor --

2 JUDGE BRYSON: Right. Yes, oleic acid.
3 And any of the oleates and oleic acids are going
4 to be, effectively, the same thing; right?

5 MR. ASHKENAZI: Well, no, there's two
6 points in there, Your Honor.

7 First, they used oleic acid as a
8 co-emulsifier. So they weren't just using it as
9 a -- it's not being used as a pH modifier. It's
10 using it as a co-emulsifier, which is separate and
11 distinct.

12 I want to be clear. If you're picking
13 oleic acid, you're not using ethanol, right.
14 They're trying to have their cake and eat it, too.
15 They want to say, Well, I'll take oleic acid from
16 Zhou, but ignore the other components of Zhou that
17 we saw, Your Honor, all of the differences between
18 Zhou and the prior art. But, also -- sorry, Zhou
19 and the claimed -- the asserted claims.

20 But, also, Your Honor, when it comes to
21 the use of oleic acid, they didn't test those
22 formulations at all in any in vivo model.

23 JUDGE BRYSON: Okay.

24 MR. ASHKENAZI: They just simply used
25 them.

1 JUDGE BRYSON: Yeah, I think we have
2 to --

3 MR. ASHKENAZI: Yes.

4 JUDGE BRYSON: -- bring in.

5 Let me go back to Mr. Aly.

6 Mr. Aly, you have, I think, just about
7 five minutes.

8 MR. ALY: Thank you, Your Honor.

9 I'd like to address four different
10 points. First is the microemulsion/emulsion.
11 I'll spend most of the time on that point. And
12 I'd like to start by sharing JTX110. That's the
13 Von Corswant reference.

14 And in that particular reference, we're
15 looking at what was disclosed in Von Corswant,
16 which is a reference that Dr. Rabinow testified
17 about, not Dr. Little. And today counsel pointed
18 the attention, if we can all see it on the screen,
19 to paragraph 9, defining the two using their
20 classic definitions.

21 But in paragraph 11, which Dr. Rabinow
22 addressed, and, again, Dr. Little did not rebut,
23 we see that there was a benefit of being a
24 microemulsion. But how the terms were used in the
25 prior art, Von Corswant discusses using the

1 example of EP258.

2 And in paragraph 11, going onto the next
3 column, exemplified that there were -- the
4 microemulsification, although it was called a
5 microemulsion in that reference, was achieved by
6 using mechanical energy input. So it is not a
7 microemulsion, according to the usual definition
8 for "microemulsion."

9 The point being that Von Corswant
10 recognized that there are classical definitions,
11 but the usage is not consistent with those in
12 several cases. This is not referencing in
13 Von Corswant the CN application. It's another
14 example of microemulsions and emulsions having
15 overlapping teachings.

16 Counsel, Mr. Ashkenazi, testified that
17 he thought that maybe different components were
18 used or different excipients. There's no evidence
19 of that. The evidence is that there's an
20 overlapping amount, which makes sense.

21 Still continue with sharing the screen
22 and looking at JTX93, it refers to -- in Table 1,
23 this is JTX93.11, the Liu reference has the
24 Table 1 which has types of commonly used
25 surfactants for injectable "microemulsions," is

1 the word used there. But the list of excipients
2 that is used overlaps substantially with the
3 CN '845 disclosures, including polysorbates,
4 specifically polysorbate 80 as an example of what
5 can be used --

6 JUDGE BRYSON: Mr. Aly, are we in Liu
7 here with this table, did you say? This is the
8 Liu reference?

9 MR. ALY: Yes. JTX93 --

10 JUDGE BRYSON: Go ahead.

11 MR. ALY: -- correct.

12 And what I was just explaining is that
13 overlaps with the CN '845. And underneath the
14 table, there's even an example called out, The
15 Sustol HS has better compatibility compared to the
16 aforesaid other surfactants and can be used for
17 intravenous administration of emulsion. So
18 referring to the fact that there's an emulsion
19 effect usage that had been established for some of
20 these experiments.

21 In Liu itself, if I can go to JTX93.9,
22 and we're going to look at the first sentence, it
23 defines "microemulsions." And then there's a
24 particle size description of 100 nanometers.

25 I call attention to that, Your Honor,

1 because Dr. Rabinow at trial, and now I'm
2 referring to Dr. Rabinow's testimony at page 161,
3 lines 3 to 14, explained that in the context of
4 CN '845, what a person of ordinary skill in the
5 art would see is CN '845 called their formulations
6 microemulsions.

7 And in that context it was clear because
8 of the size of the microemulsion. Again, 50 to
9 100 nanometers in that reference, as well. The
10 point being the microemulsion size criteria is
11 what overlapped here, the particle size, and that
12 particle size is a function of lecithin level.

13 So in combination with the transcript
14 testimony, CN '845 usage, contemporary usage, and
15 the Liu reference being an analogous reference,
16 there's no testimony or an example of something
17 that says Liu would just be completely
18 inapplicable. And it's no basis to have said that
19 either.

20 This case is, therefore, like In
21 Re: Aller, where we're looking at verifying --
22 what different variables there exist, how they are
23 known to be used, in what safe amounts had they
24 been used, and applying them to the situation at
25 hand.

1 The second point, therefore -- and I'm
2 wrapping up -- is that in the 14 percent
3 optimizing of Zhou, that there's no optimizing
4 down. There is just optimizing in terms of the KE
5 that is used to optimize in that reference versus
6 USP in the case at hand.

7 The third point I wanted to make -- and
8 Zhou did have several other stability points
9 because it was to show that promising effect of
10 stability in an emulsion, not just a theoretical
11 stability, but it did not need to be optimized for
12 USP.

13 Third or fourth point, as I conclude, is
14 the Merck work ignores the timeline and the
15 evidence. There's no evidence that said Merck
16 tried formulations to formulate aprepitant, those
17 failed, crashed out of solution, and then they
18 were stuck with fosaprepitant.

19 The evidence showed both drugs were made
20 at the same time, 1993. And by the time of the
21 priority date, CN '845 did change the state of
22 analysis.

23 Fourth and final point --

24 JUDGE BRYSON: You've reached --

25 MR. ALY: I'm sorry?

1 JUDGE BRYSON: One minute on your final
2 point, and then I'll have to stop you.

3 MR. ALY: A final point, Your Honor --

4 JUDGE BRYSON: [Inaudible].

5 MR. ALY: I'll do that, sure.

6 A final point, that as far as the
7 various reasons to increase emulsifier level,
8 counsel did not address or rebut the surface area
9 increase that was shown that Dr. Rabinow testified
10 about or the increase for particle size. And the
11 complexation was one of several reasons that also
12 Dr. Little himself agreed would be another reason
13 to increase emulsifier levels.

14 So for these reasons, Your Honor, we
15 believe judgment should be granted in favor of
16 Fresenius Kabi.

17 JUDGE BRYSON: [Inaudible].

18 MR. ASHKENAZI: Your Honor, I'm sorry, I
19 can't hear you right now.

20 JUDGE BRYSON: I'm sorry. I was just
21 wrapping up saying, I thank both counsel for a
22 very helpful presentation. I think this has been
23 informative and quite useful.

24 I will try to get -- well, I think I
25 will probably not be able to get something to you

1 very quickly. I'm going to be on vacation for
2 several weeks, but after I get back, I will hope
3 to have something for you.

4 I've already done some significant
5 amount of spadework on this. But I think, both in
6 light of your briefs and the arguments, I need to
7 do some more thinking about the issues, and I will
8 endeavor to do so.

9 I will -- after I adjourn here, I will
10 stay on the line with the court reporter and -- in
11 case he has any questions about case names or the
12 names of any of the chemicals that were discussed,
13 although I don't think there were many of them.

14 In any event, don't forget to provide us
15 with the redactions to the transcript of the trial
16 so that we can get that taken care of and then
17 other than that, thank you for your help and we're
18 adjourned.

19 MR. ALY: Thank you, Your Honor.

20 MR. ASHKENAZI: Thank you very much,
21 Your Honor. And I hope you have a great vacation.

22 JUDGE BRYSON: Thank you.

23 (Off the record at 11:39 a.m.)

24

25

1 STATE OF MARYLAND)

2 ss:

3 COUNTY OF MONTGOMERY)

4

5 I, Matthew Goldstein, Notary Public within
6 and for the State of Maryland, do hereby certify:

7

8 That I reported the proceedings in the
9 within entitled matter, and that the within
10 transcript is a true record of said proceedings.

11

12 I further certify that I am not related to
13 any of the parties to the action by blood or
14 marriage, and that I am in no way interested in the
15 outcome of this matter.

