IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,	)	
	)	
Plaintiff,	)	
	)	C.A. No. 22-228-RGA
v.	)	
	)	Trial Volume III
MSN LABORATORIES PRIVATE LIMITED, et al.,	)	
	)	
Defendants.	)	

J. Caleb Boggs Courthouse
844 North King Street
Wilmington, Delaware

Wednesday, October 25, 2023
8:30 a.m.
Bench Trial

BEFORE: THE HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL LLP
BY: ANTHONY D. RAUCCI, ESQUIRE
BY: JACK B. BLUMENFELD, ESQUIRE

-and-

WILMERHALE
BY: KEVIN S. PRUSSIA, ESQUIRE
BY: LISA J. PIROZZOLO, ESQUIRE
BY: AMY KREIGER WIGMORE, ESQUIRE
BY: JONATHAN A. COX, ESQUIRE
BY: KEVIN M. YURKERWICH, Ph.D.

For the Plaintiff

EXELIXIS 2003
Azurity v. Exelixis
IPR2025-00210

APPEARANCES CONTINUED:

HEYMAN ENERIO GATTUSO & HIRZEL LLP
BY: DOMINICK GATTUSO, ESQUIRE

-and-

WINSTON & STRAWN LLP
BY: GEORGE LOMBARDI, ESQUIRE
BY: BRYCE COOPER, ESQUIRE
BY: KURT A. MATHAS, ESQUIRE
BY: ELIZABETH GRDEN, ESQUIRE
BY: KEVIN BOYLE, ESQUIRE
BY: BRIAN O'GARA ESQUIRE

For the Defendants

Also Present:

Dr. Kondal Reddy Bairy

*** PROCEEDINGS ***

08:18:06
08:18:06
08:20:27
08:20:27 DEPUTY CLERK: All rise. Court is now in
08:30:57 session. The Honorable Richard G. Andrews presiding.
08:30:57 THE COURT: All right. Good morning, everyone.
08:30:59 Please let's continue.
08:31:08 MS. PIROZZOLO: Thank you, Your Honor. One
08:31:09 housekeeping matter, we inadvertently put up the wrong
08:31:12 version of the slide that --
08:31:13 THE COURT: That's right. I remember.
08:31:15 MS. PIROZZOLO: -- Dr. Myerson referenced, and
08:31:17 I'd agree with Mr. Lombardi that Lines 18 to 19 of Page 700
08:31:23 of the transcript could be stricken.
08:31:26 THE COURT: All right. Well, I will strike
08:31:28 those two lines, and I'm sure the court reporter will take

08:31:33 1 care of it.
08:31:35 2 MS. PIROZZOLO: Thank you, Your Honor.
08:31:36 3 DIRECT EXAMINATION (Continued)
08:31:36 4 BY MS. PIROZZOLO:
08:31:38 5 Q. Good morning, Dr. Myerson.
08:31:39 6 A. Good morning.
08:31:41 7 Q. Now, Dr. Lepore and Dr. Donovan mentioned several
08:31:44 8 references offering your obviousness opinions.
08:31:47 9 MS. PIROZZOLO: Could we put up Slide 13 of your
08:31:50 10 presentation?
08:31:50 11 BY MS. PIROZZOLO:
08:31:53 12 Q. Do any of the references discussed by Drs. Donovan
08:31:57 13 and Lepore teach the method for synthesizing cabozantinib
08:32:00 14 (L)-malate that's disclosed in the '349 patent?
08:32:03 15 A. No.
08:32:04 16 Q. Do any of the references discussed by Drs. Donovan
08:32:08 17 and Lepore teach that 1-1 could be a process impurity or a
08:32:12 18 degradation process in the synthesis of cabozantinib
08:32:17 19 (L)-malate?
08:32:17 20 A. No.
08:32:19 21 Q. Do any of the references discussed by Drs. Donovan
08:32:23 22 and Lepore teach that the 1-1 compound was genotoxic?
08:32:27 23 A. No.
08:32:28 24 Q. Do any of the references discussed by Drs. Donovan
08:32:32 25 and Lepore describe a formulation of cabozantinib (L)-malate

08:32:36 essentially free of the 1-1 impurity?
08:32:39 A. No.
08:32:40 MS. PIROZZOLO: Now, let's look more closely at
08:32:42 the Brown reference which is in -- at Tab 10 of your binder,
08:32:47 and it's Defendants' Exhibit 291. And if we can put that
08:32:53 up.
08:32:53 BY MS. PIROZZOLO:
08:32:57 Q. This is the reference that Drs. Lepore and Donovan
08:32:59 referred to; correct?
08:33:00 A. Yes.
08:33:01 Q. What is Brown directed to?
08:33:04 A. It's directed to the malate salt of cabozantinib and
08:33:11 discloses two crystalline forms of the malate salt.
08:33:14 Q. Does Brown suggest that one with -- the 1-1 impurity
08:33:18 should be minimized in its synthesis of cabozantinib
08:33:22 (L)-malate?
08:33:22 A. It does not.
08:33:24 Q. Does Brown suggest that the 1-1 is a harmful
08:33:28 impurity?
08:33:28 A. It does not.
08:33:30 Q. Now, Brown refers to the 1-1 compound; correct?
08:33:34 A. Yes.
08:33:36 Q. Dr. Lepore has offered the opinion that a skilled
08:33:39 artisan would be motivated to control for 1-1 because it is
08:33:42 a starting material in the Brown synthesis.

Do you recall that?

A. I do.

Q. Do you agree with that opinion?

A. I do not.

Q. Could you explain why not?

A. Yes. Well, of course, starting materials can carry through to the final product, but as we heard from Dr. MacMillan, we have a continuous process with multiple steps. 98 percent of the 1-1 starting material is used up at the beginning of the first step, and then there are multiple purification processes and other steps with purification processes, thus that at the end of the fifth step, we would not expect any significant amount of 1-1 to carry through. We just would expect it to be de minimis.

Q. Would a skilled artisan looking at Brown understand that the 1-1 impurity forms as a degradation process during synthesis?

A. No. Again, as we heard from Dr. MacMillan, that would not be expected by a person of ordinary skill.

Q. Now, Brown refers to the process that you discussed earlier that Exelixis referred to as the A- 2 process; correct?

A. That's correct.

Q. Is Example 1 in Brown that Dr. Lepore discussed different from the synthetic scheme for making cabozantinib

08:35:19 (L)-malate that's disclosed in the '349 patent?
08:35:22 A. Oh, yes. It's significantly different.
08:35:27 Q. Now, let's turn -- and could you describe what you
08:35:31 view as the key differences?
08:35:32 A. Well, there are multiple differences, but the key
08:35:36 difference is that the step in the Brown process that goes
08:35:42 from 1-2 to 1-3 was eliminated. There's no 1-3. You go
08:35:50 directly from 1-2 to 1-4. In addition, changes to the
08:35:55 solvent and temperature of the salt formation step were
08:35:58 made, both of those are significant changes. There are
08:36:01 other changes as well.
08:36:03 MS. PIROZZOLO: Now, let's turn to Paragraph 97
08:36:05 of Brown.
08:36:05 BY MS. PIROZZOLO:
08:36:11 Q. Dr. Lepore testified that Paragraph 97 of Brown
08:36:16 describes cabozantinib (L)-malate that is essentially free
08:36:19 of the 1-1 impurity.
08:36:22 Do you agree with that?
08:36:23 A. I do not.
08:36:26 Q. Could you explain why not?
08:36:28 A. Well, if we look at the paragraph, it's really
08:36:32 focused on crystalline form purity. That is, how much of
08:36:36 one crystalline form is present in a mixture of crystalline
08:36:39 forms. And that's the focus of this.
08:36:43 Now, what I will agree that it does say at the

very end, that some process in the purities could be present, but even with that, you can still -- it doesn't disclose something that would essentially a 1-1 impurity, but even with that, you can still -- it doesn't disclose something that would be essentially free of the 1-1 impurity.

Q. Could you explain why, even though it refers to process impurities, it doesn't disclose anything -- something that would be essentially free of the 1-1 impurity?

A. Right. Because we're talking that the 1-1 impurity, essentially free means that we have 0.02 percent of the 1-1 impurity. And you could have something that met these crystalline form purities still had 0.02 percent of the 1-1 purity. In fact, even if you say about 100 percent, about 100 percent encompasses 99.98 percent. So, I don't see how this could tell somebody that it would be essentially free of the 1-1 impurity.

Q. Does Brown disclose pharmaceutical compositions of cabozantinib (L)-malate that are essentially free of the 1-1 impurity?

A. It does not.

MS. PIROZZOLO: Now, turning to slide -- well, let me strike that.

BY MS. PIROZZOLO:

08:38:09 Q. To summarize, what are your opinions on the key
08:38:11 differences between Brown and the '349 patent?
08:38:17 A. Well, the first key difference is that the '349
08:38:21 patent has a different synthetic process which was designed
08:38:25 to minimize the 1-1 impurity at very low levels.
08:38:30 Secondly, the '349 discloses formulation of the
08:38:37 1-1 impurity that's essentially free -- I'm sorry,
08:38:41 formulation of cabozantinib (L)-malate which is essentially
08:38:45 free of the 1-1 impurity. Brown does not disclose any
08:38:49 specific formulation or discuss specific formulations.
08:38:54 Q. Okay. So, let's turn to Dr. Lepore's inherency
08:39:01 opinion.
08:39:01 MS. PIROZZOLO: And go to slide 15, please.
08:39:01 BY MS. PIROZZOLO:
08:39:04 Q. Looking at the first point on this slide, for the
08:39:11 asserted claim of the '349 patent, what must be essentially
08:39:15 free of the 1-1 impurities?
08:39:17 A. The pharmaceutical composition.
08:39:20 Q. Now, if an API has less than 200 PPM of 1-1, will the
08:39:27 formulated composition necessarily be free of the 1-1
08:39:30 impurity?
08:39:30 A. No, because as we've seen, the process of blending
08:39:36 with excipients and making it into a drug product can result
08:39:41 in increase in the 1-1 impurity. Thus, it's possible to
08:39:44 start with an API that's essentially free, but end up with a

drug product that's not essentially free due to the additional formation of the 1-1.

Q. Did Exelixis' own work show that the 1-1 impurity could form during manufacturing of a drug product?

A. Yes.

Q. Could you explain why that's your opinion?

A. Well, certainly. We first saw the excipient compatibility studies which showed that the 1-1 could -- would increase in contact with a number of different excipients. Secondly, we see the Exelixis studies that showed that the 1-1 impurity would increase when exposed to temperature, heat -- heat, moisture, and potentially physical force, which are used in manufacturing of tablets and capsules.

Q. Now, let's turn to your second point.

Do you agree with Dr. Lepore that the synthetic process in Brown does not inherently result in less than 200 PPM?

A. I do not.

MS. PIROZZOLO: Let's pull up Brown, Defendants' Exhibit 291, at paragraph 213.

BY MS. PIROZZOLO:

Q. What does this paragraph in Brown teach?

A. Okay. I'm just getting it on my...

Q. I think it's on the screen, if that's...

A. Yeah. I -- it's easier for me to read.
Q. Okay.
A. What tab is that? I'm sorry.
Q. It's -- let me get it. It's Tab 10.
A. Tab 10. And paragraph 213.
Yes. Okay. Thank you.
Q. What does this paragraph in Brown teach?
A. Well, it actually specifically says, "The foregoing disclosure has been described in some detail by way of illustration and examples for purposes of clarity and understanding."
We skip a sentence and then it says, "However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious of one of skill in the art that changes and modifications can be practiced within the scope of is the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive."
Q. Now, Dr. Lepore has testified that the Brown process inherently produces cabozantinib (L)-malate with less than 200 PPM of the impurity.
MS. PIROZZOLO: Could you turn in your binder to Tab 11, which is Plaintiff's Exhibit 38.
THE WITNESS: Yes.

BY MS. PIROZZOLO:

Q. What is -- what does this document show?

A. This is a document from the Exelixis NDA for the capsules, and it talks about batch analysis.

MS. PIROZZOLO: Could you turn to Table 1 on Page 2 of Plaintiff's Exhibit 38?

THE WITNESS: Yes.

BY MS. PIROZZOLO:

Q. What does Table 2 -- what does Table 1 show?

A. It shows five lots of cabozantinib (L)-malate that were manufactured and it looks at test results for various impurities and overall purity.

Q. Okay. Now, Dr. Myerson, do you agree with Dr. Lepore that the synthetic process does not inherently result in less than 200 PPM of the 1-1 impurity?

A. I'm sorry. Could you repeat that, please?

Q. Do you agree with Dr. Lepore that the synthetic process in Brown does not inherently result in less than 200 PPM of the 1-1 -- strike that.

Do you agree with Dr. Lepore that the Brown synthetic process inherently results in less than 200 PPM of the 1-1 impurity?

A. I do not.

MS. PIROZZOLO: Okay. And going back to Table 1 in Plaintiff's Exhibit 38.

BY MS. PIROZZOLO:

Q. Could you explain why you disagree?

A. Well, of the -- of the five lots described there, four of them are made by the A-2 process. Those are the lots listed; Regis, Regis, Regis, and Girindus.

Now, the three Regis lots show non-detected amounts of the 1-1 impurity and since the limit of detection of this test was 200 PPM, that would indicate it was below 200 PPM. While the Girindus batch showed a result of 0.06 percent, which is 600 PPM, which is not below 200 PPM.

Q. Okay. Now, you mentioned the .06 percent being 600 parts per million; is that right?

A. Correct.

Q. Now, Dr. Lepore has testified that the Girindus batch is not representative of the Brown process.

Do you agree with that?

A. I do not.

Q. Could you explain the basis of your disagreement with Dr. Lepore?

A. Yes. Well, first, the -- Exelixis in their submission to the FDA represented that the batches made by both the Regis and Girindus processes were made according to A-2, which is the Brown process -- I mean, the -- the Brown process.

In addition, while I agree the Girindus lot had

some planned deviations, those planned deviations still fall, in my opinion, within the scope of Brown.

Q. Now, you mentioned the deviations, but did you consider the deviations discussed by Dr. Lepore?

A. I did.

Q. Okay. What was the effect of the Girindus deviations in your opinion?

A. Well, all of these deviations were made with the purpose of both increasing yield and reducing the amount of impurities.

And, in fact, if we look at the total impurities at the bottom of this table, we'll see that the purest batch made of all these batches actually is the Girindus batch with 0.36 percent impurity. So, actually the planned deviations resulted in a purer batch of cabozantinib (L)-malate than was -- was obtained from the Regis batches.

Q. And how is that relevant to your opinion?

A. Well, it demonstrates that the deviations were made in such a way as to reduce the overall amount of impurities. In addition, if we look the deviations were done in steps that would not be expected to produce the 1-1 impurity.

Q. Now, in your opinion, do the deviations referenced by Dr. Lepore take the Girindus lot outside the scope of Example 1 in Brown?

A. No.

Q. Could you explain why not?
A. Again, because Example 1 -- Example 1 of Brown allows for deviation and I believe this is -- again, just falls in within the scope of Example 1.
Q. Now, turning from the Girindus batch to the Regis batches. Do you recall Dr. Lepore's testimony about GTI testing on those batches?
A. Yes.
Q. GTI specific.
Do you dispute the results of the GTI specific tests that Dr. Lepore discussed?
A. No. The GTI tests are very accurate.
MS. PIROZZOLO: Let's turn to Plaintiff's Exhibit --
THE COURT: And I'm sorry. I may have lost a thread of it here, but in terms of the three Regis batches actually producing the API with less than 200 parts per million, do you agree that -- that that's a fact?
THE WITNESS: Yes, certainly.
THE COURT: Okay.
MS. PIROZZOLO: Now, let's turn to Plaintiff's Exhibit 35, which is the Cometriq NDA.
Could you took look at Table 2 on Page 16?
THE WITNESS: Yes.
BY MS. PIROZZOLO:

Q. Does the information in this table inform your opinion on inherency?

A. Yes.

Q. Could you explain why?

A. Again, this is -- submitted to the FDA -- indicating that batches made by the A-2 process had within 35 and 411 parts per million indicating that at least some batches had more than 200 parts per million.

Q. Does that inform your opinion as to whether the Brown process would necessarily produce cabozantinib (L)-malate inherently free of the 1-1 impurity?

A. It does.

Q. Could you explain why?

A. Again, it specifically says that -- well, that API made by the A-2 process could have as high as 411 ppms over the 1-1 impurity.

Q. Okay. Now, were you here when Dr. Lepore discussed what he called the Regis process?

A. Yes.

MS. PIROZZOLO: Can we pull up Dr. Lepore's Slide 14, please?

BY MS. PIROZZOLO:

Q. Now, Dr. Lepore' Slide 14 refers to Defendants' Exhibit 38; correct?

A. Yes.

08:50:21 MS. PIROZZOLO: Let's look at Exhibit 38, that's
08:50:24 at Tab 23 in your binder.
08:50:24 BY MS. PIROZZOLO:
08:50:37 Q. What is Defendants' Exhibit 38?
08:50:38 A. That's an Exelixis document.
08:50:41 Q. Okay. Is Defendants' Exhibit 38 a Regis document?
08:50:45 A. No.
08:50:47 Q. Okay. What does Defendants' Exhibit 38 describe?
08:50:52 A. It describes information on the drug substance,
08:50:57 different properties, and then it talks about the synthetic
08:51:05 route for the preparation of XL184, which is cabozantinib.
08:51:09 Q. Were you here when Dr. Lepore testified about
08:51:12 capsules containing XL184?
08:51:14 A. Yes.
08:51:16 MS. PIROZZOLO: Okay. Let's pull up Plaintiff's
08:51:18 Exhibit 9 that Dr. Lepore referred to.
08:51:18 BY MS. PIROZZOLO:
08:51:22 Q. What is Exhibit 9?
08:51:23 A. Exhibit 9 -- done with that.
08:51:33 This is, again, from the -- it's an Exelixis
08:51:48 document talking about the drug product of XL184 with
08:51:55 cabozantinib (L)-malate in 25- and 100-milligram capsules.
08:52:00 Q. Was Defendants' Exhibit 9 in the prior art?
08:52:03 A. No.
08:52:05 Q. Does the prior art disclose capsules with the

formulation of the capsules in Exhibit 9?

A. No.

Q. Now, Dr. Lepore testified that even if Brown does not inherently teach the essentially free limitation, a person of ordinary skill would be motivated to modify Brown to obtain a pharmaceutical composition essentially free of the 1-1 impurity.

Do you agree with Dr. Lepore on that?

A. I do not.

Q. Okay. Let's go to some of your reasons for disagreeing with Dr. Lepore.

Dr. Lepore testified that a skilled artisan would have been motivated to control for 1-1 during the synthesis of the API in Brown because it was a starting material.

Do you agree with that?

A. No. As I've already noted, because it's a starting material it's essentially mainly used up in the first step and then there are multiple purification steps, an additional synthesis step with purification steps.

By the time you make cabozantinib (L)-malate, you would expect very small amounts, if any, of detectable 1-1 impurity, so there wouldn't be a motivation to control for it. Particularly since it hadn't been identified as a genotoxic impurity either.

08:53:36 Q. Now, Dr. Lepore testified that a skilled artisan
08:53:40 would have been motivated to modify Brown because they would
08:53:43 have expected the 1-1 impurity to form as a degradation
08:53:47 product.
08:53:48 Do you recall that?
08:53:48 A. I do.
08:53:49 Q. Do you agree with Dr. Lepore?
08:53:51 A. No. As we heard from Dr. MacMillan, it would not be
08:53:55 expected that the 1-1 impurity would form as a degradation
08:53:59 product.
08:54:00 Q. And how does that affect motivation?
08:54:02 A. Well, you're not motivated to control for something
08:54:05 that you don't think is going to form during your process.
08:54:11 Q. Now, Dr. Lepore testified that a skilled artisan
08:54:14 would have been motivated to monitor --
08:54:18 MS. PIROZZOLO: And we can put up Slide 20.
08:54:18 BY MS. PIROZZOLO:
08:54:21 Q. -- and control for 1-1 because it has a quinoline
08:54:24 structure. Do you agree with that?
08:54:25 A. No.
08:54:28 MS. PIROZZOLO: Can you put up Slide 20?
08:54:28 BY MS. PIROZZOLO:
08:54:31 Q. Why do you disagree with Dr. Lepore?
08:54:33 A. Well, many quinoline are actually drugs. I mean,
08:54:39 cabozantinib is a quinolines. And there are lots and lots

of quinoline drugs, so clearly not all quinolines are problematic, they're not all genotoxic.

Q. Okay. Does cabozantinib have a quinoline structure?

A. It does.

Q. Is it genotoxic?

A. No.

Q. Could you turn to Tab 13 in your binder and put up the Nagao paper that Dr. Lepore discussed?

A. Yes.

Q. Does the Nagao paper discuss the compound at issue for the '349 patent?

A. I'm sorry. I couldn't hear that.

Q. Does the Nagao paper disclose the 1-1 compound at issue for the '349 patent?

A. No.

Q. Are all the quinoline structures reported in Nagao genotoxic?

A. No.

Q. Did Nagao describe any correlation between the structure of the quinolines and genotoxicity?

A. No.

Q. Can you explain why you don't see -- let me ask this: Do you see a correlation between a quinoline structure and genotoxicity in the Nagao paper?

A. No.

08:55:48 Q. Can you explain why not?
08:55:50 A. Well, if we look in the table in the Nagao paper --
08:55:59 Q. Is this Table 1?
08:56:00 A. Yes.
08:56:02 And if, for example, we look at Compound 16 and
08:56:09 17, if we look, that the only difference between 16 and 17
08:56:19 is that in Compound 17, we have an additional chloride on
08:56:25 the -- on the wing on the bottom left. Otherwise, it's
08:56:30 identical to 16.
08:56:32 And 17 is Ames negative and 16 is Ames positive.
08:56:39 Q. And how does that impact your opinion on whether a
08:56:45 person of ordinary skill in the art would be motivated to
08:56:46 control for the 1-1 impurity because it was a quinoline?
08:56:49 A. Well, again, you can't look at these structures and
08:56:52 know if they're genotoxic or not. Very similar structures.
08:56:56 Some will be genotoxic and some will not be genotoxic. So
08:57:00 you only know when you do the AMES test.
08:57:02 MS. PIROZZOLO: So, let's turn to Defendants'
08:57:02 Exhibit 272.
08:57:02 BY MS. PIROZZOLO:
08:57:06 Q. Which is Tab 14 in your binder.
08:57:12 Did you hear Dr. Lepore discuss Defendants'
08:57:17 Exhibit 272?
08:57:17 A. I did.
08:57:19 Q. What is Defendants' Exhibit 272?

08:57:22 A. It's an EPA toxicological review of quinoline.
08:57:29 Q. Does the EPA toxicological review discuss the 1-1
08:57:34 compound?
08:57:34 A. It does not.
08:57:37 Q. In your opinion, does the EPA toxicological review
08:57:42 suggest that all of the quinoline structures are -- all
08:57:45 quinoline structures are genotoxic?
08:57:47 A. No, it does not.
08:57:48 Q. Could you explain why not?
08:57:50 A. Again, it's really just talking about quinoline.
08:57:52 It's not talking about all quinoline derivatives and
08:57:55 structures.
08:57:56 Q. Okay. Let's turn to Plaintiff's Exhibit 299 at
08:58:01 Tab 15. Is this a -- an article you considered in rendering
08:58:06 your opinions in this case?
08:58:08 A. Yes.
08:58:09 Q. Could you explain what the article describes?
08:58:12 A. Yes. This is an article from RSC Advances and it's
08:58:17 on recent advances in the chemistry and therapeutic
08:58:20 potential of functionalized quinoline motifs, a review.
08:58:26 Q. Could you -- did this paper inform your opinions in
08:58:29 this case?
08:58:29 A. Yes.
08:58:30 Q. Could you explain how?
08:58:31 A. Well, it talks about, in fact, quinolines that are

actually drugs. And if we go to Figure 1 in the paper.

Q. Is that at Page 3?

A. Yes. We have some examples of marketed drugs that are quinolines. And we see, we have antimalarials, antibacterials, anti-cancers, local anesthetics, anti-tubercular drugs, and these are just examples. There are actually a lot more quinolines that are marketed drugs.

Q. And how is this paper relevant to your opinions in this case?

A. Well, it just it generally shows that not all quinolines are genotoxic. In fact, many of them are useful as drugs.

Q. Did Dr. Lepore or Dr. Donovan provide any scientific explanation for why some quinoline structures are genotoxic and some are not?

A. No.

Q. In 2011, would a skilled artisan have been motivated to control for 1-1 simply because it was a quinoline?

A. No.

Q. Now, let's turn to the next motivation that Dr. Lepore provides to modify Brown.

These are regulatory guidances; correct?

A. Yes.

Q. Okay.

MS. PIROZZOLO: Let's put up Tab 18, which is

Defendants' Exhibit 291. Is -- sorry. Defendants' Exhibit 91.

BY MS. PIROZZOLO:

Q. Is Defendants' Exhibit 91 a guidance that Dr. Lepore discussed?

A. Yes.

Q. Could you describe your understanding of this particular guidance?

A. Yes. This is the guidance for industry on genotoxic and carcinogenic impurities in drug substances. And it talks about approaches, and it actually gives recommended limits for daily ingestion of these potential impurities in drug products.

Q. Okay. In 2011, would these guidelines have provided a skilled artisan with the motivation to control for the 1-1 impurity in drug substances and products?

A. Only if they were aware that the 1-1 impurity was genotoxic.

Q. Okay. And at the time -- does anything in the prior art disclose that the 1-1 impurity was genotoxic?

A. No.

Q. Are these guidelines applicable if the impurity is not genotoxic?

A. No.

Q. Okay. Now, Drs. Donovan and Lepore also discussed a

few other guidelines. Do any of those guidelines refer to 1-1 or describe methods for limiting byproducts or contaminants in cabozantinib (L)-malate?

A. No.

Q. So, let's go to the formulation references. Now, we've been focusing on the essentially free limitation. But Claim 3 of the '349 patent also requires certain classes of excipients; correct?

A. Correct.

Q. Do all pharmaceutical compositions have each of these four classes of excipients?

A. No.

Q. Why not?

A. Well, it really depends on the formulation and its purpose. So, for example, let's look at tablets. So, immediate release tablets, which are tablets that you take and -- and are supposed to dissolve in your body immediately always will have a disintegrant. But controlled-release tablets, which are designed to dissolve over time, don't necessarily have a disintegrant.

Capsules often do not have a disintegrant because you don't have to break apart a capsule. They sometimes can for other reasons, but that's -- this is one example. And, of course, not all formulations have to have glidants. If you have a well-flowing formulation, you don't

have to add a glidant. Generally, all capsules and -- all capsules and tablets will have fillers.

MS. PIROZZOLO: So, let's put up Claim 3 of the '349 patent.

BY MS. PIROZZOLO:

Q. Now, you heard Dr. Donovan testify that a skilled artisan would have been motivated to formulate cabozantinib (L)-malate as set forth in Claim 3.

Do you agree with that?

A. No.

Q. Could you explain why not?

A. Well, first of all, the formulation of any drug product requires you to understand the dosage form, the dose, and the physicochemical properties of the API. So, before you know how you're -- how you're going to formulate something, you have to do all that work. And then you can decide what classes of excipients you're going to employ.

Q. Okay. Have you heard the term "physicochemical properties"?

A. Yes.

Q. What physicochemical properties are important to formulation scientists?

A. Well, certainly the solubility, the permeability, the crystal size distribution, the crystal shape, the hygroscopicity, the carrying electric charge, the

compressibility, the flowability. There are probably some more but those are some of the main ones you're interested in.

Q. Is chemical stability important?

A. Yes.

Q. And why is that?

A. Well, chemical stability will determine whether the API is going to decompose, either due to interaction with the excipients or through the manufacturing process.

Q. What were some of the kinds of physicochemical properties that turned out to be important to how cabozantinib (L)-malate was formulated?

A. Well, first was the chemical stability. And second was the flowability.

Q. And why were those important?

A. Well, it turns out that cabozantinib (L)-malate could decompose to the 1-1 impurity when exposed to moisture, heat, and in the presence of certain excipients. In addition, it was poorly flowing. The API was poorly flowing.

Q. Okay. As of 2011, was the chemical stability of cabozantinib (L)-malate known in the prior art?

A. No.

Q. As of 2011, was the flowability of cabozantinib (L)-malate known in the prior art?

09:06:02 A. No.
09:06:04 Q. Okay.
09:06:05 MS. PIROZZOLO: Let's put up paragraph 82 of the
09:06:08 Brown reference, Defendants' Exhibit 291.
09:06:08 BY MS. PIROZZOLO:
09:06:11 Q. At Tab 10 in your binder.
09:06:16 Dr. Donovan referred to paragraph 82 in Brown in
09:06:20 her testimony. Do you recall that?
09:06:21 A. Yes.
09:06:23 Q. In your opinion, does paragraph 82 in Brown suggest
09:06:27 formulating cabozantinib with a glidant?
09:06:30 A. No. A glidant is not a class of excipients that's
09:06:33 listed in paragraph 82.
09:06:36 Q. Now, Dr. Donovan pointed in this paragraph to the
09:06:39 excipient talc. Do you recall that?
09:06:42 A. I do.
09:06:43 Q. Is talc listed as a glidant in this paragraph?
09:06:46 A. No, it's listed as a lubricant.
09:06:49 Q. Okay. Have you seen any reference identified by
09:06:54 Dr. Donovan that would motivate a skilled artisan to include
09:06:58 a glidant?
09:07:00 A. To include a glidant in the --
09:07:03 Q. In a composition for cabozantinib (L)-malate?
09:07:05 A. No.
09:07:12 MS. PIROZZOLO: Now, let's pull up Defendants'

Exhibit 335, which is a patent application.

BY MS. PIROZZOLO:

Q. Do you recall Dr. Donovan discussing this patent application?

A. Yes.

Q. Does this patent application relate to cabozantinib?

A. No.

Q. What, at a general level, does this patent application relate to?

A. It relates to several other APIs that are tyrosine kinase inhibitors.

Q. Does the -- does the '081 application, which is Defendants' Exhibit 35 -- 335, teach that cabozantinib (L)-malate should be formulated with a filler, disintegrant, glidant, and lubricant?

A. No.

Q. Could you explain why not?

A. Well, it's because it's about different APIs, and different APIs have different properties. It doesn't really inform you if you have formulation for a completely different API how you're going to formulate a different API. Because you don't know -- the physicochemical properties are going to be different.

Q. Now, let's turn to the Lachman reference that Dr. Donovan discussed which is Plaintiff's Exhibit 553A.

09:08:34 What is the Lachman reference?
09:08:36 A. This is a reference on pharmaceutical dosage forms.
09:08:43 Q. Did you hear Dr. Donovan testify that a skilled
09:08:46 artisan would be motivated by Lachman to formulate
09:08:50 cabozantinib (L)-malate with one or more fillers,
09:08:54 disintegrants, glidants and lubricants?
09:08:56 A. I did.
09:08:57 Q. Do you agree with Dr. Donovan's opinion?
09:08:59 A. No, Lachman is -- is a general reference on
09:09:02 formulation. And, of course, it talks about all classes of
09:09:06 excipients, but it also -- I think we saw the paragraph
09:09:10 already -- talks about how each formulation is a unique --
09:09:15 unique development project where you develop the formulation
09:09:21 based on the properties of the API.
09:09:25 MS. PIROZZOLO: So, let's turn to Page 76 of
09:09:27 Lachman, which is Page 3 of the PDF.
09:09:27 BY MS. PIROZZOLO:
09:09:33 Q. And looking at the sentence that begins with, "The
09:09:35 correct selection," is that what you're referring to,
09:09:39 Dr. Myerson?
09:09:39 A. Yes. "The correct selection and balance of excipient
09:09:43 materials for each active ingredient or ingredient
09:09:48 combination in a tablet formulation to achieve the desired
09:09:52 response (i.e. production of a safe, effective, and highly
09:09:58 reliable product) is not in practice a simple goal to

achieve."

Q. Do you agree with that statement in Lachman?

A. Yes.

Q. Could you explain why?

A. Well, because, again, each -- each formulation of a new API is a unique problem. And you might run into problems with flow or chemical stability or the ability to make a tablet that is -- doesn't break into pieces or is -- has appropriate hardness, has the right dissolution properties. So, in fact, in my own experience, you go through lots and lots of iterations of excipients and blends and tablet press pressures and various other things to make a safe and effective and reliable formulation.

Q. So, we've talked about Brown, the '081 application and the Lachman reference. Do any of those, in your opinion, provide a motivation to formulate cabozantinib (L)-malate in the manner claimed in Claim 3 of the '349 patent?

A. No.

MS. PIROZZOLO: Now, let's go to "Reasonable Expectation of Success." That's Slide 17 of your slides.

BY MS. PIROZZOLO:

Q. Going to the first point, you heard Dr. Lepore testify that a skilled artisan would have simply added a recrystallization step to the synthetic process in Brown to

achieve an API that is essentially free of the 1-1 impurity.

Do you recall that?

A. I do.

Q. Do you agree with that?

A. I do not.

Q. Do you have an opinion -- strike that.

Are there any reasons that recrystallization might be difficult in the context of cabozantinib (L)-malate?

A. Yes. So, we're trying to reduce an impurity to below 200 PPM which is 0.02 percent. And the 1-1 impurity is structurally similar to the API cabozantinib (L)-malate. And often in crystallizations, when have you structurally similar materials, the impurity substitutes in the crystalline lattice as an impurity making it very difficult to achieve that level of purification.

This is something I've been doing for more than 40 years. Crystallization is one of my main areas, and I've seen this in many cases when you're trying to reduce impurities to very low levels. They just won't be removed. So you have to come up with a different separation process or different synthetic process to achieve that level of purity.

MS. PIROZZOLO: Let's call up Plaintiff's Exhibit 494 which is Tab 21 in your binder.

BY MS. PIROZZOLO:

Q. What is Exhibit 494?

A. This is Chapter 3 of the *Handbook of Industrial Crystallization*, which is the second edition, which is a book I edited.

MS. PIROZZOLO: Let's turn to Figure 3.10 on Page 6.

BY MS. PIROZZOLO:

Q. What does Figure 3.10 show?

A. Well, this is a figure actually illustrating, among other things, the point I just made about substitution of impurities.

Q. Could you explain with reference to the circles in the figure how this would be relevant to recrystallizing cabozantinib (L)-malate?

A. Yes, so if the cabozantinib (L)-malate are the -- the white circles, and the 1-1 impurity is structurally similar -- it's A -- A can substitute in the crystalline lattice and, thus, is a substitutional impurity. And again substitutional impurities are impurities that have an affinity for the lattice, and they're very hard to reduce to very low levels.

Q. In your experience, is this kind of substitutional impurity common in crystallization of active pharmaceutical ingredients?

09:14:37 A. Yes, it's actually a problem that I work on quite
09:14:41 often and companies ask me about quite often because it's --
09:14:45 it's a difficult issue when you're trying to get an impurity
09:14:48 that to these kinds of levels.
09:14:50 Q. How does this relate to your opinion as to whether a
09:14:54 skilled artisan would have had a reasonable expectation of
09:14:57 success in recrystallizing cabozantinib (L)-malate to obtain
09:15:02 API essentially free of the 1-1 impurity?
09:15:05 A. Well, based on this mechanism, you would think they
09:15:08 wouldn't have a reasonable expectation of success. In
09:15:11 addition, of course, there's another reason. It's because
09:15:16 the 1-1 impurity is a decomposition product of the API. So,
09:15:21 when you -- it's just the act of redissolving it before you
09:15:26 recrystallize could produce additional 1-1 impurity, making
09:15:30 it even harder to get it essentially free.
09:15:35 MS. PIROZZOLO: Now, let's turn to Defendants'
09:15:39 Exhibit 304 which is Tab 22 in your binder.
09:15:39 BY MS. PIROZZOLO:
09:15:46 Q. Did you hear Dr. Lepore discuss Defendants'
09:15:50 Exhibit 304?
09:15:50 A. I did.
09:15:51 Q. What is Defendants' Exhibit 304?
09:15:54 A. It's a guidance for industry on manufacturing active
09:16:00 pharmaceutical ingredients.
09:16:01 Q. Okay. In your opinion, would this reference motivate

a skilled artisan with reasonable expectation of success to add a recrystallization step to the Brown process to achieve cabozantinib (L)-malate essentially free of the 1-1 impurity?

A. No.

Q. Could you explain your opinion?

A. Well, I mean, this -- this talks about purification and mentions that you can try to purify something via crystallization, but that wouldn't motivate a person to modify Brown because, first of all, they don't know the 1-1 impurity is a decomposition product. And, as I note, a recrystallization step could be ineffective in this type of process. So, no, I don't believe it would.

MS. PIROZZOLO: Let's go to Slide 17.

BY MS. PIROZZOLO:

Q. So, we've talked about whether there would be a reasonable expectation of success for controlling 1-1 in the API of cabozantinib (L)-malate. Let's move to controlling 1-1 in the pharmaceutical composition. Okay?

A. Yes.

Q. Without the information provided by the '349 patent, would a skilled artisan looking at the Brown reference have had a reasonable expectation of success in achieving cabozantinib (L)-malate composition with the claimed excipients free of the 1-1 impurity?

09:17:36 A. No.
09:17:36 Q. Could you explain why not?
09:17:38 A. Because the Brown process, first of all, would make
09:17:45 API with variable amounts of the 1-1 impurity, including
09:17:49 cases where the 1-1 impurity would already be greater than
09:17:54 200 PPM. But even if it was below 200 PPM, it doesn't
09:17:59 describe any information on excipient compatibility or any
09:18:05 other thing that would allow you to formulate into a drug
09:18:09 product that was essentially free.
09:18:16 Q. What were the properties of cabozantinib (L)-malate
09:18:20 that were not in the prior art that would be needed to
09:18:24 formulate cabozantinib (L)-malate essentially free of the
09:18:27 1-1 impurity?
09:18:28 A. Well, first of all, you would have to know about its
09:18:32 chemical stability. You'd have to understand whether it
09:18:38 decomposed under various conditions, and you would also have
09:18:43 to know the list of physicochemical properties I mentioned
09:18:48 before, including the excipient compatibility studies, and
09:18:56 because you're formulating it, you would still have to know
09:18:58 about the flowability and the crystal size, crystal shape,
09:19:04 all of those other things.
09:19:05 Q. Okay. Were those properties you just mentioned known
09:19:09 in the prior art?
09:19:10 A. No.
09:19:13 Q. Without knowing about these properties and without

09:19:18 the benefit of the teaching of the '349 patent, could a
09:19:21 person of skill have predicted how cabozantinib (L)-malate
09:19:26 or levels of the 1-1 impurity would be affected by
09:19:30 formulation?
09:19:30 A. No.
09:19:31 Q. Could you explain why not?
09:19:32 A. Again, there's no information on the effect of
09:19:39 excipients, heat, moisture and processing conditions on the
09:19:45 formation of the 1-1 impurity. In fact, we don't even know
09:19:48 it's a degradation product, which is the key piece of
09:19:51 information.
09:19:53 Q. Okay. Now, did you consider objective indicia in
09:19:57 rendering your opinions in this case?
09:20:00 A. I did.
09:20:02 Q. What products -- and we can look at Plaintiff's
09:20:05 Demonstrative Slide 3. What products practice Claim 3 of
09:20:12 the '349 patent?
09:20:12 A. The tablets, Cabometyx, and the capsules, Cometriq.
09:20:21 Q. Did you consider whether there was a nexus between
09:20:26 the objective indicia in Claim 3 of the '349 patent?
09:20:29 A. I did.
09:20:31 Q. What is your understanding of the nexus between the
09:20:37 '349 patent and the objective indicia.
09:20:39 A. Well, the '349 patent was crucial because it
09:20:42 disclosed a synthetic process to produce cabozantinib

(L)-malate at exceptionally low levels of the 1-1 impurity. That allowed it to be formulated into a drug product which continued to have low enough levels at of a 1-1 impurity after manufacturing and in storage to be sold and given to patients.

Q. Did you consider opinions of Dr. George?

A. I did.

Q. Okay. Dr. George will testify later, but did his opinions, as you understand them, inform your opinions in this case?

A. Yes, because Dr. George -- I relied on Dr. George for the usefulness of these formulated cabozantinib tablets and capsules for the use in treating cancer.

Q. Okay. Does the claimed invention as embodied in the Cabometyx product provide benefits over the prior art?

A. Yes. That's -- I'm relying on Dr. George for that.

Q. Were there benefits to the formulation that were relevant to patients?

A. Yes. Again, the formulation of the API that maintained formulation that was essentially free of the 1-1 impurity is a key feature of this.

Q. Now, you understand Dr. George has offered opinions that Cabometyx is a clinical success.

Does that inform your opinions?

A. Yes. Of course. The -- if the drug is clinical -- a

clinical success, a key feature of that is that it had been formulated into a drug product. It can help people.

Q. Now, did you consider the opinions of Mr. Tate?

A. Yes.

Q. What opinions of Mr. Tate did you consider?

A. Commercial success.

Q. Does Mr. -- what was Mr. Tate's opinion on commercial success that we'll hear from him later?

A. Yes. That -- that these drug products have been commercially successful in the marketplace.

Q. Okay. How did Mr. Tate's opinions relate to your ultimate opinion on obviousness?

A. Again, these have -- for -- since I'm relying on Mr. Tate for commercial success, part of the commercial success has to be due to the successful formulation of the API into the drug product.

Q. Okay. Dr. Myerson, what is your conclusion concerning whether Claim 3 of the '349 patent is obvious?

A. It's my opinion that it is not obvious.

MS. PIROZZOLO: Thank you, Dr. Myerson. I have no further questions.

THE COURT: All right. Mr. Lombardi.

MR. LOMBARDI: Your Honor, may we pass up some binders?

THE COURT: Yeah. Sure.

09:23:59 MR. LOMBARDI: Thank you.

09:24:08 CROSS-EXAMINATION

09:24:26 BY MR. LOMBARDI:

09:24:26 Q. Good morning, Dr. Myerson.

09:24:35 A. Good morning.

09:24:36 Q. My name is George Lombardi. We haven't met, have we?

09:24:39 A. Nice to meet you.

09:24:41 Q. Nice to meet you.

09:24:42 Sir, yesterday you spent a fair amount of time
09:24:45 going through various processes that had been developed by
09:24:50 Exelixis for the creation of the cabozantinib compound; is
09:24:56 that right?

09:24:56 A. Correct.

09:24:57 Q. And you started with Process A-1, I think, that was
09:25:02 the first one they had.

09:25:04 A. Yes.

09:25:04 Q. And then you went through A-2?

09:25:07 A. Yes.

09:25:08 Q. And B-1?

09:25:09 A. Yes.

09:25:10 Q. And B-2; correct?

09:25:11 A. Correct.

09:25:12 Q. And B-2, as I understood your testimony, was the one
09:25:16 that ended up getting the lowest amounts of the 1-1
09:25:19 impurity; is that correct?