16

17 IN WITNESS WHEREOF, I have hereunto set my
18 hand this 29th day of August, 2024.

19

20

21

22

23



24

Matthew Goldstein, RMR, CRR

25

A				
a.m 1:14 92:23	administering 41:18	20:10,14 23:21	application 14:22 75:4 87:13	argues 13:25
able 9:3 46:8 91:25	administration 37:1 41:1 88:17	23:24 25:2 28:9 30:24 31:3,6,13 31:17 32:16,18 32:20 33:12,18 33:21,23 36:6 36:14 39:17,21 41:24 42:2 48:7 55:6 69:11 70:6 71:10 82:7 86:5 86:6,8 88:6,9 88:11 90:25 91:3,5 92:19	applied 28:6 42:8	arguing 6:16 7:6
absolute 20:3 21:9	admits 65:15	amount 16:15,18 41:6 47:17 76:11,24 77:11 80:24 82:2 87:20 92:5	apply 27:12 38:8 49:16	argument 7:22 14:10 20:19 24:12 42:11,21 69:21 71:12,15 72:19 81:24
absolutely 21:3	advantages 40:23	amounts 12:10 49:1 50:18 64:25 69:14 74:15 75:9 76:2 89:23	applying 89:24	arguments 5:1 92:6
abstract 64:18	adverse 34:11,18 35:3,4,7,25 36:9	analogous 26:22 89:15	appreciate 10:3	arrived 30:3
accommodation 10:6	advise 5:25	analysis 25:7 27:16,18 34:1 45:17 90:22	approach 12:17 12:25 20:20,21 20:24,25 28:12 28:15 32:7 35:16 38:12 46:6 54:2 57:18 59:6 61:11 62:19,24	ARSHT 3:4
accomplish 46:8	affect 40:15	animals 25:9	approaches 25:22 60:6	art 12:24 13:3 16:22 17:3 18:20 25:5 26:22 29:9,17 29:22 30:1 38:9 38:24 39:4,5 40:7 46:10 47:5 49:15 52:2,16 53:11,21 57:15 57:17,20,23 58:3,5 62:19 69:22,24 71:8 76:8 80:8 85:18 86:25 89:5
accurately 39:4	aforesaid 88:16	answer 20:16 22:8 30:14 45:10	approaching 57:14 61:21 65:1 71:21	article 15:5 35:15 39:23
achieve 77:19	Agarwal 19:10 19:20 75:1	antagonist 12:24 45:25 53:23 54:2 55:21 56:19	appropriate 27:16	articles 34:14
achieved 87:5	agent 30:24 76:25	antagonists 54:5 54:9	approval 82:10	Ashkenazi 2:4 6:15 7:6,8,10 7:15,17,23,24 44:6,7,10,12,15 44:19,21 45:12 48:14 50:3 52:23 56:9 58:2 59:18 60:5 61:24 62:13,22 63:7 66:17,24 67:3,17,23 68:1 68:14 69:5,9,11 70:14,18,23 71:14,20 72:20 73:13,16 79:2,4 80:1 83:7 84:1 84:7,10,22,25 85:5,24 86:3 87:16 91:18
achieving 21:11	ago 55:18 61:19	anybody 5:19 49:14	approved 49:13	
acid 32:2,5,8,10 32:14 64:23 84:25 85:2,7,13 85:15,21	agree 61:19 65:12 74:23	Anyway 6:5	aprepitant 11:11 11:14 12:4,14 12:18,25 17:11 17:21 20:7,7,23 35:14,21 43:20 46:2 47:3 50:11 53:25 54:4,10 54:23,25 55:5,9 55:17 56:1,7,21 58:11,12,20,21 58:24 59:14 60:1,18 61:21 62:2,4,6,12,14 62:20 63:13,18 64:19,21 68:6 70:13 71:2,13 73:19,21 78:3 90:16	
acids 85:3	agreed 16:10 54:6 56:17 65:19 74:2 78:3 81:15 91:12	Apologies 44:16	approval 82:10	
acknowledged 25:15	agreement 24:19	apples-to-apples 39:5	approving 89:24	
action 1:5 93:13	agrees 58:8	applicability 25:1	approach 12:17 12:25 20:20,21 20:24,25 28:12 28:15 32:7 35:16 38:12 46:6 54:2 57:18 59:6 61:11 62:19,24	
actual 75:18 82:22	ahead 9:10 20:13 61:17 63:6 69:10 88:10	applicable 24:11 27:15	art 12:24 13:3 16:22 17:3 18:20 25:5 26:22 29:9,17 29:22 30:1 38:9 38:24 39:4,5 40:7 46:10 47:5 49:15 52:2,16 53:11,21 57:15 57:17,20,23 58:3,5 62:19 69:22,24 71:8 76:8 80:8 85:18 86:25 89:5	
add 27:17 32:23 75:23	akin 46:2		article 15:5 35:15 39:23	
added 32:2,12	Albano 10:9		articles 34:14	
adding 32:5 42:9	Alcon 24:12		Ashkenazi 2:4 6:15 7:6,8,10 7:15,17,23,24 44:6,7,10,12,15 44:19,21 45:12 48:14 50:3 52:23 56:9 58:2 59:18 60:5 61:24 62:13,22 63:7 66:17,24 67:3,17,23 68:1 68:14 69:5,9,11 70:14,18,23 71:14,20 72:20 73:13,16 79:2,4 80:1 83:7 84:1 84:7,10,22,25 85:5,24 86:3 87:16 91:18	
additional 43:15	alert 41:19		approval 82:10	
address 14:1 21:7 23:14 24:23 28:11 41:4 57:13 60:8 86:9 91:8	alkali 83:22,23		approved 49:13	
addressed 24:5 34:16 36:18,21 37:1 57:5 59:19 72:17 82:20 86:22	allegations 36:17		aprepitant 11:11 11:14 12:4,14 12:18,25 17:11 17:21 20:7,7,23 35:14,21 43:20 46:2 47:3 50:11 53:25 54:4,10 54:23,25 55:5,9 55:17 56:1,7,21 58:11,12,20,21 58:24 59:14 60:1,18 61:21 62:2,4,6,12,14 62:20 63:13,18 64:19,21 68:6 70:13 71:2,13 73:19,21 78:3 90:16	
addressing 20:15 20:22 53:17 57:8 81:12	Aller 89:21		approval 82:10	
adequately 50:8	allergic 34:15 36:12		approved 49:13	
adjourn 92:9	allotted 6:6 9:20		aprepitant 11:11 11:14 12:4,14 12:18,25 17:11 17:21 20:7,7,23 35:14,21 43:20 46:2 47:3 50:11 53:25 54:4,10 54:23,25 55:5,9 55:17 56:1,7,21 58:11,12,20,21 58:24 59:14 60:1,18 61:21 62:2,4,6,12,14 62:20 63:13,18 64:19,21 68:6 70:13 71:2,13 73:19,21 78:3 90:16	
adjourned 92:18	altogether 25:10 26:3		approval 82:10	
adjuster 31:19	Aly 3:12 8:7,11 8:15,16,18,25 9:11,19,22,25 13:24 14:3,14 14:16,20 15:5,8 15:10,12 19:6 19:15,19,24		approved 49:13	

<p>92:20 asked 5:7,13 27:22 51:16 54:14 asking 9:1 assert 83:8 asserted 10:13 11:6,23 43:24 45:21 55:1 63:25 68:12 76:15 85:19 asserting 12:1 84:13 assertion 34:6 82:18 83:19,21 assertions 36:17 asserts 47:19 assess 28:19 assessed 14:12 associated 34:14 34:24 assume 26:2 36:16 47:14 63:12,14 assuming 38:7 assumption 26:4 attention 63:12 77:25 86:18 88:25 attorneys 7:9,11 audio 44:17 August 1:13 93:18 authority 19:3 authors 64:6 80:16 authors' 80:22 automatically 32:15,16 available 18:2 58:15 75:21 Avenue 2:10 aware 6:3 18:14 67:20,24 awareness 6:4</p> <hr/> <p style="text-align: center;">B</p>	<p>back 39:14 51:3 52:21 53:20 60:11 61:18 70:25 84:15 86:5 92:2 back-and-forth 34:9 backwards 47:5 56:13 ball 70:20 Barr 57:6 barriers 57:16 based 13:11 16:21 67:1,3 bases 32:8 basic 27:2 32:2 basically 18:17 32:10 basing 70:8 basis 45:5 81:23 89:18 Bayer 57:7,7 behalf 2:2 3:10 10:4 believe 8:8 9:13 70:23 71:21 77:13 81:9 84:11 91:15 believes 83:22 benefit 86:23 best 19:3 30:22 56:8 67:9 73:8 better 59:1 88:15 big 42:4 45:13,14 bit 49:2,11 53:2 73:11 75:6 76:18 78:20 blends 51:2 blood 93:13 Bombardelli 19:21 bottom 64:14 68:2 83:11 bought 40:25 boxes 7:7 bread-and-but... 28:18</p>	<p>breakthrough 71:12 brick 12:15 brief 38:23 40:17 80:12 82:4 briefing 23:14 24:5 33:4 35:4 35:12,15 45:3 64:4 briefly 19:1 42:14 briefs 60:3 92:6 bright 25:12 bring 86:4 bringing 65:2 broad 65:7 66:13 68:5 broader 55:19 59:23 79:17 broadly 55:23 broke 39:13 BRYSON 1:11 5:1 6:17,21 7:13,16,20,25 8:10,16,19 9:16 9:21,24 13:23 14:9,15,17 15:3 15:7,9,11 19:1 19:11,17,23 20:4,12 23:20 23:22,25 28:8 30:21 31:2,4,8 31:14 32:13,17 32:19 33:10,14 33:20,22 36:3 36:13 39:13,20 41:19 42:1 44:5 44:9,11,13,18 45:11 48:5 50:2 52:22 55:15 57:4 59:17 60:4 61:18 62:10,16 63:5 66:14,21 67:1,13,19,25 68:13 69:3,7,10 70:11,16,19 71:6,15 72:15 73:12,15 78:25</p>	<p>79:3,24 83:5,25 84:3,8,20,23 85:2,23 86:1,4 88:6,10 90:24 91:1,4,17,20 92:22 built 67:6 burden 45:19 53:1,5,8 81:10 buyers 41:5</p> <hr/> <p style="text-align: center;">C</p> <hr/> <p>C 2:1 3:1,1 4:1,1 cake 85:14 call 6:10 8:6 24:7 25:16 52:6 88:25 called 23:6 30:13 38:22 40:16 87:4 88:14 89:5 calling 29:25 cap 23:3 care 92:16 careful 77:21 carefully 34:8 case 5:2 9:5 10:4 10:11,22 13:13 26:14 30:6 41:8 43:6 57:6,7,8 59:19 69:3 78:4 82:16,20 89:20 90:6 92:11,11 cases 55:23 57:5 87:12 categories 12:7 48:8 category 25:8 cause 36:4 80:25 caused 80:17 causes 84:13 causing 36:8 84:5 caution 20:17 cement 12:15 46:2 55:7 71:9 71:9 certain 21:3 24:17 45:24</p>	<p>69:15 80:24 84:18,19 certainly 7:1 24:16 37:15 certainty 20:3 certify 93:6,12 change 69:20,20 90:21 changed 11:21 changer 63:23 chapter 50:10 characteristics 55:4 characterize 55:23,25 56:6 57:9 58:1 characterized 57:22 71:11 chemical 38:4 chemicals 92:12 chemistry 38:3 Chicago 3:19 Chinese 14:18 choice 31:25,25 choices 68:11,11 68:18 choose 81:4 84:12 chosen 84:16 Chris 7:18 CHRISTOPH... 2:7 chunk 24:5 CINV 41:16 Cinvanti 40:25 47:2 circuit 57:4 68:24 cite 83:8 cited 60:2 69:4 cites 58:5 Civil 1:5 claim 13:19 30:2 41:14 69:1 83:3 83:12 claimed 43:14 53:16 83:9 85:19</p>
---	--	--	--	---

<p>claims 10:14 11:6 11:23 13:21 41:11,12 42:16 43:24 44:1 45:21 55:1 56:13 68:12 85:19 clamoring 35:9 clarification 9:13 class 17:20 54:9 75:20 classes 68:6 classic 86:20 classical 87:10 clear 33:6 45:20 46:17 47:25 51:16 53:4 60:11,17 65:16 69:21 73:18 75:2 76:4 80:23 81:11 82:5,6,20 83:13 85:12 89:7 clearly 50:19 82:10 Clinic 35:12 36:1 closest 39:4 40:6 closing 5:1 10:7 CN 10:13,14,21 11:1,3,8,9,22 12:2,16,23 13:2 13:7,10,25 14:4 14:11,12,21 16:22,24 17:7,8 18:2 20:18,24 21:16 22:9 23:21 27:19,23 27:25 28:7,25 29:23 30:15 31:19,20,24 36:18,21,22 37:1,3,14 38:9 39:7 41:9 42:9 46:15,18 47:12 47:15 50:13,19 52:18,25 53:12 58:16 59:8</p>	<p>63:19,22,25 64:5,15 65:6,9 65:10,19,25 66:4,7,16,17,18 67:16,20,24 68:2,19,19,23 72:3 73:17,23 74:1,4,7,12,12 74:14,16,20 76:7 78:4,6 84:17 87:13 88:3,13 89:4,5 89:14 90:21 co-counsel 8:7 co-emulsifier 10:24 68:8 85:8 85:10 coalescence 77:8 colleagues 7:5 column 83:4 87:3 combination 22:6 27:1 35:20 47:8 89:13 combinations 27:4 combine 11:3 13:7 53:7 come 5:23 15:4 20:18 29:11 47:7 48:23 comes 36:15 46:20 47:1 55:22 64:5 81:7 85:20 coming 20:19 29:25 commercial 37:17 40:18,18 60:16,25 common 10:19 35:16 50:16 commonality 20:21 commonly 33:1,9 60:12 87:24 compare 40:6 compared 39:3</p>	<p>88:15 comparison 39:6 39:22 40:1 compatibility 88:15 completely 47:23 48:20 51:13,14 89:17 complex 17:16 60:18,20 61:13 61:14,15 63:15 74:3 complexation 18:12,12 20:18 20:22 27:21 47:11,14 73:14 73:24 74:13,21 74:22 91:11 complexes 18:16 18:17 73:18,21 75:3 complexing 20:9 complexity 49:9 50:25 component 29:5 29:14 31:18 32:24 components 12:6 17:16 25:22 30:9,10 48:25 49:1 50:23 52:1 69:1 85:16 87:17 composition 14:11 compound 11:17 compounds 11:16 17:21,21 38:4 conceded 28:13 concentrate 82:13 concentration 77:4,11 concentrations 77:7 concept 47:13</p>	<p>48:15 concepts 47:6 concern 20:17 concerned 28:10 concerns 57:25 conclude 11:6 21:10,25 38:20 41:21 90:13 concluded 37:7 conclusion 41:7 42:2 43:21 80:18,20 conclusions 1:10 80:22 conditions 15:15 conduct 82:8 Conducted 1:12 conducting 8:12 confer 80:9 confidence 21:21 confidential 5:22 40:19 confines 56:2 confusion 34:7 conjecture 46:12 conjugate 32:8 conjunction 46:24 consider 51:15 considerable 24:5 consideration 37:18 38:17 considerations 11:5 30:10 34:4 41:11 consistent 13:20 87:11 consistently 76:15 consonant 31:10 constitute 24:20 construed 21:13 contain 46:18 54:17,21 63:3 65:20 contained 64:9 84:17</p>	<p>contemporary 89:14 content 82:9,15 contest 33:5 context 33:7 89:3 89:7 continue 87:21 continue- 78:24 continuum 22:23 25:11 48:18 51:19 52:3 79:12,14 contradict 82:18 contrast 65:6 controlled 40:22 convenience 10:7 conventional 49:4,6 51:19 52:6,7,17 79:18 converting 32:14 convincing 45:20 53:4 81:11 convincingly 63:17 Copying 40:16 correct 8:14,15 15:10 16:8 20:10 84:21,24 88:11 correctly 84:24 Corswant 23:17 78:17,22,25 79:9 86:13,15 86:25 87:9,13 cosolvents 60:8 cost 41:2 counsel 10:5 86:17 87:16 91:8,21 COUNTY 93:3 couple 50:15 78:2 80:1 81:8 course 21:9 25:2 28:25 court 1:1 5:16,23 10:2,8 37:21 44:21,24 92:10</p>
--	---	--	--	--

crashed 90:17	3:10 8:1,24	51:14,25 58:4	48:8 50:22	18:6,19 31:1
crashes 71:3	defines 88:23	62:16 72:25	72:16 78:15	35:8 50:8 75:7
create 46:6	defining 86:19	73:2,3 75:4	79:10	75:23 76:1
credible 68:17	definitely 36:9	79:13 86:9	distinctive 79:13	drugs 18:16 68:6
69:12	definition 87:7	87:17,18 89:22	distinguished	75:4,20 90:19
creek 72:14	definitions 86:20	difficult 46:4	42:17	due 5:10
criteria 82:24	87:10	55:5 56:22	District 1:1,2 5:3	dumping 17:10
89:10	degree 24:9 27:8	59:22 60:19	divide 6:7	dust 12:15,15
critical 30:5	40:13 53:14	63:15	doing 8:17 16:1	46:3 55:7 71:9
55:16	degrees 48:10	difficulties 63:2	36:10 61:23	71:10
criticality 29:14	Delaware 1:2 3:7	difficulty 59:25	65:4	<hr/>
30:6 53:3,9,9	4:7 5:4	DIGITAL 1:23	Dr 11:15 13:6	E
81:10	demonstrate	direct 32:7 54:14	15:22 16:16,19	E 2:1,1 3:1,1,1
CRR 1:21 93:24	67:16	directed 14:19	17:14,17 18:11	4:1,1,1
crystal 62:8 66:1	demonstrating	26:24,25	18:14 19:7	E80 64:22
82:9,15	66:22	direction 15:18	20:15,20,22	earlier 21:16
crystalline 55:10	denying 45:24	18:8,22	21:3,24 22:8,13	50:24 71:1,25
crystallize 59:2	departures 68:19	directions 21:21	22:25 23:9,12	78:20
crystallized 62:8	described 17:20	69:15	25:7,15 26:14	easier 56:25
crystals 43:20	65:5 74:17	directly 66:15	27:5,15,18	easy 60:22
46:3 55:13	describes 55:11	disagrees 80:19	28:13,17 29:10	eat 85:14
82:11	description 11:7	disclosed 86:15	29:16 30:25	effect 88:19 90:9
cure 57:14	42:14,15 43:25	disclosure 30:16	31:22 32:4,20	effective 28:24
CURTIS 1:11	82:25 83:17	31:24	33:12,24 34:1	29:3
<hr/>	88:24	disclosures 88:3	34:16,16,22	effectively 66:15
D	design 11:16,17	discuss 11:3 22:3	35:1 36:7 37:7	67:14 85:4
D 3:1 4:1	detail 49:2,8	61:6 82:7	37:20,23,25	effects 37:9 41:1
D.C 1:24 2:18	details 45:14,15	discussed 24:8,10	39:25 40:2,10	46:1,1 53:23
10:6	determine 73:6	27:23 63:9 64:3	42:7 43:9,18	56:19 81:6
Daniel 4:3 8:4	development	77:9,12 80:11	46:13 50:10	efficient 6:2
77:13	52:17 54:15,17	92:12	51:17 54:6,12	efficiently 55:12
dark 28:21	61:12	discusses 86:25	55:3,6,9 56:17	effort 10:9
data 34:20,22	difference 28:5	discussing 80:8	58:7 61:6,6,10	efforts 11:15
46:19 65:16,20	30:18 34:21	discussion 61:19	61:16,25 62:3	67:10
66:8	35:2 53:13,14	dispute 13:13	63:25 65:9,15	egg 17:11 18:15
date 11:20,23	78:18	30:11,19 31:18	65:19 67:8 71:2	18:18 29:3
16:4 37:5 49:13	differences 25:9	41:16 56:16	71:24 74:2 77:9	32:22 33:8
54:3 90:21	28:1 34:12	78:2 80:16	77:22 78:3,12	46:11,14,22
Daubert 37:22	40:13 48:10,11	82:16	79:13 80:13,19	51:10 64:22
day 41:4 45:22	81:20 85:17	disputed 16:17	81:15,19 82:18	68:21 69:16
93:18	different 12:6,9	21:1 28:12	86:16,17,21,22	73:21 74:8
days 66:2	19:14,15 22:24	30:13 45:2	89:1,2 91:9,12	eight 12:12
deal 80:10	24:8,15 25:9	distinct 34:17	dramatic 29:20	either 36:2,9
decisions 41:5	26:3 29:21	48:3,21,25	draws 78:18	41:21 89:19
declines 77:6	32:23 35:20	49:19 78:18	drew 78:15	element 42:23,24
deemed 13:3	38:4 47:24 48:3	85:11	Drive 3:17	eliminate 35:9
defendant 1:8	48:25 51:1,8,13	distinction 27:4,6	drug 10:23 17:11	Emend 35:14

41:2 46:1 54:19 emetic 55:20 emphasize 26:1 42:3 52:13 emphasized 17:17 emulsifier 10:22 17:12 18:22 22:7 23:11 27:20,20 40:9 42:10 47:17 50:18,20 63:24 64:2,25 65:7,25 67:12 68:7 74:2 75:7,9 76:2,10 76:14,19,25 77:3,4,6,11,14 77:17,20 91:7 91:13 emulsifiers 51:2,2 51:6,8 74:18 emulsion 12:3,5,8 12:11,17,21 13:10 15:2 17:3 17:5 22:21 24:21 25:13 27:1 29:6 33:7 38:12 42:8 46:10,14 47:3 51:18,19 52:17 58:19,20 59:6 63:14 64:20 65:24 75:24,24 75:25 77:1,5,7 77:14 78:14 79:17 80:18 83:24 88:17,18 90:10 emulsions 12:12 22:18 23:16 24:9,10 25:6,7 25:22 26:16 27:1 33:2 34:3 38:15 48:2,9,17 49:4,6,7,16 50:12 52:7,8,18 54:1 58:12	60:12,13,22 61:7,8,13 62:5 62:14 63:19 75:20 78:3,7,19 79:10,19 87:14 encourage 45:8 encyclopedia 10:25 endeavor 92:8 energy 87:6 entire 8:12 entirely 7:23 13:19 15:25 48:3 entitled 93:9 entry 43:23 EP258 87:1 EP279 19:20 75:1 EP825 19:10 equal 37:12 equivalent 30:16 era 38:3 ESQUIRE 2:4,5 2:6,7,8,16 3:3 3:12,13,14,15 4:3 establish 71:17 established 20:25 70:12 88:19 ethanol 17:12,13 85:13 evaluate 82:15 evaporating 17:13 event 34:18 35:6 92:14 events 34:11 35:3 35:4,7 36:9 everybody 7:21 15:21 16:10 38:14 49:7 79:9 evidence 1:23 11:18 13:6 27:10 29:20 34:12,13,20,22 35:11 36:3,6,11 38:2,5,8,14,18	40:6,7,11,14,24 42:11,13 45:20 47:11 49:12,14 52:15 53:4 65:14 76:12 81:3,12 82:17 87:18,19 90:15 90:15,19 example 35:13 39:7,8,12,18,21 40:4 42:6,18 49:20 51:17 58:5,18 63:2 65:7,22 66:14 66:18 67:7,8,15 68:20 72:6 73:25 74:1,9,9 74:9 78:17 79:9 81:14,14 87:1 87:14 88:4,14 89:16 examples 12:12 17:2 18:13,20 20:16 39:9,15 39:17 47:15 53:10 65:10 70:3 74:4,7,17 excipient 12:10 excipients 87:18 88:1 exclusively 54:22 58:10 excuse 6:1 exemplified 87:3 exhibit 33:15,16 78:25 exhibits 19:4,9,9 exist 47:7 89:22 expectation 11:4 15:19 18:23,24 20:1 21:7,8,11 38:19,24 53:7 70:7 expected 40:11 66:6 experiments 88:20	expert 21:3 experts 13:15 33:25 explain 13:9 36:7 37:24 explained 13:6 15:22 17:14 18:2,11,15 21:4 21:16 22:14,25 23:9,12,17 26:15 27:19 28:17 29:2,10 29:16 30:25 31:22 32:4,21 55:3,9 61:25 63:18 76:19 77:22 81:19 89:3 explaining 88:12 explanation 17:25 62:3 explicitly 65:20 78:18 83:12 expressly 29:2 extent 24:18 70:21 extrapolate 24:13 extremely 46:4 56:22 68:5 <hr/> F <hr/> face 40:8 facing 47:4 fact 13:25 23:15 41:1 46:8 60:7 60:12 65:15 77:2,21 80:11 81:24 82:9 88:18 factors 77:1 facts 1:10 45:24 failed 54:4 62:22 71:8 90:17 failure 37:18 38:14 59:13,13 63:8 70:8 fair 71:11	fairly 5:10 24:24 far 22:5 26:1,15 27:7 28:9 36:17 91:6 fault 24:2,2 favor 91:15 favorable 15:18 21:17 favored 55:10 FDA-approved 60:13 80:7 federal 57:4 68:24 Fell 33:2,18 fewer 46:1 field 24:19 25:6 76:6 final 90:23 91:1,3 91:6 Finally 33:1 find 22:15 62:1 finding 45:5 findings 1:10 43:24 fine 9:23 44:12 52:22 69:8 first 5:7,23 6:11 10:3 16:24 17:9 20:18,24 22:9 34:6 38:19 39:9 42:8 47:2 49:25 50:3,5 56:11 71:6 73:23 76:24 85:7 86:10 88:22 Firstly 50:7 fits 22:5 five 11:6 41:25 86:7 fix 6:21 fixated 63:19 flag 40:17 Fleischacker 2:6 7:8,18 flip 27:11 Floor 3:6 focus 10:18 16:14
---	--	---	---	--