09:25:20 A. Yes.
09:25:21 Q. And, approximately, what were the parts per million
09:25:24 on that?
09:25:24 A. It was from less than 2 PPM to 12 PPM.
09:25:28 Q. Okay. Now, you understand that we're here talking
09:25:34 about Claim 3 of the '349 patent; is that right?
09:25:39 A. Yes.
09:25:40 Q. And you're testifying specifically on whether that's
09:25:43 obvious or not; is that right?
09:25:44 A. Correct.
09:25:45 Q. So, here's Claim 3. You see it up there on the
09:25:48 screen; is that right?
09:25:49 A. Yes.
09:25:51 Q. And it does make reference in the last paragraph, as
09:25:54 you pointed out, to essentially free, which in the terms of
09:25:59 the patent means 200 PPM or less; right?
09:26:02 A. Correct.
09:26:03 Q. It does not specify any particular way of
09:26:09 accomplishing that -- that level of impurity; is that right?
09:26:14 A. In the claim itself, that's correct.
09:26:17 Q. And the claim itself is what we're determining for --
09:26:21 looking at for obviousness; is that right?
09:26:23 A. Well, the claim itself looks for obviousness but of
09:26:28 course a POSA interprets a claim based on the specification.
09:26:32 And the specification, of course, has the synthetic process

09:26:35 in it.
09:26:36 Q. Okay. So -- well, is it your testimony then that the
09:26:39 synthetic -- what is the synthetic process in this spec?
09:26:41 It's B-2 in this instance?
09:26:42 A. That's correct.
09:26:43 Q. Is it your testimony that to infringe this claim a
09:26:49 POSA would have to use B-2?
09:26:51 A. No.
09:26:52 Q. Okay. So, there is no method of controlling the
09:27:02 1-1 impurity specifically claimed in the patent; is that
09:27:05 right?
09:27:06 A. You mean -- oh, specific -- did you say specifically
09:27:10 claimed? I'm sorry.
09:27:10 Q. Yes, I did.
09:27:11 A. Yeah, not specifically in the claim. I agree with
09:27:14 that.
09:27:14 Q. Okay. And the claim -- actually, the B-2, I think
09:27:20 you just said was -- it was single digits, I think, for
09:27:23 parts per million or up to 10 perhaps?
09:27:26 A. It was up to 12. Less than 2 and up to 12.
09:27:29 Q. Okay. And so the amount that the claim calls for is
09:27:33 considerably higher than that as an upper limit on the
09:27:37 impurities; is that right?
09:27:39 A. Right. But of course, I think you're -- you're doing
09:27:43 something that happens all the time. You're talking about

09:27:45 1 the API and the claim is to the pharmaceutical composition.
09:27:49 2 Q. Yeah. And the claim is to something considerably
09:27:52 3 higher than the level that could be accomplished with B-2;
09:27:57 4 isn't that right?
09:27:58 5 A. Again, that's right, but you're connecting something
09:28:01 6 that's not exactly the same.
09:28:03 7 Q. 200 is greater than 12; is that right, Doctor?
09:28:06 8 A. 200 is in the pharmaceutical composition and the less
09:28:09 9 than 2 to 12 is in the API. But I agree with you that the
09:28:13 10 number 200 is greater than the --
09:28:15 11 Q. Thank you.
09:28:16 12 A. -- the number 12.
09:28:17 13 Q. Thank you.
09:28:17 14 Now, also in Claim 3, Doctor, there is reference
09:28:22 15 to excipients. You talked about that; correct?
09:28:25 16 A. Correct.
09:28:25 17 Q. And in the reference to the excipients, it talks
09:28:28 18 about four categories of excipients; is that right?
09:28:32 19 A. Correct.
09:28:33 20 Q. Fillers, disintegrants, glidants and lubricants; is
09:28:36 21 that right?
09:28:36 22 A. Correct.
09:28:37 23 Q. It does not specify particular excipients; is that
09:28:42 24 right?
09:28:42 25 A. That's correct.

09:28:43 Q. And -- and there are many, many fillers, for
09:28:47 instance; is that right?
09:28:48 A. Yes.
09:28:48 Q. Okay. Can you give me a ballpark?
09:28:50 A. Not really. I mean there -- there are more common
09:28:55 fillers and less common fillers. You'd have to go make a
09:28:58 list and take a look.
09:28:58 Q. Okay. There are many, many disintegrants; is that
09:29:01 right?
09:29:01 A. Actually, not many, many disintegrants, but I'll say
09:29:04 that there are a number of different disintegrants.
09:29:06 Q. Okay. There are a number of different glidants; is
09:29:09 that correct?
09:29:09 A. Again -- there are a number of different ones, yes.
09:29:13 Q. And there are a number of different lubricants; is
09:29:16 that right?
09:29:16 A. A limited set of lubricants, but there are -- there
09:29:19 are a number of different ones.
09:29:21 Q. Okay. And so for purposes of your analysis here,
09:29:25 we're not talking about specific -- it's -- they don't claim
09:29:29 in Claim 3 specific quantities of a particular filler; is
09:29:34 that right?
09:29:34 A. That's correct.
09:29:35 Q. And they don't claim specific quantities of a
09:29:38 particular filler that should be used with specific

quantities of a particular disintegrant; is that right?
A. That's correct.
Q. And it's true for all four, they don't claim an entire group of those four disintegrants where a particular disintegrant -- or excuse me. I got a word wrong. I'll start again, Doctor.
They don't -- they don't claim one group of those four excipients that specifies every excipient and the amounts of those excipients; right?
A. That's correct.
Q. They leave it to the person of skill in the art to make that determination; right?
A. Correct.
Q. And that's something well within the level of skill in the art; is that right?
A. Correct. And they do have examples in the patent that inform a POSA.
Q. Okay. And so what's at issue here is whether it would be obvious to use fillers, disintegrants, glidants, and lubricants; is that right? That's the issue?
A. No, the issue -- actually, the issue is --
Q. Well --
A. -- the entire claim.
Q. Fair enough, Doctor. Fair enough.
But with respect to the excipient part of the

09:30:43 claim --

09:30:44 MS. PIROZZOLO: Your Honor, can he finish his
09:30:46 answer?

09:30:46 THE COURT: He said it's the entire claim. That
09:30:49 is the obvious answer, I think he's done.

09:30:50 Go ahead.

09:30:51 MR. LOMBARDI: Okay.

09:30:56 BY MR. LOMBARDI:

09:30:56 Q. And so, Doctor, what's at issue here is would it have
09:30:59 been obvious on this part of the claim -- the whole claim is
09:31:02 at issue, but for this part of the claim is whether it would
09:31:04 have been obvious to use these categories of excipients;
09:31:06 correct?

09:31:06 A. You know, I -- I mean I understand what you're
09:31:15 saying, I guess. Don't you do an obvious analysis looking
09:31:19 at all the elements of the claim together?

09:31:22 So -- so, to me, it's whether they do these four
09:31:26 categories to make a pharmaceutical composition of
09:31:29 cabozantinib that's essentially free.

09:31:32 Q. Okay. Fair enough.

09:31:33 All right. Doctor, you -- as part of your
09:31:36 obviousness analysis, we know that the Brown application --
09:31:42 published application was disclosed. That's prior art;
09:31:47 correct?

09:31:47 A. Correct.

09:31:48 Q. Okay. And you talked about Brown yesterday and this
09:31:51 morning; correct?
09:31:52 A. Correct.
09:31:53 Q. And you assumed for your obviousness analysis that a
09:31:56 person of skill in the art would have known about the
09:32:00 cabozantinib crystalline malate salt based on Brown;
09:32:06 correct?
09:32:06 A. Yes. They would have known about the malate salt,
09:32:08 that's correct.
09:32:09 Q. Okay. And you would have -- they would have -- you
09:32:11 would have known a person of skill in the art -- you're
09:32:14 assuming that a person of skill in the art would know --
09:32:15 would have known that Brown teaches its use as a treatment
09:32:19 for disease; is that right?
09:32:21 A. Yes. I believe Brown discloses that.
09:32:24 Q. Okay. Given that assumption -- well, let me put up
09:32:27 on the screen just something to help guide our discussion.
09:32:32 This is --
09:32:33 MR. LOMBARDI: Could we put up the Doctor's
09:32:35 slide PDX-4.10, please.
09:32:35 BY MR. LOMBARDI:
09:32:51 Q. Doctor, this is one of your slides -- there we go.
09:32:54 This is one of your slides from early in your
09:32:57 testimony; is that right?
09:32:58 A. Yes.

09:32:59 Q. And it's --

09:32:59 MR. LOMBARDI: Just for the record, it's PDX 4.4 and it's titled "Summary of opinions."

09:33:02 BY MR. LOMBARDI:

09:33:05 Q. Did I get that right?

09:33:06 A. Yes.

09:33:07 Q. Now, given that knowledge of the person of skill in the art about cabozantinib with a crystalline form and its use as a pharmaceutical, each of these -- there it is.

09:33:26 All right. Let me step back.

09:33:28 Each of -- you put forward on this slide four things that you considered discoveries that were made by Exelixis involving the 1-1 impurity; is that right?

09:33:37 A. Yes.

09:33:39 Q. And given knowledge that cabozantinib was out there known in the art and could be used for pharmaceutical purposes, a person of skill in the art would have been motivated to do each of these things; isn't that correct?

09:33:54 A. I'm sorry. I don't think -- I think that's -- maybe I'm not following the phrasing of your question, but the first one is --

09:34:08 THE COURT: So, actually, you know, can't you rephrase the question because I think it doesn't actually make any sense.

09:34:14 MR. LOMBARDI: Maybe I got something wrong.

I'll try -- let me try again, Your Honor.

BY MR. LOMBARDI:

Q. So you set forth on this slide Exelixis' discoveries regarding the 1-1 impurity; is that right?

A. Yeah.

Q. And you talk about that Exelixis discovered the formation of a degradation product in the first bullet; right?

A. Yes. During the synthesis, right.

Q. And then discovered the degradation product when exposed to heat and water in the next one; is that right?

A. Right.

Q. And then they thought -- discovered that due to chemical interactions 1-1 could form; is that right?

A. Yes.

Q. And discovered that the 1-1 impurity is genotoxic.

Do you see that?

A. Yeah.

Q. And so my question is: Each of those discoveries -- for each of those discoveries, a person of skill in the art would have been motivated to do the work that led to them; isn't that true?

A. Well, I think that's kind of a hindsight analysis because, of course, you're not motivated to know that something is a degradation product. When you're -- when

09:35:19 you're working on development, you might discover it's a
09:35:22 degradation product but that's something you're not
09:35:26 motivated for. It's just -- it's just something you would
09:35:28 find out when you were doing further development --
09:35:32 Q. Okay.
09:35:32 A. -- of the compound.
09:35:33 Q. Okay. Well, let's talk about it. Let's talk about
09:35:35 the first one first, the first bullet point.
09:35:37 A. Yes.
09:35:38 Q. Doctor, it's the 1-1 could form as a degradation
09:35:41 product during the synthesis of the API.
09:35:44 Do you see that?
09:35:44 A. Yes.
09:35:45 Q. So, we -- we're making the assumption that
09:35:49 cabozantinib is out there and known; is that right?
09:35:52 A. Right. It's out there and known, and there's a
09:35:57 process to make it in Brown.
09:35:58 Q. And understanding the physiochemical characteristics
09:36:03 of an API is an important step in the drug development
09:36:08 process; correct?
09:36:09 A. That's correct.
09:36:09 Q. In every drug development project, the team will be
09:36:12 motivated to figure out what the physiochemical
09:36:16 characteristics of the API are?
09:36:17 A. That's correct.

09:36:18 Q. And in this case, that would be cabozantinib; right?
09:36:21 A. Correct.
09:36:22 Q. And it would be a normal progression in the drug development process for a POSA to do pre-formulation studies?
09:36:30
09:36:31 A. That's correct.
09:36:32 Q. This helps the POSA determine how to develop the product?
09:36:35
09:36:35 A. That's correct.
09:36:36 Q. And to determine suitable technologies to use the formulation, to use in the formulation?
09:36:39
09:36:41 A. That's correct.
09:36:43 Q. Now, it's important to know the degradation products that are made in the synthesis of an API?
09:36:47
09:36:51 A. That's correct.
09:36:52 Q. And a POSA would consider it important to know that?
09:36:56 A. Yes.
09:37:00 Q. And actually, a person of skill in the art would be very concerned about having degradation products in this drug that they're making because they want to make the best drug they can; right?
09:37:05
09:37:09
09:37:12
09:37:14 A. That's correct. Of course, there are -- when developing a drug and looking at degradation products, as I think I talked about a lot at my deposition, you're often looking at known impurities and unknown impurities and, in
09:37:21
09:37:24
09:37:30

fact, part of the development process might be to determine what these unknown degradation products are.

Q. And that's something formulation scientists do all the time; correct?

A. You're skipping a step. We're talking about the synthetic people, the -- which are looking at the synthetic process and then separately the formulation people do additional work that -- that we talked about.

Q. And there are -- they're both looking for degradation products; correct?

A. Yeah, at different times, for different purposes, but yes.

Q. And actually it's not just that a person of skill in the art would be motivated to find these degradation products, the FDA requires it, doesn't it?

A. Okay. So now if we talk about that, we actually -- I don't think anybody put up the actual numbers of guidance for impurities in drug products, but typically you have to identify impurities that are over a thousand PPM and those impurities that are under a thousand PPM could be listed as unknown impurities unless they're determined to be -- unless you have a reason to think they're genotoxic or carcinogenic.

Q. But have you to find the impurities. The FDA tells you to find the impurities; is that right?

09:38:52 A. No. What I just said is exactly correct. A thousand
09:38:57 PPM, you have to identify what they are. Under a thousand
09:39:01 PPM, they get listed as unknown impurities. And eventually
09:39:05 you might determine what they are particularly if they turn
09:39:10 out to be genotoxic.
09:39:12 Q. Okay. Let's put up -- I think you have this. It's
09:39:15 DTX-274 and -- and if you want your binder -- and I can put
09:39:20 it on the screen. I will put it on the screen.
09:39:22 A. I'm having a little trouble.
09:39:23 Q. With the screen? Okay.
09:39:24 A. I'd like to like look in the binder.
09:39:27 Q. Fine. DTX-274.
09:39:29 A. Yes. Right.
09:39:38 Q. Got it?
09:39:38 A. Yeah.
09:39:39 Q. Okay. Just to make sure we're on the right page,
09:39:42 Doctor, it's -- what you're looking at is the guidance for
09:39:44 industry Q3A impurities in new drug substances; is that
09:39:50 right?
09:39:50 A. Actually, I was giving you the number of this that
09:39:53 I -- that I just happened to know.
09:39:56 Q. Okay. But that's what you have in front of you;
09:39:57 right?
09:39:57 A. Yes.
09:39:58 MR. LOMBARDI: Okay. Let's go to Page 3. Yes.

09:40:07 There.
09:40:07 BY MR. LOMBARDI:
09:40:08 Q. And at the top it says, "Rationale for the reporting
09:40:10 and control of impurities."
09:40:12 Do you see that, Doctor?
09:40:13 A. I do.
09:40:14 Q. And then the first sentence says, "The applicant
09:40:19 should summarize the actual and potential impurities most
09:40:22 likely to arise during the synthesis, purification and
09:40:25 storage of a new drug substance."
09:40:28 Do you see that?
09:40:29 A. Yes.
09:40:29 Q. And when we're talking about a new drug substance,
09:40:32 we're talking about something like cabozantinib; right?
09:40:34 A. Correct. Something that hasn't been approved yet.
09:40:37 Q. Okay. And so, a person of skill in the art would be
09:40:42 motivated when they start to work with a compound that
09:40:46 they've synthesized to find degradation products during the
09:40:50 synthesis of the API; is that right?
09:40:52 A. Yes. Again, they'll see them in the HPLC. They
09:40:57 won't necessarily identify what they are.
09:41:00 Q. Okay. And, sir, when you look at the claims in this
09:41:04 case, the inventors here did not claim any new methods of
09:41:08 looking for degradation products in the synthesis of the
09:41:13 API; is that right?

09:41:14 A. I'm sorry. Maybe --

09:41:15 MR. LOMBARDI: Let's -- can we put the slide
09:41:17 back up? PDX 4.10.

09:41:21 THE WITNESS: I just didn't get the question.

09:41:22 BY MR. LOMBARDI:

09:41:22 Q. I'm going to give it to you again. I think it'll
09:41:25 help maybe. It's at -- I'm reading from the slide, so --

09:41:26 A. It might help.

09:41:27 Q. The inventors did not claim any new methods of
09:41:31 looking for degradation products that could arise during the
09:41:35 synthesis of the API?

09:41:37 A. New method, no.

09:41:39 Q. And, in fact, the inventors said use known techniques
09:41:42 to do that; is that correct?

09:41:43 A. That's correct.

09:41:44 Q. And there's nothing in the patent that says that a
09:41:46 person of skill in the art would not have been able to
09:41:49 locate the degradation products; is that right?

09:41:53 A. That's correct.

09:41:54 Q. And, in fact, the presence of reaction impurities and
09:41:58 or processing impurities may be determined by analytical
09:42:02 techniques known in the art; is that right?

09:42:04 A. That's correct.

09:42:05 Q. And actually, that's -- that was a quote from Brown;
09:42:09 right?

09:42:09 A. If you tell me it is, that's fine. But -- but I
09:42:14 agree with the statement.
09:42:15 Q. And Brown is an Exelixis patent application; correct?
09:42:19 A. Yes.
09:42:21 Q. Yes. Okay.
09:42:22 MR. LOMBARDI: Let's go to the second one.
09:42:22 BY MR. LOMBARDI:
09:42:25 Q. 1-1 could form as a degra -- de -- excuse me. 1-1
09:42:29 could form as a degradation product when cabozantinib
09:42:32 (L)-malate was exposed to heat and water.
09:42:37 Do you see that?
09:42:37 A. Yes.
09:42:38 Q. That's another one of the discoveries that you talked
09:42:40 about; correct?
09:42:42 A. Yes.
09:42:43 Q. Okay. And a person of skill in the art would have
09:42:46 been motivated to determine what the degradation products
09:42:51 would be when cabozantinib (L)-malate was exposed to heat
09:42:55 and water; is that right?
09:42:59 A. I would agree that at some point somebody would have
09:43:01 done a stress test on probably cabozantinib (L)-malate to
09:43:04 look at the effects of heat and water on the API
09:43:08 incompetent. Agree with that.
09:43:08 Q. That's routine work for formulation scientists; isn't
09:43:11 that right?

09:43:12 A. Actually, that's -- that's work that's done on the
09:43:17 API in terms of chemical stability at some point in the
09:43:22 development process. I'm not sure who's going to do it, but
09:43:26 it's done.
09:43:26 Q. Okay. You're making a distinction between perhaps a
09:43:30 chemist that does its synthesis and somebody who does the
09:43:33 formulation?
09:43:33 A. Yeah, and sometimes there's actually a material
09:43:36 science group in between.
09:43:37 Q. Okay. But persons of skill in the art would do it --
09:43:39 A. Yeah.
09:43:40 Q. -- is that right?
09:43:41 And they'd know how to do it; correct?
09:43:42 A. Yes.
09:43:43 Q. And it's another thing that the FDA requires to be
09:43:48 done; isn't that right?
09:43:49 A. At some point in development; that's correct.
09:43:53 Q. Okay. And the FDA, when it's looking for degradation
09:43:57 products, they're specifically looking for impurities that
09:44:02 result from a chemical change in the drug substance brought
09:44:05 about by the manufacture or storage of the new drug product
09:44:10 by effect of light, temperature, pH, water, things like
09:44:16 that; is that right?
09:44:16 A. Yes, because those are very important both in the
09:44:19 manufacturing and the stability of the drug on the shelf.

09:44:22 Q. Now, the patent doesn't claim any novel ways of
09:44:27 determining a degradation product when cabozantinib
09:44:32 (L)-malate was exposed to heat and water; is that correct?
09:44:36 A. That's correct.
09:44:42 Q. I'm sorry. I didn't hear you.
09:44:44 And what -- the patent assumes or says is that
09:44:53 the POSA, the person of ordinary skill in the art could use
09:44:56 known techniques to make that kind of determination; isn't
09:45:00 that right?
09:45:00 A. Sorry. Which -- what are we talking about now?
09:45:03 Q. Well, the patent doesn't claim any novel ways of
09:45:06 determining degradation products when cabozantinib is
09:45:10 exposed to heat and water; is that right?
09:45:12 A. Yes, I understand that. Yeah.
09:45:13 Q. Okay. A POSA would use known techniques; is that
09:45:17 right?
09:45:17 A. Known techniques to -- to look for degradation
09:45:21 products, yes, I agree with that.
09:45:22 Q. And the patent -- and you would expect a person of
09:45:26 skill in the art, it's within their skill to make a
09:45:29 determination of the degradation to products when
09:45:32 cabozantinib is exposed to heat and water; is that right?
09:45:35 A. Yes. Yes. It can be quite a bit of work, but that's
09:45:41 correct.
09:45:41 Q. Okay. All right.

09:45:43 MR. LOMBARDI: Let's go to the third one.
09:45:43 BY MR. LOMBARDI:
09:45:46 Q. 1-1 could form due to chemical interactions between
09:45:50 cabozantinib (L)-malate and certain excipients. That is the
09:45:55 third of the discoveries on your chart; is that right?
09:45:57 A. Correct.
09:45:58 Q. Now, we talked about preformulation. What this
09:46:04 describes -- or let me strike the question and start again,
09:46:10 Doctor.
09:46:10 Determining the chemical interactions between a
09:46:15 active ingredient and excipients is part of what we've
09:46:20 talked about being preformulation; right?
09:46:22 A. That's correct. It's -- we've heard this described
09:46:25 as excipient compatibility studies, which is what it's
09:46:28 usually described as.
09:46:29 Q. Okay. And these excipient compatibility studies is
09:46:33 part of the normal process of pharmaceutical development;
09:46:36 correct?
09:46:36 A. Yes. In this case, this is formulation development;
09:46:40 correct.
09:46:40 Q. One of the first things you do when you're -- I've
09:46:43 got the right scientists now. It's formulators now; right?
09:46:46 A. Right.
09:46:47 Q. And one of the first things you do as a formulator is
09:46:51 excipient compatibility studies; right?

09:46:53 A. Yes.
09:46:55 Q. This is what formulators do day in and day out; is
09:46:58 that right?
09:46:58 A. Every time they have a new API, they do excipient
09:47:03 compatibility studies. I agree with that.
09:47:05 Q. And then the person of skill in the art determines
09:47:07 which excipients are necessary; is that right?
09:47:10 A. After they do the excipient compatibility studies and
09:47:16 they have determined a dose and a type of drug product, they
09:47:20 then start selecting individual excipients to make -- to
09:47:26 make trial formulations.
09:47:28 Q. Okay. And you determined which excipients will be
09:47:35 compatible with a particular API; is that right?
09:47:40 The formulation scientists?
09:47:41 A. That's correct. You're looking, of course, to
09:47:43 minimize any decomposition.
09:47:46 Q. Okay. Ultimately, a POSA knows that you want to use
09:47:50 only the excipients that are physically and chemically
09:47:54 compatible with the API; is that right?
09:47:57 A. Right. That's the first step. Yes.
09:47:59 Q. Okay. And that's something that persons of skill in
09:48:02 the art are well qualified to do?
09:48:05 A. I agree with that.
09:48:07 Q. The patent doesn't claim any novel ways of
09:48:11 determining whether there's a chemical interaction between

09:48:14 cabozantinib and the excipients used; is that right?
09:48:19 A. That's correct.
09:48:21 Q. It's done using known methods; correct?
09:48:25 A. I'm sorry?
09:48:29 Q. Let me -- that was not a great question. Let me ask
09:48:32 that again.
09:48:33 The patent suggests just using known methods to
09:48:36 make that kind of determination; isn't that right?
09:48:38 A. I don't actually remember the passage related to
09:48:42 that, so we'd have to see it. But it wouldn't surprise me.
09:48:45 Q. Okay. That's consistent with your understanding as
09:48:47 an expert in this field; is that right?
09:48:50 A. (Witness nods head.) Yes.
09:48:51 Q. Now, let's go to the last one, the discovery that the
09:48:54 1-1 impurity is genotoxic, do you see that one?
09:48:57 A. Yes.
09:48:58 Q. Okay. Now, a person of skill in the art would have
09:49:01 been motivated to determine whether any of the impurities in
09:49:06 the compound -- in the composition are genotoxic; correct?
09:49:11 A. Yes. And at somewhere in the development process,
09:49:17 that would be the case.
09:49:18 Q. Okay. A POSA would have wanted to control for
09:49:23 genotoxic impurities in a formulation; right?
09:49:26 A. Yes. Generally you wish to control within certain
09:49:30 limits on genotoxic impurities.

09:49:33 Q. Okay. And genotoxic impurities, I mean, just so --
09:49:38 genotoxic is -- refers to testing that has shown that
09:49:42 something can cause the chromosomal makeup of cells; isn't
09:49:48 that right?
09:49:48 A. It -- well, it's -- a genotoxic impurity is something
09:49:53 that will interact with DNA. And the initial test, of
09:49:59 course, is a bacterial test called the Ames test.
09:50:02 Q. Okay. All right. But the idea is that you're
09:50:06 concerned with the genotoxic impurity -- if something is
09:50:09 genotoxic, it can harm DNA; is that right?
09:50:12 A. Yes; potentially harm DNA in people, though not
09:50:15 always.
09:50:16 Q. Yeah, not always. But you do laboratory tests on
09:50:19 this?
09:50:19 A. That's right.
09:50:20 Q. And genotoxic impurity can cause genetic or
09:50:23 chromosomal damages -- damage. And some of those, some
09:50:27 could be carcinogenic; is that right?
09:50:29 A. That's correct.
09:50:30 Q. And that's why a POSA is particularly interested in
09:50:33 making the determination whether impurities are genotoxic;
09:50:36 is that right?
09:50:37 A. That's correct.
09:50:38 Q. Now, a genotoxic impurity is particularly concerning,
09:50:45 isn't it?

09:50:46 A. Yes.
09:50:48 Q. Because, in the worst case, it could show that
09:50:51 something's carcinogenic; right?
09:50:53 A. Correct.
09:50:54 Q. And so when a genotoxic impurity is identified,
09:51:00 additional investigation is always warranted?
09:51:04 A. Yes.
09:51:06 Q. And the conservative approach, Doctor, is to assess
09:51:09 known genotoxic compounds as potential carcinogens, unless
09:51:14 there's experimental evidence to the contrary; is that
09:51:17 right?
09:51:17 A. Yes.
09:51:18 Q. And obviously -- I mean, a person of skill in the art
09:51:22 is obviously going to make determinations of whether
09:51:28 impurities are genotoxic; that's within the level of skill
09:51:31 in the art, isn't it?
09:51:33 A. Well, they, of course, will look for structures that
09:51:38 they think are concerning and then determine if they're
09:51:40 genotoxic. That is correct.
09:51:42 Q. Okay. That's -- that is what a person of skill in
09:51:44 the art would do, look for structures they think are
09:51:47 concerning?
09:51:47 A. At some point in the development process, that's
09:51:49 correct.
09:51:50 Q. All right. And are -- is that -- your reference to

09:51:53 structures that are concerning, is that also sometimes
09:51:56 called structural alerts?
09:51:57 A. That's right.
09:51:58 Q. Okay. And these structural alerts are known in the
09:52:02 art; is that right?
09:52:03 A. Right.
09:52:05 Q. And you can use structural alerts which you then have
09:52:11 to test out experimentally, but you can use structural
09:52:14 alerts to give you an indication about what the nature of
09:52:17 the impurity is you're dealing with; is that correct?
09:52:20 A. Well, I would -- I would phrase it this way: Use
09:52:23 structural alerts to identify compounds that you're going to
09:52:30 further test via the Ames test, do an experimental test to
09:52:33 determine genotoxicity.
09:52:35 Q. Okay. They're called alerting structures or
09:52:40 structure alerts because they're intended to give an alert
09:52:43 that there might be genotoxicity?
09:52:45 A. That's right.
09:52:46 Q. Okay. And these structural alerts are actually
09:52:50 pretty accurate in predicting whether you'll get
09:52:53 genotoxicity, not 100 percent but they're pretty accurate?
09:52:56 A. I would -- I would kind of differ -- maybe we're
09:52:59 differing about what "pretty accurate" means.
09:53:00 Q. How about 70 percent of the time?
09:53:02 A. Yeah, that's -- yes. 65, 70 percent of the time.

09:53:06 Q. Okay. And then, the next step, if the structural
09:53:11 alerts give you some indication, is to do an Ames test?
09:53:15 A. That's right. In fact, always -- always follow
09:53:19 through with the Ames test.
09:53:20 Q. And that's what a person of skill in the art would
09:53:22 do, is always follow through with an Ames test; is that
09:53:24 right?
09:53:25 A. That's right.
09:53:25 Q. And when you follow through with the Ames test, you
09:53:27 make a determination whether an impurity is genotoxic; is
09:53:30 that right?
09:53:31 A. Right. If it's positive on the AMES test, it -- it
09:53:33 at least appears to be genotoxic.
09:53:36 Q. Okay. And with respect to the regulators, regulators
09:53:44 expect to be told about whether an impurity is genotoxic or
09:53:49 not; is that right?
09:53:50 A. That's correct.
09:53:51 Q. And when the -- when an impurity is genotoxic, then
09:53:58 you take steps in the way you formulate the product; is that
09:54:04 right?
09:54:04 A. You take steps in controlling the level of that
09:54:10 impurity in the formulated product and on storage.
09:54:14 Q. Okay. Now, a POSA would have known that cabozantinib
09:54:21 was potentially genotoxic based on structural alerts; is
09:54:25 that right?

09:54:26 A. Right. Yeah. The quinoline, so you would have --
09:54:29 you would have checked. But that's right.
09:54:31 Q. Okay. So, that's -- you got one step ahead of me,
09:54:35 but 1-1 is something called a quinoline; correct?
09:54:40 A. Right. I mean, cabozantinib is a quinoline. 1-1's a
09:54:43 quinoline. And we're talking about a lot of quinoline
09:54:46 structures here.
09:54:47 Q. Okay. And a quinoline structure is a kind of
09:54:49 chemical structure?
09:54:50 A. That's right.
09:54:51 Q. And it's a kind of chemical structure that you find
09:54:54 in cabozantinib?
09:54:55 A. Yes.
09:54:56 Q. And it's in 1-1?
09:54:57 A. Yes.
09:54:58 Q. And -- and that is a red flag for a person of skill
09:55:02 in the art?
09:55:03 A. It's -- it's -- it's a structure that has to be
09:55:09 furtherly -- further evaluated. Because, of course, as we
09:55:13 know, there are lots of quinolines that are actually drugs.
09:55:17 And there are quinolines that are -- that are genotoxic. So
09:55:22 you have to -- you have to say -- you have to study each
09:55:24 particular quinoline to determine whether it's useful, not
09:55:29 harmful or harmful.
09:55:31 Q. So, to a person of skill in the art, determining that

something's a quinoline, which they could tell -- let me just ask you this first: You can tell if something's a quinoline or not by looking at the chemical structure?

A. That's right.

Q. The drawing on the page. Somebody of skill in the art could say, "That is or is not a quinoline based on that structure"?

A. That's correct.

Q. And when something is a quinoline, you actually -- that is a structural alert right there; isn't that right?

A. That's correct.

Q. So, a person of skill in the art would then take the quinoline and put it in the Ames test; is that right?

A. Yes, again, at some point, that's correct.

Q. Yeah. And the Ames test is -- it's A-M-E-S; correct? Named after a person; isn't that right?

A. That's right.

Q. Bruce Ames; right?

A. Right.

Q. And the Ames test is -- it's really one of the most famous tests out there, isn't it?

A. That's right.

Q. It's widely used?

A. Yes.

Q. Persons of skill in the art know how to use the Ames

09:56:29 test?
09:56:29 A. Yes.
09:56:29 Q. Persons of skill in the art use the Ames test routinely?
09:56:32
09:56:33 A. Yes, I would agree with that.
09:56:35 Q. And persons of skill in the art understand the results they get from an Ames test; is that right?
09:56:38
09:56:40 A. Yes.
09:56:43 Q. Okay. And a person of skill in the art, who had the 1-1 impurity, would determine -- first they determine that the API was potentially genotoxic based on the quinoline structure; isn't that right?
09:56:47
09:56:52
09:56:58
09:56:59 A. You mean the cabozantinib?
09:57:00 Q. Cabozantinib, I'm sorry. Did I say -- let me give you another -- thank you. I'll give you another question. I apologize.
09:57:03
09:57:05
09:57:06 Person of skill in the art would -- would look at the structure for the 1-1 impurity and say, "That's potentially genotoxic because it's a quinoline"?
09:57:11
09:57:15
09:57:19 A. Yes.
09:57:22 Q. And then they would do the Ames test?
09:57:24 A. Yes.
09:57:26 Q. And then they would find out in the Ames test that it's positive?
09:57:28
09:57:29 A. Yes.

09:57:30 Q. And then they would know that, in their formulation, they need to do what they can to minimize that component?
09:57:38 A. That's correct.
09:57:41 Q. Okay. Now, there's no claim made in the patent as to a novel way of determining genotoxicity; right?
09:57:46 A. Correct.
09:57:50 Q. You can use known techniques?
09:57:51 A. Correct.
09:57:52 Q. There's nothing claimed in the patent that's -- that claims a novel way of determining that there's been -- there's an impurity that is genotoxic; is that right?
09:57:56 A. Could you repeat that?
09:58:01 Q. I'm sorry. I think I'm repeating myself, so I'll just move on, Doctor.
09:58:06 Let me move to another subject here -- well, actually, Doctor, while we're here lets -- you talked about the pharmaceutical composition.
09:58:10 MR. LOMBARDI: If you could just put the Doctor's demonstrative PDX-4.15 up.
09:58:13 BY MR. LOMBARDI:
09:58:16 Q. And, Doctor, I'm just focused, for the moment, on the top one there. The essentially free limitation applies to the pharmaceutical composition; is that right?
09:58:17 A. Correct.
09:58:40 Q. Okay. And your testimony was that it's not just the
09:58:43
09:58:47
09:58:49
09:58:49
09:58:58
09:59:02
09:59:07
09:59:10
09:59:11

09:59:16 API that has to be essentially free of the impurity. It's
09:59:20 the entire pharmaceutical composition?
09:59:23 A. That's correct.
09:59:23 Q. Which would include the excipients; correct?
09:59:28 A. Pharmaceutical composition is the final drug product,
09:59:33 which includes the API plus all excipients.
09:59:36 Q. Okay. And the patent doesn't claim any novel way of
09:59:42 coming up with a composition that controls for those
09:59:47 impurities; is that right?
09:59:49 A. Other than disclosing a synthetic process that makes
09:59:54 an API exceptionally low, it doesn't then have an
09:59:59 additional -- anything additional that would control for the
10:00:03 1-1.
10:00:04 Q. And what the -- what the patent actually says is as a
10:00:08 matter of composition, people should use -- persons of skill
10:00:13 in the art should use known techniques; is that right?
10:00:15 A. I'm sorry, composition of?
10:00:17 Q. Pharmaceutical composition. The pharmaceutical
10:00:20 composition in this case, they should use known techniques?
10:00:23 A. I'm sorry. Known techniques to determine the
10:00:27 pharmaceutical composition, is that...
10:00:28 Q. To make it, yes. To make the pharmaceutical
10:00:30 composition.
10:00:30 A. Yes, that's correct.
10:00:32 MR. LOMBARDI: Okay. And if we look at the

'349 patent, which is JTX-4, again. Column 20, please.

THE WITNESS: What is that in your binder or...

BY MR. LOMBARDI:

Q. JTX-4. It's just the patent.

A. Yeah, I'm just -- I'm --

Q. In my binder, it should be -- it's around the middle of the binder I'm told.

A. I got it.

Q. Okay. And tell me when you're to Column 20, Doctor.

A. Yes, I'm there.

Q. Okay. And do you see there's a heading about halfway down that says "Pharmaceutical compositions"; is that right?

A. Yes.

MR. LOMBARDI: And at Line 40, if we could highlight that.

BY MR. LOMBARDI:

Q. You see the patent says, "Various carriers used" -- first of all, it's under the heading "Pharmaceutical compositions"; right?

A. Correct.

Q. It says, "Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions disclosed herein."

10:01:49 Do you see that?
10:01:50 A. Yes.
10:01:50 Q. That's what the patent says?
10:01:52 A. Correct.
10:01:53 Q. And it specifically cites to a couple of sources.
10:01:56 Remington is a very well-known source; is that right?
10:01:59 A. Correct.
10:01:59 Q. And Swarbrick is as well; is that right?
10:02:01 A. Correct.
10:02:02 Q. On Column 21, if you go down to Line 37, it talks -- it's talking -- tell me when you have it, Doctor.
10:02:15 A. Yes.
10:02:16 Q. Okay. You see this is the paragraph that begins "in another aspect."
10:02:21 Do you see that?
10:02:22 A. In another embodiment, yes.
10:02:25 Q. I'm reading from where it says "in another aspect." I just want to make sure we're in the same place.
10:02:31 A. Column 21 you said?
10:02:33 Q. Column 21, Line 37.
10:02:37 A. Oh, 37, yes. "In another aspect," yes.
10:02:40 Q. Got it. Okay.
10:02:41 It says, "In another aspect, the disclosure provides a pharmaceutical composition according to" various

10:02:47 tables.

10:02:48 Do you see that?

10:02:48 A. Yes.

10:02:49 Q. "The compositions are prepared according to methods

10:02:53 available to the skilled artisan."

10:02:55 Do you see that?

10:02:56 A. Yes.

10:02:57 Q. "For example, the tablet formulations are prepared by

10:03:00 combining, blending, and compacting the components of the

10:03:04 tablet compositions."

10:03:07 Do you see that?

10:03:07 A. Yes.

10:03:09 Q. "The capsule compositions are prepared by combining

10:03:11 and blending the components and then placing the blend in a

10:03:15 gelatin capsule."

10:03:16 Do you see that?

10:03:17 A. Yes.

10:03:18 Q. And so, the patent is -- well, let me go to one more

10:03:22 spot.

10:03:22 MR. LOMBARDI: Column 30, please.

10:03:22 BY MR. LOMBARDI:

10:03:28 Q. Tell me when you've got that, Doctor.

10:03:30 A. Yes.

10:03:30 Q. All right. At the very bottom -- the bottom

10:03:33 paragraph under the heading "Stability studies."

10:03:37 MR. LOMBARDI: A little bit farther down. There you go.

10:03:39 BY MR. LOMBARDI:

10:03:39 Q. "Stability studies of pharmaceutical compositions."

10:03:42 Do you see that?

10:03:42 A. Yes.

10:03:43 Q. "The pharmaceutical capsule composition of Tables 3 and 4 were prepared by mixing the ingredients according to processes known in the art."

10:03:51 Do you see that?

10:03:53 A. Yes.

10:03:54 Q. So, what the patent says in those places is that it's up to the person of skill in the art to do those kinds of tasks; isn't that right?

10:04:02 A. Yes.

10:04:04 Q. Okay. All right. Now, I'm ready to move to something else, Doctor. Get a couple things out of the way here.

10:04:17 Let me go to, again, one of your slides, just to make sure we're in the right place.

10:04:32 MR. LOMBARDI: It's the slide number PDX-4.15, please.

10:04:38 BY MR. LOMBARDI:

10:04:41 Q. And the second part of this slide, Doctor, you talked about inherency; correct?

10:04:46

10:04:48 A. Yes.
10:04:50 Q. All right. And we've had a lot of discussion about
10:04:51 inherency, both in your testimony and others; is that right?
10:04:55 A. Correct.
10:04:57 Q. Okay. And so I want to talk a little bit about
10:04:59 inherency. You talked in A about Brown Example 1 allowing
10:05:06 for variation. And I think it was in that context that you
10:05:09 put up PTX-35. And I'm going to --
10:05:15 MR. LOMBARDI: Let me put it up on the screen,
10:05:16 so you can see exactly what we're talking about.
10:05:16 BY MR. LOMBARDI:
10:05:19 Q. Do you remember this document, PTX-0035?
10:05:21 And it should be in your binder if you prefer to
10:05:24 look at that, whichever may way you prefer to do it.
10:05:27 A. Okay. I do remember the document.
10:05:28 Q. Okay. While you're looking, can you tell us what the
10:05:30 document is?
10:05:31 A. Yes. This is the Exelixis' NDA discussing
10:05:39 manufacturing processes.
10:05:43 Q. Okay. An Exelixis doc -- and you -- an Exelixis
10:05:46 document and you used this on your direct examination;
10:05:49 correct?
10:05:49 A. That's correct.
10:05:51 MR. LOMBARDI: And I want to turn to -- Page 16,
10:05:55 I believe, is specifically where you looked. There was a

10:05:59 table there called Table 2.

10:06:01 THE WITNESS: Yes.

10:06:01 BY MR. LOMBARDI:

10:06:02 Q. And you were looking -- these are those four
10:06:06 processes that you described for us in detail yesterday?

10:06:09 A. Yes.

10:06:11 Q. And you highlighted across A-2 because that was Brown
10:06:18 Example 1; right?

10:06:18 A. Correct.

10:06:19 Q. And you noted --

10:06:23 MR. LOMBARDI: Why don't we go ahead and
10:06:24 highlight across there just so we're tracking what you did
10:06:27 before.

10:06:27 BY MR. LOMBARDI:

10:06:27 Q. And you noted that there is a column for the 1 to
10:06:33 1 -- I said 1 to 1 -- it's the 1-1 impurity; is that right?

10:06:37 A. Yes.

10:06:38 Q. And in that column, it shows a range of impurities.

10:06:42 Do you see that?

10:06:43 A. Yes.

10:06:44 Q. Which you pointed out; correct?

10:06:47 A. Correct.

10:06:48 Q. And the range is 35 to 411 parts per million;
10:06:53 correct?

10:06:53 A. Correct.

10:06:54 Q. And you pointed out that 411 is above 200; correct?
10:06:58 A. Correct.
10:06:59 Q. Now, there's nothing on this document that says what
10:07:05 lot is being tested there or what lots are being tested
10:07:10 there; is there?
10:07:13 A. Not -- not in this table, that is correct.
10:07:16 Q. Okay. And have you seen the underlying data for
10:07:22 this?
10:07:22 A. I've seen lots of underlying data and this has to be
10:07:27 using the GTI specific method. And the reason I say that is
10:07:31 because the old methods could not get a number under 200.
10:07:36 Q. Okay.
10:07:36 A. So -- so, I have seen tables for the GTI specific
10:07:41 methods, but the numbers are slightly different from the
10:07:44 numbers reported in this table.
10:07:47 Q. Okay. Well, I guess what I'm referring to is you
10:07:53 don't -- have you seen the lab notebooks where the result
10:07:56 say the 411 result was received?
10:07:59 Have you seen those lab notebooks?
10:08:01 A. I've seen -- again, I've seen -- I think it was put
10:08:09 up in Court already. I've seen a document that had the --
10:08:16 result for the GTI specific method for four batches and it
10:08:21 included numbers that were consistent with these, but not
10:08:24 exactly the same.
10:08:25 Q. Okay. But -- so that's my question.