16:15 17:18 18:10 37:19 45:1 56:24 57:23 58:23 59:7,15 60:7 61:4 69:15 73:7 76:17,23 focused 16:20 52:4 58:11,16 63:21 68:4 74:12 75:18 76:23 focuses 64:15 focusing 45:12 54:22 65:2 follow-up 84:4 following 29:24 foreign 32:23 forget 92:14 forgotten 9:17 form 14:24 17:15 18:16 19:4 32:9 46:3 55:12 formally 5:14 formed 32:10 66:1 75:24,25 forming 78:13,14 formulate 12:14 12:17 46:4 90:16 formulating 25:6 formulation 11:19 12:25 17:10 21:12 25:21 26:3 27:12,13 29:4,5 30:23 37:13,15 38:5,8 40:4 41:15,17 43:5 43:12,14 46:23 47:24 48:3 51:25 52:16 53:14 54:2,18 60:6,15 64:19 73:9 formulations 18:19 25:16,20	36:22,23 39:10 42:19 43:11 53:16 64:1 81:23 84:19 85:22 89:5 90:16 formulator 37:21 37:21,24 42:7 formulators 26:10 forth 13:18 fosaprep- 62:24 fosaprepitant 46:6 54:18,21 58:7,9,25 62:25 63:3 90:18 found 37:21 66:1 68:24 80:17 four 66:2 79:25 86:9 fourth 90:13,23 FOX 3:16 frame 22:20 free 9:5 Fresenius 1:7 3:10 5:3 6:8 8:5 8:13,21 13:25 43:1 45:2,19,23 46:9 47:18 49:5 52:5 53:1,5,24 58:5 60:21 63:17 64:7,15 68:4,16 70:10 73:16 75:18 76:15,23 81:22 82:8 83:14 91:16 Fresenius' 14:4 45:16 47:4 69:21 83:15 full 42:16 Fulton 57:7,7 function 30:21 89:12 fundamental 45:16 further 18:6	52:20 58:12 93:12 <hr/> G <hr/> game 63:22 70:20 general 12:25 26:11 52:25 55:20 generally 77:22 gentleman's 10:9 genus 68:5 getting 31:9 44:17 61:18 76:2 give 9:1,5 33:10 33:14 35:18 39:15 51:17 69:18 80:5 given 5:15 37:23 53:15 57:13 70:1 74:21 gives 64:20 65:7 giving 15:19 35:18 gloss 77:2 go 6:23 9:10 20:12 27:25 35:23 39:14 40:20 45:7,13 47:21,23 49:25 51:3 52:10 56:20 57:12,19 58:11 59:9,15 60:11 61:2,12 61:17 63:5 69:10 74:5 76:20 77:17 78:9,20 82:1 86:5 88:10,21 goal 17:4 41:24 56:17 81:5 goes 55:13 70:25 going 10:18 16:12 17:6 27:5 31:16 32:14,22 34:19 35:16 44:24 49:21	50:21 52:10 56:20,24 58:10 58:23 59:2,5,7 59:14 61:11 68:20,20 69:13 71:1 72:2,6,8,8 72:9,9 73:6,7,8 73:10,10,17 74:10 77:18,21 80:10 82:11 84:12 85:3 87:2 88:22 92:1 Goldstein 1:21 93:5,24 Gonglun 77:12 good 6:12 8:3,18 8:19,19 19:17 22:3 44:19,20 54:24 granted 91:15 great 9:24 44:15 92:21 greater 46:10 GROUP 1:23 guarantee 21:5 guess 56:7,9 guidance 69:18 <hr/> H <hr/> H 3:14 Hale 11:15 37:20 55:3,6,9 61:25 62:3 71:2,24 half 41:20 Han 42:7 67:8 81:19 hand 89:25 90:6 93:18 handle 6:3 handling 7:22 happen 22:1,1 happened 29:18 42:4 57:2 happening 34:18 happens 27:12 happy 45:9 hard 12:14	Hargreaves 63:9 Hastings 2:9 7:5 7:9,11 44:22 He'll 8:11 head-scratching 47:22 hear 44:12,13 46:12 48:6 72:14 82:7 91:19 heard 11:14 45:4 45:23 53:1 61:5 69:11 76:18 79:23 hearing 5:15,16 5:17 24:1 hearings 9:17 heating 14:25 heavy 10:14 Helen 3:14 8:9 Hello 8:16 help 18:5 48:12 72:9 92:17 helped 18:19 helpful 15:17 91:22 helping 10:9 helps 30:25 hemolysis 80:17 heretofore 12:13 hereunto 93:17 Heron 1:4 2:2 5:2 6:14 7:4 11:24 16:3 26:5 29:13 29:15,19 30:6 30:17 34:25 35:12 36:1 38:18,23 40:8 40:20 42:6 43:1 43:10,16 44:22 46:9 53:2 65:24 Heron's 10:17 18:25 19:25 21:2 23:14 33:4 33:24 42:11 53:8 83:16 high 15:1 16:25
---	---	---	--	---

17:2 27:24 50:8 50:18 64:25 66:15,19 67:11 75:9 77:6,10,17 higher 18:22,23 72:8 73:11 76:2 76:10,10,14 77:18,18,21 82:1 Hill 2:7 7:18 hindsight 10:18 10:20 16:21 45:18 47:6 56:11 57:1,22 62:21 Hingorani 38:10 38:11 58:18 60:8 72:5 76:7 Honor 6:12 7:2 7:10,24 8:3,15 9:12 10:1 14:3 14:14,20 20:10 22:4 25:2 27:14 30:8 34:5 43:22 44:4,7,10,16,20 45:6,9 46:18,21 47:2,23 48:18 49:3,11,20 50:15 51:4 52:19,24 53:17 56:10 58:2,12 59:18 60:2 61:5 61:25 62:13 63:4,7,12 64:4 64:12,14,24 65:12,23 66:6 66:25 67:4,12 67:18,23,24 68:5,12 70:14 70:25 71:14,20 72:10,14,21 73:11 74:6,19 74:25 75:12 76:4,16,22 78:1 78:9,11,16 79:5 79:22 80:2,14 81:3,7 82:3,19	83:1,7,13 84:1 84:7,11 85:1,6 85:17,20 86:8 88:25 91:3,14 91:18 92:19,21 Honor's 10:5 hope 9:2 92:2,21 hour 6:7 HS 88:15 huge 68:7 human 70:1 humans 46:5,7 53:15 hydroxide 32:6 hypersensitivity 34:10,15,21,23 36:12 37:10 hypotheses 47:10 80:20 <hr/> I <hr/> idea 47:9 identified 52:2 58:13 62:10 66:3 identify 51:20 61:20 ignore 10:21 52:10 59:25 63:1 64:9 80:21 85:16 ignores 90:14 III 17:20 75:20 Illinois 3:19 illness 57:15 impermissible 45:18 implemented 5:9 implementing 30:1 imply 43:11 important 11:8 13:14 24:25 25:14 29:4,5 48:5 69:24 76:19,25 importantly 29:1	72:10 74:19 Imron 3:12 8:7 inapplicable 89:18 Inaudible 91:4 91:17 include 20:6 42:16 included 25:8 64:1 67:11 including 7:5 41:9 88:3 incorporating 24:21,21 increase 18:6,8 62:1 63:23 76:14 81:25 82:1 91:7,9,10 91:13 increased 21:5 40:9 42:10 71:17 increasing 18:5 21:4,22 23:2 40:9 76:1 77:16 77:20 indicated 62:19 indication 67:14 indicia 53:18 81:12 82:4 individual 55:11 infected 45:17 influence 77:1 influencing 7:7 inform 52:16 information 13:8 14:5,24 15:18 16:7,9 21:18 23:1 40:19 58:14 63:1 64:8 64:9 67:5 informative 91:23 infringed 44:2 infringement 41:22 44:25 45:3 82:6	ingredient 69:14 ingredients 46:24 64:20 69:15,19 72:25 73:2,3 77:23 81:17 inherency 43:5,7 inherent 43:13 inherently 32:10 32:16 inhibitors 56:4 initial 65:5 inject 47:6 injectable 11:12 12:4,17 51:7 54:17 87:25 injection 34:10 34:11,17 35:3,4 35:6,13,18,21 35:24 36:14 37:10 injection-site 35:10,17,25 36:4,8 input 87:6 inquiry 55:19 Insight 59:19 insoluble 55:7 instability 77:7 77:20 instances 84:18 intended 67:15 interactions 18:18 interactivity 68:25 interdependent 73:1 interested 54:8,8 93:14 interesting 65:23 interface 17:23 47:18 interposing 9:4 interpreted 37:25 interrupt 13:23 19:2 20:4 23:22 intravenous	88:17 introduces 35:24 invalid 10:12 43:24 invalidate 8:23 invalidity 8:22 45:1 invention 29:25 56:13 inventions 53:16 inventor 15:13 inventor's 56:12 56:12 inventors 13:16 42:12 59:15 67:4 inventors' 67:4 involved 43:23 Isaac 2:4 7:5 44:21 issue 8:22 30:5 36:25 55:22,22 57:24 59:19 71:24 81:2 issued 11:22 37:3 issues 57:25 58:4 92:7 items 24:7 26:23 IV 35:14 41:2 45:25 46:1,4,7 47:3 53:22 54:18,19 56:18 56:23 58:21 59:4,14 61:12 62:2 63:3 71:4 75:2,3,3 <hr/> J <hr/> Jenkins 4:4 8:5 Jeremy 3:3 6:13 7:3 Ji 3:14 8:9 job 28:18 joined 7:4 JTX 79:2 JTX1.18 83:3 JTX1.8 83:4
--	--	---	---	--