10:08:28 A. Yeah.
10:08:28 Q. I'm talking about the number -- I want to know what
10:08:32 the underlying documents are for the 411 and you can't help
10:08:36 me with that; is that right?
10:08:37 A. I -- I don't believe -- I mean, if we could look at
10:08:41 that GTI specific test result that was put up in Court
10:08:46 before, I'm not sure -- I don't think it was 411. It was --
10:08:51 it was over 200, but I don't remember what it was. But
10:08:54 that's the only document that I've seen that has the GTI
10:08:59 specific results for A-2 batches.
10:09:06 Q. Okay. So this document doesn't tell us, for
10:09:11 instance -- it doesn't say on the face of the document what
10:09:14 the method was that was used for that -- what the method was
10:09:19 to make that particular lot; correct?
10:09:25 A. I'm sorry. It says it's the A-2 method.
10:09:27 Q. The A-2 method. It doesn't say -- it doesn't say who
10:09:31 made the lots?
10:09:32 A. That's correct.
10:09:33 Q. So, it doesn't say whether it was Regis, for
10:09:36 instance?
10:09:36 A. That's correct.
10:09:38 Q. It doesn't say whether it was -- do you say Girindus
10:09:41 or Girindus?
10:09:42 A. I've been saying Girindus.
10:09:44 Q. Girindus. So I think --

10:09:45 A. Whatever you prefer.
10:09:46 Q. Yeah, I think we're on the same page. So I'll call
10:09:48 it Girindus.
10:09:49 So it doesn't say whether it's Girindus?
10:09:51 A. That's correct.
10:09:53 Q. We would need to see more documents to understand
10:09:57 what the testing is that's being referred to here; correct?
10:10:00 A. Again, we do have the little A next to the results
10:10:09 there that say the GTI -- that it used GTI testing. And so,
10:10:15 the only documents we have are a result that show GTI
10:10:20 testing and we'd have to match those and see how they line
10:10:23 up.
10:10:23 Q. But what we're interested here -- what you testified
10:10:27 about was whether Brown, the Brown example inherently
10:10:34 produces essentially -- impurity essentially -- composition
10:10:39 essentially free of an impurity; is that right?
10:10:41 A. That's correct.
10:10:43 Q. And we can't tell from this, what's here, what the
10:10:47 method of manufacture was?
10:10:48 A. No. I think you're misspeaking again. We know it's
10:10:53 the A-2 process. We don't know which -- which entity
10:11:02 manufactured it, but we know it was manufactured by the A-2.
10:11:05 We know two things looking at this and it's very
10:11:07 clear. We know it's made by the A-2 process and we know it
10:11:10 was tested by the GTI specific method. And because of that,

10:11:15 we know, actually by looking at another document,
10:11:20 that whether it's 35 to 411 PPM or 34 to 350 PPM, we know at
10:11:28 least one batch is above 200 PPM.
10:11:31 Q. Okay. So, just to close this out, and I think
10:11:37 maybe -- you can keep that up for one more second. Got it?
10:11:46 Okay.
10:11:47 I just want to make sure we're clear because we
10:11:50 went back and forth a little bit on that. We don't know who
10:11:54 manufactured these lots?
10:11:55 A. It doesn't -- okay. I'm going to -- I'm going to
10:12:01 phrase that slightly differently. It doesn't say who
10:12:03 manufactured these lots. But as far as I know, in all the
10:12:07 documents we've seen, the only four lots manufactured by the
10:12:11 A-2 process, that were submitted to the FDA, were the three
10:12:17 Regis batches and the one Girindus batch.
10:12:18 Q. It would help if we had the underlying lab notebooks
10:12:22 for this; right?
10:12:22 A. It would be useful, yes.
10:12:24 Q. Okay. Thank you.
10:12:25 So, sir, let me -- you mentioned Girindus, and I
10:12:31 think -- well, let me put up a document you had.
10:12:36 MR. LOMBARDI: PTX-38, please.
10:12:36 BY MR. LOMBARDI:
10:12:43 Q. And that one, it's in -- it might be easier from your
10:12:46 direct binder, it's Tab 11.

10:12:48 A. Okay.
10:12:49 Q. For you to find that.
10:13:01 Tell me when you've got it.
10:13:03 A. Okay. I do.
10:13:04 Q. All right. And I believe it's the second page? The
10:13:09 second page, I believe, was the chart you were looking at,
10:13:13 Doctor.
10:13:14 Does that look familiar?
10:13:15 A. Yes. That's -- that's the chart that makes use of
10:13:22 one -- of the older -- one of the older HPLC methods, but
10:13:25 that's correct.
10:13:26 Q. Okay. And just so that we are all back on the same
10:13:31 page, what you looked at was -- there's a -- below there,
10:13:37 just a little bit lower, for the 1-1 impurity.
10:13:41 Do you see that? And I'll try to highlight it.
10:13:43 There you go. Right there.
10:13:44 That's one of the things you highlighted; right,
10:13:47 Doctor?
10:13:47 A. Correct.
10:13:48 Q. All right. And then you noted that -- that tells you
10:13:54 how much of the 1-1 impurity is detected; right?
10:13:58 A. Well, in this particular method, it tells you if it
10:14:02 was -- if it was above or below 200 PPM, because that's the
10:14:07 limit of detection of this particular test.
10:14:08 Q. Fair enough. And if it's ND, then it's below 200?

10:14:13 A. Correct.
10:14:14 Q. All right. And you noted in the far right column,
10:14:19 that's the Girindus lot; that right?
10:14:24 A. Correct.
10:14:25 Q. And the Girindus lot had something above 200;
10:14:30 correct?
10:14:30 A. Correct.
10:14:31 Q. And the .06 translates to 600 parts per million; is
10:14:35 that right?
10:14:36 A. Correct.
10:14:37 Q. And you said, you pointed out, well look, it's --
10:14:40 it's also got a difference in total impurities, do you see
10:14:44 that?
10:14:45 A. Yes.
10:14:45 Q. And you said the total impurities -- you were
10:14:48 pointing down at the bottom, at the 0.36; is that right?
10:14:52 A. Correct.
10:14:52 Q. Now, so, Girindus comes out differently than Regis;
10:14:58 is that right?
10:14:59 A. It's actually purer than Regis.
10:15:02 Q. Okay. And Regis used exactly the method of example
10:15:09 two; is that right?
10:15:10 A. Well, when you say "exactly," what you mean is they
10:15:15 followed Example 2 of the -- of Brown. But, of course, in
10:15:22 any long synthetic process, there's always variability. So,

10:15:27 they followed Brown within the variability of Brown.
10:15:33 Q. The language used by Exelixis in its IND to describe
10:15:38 how the clinical material was manufactured is identical to
10:15:43 Example 1 Brown; is that right?
10:15:45 A. That's right. But Example 1 of Brown, as we've
10:15:48 heard, says the word about 27 times, which means it's
10:15:52 variable. In fact, all synthetic processes are variable.
10:15:56 Q. Yeah, well -- right. So, sir, about that, the word
10:16:00 -- it's actually the word "approximately."
10:16:01 A. I'm sorry, I should have said "approximately."
10:16:03 Q. And you didn't express any opinion on approximately
10:16:06 before in this case; right?
10:16:08 A. I didn't express an opinion about approximately in
10:16:13 the example, that's true. Though, I did quote from other
10:16:16 parts of the patent. And I also, in my deposition, noted
10:16:19 that synthetic processes vary from batch to batch.
10:16:25 Q. Yeah. You have didn't testify about the word
10:16:26 "approximately," did you?
10:16:27 A. I would agree with that.
10:16:28 Q. Okay. So this is the first you're talking about
10:16:31 approximately?
10:16:31 A. Yes. But I've actually sat in the courtroom and
10:16:34 heard testimony about the term "approximately."
10:16:37 Q. And -- and did you know that the word "approximately"
10:16:40 is used in the '394 patent?

10:16:45 A. In the 39 -- in the '394 patent, probably. I would
10:16:50 expect it is used.
10:16:51 Q. '349, I'm sorry.
10:16:53 A. '349.
10:16:54 And it goes to the fact that synthetic processes
10:16:57 are never exactly the same when done every time. There's
10:17:02 always variability in a synthetic process.
10:17:06 Q. Well, for something --
10:17:06 A. And we don't have a batch record. You know, no one
10:17:12 has actually discussed this in this case. But the reason,
10:17:15 when you manufacture a batch, you have something called a
10:17:18 batch record, is it has -- it has a procedure. And then
10:17:23 next to it somebody has to write in pen what the actual
10:17:27 conditions were.
10:17:28 And so, it says, you know, heat to 70 degrees.
10:17:31 And it might say we heat it to 68 degrees. Right. And so
10:17:36 that's how -- that's how synthetic processes are done.
10:17:40 Unfortunately, we've never seen a batch record for any of
10:17:42 these.
10:17:46 Q. That's -- Exelixis would have those; right?
10:17:48 A. I've never seen a batch record for any of the four
10:17:51 processes.
10:17:51 Q. Okay. Now, "approximately" is used all the time in
10:17:55 pharmaceutical -- in pharmaceutical formulations; correct?
10:17:59 That -- that term is used frequently?

10:18:01 A. I think we're talking about synthetic processes, not
10:18:04 formulations.
10:18:05 Q. Okay. Fair enough.
10:18:06 A. And it's used all the time.
10:18:08 Q. Yeah. And it's used when the quantities in question
10:18:11 do not have to be precise; is that right?
10:18:14 A. Its quantities, its temperature, and its time.
10:18:18 Q. Right. Correct. And they use it when those -- those
10:18:22 parameters don't have to be precise; is that right?
10:18:25 A. They use it to say you want to be in this range, but
10:18:31 they don't have to be exactly the same.
10:18:33 Q. Right. Because there are other places where precise
10:18:37 quantities are used; isn't that right?
10:18:39 A. There are places where the word "approximately"
10:18:44 doesn't appear, and it will say something very precise, I
10:18:47 agree with that.
10:18:48 Q. Right. So the -- and you know that's the case for
10:18:52 the Brown formulation, too, for the -- for Example 1 of
10:18:56 Brown; isn't that right?
10:18:57 A. Yeah. Again, you're using the word "formulation."
10:18:59 Q. I apologize. I apologize. I'll start again so that
10:19:02 you can get a clean question.
10:19:04 A. Yeah.
10:19:05 Q. In Brown, Example 1, the word "approximately" is not
10:19:09 used with respect to all quantities; is that right?

10:19:12 A. That's correct.
10:19:14 Q. Okay. In fact, precise numbers are used with some of
10:19:19 the quantities; is that right?
10:19:21 A. That's correct.
10:19:22 Q. Now, you agree that the Regis process -- well, the
10:19:31 Regis process and Girindus got different results in this
10:19:35 Table 1 that you put up; is that right?
10:19:37 A. I mean, they -- they have different amounts of the
10:19:43 1-1 impurity, certainly, that we talked about. And the
10:19:47 overall purity is different, meaning that the Girindus is
10:19:52 purer than the -- than the three Regis batches.
10:19:55 Q. Okay. So, the Girindus 1-1 is, what, it's at least
10:20:02 three times as much, at least three times as much as what's
10:20:06 detected in the Regis batches; is that right?
10:20:09 A. Yeah, using -- using this HPLC method, of course, we
10:20:14 actually have more accurate data on this, using the GTI
10:20:19 method. And so your -- your multiplier would be better than
10:20:23 three, you know, if we looked at that, but they're certainly
10:20:26 different.
10:20:26 Q. Okay. Well, I'm just using your exhibit; right?
10:20:29 A. Right.
10:20:29 Q. And your exhibit, you said --
10:20:31 A. Yeah.
10:20:32 Q. -- that there's more for Girindus than for the Regis;
10:20:35 is that right?

10:20:36 A. That's correct.
10:20:37 Q. And it's over 200. And it's 600; is that right?
10:20:42 A. In -- in this method, yes. It says 600.
10:20:45 Q. Okay. There were no deviations in the Regis process
10:20:53 from Example 1 in Brown; is that right?
10:20:56 A. I don't believe that's what it says in the document.
10:21:00 I've seen a document at some point that does say there were
10:21:06 deviations. And, actually, Dr. Lepore was cross-examined
10:21:09 about that and was shown a document that was up in Court
10:21:14 that said there were deviations.
10:21:16 Q. Sir, it's correct that the Regis process does not
10:21:19 include deviations from Example I of Brown; correct?
10:21:23 A. You're quoting my deposition because I hadn't seen
10:21:27 that document before. But, of course, I've been sitting in
10:21:29 court and I get to watch what goes on, and there is a
10:21:32 document that says there are deviations, so that's a factual
10:21:36 statement.
10:21:36 You know, I can't not know what I saw in Court.
10:21:39 So, if you want to impeach me with what I said in my
10:21:43 deposition, that's fine. But I learned something in Court,
10:21:45 which I'm aloud to talk about.
10:21:46 Q. Okay. Well, I think you handled it for me, which is,
10:21:48 you testified at your deposition differently than you're
10:21:52 testifying today --
10:21:52 A. Right.

10:21:53 Q. -- on that point; is that right?
10:21:54 A. Right, because I saw something with -- it's a factual
10:21:57 statement that was brought out in Court that I saw, and it
10:22:00 does say that.
10:22:01 Q. Okay. You admit that there are deviations in the
10:22:05 Girindus process, deviations from Brown Example 1?
10:22:09 A. Sure.
10:22:09 Q. And there are a number of things called planned
10:22:14 deviations in Girindus; is that right?
10:22:16 A. That's correct.
10:22:17 Q. And I don't think we have to go through them all, but
10:22:20 you're aware that Dr. Lepore, during his testimony, went
10:22:26 through and pulled out some of those -- or all of those
10:22:29 deviations; is that right?
10:22:30 A. That's correct.
10:22:31 Q. And -- and you don't disagree with the things he
10:22:34 pulled out that were called planned deviations; is that
10:22:37 right?
10:22:37 A. Yes, they're clearly listed in the Girindus document
10:22:40 as planned deviation. And they are deviations.
10:22:43 Q. Okay. And so, we have planned deviations in Girindus
10:22:47 from the Brown Example 1 method; is that right?
10:22:50 A. That's correct.
10:22:51 Q. And when we do those planned -- we test that batch
10:22:56 with the planned deviations, we get different results; is

10:23:00 that right?
10:23:01 A. The results are different, I agree with that.
10:23:03 Q. And the results are well above the 200 parts per
10:23:07 million; is that right?
10:23:08 A. Correct.
10:23:09 Q. And there's a difference in the overall purity; is
10:23:13 that correct?
10:23:13 A. Correct.
10:23:25 Q. And I think I just have one other thing for you,
10:23:29 Doctor. Just one moment. Just a couple of questions.
10:23:44 MR. LOMBARDI: And we can take that down now.
10:23:44 BY MR. LOMBARDI:
10:23:46 Q. You gave some testimony about crystallization and
10:23:50 recrystallization; is that right?
10:23:53 A. Yes.
10:23:53 Q. And you talked about -- you've talked about
10:23:56 crystallization and recrystallization in your reports; is
10:23:59 that right?
10:24:00 A. Yes.
10:24:00 Q. And you talked about it in your testimony; is that
10:24:02 right?
10:24:02 A. Yes.
10:24:03 Q. And crystallization is recommended by the FDA; is
10:24:09 that right?
10:24:09 A. That's right.

10:24:11 Q. For all impurities at or above .1 percent; is that
10:24:15 right?
10:24:16 A. I'm -- I -- I -- it's recommended -- it's recommended
10:24:23 as a final purification step irregardless if they're below
10:24:27 or above 1 percent. It's actually usually the final
10:24:31 purification step in the manufacture of any API purification
10:24:35 step.
10:24:35 Q. And you -- there's a -- are you familiar with the
10:24:38 Robinson reference you cited in your expert report?
10:24:41 A. Yes.
10:24:41 Q. Okay. And in the Robinson reference, you saw that it
10:24:47 says, "Conventional processes such as fractional
10:24:51 crystallization and recrystallization can be used"; is that
10:24:54 right?
10:24:55 A. Correct.
10:24:55 Q. And you agree that those are conventional processes;
10:24:59 is that right?
10:24:59 A. That's correct.
10:25:00 Q. And actually one method for dealing -- you said in
10:25:03 your report, one method for dealing with removing genotoxic
10:25:08 impurities is recrystallization; correct?
10:25:10 A. There's always something that you're -- that you're
10:25:13 interested in doing, but, of course, as I noted, it doesn't
10:25:17 always work.
10:25:17 Q. Okay. As a general rule, crystallization will

improve purity; is that right?

A. As a general rule, it will -- it will improve overall -- overall purity, but won't necessarily improve the purity of each individual component if there are multiple impurities.

Q. Is it true that more often than not in your experience crystallization improves the overall purity of a material?

A. Oh, yeah. Generally it will improve the overall impurity, but, again, might have problem with the specific impurity.

Q. A person of skill in the art would have known how to perform crystallization; is that right?

A. Certainly.

Q. And they would have known how to perform recrystallization?

A. Yes.

Q. And the patents don't claim a novel method of recrystallization; is that right?

A. Correct.

Q. And they don't claim a novel method of crystallization; is that right?

A. Correct.

Q. Okay.

MR. LOMBARDI: No further questions, Your Honor.

10:26:16 THE COURT: All right. So, I think we need to take our morning break here. So we'll take a 15-minute break.

10:26:21 THE CLERK: All rise.

10:26:27 (Recess was taken.)

10:43:45 DEPUTY CLERK: All rise.

10:43:46 THE COURT: All right. Redirect.

10:43:47 Everyone be seated.

10:43:48 MS. PIROZZOLO: Thank you, Your Honor.

10:43:49 REDIRECT EXAMINATION

10:43:49 BY MS. PIROZZOLO:

10:43:49 Q. Could we pull up Plaintiff's Exhibit 38, which is Tab 11, Dr. Myerson?

10:43:57 MS. PIROZZOLO: And go to the page with Table 1.

10:44:01 A. Yes.

10:44:02 Q. Now, you were asked questions about Table 1; correct?

10:44:05 A. Yes.

10:44:07 Q. Now, focusing on the columns for the Regis batches, let's go to the line on total impurities.

10:44:17 Do total impurities vary among the different Regis batches?

10:44:22 A. Yes. They vary significantly between 0.87 percent to 0.54 percent.

10:44:30 Q. Why would that occur if Regis was using the same A-2 process?

10:44:35 A. Again, they're always -- they're -- there's always
10:44:39 variations in synthetic processes so you never get exactly
10:44:42 the same purity or impurity profile when going through any
10:44:47 five-step synthetic process.
10:44:50 Q. Did the invention of the '349 patent include solving
10:44:54 the problem of the genotoxic impurity identified by
10:44:59 Exelixis?
10:44:59 A. It did.
10:45:00 Q. How did Exelixis solve that problem?
10:45:02 A. By developing the B-2 process, that consistently made
10:45:09 cabozantinib (L)-malate with exceptionally low levels of a
10:45:14 1-1 impurity from below 2 to 12 parts per million.
10:45:18 Q. And the B-2 process is the process described in the
10:45:21 '349 patent?
10:45:21 A. Correct.
10:45:23 Q. Have you seen any evidence that adding a
10:45:27 recrystallization step to the Brown process would have
10:45:30 resulted in the claimed purity levels for cabozantinib
10:45:33 (L)-malate?
10:45:33 A. No.
10:45:36 MS. PIROZZOLO: No further questions.
10:45:38 THE COURT: All right. Dr. Myerson, thank you.
10:45:40 You may step down. Watch your step.
10:45:43 MS. PIROZZOLO: May I move for the admission of
10:45:46 Plaintiff's Exhibit 773, Plaintiff's Exhibit 38, PTX-299,

PTX-494, and Joint Exhibit 8.

MR. LOMBARDI: No objection. Your Honor.

THE COURT: All right. Admitted without objection.

(PTX Exhibit Nos. 773, 38, 299, and 494 were admitted into evidence.)

(JTX Exhibit No. 8 was admitted into evidence.)

THE COURT: Dr. Koleng, you're still sworn, all right.

THE WITNESS: Yes, sir.

MR. YURKERWICH: May it please the Court, Kevin Yurkerwich on behalf of Exelixis.

DIRECT EXAMINATION

BY MR. YURKERWICH:

Q. Good morning, Dr. Koleng.

A. Good morning.

Q. You testified earlier in the trial on the issue of infringement of the '349 patent; correct?

A. Correct.

Q. What patents will you address today?

A. The crystalline (L)-malate salt patents.

MR. YURKERWICH: Can we pull up PDX-5.2, please?

BY MR. YURKERWICH:

Q. What is the relationship between these patents?

A. They share a common specification and priority date.

10:47:19 Q. What is that priority date?
10:47:21 A. As highlighted here, January 16, 2009.
10:47:26 Q. At a very high level, can you remind us of your
10:47:30 experience with formulation development?
10:47:31 A. Yes, I'm a pharmaceutical scientist that's
10:47:34 responsible for working with drug substances and drug
10:47:38 products to create useable drug products.
10:47:41 Q. And what is the -- just stepping back a moment, what
10:47:44 is the relationship between these three patents?
10:47:45 A. Again, they all relate to the crystalline (L)-malate.
10:47:49 They share a common specification.
10:47:51 Q. Do you have -- and turning to your experience for a
10:47:53 moment, do you have experience with poorly water soluble
10:47:56 compounds?
10:47:56 A. Yes.
10:47:57 Q. What is your experience?
10:47:58 A. Most of my career has actually been addressing
10:48:02 performance issues associated with what would be called
10:48:06 poorly soluble drugs.
10:48:07 Q. What experience do you have with the preparation of
10:48:09 pharmaceutical salts?
10:48:10 A. I've executed programs throughout my career where we
10:48:14 have evaluated possible salt formation as one way to address
10:48:19 problems with a drug substance.
10:48:21 Q. Do you have any experience with salt screening?

10:48:23 A. Yes, I do.
10:48:24 Q. Could you tell us about your experience?
10:48:25 A. I have executed -- salt screen, first, is a broad
10:48:30 term encompassing a large set of experimentation where we --
10:48:35 in cases where we were interested in pursuing a potential
10:48:38 salt, we would utilize a salt screen type of experiment as a
10:48:43 first step on the road to potentially selecting one, if
10:48:47 available.
10:48:48 Q. How many compounds have you tested in services?
10:48:50 A. Ten.
10:48:51 Q. Have you ever consulted for a pharmaceutical company
10:48:55 for the purpose of identifying the best salt for a
10:48:58 particular drug?
10:48:58 A. Yes.
10:49:00 MR. YURKERWICH: Let's turn to PDX-5.3, please.
10:49:00 BY MR. YURKERWICH:
10:49:04 Q. Looking at the slide, what opinions will you offer
10:49:08 here today?
10:49:08 A. The preparation of pharmaceutical salts is
10:49:11 unpredictable, that the (L)-malic acid would not have been
10:49:15 selected for cabozantinib as a counterion and that
10:49:19 identifying a suitable pharmaceutical salt for development
10:49:22 depends upon a wide range of considerations.
10:49:25 Q. Are you offering an ultimate opinion on validity with
10:49:27 respect to any of the asserted patents?

10:49:29 A. No, sir.

10:49:30 MR. YURKERWICH: Can we turn to PDX-5.4?

10:49:30 BY MR. YURKERWICH:

10:49:34 Q. What is shown here?

10:49:35 A. These are the definitions of a person of ordinary skill in the art proffered by Exelixis and MSN in this case.

10:49:42 Q. Which definition did you apply?

10:49:44 A. Exelixis'.

10:49:45 Q. At the time of the invention, would you have qualified as a person of skill in the art under either of the definitions?

10:49:52 A. Yes.

10:49:54 Q. Would your opinions change depending on which definition was applied?

10:49:57 A. No.

10:49:59 Q. Let's introduce the concepts you'll be addressing very briefly. What is a drug substance?

10:50:04 A. At the highest level we've heard it's the active pharmaceutical ingredient, API. It's the active -- it's the chemical that is attributed with the therapeutic activity.

10:50:15 Q. Dr. Steed discussed salt screening. Is salt screening the only approach to formulating low solubility compounds?

10:50:21 A. No.

10:50:22 Q. What other approaches are there?

10:50:23 A. There's a host of other approaches, including things like nanomilling, micronization, lipid base formulation approaches, solid amorphous dispersion, cyclodextrin complexation, among others.

10:50:37 Q. Were those techniques known in 2009?

10:50:39 A. Yes.

10:50:40 Q. Could those techniques have been used to formulate low solubility compounds?

10:50:43 A. Yes.

10:50:46 Q. What experience do you have with those techniques?

10:50:48 A. I've used them continuously and continue to do so throughout my career.

10:50:53 Q. How would a skilled artisan have evaluated which of those techniques to pursue?

10:50:58 A. Well, they would have had to take a holistic approach in assessing one, what problem they were trying to solve. And then, with an eye toward potential limitations associated with the starting materials, as well as taking into consideration the requirements of the entire product development program.

10:51:18 MR. YURKERWICH: Now, if we turn to PDX-5.5.

10:51:18 BY MR. YURKERWICH:

10:51:22 Q. Can you describe for the Court how a salt is formed?

10:51:25 A. Sure. We've seen this slide several times already. It's the reaction between an acid and a base.

10:51:32 Q. And remind us, what is a salt screen?
10:51:35 A. A salt screen generally is a general term for a set
10:51:38 of -- a set of experiments with very specific conditions and
10:51:42 considerations that is used to evaluate if a salt can be
10:51:46 formed. And if formed, what, if any, physical properties
10:51:50 that material may have.
10:51:52 Q. Now, is a salt -- is every salt screen carried out
10:51:55 the same way?
10:51:55 A. No.
10:52:04 Q. How many counterions are typically tested in a salt
10:52:07 screen?
10:52:07 A. There's no defined number. But I would say you -- it
10:52:12 could be as -- be as many as a few up to several. My
10:52:17 experience has been it could be, like I said, a couple up to
10:52:21 maybe 10 to 20.
10:52:23 MR. YURKERWICH: Now, if we turn to PDX-5.6.
10:52:23 BY MR. YURKERWICH:
10:52:26 Q. Can you -- can we talk about salt formation and how
10:52:30 that can be impacted by different variables?
10:52:33 Can you describe what's on the slide?
10:52:35 A. These are all variables that have to go in that are
10:52:38 all considered when performing what's been termed a salt
10:52:41 screen.
10:52:42 Q. Directing your attention to the top left, how does
10:52:45 the active ingredient affect salt formation?

10:52:50 A. This is quite key. The first assessment a POSA has
10:52:53 to do is to have a reasonable assessment of whether or not
10:52:55 the compound will even form a salt. And if it -- if it has
10:52:58 functionality that may support salt selection or salt
10:53:02 formation, then they have to assess whether or not that's an
10:53:05 acid or a base, for instance. An assessment or an idea of
10:53:10 chemical liability, say stability is also a key -- is also a
10:53:12 key here.
10:53:14 Q. Now, over the course of the trial we've heard the
10:53:17 term pK_a. Could you describe what a pK_a is at a very high
10:53:21 level?
10:53:21 A. Generally, it's a numeric number given to an acid
10:53:25 that allows you to compare whether or not it's a relatively
10:53:29 weak or strong acid.
10:53:31 Q. Do you recall Dr. Steed's testimony that differences
10:53:33 in pK_a can impact salt section?
10:53:37 A. Yes.
10:53:38 Q. What's your response to that testimony?
10:53:40 A. It's only one of many factors that need to be
10:53:42 considered in salt selection.
10:53:44 Q. In 2009, could a skilled artisan have predicted
10:53:48 whether a salt formation would occur based on the
10:53:51 differences between the pK_a, the counterion, and the active
10:53:54 ingredient?
10:53:54 A. No.

10:53:56 Q. What are the reasons for your opinion?
10:53:57 A. First that, again, the -- the differences are only
10:54:02 one consideration. The other is then looking at all the
10:54:05 different considerations here, including the specific
10:54:09 attributes of the starting material.
10:54:11 Q. Now, in 2009, could a person of skill in the art have
10:54:15 predicted the properties of any salt that was produced based
10:54:18 on the differences between the pK_a, the counterion, and the
10:54:21 active ingredient?
10:54:22 A. Not at all.
10:54:25 Q. Let's turn our attention to solvents.
10:54:28 How does the solvent affect salt formation?
10:54:30 A. So the solvents are quite key in a salt screen.
10:54:35 First, the reaction that we just discussed is typically
10:54:37 conducted in solution. So there's a requirement that the
10:54:39 starting material be in solution, as well as the
10:54:42 corresponding counterion. The choice of solvent will also
10:54:48 drive whether, you know, can affect certain properties of
10:54:50 the materials as well. And it also, as we've learned
10:54:54 through testimony, that the choice of salts can impact the
10:54:58 characteristics of whatever solid material you may
10:55:01 ultimately recover.
10:55:02 MR. YURKERWICH: Can I direct your attention to
10:55:05 Tab 2 in your binder, where you'll find PTX-0087?
10:55:10 BY MR. YURKERWICH:

10:55:10 Q. Would you please identify this document?
10:55:13 A. This is the Pharmorphix report, I believe it's been
10:55:18 shared previously, on the salt screen for EXEL-7184.
10:55:23 MR. YURKERWICH: Can we turn to Page 6 where
10:55:25 you'll find Table 2 of this document?
10:55:25 BY MR. YURKERWICH:
10:55:26 Q. What is the name of Table 2?
10:55:28 A. "Solvents used in solvent screen."
10:55:32 Q. And what information is provided in Table 2?
10:55:34 A. So these are -- this is first, it provides a list of
10:55:38 solvents that were evaluated to assess the solubility of the
10:55:43 cabozantinib free base and it also -- and it has a row --
10:55:47 column with the Xs and checkmarks where they've determined
10:55:51 whether or not those solvents exhibited suitable solubility
10:55:54 to continue with the salt -- with this experiment.
10:55:56 Q. Would a person of ordinary skill in the art have been
10:55:59 familiar with the solvents here in Table 2?
10:56:00 A. Yes.
10:56:03 Q. Do all the solvents in Table 2 share the same
10:56:06 properties?
10:56:06 A. Not at all.
10:56:07 Q. How do the properties vary among the solvents?
10:56:10 A. They vary widely in properties, such as melting
10:56:13 point, boiling point, dielectric constant, densities among
10:56:16 others, admissibility with each other for instance.

10:56:19 Q. How many solvents were tested in Table 2?
10:56:28 A. I believe 27.
10:56:29 Q. And focusing on the column with results, how many
10:56:33 solvents were deemed acceptable?
10:56:34 A. Just two, THF, tetrahydrofuran and acetone.
10:56:39 Q. What were the results of the other solvents?
10:56:41 A. They were deemed not -- not suitable or providing
10:56:44 sufficient solubility.
10:56:45 Q. In 2009, how many solvents were available for a
10:56:49 skilled artisan to have used in a salt formation experiment?
10:56:53 A. I think the list could be two times this, maybe
10:56:58 three.
10:56:59 Q. Could a skilled artisan have formed a reasonable
10:57:01 expectation in advance as to which, if any, of the solvents
10:57:05 tested would have been successful?
10:57:06 A. No. That's why we do this work.
10:57:08 MR. YURKERWICH: Now, if we turn back to the
10:57:10 demonstratives about salt formation.
10:57:10 BY MR. YURKERWICH:
10:57:14 Q. Can you discuss experimental conditions and how
10:57:17 experimental conditions can -- can affect salt formation?
10:57:21 A. Of course. Experimental conditions, first, I'll --
10:57:25 well, they typically include things like determining the
10:57:27 concentration of the materials to use, the temperatures at
10:57:31 which the reactions are run, whether or not the samples are

10:57:36 agitated, for instance, and say how long they're -- they're
10:57:38 reacted.
10:57:39 Q. And how, if at all, does an experimental procedure
10:57:43 and the conditions used affect whether a salt will form or
10:57:46 not?
10:57:46 A. They can directly impact it. They can either -- they
10:57:49 can inhibit it, facilitate it, or -- and potentially change
10:57:53 the outcome.
10:57:55 Q. What expectations, if any, would a skilled artisan
10:57:57 have had regarding the conditions necessary for salt
10:58:01 formation?
10:58:01 A. They wouldn't have had an expectation. They would
10:58:04 have had to have started with something and then made
10:58:07 adjustments through the experimentation.
10:58:10 Q. Do you agree with Dr. Steed's testimony that salt
10:58:14 screening involves routine experimentation?
10:58:15 A. No, I do not.
10:58:17 Q. What are the reasons you disagree?
10:58:18 A. As we just discussed, salt screening is a very
10:58:22 generic term that describes a very complex and
10:58:24 individualized set of experiments for a given API.
10:58:27 Q. Can you give us an example from your own experience
10:58:29 where a salt -- a salt screen led to unpredictable and
10:58:33 unexpected results?
10:58:34 A. Of course. We were working with one client on three

structurally related compounds where we were asked to consider salt screening as part of development.

We actually did this work at Pharmorphix, as well. We chose -- we did a very similar assessment. We chose about, I think, 15 or 16 counterions per active ingredient. We executed the study for two of the three. We actually nominated the free form or the starting form because it -- the salts that were formed didn't have any better properties. And for the third, it was only one of two that formed and it showed some beneficial properties that was nominated for progression.

Q. Were the results of your salt screening experiments consistent?

A. No.

Q. Were they predictable?

A. No.

MR. YURKERWICH: Turning to PDX 5.8.

BY MR. YURKERWICH:

Q. At a high level, can you describe what's on the screen and why a person of skill in the art -- well, can you describe what's on the screen?

A. Yeah. So this is a -- this stems from my second point that malic acid would not have been selected as a counterion and that's based on three reasons. First, that malic acid was -- is a weak acid. There are hierarchical

10:59:51 1 approaches that favor stronger, more commonly used acids
10:59:55 2 that a POSA would understand. And, again, malic acid
10:59:58 3 stemming from that is a rarely used acid.
11:00:02 4 Q. Now, before we dig into your opinions here, can we
11:00:06 5 step back and take a moment to talk about the properties of
11:00:09 6 cabozantinib.
11:00:10 7 MR. YURKERWICH: Can we pull up PDX-5.9?
11:00:10 8 BY MR. YURKERWICH:
11:00:14 9 Q. What is shown here?
11:00:15 10 A. This is the chemical structure of cabozantinib base.
11:00:19 11 Q. In 2009, would a skilled artisan have known the
11:00:23 12 aqueous solubility of cabozantinib based on this structure?
11:00:27 13 A. No.
11:00:27 14 Q. Was there any information in the prior art indicating
11:00:31 15 that there were any concerns about the solubility of
11:00:33 16 cabozantinib?
11:00:33 17 A. No.
11:00:35 18 Q. What, if any, information about cabozantinib's pK_a
11:00:38 19 was disclosed in the prior art?
11:00:40 20 A. None.
11:00:42 21 MR. YURKERWICH: Turning to the next
11:00:43 22 demonstrative, PDX 5.10.
11:00:43 23 BY MR. YURKERWICH:
11:00:46 24 Q. In 2009, what, if any, information would a skilled
11:00:49 25 artisan have been able to understand about whether

11:00:52 cabozantinib was an acid or a base based on its structure?
11:00:55 A. As I discussed previously, a POSA would look at the
11:00:59 structure to look for certain functional groups. They would
11:01:03 identify the clinical group that's highlighted in blue and
11:01:06 recognize that it was basic.
11:01:09 Q. Now that we've talked about the properties of
11:01:14 cabozantinib, let's turn back to the opinions on your
11:01:17 earlier demonstrative.
11:01:20 MR. YURKERWICH: And I'd like to turn our
11:01:21 attention to PDX-5.11.
11:01:21 BY MR. YURKERWICH:
11:01:24 Q. What is your first reason why a skilled artisan would
11:01:26 not have been motivated to pursue malic acid?
11:01:28 A. Malic acid is a weak acid.
11:01:32 MR. YURKERWICH: If you turn in your materials
11:01:33 to Tab 3.
11:01:33 BY MR. YURKERWICH:
11:01:38 Q. Let me know when you're there.
11:01:40 A. I'm there.
11:01:41 Q. Could you identify the document marked as PTX-373?
11:01:45 A. Yes. This is the *CRC Handbook of Chemistry and*
11:01:49 *Physics*, edited by David Lide.
11:01:53 MR. YURKERWICH: Would you turn in this exhibit
11:01:54 to Page 6.
11:01:54 BY MR. YURKERWICH:

Q. Could you describe the table of information beginning at Page 6?

A. Yeah. This is a reference on dissociation constants of organic acids and bases.

MR. YURKERWICH: Now, turning to Page 13.

BY MR. YURKERWICH:

Q. I'd like to direct your attention to the third row of the left-hand column.

A. I'm there.

Q. Do you see the reference to quinoline?

A. I do.

Q. What is the pK_a of a quinoline?

A. As shown here, 4.90.

Q. What does that tell you about a quinoline?

A. That it's a weak base.

MR. YURKERWICH: Now, I'd like to direct your attention to the bottom right of Page 7 in this exhibit. And it will be, I think, eight lines from the bottom.

BY MR. YURKERWICH:

Q. Do you find malic acid?

A. Yes.

Q. What is the relevant pK_a of malic acid?

A. The relevant pK_a is 3.40.

Q. What would that have indicated to the skilled artisan about malic acid?

11:03:08 A. That it's a weak acid.
11:03:11 Q. Do you recall Dr. Steed's testimony about the
11:03:13 Rule-of-2?
11:03:14 A. Yes.
11:03:16 Q. Were you aware of the Rule-of-2 before this case?
11:03:18 A. I was generally aware of rules related to -- or
11:03:23 recommendations related to differences in pK_a values. I was
11:03:28 generally aware of differences of two to three or more in
11:03:32 looking at counterions.
11:03:34 Q. Now, if we pull up from the Lide reference, the
11:03:38 entries for malic acid and quinoline, in view of the pK_a
11:03:45 information for malic acid and quinoline, what, if anything,
11:03:49 would the Rule-of-2 have told a POSA about whether or not to
11:03:52 pursue a malic salt of a quinoline-containing compound?
11:03:56 A. Based upon the information available to a POSA in the
11:03:59 literature, it would not have satisfied at least the
11:04:02 Rule-of-2.
11:04:02 Q. Now, does the combination of malic acid and
11:04:05 cabozantinib ultimately satisfy the Rule-of-2?
11:04:07 A. That's my understanding, yes.
11:04:09 Q. Could that have been reasonably expected beforehand?
11:04:12 A. No.
11:04:13 Q. Does a less than two pK_a unit difference mean that a
11:04:16 salt will not form?
11:04:17 A. No.

11:04:17 Q. Does a greater than two pK_a unit difference mean that
11:04:20 a salt will form?
11:04:21 A. No.
11:04:24 Q. Turning to PDX 5.12. What is your second reason why
11:04:29 a person of skill in the art would not have been motivated
11:04:32 to select malic acid in a salt screen?
11:04:34 A. Well, so a POSA would have been aware of hierarchical
11:04:38 approaches that favored stronger, more commonly used acids.
11:04:42 Q. What does the term "hierarchical approach" refer to?
11:04:45 A. A stepwise approach.
11:04:48 Q. Was that approach described in the literature?
11:04:50 A. Yes, it was.
11:04:53 Q. Would you turn in your binder to Tab 4 where you'll
11:04:56 find DTX-167?
11:04:59 A. I'm there.
11:05:00 Q. Would you please identify this document?
11:05:01 A. This is the Bighley reference.
11:05:10 Q. Turning to Page 480 of Bighley -- or Bighley, we'll
11:05:14 go with Bighley -- can you read when we get there -- let me
11:05:18 know when you're at Page 480.
11:05:20 A. 480?
11:05:21 Q. 4 -8 -0.
11:05:23 And I'll direct your attention to the last two
11:05:26 sentences of the first paragraph.
11:05:33 A. Okay, I'm there.

11:05:36 Q. Would you please read the last two sentences of the
11:05:38 first paragraph on Page 480 of Bighley?
11:05:41 A. "Hence, there is a need for a decision tree to create
11:05:45 a prototype thought process whereby a suitable salt form can
11:05:49 be chosen in an efficient and timely manner with few false
11:05:54 starts and the minimum expenditure of resources. The
11:05:58 following decision tree (Figure 1) is proposed to aid in
11:06:01 this selection."
11:06:03 Q. Now, if we turn to the next page, 481 in Bighley,
11:06:09 what's shown here?
11:06:09 A. This is the decision tree that was referenced in the
11:06:14 passage we just read.
11:06:16 Q. How, if at all, does this decision tree and this
11:06:18 excerpt from Bighley compare with your personal experience
11:06:22 with salt screening?
11:06:23 A. It's consistent.
11:06:24 Q. Based on the approach shown in Bighley, would a -- or
11:06:28 which acid would a skilled artisan have begun with?
11:06:30 A. Hydrogen chloride.
11:06:32 Q. And what are the reasons that a skilled artisan would
11:06:34 have begun with hydrogen chloride?
11:06:36 A. As we've heard during testimony, it's a very strong
11:06:39 acid. It's very common in pharmaceutical salts. And the
11:06:44 counterion, the chloride, is not one that would be expected
11:06:47 to react readily with other parts of the compound.

11:06:52 Q. Based on the approach shown in Bighley, where would a skilled artisan have turned after hydrogen chloride?
11:06:56
11:06:59 A. As we look down, to other mineral acid salts.
11:07:04 Q. And what are mineral acid salts?
11:07:08 A. There's salts of mineral acids where mineral acids are also -- often called inorganic acids.
11:07:10
11:07:13 Q. What are inorganic acids?
11:07:15 A. Those that typically don't include carbon.
11:07:22 Q. Can you please provide an example or two of some inorganic acids or mineral acids?
11:07:25
11:07:28 A. Sure. Other examples include hydrogen bromide, for instance. Sulfuric acid, nitric acid, phosphoric acid, among others.
11:07:32
11:07:36
11:07:37 Q. What are the reasons a skilled artisan would have considered inorganic acids or mineral acids at this stage in the decision tree?
11:07:39
11:07:42
11:07:43 A. First, they're still very strong acids. The other reason would be that they didn't find -- they weren't either able to form a salt with the hydrogen chloride. Or any resulting salt didn't display any beneficial properties.
11:07:47
11:07:51
11:07:54
11:07:59 Q. Now, I'd like to you to turn in Bighley to Page 486. It's a little bit further into the reference. And I'll direct your attention to the paragraph under preparation of organic salts.
11:08:03
11:08:09
11:08:13
11:08:15 Do you see that section?

11:08:15 A. I do.
11:08:16 Q. Do you recall Dr. Steed's testimony that a skilled
11:08:18 artisan would have disfavored inorganic acids based on this
11:08:22 excerpt from the Bighley reference?
11:08:23 A. I do.
11:08:24 Q. What's your response to that testimony?
11:08:25 A. I believe that it's misplaced. If we consider the
11:08:29 context of this entire paragraph, the POSA would recognize
11:08:34 that it's specifically addressing an issue associated with
11:08:37 salt selection for injectable drugs, those that are
11:08:41 typically administered as solutions and injected directly
11:08:45 into the body.
11:08:46 Q. Are -- this is straightforward, but are oral dosage
11:08:50 forms injectable drugs?
11:08:51 A. No.
11:08:51 Q. Is Cabometyx an injectable drug?
11:08:54 A. No.
11:08:58 Q. Now, if we turn back to the decision tree, which I
11:09:01 believe is on Page 481. As part of the hierarchical
11:09:09 approach, described in Bighley, would a skilled artisan have
11:09:13 considered organic acids?
11:09:14 A. Potentially.
11:09:15 Q. Under what circumstances would a skilled artisan have
11:09:18 considered organic acids?
11:09:19 A. Well, we have, one, if you're developing an

injectable product. Number two, you weren't able to obtain either salts with the inorganic acids. Or there's any salt that was obtained didn't have desirable properties.