JTX105 61:2	67:1,13,19,25	knew 28:25	length 64:3	24:14 25:1
JTX105.25 60:10	68:13 69:3,7,10	know 9:8,19 13:3	let's 6:5 8:23	27:15,17 41:9
JTX110 79:3	70:11,16,19	20:17 23:1	48:14 49:10	49:18,18,22
86:12	71:6,15 72:15	28:22 30:20,22	50:15 59:9	50:6 51:4 52:25
JTX112 33:3,18	73:12,15 78:25	31:8,18 39:22	60:10 63:12,13	78:2 87:23 88:6
JTX113 17:19	79:3,24 83:5,25	45:6 57:4 59:3	69:21 73:18	88:8,21 89:15
JTX113.9 75:16	84:3,8,20,23	60:15 61:11	76:4 80:23	89:17
JTX114 19:20	85:2,23 86:1,4	72:3,4 73:7	level 11:17 23:11	LLC 1:7 3:11 5:3
JTX115 15:13	88:6,10 90:24	79:10,17 82:19	25:18 49:8,9	LLP 2:9 4:4
21:19 64:13	91:1,4,17,20	knowing 52:23	89:12 91:7	load 75:20
JTX21 38:12	92:22	58:24 80:5,5	levels 16:25 17:3	loading 75:22,25
JTX67 19:20	judgment 82:21	knowledge 13:8	17:18 18:9,22	localized 34:17
JTX71 11:9	91:15	18:11 50:17	21:18 26:6	long 12:21 28:14
64:14 68:3	Julie 3:15 8:9	67:6	27:24 91:13	long-felt 34:7
JTX74 19:21	Jumaa 33:2,6,21	known 21:1 23:8	lifting 10:14	35:9 36:2,16,18
JTX76 33:3,19	33:25 80:23	28:23 29:4,16	light 92:6	37:3,8
JTX79 77:13	jump 70:5	50:18 81:1	limit 21:6 22:10	look 10:21 13:2
JTX88 33:3,6,21	Justin 2:6 7:18	89:23	68:21	13:16 15:14
JTX91 29:7		Kruse 2:8 7:19	limitation 55:1	16:18 22:14
76:20	K		limitations 13:19	26:6,7,10 28:19
JTX93 22:5	K 14:18,22 15:3	L	line 25:12 50:4,4	29:19 40:7
49:22 51:3	15:16 16:2,12	L-I-U 19:13 22:5	50:5 83:4 92:10	42:12 43:20
87:22 88:9	16:13 46:21	lab 40:3	lines 89:3	47:5 49:15,18
JTX93.11 87:23	Kabi 1:7 3:10 5:3	label 35:2	linked 35:5	49:22 50:21,22
JTX93.9 88:21	8:5 91:16	lack 24:19 43:25	lip 64:7	51:4,7 54:25
JUDGE 1:11 5:1	Kabi's 43:1	large 75:21	list 7:14 30:15	57:15 60:9,10
6:17,21 7:13,16	Kamantz 60:10	largely 9:3 55:7	51:5 88:1	65:6 66:12 68:1
7:20,25 8:10,16	Karavas 58:6	lattice 55:14	listed 61:8	72:22,23 73:1,5
8:19 9:16,21,24	Karthik 2:16	law 82:20	listening 34:8	73:20,25 74:4
13:23 14:9,15	7:17	lead 15:13 62:14	literature 49:16	75:14,16 78:12
14:17 15:3,7,9	Kasaraneni 2:16	77:20	little 21:3,24	78:17 81:19
15:11 19:1,11	7:17,18	leading 8:8,11	23:12 25:15	82:14 88:22
19:17,23 20:4	Katzenstein 4:4	lecithin 16:15,18	27:5 28:13	looked 11:14 17:7
20:12 23:20,22	8:4	16:21,25 17:4	29:16 33:12,24	17:7 22:9,13
23:25 28:8	KE 15:2 16:5	17:12,18 18:8	37:23,25 43:9	33:2 73:2 76:13
30:21 31:2,4,8	21:20 64:8 90:4	18:15,18 20:9	43:18 49:2,10	looking 12:23
31:14 32:13,17	keep 12:21 31:16	21:4,18,22 23:2	50:10,24 53:2	16:21 23:18
32:19 33:10,14	77:18	26:12,18 28:23	53:19 61:6,10	27:25 28:7,25
33:20,22 36:3	Kevin 3:13 8:8	29:3,17 46:11	64:2 65:11 75:6	29:9 43:3 47:14
36:13 39:13,20	key 33:4 46:11	46:14,16,23	76:18 77:22	54:20 57:22
41:19 42:1 44:5	71:5	51:11 64:22	78:20 79:25	59:23 63:18
44:9,11,13,18	Khan 29:1,7	68:21 69:16	86:17,22 91:12	67:2 73:17
45:11 48:5 50:2	76:17,18,23	73:22 74:8 82:2	Little's 40:2	86:15 87:22
52:22 55:15	kind 24:9,15 25:9	89:12	82:18	89:21
57:4 59:17 60:4	26:3 27:9 48:11	left 78:23	Liu 19:13 22:3,13	looks 49:7
61:18 62:10,16	53:13 57:5	left-hand 61:4	22:16,17,24	lot 11:18 55:22
63:5 66:14,21	kinds 12:15 38:4	lended 59:22	23:4,10,13 24:8	75:12

low 77:24	51:9 78:1 79:22	53:23 56:19	moved 54:4	45:25 53:22
lower 83:19	mentioned 22:4	81:5	moving 28:2 34:4	54:1,5,8 55:21
Ls 31:7	47:12 50:23	minimum 26:22	multiphase 72:17	56:3,18
<hr/>	55:18 60:7	minute 76:17	multiple 73:2	noninfringement
M	78:19	91:1	<hr/>	11:7 42:15,22
M 1:24 2:17	mentions 73:23	minutes 9:9,14	N	45:5
magnification	Merck 11:17 38:5	9:22 41:20,25	N 2:1 3:1,1,1 4:1	nonobvious 69:2
43:7	46:5 54:3 61:19	44:6,25 66:11	4:1,1	North 3:5
maintain 72:2,13	76:6 90:14,15	79:25 86:7	naked-eye 43:17	Notary 93:5
maintained 15:16	Merck's 37:19	misconstrue	43:19	note 51:9
making 12:5,24	met 69:18 81:10	83:14	named 13:16	notebook 40:3
24:12 25:22	meter 81:20	missed 39:13	31:21	notes 5:6
26:25 33:24	method 41:15,17	69:4	names 92:11,12	number 7:11 9:9
52:9 62:4,6	61:21	missing 70:16,20	nanometers	25:5,24,25
63:3 72:19	micro- 80:5	misspoke 50:24	88:24 89:9	29:15 30:7
manageable	microemulsific...	mistake 52:5,9	narrowly 58:15	56:22 58:4,23
37:11	87:4	misunderstand	59:15	59:5 65:2 68:11
manual 26:9,9	microemulsion	19:12	natural 23:7	74:7 79:1
Mark 2:5 7:18	22:20 23:13	mix 16:4	32:24	numbers 33:15
market 3:5 41:3	24:18 25:13	model 85:22	naturally 22:10	33:17
47:3	26:17 48:15,16	Moderna 68:25	nature 5:16	NW 1:24 2:17
Markman 34:16	49:13,15 51:20	69:5,7	near 49:8 75:7	<hr/>
37:7	52:6,16 78:14	modification	necessarily 14:13	O
marriage 93:14	86:24 87:5,7,8	81:16	necessary 56:1	O 3:1 4:1
Maryland 93:1,6	89:8,10	modifier 81:2	71:17 75:19	objective 45:24
match 16:4	microemulsion...	85:9	need 16:5 34:7,8	53:18 81:12
materials 37:25	86:10	molecule 46:4	35:9 36:2,16,18	82:4
matter 6:3 27:8,9	microemulsions	59:21,22 60:18	37:3,8 45:24	observations
28:4 38:17	22:17 23:15	molecules 55:11	53:22 69:23	43:18,20
45:22 72:9 73:4	24:6,22 25:16	moment 13:24	76:9 81:9,25	obtain 12:3 28:20
81:22 93:9,15	47:24 48:2,9,23	53:21 55:18	82:1,1 90:11	obtained 11:25
Matthew 1:21	49:9 50:7,16,22	61:19 72:23	92:6	obvious 10:12
93:5,24	51:1,7 52:8	73:14 75:12,14	needed 42:24	15:25 31:23,25
Mayo 35:12,25	61:7 78:5,8,19	MONTGOME...	needle 34:19	41:12,13,17
mean 14:8 52:9	79:11,19 80:6,7	93:3	needs 69:18	43:25 45:21
means 43:6 69:24	87:14,25 88:23	morning 6:13 8:3	neither 17:22	47:7 57:19 69:2
measurement	89:6	8:18,19 44:20	21:6	obviously 78:13
15:16	microfluidizer	Morris 3:4 6:13	Nelson 3:13 8:9	obviousness
mechanical 87:6	25:17	7:3	never 30:13	10:13 11:5
mechanism 18:3	microscope 43:3	motivate 69:13	new 2:11,11	40:15 41:7,8
medically 37:10	microscopic	motivation 11:3	20:19 29:25	42:3,13 45:13
medicinal 38:3	25:18 42:25	13:7 18:8 53:7	42:7 47:6	45:17 53:4
meet 21:22	microscopy 42:24	56:17 59:24	Nichols 3:4 6:13	55:23 81:11
meets 21:12,13	43:18	motivations 20:1	7:3	83:21
member 5:12,25	mid-1990s 11:16	move 30:8,9	night-and-day	occurred 42:5
members 5:25	11:19	40:18 46:5	28:5	occurs 77:7
mention 33:25	minimal 45:25	52:20 62:23	NK-1 12:24	Oh 6:20 9:16