Q. Can you please provide an example or two of an organic acid?

A. Sure. These would be things like maleic acid, methane sulfonic acid, for instance.

Q. Now, what type of organic acids would have been considered at this stage in the decision tree?

A. Stronger ones, like the examples I gave.

Q. And why is that?

A. Again, because you're still looking for stronger acids.

Q. Would you turn to PDX 5.13, please?

What's displayed on the demonstrative?

A. So organic acids have limitations in their use as counterions. This is a list of four that a POSA would need to consider.

Q. Could you describe some of the limitations?

A. Sure. They're usually weaker. They have higher pK_as than the inorganic acids. They themselves have reduced aqueous solubility. They typically include multiple functional groups that can complicate the chemistry or have side reactions, things of that nature. And they usually have larger molecular weights, which add bulk to the API

11:10:42 which can create issues in formulating products.
11:10:45 Q. Have organic acids been used in pharmaceutical salts?
11:10:48 A. Yes, they have.
11:10:49 Q. Turning to PDX-5.14. What were the most common
11:10:54 organic acids used?
11:10:56 A. As shown here, mesylate, maleate, the citrate,
11:11:00 tartrate, and acetate.
11:11:02 Q. What type of acid is malic acid?
11:11:05 A. Organic.
11:11:06 Q. Is malic acid included in the list of the five most
11:11:11 common organic acids on PDX-5.14?
11:11:14 A. No.
11:11:16 Q. Did you hear Dr. Steed's testimony that malic acid
11:11:18 would have been favored over other potential acids because
11:11:21 it was identified as generally recognized as safe?
11:11:24 A. I recall that testimony.
11:11:26 Q. Have you ever considered a GRAS designation in
11:11:30 identifying a counterion for selection in a salt screen?
11:11:32 A. No.
11:11:33 Q. What are the reasons for that?
11:11:34 A. Mainly that the GRAS designation, GRAS regulations
11:11:38 are related to food additives of the pure materials. It's
11:11:42 really not directly applicable to pharmaceuticals. The
11:11:46 other consideration is that the combination of a counterion
11:11:50 and the active ingredient are qualified together. So that

it's the safety and toxicity of the salt, not the starting counterion acid in this case.

It's a particularly -- particularly interesting to note that the two most common anions listed here, actually their corresponding acids are non-GRAS designated.

Q. Now, turning to PDX-5.15.

Do you agree with Dr. Steed that malate salts were commonly used in pharmaceutical compounds?

A. No, I do not agree with him.

Q. What are the reasons you disagree?

A. Mainly that the information that -- part of what's already been put up during this trial shows that it was only rarely used.

Q. Now, I want to direct your attention to -- back to Tab 4 in your materials, which is DTX-167, the Bighley reference we discussed earlier.

A. Yes, sir.

Q. Can you turn to Page 453?

A. I'm there.

Q. And turning your attention to the second-to-last paragraph on the page, what information is addressed in Table 1 in Bighley?

A. "Salt forms that have been clinically evaluated in humans or were commercially marketed through 1993."

Q. Now, turn the page to Pages 454 and 455.

11:13:12 Do you find Table 1?
11:13:13 A. I do.
11:13:15 Q. What is the name of Table 1?
11:13:16 A. Anionic pharmaceutical salt forms currently in use.
11:13:21 Q. And what is an anionic pharmaceutical salt form?
11:13:25 A. So this is a salt where the active ingredient is a
11:13:29 base and the corresponding counterion comes from an acid,
11:13:33 like cabozantinib (L)-malate.
11:13:36 Q. Have you analyzed the salts in Table 1?
11:13:38 A. I have.
11:13:40 Q. Can you turn to Tab 5 in your materials, where you'll
11:13:43 find PTX-782?
11:13:48 Can you please identify this document?
11:13:50 A. Yeah, so this is the data from Table 1 that we just
11:13:55 reviewed. Table 1 presented it alphabetically. This table
11:14:00 that shows the -- the same salt, the same anionic salts but
11:14:07 ranked by frequency of occurrence.
11:14:09 Q. So, I think you may have just said two different
11:14:12 things.
11:14:12 How are the salts arranged in this table on
11:14:15 PTX-782?
11:14:17 A. By order of occurrence. So, from most current to
11:14:21 least current, least -- most frequent to least frequent.
11:14:24 Q. Now, focusing on the anionic salts in PTX-782, how
11:14:30 many salts are listed here?

11:14:31 A. I believe 113.

11:14:36 MR. YURKERWICH: Mr. Lee, can you write the number 113 on the -- PTX-782?

11:14:37 BY MR. YURKERWICH:

11:14:45 Q. Are these 113 salts all pharmaceutically acceptable salts?

11:14:49 A. Yes.

11:14:52 Q. Now, I want to direct your attention to the bottom left of the table. And focus your attention on the malate salt.

11:14:54 How often was the malate salt used in pharmaceutical -- anionic pharmaceutical salts?

11:15:02 A. As highlighted here, it's 0.26 percent.

11:15:07 Q. Now, coming back and taking a look at the whole chart, how many anions used in 1 percent or fewer pharmaceutical salts?

11:15:10 A. I believe it's about 98.

11:15:13 Q. Would you turn in your materials to Tab 6. We're going to take a quick look at another reference that's been discussed. You'll find DTX-177.

11:15:18 Would you please identify that document?

11:15:19 A. This is the Paulekuhn reference that's been in evidence.

11:15:29 Q. Now, if you look on -- farther down on the first page of this reference, do you see the section "Study Design"?

11:15:34

11:15:36

11:15:40

11:15:41

11:15:46

11:15:46

11:15:50

11:15:52 A. I do.
11:15:57 Q. What kind of compounds were studied in the Paulekuhn
11:16:00 reference?
11:16:00 A. So as they note here, they studied chemically
11:16:03 well-defined APIs. They would be drug substances. They
11:16:06 represent about 1,300 from the FDA Orange Book at the time.
11:16:11 Q. Now, turning two pages forward to Page 6667, do you
11:16:16 find Table 2.
11:16:17 A. I do.
11:16:19 Q. What is the title of Table 2?
11:16:20 A. "Distribution of Anions Used in APIs of Category I."
11:16:27 Q. Can you remind us, what is Category I?
11:16:30 A. Yes. These would be the same sorts of anionic
11:16:33 pharmaceutical salts we just discussed. The API is basic.
11:16:36 The counterion comes from an acid.
11:16:39 Q. Now, focusing on the first column in Table 2 and
11:16:43 looking at the malate entry, how often was the malate salt
11:16:48 used in terms of the overall sample studied?
11:16:51 A. 0.4 percent. I believe you have the -- there we go.
11:16:56 Q. And if you look to the right-hand side of the
11:16:59 column -- or the right -- far right column in Table 2, how
11:17:04 often was the malate salt used between 2002 and 2006?
11:17:08 A. Once. It was roughly 3 percent of 36 drugs approved
11:17:13 during that period.
11:17:14 Q. Did you reach any conclusions based on your review of

11:17:16 the Bighley and Paulekuhn references?
11:17:19 A. Yes, that the malate salt is only rarely used.
11:17:22 Q. How does that compare with your experience?
11:17:24 A. It compares correctly. It's not one I've ever
11:17:28 considered.
11:17:29 Q. How many of your salt screen projects included malic
11:17:32 acids among the acids tested?
11:17:34 A. None.
11:17:36 Q. By 2009, how many acids were known and could have
11:17:39 been considered by a skilled artisan in attempting to form a
11:17:42 pharmaceutically acceptable salt?
11:17:44 A. Bighley lists at least 113.
11:17:49 Q. Can you please turn to Tab 7 in your binder where
11:17:52 you'll find DTX-287? Would you please identify this
11:17:57 document?
11:17:58 A. This is the Sutent product label.
11:18:03 Q. What is Sutent?
11:18:05 A. It's a pharmaceutical composition comprising
11:18:08 sunitinib malate.
11:18:10 Q. Do you recall Dr. Steed's testimony that a skilled
11:18:12 artisan would have been motivated to use malic acid because
11:18:15 the active ingredient in Sutent is in the form of malate
11:18:20 salt?
11:18:20 A. I recall that.
11:18:22 Q. What's your response to that?

11:18:24 A. I disagree. Although Sutent has a similar
11:18:29 indication, a POSA doesn't select counterions based on
11:18:34 indication. It's based upon the actual attributes of the
11:18:39 chemical that they're studying.
11:18:40 Q. Well, let's talk about some of those attributes. I
11:18:43 want to direct your attention to the second paragraph on the
11:18:44 first page of DTX-287. Would you please read the first
11:18:48 sentence in that paragraph?
11:18:49 A. "Sunitinib malate is a yellow to orange powder with a
11:18:54 pK_a of 8.95."
11:18:57 Q. How do the chemical properties of sunitinib compare
11:19:01 to cabozantinib?
11:19:02 A. With this pK_a, sunitinib would be would have been
11:19:08 considered a strong base even relative to cabozantinib.
11:19:11 Q. And what are the consequences of that difference.
11:19:15 A. Well, first, the choice of acids that one would
11:19:18 consider would be different. And then the like -- the
11:19:23 likely outcomes would be different.
11:19:28 Q. Turning to PDX-5.16, what is your third opinion
11:19:32 you're offering here today?
11:19:33 A. Pharmaceutical development is a complex process.
11:19:38 There has to be a range of considerations that go into
11:19:42 identifying the pharmaceutical salt, if selected, that
11:19:46 ultimately goes into the final products.
11:19:48 Q. Can you give us some examples of considerations or

11:19:52 1 factors in development that would have been considered in
11:19:55 2 the course of salt development in 2009?
11:19:58 3 A. Yes. I believe we've heard several already. They
11:20:02 4 include elements such as bioavailability, solubility,
11:20:06 5 dissolution, physical and chemical stability, the PK
11:20:11 6 potentially resulting from that particular salt.
11:20:14 7 Manufacturability is key as well, among others.
11:20:17 8 Q. Now, let's assume the skilled artisan wanted to make
11:20:19 9 a salt with a favorable solubility. Could a skilled artisan
11:20:23 10 have had a reasonable expectation as to what salt would give
11:20:26 11 the best solubility?
11:20:28 12 A. No.
11:20:30 13 Q. In your experience, does making a salt result in
11:20:33 14 improved solubility relative to the free form of the active
11:20:37 15 ingredient?
11:20:37 16 A. No. Not always.
11:20:40 17 Q. Dr. Steed testified that a skilled artisan would have
11:20:42 18 been motivated to pursue a malate salt of cabozantinib to
11:20:45 19 improve solubility. What impact did forming a malate salt
11:20:48 20 actually have on solubility of cabozantinib?
11:20:51 21 A. As we've learned, the solubility in biorelevant media
11:20:57 22 which is more predictive of bioavailability, was not
11:21:00 23 greater.
11:21:00 24 Q. How, if at all, does that bear on your opinion
11:21:03 25 regarding reasonable expectation of success?

11:21:05 A. Again, I don't believe it supports a POSA having a
11:21:09 reasonable expectation of success.
11:21:10 Q. What is your overall response to Dr. Steed's
11:21:13 testimony that it would have been obvious to prepare the
11:21:17 (L)-malate salt of cabozantinib as part of a salt screen?
11:21:19 A. First, I don't think, from everything we just
11:21:22 discussed, they wouldn't have been motivated to evaluate it.
11:21:26 And they wouldn't have had a reasonable expectation of
11:21:29 success.
11:21:30 MR. YURKERWICH: Thank you, Dr. Koleng. I have
11:21:32 no further questions for you at this time.
11:21:33 Your Honor, Exelixis would move to admit
11:21:36 PTX-373, PTX-782, and DTX-287.
11:21:43 MR. MATHAS: No objection, Your Honor.
11:21:44 THE COURT: Admitted without objection.
11:21:46 (PTX Exhibit No. 373 and 782 were admitted into
11:21:46 evidence.)
11:21:46 (DTX Exhibit No. 287 was admitted into
11:21:52 evidence.)
11:21:52 MR. MATHAS: Your Honor, may we hand up a cross
11:21:54 binder?
11:21:55 THE COURT: Sure.
11:22:05 THE WITNESS: Are you going to reference
11:22:06 anything in here? Otherwise, I'll put it on the floor.
11:22:09 MR. MATHAS: I may. So go ahead and keep it

handy. This other one is small.

THE WITNESS: Thank you, sir.

CROSS-EXAMINATION

BY MR. MATHAS:

Q. All right. Good morning, Dr. Koleng.

A. Good morning, sir.

Q. Now, as of 2009, the basic principles associated with salt formation reactions were understood; isn't that true?

A. I believe acid base reactions were reasonably understood.

Q. All right. And by 2009, salt screening was a known technique for identifying salt forms of compounds; true?

A. It's a -- it's a way to identify salt forms, yes.

Q. All right. And it was a known technique as of 2009; right?

A. Yes.

Q. And you yourself, as of 2009, were involved in doing salt screening; right?

A. Correct.

Q. And as of 2009, a salt screen would have been a tool in the formulator's toolbox; isn't that true?

A. Yes.

Q. All right. Now, I want to -- you gave some opinions about variables -- excuse me -- variables that would be considered in setting up a salt screen.

11:23:24 Do you recall that?
11:23:25 A. I do.
11:23:25 Q. And you testified, I believe, that salt screening is
11:23:32 unpredictable because you couldn't predict or guarantee the
11:23:35 results of the salt screen; is that your testimony?
11:23:38 A. It's unpredictable. Yes.
11:23:41 Q. Okay. And because you say it's unpredictable, you
11:23:44 say you can't guarantee that a salt will form; right?
11:23:47 A. Correct.
11:23:48 Q. And you say you can't guarantee what the properties
11:23:51 of the salt will be in advance; right?
11:23:53 A. Correct.
11:23:55 Q. Okay. Now, a person of ordinary skill in the art
11:23:58 would have been able to assess these variables that you
11:24:01 talked about and select suitable conditions to conduct a
11:24:05 salt screen, wouldn't they?
11:24:06 A. I believe they would have the capability to, you
11:24:12 know, set up the experiment, react to the data, make the
11:24:16 necessary changes on a trial and error basis, yes.
11:24:19 Q. And they would have been able to do that as of 2009,
11:24:21 wouldn't they?
11:24:22 A. Yes.
11:24:24 Q. You also talked about a hierarchical order of
11:24:30 proceeding through a salt screen.
11:24:31 Do you recall that?

11:24:32 A. I do.
11:24:33 Q. And you pulled up the Bighley reference, and there
11:24:35 was a decision tree in there that you talked about; right?
11:24:38 A. Correct.
11:24:40 Q. Now, but you agree, don't you, Dr. Koleng that a
11:24:43 person of ordinary skill in the art as of 2009 would not
11:24:46 have been beholden to following prior art decision trees in
11:24:51 a hierarchical order in setting up a salt screen?
11:24:55 A. Correct.
11:24:56 Q. All right. You also talked about the fact that malic
11:25:01 acid was a weak acid; right?
11:25:02 A. Correct.
11:25:03 Q. Okay. Now, you agree that there are a significant
11:25:06 number of organic acids that have been used to make
11:25:10 pharmaceutically acceptable salts, don't you?
11:25:12 A. Bighley shows a fair number, yes.
11:25:16 Q. All right. And you highlighted a couple of those in
11:25:18 your testimony; right?
11:25:19 A. Correct.
11:25:20 Q. Okay. And you also talked a little bit about the
11:25:32 Tong's Rule-of-2 and the use of pK_a during your direct;
11:25:36 right?
11:25:36 A. I don't think I specifically addressed Tong's
11:25:39 Rule-of-2. I said I acknowledge that I heard Dr. Steed's
11:25:43 testimony and I was aware of the principle.

11:25:46 Q. Okay. So you're aware of the principle of using pK_a for selecting salts for a salt screen; right?

11:25:49 A. As one variable, yes.

11:25:51 Q. And that was something you were aware of back in 2009; right?

11:25:53 A. Correct.

11:25:55 Q. And something that the POSA would have been aware of back in 2009?

11:25:56 A. I believe so, yes.

11:25:57 Q. Okay. Now, it's true, isn't it, Dr. Koleng, that a POSA could have determined the pK_a of a compound by performing a titration test; right?

11:25:59 A. Potentially, yes.

11:26:00 Q. And that's a routine test that POSAs like yourself as of 2009 would have been able to perform and interpret; right?

11:26:01 A. It was a test in use at that time, yes.

11:26:05 Q. Okay. Now, you showed us an entry on quinolines in connection with their pK_a; is that right?

11:26:09 A. Correct.

11:26:11 Q. And you didn't show us an entry on the pK_a of cabozantinib; isn't that right?

11:26:13 A. That's correct. It wasn't available at the 2009 time.

11:26:17 Q. Right. And so when you said that the quinolines

11:26:43 wouldn't have fallen within the pK_a of a Rule-of-2, that was
11:26:49 quinolines generally. You weren't saying that cabozantinib
11:26:52 wouldn't fall within the Rule-of-2; right?
11:26:53 A. That's correct. It's what would have been available
11:26:56 without experimentation.
11:26:58 Q. Right. And you're not disputing, are you, sir, that
11:27:01 cabozantinib falls within the Rule-of-2?
11:27:03 A. Ultimately, correct.
11:27:05 Q. Okay. And I think you said this, but just so the
11:27:17 record is very clear, you agree, Dr. Koleng, that malate
11:27:22 salt is a pharmaceutically acceptable salt; right?
11:27:25 A. Yes.
11:27:26 Q. And you agree that as of 2009, malate salt had been
11:27:30 used in FDA-approved drugs; right?
11:27:32 A. A small number, yes.
11:27:35 Q. They had been used in FDA-approved drugs since at
11:27:37 least the 1970s; true?
11:27:39 A. I believe there's one going that far back, yes.
11:27:41 Q. Okay. And malate salt had been used in FDA-approved
11:27:44 drugs in the decade leading up to the priority date here;
11:27:47 right?
11:27:47 A. In the small numbers that I showed, yes.
11:27:50 Q. Okay. Now, there was some discussion about malic
11:27:53 acid and whether it was GRAS or not.
11:27:56 Do you recall that?

11:27:56 A. I do.
11:27:57 Q. And that's G-R-A-S, generally recognized as safe;
11:28:01 right?
11:28:01 A. Right.
11:28:02 Q. And I think what you said on your direct was, "Well,
11:28:06 GRAS isn't relevant because that's just something that
11:28:08 matters for food additives"; is that right?
11:28:10 A. No. I said that GRAS status is specific for foods
11:28:14 and it's not a consideration that I've ever taken into
11:28:18 account.
11:28:18 Q. Okay. Now, but persons of ordinary skill as of 2009
11:28:22 did take into account the GRAS status of counterions in
11:28:26 selecting salts for salt screening. Didn't they?
11:28:28 A. I don't think I'd agree with that generally.
11:28:31 Q. Okay. Now -- well, let me ask you this: As of 2009,
11:28:35 isn't it true that the literature taught the GRAS status of
11:28:38 counterions and to consider it in selecting salts for
11:28:42 development?
11:28:43 A. So they have GRAS designation like in some of the
11:28:47 experiment -- like in some of the literature that's been put
11:28:49 up? It was -- it wasn't -- not every salt was GRAS. I
11:28:54 think it's one of consideration, if it was important to a
11:28:56 POSA. But it's obviously not -- it doesn't -- it's not a
11:29:01 definitive no if it's not GRAS designated.
11:29:04 Q. All right. So let's look at -- let's look at some of

that literature then.

MR. MATHAS: Can we pull up PTX-610, please?

BY MR. MATHAS:

Q. And we'll put it on the screen here, Dr. Koleng.

This is the Stahl reference that's been discussed --

MR. YURKERWICH: Your Honor.

THE COURT: Yes.

MR. YURKERWICH: We object. The document now before the witness isn't in the cross binder.

MR. MATHAS: We can hand up a copy, Your Honor, if we may.

THE COURT: Okay.

MR. MATHAS: It's in a bunch of these other binders. I didn't know we were going to talk about it, but here we are.

BY MR. MATHAS:

Q. All right. So this is the Stahl reference, Dr. Koleng?

A. Is that a question or a statement?

Q. Either. That's what it is; right?

A. Yes.

Q. And you were in the courtroom for Dr. Steed's testimony about this?

A. Yes.

11:29:49 Q. And you referenced in an answer a moment ago that
11:29:51 there might be some tables that had GRAS status indicated;
11:29:55 right?
11:29:55 A. Yes.
11:29:55 Q. Okay. Now, this -- this reference is -- it's in the
11:29:59 *Handbook of Pharmaceutical Salts*; right?
11:30:01 A. I'm sure we're going to get to that.
11:30:05 Q. All right. It's not the *Handbook of Food Additives*;
11:30:09 right?
11:30:09 A. Agreed.
11:30:10 Q. Okay. And let's go back to one of the tables that
11:30:13 Dr. Steed showed that maybe you were -- you were referring
11:30:17 to a moment ago.
11:30:18 MR. MATHAS: And I think we can find that back
11:30:20 in Table 2, which begins on Page 336 of the exhibit.
11:30:33 THE WITNESS: So 336?
11:30:34 BY MR. MATHAS:
11:30:34 Q. Well, it's -- it's the Bates page 33 -- or the
11:30:37 Exhibit Page 336, Document Page 334.
11:30:40 A. I'm looking for the document page. Yeah.
11:30:46 Q. The page number on the bottom middle of the page has
11:30:49 the 336.
11:30:50 A. All right.
11:30:56 Q. Did you find Table 1 there?
11:30:57 A. Well -- oh, you're -- it's 334 on the document.

11:31:05 Yes, I'm there.
11:31:06 Q. Okay. So Table 1 starts there on -- on Exhibit
11:31:12 Page 336. And then if you go forward, Table 2 starts on
11:31:17 Exhibit Page 338.
11:31:19 Are you with me?
11:31:20 A. Table 2 on 336 you said. Okay. Yeah.
11:31:25 Q. All right. And Table 2 is a list of acids sorted by
11:31:29 increasing pK_a value. That's been looked at; right?
11:31:33 A. The table says "Acids sorted by increasing pK_a
11:31:38 value."
11:31:38 Q. Okay. And in this list of acids in this textbook on
11:31:43 pharmaceutical salts, in the far right-hand there's a column
11:31:47 on GRAS status; right?
11:31:48 A. I see that.
11:31:50 Q. All right. And that's information that would have
11:31:51 been available to the person of ordinary skill in the art as
11:31:55 of 2009; right?
11:31:57 A. This reference would suggest so.
11:31:59 Q. Okay. And persons of ordinary skill in the art could
11:32:03 have used this information about whether or not a compound
11:32:06 was GRAS or not in determining counterions to include in a
11:32:13 salt screen; right?
11:32:14 A. If they were concerned about the GRAS status, yes.
11:32:17 MR. MATHAS: Okay. And if we can go to Page 334
11:32:20 of the exhibit.

11:32:20 BY MR. MATHAS:

11:32:27 Q. You see there there's a section GRAS and ADI?

11:32:32 A. Okay.

11:32:32 Q. All right. And so --

11:32:34 A. Sorry. What page?

11:32:37 Q. Your -- it's?

11:32:37 A. Now we're in text. I thought you said the table. I'm sorry. Oh, here we go. Okay.

11:32:41 Q. Yeah. There's a section here, GRAS and ADI.

11:32:45 Are you with me?

11:32:46 A. I do.

11:32:47 Q. Okay. And this is a section on GRAS in this -- in this text on the *Handbook of Pharmaceutical Salts*; right?

11:32:54 A. Okay.

11:32:56 Q. And so this -- this textbook that would have been known to the POSA about selecting pharmaceutical salts includes a section on GRAS; right, Dr. Koleng?

11:33:05 A. Yes.

11:33:07 Q. Actually -- oh, sorry.

11:33:07 A. As shown here.

11:33:08 Q. And look at second sentence there.

11:33:11 MR. MATHAS: Let's call that out.

11:33:11 BY MR. MATHAS:

11:33:12 Q. This textbook says that, "Some substances may be considered unobjectionable because they are used profusely

11:33:18 in food processing"; right?
11:33:21 A. Okay.
11:33:22 Q. That's what it says. You agree?
11:33:23 A. I see the words. I agree with the words.
11:33:25 Q. And you --
11:33:26 A. I agree the words are there.
11:33:28 Q. Right. And this is talking about substances being
11:33:32 unobjectable for use as pharmaceutical salts because of
11:33:34 their GRAS status; isn't that right?
11:33:37 A. No. I'm going to say that it's -- some substance
11:33:41 here refer to the acid not the pharmaceutical salt.
11:33:44 Q. Okay.
11:33:45 A. Which includes the combination of the API and the
11:33:48 base and the salt.
11:33:49 Q. Okay. So, the -- the acids may be considered
11:33:54 unobjectionable in the salt screen because of their GRAS
11:33:57 status. That's what it's teaching?
11:33:59 A. Well, they would be unobjectable on themselves, how
11:34:04 they're used in a salt screen, et cetera, within it.
11:34:07 Ultimately, the resulting drug substance would still have to
11:34:09 be assessed.
11:34:10 Q. All right. Now, in -- and you're not disputing that
11:34:12 malic acid was known and recognized as GRAS as of the
11:34:16 priority date here; right?
11:34:17 A. No, I'm not.

11:34:19 MR. MATHAS: No further questions.

11:34:20 THE COURT: Dr. Koleng --

11:34:24 THE WITNESS: Yes, sir.

11:34:25 THE COURT: -- if you had a base and you didn't know what its pK_a was, how much effort goes into determining that?

11:34:34 THE WITNESS: It can be quite a bit. So, you can start with what's known about the functionality and then you can then work from there. So, that gives you an idea of the -- functionality gives you an idea where to start and then I don't disagree that you could run experimentation to identify the pK_a ultimately. Yeah, the ionization constant for that base.

11:34:59 The issue would be is that it depends on the conditions under which it's conducted and the -- and the test to do it. So, you would still have to do enough experimentation to gets an accurate value, so there's -- you may be able to improve the estimate, but work would continue to try to fine tune that.

11:35:15 THE COURT: So if you wanted to do that and you had a fully equipped lab and you were a person of ordinary skill, how many days, weeks, months, years would you set aside to do that?

11:35:26 THE WITNESS: I would say a couple weeks.

11:35:31 THE COURT: All right. The solvent streams

where if you had, again, your base and you wanted to find out what solvent would work with it, how long does it take to do the solvent screening?

THE WITNESS: The solvent screenings can take on the order of a couple weeks as well because you have to select the solvent, you have to prep the samples, have analytical methodology in order to assess the amount that is dissolved, prepare the samples, analyze the samples, and then get the results.

THE COURT: All right.

MR. YURKERWICH: No redirect, Your Honor.

THE COURT: Okay. All right. Dr. Koleng, thank you. You're done. Please watch your step.

THE WITNESS: Thank you, sir.

MR. PRUSSIA: Your Honor, Plaintiffs call Dr. Bernhardt Trout.

THE COURT: All right.

DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: Bernhardt Trout. B-E-R-N-H-A-R-D-T, T-R-O-U-T.

BERNHARDT TROUT, the witness herein, after having been duly sworn under oath, was examined and testified as follows:

THE WITNESS: Yes, I do.

11:37:19 MR. PRUSSIA: May I proceed?

11:37:12 DIRECT EXAMINATION

11:37:12 BY MR. PRUSSIA:

11:37:21 Q. Good morning. Would you please introduce yourself to
11:37:24 the Court?

11:37:24 A. Good morning. My name is Bernhardt Trout.

11:37:28 Q. Dr. Trout, have you been retained by Exelixis as an
11:37:31 expert witness in this case?

11:37:32 A. Yes, I have.

11:37:33 Q. Are you being compensated for your work in this case?

11:37:35 A. Yes, I am.

11:37:37 Q. Does your compensation depend on the outcome or the
11:37:40 substance of your opinions?

11:37:41 A. No.

11:37:41 MR. PRUSSIA: Let's please have PDX-2.

11:37:44 BY MR. PRUSSIA:

11:37:44 Q. Where do you work, sir?

11:37:45 A. I work at MIT. It's Massachusetts Institute of
11:37:48 Technology.

11:37:50 Q. And what is your position at MIT?

11:37:51 A. I'm a professor of chemical engineering.

11:37:54 Q. And how long have you been a professor of chemical
11:37:56 engineering?

11:37:57 A. Over 25 years.

11:37:59 Q. What is your educational background?

11:38:00 A. Well, I got my undergraduate degree and my master's
11:38:03 degree at MIT. My Ph.D. at the University of California,
11:38:07 Berkeley in 1996. All in chemical engineering.
11:38:11 And then I did a post-doctoral research at the
11:38:13 Max-Planck Institute in Stuttgart, Germany.
11:38:17 Q. Generally, what are your job responsibilities as a
11:38:20 professor of chemical engineering at MIT?
11:38:23 A. Well, generally there are three aspects. One is
11:38:24 research, run a research lab. Another is education, meaning
11:38:30 specifically classroom room teaching, which I also do. And
11:38:33 then the third area is service, helping the department, and
11:38:37 the institute in committees and other ways.
11:38:39 Q. You mentioned teaching. What is the primary focus of
11:38:42 your teaching?
11:38:42 A. Well, chemical engineering.
11:38:44 Q. And are there any courses that you've taught that are
11:38:46 relevant to the issues in this case?
11:38:47 A. Yeah. Yes, there are. I've taught, for example,
11:38:50 thermodynamics at the undergraduate and graduate level.
11:38:54 I've taught chemical kinetics and reactor design, again, at
11:38:57 the undergraduate and graduate level. I've taught process
11:39:01 laboratory and a whole host of other courses.
11:39:03 Q. You mentioned research. What is the focus of your
11:39:06 research?
11:39:06 A. Well, the focus is pharmaceutical development and

11:39:10 manufacturing research.
11:39:11 Q. What experience do you have with crystalline
11:39:14 pharmaceutical salts?
11:39:15 A. Well, I have quite a bit of experience in my own lab
11:39:18 at MIT and also as a consultant with pharmaceutical
11:39:22 companies.
11:39:23 Q. What type of consulting work do you do?
11:39:25 A. Well, there are two aspects. One is kind of
11:39:29 higher-level consulting as, for example, serving on a
11:39:32 scientific advisory board. And then the other aspect is
11:39:36 helping companies solve kind of targeted technical problems.
11:39:39 Q. And generally what type of companies do you work
11:39:42 with?
11:39:42 A. Generally larger companies, companies we'd be
11:39:47 familiar with. But also medium size and smaller and
11:39:50 startups.
11:39:50 Q. If you could please take a look at your binder at
11:39:54 Tab 1, it's PTX-774.
11:39:56 Would you please identify it?
11:39:56 A. Yes. That is my CV.
11:40:02 Q. And does it contain an accurate summary of your
11:40:04 education and professional experience?
11:40:06 A. Yes.
11:40:07 MR. PRUSSIA: With that, Your Honor, I tender
11:40:08 Dr. Trout as an expert in pharmaceutical development and

11:40:11 manufacturing, including with respect to crystallization of
11:40:14 pharmaceutical salts.
11:40:17 MR. LOMBARDI: No objection.
11:40:18 THE COURT: All right. You may proceed.
11:40:18 BY MR. PRUSSIA:
11:40:19 Q. Let's move into your opinions, sir.
11:40:20 MR. PRUSSIA: Let's please have PDX-3.
11:40:20 BY MR. PRUSSIA:
11:40:22 Q. What issues will you be addressing today?
11:40:24 A. Well, I'm going to be responding to MSN's experts
11:40:28 and, in particular, Dr. Steed with respect to written
11:40:32 description, and also obviousness-type double patenting.
11:40:34 MR. PRUSSIA: Can I have the next slide, please,
11:40:36 PDX-4?
11:40:36 BY MR. PRUSSIA:
11:40:37 Q. What does this slide show?
11:40:38 A. Well, this shows the cover page of the three asserted
11:40:42 crystalline malate salt patents. The '439, the '440, and
11:40:47 the '015, together with the cover page of the respective
11:40:52 file histories.
11:40:52 Q. And have you reviewed the file histories for these
11:40:55 patents?
11:40:55 A. Yes, I have.
11:40:57 Q. And if you look in your binder at Tabs 2, 3, and 4,
11:41:00 they are JTX-1, 2, and 3.

Could you just briefly identify what those are?
A. Yes. 2, 3, and 4 are respectively those three patents in the same order.
Q. And what do these patents generally disclose?
A. Well, they generally disclose crystalline cabozantinib malate.
Q. What is the priority date for these patents?
A. Priority date is January 16th, 2009.
Q. And have you offered an opinion regarding the qualifications of a person of ordinary skill in the art for these patents as of that date?
A. Yes, I have.
MR. PRUSSIA: And if we turn to PDX-5.
BY MR. PRUSSIA:
Q. What qualifications would that person have?
A. Well, that person would have had at least a bachelor's degree in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline. Along with several years of experience working in pharmaceutical development and/or solid-state chemistry.
And a POSA would have also been part of a team which would have included synthetic organic chemists and process chemists, formulation scientists, and analytical scientists, and clinicians.
Q. And did you apply this definition of a person of

skill in connection with forming your opinions in this case?
A. Yes, I did.
Q. And you understand that MSN has in -- and its expert has offered a different opinion?
A. Yes, I do.
Q. And would your opinions change regardless of which definition is adopted?
A. No, they wouldn't.
Q. And as of the priority date, did you meet the qualifications of a person of ordinary skill in the art under either side's definition?
A. Yes.
Q. Now, let's move into -- before moving into your opinions, let's briefly cover some background concepts, okay?
A. Okay.
MR. PRUSSIA: Let's move to PDX-6.
BY MR. PRUSSIA:
Q. What is shown on this slide?
A. This is a very high-level slide, Your Honor. But it, I think, presents the starting point for understanding these patents. I think we're all familiar, but the starting point here is that there are three important states of matter. Solid, liquid, and gas.
Q. And what's the relevant state for this case?

11:42:57 A. It's a solid.

11:42:58 MR. PRUSSIA: And if we could turn to PDX-7.

11:42:58 BY MR. PRUSSIA:

11:43:01 Q. What are the different types of solids?

11:43:02 A. Well, there are two different types of solids. I think Your Honor's heard that throughout the first part of the week here.

11:43:09 On the left, I have the crystalline solid. You can see in the large circle, it's a cartoon emblematic of the repeating pattern of the atoms and molecules over three dimensions in crystalline material. And that smaller insert is an actual picture of an actual crystal, you can see the facets there.

11:43:33 On the other hand, there's amorphous material, and you can see that on the right side. So the amorphous material does not contain long-range order. There's a randomness there. And then you can see there's a picture, again, from -- a microscope picture of an amorphous material. It looks very different.

11:43:52 MR. PRUSSIA: So let's turn to PDX-8.

11:43:52 BY MR. PRUSSIA:

11:43:54 Q. What is shown here?

11:43:55 A. These are the asserted claims of the crystalline malate salt patents.

11:43:59 Q. And what are the common elements of the three

11:44:01 asserted claims?
11:44:02 A. Well, first of all -- well, you can see highlighted
11:44:05 here, crystalline, also the chemical formula cabozantinib,
11:44:09 and then the malate.
11:44:12 MR. PRUSSIA: Can we turn to JTX-1. It's Tab 2
11:44:15 in the binder. It's the '439 patent. And if we turn to
11:44:18 Scheme 1. Which begins at Column 19.
11:44:18 BY MR. PRUSSIA:
11:44:23 Q. What is Compound I?
11:44:25 A. Compound I is cabozantinib (L)-malate.
11:44:33 MR. PRUSSIA: And if we turn to Column 5 of the
11:44:35 patent, there's a structure starting at Line 50.
11:44:35 BY MR. PRUSSIA:
11:44:40 Q. What is that structure?
11:44:40 A. That structure is (L)-malic acid.
11:44:45 MR. PRUSSIA: And if we turn to the next column,
11:44:47 there's a structure starting at Line 1.
11:44:47 BY MR. PRUSSIA:
11:44:50 Q. What is that structure?
11:44:51 A. That structure is (D)-malic acid.
11:44:55 Q. And what is the difference between the (L)- and the
11:44:58 (D)-malic acid?
11:44:58 A. Well, the two are mirror images of each other.
11:45:02 MR. PRUSSIA: Let's go back to Column 6 and look
11:45:06 at a paragraph that starts at about Line 56.

BY MR. PRUSSIA:

Q. Do you see the phrase "this disclosure relates to malic salts"?

A. Yes.

Q. What malic salts are disclosed in this paragraph of the patents?

A. Well, there are three starting at Line 59; the (L)-malate salt of cabozantinib, the (D)-malate salt of cabozantinib, and the (DL)-malate salt of cabozantinib.

Q. So, what, if any, significance would a skilled person have attributed to the patent's use of the term "malate salts" here?

A. Well, as the patent shows right here, the malate salts are those three salts.

MR. PRUSSIA: If we turn to Column 7.

BY MR. PRUSSIA:

Q. What does the first sentence in the paragraph beginning at Line 10 say about the malate salts addressed in these patents?

A. That line says, "The salts of cabozantinib, and particularly Compound I" -- again, that's the cabozantinib (L)-malate -- "have a preferred combination of pharmaceutical properties for development."

Q. And if we turn to the second sentence, what properties are described there?

11:46:16 A. Well, under two different conditions of temperature
11:46:20 and relative humidity, Compound I, again, cabozantinib
11:46:24 (L)-malate, showed no change in assay, purity, moisture, and
11:46:29 dissolution.
11:46:31 Q. And continuing to the next sentence, at Line 16, what
11:46:34 properties are described there?
11:46:35 A. "The DSC/TGA" -- so those are thermal analytical
11:46:41 methods -- "showed the Compound (I) to be stable up to
11:46:44 185 degrees Celsius.
11:46:46 Q. So what, if any, significance would a skilled person
11:46:49 have attributed to these disclosures in the crystalline
11:46:52 malate salt patent?
11:46:53 A. Well, the crystalline cabozantinib (L)-malate is
11:46:59 stable and, in general, it has good pharmaceutical
11:47:03 properties for development.
11:47:05 Q. Now, if we turn to the sentence beginning at Line 21
11:47:09 of this same paragraph, and it starts with "the (L)-malate
11:47:13 salt," what properties are described there?
11:47:16 A. Well, it says the (L)-malate salt was synthesized
11:47:21 with good yield and purity and had sufficient solubility for
11:47:24 use in a pharmaceutical composition.
11:47:27 Q. And what, if any, significance would a person of
11:47:30 skill have attributed to that disclosure in the patent?
11:47:33 A. Well, again, that is suitable for a
11:47:34 manufacturability, it could be manufactured. And it had

suitable properties for use in a pharmaceutical composition, in particular, solubility.

Q. Look at the last sentence of this paragraph, at Column 7, Lines 26 to 31. What does this sentence convey to a skilled person regarding the (D)- and (L)-malate salts?

A. Well, this sentence says, "The (D)-malate salt of cabozantinib will have the same properties as the (L)-malate salt of cabozantinib."

MR. PRUSSIA: If we move over to Column 8 at Lines 34 to 39.

BY MR. PRUSSIA:

Q. What does this passage disclose about the properties of the crystalline cabozantinib (D)-malate?

A. Yeah. Okay. It says, "As known in the art, the crystalline (D)-malate salt will form the same crystalline form and have the same properties as crystalline compound (1)" -- in other words, the (L)-malate salt.

MR. PRUSSIA: Let's take a look at Table 1 in this patent. Table 1 spans two columns. I want to focus on the right-hand side, which is on Column 8.

BY MR. PRUSSIA:

Q. Do you see the reference to (L)-malate salt in the bottom row?

A. Yes, I do.

Q. What information does Table 1 disclose concerning the

11:48:51 (L)-malate salt of cabozantinib?
11:48:52 A. Well, it discloses the solubility. And then it says
11:48:55 that it's crystalline, nonhygroscopic with no indication of
11:49:00 hydrate formation. It's got suitable solubility. And
11:49:03 chemical and physical stability.
11:49:05 Q. How do the properties of the (L)-malate salt compare
11:49:08 to the properties of the other salts disclosed in Table 1?
11:49:10 A. Well, as the patent teaches, the properties
11:49:13 altogether show that it has the most suitable suite or
11:49:16 combination of properties for pharmaceutical development.
11:49:20 Q. Was cabozantinib malate the most soluble salt?
11:49:22 A. No.
11:49:23 Q. And were you here in Court yesterday for the
11:49:25 testimony of Dr. Khalid Shah?
11:49:27 A. Yes, I was.
11:49:28 Q. What was the explanation he provided for why Exelixis
11:49:31 pursued the (L)-malate salt despite its low solubility?
11:49:35 A. Well, even though it doesn't have the best solubility
11:49:37 and, in general, has a low solubility, it has the best
11:49:41 combination of properties.
11:49:43 Q. Staying on Column 8, there's a paragraph right below
11:49:45 this table. Please read the first sentence there beginning
11:49:49 at Line 25.
11:49:50 A. Certainly. "Another aspect of this disclosure
11:49:53 relates to crystalline forms of Compound (I), which include

11:49:57 the N-1 and/or the N-2 crystalline form of Compound (I), as
11:50:02 described herein."
11:50:04 Q. So, a couple things on this sentence. First, there's
11:50:06 a reference to crystalline form, we're seeing that for the
11:50:09 first time. What is a crystalline form?
11:50:11 A. Well, a crystalline form is a particular polymorph or
11:50:15 a particular repeating pattern of a given crystal.
11:50:19 Q. Now, this sentence starts with the phrase "another
11:50:23 aspect." What, if any, significance would a skilled person
11:50:26 attach to the use of the term "another aspect of this
11:50:28 disclosure"?
11:50:29 A. Well, the skilled person would understand that the
11:50:31 inventors are saying in addition and separate to crystalline
11:50:37 cabozantinib (L)-malate salt, another aspect of the
11:50:41 disclosure relates to the specific crystalline polymorphic
11:50:46 forms, the N-1 and the N-2.
11:50:49 Q. Can you please read the next sentence?
11:50:51 A. Certainly. "Each form of Compound (I) is a separate
11:50:55 aspect of the disclosure."
11:50:58 Q. What, if any, significance would a skilled person
11:51:01 attach to the patents' use of the term "separate aspect of
11:51:04 the disclosure"?
11:51:05 A. Well, I think this is -- just reinforces the previous
11:51:08 sentence that, again, it's a separate aspect of the
11:51:11 disclosure or separate aspect of the invention. The

specific crystalline polymorphic forms, the N-1 and N-2, separate from crystalline cabozantinib (L)-malate.

Q. Now, do any of the crystalline malate salt patents contain claims to an N-1, N-2, or any other crystalline forms?

A. No.

Q. Let's talk more about the word "crystalline." What is the plain and ordinary meaning of the term "crystalline" in the context of the asserted claims?

A. Well, it's what I just said when we had the slide up for crystalline. It's a solid material in which there's a regular repeating pattern over -- many over three dimensions and over large spatial dimensions in contrast to an amorphous form. And it's consistent with what I heard Dr. Steed say yesterday.

Q. Dr. Steed used slightly different words. He said -- I wrote it down -- "a crystal in which the structural units are repeated regularly in three dimensions."

Do you remember that testimony?

A. Yes, I do.

Q. Is there a meaningful difference between that and your plain and ordinary meaning?

A. No.

Q. How many crystalline cabozantinib salts exist?

A. Well, there are three. There's the (L)-malate, the

(D)-malate and the (DL)-malate.

Q. And what is the basis for that opinion?

A. Well, that's what's written and disclosed in the patent.

MR. PRUSSIA: And if you pull back up Column 6, Line 56.

BY MR. PRUSSIA:

Q. Is this the passage that you're referring to?

MR. PRUSSIA: We can highlight "this disclosure related to" -- yeah.

THE WITNESS: Yes, it is. Again, that's the disclosure of malate salts.

BY MR. PRUSSIA:

Q. Now, Dr. Steed testified yesterday that the claims require a genus of crystalline malate salt forms.

Do you remember that?

A. Yes. I do.

Q. Do the claims require a genus of crystalline malate salt forms?

A. No.

Q. And why not?

A. Well, the word "form," first of all, is not in the claims. And the claims do not require a particular genus of specific polymorphs. They just require the property of crystalline and, of course, cabozantinib malate.

11:53:21 MR. PRUSSIA: Let's look back at the claims, PDX-8.

11:53:23 BY MR. PRUSSIA:

11:53:24 Q. And just to be clear, you just testified to this, but I have to ask the question: Do any of the asserted claims contain the word "form"?

11:53:30 A. No.

11:53:32 MR. PRUSSIA: Let's turn to PDX-9.

11:53:32 BY MR. PRUSSIA:

11:53:35 Q. What is shown here?

11:53:35 A. Well, this is Claim 1 on the right and left of two different patents, not the asserted crystalline malate cabozantinib patents. This on the left is the '776 patent, and on the right is the '549 patent. These are in the same family as the asserted crystalline cabozantinib and malate patents, and they have the same specification.

11:54:03 Q. Do the claims in these patents contain the word "form"?

11:54:06 A. Yes.

11:54:08 Q. How, if at all, does that bear on your opinions in this case?

11:54:10 A. Well, again, this is from the same inventors and the same family, so it shows, I guess, as additional evidence of what I was talking about before, that the inventors could have claimed forms if they wanted to, and, in fact, they

11:54:26 did.

11:54:27 MR. PRUSSIA: So returning to PDX-8, and we're looking at the claims of the crystalline malate salt patents.

11:54:33 BY MR. PRUSSIA:

11:54:34 Q. How was the term "crystalline" being used in the asserted claims?

11:54:38 A. Well, crystalline meaning that they're a solid. They're crystalline as I've been defining it, and they're not amorphous.

11:54:47 Q. Now, as of the priority date, would a skilled person have been able to distinguish between a crystalline material and an amorphous material?

11:54:54 A. Yes.

11:54:56 MR. PRUSSIA: Let's have PDX-10, please.

11:54:56 BY MR. PRUSSIA:

11:54:59 Q. Just explain for the Court, please, how a skilled person would have done that.

11:55:02 A. Well, this is an example of via microscopy. That's one method. And the Court can, I think, see and distinguish, but between the amorphous and crystalline, just by looking at it. The crystalline has these facets. That's a consequence of the regular repeating pattern where the amorphous does not.

11:55:24 Q. Yesterday we heard some discussion about different

forms. Now, as of the priority date, could a person of skill in the art identify a crystalline salt without knowing what specific form the salt was in?

A. Yes.

Q. And how does this relate to your opinions regarding written description?

A. Well, again, because crystalline is exactly as I've been explaining it -- and this is an example of a method that the skilled person could use to distinguish between crystalline and amorphous without knowing, you could see it quite plainly there without knowing what specific crystalline or amorphous material it is.

Q. Now, what would a skilled person have done if the -- that person wanted to evaluate the particular polymorph, polymorphic form?

A. Well, the person could use other techniques, for example, more detailed analysis with X-ray powder diffraction. I think the Court might be familiar with this. It was discussed earlier this week.

Q. Now -- so let's turn now to your opinions regarding written description, and what is your opinion regarding whether the specification conveys that the inventors possessed the claimed invention?

A. Well, my opinion is, for the reasons that I've been given, that the inventors did possess the claimed invention.

11:56:39 Q. Is there any dispute that the specification discloses
11:56:42 cabozantinib?
11:56:43 A. No.
11:56:44 Q. Is there any dispute that the specification discloses
11:56:47 cabozantinib malate salts?
11:56:48 A. No.
11:56:50 MR. PRUSSIA: Let's turn to the crystalline
11:56:51 limitation, and let's have PDX-11.
11:56:51 BY MR. PRUSSIA:
11:56:54 Q. Does the specification disclose crystalline salts?
11:56:57 A. Yes. And I have here in this table a summary of the
11:57:02 various places in the patent specification in which it's
11:57:06 disclosed. You can see there are quite a few. I won't list
11:57:10 all of them verbally.
11:57:11 Q. You have a reference to preparative examples on the
11:57:15 right-hand side of this table. What is disclosed by the
11:57:20 preparative examples?
11:57:21 A. Well, by preparative examples, I mean, the examples
11:57:25 in the patent that are named and listed as examples in which
11:57:29 they describe actual chemical processes to generate
11:57:34 crystalline cabozantinib (L)-malate. And for that matter
11:57:38 one of the examples generates the amorphous version of the
11:57:41 material.
11:57:42 MR. PRUSSIA: If we could put up DDX Steed 13.
11:57:42 BY MR. PRUSSIA:

11:57:45 Q. Now, yesterday Dr. Steed offered the opinion that no two forms are representative of one another because of the different intrinsic properties of crystalline salt forms.

Do you recall that?

A. Yes, I do.

Q. Now, two questions about this. First, is that opinion relevant under the plain and ordinary meaning of crystalline?

A. No.

Q. Second, is that opinion correct?

A. No.

Q. And can you explain why?

A. Yes. Certainly. So, as I said, under the -- plain and ordinary meaning of crystalline, it's not relevant at all. But if we assume for some reason that form is read into the claim, then the patents disclosed representative species of those crystalline forms.

Q. So, let's turn to that.

Would your opinion concerning written description change if Dr. Steed's version of the claims were applied?

A. No.

Q. Let's have PDX-12, please. And at a high level, what are the reasons that your opinion is unchanged under his view?

11:58:41 A. Well, as I just said, representative crystalline
11:58:44 forms are disclosed in the specification. In addition to
11:58:48 that, the purported forms that the Court heard about
11:58:52 yesterday are not distinct forms.
11:58:55 And, finally, there are common structural
11:58:57 features disclosed in the specification.
11:58:59 Q. So if you go to PDX-13 and start with your first
11:59:03 reason, what are the representative forms of cabozantinib
11:59:06 salts?
11:59:07 A. Well, those are the N-1, N-2 forms explicitly
11:59:11 disclosed in the specification which are the
11:59:14 pharmaceutically most relevant forms.
11:59:15 Q. And what makes forms N-1 and N-2 representative
11:59:19 polymorphs?
11:59:20 A. Well, they exhibit properties that make them suitable
11:59:23 for pharmaceutical development.
11:59:25 Q. What are those properties?
11:59:26 A. Well, the properties are what we discussed before.
11:59:29 They're crystalline, so they have good crystallinity.
11:59:33 Nonhygroscopic, they have good stability, both chemical and
11:59:37 physical.
11:59:38 Q. Generally, you mentioned stability. Generally what
11:59:40 role does stability play in identifying a pharmaceutically
11:59:43 relevant form?
11:59:44 A. Well, stability is very important. The API, as we've

heard throughout the week, in its pharmaceutical composition, needs to be stable over the lifetime of the drug. Otherwise, it wouldn't be a good drug. It wouldn't be useable.

Q. Now, we walked through the specification of the crystalline malate salt patents. There are also figures. We didn't show the Court those, but have you considered the figures?

A. Yes, I have.

Q. What do the figures disclose regarding the stability of forms N-1 and N-2?

A. Well, the figures disclose that they have good thermal stability. So they're stable thermally.

MR. PRUSSIA: Let's turn to PDX-14.

BY MR. PRUSSIA:

Q. And your second reason, what is your response regarding the other purported forms that he identified?

A. Well, I went through those forms in detail that Dr. Steed identified yesterday. They're all disclosed in my report. My conclusion is that those purported forms are not distinct forms, at least there's no clear evidence that they're distinct forms.

MR. PRUSSIA: Can we have the next slide, PDX-15?

BY MR. PRUSSIA:

12:00:47 Q. Now, there's a reference to XRPD overlay. Could you
12:00:51 start please by explaining to the Court what that is?
12:00:53 A. Yes. And I think Your Honor is familiar with XRPDs.
12:00:59 I'm sure you've heard of them before and earlier this week.
12:01:02 So these are diffractograms or the products of an X-ray
12:01:07 powdered fraction experiment, and actually it might be
12:01:11 helpful.
12:01:11 THE WITNESS: May I use my laser pointer?
12:01:13 THE COURT: Sure, yes.
12:01:14 THE WITNESS: Okay. So, again, I know it's
12:01:17 basic, but there are various peaks. I'll focus on the
12:01:20 bottom one, and this combination of peaks across the X-axis
12:01:25 gives an indication of a specific crystalline or polymorphic
12:01:30 form. And the overlay is if I take two of these and put
12:01:35 them together, make sure the x-axis is the same scale, and
12:01:39 so, that's what I've done here on this slide.
12:01:42 Q. Now, who prepared this overlay?
12:01:44 A. I did.
12:01:44 Q. And based on what data?
12:01:46 A. Well, the blue curve is based on MSN's data for their
12:01:51 purported form M. And the orange curve is based on
12:01:55 Exelixis' data for its free base Form 3. In other words,
12:02:00 not cabozantinib (L)-malate.
12:02:02 Q. So, what conclusions did you reach about whether form
12:02:07 M is a true crystalline salt form of cabozantinib malate?

12:02:11 A. Well, that it's not. You can see from the overlay
12:02:14 the peaks match. In other words, MSN's purported form M is
12:02:19 a free base form, the free base Form III, not a salt, not a
12:02:26 malate salt.
12:02:26 Q. Now, did Dr. Steed point to form M as a purported
12:02:30 form?
12:02:30 A. He did originally.
12:02:32 Q. And what's your understanding of his reliance on form
12:02:35 M now?
12:02:36 MR. LOMBARDI: So, Your Honor, I'm just going to
12:02:37 object because now Dr. Steed didn't present this at trial.
12:02:41 So, it's irrelevant, I guess.
12:02:45 There shouldn't be any mistake. Dr. Steed did
12:02:48 not present anything about form M at trial, didn't say it
12:02:51 was crystalline form.
12:02:52 THE COURT: I forget what I'm -- is that like
12:02:55 form S or something?
12:02:57 MR. LOMBARDI: Yes, form S.
12:02:59 So this is something that was never presented.
12:03:01 THE COURT: Right. I think the relevant
12:03:03 universe is the 111 that he did present.
12:03:06 MR. PRUSSIA: Your Honor, the next question will
12:03:09 get to the point of this; right?
12:03:09 BY MR. PRUSSIA:
12:03:10 Q. So he initially relied on it, but now he doesn't

because of why?

Why doesn't -- why doesn't Dr. -- why -- what's your understanding as to why Dr. Steed did not present this form to the Court, even though he initially presented it in his opinions?

MR. LOMBARDI: Your Honor, that would have been a question for Dr. Steed.

THE COURT: Well, I tend to think it is but it's hard to say without hearing what the answer is. So, I reserve the right to strike the answer after I hear it.

So, I'm sorry. You may want the question re-asked.

THE WITNESS: Maybe one more time, counsel, please.

BY MR. PRUSSIA:

Q. What is your understanding as to why Dr. Steed no longer relies on this form?

A. I think he agrees with me that it's not a true form. It's actually not a form of cabozantinib (L)-malate salt.

MR. PRUSSIA: Let's have PTX-16.

THE WITNESS: Polymorphic forms.

THE COURT: So I'm not going to strike it, it's just irrelevant. So we'll just continue.

MR. PRUSSIA: PDX-16, please.

BY MR. PRUSSIA:

12:04:01 Q. What does this slide show?
12:04:02 A. Okay. So this is XRPD pattern for purported Mylan
12:04:07 form M-1. Dr. Steed did have this explicitly in his table,
12:04:12 although he didn't show the Court this particular
12:04:16 diffractogram.
12:04:16 Q. And what conclusions did you reach whether form M-1
12:04:19 is a true form?
12:04:20 A. Well, I think you can see in contrast to the previous
12:04:26 XRPD diffractograms, this has this broad halo indicative of
12:04:32 amorphous material. It does have some broad features here
12:04:36 which show that there's some kind of crystalline material.
12:04:40 It's not fully amorphous, it seems primarily amorphous, but
12:04:44 it's unclear what this material is. Certainly not clear
12:04:47 that it's a new form.
12:04:50 Q. Now --
12:04:51 A. It's not a new crystalline polymorphic form. I
12:04:55 should be careful myself.
12:04:56 That's not a new crystalline polymorphic form.
12:04:56 Q. So, generally, what is your opinion regarding form
12:04:58 M-1 and the other forms that Dr. Steed identified?
12:05:00 A. Well, I went through them in some detail. Again, I
12:05:05 outlined it in multiple pages of my report.
12:05:08 In going through each of those forms from Mylan
12:05:10 and Cipla, my conclusion is there's no clear evidence that
12:05:14 these are new or distinct forms. The evidence says that

they're not.

Q. Now, do you recall Dr. Steed's testimony concerning solvates?

A. Yes.

Q. And what is your response to that?

A. Well, there's no evidence that there's actual solvates of crystalline cabozantinib (L)-malate.

MR. PRUSSIA: Let's have PDX-17.

BY MR. PRUSSIA:

Q. Move to your third point.

What is that?

A. That there are common structural features disclosed in the specification.

MR. PRUSSIA: And let's have PDX-18.

BY MR. PRUSSIA:

Q. What are those common structural features?

A. Well, there's the structure, meaning that they're crystalline, as opposed to amorphous. There's the formula, like what you can see up on the screen. The cabozantinib malate. And then there's the actual name, the chemical name also in the specification.

Q. Now, to just be clear, what's -- when you reference structure, what are you referring to?

A. Oh, that it's crystalline.

Q. Now, do these structural features allow a skilled

12:06:14 artisan to recognize and identify other crystalline
12:06:18 cabozantinib salts?
12:06:19 A. Yes.
12:06:19 Q. Which, if any, of these structural features are
12:06:21 present in form N-1?
12:06:23 A. All of them.
12:06:24 Q. Which are present in form N-2?
12:06:26 A. All of them.
12:06:27 Q. Which are present in MSN's form S?
12:06:29 A. All of them.
12:06:30 Q. Which, if any, of these structural features are
12:06:34 present in the other purported forms discussed by Dr. Steed?
12:06:37 A. Well, to the extent that they're crystalline
12:06:40 cabozantinib (L)-malate or malate broadly, then they're
12:06:44 present.
12:06:45 Q. So just to recap: What is your opinion regarding
12:06:47 whether the inventors possessed the full scope of the claims
12:06:50 under Dr. Steed's interpretation?
12:06:52 A. My opinion is that they did.
12:06:54 Q. Let's shift topics now and move to obviousness-type
12:06:57 double patenting.
12:06:58 Now, have you formed an opinion on whether the
12:07:00 asserted claims are patentably distinct over Claim 5 of --
12:07:04 over -- of the '473 compound patent?
12:07:07 A. Yes, I did.

12:07:07 Q. And what is your opinion?
12:07:08 A. My opinion is that they are, indeed, patentably
12:07:11 distinct over Claim 5 of the '473 patent.
12:07:15 MR. PRUSSIA: Let's please have PDX-19.
12:07:15 BY MR. PRUSSIA:
12:07:17 Q. At a high level, what are the reasons for your
12:07:19 opinion?
12:07:19 A. Well, first of all, there are very significant
12:07:21 differences between claims and there's no motivation to
12:07:27 pursue the salt based on the prior art. Even if there were,
12:07:31 there was no motivation to include malic acid in the salt
12:07:35 screen based on the prior art.
12:07:36 Even if the skilled person were to pursue a salt
12:07:41 screen with malic acid, there was no reasonable expectation
12:07:43 of success.
12:07:44 And then finally, objective evidence confirms
12:07:47 non-obviousness.
12:07:48 Q. So, let's take each one of these in turn and start
12:07:51 with your first reasoning for that.
12:07:54 MR. PRUSSIA: And we'll pull up PTX-252. It's
12:07:58 Tab 6 in the binder.
12:07:58 BY MR. PRUSSIA:
12:07:58 Q. And what is this document?
12:08:01 A. This document is the '473 patent.
12:08:07 Q. What is the issue date of the '473 patent?

12:08:09 A. That's August 25th, 2009.
12:08:13 Q. Have you offered an opinion on whether the '473 patent is prior art to the asserted claims?
12:08:16 A. Yes, I have.
12:08:18 Q. What is your opinion?
12:08:18 A. It is not prior art.
12:08:19 Q. And in your opinion, when were the asserted claims reduced to practice?
12:08:21 A. Well, we heard from Dr. Shah yesterday they were reduced to practice a lot earlier, I believe 2004.
12:08:25 Q. And what is the priority date of the asserted claims?
12:08:29 A. The priority date of the asserted claims is January 16th, 2009.
12:08:33 Q. Now, let's look at Claim 5 itself.
12:08:35 MR. PRUSSIA: If we turn to Column 412 of the '473 patent.
12:08:39 BY MR. PRUSSIA:
12:08:41 Q. What is Claim 5 directed to?
12:08:43 A. Well, it's directed to cabozantinib, that's, again, the molecular structure that is on the screen. That's the free base or a pharmaceutically acceptable salt thereof.
12:08:48 Q. Does Claim 5 require a pharmaceutically acceptable salt?
12:08:48 A. No.
12:08:49 MR. PRUSSIA: Let's have PDX 20.
12:08:50
12:08:54
12:08:59
12:09:03
12:09:07
12:09:07
12:09:08

12:09:08 BY MR. PRUSSIA:
12:09:11 Q. What are the differences between Claim 5 of the
12:09:15 '473 patent and the asserted claims?
12:09:17 A. Well, quite a few differences and forgive me --
12:09:20 forgive us, Your Honor, for including a whole bunch of
12:09:24 different colors.
12:09:24 But just to point out the differences here, in
12:09:27 yellow there's the malate salt, (L) or (D) for example. In
12:09:33 red, pharmaceutical composition. Neither of those, I should
12:09:38 make clear, are in Claim 5 of the '473.
12:09:41 Crystalline, in blue, is also not in Claim 5 of
12:09:45 the '473. And the method of treating cancer where said
12:09:50 cancer is kidney cancer, that's in green in the asserted
12:09:54 malate crystalline salt patents, also is not in Claim 5 of
12:09:58 the '473.
12:10:00 Q. So just on a pure comparison of the claims, in your
12:10:04 opinion, are the claims of the crystalline malate salt
12:10:06 patents patentably distinct from Claim 5?
12:10:09 A. Yes.
12:10:10 Q. Now, let's focus on the disclosures of the
12:10:13 '473 patent specification. What, if any, cabozantinib salts
12:10:17 are exemplified in the '473 patent?
12:10:19 A. Well, there's a -- oh, cabozantinib salts? None.
12:10:25 Q. So what, if any, information is disclosed in the
12:10:29 '473 patent regarding a (L)-malate salt of cabozantinib?

12:10:30 A. Nothing.
12:10:32 Q. What, if any, information is disclosed in the
12:10:36 '473 patent regarding a (D)-malate salt of cabozantinib?
12:10:38 A. Nothing.
12:10:39 Q. What crystalline cabozantinib is exemplified
12:10:43 in the '473 patent?
12:10:44 A. None.
12:10:45 Q. What, if any, information does the '473 patent
12:10:48 disclose about crystalline polymorphs of any crystalline
12:10:53 cabozantinib salt?
12:10:53 A. Nothing.
12:10:55 Q. What, if any, pharmaceutical compositions of
12:10:58 cabozantinib are exemplified in the '473 patent?
12:11:01 A. None.
12:11:02 Q. What, if any, methods of treating kidney cancer with
12:11:04 cabozantinib are exemplified in the '473 patent?
12:11:07 A. None.
12:11:09 Q. Let's turn back to Claim 5 itself. And now I want to
12:11:13 focus on the language regarding a pharmaceutically
12:11:15 acceptable salt.
12:11:17 A. Okay.
12:11:17 Q. What information is disclosed in the '473 patent
12:11:21 regarding a pharmaceutically acceptable salt?
12:11:22 A. Well, there's a definition of pharmaceutically
12:11:26 acceptable salts or particular acids that could be used to

12:11:30 form pharmaceutically acceptable salts in the patent.

12:11:33 MR. PRUSSIA: Let's turn to Column 270, Lines 15 through 25.

12:11:37 BY MR. PRUSSIA:

12:11:42 Q. What is listed -- what is identified at this portion of the '473 patent specification?

12:11:46 A. Well, starting at Line 15 -- yeah, and I think we can just start at Line 15 there -- "pharmaceutically acceptable acid addition salt," that's under the definition section in the patent; that's in quotes. And so, this is the definition of pharmaceutically acceptable acid addition salts.

12:12:08 Q. And how many acids are listed by name in this definition?

12:12:11 A. Twenty-four.

12:12:15 MR. PRUSSIA: Can we write 24 on the screen?

12:12:15 BY MR. PRUSSIA:

12:12:17 Q. Now, does the '473 patent identify malic acid as a pharmaceutically acceptable acid addition salt?

12:12:27 A. No, it's not identified in this list.

12:12:30 Q. And what acids would -- a skilled person looking at the '473 patent specification, what would they have started with as a potential counterion for cabozantinib?

12:12:40 A. Well, the acids that are identified in this list.

12:12:44 Q. Now, what is your response -- you heard Dr. Steed's

12:12:49 testimony about "the words at the end" and the like?
12:12:52 A. Yes.
12:12:52 Q. What is your response to that testimony?
12:12:54 A. Well, Dr. Steed said "and the like" might mean 50
12:12:58 other acids. We heard today from the Bighley reference that
12:13:02 there were 113. Of course, some of these were on that list,
12:13:06 but all in all there are over 113. I think that would be
12:13:10 the reasonable way of thinking of "and the like."
12:13:13 Q. So, would a skilled person reading Claim 5 of the
12:13:20 '473 patent and its definition of a pharmaceutically
12:13:22 acceptable salt, would that person have a immediately
12:13:26 envisioned cabozantinib malate salt from that genus?
12:13:29 A. No.
12:13:30 Q. And what are the reasons for that?
12:13:32 A. Well, again, the genus is very large, over 113, at
12:13:35 least, potential salts.
12:13:38 Q. Now, you just heard Dr. Koleng's testimony about 113
12:13:42 pharmaceutically acceptable anionic salts; right?
12:13:45 A. Correct.
12:13:46 Q. Does that reflect the entire genus of
12:13:48 pharmaceutically acceptable salts that were known as of the
12:13:51 priority date?
12:13:51 A. No, that was just from that one reference. There are
12:13:54 additional ones.
12:13:56 MR. PRUSSIA: Let's have PDX 21, please. And

turn to your opinions regarding motivation to pursue a salt.
BY MR. PRUSSIA:
Q. Now, first, what -- when you were here yesterday, what opinions did you hear from Dr. Steed regarding a motivation to form a salt?
A. Frankly, I don't recall hearing any opinions. He had mentioned solubility, but I wasn't sure even if that was the motivation. But that was the closest that he mentioned.
MR. PRUSSIA: Can we have PDX-22, please. And let's turn to your opinions on this point.
BY MR. PRUSSIA:
Q. At a high level, what are the reasons that a skilled person would not have been motivated to pursue a salt?
A. Well, overall, first of all, there were no reported problems with cabozantinib in the prior art. Even if one were to focus in on solubility, solubility is not determinative of oral bioavailability. And even if one wanted to improve solubility, there were multiple methods to improve solubility.
Q. So as of the priority date, what, if any, information was disclosed in the prior art regarding the reasons to form a salt with cabozantinib?
A. Nothing.
Q. Does the '473 disclose anything regarding the reasons to form a salt with cabozantinib?

12:15:07 A. No.
12:15:09 Q. As of the priority date, what, if anything, was known
12:15:11 about cabozantinib's bioavailability?
12:15:13 A. Nothing.
12:15:15 Q. As of the priority date, what, if anything, was known
12:15:17 about cabozantinib's solubility?
12:15:19 A. Nothing.
12:15:20 Q. Does the '473 disclose anything about cabozantinib's
12:15:24 bioavailability or its solubility?
12:15:26 A. No.
12:15:27 MR. PRUSSIA: Let's have PDX-23, please.
12:15:27 BY MR. PRUSSIA:
12:15:30 Q. What is your second reason that a skilled person
12:15:32 would not have been motivated to pursue a salt of
12:15:35 cabozantinib?
12:15:35 A. Well, even if one did want to focus on solubility,
12:15:40 solubility itself is not determinative of oral
12:15:43 bioavailability.
12:15:44 Q. And just taking a step back, what are the reasons
12:15:47 that oral bioavailability -- what's the reason that it's
12:15:49 relevant to your opinion?
12:15:50 A. Well, it's quite relevant. This is an oral drug, so
12:15:55 it would be taken through the mouth into the GI system and
12:15:58 then absorbed into the body. And the degree to which it's
12:16:02 absorbed and then can reach the therapeutic site is its

bioavailability.

MR. PRUSSIA: And if we could have PTX-625, Tab 16 in the binders.

BY MR. PRUSSIA:

Q. What is this document?

A. This is the Takagi reference.

Q. And what is the title?

A. Title is "A Provisional Biopharmaceutical Classification of the Top 200 Oral Drug Products in the United States, Great Britain, Spain, and Japan."

Q. And what is the date?

A. The date is February 21st, 2006.

MR. PRUSSIA: And if we turn to Figure 2.

BY MR. PRUSSIA:

Q. What does this chart disclose to a person of skill as of the priority date?

A. This is a histogram, and you can see in the Y axis, it's percentage of immediate-release oral drugs. So those are the relevant drugs that we're talking about here. So it goes from 0 to about 45 percent. On the left side is the categories. The different colors just mean the different countries or jurisdictions. It shows very soluble.

And then at the end, not available. So that's not so important here. But the far end -- or sorry, one next to the far end, practically insoluble, is the lowest

12:17:19 1 category. And one can see that the practically insoluble,
12:17:24 2 on average, is about 40 percent of all immediate-release
12:17:28 3 oral drugs, or at least the top ones.
12:17:31 4 Q. So can a compound with poor water solubility
12:17:33 5 nonetheless be bioavailable.
12:17:35 6 A. Yes.
12:17:36 7 Q. If you turn to PDX-24.
12:17:39 8 At a high level, what are the reasons that a
12:17:41 9 compound with poor water solubility could nonetheless still
12:17:44 10 have sufficient bioavailability?
12:17:45 11 A. Well, as I've been saying, poor water or aqueous
12:17:50 12 solubility is not determinative of bio -- oral
12:17:53 13 bioavailability. There's also potency, permeability, and
12:17:58 14 solubility in bio-relevant media.
12:18:01 15 Q. And what's known today about the role that potency
12:18:03 16 plays in the bioavailability of cabozantinib?
12:18:05 17 A. Well, as Dr. Shah testified yesterday, it turns out
12:18:09 18 that cabozantinib has high potency.
12:18:11 19 Q. What is known today about the role that permeability
12:18:15 20 plays in the oral bioavailability of cabozantinib?
12:18:17 21 A. Well, again, as we heard from Dr. Shah yesterday,
12:18:21 22 cabozantinib is highly -- or is -- is absorbed very well, so
12:18:27 23 it's considered highly permeable.
12:18:29 24 Q. What does solubility in bio-relevant media refer to?
12:18:33 25 A. So we've been talking earlier about aqueous

12:18:36 solubility. So, solubility just in water, per se. But
12:18:40 solubility in bio-relevant media would be in media that's
12:18:45 made to mimic various kind of places in the body. For
12:18:49 example, simulated stomach fluid and also simulated
12:18:53 intestinal fluid.
12:18:55 Q. So, to be clear, though, as of the priority date, was
12:18:57 there any information in about cabozantinib's solubility,
12:19:01 its permeability, or its in vivo potency?
12:19:04 A. No.
12:19:04 Q. And were you here -- again, you heard Dr. Steed
12:19:06 testify that a skilled person could have identified the
12:19:10 water solubility of cabozantinib experimentally?
12:19:13 A. Yes.
12:19:14 Q. But I think he said they wouldn't go beyond that, do
12:19:18 you remember that?
12:19:18 A. Right.
12:19:18 Q. Just focusing on whether, if that is correct, that a
12:19:22 skilled person could have experimentally identified the
12:19:26 water solubility, in your opinion, would that POSA have
12:19:29 continued to -- continued to experimentally identify the in
12:19:36 vivo potency, the permeability, and the solubility and
12:19:39 bio-relevant media of cabozantinib?
12:19:41 A. They could have.
12:19:42 Q. And if that skilled person did so, what would -- what
12:19:46 would they have learned with respect to the need to form a

12:19:49 salt with cabozantinib?
12:19:50 A. Well, again, under that assumption, as we now know
12:19:54 after the fact, that there wasn't an issue actually with
12:19:59 solubility, per se.
12:20:01 MR. PRUSSIA: Let's turn to PDX-25.
12:20:01 BY MR. PRUSSIA:
12:20:03 Q. What is your third reason that a skilled person would
12:20:05 not have been motivated to pursue a salt of cabozantinib?
12:20:08 A. Well, even if the skilled person did want to improve
12:20:12 solubility for cabozantinib or another drug, there were
12:20:17 multiple methods to improve solubility.
12:20:20 Q. And generally, as of the priority date, what sorts of
12:20:22 methods existed to do so?
12:20:23 A. Well, again, Dr. Koleng testified just a little while
12:20:27 ago, so I won't go through all of them again, but one is,
12:20:31 for example, to make it into amorphous material. Another is
12:20:35 to try to reduce particle size, if you wanted to keep it in
12:20:38 crystalline, for example.
12:20:40 MR. PRUSSIA: So, let's shift gears and move to
12:20:42 PDX-26.
12:20:42 BY MR. PRUSSIA:
12:20:44 Q. What is the next reason for your opinion that there
12:20:47 is no obviousness-type double patenting?
12:20:49 A. Well, even if one did want to pursue a salt, there
12:20:52 was no motivation to include malic acid in the salt screen.

MR. PRUSSIA: And if we turn to PDX-27.

BY MR. PRUSSIA:

Q. How do Dr. Koleng's opinions relate to your opinion on whether a skilled person would have included malic acid in a salt screen?

A. Well, again, these are Dr. Koleng's opinions just from a little while ago. I won't repeat them. But I would agree with those opinions.

MR. PRUSSIA: And if we go to PDX-28.

BY MR. PRUSSIA:

Q. Do you have additional reasons -- strike that.

Do you have additional responses to Dr. Steed's opinions regarding use of malic acid?

A. Yes. The Rule-of-2 we've heard about is just one guideline. It's also not an absolute rule. And, furthermore, properties of malic acid would not have said -- would not have led the POSA to seek malate salts.

Q. Let's focus on the first one first. What's your opinion regarding Dr. Steed's reliance on the Rule-of-2?

A. Well, I think Dr. Steed himself said that it's a starting point or it's a starting point for a scale. So, Rule-of-2 is a guideline. There are other rules.

Q. You mentioned there are other rules. What is -- you heard some discussion yesterday about the Rule-of-3. Were you familiar with that?

12:22:01 A. I did, Counsel, and I was familiar with that. Yes.
12:22:06 Q. And if a skilled person would have followed the
12:22:11 Rule-of-3, what conclusions would that person have reached
12:22:14 regarding malic acid as a potential counterion for
12:22:17 cabozantinib?
12:22:17 A. Well, I think you showed yesterday that the skilled
12:22:20 person following the Rule-of-3, again, just another
12:22:24 guideline. If the person did follow that absolutely, malic
12:22:28 acid would have been excluded.
12:22:30 Q. Just to be clear, though, in your opinion, would a
12:22:32 person of skill have been motivated to follow either
12:22:35 Rule-of-2 or a Rule-of-3 in identifying counterions to
12:22:39 potentially pair with cabozantinib in a salt screen?
12:22:41 A. No, those are guidelines. The skilled person
12:22:45 certainly would have taken them into account, but they would
12:22:47 not have been determinative of the choice of potential
12:22:50 counterions.
12:22:51 MR. PRUSSIA: Let's have PDX-29, please.
12:22:51 BY MR. PRUSSIA:
12:22:55 Q. How do Dr. Koleng's opinions relate -- relate to
12:22:58 yours regarding the properties of malic acid?
12:23:00 A. Well, again, malic acid, even if one were to pursue
12:23:06 the salt screen, had some properties that would have made it
12:23:09 undesirable. Dr. Koleng just talked about the weak acidity
12:23:13 and the heavy molecular weight. Those would have made it

undesirable.

In addition to that, malic acid actually has two acid groups so it's doubly ionizable. That can create complexity and would make it less favorable. In addition to that, it's subject to pseudodimerism so two molecules of malic acid could actually react to each other to form one larger molecule which would have also turned away the skilled person from malic acid.

MR. PRUSSIA: If I could have DTX Steed 26, please.

BY MR. PRUSSIA:

Q. Do you recall Dr. Steed's testimony regarding how hydrogen bonds would have informed salt selection for a skilled artisan?

A. I do.

Q. Do you agree that the potential for an eight atom hydrogen-bonded ring would have led a person of skill to select malic acid in a salt screen?

A. No, and Dr. Steed didn't give any reference for this. I presume he made it himself, but as far as I can tell, it's not based on data. And at any rate it's retrospective. It wouldn't have been known ahead of time.

Q. And if Dr. Steed is correct about this -- this rationale, what would it do to some of the status of what -- strike that.

12:24:22 If Dr. Steed's theory with respect to hydrogen
12:24:26 binding and its role in identifying counterions were
12:24:28 correct, what would it do -- what would be the result for
12:24:30 the -- as the status of some of the more commonly used
12:24:34 counterions for -- as potential salt formers?
12:24:37 A. Well, the more commonly used ones could also form
12:24:40 such structures, just an acid group that Dr. Steed has
12:24:43 there. Maybe I'll point it out to the Court. This is just
12:24:46 a general acid group, so any organic acid could form this
12:24:50 making this assumption.
12:24:53 MR. PRUSSIA: Now, let's turn to PDX-32, please,
12:24:56 and move to your opinions regarding expectation of success.
12:24:56 BY MR. PRUSSIA:
12:24:59 Q. At a high level what's your basis for why a skilled
12:25:01 person would not have had a reasonable expectation of
12:25:03 success?
12:25:04 A. Well, there's no expectation of salt formation as
12:25:07 such or isolation of salts. There's no expectation of
12:25:10 crystalline salt formation even if the skilled person could
12:25:14 form a salt. And even if a skilled person formed
12:25:18 crystalline salt of cabozantinib (L)-malate, there would be
12:25:21 no expectation that that salt would have properties suitable
12:25:25 for pharmaceutical development.
12:25:27 MR. PRUSSIA: And if we have PDX-33.
12:25:27 BY MR. PRUSSIA:

12:25:29 Q. Focusing on your first point, how do Dr. Koleng's
12:25:33 opinions relate to yours on reasonable expectation of
12:25:35 success?
12:25:36 A. Well, I think Dr. Koleng said it quite well
12:25:38 explaining the complexity of salt formation and Your Honor
12:25:42 already saw that. I won't go through it again.
12:25:44 MR. PRUSSIA: If we move to PDX-34 to your
12:25:47 second point.
12:25:47 BY MR. PRUSSIA:
12:25:47 Q. If the skilled person had chosen to perform a salt
12:25:50 screen on cabozantinib. What, if any, expectations would
12:25:52 they have had for obtaining a crystalline cabozantinib
12:25:56 malate salt?
12:25:56 A. There wouldn't have been an expectation. Could have
12:26:00 been amorphous, or oily or not crystalline.
12:26:03 Q. And generally can you say more about what your
12:26:05 reasoning is for why a person of skill would not have had an
12:26:08 expectation about obtaining crystalline material?
12:26:11 A. Yes. Because it's not predictive.
12:26:13 Q. And do you recall Dr. Steed's testimony regarding the
12:26:16 Tong Rule-of-2 as providing a person of skill with such
12:26:19 expectation?
12:26:20 A. Yes.
12:26:21 Q. Do you agree with him?
12:26:22 A. No. I think --

12:26:23 Q. What are the reasons?
12:26:24 A. Oh, sorry.
12:26:25 Q. It's okay.
12:26:26 A. Again, it's -- thank you, counsel.
12:26:28 It's one guideline that could be used, and again
12:26:32 as you asked Dr. Steed about this yesterday in the Tong
12:26:36 paper itself, two of the six examples didn't end up forming
12:26:41 crystalline salt.
12:26:43 MR. PRUSSIA: If we can have PDX-35.
12:26:43 BY MR. PRUSSIA:
12:26:45 Q. What is your third reason for why a skilled artisan
12:26:47 would not have had a reasonable expectation of success?
12:26:50 A. Well, even if the skilled person did form a
12:26:52 crystalline salt, there was no expectation that the
12:26:55 properties would be suitable for pharmaceutical development.
12:26:58 One couldn't have predicted those properties in advance.
12:27:01 MR. PRUSSIA: If you go to PDX-36.
12:27:01 BY MR. PRUSSIA:
12:27:03 Q. What properties go into identifying the best salt
12:27:06 from the salt screen?
12:27:06 A. Well, just a few key properties are the ease of
12:27:11 formation. It's important for manufacturability.
12:27:15 Solubility, we've been talking about. Still important.
12:27:19 Yield. Stability. Hygroscopicity. Flowability. The type
12:27:24 of drug product. Dosage form, for example, tablet. And the

12:27:28 expected dose.

12:27:30 MR. PRUSSIA: If we could please go to PTX-327.
12:27:34 It's Tab 10 in the binders. Please identify this reference
12:27:37 for the Court.
12:27:37 BY MR. PRUSSIA:
12:27:37 Q. Please identify this reference article.
12:27:37 A. This is the Berge article -- sorry, Counsel, which
12:27:40 tab did you say it was?
12:27:42 Q. Tab 10 in the binders.
12:27:42 A. Got it. Thank you.
12:27:52 Q. And sorry. I don't know.
12:27:54 A. I'm there. Yes.
12:27:55 Q. Okay. And what does what is the date of this
12:27:58 reference?
12:27:59 A. It's 1977. January 1977.
12:28:02 Q. And if we go to the first full paragraph on under
12:28:07 the -- yeah, right there.
12:28:09 What does Berge disclose about choosing the
12:28:13 appropriate salts?
12:28:13 A. Well, just that second sentence there at the bottom,
12:28:17 "choosing the appropriate salts, however, can be a very
12:28:20 difficult task, since each salt imparts unique properties to
12:28:24 the parent compound."
12:28:26 Q. How does this disclosure relate to your opinions in
12:28:28 this case?

12:28:28 A. Well, it's consistent with my opinions.
12:28:31 Q. If we turn to the next paragraph and focusing on the
12:28:34 sentence beginning with "unfortunately."
12:28:37 A. Okay.
12:28:37 Q. What does Berge disclose to a skilled artisan about
12:28:40 salt selection?
12:28:41 A. Well, Berge says, "Unfortunately, there is no
12:28:44 reliable way of predicting the influence of a particular
12:28:48 salt species on the behavior of the parent compound."
12:28:52 Q. How does this disclosure relate to your opinions in
12:28:55 this case?
12:28:56 A. Well, again, it's consistent with what I've been
12:28:59 saying.
12:29:00 MR. PRUSSIA: Now, you can pull that down.
12:29:00 BY MR. PRUSSIA:
12:29:02 Q. You testified earlier that there were more than 113
12:29:05 pharmaceutically acceptable salts that were known as of the
12:29:08 priority date; right?
12:29:08 A. Yes.
12:29:09 Q. Now, what, if any, information is disclosed in the
12:29:14 '473 patent regarding the desired properties of a
12:29:16 cabozantinib salt?
12:29:16 A. Nothing.
12:29:18 Q. And as of the priority date, what information was
12:29:20 disclosed regarding the problems that needed to be addressed

12:29:23 by forming a salt with cabozantinib?
12:29:26 A. None.
12:29:27 Q. So what information would have been available to
12:29:29 identify which of the entire genus of pharmaceutically
12:29:32 acceptable salts would have resulted in the right salt for
12:29:35 cabozantinib?
12:29:36 A. Nothing.
12:29:39 MR. PRUSSIA: If we turn to PDX-37, please.
12:29:39 BY MR. PRUSSIA:
12:29:42 Q. What is your fifth reason for why the claims are not
12:29:45 invalid for obviousness-type double patenting?
12:29:47 A. That objective evidence also confirms
12:29:51 non-obviousness.
12:29:51 MR. PRUSSIA: And if we go to PDX-38, please.
12:29:51 BY MR. PRUSSIA:
12:29:53 Q. At a high level what objective indicia did you
12:29:56 consider?
12:29:56 A. Well, there are unexpected results technically. That
12:30:01 is, the malate unexpectedly featured the best suite of
12:30:05 properties, as I've been talking about, and that's despite
12:30:09 the undesirable properties of the malate that I just talked
12:30:12 about a little bit earlier.
12:30:14 And as we heard from Dr. Shah yesterday,
12:30:17 crystalline cabozantinib malate has surprisingly better
12:30:20 dissolution properties than amorphous cabozantinib malate.

12:30:25 Q. So starting with your first point, what are the
12:30:27 reasons that it would have been unexpected that the malate
12:30:29 salt would have provided the best suite of properties?
12:30:32 A. Well, as I -- as I said, there's no way to predict
12:30:35 what the pharmaceutical properties would be until the salt
12:30:39 is made and characterized. And it turns out that the malate
12:30:44 salt featured the best suite of properties despite the
12:30:48 potential issues with the low acidity, the high molecular
12:30:52 weight, the tendency to form pseudodimerism and also the
12:30:55 fact that it has two acid groups.
12:30:59 Q. Focusing on your second point, what is your second
12:31:02 point?
12:31:02 A. Well, okay. So, again, that is from Dr. Shah's
12:31:08 testimony yesterday having to do with the fact that it turns
12:31:11 out unexpectedly the crystalline material has better
12:31:15 dissolution properties than the amorphous material.
12:31:17 MR. PRUSSIA: If we go to PDX --
12:31:19 THE COURT: Mr. Prussia, excuse me a second.
12:31:21 Dr. Trout, the thing you said a minute ago, that malate
12:31:24 features the best suite of properties, that's based on the
12:31:27 salt screen; right?
12:31:28 THE WITNESS: That's -- that's -- yes,
12:31:30 Your Honor. It's based on the salt screen as disclosed in
12:31:32 the asserted patents here. Correct. It wouldn't have been
12:31:36 known before that.

12:31:36 THE COURT: Okay. Right. Okay.

12:31:38 Sorry, go ahead.

12:31:40 MR. PRUSSIA: That's okay. It's for you, Your Honor. Any questions you have, please feel free.

12:31:44 PTX-225, please.

12:31:44 BY MR. PRUSSIA:

12:31:46 Q. What is this document?

12:31:47 A. That's the Shah declaration that Dr. Shah testified about yesterday.

12:31:52 MR. PRUSSIA: It's Tab 14 in the binders. If we could turn, please, to Figure 2.