<p>15:7 19:17 31:8 52:3 76:9 77:17 79:3 83:16 oil 10:23 17:22,24 27:2,4 50:7,11 52:7 55:2 64:21 oil-in-water 49:5 52:7 61:7,8,13 79:19 okay 7:13,20 8:1 8:10,20 9:16 15:7,11 19:17 19:23 20:12 28:8 31:15 33:22 36:13 39:20,20 42:1 44:18,24 59:17 67:21,25 69:7,8 72:20 73:6,12 80:1 83:25 85:23 oleate 30:11,19 31:17,23 32:7,9 32:9,21 33:1,5 33:7 68:22 69:16 80:15,17 80:25 81:1,2 84:5,6,12,13,16 84:18,23 oleate's 34:2 oleates 85:3 oleic 32:2,5,8,10 32:14,15 64:22 84:25 85:2,3,7 85:13,15,21 once 12:20 13:2 18:1 20:4 opening 38:22 opinion 39:25 opportunity 9:2 37:23 opposed 35:18 48:11 optimal 46:23 64:19 73:8 optimism 15:19 optimization</p>	<p>10:16 11:25 12:22 15:23 16:1,19 22:6,12 28:10,11 30:4,5 46:22 68:17 71:16 optimize 13:11 14:7 46:21 69:23 73:9,10 90:5 optimized 46:16 64:6 72:24 90:11 optimizing 28:17 28:23 29:9,22 29:24 65:2 90:3 90:3,4 option 47:5 options 30:16 58:17 oral 35:14,22 orally 35:19 order 9:14 33:3 61:11 62:1 75:20 ordered 55:14 ordinary 89:4 osmolality 30:25 31:2,3,5,6,11 31:13 osmolarity 31:5 outcome 93:15 overlap 25:19 overlapped 89:11 overlapping 22:21 23:16 48:10 87:15,20 overlaps 88:2,13 owner 10:19</p> <hr/> <p style="text-align: center;">P</p> <hr/> <p>P 2:1,1 3:1,1 4:1 4:1 page 49:23 51:3 61:3 64:14 68:3 76:20 79:5 89:2 pages 80:12</p>	<p>paint 60:21 pallor 36:10 paragraph 76:22 86:19,21 87:2 parallel 23:19 parameter 14:8 parameters 29:11 Park 2:10 parse 72:16 part 22:17 23:15 62:11 70:12,22 70:24 participate 5:14 5:14 particle 88:24 89:11,12 91:10 particles 25:18 43:1 particular 10:11 13:1 18:15 20:23 21:15 23:6 29:6,14,23 31:20 41:6 55:22 57:14 69:19 86:14 parties 5:7 45:7 93:13 parts 58:23 party 8:21,22 patent 8:23 10:19 13:21 14:18,21 15:9 30:16 37:5 37:5 39:18,18 39:24 41:12,15 42:17,23 44:1 83:3 84:6,9 patented 56:13 patents 10:12 11:25 39:10,22 patents-in-suit 53:11 65:23 pathways 57:16 patients 35:23 Paul 2:9 7:5,9,11 44:22 pays 64:7 PDX4-4 74:5</p>	<p>PDX5- 83:2 PDX5-1 64:11 66:10 PDX5-3 78:21,22 PEG 74:10 people 5:17 23:18 25:15 26:12 31:6 48:1 52:5 58:3,4 59:10 79:18 percent 17:1,4 21:18 22:9,11 23:2,5,10 26:12 26:18 27:19 28:2,3 30:2 35:7 46:11,14 46:16,22 63:24 64:2,21,21,22 65:3,8,11,25 66:20 67:15 68:8,9,21 69:16 72:6 73:9 74:1 74:2 75:10 77:13,14,15,15 80:6 90:2 perfectly 9:22 44:14 period 53:15 70:3 71:8,24 permission 5:13 person 52:14 89:4 pertinent 37:4 pH 31:19 32:2,6 32:13 39:6,8,10 39:24 40:4 66:2 81:2,15,20 83:10,19 85:9 Pharmaceuticals 57:6 phase 50:7 phases 17:24 27:2 phospholipid 23:5 32:22 73:21 phospholipids</p>	<p>23:6 33:8 51:10 phrases 12:16 pHs 39:16 42:17 physical 13:18 55:4 physically 13:20 21:14 42:18,23 43:13 pick 69:16 picking 85:12 picture 45:14,14 60:21 piece 52:2,14 pile 55:12 place 22:3 38:19 plaintiff 1:5 2:2 6:11 44:22 plan 9:14 11:2,6 please 10:2 44:21 61:3 64:11 66:10 76:21 79:21 83:1,2 point 5:12 11:13 11:20,21 18:10 21:1 22:19 24:17 25:5,23 25:25 26:5,21 33:4,23 35:11 39:14 40:17 41:14 43:9 49:21 50:9 51:12 60:12 63:20 70:6 71:18 72:21 74:11 77:16 80:15 81:1 84:10,17 86:11 87:9 89:10 90:1 90:7,13,23 91:2 91:3,6 pointed 21:20 46:9,21 65:13 86:17 pointing 77:10 points 18:21 20:15 43:16 45:14 50:16</p>
---	--	--	--	--

<p>56:10 80:2 81:9 85:6 86:10 90:8 poloxamer 74:8 polysorbate 34:14,24 35:5 36:10,20,23,24 37:13 54:18,22 63:4 74:9 88:4 polysorbates 88:3 poorly 55:1 portion 5:23 64:15 68:4 75:17 78:12 79:6 83:11 portions 72:17,18 POSA 10:15 12:13 13:3,5,9 13:9,14,16 15:22 16:14,18 16:20,23 17:7 17:18 18:1,7,11 18:14 22:7,10 22:14 23:1 26:6 27:25 28:22,24 29:8 30:3 32:5 47:9,13 50:19 52:9 53:24 54:7 54:20,24 56:18 58:8,14 59:6,24 62:25 63:13,14 63:18,21 66:6,8 68:10,18 69:13 73:17,20 80:21 81:3 83:21 84:11,12,15 POSA's 28:16,18 POSAs 54:8 position 10:12,17 10:20 14:4 26:4 positive 14:24 21:21 possession 42:20 possible 57:13 77:24 possibly 48:20 post 75:20 post-trial 45:3</p>	<p>posting 5:11 potential 35:24 preassembled 11:1 precise 14:21 22:22 26:15 predict 20:3 preferred 36:23 prepared 5:11 preposterous 83:10,20 prescreening 65:4 present 5:15 7:16 9:5 49:17 presentation 8:8 8:11,12 9:2 11:2 45:1,7 52:21 91:22 previous 64:6 73:6 pricing 40:21 41:5 primarily 37:20 prior 16:22 17:3 18:20 29:9,17 29:22 30:1 38:24 39:4,4 40:6 46:10 47:5 52:2 53:11 57:15,17,20,23 58:3,5 62:18 69:22,24 71:8 76:8 80:8 85:18 86:25 priority 11:20,22 37:5 49:13 54:3 90:21 pro-drug 46:6 62:24 probably 74:19 91:25 problem 7:1 11:10,11 26:24 28:11 34:21 45:16 53:24 55:16,20,24,25</p>	<p>56:6,15 57:5,10 58:1,22 59:3,20 61:20,22 62:11 62:18,20 70:22 70:24,24 71:1 72:17 80:25 problematic 36:11 84:9 problems 41:4 52:24,24 57:8 84:5,14 procedure 17:8 proceed 9:23 proceeding 5:24 proceedings 93:8 93:10 process 10:10 product 15:1 40:22 43:2 60:16 71:4 82:11 products 23:7 61:1 75:3 project 42:4 promising 90:9 pronounce 74:10 propensity 46:3 proper 71:21 properties 43:6 43:11 46:2 49:20 59:1,21 59:25 60:19 72:22 81:8 property 43:13 proposed 57:20 proposition 19:5 19:7 prove 53:2,3,6,9 83:17 provide 5:8 38:23 92:14 provided 34:2 36:7 72:4 79:15 81:22 82:17 provides 64:8 proving 45:20 81:11 82:9</p>	<p>public 5:13,16,24 6:1,4 93:5 publication 14:19 publish 63:8 published 38:6 38:10,11 47:20 76:5 pull 49:21,23,24 54:7,11 55:8 64:11 65:18 66:10 83:1 pulled 10:25 pure 62:21 purpose 16:18 31:9 41:18 62:9 pursue 16:11 37:14,16 pursued 13:14 15:23 pursuing 16:12 put 11:11 17:11 42:6 45:19 47:1 56:1,7,8 59:3 81:17 83:2 puts 49:5</p> <hr/> <p style="text-align: center;">Q</p> <hr/> <p>question 9:4 12:19,23 13:1 14:2 20:14 22:8 24:4,24,25 27:22 37:4 39:2 46:17 48:1,6 54:13,13 56:8 57:19 59:23 62:17,25 70:15 72:1,11 78:6 84:4 questions 9:1 45:8 52:20 92:11 quick 5:5 80:15 81:8 quickly 77:2,5,6 80:2 92:1 quite 15:20 91:23</p>	<p style="text-align: center;">R</p> <hr/> <p>R 2:1,16 3:1 4:1 Rabinow 13:6 15:22 16:16,19 17:14,17 18:11 18:14 19:7 20:15,20,22 22:8,13,25 23:9 26:14 27:18 28:17 29:10 30:25 31:22 32:4,20 34:1 40:10 46:13 51:17 54:6,12 56:17 58:7 61:6 61:16 63:25 65:9,15,19 74:2 77:9 78:3,12 79:13 80:19 81:15 86:16,21 89:1 91:9 Rabinow's 25:7 27:15 39:25 80:13 89:2 raise 32:6 range 23:11 42:16 50:19 55:19 56:3 65:3 65:7,8 66:3,12 66:15,19,22,23 67:12 68:2 72:25 74:21 83:9,12,22,23 ranges 12:9 53:3 66:13 68:7 73:3 74:17 83:19 rapid 77:8 rarely 60:15,25 ratio 75:5,8 ratios 17:1 48:25 re-creation 81:14 reached 84:2 90:24 reaction 34:15 reactions 34:11 35:10,17,25 36:5,12</p>
--	---	---	--	---

readily 55:11 59:1	record 6:18 19:19 92:23 93:10	31:9 75:4 93:12	28:15,20 29:12 38:16 39:2,3 40:5,9,15	saw 40:16 54:3 56:16 60:4 85:17
ready 9:23	redact 40:21	relation 76:3	reviewing 35:15	saying 8:10 16:4 22:1 35:22 40:8 58:14 64:24 67:21 76:24 77:19 83:18 84:15 91:21
real-world 29:19 42:6,13	redactions 5:8,10 92:15	relationship 47:17	right 6:5,23 7:20 7:25 9:21 14:15 14:16 15:18 19:18 20:7,9,12 31:4,9,10,11,12 31:13 32:19 33:16,20,22 45:11 57:18 60:4 62:21 63:5 66:2,19 68:13 70:17,22 71:7 72:25 83:10 85:2,4,13 91:19	says 29:19 31:20 49:18 50:7 52:3 53:24 68:7 72:24 73:5,16 75:15,23 76:14 89:17
realize 73:20	redline 29:16	relied 34:22 43:5 43:9,17	right-hand 79:7	schedule 10:5
realized 6:18	refer 40:20	relies 43:10	RMR 1:21 93:24	Schiff 3:16 8:7
really 10:3 16:17 23:3 24:13 45:1 45:2,4,8 55:10 55:15 69:1,12 69:17,23 76:19	reference 10:23 10:24 12:2 17:19,20 19:10 19:13,14,15,21 21:16 22:4,14 22:15 23:10 26:11,17 27:15 29:7 32:1,2 38:11 46:13 50:11 51:10 52:11 58:6 63:10 64:5,13 64:18 76:17 77:10,12 86:13 86:14,16 87:5 87:23 88:8 89:9 89:15,15 90:5	remain 15:2	Roeland 34:16,22 35:1 36:7	science 52:10
reason 17:3,17 21:10,25 22:25 26:19 28:6 32:20 37:14,15 37:16 91:12	referenced 36:1 68:22 74:24 80:12 84:20,24	remained 12:19	roll 6:10 7:14	scope 24:20,20 57:9,10 62:17
reasonable 11:3 15:19 18:24 20:1 21:7,8,9 21:11 53:7 70:7	references 18:13 20:6 24:10 26:25 41:10 58:13 59:8,10 60:14 75:1 76:8 78:17	remains 27:18 47:2	routine 10:16 11:24 12:22 16:1,19 22:6,11 28:9,11,14,15 30:4 68:16 71:16	screen 6:15 7:7 49:24 50:1 86:18 87:21
reasons 13:22 16:20 18:21 21:15 22:15 23:9 27:14 38:13 40:25 54:24 91:7,11 91:14	referencing 87:12	Remington's-t... 26:9	routineness 28:12	sea 58:14
rebut 86:22 91:8	referred 55:6 61:10	remote 10:8	run 7:13 29:11	second 5:12 6:17 17:17 23:23 37:17 44:8,16 49:14 50:4,5 73:25 90:1
rebuttal 9:7 41:25	referring 19:8 88:18 89:2	Remotely 1:12	Russell 2:5 7:19	second-to-last 61:9
rec- 74:14	refers 87:22	render 69:1		second-to-most 61:14
recall 84:24	refined 10:15	replicate 66:18	S	secondary 11:4 30:9 34:4 37:17 38:16 41:11
receptor 45:25 54:2,5,9 56:18	reflecting 22:22	replicated 39:4	S 2:1,4 3:1 4:1	seconds 44:8
recited 33:17	regarding 18:12 36:18 38:3	report 39:24 40:1	safe 23:8 26:6,13 26:18 33:6,7 89:23	Section 65:5
recognition 54:19 59:20	regardless 53:9	reported 1:21 21:16 35:7 93:8	safety 23:2 26:1 26:19 34:2 80:3 80:3	see 6:15 7:7 18:1 30:12 38:13 52:18 54:15,16 55:8 58:3,4,6 60:14,24 61:6 64:17 67:10 70:3 73:8 74:6 77:3 78:23 83:10 86:18,23
recognize 18:1	reign 9:5	reporter 10:8 92:10	sales 40:22	
recognized 17:8 87:10	related 20:8 22:23 25:5 31:7	representing 6:10	salt 32:9 62:4,6	
recognizing 28:1 59:12 60:25		requirement 82:22	satisfied 45:19 82:24	
reconcile 73:19		reserve 9:15 41:24 44:3	satisfies 71:19	
reconciled 47:11 47:13 74:13,15 74:16 83:20		resist 9:4	save 9:7 41:21	
		respect 8:21 24:25 55:21 60:5 78:1 80:3 80:14 81:13 82:3,25		
		respond 25:3		
		responded 26:5 54:16		
		response 14:9 18:25 19:25 21:2,24 23:12 29:13 33:12 40:17 54:12,13		
		rest 44:3		
		restrain 8:25		
		result 28:24 29:2 38:20,25		
		results 10:17		

<p>89:5 seeing 79:8 seek 82:10 seeking 8:23 seen 66:9 select 69:13,14 sense 35:16 51:21 51:23 62:21 87:20 sensitive 5:22 sentence 50:5 76:24 88:22 separate 85:10 separately 48:20 September 11:23 37:6 serve 30:22 service 64:7 set 18:23 29:10 50:19 93:17 sets 13:18 setting 37:22 seven 41:20 share 47:9 sharing 86:12 87:21 shift 53:1 63:11 shifting 32:25 shooting 28:21 short 9:9 30:14 71:23 shortly 62:8 show 11:5 12:2 18:13 20:25 21:21 25:12 30:6,17 38:25 42:9 81:9 82:23 90:9 showed 10:13 12:3,4,6,9,16 13:6 15:16 23:4 23:7 27:10 29:13,15,20 35:8 39:10 40:3 40:11 42:11 63:15 80:24 90:19</p>	<p>showing 14:6 15:1 16:22 26:17,23 27:20 34:2 42:20,25 59:10 63:23 83:15 shown 37:9 39:18 52:15 53:10 57:15 66:22,23 80:21 81:22 91:9 shows 40:9 67:18 72:6 82:13 sic 62:8 side 6:6,7,10 7:21 9:14 37:9 40:25 44:17 46:1,1 53:23 56:19 61:5 78:23 79:7 81:5 sides 10:4 significant 92:4 similar 57:2 similarity 25:21 43:10 simple 60:23 83:8 simpler 61:12 simplest 56:14 simply 20:2 33:23 37:7 39:25 42:22 45:19 47:1,20 48:10 49:17 57:12 77:17 85:24 single 46:10,13 51:17 52:2,14 52:14 73:24 site 34:10,11,18 35:3,4,6 36:14 37:10 situation 89:24 size 47:18 88:24 89:8,10,11,12 91:10 skill 89:4 skin 34:19 small 28:1</p>	<p>Smith 4:4 8:4 snaps 48:22 51:25 sodium 30:11,19 31:17,23 32:5,7 32:9,9,11,21 33:1,5,6 34:2 68:22 69:16 80:14,17,25 81:1,2 84:5,5 84:12,13,16,18 84:23 solubility 50:8 62:2 72:2 solubilize 18:6 62:12 70:13 71:2,8,13 72:7 solubilized 71:7 71:23,23 72:5 72:22 solubilizing 61:21 61:24 62:14,20 72:11 soluble 17:22,23 50:11 55:2 71:3 solution 11:12,14 12:4,18 55:17 56:2,7 57:14,17 57:20,21 62:7 90:17 solutions 56:25 solve 53:24 55:20 56:14 solved 11:9,10 55:16 56:6 58:1 59:20 70:21,24 somebody 16:5 18:1 38:24 52:15 soon 5:10 sooner 62:7 sorry 6:25 19:15 23:24 33:14 49:9,23,25 61:17 72:14 83:2 84:22 85:18 90:25</p>	<p>91:18,20 sort 24:6 48:22 48:23 sorts 25:8 sound 31:5 South 3:17 soybean 64:21 spadework 92:5 speaking 7:12 specific 49:11 64:20 69:14 78:7 specifically 18:9 30:4 34:3 79:5 81:21 88:4 specification 42:17 82:10 83:9,11,16,16 spend 44:25 86:11 Sperling 2:5 7:19 ss 93:2 stability 13:15,19 14:5,6,7,23,24 15:14 18:9,23 21:5,19 27:21 27:24 28:13 29:6 40:10 42:10 46:18 47:18 66:7 69:23 70:17 71:17 72:13 76:3,15 77:5,19 80:4,10 82:1 90:8,10,11 stability-orient... 16:7,9 stabilize 18:19 stable 12:19 13:20 14:1,11 21:12,14 27:6 39:10 40:13 42:19,23 43:13 48:17,19,24 51:24 53:15 63:24 64:1 65:10,13,14,15</p>	<p>66:7,9 69:22 70:2 81:23,25 stacking 55:13 stage 71:6 standard 14:12 14:17 15:4 16:2 16:13 28:20 49:6 69:17 standards 13:11 15:20 21:23 start 6:8,24 8:24 24:1 48:14 63:17 86:12 started 5:5 6:5,9 43:22 starting 29:23 43:21 63:20 state 12:24 13:3 38:9 53:21 78:11 83:12 90:21 93:1,6 stated 47:20 statement 71:12 STATES 1:1 stay 92:10 step 16:11 17:9,9 45:18 53:20 58:11 81:16 Stephen 2:8 7:19 steps 58:19 sterilization 14:25 21:17 stop 91:2 straight 53:25 54:1 56:21 59:5 59:9 straightforward 60:23 strategic 40:21 41:4 strategy 60:15 Street 1:24 2:17 3:5 4:5 Strickley 60:9,10 60:14,24 61:3 stringent 82:8,19 strong 41:8</p>
--	--	---	---	--

<p>structure 55:10</p> <p>stuck 90:18</p> <p>study 15:14 21:19 36:1</p> <p>subE 14:18,23 15:3,16 16:2,12 16:13 46:21</p> <p>subject 6:4</p> <p>submissions 16:3</p> <p>subsets 25:10</p> <p>substance 14:10</p> <p>substantially 88:2</p> <p>succeeded 61:23</p> <p>success 11:4 15:20 20:2 21:7 21:8,11 40:18 40:18 53:8 70:7</p> <p>sucrose 30:10,12 30:15,22</p> <p>suddenly 27:10</p> <p>sufficient 70:2</p> <p>sufficiently 74:3</p> <p>sugar 30:18</p> <p>suggest 66:5 76:13</p> <p>suggested 57:23</p> <p>Suite 1:24 3:18 4:6</p> <p>summary 82:21</p> <p>support 79:15</p> <p>supports 42:13</p> <p>sure 5:18,19 6:20 7:15 9:18 20:3 31:10 33:16 44:9 48:14 73:15 79:2 91:5</p> <p>surface 18:5 75:21 76:2 91:8</p> <p>surfactant 76:10</p> <p>surfactants 51:6 60:8 87:25 88:16</p> <p>surprised 30:12</p> <p>Sustol 88:15</p> <p>switch 44:8</p> <p>switched 27:11</p>	<p>35:13</p> <p>switching 32:1</p> <p>system 47:24 48:17 51:13 60:20 63:16</p> <p>systemic 34:15</p> <p>systems 48:4 49:19 79:20 80:24</p> <hr/> <p style="text-align: center;">T</p> <hr/> <p>T 2:6 3:1 4:1</p> <p>table 51:5,5 61:5 87:22,24 88:7 88:14</p> <p>take 8:13 9:19 10:20 18:7 50:14,15 51:22 52:10 53:20 65:21 68:15 75:14 79:21 85:15</p> <p>taken 66:14,21 92:16</p> <p>takes 28:14</p> <p>talk 41:22 53:21 64:7,19,25 68:20 69:11 75:11 79:11,12 79:18</p> <p>talking 11:15 12:20 19:13 20:8,16 24:1,2 24:14 26:23,24 50:6 58:7 60:20 61:17 62:5,6 74:13 75:8 78:23 79:16,20</p> <p>talks 68:16</p> <p>tandem 41:3</p> <p>taught 16:22</p> <p>Taylor 4:3 8:3,4 8:14</p> <p>teaches 75:13</p> <p>teaching 74:20 75:18</p> <p>teachings 26:1</p>	<p>87:15</p> <p>technically 22:22</p> <p>techniques 58:19</p> <p>tell 7:8 31:6 72:4 72:7,8 80:9 83:5</p> <p>temperature 15:1 15:15</p> <p>term 13:20 21:13 30:3 43:13 48:1</p> <p>terminal 21:17</p> <p>terminology 47:25 52:4</p> <p>terms 22:23 23:16 39:6 86:24 90:4</p> <p>test 14:7 28:19 38:20 39:1,2,23 40:3 42:25 43:1 46:19 65:20 82:8,12,13,19 82:22,24 85:21</p> <p>tested 30:17 65:3 66:2,8 78:7 81:17</p> <p>testified 16:16 35:1 42:7 61:16 67:9 78:5 86:16 87:16 91:9</p> <p>testimony 19:7,8 22:2 23:7 40:2 79:6 80:13 82:17 89:2,14 89:16</p> <p>testing 14:23 23:11 28:14 65:16</p> <p>tests 14:25 29:11 42:9 43:4,16</p> <p>thank 9:11,25 10:1,5 19:24 33:22 39:20 43:22 44:3,5,10 69:9 86:8 91:21 92:17,19,20,22</p> <p>theoretical 90:10</p> <p>Therapeutics 1:4</p>	<p>2:3 5:2 44:22</p> <p>thermodynamic 80:4</p> <p>thermodynami... 48:16,19 51:24</p> <p>thing 8:17 14:6 15:23,24 34:24 47:23 51:9 72:12 73:23 79:23 85:4</p> <p>things 25:3 37:24 48:21 58:24 59:11 63:9 65:1 78:2</p> <p>think 5:7,9,20 6:2 6:6 47:22 50:24 57:6 68:17 71:11 82:4 84:1 86:1,6 91:22,24 92:5,13</p> <p>thinking 62:17 92:7</p> <p>third 10:24 18:10 19:4,6 26:21 90:7,13</p> <p>thought 12:14 36:8 87:17</p> <p>thousand 82:13</p> <p>three 16:20,24 18:21 19:8,9 20:6 25:3 27:14 33:16 74:25</p> <p>threshold 38:17</p> <p>Thursday 1:13</p> <p>tie 37:24</p> <p>Tigan 3:3 6:12,13 6:17,20,24 7:1 7:3</p> <p>tight 77:4</p> <p>time 6:7 9:7,20 11:21,24 15:15 22:19,20 24:17 28:14 36:25 41:6,21 42:8 43:23 44:3 54:14 70:2 71:24 72:13</p>	<p>81:21 84:2,11 86:11 90:20,20</p> <p>timeline 90:14</p> <p>times 82:13</p> <p>title 79:17</p> <p>today 7:12 11:2 24:18 34:9 45:4 45:23 53:2 86:17</p> <p>tonicity 30:24</p> <p>top 50:1,4 64:12 64:17 66:23</p> <p>totally 34:1</p> <p>touch 73:13</p> <p>transcript 5:8,11 89:13 92:15 93:10</p> <p>treat 41:16</p> <p>trial 10:6 11:15 11:20 16:10 25:11 28:13 30:14,20 33:13 33:25 34:12,13 36:7 38:2 40:2 43:17 45:3 64:3 89:1 92:15</p> <p>tried 11:16 38:6 38:15 58:18 62:1 65:24 72:3 83:14 90:16</p> <p>tries 53:1 60:21</p> <p>true 21:6 43:7 93:10</p> <p>truly 63:15</p> <p>try 8:25 9:4 22:10 47:21 58:19,20 70:4 73:8 74:10 91:24</p> <p>trying 53:24 59:10,13 72:16 85:14</p> <p>TUNNELL 3:4</p> <p>turn 68:14 76:16 77:25</p> <p>turning 65:22</p> <p>two 5:5 17:16,24 22:16,23 26:25</p>
--	---	--	--	---