12:31:54 BY MR. PRUSSIA:

12:31:59 Q. What does this figure show?

12:32:01 A. Well, this is a figure -- again, I think the Court saw this yesterday. So, this is dissolution, percentage dissolution from zero to a hundred. It goes up a little farther, but it's basically zero to a hundred as a function of time in minutes.

12:32:20 And you can see the curve with the squares, zero percent amorphous. In other words, a hundred percent crystalline. It dissolves very quickly, and in about 15 minutes that's very rapid. And by contrast, with 20 percent amorphous, this lower curve hardly dissolves or at least a small fraction dissolves even after an hour and a half.

12:32:44 Q. And what conclusions did you reach regarding this
12:32:48 data?
12:32:48 A. Well, this was unexpected for a couple reasons. One
12:32:52 is that in general, the skilled person would think that the
12:32:56 amorphous material would dissolve more quickly than the
12:32:59 crystalline material. And then, secondly, just the sheer
12:33:03 fact that the crystalline material, even given its low
12:33:07 solubility, dissolves fully within 15 minutes would have
12:33:11 been unexpected.
12:33:12 Q. You mentioned low solubility. Did you hear
12:33:16 Dr. Steed's testimony yesterday that a person of skill would
12:33:18 expect that low water solubility will correlate with the
12:33:21 slow dissolution rate?
12:33:22 A. Yes.
12:33:23 Q. How does that statement from Dr. Steed relate to your
12:33:26 opinions regarding unexpected results?
12:33:27 A. Well, that's the second aspect of my opinions on this
12:33:30 figure. Despite the low solubility, it dissolves completely
12:33:35 within 15 minutes. That's very rapid.
12:33:37 MR. PRUSSIA: If we go to JTX-5, which is Tab 17
12:33:40 in its binders.
12:33:40 BY MR. PRUSSIA:
12:33:41 Q. What is this document?
12:33:42 A. This is part of a file history.
12:33:47 MR. PRUSSIA: And if we go to Page 373 of JTX-5.

12:33:47 BY MR. PRUSSIA:

12:33:53 Q. What is this portion of the prosecution history?

12:33:55 A. This is an office action summary.

12:34:00 MR. PRUSSIA: If we go to the next page, 374.

12:34:00 BY MR. PRUSSIA:

12:34:03 Q. How did the examiner respond to the evidence submitted in the Shah declaration?

12:34:08 A. Well, if we look right under the heading -- and thank you for highlighting that -- "Declaration of Khalid Shah," it says, "The declaration of Khalid Shah" -- and I won't read the legal aspect of it -- "filed March 19, 2021, is sufficient to overcome the rejection of Claims 16-20 based upon" -- and then again the legal -- "as being unpatentable over Bannen in view of Berge."

12:34:36 Q. Now, let's focus on that. There's a reference to a Bannen patent application ending in the Number '928 and a Berge reference. Do you see that?

12:34:44 A. Yes.

12:34:45 Q. Are those the same, '928 patent application and the Berge reference, that Dr. Steed relied upon during his testimony to the Court?

12:34:52 A. Yes.

12:34:52 Q. So, what happened after submission of the Shah declaration during prosecution?

12:34:58 A. Well, based on the Shah declaration, the patent

examiner concluded that that evidence made it sufficient to overcome the rejection of the claims. In other words, allowed the claims of the patent.

MR. PRUSSIA: Okay. If you could turn to PTX-421, Tab 15 of the binders.

BY MR. PRUSSIA:

Q. What is this document?

A. Well, this is the cover page of an edited volume. The relevant chapter that we'll talk about is by Guillory.

MR. PRUSSIA: And can we go to that chapter on Page 3 of the document.

BY MR. PRUSSIA:

Q. Who is the author?

A. Again, Keith Guillory.

MR. PRUSSIA: And if we turn to Page 208, under the section titled, "Methods employed to obtain amorphous materials."

BY MR. PRUSSIA:

Q. Focusing on the very bottom of that page, what does Guillory disclose regarding the relationship between the dissolution rate of crystalline amorphous solids?

A. Well, again, Guillory discloses what the skilled person would expect. He says, "While crystalline solids offer the advantages of chemical and thermodynamic stability, amorphous solids are occasionally preferred

because they undergo dissolution at a faster rate."

Q. Okay. Just a few more questions, Dr. Steed.

MR. PRUSSIA: Can we have PDX-39, please.

THE WITNESS: Trout.

BY MR. PRUSSIA:

Q. Oh, Dr. Trout. Sorry about that.

What are your opinions on clinical and commercial success?

A. Well, again, the Court's heard this, that Cabometyx is the commercial or marketed pharmaceutical in which the cabozantinib -- the crystalline cabozantinib (L)-malate is incorporated as the API.

And as I've read from Dr. George's report and Mr. Tate's report, it is both a commercial and clinical success.

Q. Now, what is the commercial embodiment of the asserted crystalline malate salt patents?

A. Well, again, that's the Cabometyx. That's the brand name.

Q. And what is the API in Cabometyx?

A. Crystalline cabozantinib (L)-malate.

Q. What benefits does the crystalline cabozantinib (L)-malate invention provide?

A. Determinative benefits, it allows it to be manufactured and it allows it to be formulated or developed

12:37:22 into a formulation that's stable and safe and effective for
12:37:26 patients.
12:37:28 MR. PRUSSIA: Thank you, Dr. Trout.
12:37:29 Your Honor, Plaintiffs would proffer the
12:37:30 following exhibits: JTX-1, JTX-2, JTX-3, JTX-5, 6, 7, 9,
12:37:41 10. PTX-283, 225, 252, 258, 327, 421, 625, 774, and 783.
12:38:00 And with that, I pass the witness.
12:38:02 MR. LOMBARDI: No objections to any of them.
12:38:03 THE COURT: All right. Well, why don't we admit
12:38:05 them without objection.
12:37:32 (JTX Exhibit Nos. 1, 2, 3, 5, 6, 7, 9, 10, were
12:37:32 admitted into evidence.)
12:37:32 (PTX Exhibit Nos. 225, 252, 258, 283, 327, 421,
12:37:53 625, 774, and 783, were admitted into evidence.)
12:38:06 THE COURT: And since I was going to take a
12:38:08 lunch break in five minutes anyhow, why don't we take the
12:38:11 lunch break now and we can have cross-examination when we
12:38:13 return.
12:38:14 So, we'll take an hour and we'll start again at,
12:38:18 by that clock, 20 minutes of 2.
12:38:22 All right. We'll be in recess.
12:38:25 DEPUTY CLERK: All rise.
01:39:52 (Recess was taken.)
01:39:52 Deputy CLERK: All rise.
01:39:53 THE COURT: All right. Let's sit down and

continue.

MR. LOMBARDI: Your Honor, we're taking care of cross binders right now, if that's okay.

THE COURT: It's okay.

CROSS-EXAMINATION

BY MR. LOMBARDI:

Q. Good afternoon, Dr. Trout.

A. Good afternoon.

Q. I'm George Lombardi. We haven't had a chance to meet.

A. No. Nice to meet you.

Q. Nice to meet you.

Dr. Trout, you talked a lot about crystalline salts today; is that right?

A. Crystalline salts, yes.

Q. Crystalline salts may exist in multiple different polymorphic forms; is that right?

A. Yes.

Q. It is important in the pharmaceutical industry to identify and isolate different polymorphs of a crystalline salt; true?

A. Broadly speaking, true.

Q. This is because the fact that significant differences in chemical and physical characteristics may arise with changes in crystalline form; true?

01:41:56 A. Yes.
01:41:59 Q. These difference can affect the manufacturability,
01:42:02 the performance, and the quality of a drug product; correct?
01:42:08 A. Correct. They may.
01:42:11 Q. Different crystalline forms of a salt can be
01:42:14 characterized in various ways; is that right?
01:42:18 A. Yes.
01:42:19 Q. There are various ways that are available this to the
01:42:25 person of skill in the art; correct?
01:42:27 A. Yes.
01:42:28 Q. One method is XRPD; correct?
01:42:30 A. Yes.
01:42:33 Q. And you talked about that this morning, that's with
01:42:35 the peaks; right?
01:42:36 A. Correct.
01:42:39 Q. And there are others, but different forms create
01:42:43 different XRPD -- are they called diffractograms, is that
01:42:51 what you call the result of the next part of the XRPD
01:42:52 analysis?
01:42:52 A. Yes, diffractogram is the word.
01:42:54 Q. Okay. So different forms -- crystalline forms create
01:42:57 different XRPD diffractograms; correct?
01:43:00 A. Generally correct.
01:43:03 And, Counsel, it's important that you clarify
01:43:05 crystalline forms because we know without that crystalline

01:43:09 modifier it has a different meaning.
01:43:12 Q. I've been asking you about crystalline forms. You
01:43:15 understand that?
01:43:15 A. Yes.
01:43:16 Q. Okay. A substance can be identified by its
01:43:20 characteristic XRPD peaks; correct?
01:43:21 A. A particular polymorph generally can be, yes.
01:43:27 Q. And XRPD gives unique fingerprints of a crystalline
01:43:31 form; correct?
01:43:34 A. Again, generally correct.
01:43:35 Q. There are other ways to identify crystalline forms or
01:43:39 other ways that can be used to characterize crystalline
01:43:42 forms?
01:43:42 A. Yes.
01:43:45 Q. Such as thermal characterization. You can do thermal
01:43:51 characterization of a crystalline form?
01:43:53 A. Yes.
01:43:53 Q. You can do differential scanning calorimetry; is that
01:43:59 right?
01:43:59 A. Yes. It's a type of thermal method, as you
01:44:02 mentioned.
01:44:02 Q. Moisture absorption is another one you can use?
01:44:06 A. Yes.
01:44:06 MR. LOMBARDI: Okay. Now, you talked about the
01:44:09 patent here, so let me pull up JTX-1, which is the

01:44:09 '439 patent.
01:44:09 BY MR. LOMBARDI:
01:44:15 Q. I'm going to put it on the screen. If you want to
01:44:18 pull it up in front of you, you can. I'm just going to be
01:44:22 showing you the claims, so... If that helps you in
01:44:24 determining what you want to do.
01:44:26 A. Okay. If you could just point me to the place in the
01:44:29 binder, too, that would be helpful.
01:44:30 Q. It should be the first one in the first binder, I
01:44:33 think.
01:44:34 A. Perfect.
01:44:35 Q. Got it?
01:44:36 A. Yes. Thank you.
01:44:37 Q. Okay. So, let's go to where the claims are.
01:44:42 A. Oh, I apologize, Counsel. The first one is the '473.
01:44:46 Is that what you...
01:44:47 Q. It should -- is that Binder 1?
01:44:52 A. Yes.
01:44:58 Q. Excuse me. My mistake. It's about halfway through
01:45:00 Volume I. My mistake.
01:45:05 Do you have the number? JTX-1. It will say it
01:45:09 on the tab.
01:45:11 A. Okay. I've got it now. Thank you.
01:45:22 Q. Okay. All right. And -- and I'm back at the claims
01:45:27 at the very end, Doctor.

01:45:38 Are you there?
01:45:38 A. Yes.
01:45:39 Q. Okay. And that's what's displayed on the screen;
01:45:41 right?
01:45:42 A. Yes.
01:45:43 Q. And which claim is at issue here?
01:45:45 A. That's claim -- well, the asserted claim is 4.
01:45:50 Q. Right. And then it -- it's dependent and it goes
01:45:53 back up, eventually, to 1; is that right?
01:45:55 A. Correct.
01:45:55 Q. And 1 is where you see the word "crystalline"; right?
01:45:59 A. Yes.
01:45:59 Q. And that carries through all the way down to Claim 4;
01:46:02 correct?
01:46:03 A. Yes.
01:46:06 Q. Okay. So, if you -- I want you to -- I'm going to
01:46:10 give you a hypothetical, Doctor. I want you to assume that
01:46:15 Claim 1 says "Wherein said salt is a crystalline form."
01:46:21 Okay?
01:46:22 A. Okay.
01:46:23 Q. Would that cover all forms -- crystalline forms of
01:46:30 the malate salt of the -- is that the (L)-malate salt -- of
01:46:36 the malate salt?
01:46:40 A. All polymorphic forms you're asking about?
01:46:43 Q. I'm asking if it would cover all forms -- all

crystalline forms of the malate salt, if it had the word "form" after crystalline?

A. Well, again, under this hypothetical, if you read in form, it would incorporate at least the forms that we know today, the N-1, N-2, and the S.

Q. Okay. And any forms that arose in the future; right?

A. It could. One would have to do the analysis.

Q. Okay. Now, if you read it without my hypothetical, if you read it and it says "Wherein said salt is crystalline," it will still cover all crystalline forms; isn't that correct, as you understand it?

A. No, Counsel. I don't think that's the way to think about it. It covers cabozantinib malate, which is crystalline having the property of crystalline.

Q. Does it cover form S?

A. Yes.

Q. Does it cover form N-1?

A. Yes.

Q. Does it cover form N-2?

A. Yes.

Q. Does it cover every form that we know to exist today?

A. Yes.

Q. Will it cover every form that comes to being in the future?

A. That I'm not sure about.

01:48:08 Q. Okay. At least it would literally fall within those
01:48:11 words; correct?
01:48:12 A. In -- on a high level, yes.
01:48:18 Q. Okay. So, the asserted claims in this patent, the
01:48:25 '439 patent, are not limited to forms N-1 and N-2; is that
01:48:31 right?
01:48:31 A. Yes.
01:48:37 Q. And I think you've said this, but just to be sure:
01:48:39 It covers MSN's form S; correct?
01:48:44 A. Yes.
01:48:46 Q. All right. Now, we know, as a factual matter,
01:48:50 Doctor, that Exelixis did not invent form S.
01:48:58 We know that as a factual matter; correct?
01:49:00 A. That's my understanding. Yes.
01:49:03 Q. And we know that the -- the inventors actually did
01:49:07 not -- the Exelixis inventors actually did not invent any
01:49:10 forms beyond N-1 and N-2; correct?
01:49:13 A. Speaking of polymorphic forms, that's correct.
01:49:17 Q. And if we look at the specification, and you're
01:49:21 welcome to look at it if you want to, I think you'll be able
01:49:24 to answer this without, but there is extensive description
01:49:28 of the forms that were invented by Exelixis in the
01:49:32 specification; correct?
01:49:33 A. Again, crystalline or polymorphic forms. Yes.
01:49:38 Q. And you used those terms synonymously; right?

01:49:41 A. Yes.
01:49:43 Q. Okay. And there's an extensive description -- in the
01:49:48 specification, there is a disclosure of techniques used to
01:49:53 identify forms N-1, and N-2; is that right?
01:49:57 A. Yes.
01:49:58 Q. And then they are, in fact, identified according to
01:50:02 those techniques as N-1 and N-2; correct?
01:50:05 A. Correct.
01:50:06 Q. And the techniques are XRPD; correct?
01:50:09 A. Yes.
01:50:11 Q. Thermal characterization; correct?
01:50:13 A. Yes.
01:50:14 Q. Differential scanning calorimetry; correct?
01:50:17 A. Yes.
01:50:18 Q. If I say -- am I saying that wrong?
01:50:20 A. Differential scanning calorimetry.
01:50:24 Q. Calorimetry.
01:50:25 A. They're a type of thermal method.
01:50:27 Q. And moisture selection; correct?
01:50:29 A. Yes.
01:50:29 Q. All right. And the specification gives very specific
01:50:36 descriptions of how to prepare N-1 and N-2; is that correct?
01:50:40 A. Yes.
01:50:41 Q. And there's no question that the inventors have
01:50:45 provided sufficient information to identify N-1 and N-2; is

01:50:52 that correct?
01:50:52 A. Correct.
01:50:53 Q. Okay. There's no reference in the specification to
01:50:56 form S; is that correct?
01:50:58 A. Correct.
01:50:59 Q. There's no reference in the specification to any form
01:51:03 other than N-1 and N-2; correct?
01:51:05 A. And again, I -- I apologize, but it's important that
01:51:08 we differentiate salt form from crystalline form. That's
01:51:13 why if you say form --
01:51:14 Q. And I'm not meaning to make it -- if I short -- I'll
01:51:17 try not to shortcut it. I'll try not to shortcut it.
01:51:20 There's no description in the specification of
01:51:23 any crystalline form other than N-1 and N-2; is that right?
01:51:27 A. Correct.
01:51:29 Q. And the working examples in the specification relate
01:51:32 only to N-1 and N-2; correct?
01:51:34 A. Those -- no, not correct.
01:51:41 Q. Okay. Well, the only forms described in example --
01:51:47 working examples of the specification are forms N-1 and N-2,
01:51:51 the only crystalline forms are N-1 and N-2; is that correct?
01:51:54 A. With that adjective, correct. Crystalline
01:51:58 polymorphic forms, yes.
01:52:00 Q. There are no examples in the specification of how to
01:52:03 make the crystalline forms of cabozantinib (L)-malate other

than forms N-1 and N-2; correct?
A. Crystalline forms, yes.
Q. Okay. There is, also -- so you've got forms N-1 and N-2 described in the specification. My question now is: There's -- a person of skill in the art would not know whether other forms -- crystalline forms even existed based on the disclosure of the specification; isn't that right?
A. Yes.
Q. Is there is nothing in the specification that enables the person of skill in the art to predict whether there would be other forms?
A. Correct.
Q. A person of skill in the art cannot predict additional polymorphic forms based on the knowledge of forms N-1 and N-2; correct?
A. That's generally correct. And, I apologize, just to make the very clear, I'm assuming for all this, when you say "form" without the proviso, you don't mean salt form, you mean polymorphic form.
Q. I'm talking about crystalline form.
A. I know, but it's very important to make sure that we understand that that's what we're talking about.
Q. Okay. And even if one had a crystalline form in hand, there would be no way to predict in advance what other crystalline forms of the same compound you might obtain;

01:53:43 correct?
01:53:44 A. Without any information, no.
01:53:47 Q. There is just no way a person of skill in the art can
01:53:51 predict which polymorph can be obtained before starting
01:53:55 actual testing; is that right?
01:53:57 A. Correct. Not with accurate -- not with great
01:54:00 accuracy, correct.
01:54:01 Q. It's only through actual testing that one can
01:54:05 determine whether there are other polymorphic forms; is that
01:54:10 correct?
01:54:10 A. Yes.
01:54:12 Q. There is no way to know how many polymorphs there
01:54:16 will be based simply on the compound itself; correct?
01:54:20 A. I don't think that's fully correct.
01:54:24 Q. Okay.
01:54:25 A. In broad terms.
01:54:26 Q. Okay. There are many factors that can influence
01:54:36 crystallization; correct?
01:54:37 A. Yes.
01:54:46 Q. Just one moment, Doctor. Oops.
01:54:58 There are many factors that can influence
01:55:00 crystallization and that makes the process of identifying a
01:55:05 given crystalline form highly unpredictable; correct?
01:55:10 A. Again, you mean in the absence of any information? I
01:55:16 mean, you can identify a sample with the methods we've been

01:55:20 talking about.
01:55:21 Q. You can identify the sample. I'm talking about
01:55:24 identifying other crystalline forms of a compound that you
01:55:28 don't know about yet.
01:55:29 I'll give you the question again: There are
01:55:31 many factors that can influence the crystallization process,
01:55:36 and you said yes to that; right?
01:55:38 A. Yes.
01:55:39 Q. And the process of identifying a given crystalline
01:55:44 form is highly unpredictable; correct?
01:55:47 A. Again, if -- if you mean discover a new form, yes.
01:55:54 Q. Okay. That's what I mean. Thank you.
01:55:56 And there's no way to know how many polymorphs
01:56:06 can be obtained from a particular compound before doing the
01:56:11 actual testing; is that right?
01:56:12 A. Well, I don't think that's fully correct.
01:56:17 Q. Okay. Why is that not correct?
01:56:19 A. Because, as we talked about before, about half of
01:56:25 crystalline materials have only one polymorph. Most of the
01:56:30 others just have a handful. And I think we talked about the
01:56:33 extreme number was 14. So, you may not know the exact
01:56:37 number, but you have a ballpark that it's going to be
01:56:41 relatively small.
01:56:42 Q. You can't know until you actually do the testing,
01:56:45 though; correct?

A. You can't know the results of the test, but again, you have the ballpark, as I've explained.
Q. Okay. There are many factors that affect the formation of crystalline forms; correct?
A. In broad terms, yes.
Q. And the some of those factors include the process of manufacture; right?
A. Yes. I mean --
Q. Evaporation can effect --
A. Okay. Now I understand what you're saying. Yes.
Q. Melting can have an effect?
A. Again, your question is -- I think you mean process parameters. I'm --
Q. If that makes --
A. -- you are --
Q. If that makes it easier for you, Doctor.
A. Okay.
Q. Did you answer that one?
Melting can have an effect on the formation of polymorphs?
A. Again, how you do the melting, I think, is what you're getting at. I wouldn't -- it doesn't quite fit the way you're asking it.
Q. Well, there are a multitude of factors that can influence the crystallization of a salt; correct?

01:58:08 A. Yes.
01:58:09 Q. And among those factors are evaporation, melting --
01:58:21 A. Again, I would say it that way, Counsel.
01:58:23 Q. Well, let's -- well, let me complete the list.
01:58:29 Melting. Grinding could have an effect?
01:58:32 A. Again, I think you're asking the way you do each of
01:58:35 those might have an effect. And the answer is yes, if
01:58:38 that's what you're asking.
01:58:39 Q. That's what I'm asking.
01:58:40 A. Yes.
01:58:41 Q. Sublimation?
01:58:42 A. The way you do it might have an effect, yes.
01:58:45 Q. Okay. They could -- these kinds of methods can have
01:58:48 an effect on the formation of polymorphs; correct?
01:58:52 A. Yes.
01:58:55 Q. And there were a large number of other factors that
01:58:58 can influence the crystallization of a salt; correct?
01:59:02 A. Yes.
01:59:03 Q. Such as concentration of salt in solution?
01:59:06 A. Yes.
01:59:08 Q. Such as types of solvent used?
01:59:10 A. Yes.
01:59:12 Q. Such as seeding and agitation?
01:59:15 A. Yes.
01:59:16 Q. Such as interconversion of solid forms?

01:59:18 A. I mean, that's not a choice. That's a result.
01:59:24 Q. Okay. But all of those things can or -- well, the
01:59:29 presence of additives or impurities can have an effect, too;
01:59:33 right?
01:59:34 A. I didn't hear the --
01:59:35 Q. The presence of additives and impurities can have an
01:59:39 effect, too; is that right?
01:59:40 A. Yes.
01:59:41 Q. Okay. Solid forms of compound or salt are affected
01:59:46 by how they are prepared; correct?
01:59:49 A. They might be or might not be.
01:59:53 Q. Okay. You just don't know until you do it; correct?
01:59:57 A. You have to do the experiment, correct. Or have
02:00:00 information already.
02:00:01 Q. Okay. Okay.
02:00:04 So, Doctor, one moment.
02:00:19 In short, many factors can influence the
02:00:23 crystallization of a molecule; correct?
02:00:24 A. Yes.
02:00:26 Q. And that makes the process of identifying a given
02:00:30 crystalline form highly unpredictable and far from routine;
02:00:34 correct?
02:00:34 A. Yes, assuming you don't have information, again.
02:00:41 Q. Okay. Now, just to give us more real-world examples
02:00:51 of different polymorphs -- different polymorphs are created

through different manufacturing processes, we talked about that; right?

A. Yes, for example.

Q. And so form N-1 is created one way; is that right?

A. Yes.

Q. And form N-2 is different in the way it's created; correct?

A. Yes.

Q. And form N-1 is actually not equivalent to form N-2; correct?

A. Well, I think, as I've said, they have similar properties and they can be representative of each other.

Q. Okay. But, for instance, N-2 is by -- is not bioequivalent to N-1; correct?

Do you know?

A. I'm not sure about that.

Q. Okay. Well, do you know that a batch of N-2 is not bioequivalent to a batch of N-1; do you know one way or the other?

A. I don't know. I know the company decided to pursue N-2.

Q. Okay. And you know that form S, MSN's form S is manufactured differently than form N-2; correct?

A. Correct.

Q. And you know that it differs -- well, do you know

what part of the manufacturing process is different in that instance?

A. I've read. I don't have them memorized.

Q. Okay. But there is a difference which leads to the difference in the crystalline structure; correct?

A. Correct.

Q. All right. Now, there are other polymorph forms that exist beyond form S -- well, you agree that form S is a different polymorphic form, a different crystalline structure than N-1 and N-2; correct?

A. Yes.

Q. Okay. There are other forms beyond that; correct?

A. Well, I think I've called into question that, and I can elaborate more if you'd like. But I think that those are the three known or bona fide forms.

Q. Okay. Well, you have testified, or you were involved in the first case involving cabozantinib; correct?

A. Yes.

Q. And in that first case, you provided an expert report; correct?

A. Yes.

Q. And in that expert report, you talked about the number of reported forms of the malate crystalline salt correct?

A. I did talk about, I think, the same ones we've been

02:03:24 talking about in this trial; correct.
02:03:25 Q. And in that expert report, you stated that there --
02:03:31 well, why don't we just put this up?
02:03:34 MR. LOMBARDI: Let's go to the Cabo rebuttal
02:03:36 report on Paragraph 313.
02:03:54 THE WITNESS: And, counsel, could you -- it's a
02:03:55 little easier for me to read it, if you don't mind.
02:03:58 BY MR. LOMBARDI:
02:03:58 Q. Okay. Your rebuttal report is going to be, I think,
02:04:00 at the back of the second volume.
02:04:01 A. Okay. Thank you.
02:04:05 Oh, yes.
02:04:06 Q. Tell me when you're ready, Doctor.
02:04:28 A. I'm ready.
02:04:28 Q. Okay. I'm at Paragraph 313. It should be Page 108.
02:04:43 A. I'm there.
02:04:44 Q. Okay. And you note what -- you were testifying on
02:04:48 behalf -- providing expert report on behalf of Exelixis in
02:04:52 that case; correct?
02:04:53 A. Correct.
02:04:54 Q. And about -- one, two, three -- fourth line down, you
02:04:58 see, "As Dr. Steed concedes."
02:05:00 Do you see that?
02:05:01 A. Oh, yes.
02:05:07 Q. And it says, "As Dr. Steed concedes, the BMS team

02:05:11 reports form N-1, N-5 and several others."

02:05:16 BMS refers to what?

02:05:17 A. Well, that's a company that did a polymorph screen.

02:05:22 Q. And the company --

02:05:23 A. Oh, Bristol-Myers-Squibb.

02:05:25 Q. Thank you.

02:05:26 "Further, and as explained above, additional documents identified in discovery make clear that there are at least 12 reported forms of the cabozantinib (L)-malate salt."

02:05:38 Do you see that?

02:05:39 A. Yes.

02:05:40 Q. And then it says, "Form M and form S, that MSN represents it has created M-1 to M-4 forms and C-2 to C-5 forms in addition to form N-1 and N-2."

02:05:55 Do you see that?

02:05:55 A. Yes.

02:05:55 Q. And then you say, "Thus discovery plainly refutes Dr. Steed's opinion."

02:06:01 Correct?

02:06:02 A. That's what's written, yes.

02:06:04 Q. Okay. And then on page -- the next paragraph, paragraph -- or excuse me, two paragraphs down, Paragraph 315. This will be more towards the top, about -- let's see, again, four lines down.

02:06:26 Doctor, we'll highlight it. It begins, "As discussed above."

02:06:30 Do you see that?

02:06:30 A. Yes.

02:06:31 Q. And you said, "As discussed above, there are at least 12 reported forms of the (L)-malate salt: Form M and form S that MSN represents it has created, M-1 to M-4 forms and C-2 to C-5 forms, in addition to form N-1 and N-2."

02:06:52 Do you see that?

02:06:53 A. Yes. Yes.

02:06:54 Q. And this is what you said in that litigation; correct?

02:06:57 A. Yes. And in this litigation, Dr. Steed also thought that was the case and I did a deeper analysis, as I elaborated in my reports, and unfortunately that calls into question those documents.

02:07:11 Q. Okay. Well, Doctor, at this time, it was in Exelixis' interest -- well, at this time, I mean, at the time you wrote the report we have on the screen. Got that time -- time frame; right?

02:07:25 A. Yeah. Let me just confirm just to make sure I have the exact date, but yes, I have the time frame, but let me just look at the date.

02:07:39 Okay. I've got it. Thank you.

02:07:41 Q. So, you were involved in the *Cabo I* case, and you

02:07:44 filed an expert report?
02:07:45 A. Correct.
02:07:46 Q. And at that time, it was in Exelixis' interest that
02:07:52 you recognized 12 reported forms; is that right?
02:07:56 A. Counsel, I'm trying to report the best science I
02:07:59 could. That's what everyone thought at the time, including
02:08:03 Dr. Steed, as of a few months ago. A deeper analysis that I
02:08:08 did calls into question the clarity of that and those
02:08:12 documents.
02:08:13 Q. Okay. And so, in this litigation, it's in Exelixis'
02:08:17 best interest for you to say there are a smaller number of
02:08:21 forms; is that right?
02:08:22 A. I tried to do the scientific analysis. Exelixis'
02:08:27 interest is their own business. I went through those in
02:08:31 some depth over many pages, and I can demonstrate to you and
02:08:35 the Court why in additional depth these putative forms are
02:08:40 at least not clearly new forms.
02:08:42 Q. Now, Doctor, I understand and you -- what you showed
02:08:46 the judge this morning, what you chose to show was form M;
02:08:50 right?
02:08:50 A. From Mylan?
02:08:53 Yeah, well, there are two form Ms. It's a
02:08:58 little confusing. One was form M from MSN. And one was
02:09:03 form M-1 from Mylan.
02:09:05 Q. And it was form M-1 from Mylan that you showed the

judge this morning; is that right?

A. Well, I showed both, but, yes, including M-1, correct.

Q. Okay. All right. Now, in any event, as you agree that -- well, strike the question.

Now, polymorphs -- properties of polymorphs differ; is that right?

A. In general, they -- they can differ. The question is: Is it significant?

Q. Okay. And the physical properties of a crystalline salt can differ; is that right?

A. I'm sorry. Again, you're talking about polymorphs?

Q. Yes. Polymorphic forms, crystalline forms.

A. Okay.

Q. Their properties can differ; right?

A. They -- they might differ. They might not significantly.

Q. Okay. Different crystal forms of a particular salt can have different chemical properties; correct?

A. They can. Again, the question is: Are they significantly different?

Q. Okay. Crystalline solids -- and you don't find that out until you do the testing; right? Whether they're significantly different or not?

A. Yes.

02:10:29 Q. You don't find -- you agree? You don't find out
02:10:32 until you do the testing; correct?
02:10:33 A. Agreed.
02:10:35 Q. Crystalline solids have the same chemical composition
02:10:38 but different crystal structures. And, therefore, different
02:10:42 properties; correct?
02:10:43 A. Again, I think I know what you mean, but you're not
02:10:49 using the terminology properly. I think you mean different
02:10:53 crystalline polymorphs. But ask your question as you will.
02:10:58 I'll answer it.
02:10:59 Q. Crystalline solids have the same chemical
02:11:01 composition, but different crystalline structures. That
02:11:05 much is right; correct?
02:11:06 A. Again, I think to be precise, you're saying different
02:11:14 crystalline polymorphs, not just -- I think that's what you
02:11:18 mean, but...
02:11:18 Q. Okay. Crystalline solids --
02:11:20 A. Yes.
02:11:21 Q. -- can be classified into polymorphs; correct?
02:11:23 A. If you -- if you divide them up into polymorphs, yes.
02:11:29 Q. And those are forms having the same chemical
02:11:32 composition but different crystal structures; correct?
02:11:35 A. Crystalline forms, yes.
02:11:37 Q. And, therefore, they can have different densities?
02:11:40 A. They can.

Q. They can have different melting points?
A. Yes.
Q. They can have different solubilities?
A. Yes.
Q. And they can differ in other properties as well; correct?
A. They can, yes.
Q. They could be different in hygroscopicity; correct?
A. They can be.
Q. They can be different in solubility; correct?
A. Yes.
Q. They can be different in stability; correct?
A. They can be.
Q. They can be different in vapor pressure; correct?
A. They can be.
Q. They can be different even in color; correct?
A. Correct.
Q. Changes in a polymorphic form of a pharmaceutical compound can impact chemical stability?
A. Changes, meaning there's a transformation, if that's the --
Q. Changes in the polymorphic form.
A. Yes. Yes.
Q. Okay. It is true, sir, that in addition to these differences in polymorphic form affecting those properties,

the result can be a difference -- it could be variable potency of a compound.

A. That's a possibility. Yes.

Q. And by "potency," you mean how strong the compound is?

A. Well, I guess bioavailability perhaps, yes.

Q. Okay. Which is important in the pharmaceutical world; correct?

A. Yes.

Q. Very important in the pharmaceutical world?

A. Yes.

Q. And the prior art taught that the range and combinations of crystal growth conditions are virtually infinite; isn't that right?

A. Yes.

Q. And there is no way to guarantee the preparation of additional polymorphs of a substance, much less the generation of all of them; correct?

A. Could you please repeat that?

Q. Well, let me -- you actually wrote that -- you quoted somebody in your -- in your expert report in the prior case; correct?

A. I just didn't hear the first part of the statement.

Q. Okay. Well, let me show it to you.

MR. LOMBARDI: Let's go to the rebuttal report

at Paragraph 277. It's the same report you were looking at before if you want to look at it.

A. Okay.

Q. Do you see 277?

A. I do. Yes.

Q. Okay. And we can just start this at the beginning. This is your report, and let's make sure that your opinions are the same today, okay?

A. Oh, absolutely correct.

Q. "Further, even if a crystalline form is attained, there was no way at the priority date to predict in advance what crystalline form (or forms) that compound would assume."

You agree with that today?

A. Yes.

Q. Okay. "Critically, as explained" -- and then you have a reference to a section -- "solid forms of a compound or salt are affected by how they are prepared, which include factors such as solvents, temperatures, concentration, agitation, and pH."

Do you still have that opinion today?

A. Yes.

Q. "There is no standard approach, and there was no teaching in the prior art regarding the parameters to use in forming an (L)-malate salt of cabozantinib."

That's still true today?

A. Yes.

Q. "Without information, there was no way a POSA would have had any reasonable expectation of which form" -- "solid form" -- I'm sorry -- "which solid form, if any, would be obtained, nor any reasonable expectation of preparing the N-2 crystalline form."

Is that your opinion still today?

A. Yes.

Q. And then as the prior art taught -- and here you quote. Okay?

The range and combinations of crystal growth structures are virtually infinite and there is no way to guarantee the preparation of additional polymorphs of a substance, much less the generation of all of them.

Is that still your opinion, today?

A. Yes.

Q. Now, not every crystalline form or polymorph -- well, you're using those synonymously; right?

A. Yes. Yes.

Q. Okay. Can be used in a pharmaceutical composition; right?

A. I mean, it's a very general question. So, yes.

Q. Let me make sure -- I might have put a negative in there. I just want to make sure we're clear.

02:16:41 It is true that you cannot use every crystalline
02:16:47 form of a particular compound in a pharmaceutical
02:16:50 composition; is that right?
02:16:51 A. Oh. Maybe or maybe not, it depends on the situation.
02:16:58 Q. And you'd have to do the testing to know; right?
02:17:01 A. Yes, if you had no other information.
02:17:03 Q. Okay. And the FDA actually requires manufacturers to
02:17:10 provide information about polymorphic forms; correct?
02:17:14 A. I mean, there's guidelines but you could say de facto
02:17:21 requirements. Technically, they're guidelines. But yes,
02:17:24 guidelines.
02:17:24 Q. And significant differences and -- well, strike the
02:17:28 question.
02:17:28 And in the guidelines, they talk about the fact
02:17:32 that the manufacturer must make a determination whether
02:17:39 there are multiple solid state forms; right?
02:17:44 You have to do that. You have -- a solid state
02:17:46 form refers to something like crystalline forms; right?
02:17:48 A. Correct.
02:17:50 Q. Okay. Whether there are multiple solid state forms
02:17:53 and whether these affect the dissolution and bioavailability
02:17:57 of the drug?
02:18:00 A. Yes. That's correct. Yes.
02:18:02 Q. Okay. And they want you to do that because not every
02:18:06 polymorph will have an effect?

02:18:11 A. Again, the concern is that might be the case.
02:18:13 Q. And you can only know by doing the testing; is that
02:18:18 correct?
02:18:18 A. Yes.
02:18:20 Q. Okay. Now, there are examples of polymorphs that
02:18:27 worked for pharmaceutical purposes and polymorphs of the
02:18:31 same compound that didn't work; correct?
02:18:34 You've talked about this before; right?
02:18:37 A. I'm sure I have. And, yes, there are.
02:18:40 Q. Okay. And I just ask again: I mean, you understand
02:18:43 that N-1 is -- is not used in a pharmaceutical composition.
02:18:49 Form N-1 from Exelixis; correct?
02:18:50 A. That's my understanding. Exelixis commercialized
02:18:55 form N-2, yes.
02:18:56 Q. Right. Okay.
02:18:57 And so, that's one example of a polymorph for
02:19:00 the same compound where one -- polymorphs of the same
02:19:04 compound where one worked and one didn't work; correct?
02:19:07 A. No, I wouldn't say that.
02:19:09 Q. Oh, okay. All right. Well, how about -- Norvir is
02:19:13 an example that you've talked about; correct?
02:19:15 A. Yes.
02:19:16 Q. And Norvir was a situation where one polymorph of a
02:19:19 compound worked for pharmaceutical purposes in a
02:19:24 pharmaceutical composition; right?

02:19:26 A. Yes.
02:19:27 Q. And another polymorph emerged which did not work; is
02:19:32 that right?
02:19:32 A. I think that's right. I'm trying to remember
02:19:34 specifically Norvir, but that sounds right.
02:19:37 Q. Okay. Now, form S is, in fact, different than forms
02:19:46 N-1 and N-2 in several ways; isn't that right?
02:19:51 A. There are differences and there are similarities.
02:19:56 Q. Okay. Form S is hygroscopic?
02:19:59 A. It's been characterized as hygroscopic, yes.
02:20:02 Q. Form N-2 is not -- I'm sorry. I didn't mean to
02:20:04 interrupt you.
02:20:05 A. Sorry. I just wanted to make sure it's clear to the
02:20:07 Court, it's nonhygroscopic enough to be used in MSN's
02:20:13 product.
02:20:15 Q. And form N-2 is not hygroscopic; right?
02:20:19 A. That's how it's been characterized, correct.
02:20:22 Q. Form S has a low melting point; is that correct?
02:20:25 A. No, I wouldn't say it that way.
02:20:28 Q. Well, it has a -- it has a melting point lower than
02:20:31 186 to 187; correct?
02:20:33 A. That's correct.
02:20:35 Q. And you would characterize that -- that would be
02:20:37 considered -- well, that would be considered lower than the
02:20:40 form N-1, N-2 melting point; isn't that right?

02:20:43 A. Well, it has a lower melting point than the form N-1
02:20:48 or N-.2, I think I explicitly didn't say it's a low melting
02:20:54 point.
02:20:54 Q. Okay. And you talked about, I think you said, and I
02:20:59 might get the words wrong, but -- correct me if I've got it
02:21:02 wrong, but I think you said that form N-2 is the very best
02:21:05 in terms of stability of the polymorphs, the crystalline
02:21:09 forms of the cabo malate salt; is that right?
02:21:14 A. I don't think that's what I said. I think that
02:21:16 overall -- well, first of all, I think I said overall the
02:21:20 crystalline (L)-malate has the best suite or combination of
02:21:23 properties.
02:21:24 Q. Okay. And are you aware that Exelixis has said that
02:21:27 form S has a lower stability than N-2, a lesser stability?
02:21:31 A. I don't remember the specific document. But if you
02:21:38 say so, I'm sure that's the case. MSN says it's stable
02:21:42 enough to be a product.
02:21:52 Q. Just a few questions on your obviousness-type double
02:21:56 patenting. So, I'm changing gears, just so you know.
02:22:00 Obviousness-type double patenting now, Doctor.
02:22:03 So, the malate salt was known for use in
02:22:09 pharmaceutical compositions as of the priority date in this
02:22:12 case; is that right?
02:22:13 A. Again, your question -- I think what you mean is
02:22:20 malic acid, but...

02:22:22 Q. Well, or the malate salt that results from use of
02:22:25 malic acid.
02:22:26 A. There were, as we heard this morning, a small number
02:22:30 of examples in the past, yes.
02:22:31 Q. Yeah. (L)-malate salt was known to be a
02:22:35 pharmaceutically acceptable salt as of the early 2000s; is
02:22:38 that right?
02:22:39 A. Again, I'm just trying to help you with -- yes, for
02:22:45 specific compounds.
02:22:48 Q. Okay. And a person of skill in the art -- well, and
02:22:54 Sutent -- S-U-T-E-N-T, I think it is -- you've heard of
02:22:58 that; correct?
02:22:58 A. Yes.
02:22:59 Q. That's a pharmaceutical product?
02:23:00 A. Yes.
02:23:01 Q. And it's a pharmaceutical product that's an example
02:23:04 of a malic acid -- or being used in a formulation of
02:23:10 crystalline malate salt; correct?
02:23:12 A. It's a malate salt. I think that's the way to say
02:23:18 it.
02:23:18 Q. Okay. And that -- and it's used for treating cancer;
02:23:21 is that right?
02:23:21 A. Yes.
02:23:22 Q. And it's right there on the label of the Sutent
02:23:26 pharmaceutical product, that it's described as an (L)-malate

02:23:29 salt; correct?
02:23:30 A. Correct. And it's a different molecule than
02:23:32 cabozantinib.
02:23:33 Q. Right. Exactly.
02:23:34 So -- and so, you talked a little bit about some
02:23:44 lists -- some articles that listed potential counterions for
02:23:51 use in making salts; correct?
02:23:52 A. Yes.
02:23:55 Q. And when -- just so for vocabular purposes, when we
02:23:59 talk about counterions we're talking about something like
02:24:02 malic acid; right?
02:24:03 A. Yeah. Ionized form, yes.
02:24:05 Q. And that's what will react with the base and
02:24:07 hopefully make the salt, if that's what is going to happen;
02:24:10 correct?
02:24:10 A. The nonionized form reacts with the base to hopefully
02:24:16 make the ionized salt.
02:24:17 Q. Okay. And one of the -- you actually cited an
02:24:24 article in your expert report concerning discussions of
02:24:30 counterions that might be suitable for use; correct?
02:24:33 A. There were several articles cited. Yes.
02:24:37 Q. And -- yeah. And you took a chart -- a table out of
02:24:40 one of those articles; correct?
02:24:42 A. You mean the Stahl article?
02:24:46 Q. Yes, exactly.