<p>27:1,3 30:8,10 31:7 41:3 56:9 58:13,22 59:5,7 60:13 85:5 86:19 two-minute 41:1 type 51:13 types 51:8 87:24 typically 51:6 57:21</p> <hr/> <p style="text-align: center;">U</p> <hr/> <p>U 3:1 4:1 ubiquitous 50:17 ultimately 36:15 37:2 40:5,12 48:7 61:23 ultracentrifuga... 82:12 underneath 88:13 understand 13:9 24:16 70:20 72:15,19 understood 31:14 71:7 undisputed 12:11 unexpected 38:16 38:21,25 40:5,8 40:15 81:7 unfortunately 23:14 uninterrupted 9:3 UNITED 1:1 unpredictable 68:25 unrebutted 17:15 34:1 untested 47:10 unworkable 66:23 upper 21:6 22:10 USA 1:7 3:11 5:3 usage 87:11 88:19 89:14,14 use 12:16 32:7,21</p>	<p>32:22 43:19 46:5,7 48:1,24 50:17 51:1,2,6 69:19 74:8 76:14 77:23 81:2 82:22 84:16 85:21 useful 10:10 26:20 48:13 91:23 uses 51:25 66:19 82:12 USP 13:11,11,12 13:14,17 14:6,7 14:13 15:2,20 15:23 16:9,13 16:13 21:12,12 21:22 27:24 29:24 30:4 69:12,13,17 71:19 90:6,12 usual 87:7</p> <hr/> <p style="text-align: center;">V</p> <hr/> <p>v 1:6 vacation 92:1,21 valuable 10:8 value 40:8 values 22:11 32:25 variable 28:24 29:3 variables 15:15 28:19 51:14 89:22 various 25:8 69:1 91:7 verifying 89:21 Vernon 3:15 8:9 verse 50:10 version 35:22 versions 35:21 versus 25:13 41:6 69:5 90:5 view 31:23 41:10 70:19 visible 42:25</p>	<p>visual 83:8 vivo 85:22 vocabulary 25:15 25:23 volume 82:14 Von 23:17 78:17 78:22,25 79:9 86:13,15,25 87:9,13</p> <hr/> <p style="text-align: center;">W</p> <hr/> <p>Wacker 3:17 Wan 33:2,18 80:16,16 want 5:19 7:13 9:7 24:7 31:10 33:15 41:19,22 42:3 46:17 47:25 51:16 52:13 53:20 60:7,17 63:11 65:16 66:12 70:5 73:13 75:2 75:13 76:17 77:23 78:1 79:22 80:15 81:8 82:6 83:1 83:13 85:12,15 wanted 23:1 26:6 90:7 warning 35:2 Washington 1:24 2:18 17:19,20 18:2,4,7 41:10 47:19 52:25 75:11,13,17,19 76:5,9,13,14 wasn't 11:13 16:17 35:20 71:24 water 17:22,24 27:2,4 55:2 way 6:2 9:5 10:21 12:3 17:15 36:2 37:8 45:18 56:8 56:14 66:22 71:21 72:4 75:9</p>	<p>80:7 93:14 ways 12:5 22:21 57:13 62:1 we'll 6:7 9:19 46:24 47:15,21 49:1 51:9 53:18 74:6 we're 9:23 12:20 26:23,24 50:21 60:17,19 62:5,6 68:20 73:10 75:8 78:13,13 78:14 79:8,16 79:19 83:15,18 84:13 86:14 88:22 89:21 92:17 we've 45:23 65:13 week 9:17 43:3 weeks 92:2 weigh 41:8 went 18:4,4 50:10 weren't 72:18 85:8 West 4:5 whatsoever 69:19 79:15 wheelhouse 28:16 WHEREOF 93:17 white 40:16 WILLIAM 1:11 Wilmington 3:7 4:7 6:14 7:4 window 11:24 77:4 wish 5:9 WITNESS 93:17 wondering 67:13 word 16:6 22:20 22:20 25:11 73:24 88:1 words 67:19 work 37:19 38:3</p>	<p>38:5,8 55:5 56:12,13,21,22 59:22 60:19,22 61:20 64:6 65:5 67:4,10,11,16 67:21 70:9,11 73:7 83:20,23 90:14 worked 12:8 18:3 27:20 35:23 69:25 70:21 working 13:10 23:11 39:9 41:3 42:8 56:25 58:3 58:8 59:25 63:2 63:13,14 76:6 world 11:21 26:16 57:12 worried 56:3 wouldn't 47:14 wrapping 90:2 91:21 written 11:7 42:14,15 43:25 82:25 83:17</p> <hr/> <p style="text-align: center;">X</p> <hr/> <p>X 1:3,9</p> <hr/> <p style="text-align: center;">Y</p> <hr/> <p>Y-U-E 19:16,17 yeah 9:16 19:6 32:17 41:24 44:11,13 50:3 61:24 70:18 79:2 83:7 86:1 years 56:23 71:25 yolk 17:11 18:15 18:18 29:3 32:22 33:8 51:10 64:22 73:22 74:8 York 2:11,11 Yue 19:9,11,20 75:1</p> <hr/> <p style="text-align: center;">Z</p> <hr/>
---	--	--	---	---

<p>zero 82:11 Zhou 15:4,5,12 15:13 21:19 31:25 32:1,1 38:10 39:23 41:9 46:15,20 47:15 50:13 52:18 53:12 58:16 59:8 64:4 64:13,18 65:1 72:23,24 73:1,5 73:5 76:7 78:8 81:15,16 84:20 84:24 85:16,16 85:18,18 90:3,8 Zoom 23:25 24:3</p> <hr/> <p style="text-align: center;">0</p> <hr/> <p>0 74:22 0.125 64:23 0.25 64:21 0.5 50:20 64:2 65:8 68:8 74:1 74:2 77:13,15</p> <hr/> <p style="text-align: center;">1</p> <hr/> <p>1 13:11 16:13 17:1,4 21:12 25:5,24 35:7 68:8 72:6 75:7 75:8 87:22,24 1.1 50:4 10 13:21 17:1 21:18 22:9,11 23:2 27:19 28:2 41:11,12 46:11 46:14 49:24 50:20 63:24 65:1,8 66:20 67:15 68:8,9,21 74:22 75:10 77:15 10:00 1:14 100 88:24 89:9 1000 4:5 100X 43:8 10166 2:11</p>	<p>10X 43:8 11 28:2 49:23 51:3 65:18 86:21 87:2 11:39 92:23 12 28:2 1201 3:5 127 54:11 13 28:2 64:14 68:3 14 28:3 30:2 69:16 89:3 90:2 15 28:3 64:21 71:25 1501 4:6 161 89:2 161:3 78:10 162:4 78:10 16th 3:6 17 54:11 1730 1:24 19801 4:7 19899 3:7 1990s 37:19 38:3 1993 90:20 1996 47:20 76:5</p> <hr/> <p style="text-align: center;">2</p> <hr/> <p>2 17:4 25:25 65:4 74:9 2.1 65:5 2.5 46:16,22 64:22 65:3 73:9 20 56:23 75:8 200 2:10 20036 1:24 2:18 2012 11:22 15:8 37:4 38:9 2014 11:23 22:19 37:6 53:22 63:22 84:16 202 1:25 202.551.1901 2:19 2024 1:13 93:18 2050 2:17 21 41:11,14</p>	<p>212.230.7892 2:12 22 55:8 22-985 5:2 22-cv-00985-W... 1:6 229 41:12,15 23 79:7 232-0646 1:25 233 3:17 24 54:11 78:10 26 61:3 29 1:13 29th 93:18</p> <hr/> <p style="text-align: center;">3</p> <hr/> <p>3 35:7 74:9 75:6,6 75:6 79:5 89:3 30 23:5,10 26:12 26:18 44:8 80:6 302.425.3096 3:8 302.504.1688 4:8 312.258.5523 3:20 318 65:18 341:1 79:7 341:24 80:13 342:11 80:13 395 54:7</p> <hr/> <p style="text-align: center;">4</p> <hr/> <p>4 39:8 42:18 53:10 65:4,22 66:14 67:7,8,15 70:3 83:4 40X 43:8 45 9:14,16,18,22 44:6 49 17:1 72:18 4X 43:8</p> <hr/> <p style="text-align: center;">5</p> <hr/> <p>5 23:10 39:12,21 40:4 53:10 65:11 70:3 76:20 77:14 81:14,14</p>	<p>50 89:8</p> <hr/> <p style="text-align: center;">6</p> <hr/> <p>6 54:7 66:3 73:25 74:1 6.5 40:4 60606 3:19 65 83:4 67 83:4</p> <hr/> <p style="text-align: center;">7</p> <hr/> <p>7 32:13 39:8,18 7.3 32:3 7.5 42:16,20 7100 3:18 729 13:12 16:13 21:12 794 13:21 41:13 42:23 44:1</p> <hr/> <p style="text-align: center;">8</p> <hr/> <p>8 42:18,20 55:8 66:3 74:9 83:3 8.7 39:19 8.74 42:19 8.8 39:11 8.9 39:19 8.92 42:19 80 34:14,24 35:5 36:10,20,23,24 37:13 54:18,22 63:4 88:4 812 1:24 845 10:13,14,21 11:1,3,8,9,22 12:2,16,23 13:2 13:7,10,25 14:4 14:11,12,21 15:9 16:22,24 17:7,8 18:2 20:18,24 21:16 22:9 23:21 27:23,25 28:7 29:23 30:15 31:20,24 36:18 36:21,22 37:1,3 37:14 38:9 39:7</p>	<p>41:9 42:9 46:15 46:18 47:12,15 50:13,19 52:18 52:25 53:12 58:16 59:8 63:19,22,25 64:5,15 65:6,10 65:19,25 66:4,7 66:16,17,18,23 67:2,16,20,24 68:2,19,19,23 72:3,18 73:17 73:23 74:1,4,7 74:12,12,14,16 74:20 76:7 78:4 78:6 84:17 88:3 88:13 89:4,5,14 90:21</p> <hr/> <p style="text-align: center;">9</p> <hr/> <p>9 13:21 41:11,12 54:7 65:18 86:19 9.0 42:16 9.95 65:25 66:19 901:17 55:4 902:5 55:4 903 55:8</p>
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