02:24:47 A. Yes.
02:24:47 Q. The Stahl article.
02:24:48 MR. LOMBARDI: So let's put the Stahl article up
02:24:50 on the screen, PTX-610.
02:24:54 THE WITNESS: Again, please point me to the --
02:24:54 BY MR. LOMBARDI:
02:24:55 Q. I'm sorry. Volume II, and look at the tabs. It
02:25:00 will -- the tabs will tell you.
02:25:02 A. I got it. I got it. Thank you.
02:25:11 Oh, actually, I went to my report. You want to
02:25:13 go to the article. Do you know the PTX?
02:25:23 Q. It's PTX-610.
02:25:30 A. Okay. I got it. Thank you.
02:25:32 Q. Okay. Tell me when you're there.
02:25:34 A. I'm there.
02:25:35 Q. Okay. And this is the Stahl article, S-T-A-H-L;
02:25:40 correct?
02:25:41 A. Yes.
02:25:43 Q. And this is the one you cited in your report;
02:25:46 correct?
02:25:46 A. I believe so. Yes.
02:25:53 MR. LOMBARDI: And Stahl, at Page 333 -- Exhibit
02:26:04 Page 333.
02:26:04 BY MR. LOMBARDI:
02:26:04 Q. That's in the middle at the bottom, Doctor.

02:26:09 A. Okay.
02:26:13 Q. On that page, he refers to other reviews of
02:26:17 pharmaceutical salts; correct?
02:26:19 A. The first sentence.
02:26:21 Q. Yes, exactly. That first sentence.
02:26:24 And he talks about comprehensive reviews on
02:26:26 pharmaceutical salts by -- you say that Berge. Is that how
02:26:30 you say it?
02:26:31 A. I think there's been some debate this week whether
02:26:35 Berge or Berge.
02:26:36 Q. Whichever you want is fine with me.
02:26:38 A. French or German, I would say. Whatever.
02:26:40 Q. All right. Berge, Bighley and Monkhouse.
02:26:44 Do you see that?
02:26:44 A. Yes.
02:26:45 Q. And I think you said you've been here during trial
02:26:51 and you saw the counsel for Exelixis discussed Bighley with
02:26:57 Dr. Steed, I believe it was.
02:26:58 Do you remember that?
02:26:58 A. Yes.
02:27:00 Q. And you remember putting a chart up based on Bighley?
02:27:02 A. Yes.
02:27:03 Q. Okay. And if you go down to the third line in the
02:27:08 middle. It says, "While these authors presented the results
02:27:11 of a survey on the approval status of drug salts 25 years

ago, the present-day situation is different."

Do you see that?

A. Yes.

Q. "And accumulated knowledge and experience has led to a reduction of the number of acids and bases regarded as innocuous."

Do you see that?

A. Yes.

Q. "Therefore, it was" -- I'm skipping a line.

"Therefore, it was deemed timely to put up a revised list of useful salt-forming acids and bases."

Do you see that?

A. Yes.

Q. And is that one of the reasons you selected Stahl for your expert report, was its updated information?

A. I selected Stahl because of the table and what I discussed in my report.

Q. Okay. And it talks about -- in Stahl, it talks about -- well, let me strike the question.

A person of skill in the art would have been aware of something called Tong's Rule-of-2?

A. Yes. They've we've talked about that.

Q. Okay. And you talked about that.

It's a well-known rule of thumb; correct?

A. That's fair.

02:28:22 Q. And it was well-known in the early 2000s?
02:28:24 A. Yeah. Somewhere in the early 2000s, yeah.
02:28:31 Q. And a person of skill in the art would have been
02:28:33 aware of the Tong reference in that time frame; correct?
02:28:35 A. Yes.
02:28:38 Q. And a person of skill in the art would have been
02:28:42 motivated to select a counterion for salt screening with a
02:28:48 pK_a at least two units lower than the base, based on Tong's
02:28:53 rule of thumb; correct?
02:28:56 A. No, Counsel. I can't agree with that. I think I've
02:28:58 talked about that extensively.
02:29:01 Q. Okay. Well, let me just make sure that we're talking
02:29:05 about the same thing here so that there's no confusion.
02:29:23 Do you agree that a person of skill in the art
02:29:26 would have been motivated to select counterions for
02:29:30 screening that had a pK_a of at least two pH units lower than
02:29:35 the compound being screened?
02:29:38 Do you agree with that?
02:29:39 A. I think that would be a consideration that would not
02:29:44 be -- it would not be exclusive as we've been talking about
02:29:47 today.
02:29:48 Q. Okay. Okay. And -- but it's something that a person
02:29:51 of skill in the art would consider in determining what acid
02:29:56 to choose in trying to make a salt; correct?
02:29:59 A. The skilled person would know it and taking it into

account, and it wouldn't be exclusive.

Q. Okay. And there were techniques at the time that a person of skill in the art would be able to undertake to determine pK_a; right?

A. Yes.

Q. That was within the level of skill in the art at the time; is that right?

A. If the person wanted to, yes.

Q. And I think you've said you've heard in Court, but just so we say it, the pK_a for cabozantinib is 5.9, or around there at least?

A. That's the number Dr. Steed used. He never referenced that, but...

Q. Right. And the acceptable acids or counterions under the rule of thumb would have a pK_a of 3.9 or more; is that right?

A. Again, I think you mean less, but...

Q. I do.

A. Just trying to help you.

Q. Yeah, that's fine. That's fine. Do you want me to restate the question?

THE COURT: I think we've got it.

MR. LOMBARDI: Okay. That's fine.

BY MR. LOMBARDI:

Q. So -- so, a person could determine -- well, let me

02:31:10 just ask this: The Stahl chart also has a column that
02:31:16 indicates G-R-A-S; correct?
02:31:19 A. Yes.
02:31:21 Q. Okay. And G-R-A-S stands for generally regarded as
02:31:25 safe; correct?
02:31:26 A. Yeah, technically it's generally recognized as safe.
02:31:30 I think that's what we've been talking about. I know it
02:31:33 says "regarded" in the reference, but just to be clear.
02:31:36 Q. Okay. That's fine.
02:31:37 A. But that's close enough.
02:31:38 Q. And I'm not going to make you repeat this because
02:31:41 you've done it already, but you've gone through in
02:31:44 questioning at a deposition and determined kind of the
02:31:47 overlap between G-R-A-S and Tong's Rule-of-2 for that chart
02:31:54 in Stahl; is that right, with respect to cabozantinib?
02:31:56 A. I was asked GRAS --
02:32:03 Q. Yeah.
02:32:03 A. -- during my deposition; I do recall that.
02:32:05 Q. And when you find things that fit within the rule of
02:32:07 thumb and things that are G-R-A-S from that chart, the Stahl
02:32:12 chart, you come up with about nine acids; is that right?
02:32:16 Do you remember? If you don't remember...
02:32:18 A. I don't remember the exact number, as I testified in
02:32:21 my deposition. That would not exclude the skilled person
02:32:25 from incorporating others. So, it's not a really accurate

number.

Q. Okay. Okay.

MR. LOMBARDI: No further questions, Your Honor.

THE COURT: All right. Any redirect?

MR. PRUSSIA: Briefly, Your Honor.

REDIRECT EXAMINATION

BY MR. PRUSSIA:

Q. So, Dr. Trout, you were asked some questions about paragraph 277 of your report in the first MSN case, do you recall that?

A. Yes.

Q. And the issue that you were addressing in that portion of your report was obviousness, do you remember that?

A. Yes.

Q. And in the MSN one litigation, Dr. Steed was offering the opinion that it was routine and predictable to arrive at form N-2; does that refresh your memory?

A. Yes.

Q. And in this litigation, MSN and Dr. Steed are arguing the direct opposite, that obtaining polymorphs would be unpredictable; right?

A. Yes.

Q. Now, for 103, which was the issue that you were discussing in your report, what's your understanding of

whether the person of ordinary skill in the art would have had the benefit of the teachings of the specification of the crystalline malate salt patent?

A. The person would not have had the benefit of those teachings and even under 103.

Q. Thank you.

So in -- at the time you were making those statements, about what a person of ordinary skill in the art would have expected, was that with or without the benefit -- with or without the benefit of the teachings of the specification of the crystallize malate salt patents?

A. That's without the benefit of those patents, the asserted patents here.

Q. And the issue that you're addressing in this case is you're responding to their arguments with respect to written description; right?

A. Correct.

Q. And what role does the specification play in determining whether the inventor has had possession of the invention under written description?

A. Well, as I explained in my direct, there's a whole host of detail in the specification, including experimental detail -- I think there are 27 figures -- a lot of data, a lot of information, including the text that we went over, which demonstrate that the inventors possessed crystalline

cabozantinib malate.

Q. Now, with the guidance that's identified in the common specification, coupled with the knowledge of a person of ordinary skill in the art, would that have allowed a person of skill to perform a polymorph screen, and with a routine expectation of success, obtain and characterize additional polymorphs of crystalline cabozantinib (L)-malate?

A. If they were routine polymorphs from a routine screen, yes, they could have used the teaching to do that.

Q. And did MSN cite the crystalline malate salt patents in its patent application for form S?

A. Yes.

Q. And did Mylan and Cipla?

A. Yes.

Q. Now, you were asked some questions about form S. And just to make sure we're talking about the same thing, does -- what is the form of crystalline malate that's in the MSN ANDA product?

A. That's the MSN form S.

Q. And what form of crystalline cabozantinib malate is used in Cabometyx?

A. That's form N-2.

Q. And you understand that MSN has submitted an application to the FDA to market a generic version of

Cabometyx; do you understand that?

A. Yes.

Q. And has MSN represented to the FDA that its form S is bioequivalent to form N-2?

A. Yes.

MR. PRUSSIA: Nothing further.

THE COURT: All right. Dr. Trout, thank you. You may step down. Watch your step.

THE WITNESS: Yes. Thank you.

MS. WIGMORE: Your Honor, Exelixis calls for its next witness Dr. Daniel George.

THE COURT: All right.

DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: Yes, it's Dr. Daniel James George. It's D-A-N-I-E-L J-A-M-E-S G-E-O-R-G-E.

DANIEL JAMES GEORGE, the witness herein, after having been duly sworn under oath, was examined and testified as follows:

THE WITNESS: I do.

MS. WIGMORE: May I proceed, Your Honor?

THE COURT: Yes.

DIRECT EXAMINATION

BY MS. WIGMORE:

Q. Good afternoon, Dr. George. Would you please

02:37:29 introduce yourself?
02:37:29 A. Hi, I'm Dr. Daniel George.
02:37:33 Q. Have you been retained by Exelixis, Inc., as an
02:37:35 expert in this case?
02:37:36 A. I have.
02:37:38 Q. Generally speaking, what issues have you been asked
02:37:40 to address?
02:37:41 A. I've been asked to address the clinical success
02:37:44 associated with Cabometyx and the nexus between this
02:37:47 clinical success and the patents in question.
02:37:50 MS. WIGMORE: Let's have PDX-7.2.
02:37:50 BY MS. WIGMORE:
02:37:53 Q. What is shown on this slide?
02:37:54 A. That's a picture of me and my -- summary of my
02:37:57 education and experience.
02:37:58 Q. Where are you employed?
02:37:59 A. I am at Duke University.
02:38:01 Q. What do you do at Duke?
02:38:02 A. I'm a medical oncologist. I specialize in
02:38:06 genitourinary cancers. So kidney, bladder, prostate cancer.
02:38:10 And I also do research. I'm a professor of medicine.
02:38:12 Q. Have you been involved in any work involving tyrosine
02:38:16 kinase inhibitors?
02:38:16 A. I have. Yes.
02:38:18 Q. Can you give us some examples?

A. Sure. Yeah, since my -- finishing my fellowship in 1998. I was at Dana-Farber, did some early experiments with the early clinical trials with VEGF tyrosine kinase inhibitors. I moved to Duke and I've continued that work on up to the current day.

Q. For how long have you been researching tyrosine kinase inhibitors?

A. 25 years.

Q. Approximately what portion of your work involves treating patients?

A. About 40 percent.

Q. For how long have you been treating patients with kidney cancer?

A. For 25 years.

MS. WIGMORE: Let's please have PDX-7.3.

BY MS. WIGMORE:

Q. Dr. George, have you received any honors for your clinical work?

A. Yeah, overall, I mean, for my work at Duke, I was recently awarded Eleanor Easley Distinguished Chair in School of Medicine. I've also been recognized as a fellow of American Society of Clinical Oncology. In 2021, I was elected the chair of the Medical Steering Committee for the Kidney Cancer Association.

Q. What is the Kidney Cancer Association?

02:39:17 A. It's a non-profit advocacy group for patients with
02:39:21 kidney cancer.
02:39:22 Q. If you could please turn to Tab 1 in your binder.
02:39:24 MS. WIGMORE: And pull up PTX-775.
02:39:24 BY MS. WIGMORE:
02:39:29 Q. What is this document?
02:39:31 A. That's my CV.
02:39:34 Q. Is this an accurate representation of your
02:39:35 experience, publications, and honors and awards?
02:39:38 A. It is.
02:39:39 MS. WIGMORE: Your Honor, we offer Dr. Daniel
02:39:41 George as an expert in the treatment of cancer, including
02:39:45 renal cell carcinoma.
02:39:47 MR. COOPER: No objection.
02:39:48 THE COURT: You may proceed
02:39:50 BY MS. WIGMORE:
02:39:51 Q. Dr. George, are you familiar with the patent claims
02:39:52 asserted in this case?
02:39:54 A. I am.
02:39:54 Q. Were you here when Dr. Trout testified the asserted
02:39:57 claims of the crystalline malate salt patents cover
02:40:00 Cabometyx?
02:40:01 A. Yes.
02:40:02 Q. And do you understand that Claim 3 of the low
02:40:04 impurity patent covers Cabometyx?

02:40:06 A. Yes.
02:40:07 Q. Are you offering an ultimate opinion on the validity
02:40:10 of any of the asserted claims?
02:40:12 A. Not an ultimate opinion.
02:40:14 MS. WIGMORE: Let's have PDX-7.4.
02:40:14 BY MS. WIGMORE:
02:40:17 Q. Could you briefly describe your opinions?
02:40:19 A. Yeah, I have three opinions: One that Cabometyx is
02:40:23 and has been a clinical success in kidney cancer, that
02:40:28 Cabometyx satisfies a long-felt unmet need in patients, and
02:40:33 that there's a direct nexus between this clinical success
02:40:37 and the asserted claims.
02:40:39 Q. And we'll come to those in detail momentarily.
02:40:42 MS. WIGMORE: But if we could please have
02:40:44 PDX-7.5.
02:40:44 BY MS. WIGMORE:
02:40:45 Q. What information did you consider in forming your
02:40:47 opinions?
02:40:47 A. I based this on a review of the literature as well as
02:40:51 my extensive clinical experience as well as conversations
02:40:55 with my colleagues, Dr. Trout and Dr. Myerson.
02:40:57 Q. Are you familiar with defendants' expert, Dr. Anthony
02:41:01 Mega?
02:41:02 A. I am.
02:41:02 Q. Have you reviewed the opinions he has offered in this

02:41:05 case?
02:41:05 A. Yes, I have.
02:41:07 Q. Are you prepared to respond to those today?
02:41:08 A. Yes.
02:41:10 MS. WIGMORE: Let's have PDX-7.6.
02:41:10 BY MS. WIGMORE:
02:41:13 Q. What is Cabometyx?
02:41:13 A. This is Cabometyx. It's a product that we prescribe
02:41:18 regularly in clinic to patients with advanced kidney cancer.
02:41:22 And shown here in three formulations, 60 milligrams,
02:41:26 40 milligrams and 20 milligrams.
02:41:27 Q. Are you familiar with Cometriq?
02:41:29 A. I am. Yes.
02:41:30 Q. And what is Cometriq?
02:41:31 A. Cometriq is a capsule form of cabozantinib similar to
02:41:36 Cabometyx, and it's prescribed for the treatment of
02:41:39 medullary thyroid cancer.
02:41:41 Q. What is the active ingredient in Cabometyx and
02:41:43 Cometriq?
02:41:43 A. It's crystalline Cabometyx (L)-malate.
02:41:47 Q. And is that cabozantinib?
02:41:49 A. Sorry. Yes. Crystalline cabozantinib (L)-malate.
02:41:52 Q. Now, for the purpose of your testimony today, will
02:41:54 you focus on Cabometyx?
02:41:56 A. I will, yes.

02:41:57 Q. When was Cabometyx first approved by the Food & Drug Administration?
02:42:01 A. In 2016.
02:42:01 Q. Please turn to Tab 2 in your binder, which is PTX-1.
02:42:04 What is this document?
02:42:08 A. This is a patent for the -- for cabozantinib.
02:42:11 Q. I think you might be at the wrong tab. We're looking at PTX-1.
02:42:22 A. Oh, sorry. Oh, 1. Sorry.
02:42:24 Q. What is PTX --
02:42:25 A. Oh, yeah, yeah. Sorry, it's up on the screen. This is the prescribing information for Cabometyx.
02:42:28 Q. Is this sometimes referred to as the label or the package insert?
02:42:29 A. That's right.
02:42:31 Q. Now, if you could focus on the section in the left-hand side of the first page titled "Indications and Usage."
02:42:35 Do you see that?
02:42:37 A. I do. Yes.
02:42:38 Q. Are you familiar with the approved indications for Cabometyx?
02:42:39 A. I am. Yes.
02:42:42 Q. What indications are you focusing on in your testimony here today?
02:42:45
02:42:46
02:42:47
02:42:48
02:42:51
02:42:51
02:42:53
02:42:55

02:42:56 A. The first two, where one is for advanced renal cell
02:43:02 carcinoma.
02:43:02 Q. And what are those specific indications.
02:43:05 A. The first is for patients with advanced renal cell
02:43:08 carcinoma, and the second is for patients with advanced
02:43:09 renal cell carcinoma as a first-line treatment in
02:43:12 combination with nivolumab.
02:43:15 Q. What is renal cell carcinoma or RCC?
02:43:17 A. Renal cell carcinoma refers to the most common form
02:43:20 of kidney cancer. It's over 90 percent of kidney cancers
02:43:24 and its tumors are cancers that originate out of the kidney.
02:43:27 Q. What is first-line treatment?
02:43:28 A. First-line treatment refers to treatment that we give
02:43:32 to patients who have not received any prior systemic therapy
02:43:35 for advanced renal cell carcinoma.
02:43:37 Q. What is subsequent line treatment?
02:43:39 A. So subsequent line treatment refers to any treatment
02:43:42 that patients received after receiving a first-line
02:43:45 treatment.
02:43:45 Q. What is nivolumab?
02:43:47 A. Nivolumab is an immunotherapy. It's an antibody
02:43:51 targeted against a protein PD-1. It's also referred to as
02:43:55 an immuno checkpoint inhibitor.
02:43:57 Q. Now, we'll focus on kidney cancer today, but
02:44:00 generally speaking is Cabometyx approved for any other

02:44:03 cancers?
02:44:03 A. It's also approved, yes, for hepatocellular carcinoma
02:44:08 and differentiated thyroid cancer.
02:44:11 Q. Are you familiar with a concept of breakthrough
02:44:14 therapy designation?
02:44:14 A. I am, yes.
02:44:15 Q. What is that?
02:44:16 A. That's an FDA distinction for new drugs undergoing
02:44:21 review for indication. It's regulatory approval --
02:44:26 regulatory process to accelerate the approval process. And
02:44:29 it's granted at the request of the -- of the sponsor.
02:44:33 Q. How, if at all, does breakthrough therapy designation
02:44:36 apply to Cabometyx?
02:44:38 A. Cabometyx received breakthrough designation when it
02:44:42 was under review for the first indication of advanced renal
02:44:46 cell carcinoma.
02:44:46 Q. Did Cabometyx receive that designation for any other
02:44:49 indication?
02:44:49 A. Yes. Also when it was under review for
02:44:54 differentiated thyroid cancer.
02:44:56 MS. WIGMORE: If we could turn to Tab 3 in your
02:44:58 binder which is PTX-528. I'd like to move to your first
02:45:03 opinion regarding clinical success.
02:45:03 BY MS. WIGMORE:
02:45:06 Q. What is PTX-528?

02:45:08 A. This is the NCCN, or *National Comprehensive Cancer Network Practice Guidelines for Kidney Cancer*.
02:45:15 Q. What is the date of the document?
02:45:16 A. June 21, 2023.
02:45:19 Q. How is this document used by clinicians?
02:45:22 A. You know, this is helpful for clinicians in two ways. One, it really helps guide our practice. It gives us a -- a reference in which to justify or back up the treatments that we choose for our patients. It also helps with approval process with -- with papers.
02:45:39 MS. WIGMORE: If we could please turn to Page 15 that ends in Bates Number 1680.
02:45:41 BY MS. WIGMORE:
02:45:45 Q. What is clear cell histology?
02:45:48 A. Yeah. Clear cell histology refers to the most common form of renal cell carcinoma. It's about 75, 80 percent of renal cell carcinomas.
02:46:01 Q. Generally speaking, what does this table on Page 15 of the NCCN Guidelines address?
02:46:07 A. So, this table is sort of a summary, if you will, of the recommendations from the panel. You'll see on the far left, risk categories. This refers to the prognostic status of patients. Favorable risk is obviously better than the patients who have poor or intermediate risk features, and then next to that is a column for preferred regimens. These

are the recommendations from the panel consensus recommendations.

Q. Now, how does this table address Cabometyx specifically?

A. Yeah, Cabometyx is in several of these recommendations. You'll see for favorable risk preferred regimens, cabozantinib or Cabometyx is listed in combination with nivolumab. It's a Category I recommendation, which is the highest recommendation. And then you'll see it listed twice in the poor and intermediate risk categories, once again, with -- in combination with nivolumab is Category I. And then it's the only VEGF tyrosine kinase inhibitor listed as a single agent in this category by itself as monotherapy.

Q. Now, you've referred to this combination of Cabometyx and nivolumab.

A. Yes.

Q. How, if at all, does Cabometyx contribute to the success of that combination?

A. Yeah, that combination is the most recent clinical data around cabozantinib and nivolumab in the front-line setting, and it demonstrated a significant improvement in the delay to disease progression in overall survival for patients. In that study, the results of that combination outperformed what either cabozantinib alone or what nivolumab alone had been able to show. So it was really the

combination of both drugs working together to produce those results.

Q. Now, you pointed out that that table refers to cabozantinib. Is there any other form of cabozantinib approved to treat kidney cancer besides Cabometyx?

A. No, there is not.

Q. Could you please explain how Cabometyx has impacted your patients?

A. Yeah. You know, for our patients since 2016, when this first became available, Cabometyx really changed the landscape for our patients. This created a treatment option for the first time that extended survival for patients for the majority of patients in the subsequent lines of therapy. And it was really a life extending therapy for patients. It gave them hope.

Since then we've been able to use this drug now in the first-line setting where we're seeing extended disease periods of control near complete responses in patients. I have patients now on this drug literally for years. It's changed the life of patients with kidney cancer.

Q. If you could please turn to Tab 4 in your binder which is PTX-363.

What is this document?

A. This is the *Lancet Oncology* publication for the

02:49:00 1 METEOR study. This was the pivotal trial that led to the
02:49:03 2 first FDA indication for Cabometyx.
02:49:07 3 Q. And what was compared in this study?
02:49:09 4 A. So this is a Phase 4 study comparing cabozantinib
02:49:12 5 versus everolimus in patients with advanced renal cell
02:49:16 6 carcinoma treated with one or more prior VEGF tyrosine
02:49:20 7 kinase inhibitors.
02:49:20 8 Q. If you could turn, please, to the section titled
02:49:23 9 "Interpretation" toward the bottom of the first page.
02:49:26 10 A. Yes.
02:49:27 11 Q. Please read the first two sentences in that
02:49:29 12 paragraph.
02:49:29 13 A. "Treatment with cabozantinib increased overall
02:49:32 14 survival, delayed disease progression, and improved the
02:49:36 15 objective response compared with everolimus. Based on these
02:49:40 16 results, cabozantinib should be considered a new standard of
02:49:44 17 care treatment option for patients previously -- previously
02:49:47 18 treated patients with advanced renal cell carcinoma."
02:49:50 19 Q. If you could turn, please, to Tab 5 in your binder,
02:49:53 20 which is PTX-366.
02:49:56 21 What is this document?
02:49:56 22 A. This is the *Journal of Clinical Oncology*, or JCO,
02:50:01 23 publication for the CABOSUN study, a comparison of
02:50:05 24 cabozantinib versus sunitinib as initial therapy for
02:50:08 25 patients with advanced renal cell carcinoma.

02:50:11 Q. What is sunitinib?
02:50:12 A. Sunitinib has otherwise been referred to as Sutent.
02:50:15 This is another spectrum selective VEGF tyrosine kinase
02:50:19 inhibitor that was really the standard of care in the
02:50:23 first-line treatment of patients with advanced renal cell
02:50:26 carcinoma at the time.
02:50:26 Q. Could you please turn to the conclusion section on
02:50:29 the first page of this document, and read the conclusion for
02:50:33 the record?
02:50:34 A. "Cabozantinib demonstrated a significant clinical
02:50:37 benefit in the progression free survival in overall response
02:50:42 rate over standard of care sunitinib as first-line therapy
02:50:46 in patients with intermediate or poor risk metastatic renal
02:50:50 cell carcinoma."
02:50:50 Q. Let's turn to Tab 6 in your binder, which is PTX-367.
02:50:55 What is this document?
02:50:55 A. This is the *New England Journal of Medicine*
02:51:00 publication for the CheckMate 9ER study. This was a Phase 3
02:51:03 study comparing the combination of nivolumab plus
02:51:07 cabozantinib versus sunitinib for patients with advanced
02:51:09 renal cell carcinoma.
02:51:11 Q. Could you please turn to the conclusions section?
02:51:14 A. Yes.
02:51:14 Q. And what does the first sentence of the conclusion of
02:51:18 the study show?

02:51:19 A. Nivolumab plus cabozantinib had significant benefits
02:51:23 over sunitinib with respect to progression free survival,
02:51:27 overall survival and likelihood of response in patients with
02:51:31 previously untreated advanced renal cell carcinoma.
02:51:34 MS. WIGMORE: Let's turn to Tab 7 in your
02:51:36 binder, which is PTX-470.
02:51:39 THE WITNESS: Yes.
02:51:39 BY MS. WIGMORE:
02:51:39 Q. What is this document?
02:51:40 A. This is the Contact-03 publication from this year in
02:51:45 the journal *Lancet*, and it was a comparison -- a Phase 3
02:51:49 study comparing the combination of atezolizumab plus
02:51:53 cabozantinib versus cabozantinib monotherapy for patients
02:51:57 with renal cell carcinoma after progression with previous
02:52:00 immune checkpoint inhibitor.
02:52:02 Q. What is atezolizumab?
02:52:04 A. Atezolizumab is another immune checkpoint. It's
02:52:10 monoclonal antibody targeting the PD-L1 protein, which is
02:52:12 the protein that activates the PD1 receptor, so similar
02:52:17 pathway.
02:52:17 Q. Similar pathway to?
02:52:19 A. To nivolumab sulfate.
02:52:21 MS. WIGMORE: If you could turn to the findings.
02:52:21 BY MS. WIGMORE:
02:52:23 Q. And I want to direct your attention to the sentence

beginning "median."

Do you see that?

A. I do. Yes.

Q. What does that sentence convey about cabozantinib versus the combination of cabozantinib and atezolizumab?

A. Yeah. So the top level results from the study demonstrated that the median progression free survival for the combination with atezolizumab and cabozantinib was 10.6 months, but for cabozantinib monotherapy it was 10.8 months. Essentially, overlapping results in terms of the effectiveness of these two arms, but with greater side effects associated with the combination.

Q. Does that mean that this was a failed study?

A. Not at all. I mean, clinical trials are designed to answer a question and the question here was: Is there value to continuing with an immune checkpoint inhibitor in this subsequent line of therapy, and this definitively answered the question, just the answer is no, that cabozantinib monotherapy was really as effective as any other -- as the combination would be in this setting.

Q. What, if anything, did this study reveal about treatment with cabozantinib alone?

A. Well, you know, this is the new landscape of renal cell carcinoma. When the METEOR study was done, there were very few immune checkpoint inhibitor patients treated, so

now we're in a new situation where immune therapies are really the standard of care. This really provides a context for what we can expect for patients receiving Cabometyx now in this subsequent line therapy. And the results were actually better than what we saw with METEOR. If anything, this agent is even more relevant than it was seven years ago.

Q. Dr. George, from your perspective as a clinician, has Cabometyx been clinically successful?

A. Absolutely.

Q. How does that clinical success bear on your decision to prescribe Cabometyx?

A. Yeah. I prescribe Cabometyx routinely for my patients, either in the first line or in the subsequent line therapy, over 90 percent of my patients are receiving Cabometyx at some point in their journey.

Q. Would an oncologist continue to prescribe a drug that does not work?

A. No. Oncologists base their decisions on both the literature that we've just reviewed, as well as their own clinical experience. If a drug is not performing in their experience with patients, if they're not tolerating it or if the drug is not demonstrating clinical benefit, they're going to stop using it.

MS. WIGMORE: Let's turn to PDX-7.7.

BY MS. WIGMORE:

Q. Now, what is the second opinion you're offering in this case?

A. That Cabometyx satisfied a long felt, unmet clinical need.

Q. As of 2011, was there a need for improved kidney cancer therapies?

A. Absolutely.

Q. Was the same true as of 2009?

A. Yes.

Q. How, if at all, did Cabometyx address that need?

A. Well, you know, at the time we had really kind of a handful of these VEGF targeted TKIs or mTOR inhibitors, like everolimus. But the truth was if you look at our Medicare data from that time, median survivals were about a year. Our best patients, from clinical trial data, the median survivals were a little over two years. This isn't long enough. And these patients were all progressing on these first line therapies within a year or so. They needed other therapy.

Everolimus, at the time, was the only approved therapy and it was based on modest delay of progression of disease with no survival benefit. Cabometyx met that need. It demonstrated greater survival, greater disease -- delay in disease progression, and response.

02:55:57 Q. To the extent Dr. Mega suggests that Cabometyx
02:56:00 offered only a difference of degree in comparison to
02:56:05 existing therapies, do you agree?
02:56:06 A. No. I don't.
02:56:07 Q. What are the reasons you do not agree?
02:56:09 A. Well, first off, this is a different drug. Now, I
02:56:12 know all the VEGF inhibitor TKIs vary, but this is the only
02:56:16 one that was intentionally selected to be both a MET
02:56:20 inhibitor and a VEGF inhibitor. And the reason for that was
02:56:23 the biology of MET, which we went over in the last trial,
02:56:26 and the reason why that was important in kidney cancer,
02:56:29 particularly kidney cancer that was resistant, where did
02:56:32 this study show the benefit first? In exactly that patient
02:56:35 population.
02:56:35 And then we studied it in the other population,
02:56:38 the patients with the intermediate and poor risk patients
02:56:41 that were rapidly progressing on sunitinib in the front line
02:56:45 setting, and we demonstrated a superiority there that no
02:56:47 other VEGF tyrosine kinase inhibitor had been able to show
02:56:51 superiority versus sunitinib, even though others had tried.
02:56:55 So the clinical data really spoke to this drug
02:56:58 demonstrating unmet needs and also benefits that no other
02:57:02 VEGF TKI had shown.
02:57:04 Q. Is there a need for additional kidney cancer
02:57:06 therapies today?

02:57:07 A. Absolutely.
02:57:09 Q. Does that change your opinion about whether Cabometyx
02:57:12 fulfilled a long felt, unmet need?
02:57:14 A. Absolutely not.
02:57:15 Q. Why not?
02:57:16 A. Well, the truth is that our patients are still dying
02:57:20 today and the death rate associated with kidney cancer
02:57:23 hasn't gone down. We've delayed that time, but -- and
02:57:26 people are living longer than ever, but they're still dying
02:57:29 from this disease.
02:57:30 What Cabometyx has done is it's changed the
02:57:32 landscape, it's allowed patients to live longer and that
02:57:36 matters. Anybody that's known somebody who has died from
02:57:39 metastatic cancer, whether it's kidney cancer or any cancer,
02:57:42 knows that prolonging survival matters and it doesn't matter
02:57:46 if it's a few months or a year. That time matters.
02:57:49 So having drugs that can do that, that can be a
02:57:51 bridge to another therapy, it's hope. It's what our
02:57:55 patients are really after.
02:57:56 MS. WIGMORE: Let's go to PDX-7.8.
02:57:56 BY MS. WIGMORE:
02:58:00 Q. Have you considered whether there's a nexus between
02:58:02 the asserted claims in this case and the clinical benefits
02:58:06 of Cabometyx?
02:58:06 A. I have.

02:58:07 Q. What is your opinion?
02:58:08 A. Well, Cabometyx is what has worked in our clinic.
02:58:12 Cabometyx is what I prescribe. It's what our patients are
02:58:15 taking and they're taking it in the context -- not of a
02:58:18 clinical trial or controlled environment, but in real life
02:58:21 and they're dealing with it with the medications and the
02:58:26 concomitant drugs they have to take with the delays in
02:58:28 discontinuations they have to go through for other medical
02:58:31 issues and the travel or whatever circumstances they're
02:58:34 living in. The drug is stable. The drug is effective. The
02:58:37 drug is safe. The fact that we don't have this risk of --
02:58:44 you know, of genotoxic impurities. All of this matters for
02:58:50 our patients.
02:58:51 Q. You mentioned genotoxic impurities. Just briefly
02:58:53 remind us what that is.
02:58:54 A. Yeah. So that refers to chemical degradated products
02:58:59 from -- from the compound, in this case Cabometyx, that
02:59:02 could be harmful, particularly damaging to DNA.
02:59:05 Q. Are genotoxins the same as side effects?
02:59:08 A. No. Side effects refer to complications that
02:59:11 patients experience from the active pharmaceutical
02:59:15 ingredient, in this case Cabometyx. And typically from
02:59:19 effects that are on targets, meaning when we block this VEGF
02:59:23 receptor, we're having effects not just on the cancer but in
02:59:26 the whole body. That's why when we block that -- it

02:59:28 tightens the blood vessels, it's why we get diarrhea or high
02:59:31 blood pressure because we're blocking water absorption and
02:59:34 things like that.
02:59:35 Q. And is genotoxic -- a genotoxic side effect different
02:59:39 from that?
02:59:39 A. Yeah. So genotoxic side effects are silent, patients
02:59:42 don't feel them. Like they can't tell if something like
02:59:45 that is going on, but it could be going in insidiously in
02:59:48 their body and in their cells, and it has the risk over time
02:59:51 of ultimately causing cancer.
02:59:53 Q. Have genotoxic impurities presented challenges for
02:59:57 any other drug products?
02:59:58 A. Yeah, they have.
02:59:59 Q. Can you give us an example?
03:00:01 A. Yeah. One that I'm aware of is this drug valsartan
03:00:05 or Diovan. It was an antihypertensive drug that we used in
03:00:08 clinic and it got pulled because it was associated with --
03:00:11 it was found to have genotoxic impurities that were
03:00:14 increasing the risk of cancer.
03:00:16 Q. Now what, if any, role does the formulation of
03:00:19 Claim 3 of the '349 patent play in the clinical success of
03:00:23 Cabometyx?
03:00:24 A. Well, when I treat patients with Cabometyx,
03:00:27 I don't -- I don't worry about, you know, what form this is.
03:00:31 I know this is coming from -- you know, from Exelixis. I

know what this is. This is the crystalline form of cabozantinib (L)-malate and that gives me confidence. I know what I'm prescribing to these patients and I know that it's safe.

I know it has side effects and not everyone is going to tolerate it, but I can manage those things. It's the things that we don't know, the things that we can't measure that worry us, particularly now that we're using a drug in a setting where patients are living potentially for years on this drug.

Q. Now, in the previous trial against MSN concerning the '473 patent, you testified that the cabozantinib compound contributed to the success of Cabometyx.

Do you recall that?

A. I do.

Q. Does the fact that the cabozantinib compound impacts clinical success mean -- mean that the other features of Cabometyx do not?

A. Not at all.

Q. Why not?

A. Well, you know, cabozantinib (L)-malate in the crystalline form, I mean that's -- that's the whole molecule. What we study in the laboratory, what was designed and originally selected for, that -- that's not the drug product that we're ultimately treating patients with.

It's Cabometyx. It's the whole combination that ultimately is playing out in our patients and that's important.

I can't distill down the pieces of this and put percentages on what -- you know, how much -- what each is working. I just need to know that what I'm prescribing for patients is associated with the clinical data that we've studied and that I'm seeing play out on my patients individually.

MS. WIGMORE: Thank you, Dr. George. I have no further questions.

I would move to admit PTX-775, PTX-528, PTX-363, PTX-366, PTX-367 and PTX-470.

MR. COOPER: No objection.

THE COURT: Admitted without objection.

(PTX Exhibit Nos. 363, 366, 367, 470, 528, and 775, were admitted into evidence.)

MR. COOPER: May I proceed?

THE COURT: Yeah.

CROSS-EXAMINATION

BY MR. COOPER:

Q. Good afternoon, Dr. George. Good to see you again?

A. Good to see you, too.

Q. Now, Doctor George, in forming your opinions for this case, you believed that any drug that extends the lives of patients beyond previously available therapies is meeting a

long felt, unmet need; correct?

A. Yes.

Q. And of course you'd agree that there were drugs available that were approved before Cabometyx that extended the lives of patients beyond the available RCC treatments that were then available; correct?

A. Actually that's not true.

Q. Well, let me ask you this: After Cabometyx was approved, there have been about six new regimens that have extended the lives of RCC patients beyond previously available therapies; correct?

A. That's true.

Q. And there is still an unmet need today to improve RCC treatment on both the front line and subsequent line treatments for RCC; correct?

A. Yes.

Q. All right. Let's go back to 2009.

By 2009, there were eight TKIs that had been approved for cancer treatment other than cabozantinib; correct?

A. Yes.

Q. Those are imatinib; yes?

A. I'm sorry?

Q. Imatinib?

A. No, imatinib wasn't approved in renal cell carcinoma.

Q. That was -- my question was for cancer?
A. Oh, for cancer, yes, absolutely. Sorry.
Q. Gefitinib; right?
A. Yes.
Q. Erlotinib?
A. Yes.
Q. Sorafenib?
A. Yes.
Q. Sunitinib?
A. Yes.
Q. Dasatinib?
A. Yes.
Q. Nilotinib?
A. Yes.
Q. Pazopanib; correct?
A. Yes.
Q. And as a group by 2009, these TKIs had demonstrated clinical efficacy or benefits in several tumor types, including kidney cancer, lung cancer, breast cancer, and chronic leukemia; correct?
A. Yes.
Q. And each of those eight TKIs I just mentioned, except Gefitinib and erlotinib are known to be spectrum selective; correct?
A. That's correct.

03:05:11 Q. And the term "spectrum selective," that refers to a
03:05:14 drug that simultaneously inhibits multiple kinases that are
03:05:19 implicated in various forms of cancer; correct?
03:05:21 A. That's correct.
03:05:23 Q. And then there are also TKIs that were approved after
03:05:28 2009 to treat various forms of cancer that are spectrum
03:05:32 selective as well; correct?
03:05:34 A. That's right.
03:05:34 Q. And a few of those are vandetanib, lenvatinib, and
03:05:39 axitinib are just a few; correct?
03:05:41 A. Yes.
03:05:41 Q. And each of the spectrum-selective TKI drugs has its
03:05:47 own unique inhibition profile when it comes to their TKI
03:05:52 targets; correct?
03:05:53 Except for erlotinib and Gefitinib, of the ones
03:05:57 that I've -- we just talked about; is that true?
03:05:59 A. Yeah, that's generally true, yes.
03:06:01 Q. And even though none of them have the exact same TKI
03:06:05 targets, other TKIs have some overlapping targets with
03:06:10 cabozantinib; true?
03:06:11 A. Yeah. None of the ones you mentioned block MET.
03:06:16 Q. Right. But there are other overlapping TKI targets
03:06:19 that the -- that some of the other TKIs have with
03:06:23 cabozantinib; correct?
03:06:24 A. That's true.

03:06:26 Q. Now, one of the TKI targets you mentioned that
03:06:29 Cabometyx inhibits is VEGFR; right?
03:06:32 A. Yes.
03:06:33 Q. And both in 2009 and at the time later at Cabometyx's
03:06:38 approval, anti-VEGFR treatment was the standard of care for
03:06:43 RCC therapy; correct?
03:06:44 A. That's right.
03:06:46 Q. And -- but sunitinib, sorafenib, and pazopanib, those
03:06:50 were the first three anti-VEGFR TKIs to be approved for
03:06:55 front line RCC treatment; right?
03:06:58 A. Yes. Sorafenib, actually, after cytokine therapy,
03:07:02 but the other two, yes.
03:07:04 Q. And cabozantinib entered the market after those VEGFR
03:07:07 inhibitors; correct?
03:07:08 A. That's right.
03:07:09 Q. Cabometyx received an indication for RCC first-line
03:07:13 therapy in 2017; true?
03:07:15 A. In 20 -- the first-line treatment --
03:07:18 Q. First line?
03:07:19 A. -- on the -- I think it was 2019.
03:07:21 Q. Oh, okay. Thank you.
03:07:22 So, let's -- looking at about the 2015 to 2017
03:07:27 time frame, before and after Cabometyx was first initially
03:07:30 approved at all, you prescribed sunitinib to about 40 to
03:07:35 50 percent of your RCC patients; correct?

A. Yes.
Q. And in that same time frame, both before and after Cabometyx was approved, you prescribed pazopanib to around 30 percent of your RCC patients; true?
A. Roughly, yes.
Q. You showed us the NCCN guidelines, and so I'd like to pull those up at PTX-528.
MR. COOPER: Let's pull up the charts on Pages 15 to 16.
BY MR. COOPER:
Q. And so, you talked to us about some of the recommended regimens here, do you recall that?
A. I do. Yes.
Q. And for first-line treatment of RCC, cabozantinib is not the only preferred regimen here; agreed?
A. Agreed.
Q. For instance, axitinib and pembrolizumab combo therapy is one of the preferred regimens; right?
A. Something like that, yes.
Q. Thank you.
And you prescribed that combo therapy as first-line therapy for both your favorable risk and your poor or intermediate risk patients; correct?
A. I have. Yes.
Q. And same thing with the lenvatinib and pembrolizumab

combination therapy; correct?

A. Yes, it's -- it's pembrolizumab.

Q. Thank you for that.

But what you also did is you highlighted, in the top -- the top box there, cabozantinib, and you pointed out that that's the only monotherapy that is a preferred -- down in the intermediate box is what we're highlighting. There, cabozantinib by itself is the only monotherapy that is available that is in the preferred regimens, you remember talking about that?

A. I'm with you, Bryce.

Q. Thank you. Thank you.

But for most of your RCC patients, you don't prescribe cabozantinib as monotherapy for first-line treatment; correct?

A. Yeah, that -- that's really for patients who are not eligible or can't tolerate immunotherapy. We have patients with severe autoimmune diseases and whatnot. And cabozantinib there fills a really important unmet need.

Q. Sure. But I'm saying that you've got a list of preferred regimens, and for most of your patients, you don't prescribe cabozantinib as monotherapy for first-line treatment; is that correct?

A. That's correct.

Q. And then looking at the other recommend regimens

there are drugs like pazopanib and sunitinib, those are other TKIs that are listed for first-line treatment; correct?

A. Yes.

Q. And then in the subsequent line therapy chart, you see that cabozantinib is one of the recommended regimens for prior IO therapy patients; correct?

A. Yes.

Q. And -- but there are three other TKIs in there -- or three other regimens in there as well; correct?

A. Yes.

Q. And for patients in that category, you prescribe each of those regimens to your patients in that category; correct?

A. Yes.

Q. Okay. You mentioned the CABOSUN trial, and that's the trial that compared cabozantinib against sunitinib in first line -- for first-line RCC treatment; right?

A. That's correct.

Q. Now -- and you were involved in that trial right?

A. Yes, yes.

Q. There's never been a head-to-head study comparing overall survival or progression-free survival for cabozantinib versus any other TKI drug other than sunitinib; correct?

03:11:00 A. That's true.
03:11:02 Q. And so you aren't offering an opinion that Cabometyx
03:11:04 has been shown to be more effective than pazopanib, for
03:11:09 instance, for first-line RCC treatment; right?
03:11:12 A. Yeah, I -- you know, I would just say that, you know,
03:11:15 on -- on my own experience, and based on the fact that
03:11:19 pazopanib, or what we call pazopanib, had been studied
03:11:24 head-to-head against sunitinib in a large Phase 3 study, and
03:11:28 demonstrated no difference between those two agents that --
03:11:32 like we do often in cancer.
03:11:34 And we have to pick a treatment without Level 1
03:11:37 head-to-head evidence that extrapolate -- extrapolate from
03:11:41 that data to say that cabozantinib was superior to sunitinib
03:11:46 in the setting. And there's no other agent that's superior
03:11:50 to sunitinib. So it's my treatment of choice for those
03:11:53 patients in the front-line setting that can't receive
03:11:55 immunotherapy.
03:11:56 Q. And, Doctor, I want to ask you about the opinions
03:11:58 you're offering in this case, so if you could listen
03:12:01 carefully?
03:12:01 A. Okay.
03:12:02 Q. You're not offering an opinion that Cabometyx has
03:12:04 been shown to be more effective than pazopanib as first-line
03:12:08 therapy for RCC; is that fair?
03:12:09 A. No, I'm not.

Q. And I don't think we mentioned, but the CABOSUN trial was performed only with the intermediate or poor risk patients population; correct?

A. That's correct.

Q. So there's actually never been any head-to-head study between Cabometyx and another TKI for RCC patients with favorable risk; correct?

A. The Cabometyx and nivolumab versus as sunitinib --

Q. I said monotherapy.

A. Oh, monotherapy. No, you're correct.

Q. But getting to the point -- your point, that Cabometyx has been now approved --

MR. COOPER: You can take that down. Thank you.

BY MR. COOPER:

Q. -- been approved for combination therapy with nivolumab as a first-line treatment for RCC; correct?

A. That's correct.

Q. And you mentioned the CheckMate trial, we put that up real quick. And that compared Cabometyx plus nivolumab versus sunitinib; correct?

A. That's correct.

Q. Now, the combination therapy aspect of that is important; right?

A. Absolutely.

Q. Right. Because the IO drug that's part of that

combination therapy has been instrumental in improving patient outcomes; correct?

A. Yes.

Q. There's no study testing the TKIs sunitinib or pazopanib in combination with nivolumab as first-line therapy to treat RCC; yes or no?

A. That's because they were not tolerated.

Q. Okay.

Is my question true?

A. Yes, it's true.

Q. Okay. So the CheckMate trial -- and, also, the CheckMate trial wasn't the first study that compared a TKI and an IO combo therapy against just a TKI monotherapy; right?

A. That's true.

Q. Right. So there have been pembrolizumab plus axitinib that had also been shown to be more effective than sunitinib alone; right?

A. Yes.

Q. And avelumab and axitinib, that had also been shown to be more effective than sunitinib alone; correct?

A. Yes.

Q. Okay. So, this wasn't particularly unusual when you take into account there were two others; right?

A. It has differences in outcomes that we can go into if

03:14:17 you like.
03:14:18 Q. Okay. Now, you also talked about the METEOR trial,
03:14:25 you recall that?
03:14:25 A. Yes.
03:14:26 Q. You were involved in that trial, the working of that
03:14:29 trial as well; correct?
03:14:30 A. That's true, yes.
03:14:31 Q. And that one was where cabozantinib was tested
03:14:33 against everolimus -- you know, I did better in these in
03:14:37 your deposition -- cabozantinib versus everolimus?
03:14:41 A. Yes.
03:14:41 Q. And that was for second-line treatment; correct?
03:14:43 A. It was in subsequent --
03:14:45 Q. Subsequent line?
03:14:46 A. -- yeah, so one or more prior TKIs.
03:14:48 Q. And your -- other than with everolimus, there's never
03:14:53 been any head-to-head trials between Cabometyx and any other
03:14:56 TKI as subsequent-line RCC treatment; correct?
03:14:59 THE WITNESS: That's true.
03:15:01 Q. And you agree that other TKIs, like sunitinib and
03:15:05 sorafenib, have also been shown to successfully treat RCC
03:15:09 patients; correct?
03:15:10 A. Only in the front-line setting.
03:15:12 Q. All right. And you also showed us real quick the
03:15:16 CONTACT-03 trial. Do you recall that?

A. I do.
Q. And that was the trial where the cabozantinib combo therapy performed about as well as the cabozantinib monotherapy; right?
A. Yes.
Q. Doctor, one of your opinions on objective indicia is that Cabometyx is "a clinical success." That's what you've termed it; right?
A. Yes.
Q. And you formed an opinion on this subject because you received an instruction that quote/unquote clinical success can serve as objective evidence of non-obviousness of a patent. That's why you did that; right?
A. Well, I was asked to speak on the clinical success of this drug. I --
Q. Okay.
A. -- I didn't make it up. It's real.
Q. Right. What I'm saying is that the reason you're talking about it today is because you were instructed that is an actual objective indicia.
A. Yes.
Q. Okay. Now, cabozantinib does not improve clinical outcomes for all patients it's prescribed to; correct?
A. Absolutely. No drug does.
Q. And we can agree that RCC patients develop a

resistance to cabozantinib; correct?

A. Most do.

Q. Yeah. And they -- just like other TKIs; right?

A. Absolutely, yeah.

Q. Some patients cannot tolerate Cabometyx; is that true?

A. That's true.

Q. And Cabometyx has a similar toxicity profile to other TKIs; correct?

A. Yes.

Q. You -- very briefly, you mentioned that Cabometyx had received FDA -- had been designated as a breakthrough therapy by FDA; is that right?

A. Yes.

Q. And that's a regulatory designation that the FDA gives to certain drugs in development; is that true?

A. That's true.

Q. And but the definition for giving that breakthrough therapy designation is that it's for a drug that treats a serious or life-threatening condition; correct?

A. That's right.

Q. And we can agree that cancer is a serious or life-threatening condition; right?

A. Yes, but not all cancer therapies get breakthrough.

Q. I understand that, but that's -- that then allows

accelerated review by the FDA of the drug; correct?
A. Yes.
Q. Okay. You're -- shifting to just two questions about: You're familiar with MSN's expert, Dr. Mega; correct?
A. Yes.
Q. You consider him a respected researcher in the oncology field as well; yes?
A. I do.
Q. You mentioned at the end of your testimony a few opinions about genotoxicity. Do you recall that?
A. I do.
Q. You agree that in formulating a drug product, a research team is motivated to avoid or minimize genotoxic impurities as much as possible; correct?
A. Yes.
Q. And genotoxic impurities can, as I think you said, increase the chances of lifetime risks of secondary cancer; correct?
A. That's right.
Q. And regulatory agencies, I think you also said, such as the FDA, provide guidelines for limits of genotoxic impurities in drug substances and products; right?
A. Yes.
Q. And a research team who's developing a drug, they're

motivated to prepare a drug product under those FDA limits when possible; correct?

A. Sure.

MR. COOPER: No further questions. Thank you.

MS. WIGMORE: No redirect, Your Honor.

THE COURT: All right. Dr. George, thank you. Watch your step stepping down.

All right. So why don't we take the break until 25 minutes of 4:00.

All right?

DEPUTY CLERK: All rise.

(Recess was taken.)

DEPUTY CLERK: All rise.

THE COURT: All right. Let's be seated and --

MS. PIROZZOLO: Plaintiffs call Michael Tate.

THE COURT: Okay. Tate.

DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: It's Michael, M-I-C-H-A-E-L, Tate, T-A-T-E.

MICHAEL TATE, the witness herein, after having been duly affirmed under oath, was examined and testified as follows:

DIRECT EXAMINATION

BY MS. PIROZZOLO:

Q. Good afternoon, could you please introduce yourself?
A. Good afternoon my name is Mike Tate.
Q. Mr. Tate, have you been retained by Exelixis as an expert in this case?
A. I have, yes.
Q. What issues have you been asked to address?
A. So, I'm going to discuss the commercial success of the cabozantinib products and in particular Cabometyx.
MS. PIROZZOLO: Let's put Plaintiff's Demonstrative Exhibit 8 on the screen and go to Slide 2.
BY MS. PIROZZOLO:
Q. What is your educational background?
A. So I about have a BBA in finance. That is a bachelor of business administration degree from the University of Houston. And then I entered -- upon graduating from U of H, I entered the Krannert School of Management at Purdue University where I received a master of science in industrial administration degree which is similar to an MBA.
Q. Where do you work?
A. I am a vice president in the intellectual property practice of Charles River Associates. Charles River Associates is an economic business consulting firm.
Q. And what is the nature of your work at Charles River Associates?
A. So most of what I do involves the preparation of

financial and economic analyses for the purpose of determining damages or assessing commercial success in patent infringement cases.

Q. Okay.

MS. PIROZZOLO: Let's put Plaintiff's Exhibit 778 on the screen, and that's Tab 1 in your binder.

Q. Could you identify Exhibit 778?

A. Sure. This is my current CV.

Q. Does this exhibit provide an accurate summary of your education and professional experience?

A. It does, yes.

MS. PIROZZOLO: Your Honor, Exelixis offers Mr. Tate as an expert in the field of economic analysis as it pertains to commercial success.

MS. GRDEN: No objection.

THE COURT: All right. You may proceed.

BY MS. PIROZZOLO:

Q. Did you focus on any particular product in your analysis of commercial success?

A. So I looked at both products, Cometriq and Cabometyx, but for purposes of today, I'm going to focus on Cabometyx, which represents about 95 percent of the revenue that Exelixis has generated from the sale of the cabozantinib products.

Q. Do the Cabometyx tablets practice each of the four

asserted patents?

A. That's my understanding. Yes.

Q. At a high level what did you conclude with regard to commercial success?

A. So based on the analyses that I did, I determined that the Cabometyx product was a commercial success.

MS. PIROZZOLO: Let's pull up Slide 3, Plaintiff's Demonstrative 8.3.

BY MS. PIROZZOLO:

Q. Could you explain the factors that you considered in your analysis?

A. So, I did a number of different analyses. First, I determined the number of patients treated with the cabozantinib products. Then I identified and analyzed the relevant markets for Cabometyx. And then within each of those markets, I looked at various measures of market share, and then lastly I determined the amount of revenue that Exelixis generated from the sale of the product in the U.S. marketplace.

MS. PIROZZOLO: Let's turn to Plaintiff's Exhibit 824 which is Tab 2 in your binder.

BY MS. PIROZZOLO:

Q. Could you describe what Plaintiff's Exhibit 824 shows?

A. Sure. So, this is an internal Exelixis business

record. And this shows the cumulative number of patients treated by quarter with the cabozantinib product. And if I could focus everyone on the last bar on the right-hand side, that represents the number of patients treated in total as of about the end of April 2023. And you can see at the very top of the bar, there were approximately 55,000 patients treated with the cabozantinib products over the course of the products' life cycle.

Q. Now, one of the indications for Cabometyx is renal cell carcinoma; is that right?

A. That's correct. Yes.

Q. What percentage of Cabometyx prescriptions are for renal cell carcinoma?

A. So depending on the time period, it varies a bit, but I think greater than 92 or 93 percent of the patients of the usage is in the RCC segment of the marketplace. So that's the largest segment of use.

MS. PIROZZOLO: Let's put Plaintiff's Exhibit 823 on the screen, which is Tab 4 in your binder, and direct your attention to the second page of the exhibit on the right-hand side.

THE WITNESS: Okay.

BY MS. PIROZZOLO:

Q. What does this page show?

A. So, this again, is an internal Exelixis business

record, and this shows the TRX share of a market called CISVL.

And the CISVL is the acronym, Your Honor, for the products that you see listed in the key. Each one of those products is in this particular marketplace. And those products are in this marketplace because they are all TKIs or tyrosine kinase inhibitors. And so this is one way that Exelixis monitors the market for Cabometyx and the performance of Cabometyx.

Q. Okay. And does this graph pertain to certain indications for Cabometyx?

A. Yes. My understanding is this relates to the RCC indication in the U.S. marketplace.

Q. What did you learn about the market share of Cabometyx based on the data in exhibit -- Plaintiff's Exhibit 823?

A. So, if we could focus on the bottom of the chart, you'll see the blue shaded areas. Each one of these bars is the quarterly -- represents quarterly market shares. And you can see that the blue shaded area, that's Cabometyx. And we -- if we look at the left-hand bar -- the very left-hand bar, you see in Quarter 3 of 2020, Cabometyx's share in this particular market segment was 26 percent.

Now, that share grew a quarter -- over the quarter until we get out into the 2022 time frame and it

maintained itself at about 39 percent, beginning of the fourth quarter of 2022 into the first two quarters of 2023.

And as we can see, in this particular segment of the market, Cabometyx has achieved market leadership position in terms of TRxs and a TRx is the total number of prescriptions written in the marketplace. So Cabometyx has a 39 percent share of that marketplace relative to the other TKIs in the market.

Q. Was Cabometyx the first tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma?

A. It was not. It was the third or fourth product which received approval in that marketplace. So it was able to achieve these shares in spite of competition from products that existed in the marketplace prior to its launch in 2016.

Q. How, if at all, does that impact your analysis of commercial success?

A. Well, it shows me -- it's an indicator of commercial success given that Cabometyx was able to grow and then maintain its share and become the market leader.

Q. Now, we've been discussing a comparison of Cabometyx to other tyrosine kinase inhibitors. Did you also look at Cabometyx's share of the broader market for renal cell carcinoma treatments?

A. I did. Yes.

MS. PIROZZOLO: Let's put up Plaintiff's

Demonstrative 8.4.

BY MS. PIROZZOLO:

Q. What does this chart show?

A. So this charts reflects the overall RCC market and it's based on what's called new patient share. And I've pictured on the chart at the top, I think, nine products in the marketplace, but there are, depending on the time frame, 13 to 16 total products in the marketplace. But I put the top nine performers on the chart that you see here.

And so, this reflects the market shares of these products from Quarter 4 of 2019 through Quarter 4, 2022. And Cabometyx is found in two places on this chart, it's reflected in two places.

One is the solid red line, which is about -- if you look at about halfway down the chart, you see the solid red line. That's the share for Cabometyx in the overall RCC market when used as a monotherapy, so when used alone. And you can see that during the first half of the period reflected here, the share varied between 10 and 15 percent. And then that share grew in the latter half of the period to the 15 to 20 percent range.

Now, the second place that we need to focus on is the dashed red line, which is toward the bottom of the chart. That is the market share Cabometyx used in combination with Opdivo, that's the combination product. As

you can see in the first half of the period, the share varied between 1 and 4 percent and then it increased to the 5 to 8 percent range in the latter half of the chart.

Now, Cabometyx used a monotherapy, you can see ranked second or third in the marketplace, depending on the quarter that we're looking at. But if you add the two usages together, the monotherapy with the combination product, you would find that in the latter period, in the 2022 period, Cabometyx became the market leader.

MS. PIROZZOLO: Now, let's put up Plaintiff's Demonstrative Exhibit 8.5.

BY MS. PIROZZOLO:

Q. Could you explain what this chart shows?

A. Sure. So this is a similar chart and it is -- except it's not the overall market. Now, we're looking at the second line segment of the market and we heard Dr. George explain what -- what second-line therapy meant during his testimony. But here, again, we focus on two lines. One is the very top line that is the solid red line, that's Cabometyx used as a monotherapy. And you can see here that the share varied depending on the quarter between 20 percent and 35 percent. But Cabometyx was the clear market leader, even if we only look at the monotherapy alone.

But let's also focus then on the -- on the bottom of the chart where the dashed red line is. That,

again, reflects Cabometyx used in combination with Opdivo. And there we can see the share varied depending on the quarter between 2 and 5 or 6 percent. And so, in the second-line therapy, Cabometyx was the clear market leader throughout the time frame that we're looking at here.

Q. Now, did you also look at the revenue for Cabometyx?

A. I did. Yes.

MS. PIROZZOLO: Okay. Let's put Plaintiff's Demonstrative Exhibit 8.6 up.

BY MS. PIROZZOLO:

Q. Can you describe what is shown here?

A. Sure. So, this is a chart that reflects the annual net product revenue for the Cabometyx product sold in the U.S. We start in 2016, which was the launch year, and we see that year over year there was growth in net revenue in the U.S. marketplace. And we get to 2022 and we see approximately $1.4 billion of revenue for 2022. So, pretty significant growth between the launch in 2016 and -- and the most recent four-year data that we had in 2022.

Now, in total, for this time frame, there was $4.9 billion of revenue generated in the U.S. market by Exelixis from the sale of Cabometyx.

Q. What sources did you use to prepare the summary of revenue on PDX-8.6?

A. Yeah. So this -- this source here is PTX-802, which

is the profit and loss statement for Cabometyx. It's Exelixis' internal accounting document.

Q. Mr. Tate, do you have an understanding of whether there is a nexus between the commercial success of Cabometyx and the asserted claims?

A. I do. Yes.

Q. In summary, what did you -- and what is that understanding?

A. So, my understanding, the way I look at nexus in this case is I'm relying on the technical experts for the clinical benefits that -- the technical benefits that the product provides. It's those benefits that contribute to the clinical success that you heard Dr. George speak of. The clinical benefits then drive Dr. George, or oncologists like him, to prescribe the product to the relevant patient group. Not all patients, but the relevant patient group. Those prescriptions when filled, then generate the revenues and market shares that you saw on the slides that I presented here today. And so, there's a direct link between the technical aspects, the claims of the patent, and the revenue that is generated.

MS. PIROZZOLO: Thank you, Mr. Tate.

Your Honor, we would like to move the following exhibits used with Mr. Tate into evidence: Plaintiff's Exhibit 778, Plaintiff's Exhibit 824, Plaintiff's

Exhibit 823, Plaintiff's Exhibit 791, Plaintiff's Exhibit 853, and Plaintiff's Exhibit 802.

MS. GRDEN: No objection.

THE COURT: All right. Admitted without objection.

(PTX Exhibit Nos. 778, 791, 802, 823, 824, 853, were admitted into evidence.)

THE COURT: Thank you.

MS. GRDEN: We'll pass up some cross binders, Your Honor, with your permission.

THE COURT: Yeah.

CROSS-EXAMINATION

BY MS. GRDEN:

Q. Good afternoon, Mr. Tate. Nice to see you again.

A. Good afternoon.

Q. Mr. Tate, the last question that your counsel asked you was whether or not there is a nexus to the claimed invention of the patents in this case; right?

A. That's correct.

Q. You opine that there is; yes?

A. That's correct.

Q. You've opined on the commercial success of Cabometyx before this case; right?

A. I did. Yes.

Q. That was the case that we have been calling

Cabozantinib 1 case?

A. And MSN 1 or -- yes. That's correct.

Q. And one of the patents at issue there was the '473 patent that we've also heard a bit about during this case?

A. Correct. It was.

Q. And in that case you said there was a nexus between the '473 patent and Cabometyx; correct?

A. I said in part, yes. That part of the success was attributable to that patent, yes.

Q. Well, in fact, you concluded that the -- that Cabometyx was a commercial success and that the success was attributable to Claim 5 of the '473 patent; correct?

A. That's correct.

Q. And you went a little bit further. Isn't it right that you testified in Court there was a direct roadmap from Claim 5 of the '473 patent to revenue generation for Cabometyx; correct?

A. That's correct. All of these patents in combination work together. So, yes. That is correct.

MS. GRDEN: Thank you.

No further questions.

THE COURT: All right. Mr. Tate, you can step down.

Right? There's nothing more?

MS. PIROZZOLO: Plaintiff's rest, Your Honor.

THE COURT: Okay. So, watch your step.

THE WITNESS: Thank you.

THE COURT: All right. Defendant?

MR. COOPER: MSN calls Dr. Anthony Mega.

DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: Yes. Anthony Emmanuel Mega. A-N-T-H-O-N-Y, E-M-M-A-N-U-E-L, M-E-G-A.

ANTHONY MEGA, the witness herein, after having been duly sworn under oath, was examined and testified as follows:

THE WITNESS: I do.

MR. COOPER: May it please the Court?

DIRECT EXAMINATION

BY MR. COOPER:

Q. Good morning. Could you please introduce yourself to the Court?

A. Yes. I'm Anthony Mega, M.D.

Q. Dr. Mega, have you prepared slides to assist in your testimony today?

A. Yes, I did.

Q. For the record, those slides are on the screen marked in the bottom right-hand corner as DDX Mega, and then the slide number.

MR. COOPER: Could we please pull up DTX-536, and call out the second page.

BY MR. COOPER:

Q. Dr. Mega, could you please identify this exhibit?

A. Yes. This is my curriculum vitae dated June 2023.

Q. Does it accurately reflect your employment credentials and education?

A. Yes, it does.

MR. COOPER: Can we turn to Slide DDX 2.

BY MR. COOPER:

Q. Dr. Mega, are you a board certified physician?

A. Yes. I am board certified in medical oncology.

Q. How long have you been practicing in the field of medical oncology?

A. Nearly 30 years.

Q. Can you please briefly describe your current employment?

A. I'm a associate professor of medicine at Brown University. My clinical practice is via the Lifespan Cancer Institute. I'm employed by Brown Physicians, Incorporated, as part of that practice. So I'm medical director of genitourinary oncology within that group and I direct the multidisciplinary clinics in genitourinary oncology. I'm a staff oncologist practicing at the Lifespan Cancer Institute.

Q. So as part of your work, do you treat and -- see and treat cancer patients?
A. Yes, I do.
Q. Have you published any articles over the course of your career?
A. Yes, I have. I've published over 50 peer-reviewed articles and over 20 abstracts.
Q. Approximately how many times have you given testimony as an expert in the field of medical oncology?
A. I would say approximately 20 times.
MR. COOPER: Your Honor, defendants proffer Dr. Anthony Mega as an expert in the field of medical oncology.
MS. WIGMORE: No objection.
THE COURT: All right. You may proceed.
MR. COOPER: Thank you. You can take that down.
BY MR. COOPER:
Q. Dr. Mega, have you reviewed the four patents-in-suit in this case?
A. Yes, I have.
Q. Have you reviewed the claims that Exelixis has asserted against MSN?
A. I have.
Q. Were you present in Court and did you hear the entire testimony of Exelixis' expert Dr. George?

A. I have.

Q. Have you been engaged by MSN to provide opinions on certain objective indicia related to those asserted claims, namely long-felt and unmet need and what Dr. George has termed clinical success?

A. Yes.

Q. All right. Let's start with your brief background discussion. Dr. Mega, we've heard this term before, but can you please briefly describe what a tyrosine kinase is?

A. Yes. A tyrosine kinase is an enzyme that regulates cell growth through signal transduction. So, it will bind to proteins ligands, get -- get turned on. And then subsequently signal the cells to either proliferate, differentiate, turndown, program cell death, increase cell growth.

Q. What is the relationship between tyrosine kinases and cancer development?

A. Well, tyrosine kinases themselves are normal -- regulate normal functioning cells. But there are certain mutations that can occur that turn on these tyrosine kinases and don't allow them to get turned off, would be one example of such mutation.

In that situation, you get dysregulated cell growth, which we -- often then would lead to malignant or cancerous situations.

Q. What are tyrosine kinase inhibitors or TKIs?
A. Tyrosine kinase inhibitors block this activation of tyrosine kinases through pathways such as phosphorylation.
Q. We've heard from Dr. George that cabozantinib is a TKI. Had TKI drugs been developed to treat cancer before cabozantinib?
A. Yes, absolutely, yes.
MR. COOPER: Can we go to DDX-3?
BY MR. COOPER:
Q. What was the first TKI drug approved to treat cancer?
A. Yes, imatinib or the brand name Gleevec was the first TKI. This was launched in 2001. And it's indicated by, you know, what was really a momentous moment, even in my now increasingly lengthy career, which is this TIME magazine acknowledgment, that this represented a really profound advancement. It was new ammunition in cancer, just by the mechanism in which it worked for chronic myelogenous leukemia.
Q. How did imatinib compare to the previous ways of treating cancer?
A. Extraordinary first in efficacy. When you -- at that point in my career, I was taking care of patients with chronic myelogenous leukemia. And this was a situation where this was a uniformly lethal disease within a three to five-year period of time. And this -- this mechanism to

block tyrosine kinase pathways really led to a profound difference in regards to the outcomes for people with this leukemia. So, that -- the efficacy component was certainly one of the components. But there were others. It was an oral agent.

Q. As -- sorry.

A. So it was an oral therapy for leukemia which was, you know, one of the few oral therapies that you could effectively treat cancer with. And it had a much better side effect profile comparatively to chemotherapy.

Q. Were there in -- any other TKIs that were subsequently approved by FDA to treat cancer by 2009?

A. Yeah, I think the -- the advent of imatinib then just opened the door, and we had then another sequence of TKIs that subsequently were approved, which I have listed here. Gefitinib, erlotinib, sorafenib, dasatinib, sunitinib, lapatinib, nilotinib, and vandetanib.

Q. And we heard about each of these -- some of these drugs, I should say, are spectrum selective. Do you recall that testimony from Dr. George?

A. Yes.

Q. Can you remind us what that means?

A. Well, spectrum selective is a -- there are multiple pathways that -- tyrosine kinase pathways that these agents affect, with the exception of the -- of some of the

EGFR-specific agents. But -- so there were multiple pathways that can be affected by these tyrosine kinases.

Q. Does --

A. Inhibitors.

Q. And Dr. George mentioned that cabozantinib affects c-Met as one of its pathways, do you recall that?

A. Yes.

Q. Does each TKI pathway play a different role in tumor growth?

A. Well, the pathways themselves are distinct. But they often merge together into more prominent pathways that then influence cellular proliferation and growth, similar to, say, secondary roads leading into interstate highways.

Q. Okay.

MR. COOPER: Can you take that down. Thank you.

BY MR. COOPER:

Q. Dr. Mega, let's turn to your opinion regarding long-felt and unfelt need.

Can you please first just summarize for the Court the opinions you are going to testify about on that subject?

A. Yes. That cabozantinib did not meet a long-felt unmet need in the treatment of cancer, specifically the treatment of advanced renal cancer, or kidney cancer, and the treatment of advanced kidney cancer in combination with

immune checkpoint inhibitor.

Q. Now, has cabozantinib benefited individual RCC patients?

A. Oh, absolutely. They -- the drug has had a benefit for patients with advanced renal cell carcinoma, so there have been individual patients that have certainly benefited from it.

Q. In your opinion, does that clinical effect represent a difference in kind in the treatment of RCC?

A. It does not. I think it's an incremental improvement in therapy that represents a difference in degree.

Q. Okay. Can we go to -- you recall the two -- the indications that Dr. George referred to that Cabometyx treats; is that right?

A. Yes.

Q. Were there treatment options available for RCC, specifically, before cabozantinib received FDA approval for that indication?

A. Yes, there were -- there were numerous treatment options, several within that category of tyrosine kinase inhibitors.

Q. Were there any other categories of drugs that were -- that treated RCC when Cabometyx -- or by 2009?

A. Yes. There was the angiogenic agent, bevacizumab. There were cytokine agents, such as alpha interferon and

interleukin, too. And there was also the mTOR inhibitors.
Q. Since FDA first approved cabozantinib to treat RCC, have there been new TKIs and other types of treatment that have entered the market?
A. Yes. The growth has continued on a steady pace in regards to newer tyrosine kinase inhibitors, and also the advent of the immune checkpoint inhibitors within this treatment space.
Q. Dr. George discussed the NCCN guidelines for kidney cancer. Do you use those as part of your practice as well?
A. I do use them as part of my practice in a similar way that Dr. George noted.
MR. COOPER: Can we please pull up PTX-528? And let's go to Page 15 and call out the chart. All right.
BY MR. COOPER:
Q. Do you discuss -- do you recall Dr. George discussing this chart?
A. Yes, I do.
Q. Could you describe what types of consensus recommendations are provided by these guidelines?
A. Yes. We can see these recommendations sort of listed as preferred regimens, other recommended regimens, and useful and in certain circumstances. And there are a variety of factors considered.
Q. What are the criteria used for determining what

category a treatment regimen is placed in by the NCCN guidelines?

A. Well, it's a consensus determination that takes into consideration efficacy, toxicity, maturation, you know, where the data is from a maturation standpoint, affordability.

Q. And so are there criteria related to things other than efficacy and safety that are taken into consideration?

A. Yes, there are.

Q. And Dr. George highlighted where cabozantinib falls on this chart. Are there other preferred and recommended options for treatment of RCC in each of the patient risk categories?

A. Yes, we can see a number of options. Principally, axitinib, lenvatinib, and cabozantinib being in combination with immune checkpoint inhibitor.

Q. And can you describe exactly what an immune checkpoint inhibitor is?

A. Sure. And immune checkpoint inhibitor is a class of agents that essentially turn the switch on for our immune system to detect and to use our own body's host defenses to kill cancer cells. And so it draws the curtain away from the cancer cells so our own immune system can be activated against it.

Q. Is there a preferred standard -- or is there a

04:04:15 standard of care for treatment of RCC today?
04:04:18 A. Yes. I think the standard of care today is that all
04:04:22 patients that are appropriate should receive a combination
04:04:26 of an immune checkpoint inhibitor plus a tyrosine kinase
04:04:30 inhibitor.
04:04:31 Q. And Dr. George identified one of these combination
04:04:35 therapies that includes cabozantinib. In your opinion, are
04:04:39 any of the combination regimens in the preferred regimens
04:04:42 category or poor intermediate category better than the
04:04:47 others?
04:04:47 A. Even the consensus is that they're all on relatively
04:04:54 equal footing. And in regards to these reg -- these
04:04:58 combination regimens, they're either preferred regimens or
04:05:03 other recommended regimens.
04:05:04 Q. We noticed that cabozantinib is a monotherapy that's
04:05:07 in a poor intermediate risk group for a preferred regimen.
04:05:12 Are physicians typically prescribing cabozantinib
04:05:15 monotherapy for first-line treatment today?
04:05:18 A. Generally speaking, that first-line monotherapy is
04:05:21 not being utilized today.
04:05:22 Q. And with regards to first-line RCC therapy, do you
04:05:27 recall Dr. George testified about the Sunitinib trial?
04:05:30 A. Yes.
04:05:32 Q. Generally what did the CABOSUN study show?
04:05:34 A. Well, the CABOSUN trial was a randomized Phase II

04:05:39 study that looked at sunitinib versus cabozantinib as a
04:05:46 first-line therapy for advanced renal cell carcinoma in
04:05:52 previously untreated patients.
04:05:54 Q. And what did the -- and what did the results show?
04:05:57 A. Well, the results showed that there was a -- there
04:06:01 was a statistically significant, albeit modest, difference
04:06:05 in -- in progression-free survival, with cabozantinib being
04:06:11 approximately eight and a half months to five and a half
04:06:14 months for -- for sunitinib. But there was no overall
04:06:19 survival benefit, because the study really wasn't designed
04:06:24 to be powered to show a survival benefit.
04:06:26 Q. How did sunitinib perform in CABOSUN -- in the
04:06:29 CABOSUN trial compared to other trials that had included
04:06:34 sunitinib?
04:06:34 A. CABOSUN truly underperformed in this study, even if
04:06:39 we -- if we look at other comparable studies in which
04:06:44 sunitinib was used as a -- was used as the control arm, the
04:06:51 progression-free survival rates were much better than what
04:06:54 it showed in the CABOSUN trial.
04:06:55 Q. Now, cabozantinib has also been tested in combination
04:06:59 with nivolumab against sunitinib. Did you hear Dr. George's
04:07:04 testimony about the CheckMate study?
04:07:06 A. Yes, I did.
04:07:09 Q. And, again, what type of drug is nivolumab?
04:07:11 A. That's one of those immune checkpoint inhibitors.

04:07:14 Q. Was the check point -- CheckMate study -- if I said
04:07:17 check point, I apologize -- CheckMate study the first study
04:07:21 comparing a combination drug regimen of a checkpoint
04:07:24 inhibitor and TKI drug versus sunitinib?
04:07:26 A. No. There were other studies that had reported out
04:07:33 pembrolizumab plus axitinib, which was a keynote study. And
04:07:38 then nivolumab plus axitinib, and sort of simultaneously was
04:07:42 a study using the tyrosine kinase lenvatinib with the
04:07:48 pembrolizumab.
04:07:49 Q. Have those TKI and IO combination regimens also shown
04:07:54 superiority against sunitinib?
04:07:56 A. Yes, they have.
04:07:57 Q. And just to make sure it's clear for the record, what
04:08:01 is an IO?
04:08:03 Was that referred to?
04:08:03 A. Yeah, that's an immuno oncology agent.
04:08:08 Q. And so that's a checkpoint inhibitor?
04:08:09 A. That's a checkpoint inhibitor.
04:08:11 Q. So was there anything new or unexpected about the
04:08:14 fact that cabozantinib plus nivolumab combination therapy
04:08:19 performed better than sunitinib alone in the CheckMate
04:08:21 study?
04:08:22 A. No, I think there was already a lead-in that -- that
04:08:25 there was evidence that -- well, first of all, to just take
04:08:28 a step back. We all -- even we knew going in that immune

checkpoint inhibitors as a single-class therapy was very active in renal cell carcinoma, almost to the extent of, you know, speaking to it as ground-breaking activity because of the potential durable responses.

So, then, the addition of a tyrosine kinase inhibitor to get what scientifically we believed is a synergistic effect by blocking angiogenesis, affecting immune modulation and then adding on top of that an immune checkpoint inhibitor, I think was -- it was expected that this combination was going to give us better response rates, and it was evident that that was happening even before the CheckMate 9ER study reported out.

Q. Now, shifting to second-line treatment of RCC. Dr. George identified cabozantinib as an option to treat patients for that category.

Do you recall that?

A. Yes.

Q. Are there other recommended options that physicians use in order to treat patients in that category?

A. Yes, I think if we look again at the NCCN guidelines.

Q. Sure.

A. You see that --

Q. That's PTX-528, Page 16.

Okay. Go ahead.

A. And we can see in those, I think, exceedingly

decreasing number of people who are -- who have not received immune checkpoint inhibitor therapy we then have the option of adding an immune checkpoint inhibitor. And then the people that, I think, is now the larger category, the ones that have received prior immune oncology therapy, we can see that there are four different tyrosine kinase -- tyrosine kinase therapies that are recommended.

Q. Do you recall Dr. George showed the METEOR study that tested cabozantinib as subsequent-line RCC therapy?

A. Yes, I do.

Q. Could you briefly remind us what that study showed?

A. Yeah. So the METEOR study was a Phase 3 randomized control trial comparing patients who had received at least one prior VEGF inhibitor therapy or tyrosine kinase inhibitor therapy and randomized them to compare cabozantinib not to another tyrosine kinase inhibitor, but to an mTOR inhibitor everolimus.

Q. Has cabozantinib been tested head to head against any TKIs for second-line treatment of RCC?

A. No, it has not.

Q. Dr. George also talked about the CONTACT-03 study. Can you remind us what the objective of that study was?

A. Yeah, the CONTACT-03 study was a study that was to answer a very important question that -- many of us had wondered if continuing -- continuing immune checkpoint

inhibitor therapy after you failed the regimen was still beneficial say if you've changed the partner, the tyrosine kinase inhibitor, and this was a study of continuation of immune checkpoint inhibitor therapy with a TKI, namely, cabozantinib versus just TKI therapy as monotherapy. And so the aim of the study was really to look at the benefit of continuing the immune checkpoint inhibitor, and there was no benefit in continuing it. And it was more toxic.

Q. Dr. Mega, in your opinion, is there a -- was there a long-felt unmet need for additional or improved treatment options for treating patients with RCC in a first or second-line therapy?

Strike that. Let me ask that --

In your opinion, does there remain a long-felt and unmet need today for additional or improved treatment options for treating patients with RCC in the first or subsequent lines?

A. I agree with Dr. George that the need remains for us to continue to try to build on the therapies that have advanced our options for treatment. So, yes, I still believe there is a an unmet need in the treatment for advanced renal cell carcinoma.

Q. How does cabozantinib's toxicity profile compare to other TKIs?

A. As a class of agents, they have their issues with

toxicity and patients usually will be experiencing side effects and that includes cabozantinib.

Q. Now, Dr. George provided an opinion on what he termed clinical success.

Did you hear that testimony?

A. I did.

Q. And he talked about his personal experience with his patients. How does your experience with cabozantinib or cabozantinib compare?

A. Like many of the tyrosine kinase inhibitors available for therapy, I've seen patients individually benefit and some benefit significantly, and that's what cabozantinib and a number of other agents -- as we have listed.

But I've also seen it not -- them not work, including cabozantinib, and, unfortunately, a large number of patients. And I've seen them have significant toxicity in a lot of patients.

Q. So with respect to your opinions on the objective indicia that you addressed, what is your opinion as to whether Cabometyx represents a different kind of treatment in the treatment of RCC?

A. It's my opinion that it does not represent a different kind of treatment. There remains an unmet need that it represents an incremental therapeutic growth and is really just a difference in degree rather than a difference

in kind.

MR. COOPER: Thank you, Dr. Mega. I pass the witness.

THE COURT: So, before you begin, Doctor, so is it your opinion that there's been a long-felt, unmet need basically for a long period of time?

THE WITNESS: For advanced renal cell carcinoma? Through my career, yes.

THE COURT: And so -- but your opinion is Cabometyx didn't meet it?

THE WITNESS: No. Cabometyx didn't meet it. And I think the major advancement has been in immunotherapeutics, not just for renal cell carcinoma, but for a whole host of malignancies because of the ability to get these very durable responses with treatment or that can last for years.

THE COURT: All right. Thank you. Go ahead.

CROSS-EXAMINATION

BY MS. WIGMORE:

Q. Good afternoon, Dr. Mega. You have prescribed Cabometyx to treat patients with advanced renal cell carcinoma; correct?

A. Yes, I have.

Q. And you do not dispute that Cabometyx had clinical success in some patients; correct?

04:15:59 A. No, I -- I agree that it did.
04:16:01 Q. You have observed Cabometyx improve outcomes for
04:16:05 certain patients; correct?
04:16:06 A. I have similar to other TKIs, yes.
04:16:10 Q. And you continue to prescribe Cabometyx today;
04:16:12 correct?
04:16:13 A. I do along with other TKIs yes.
04:16:16 Q. You would not continue to prescribe an oncology
04:16:19 therapy that was not effective; correct?
04:16:21 A. No, I would not.
04:16:24 Q. Multiple characteristics can contribute to the
04:16:26 clinical success of a drug product; correct?
04:16:29 A. I'm not sure I understand the multiple -- what
04:16:35 multiple characteristics we're speaking of, but I could -- I
04:16:38 could see how they could contribute to the success, yes.
04:16:41 Q. Consistent dosage is critical to patient treatment;
04:16:44 correct?
04:16:45 A. Are you speaking about consistent absorption of a
04:16:51 drug or -- when you say dosage, because every drug has a
04:16:55 consistent dose. So, I would say correct, yes.
04:16:59 Q. Now, having a drug product optimized to promote
04:17:03 absorption of the drug substance can be critical to the
04:17:05 success of a cancer therapy; correct?
04:17:07 A. I think consistency in all absorption is important,
04:17:12 correct.

04:17:12 Q. A cancer therapy would not be useful if it were packaged in a drug product that prevented its absorption in the patient's body; correct?
04:17:21 A. No, you would need to get the absorbed -- the drug absorbed for it to be useful, yes.
04:17:27 Q. A successful cancer therapy requires a compound that remains stable during the drug manufacturing process; correct?
04:17:34 A. I have limited knowledge about manufacturing, but I would say that stability would be important, yes.
04:17:43 Q. Preventing degradation of a drug substance is necessary in order to administer the drug; correct?
04:17:48 A. Again, the manufacturing process is not -- in my area of expertise but I think that would be important to have an effective drug, yes.
04:17:58 Q. A genotoxic impurity can lead to secondary cancer; correct?
04:18:03 A. Yes, it can.
04:18:04 Q. It is important to reduce genotoxic impurities in drug development; correct?
04:18:10 A. I believe it's uniformly important not just with tyrosine kinase inhibitors, but a whole host of agents, yes.
04:18:19 Q. If a patient is on a particular drug for a longer duration, the risk of any genotoxic impurities goes on for a longer period of time; correct?

04:18:29 A. Yes, that's correct.
04:18:31 Q. Now, resistance occurs when a patient stops
04:18:34 responding to a particular therapy; correct?
04:18:36 A. Well, or does -- yeah, resistance would be not
04:18:41 responding. Refractory would be never responding.
04:18:45 Q. And every day in your practice, you see patients that
04:18:47 have developed drug resistance; correct?
04:18:50 A. Yes, I do.
04:18:52 Q. Having second and third-line therapies available is a
04:18:55 very important option for individuals suffering from
04:18:59 advanced renal cell carcinoma; correct?
04:19:01 A. That is correct.
04:19:04 Q. The treatment that might work best for one patient
04:19:07 will not necessarily work best for another; correct?
04:19:10 A. Generally correct. I mean, there are -- sometimes
04:19:16 the context is that changing a drug category, not just
04:19:22 changing a drug within a category is a more preferable way
04:19:27 to manage subsequent therapies.
04:19:29 Q. It is helpful for oncologists to have multiple
04:19:32 therapies available to treat patients; correct?
04:19:34 A. It is helpful, yes.
04:19:37 Q. Now, you testified about the NCCN guidelines. For
04:19:41 people who cannot tolerate immuno-oncology drugs, Cabometyx
04:19:45 is an important first-line option; correct?
04:19:48 A. Cabo -- Cabometyx and all of the tyrosine kinase

04:19:53 inhibitors that were in recommended options would be
04:19:58 considered options, yes.
04:19:59 Q. Cabometyx is the only preferred option for the
04:20:03 unfavorable risk patients who cannot tolerate
04:20:06 immuno-oncology; correct?
04:20:08 A. Speaking to the NCCN guidelines?
04:20:11 Q. Yes.
04:20:11 A. Yes.
04:20:13 Q. Now, your opinion is that Cabometyx offers a
04:20:15 difference in degree, but not a difference in kind; is that
04:20:19 right?
04:20:19 A. Yes, it is.
04:20:19 Q. A treatment's ability to extend the overall survival
04:20:23 of a cancer patient can be a difference in kind in some
04:20:27 circumstances; correct?
04:20:28 A. In -- I think there are noteworthy circumstances
04:20:34 where that is true, but a lot of agents that are -- are
04:20:41 brought into the marketplace do show these smaller benefits
04:20:46 that are worthwhile, but don't represent a difference in
04:20:49 kind.
04:20:50 Q. Every single month of increased survival matters to a
04:20:53 patient; correct?
04:20:53 A. That could be a profound ethical discussion. I would
04:21:00 say to you that a lot of factors play into that, including
04:21:07 quality of life. Existential pain because, you know, you're

dying plays into that. So, I think that it's a much more complicated answer than yes or no.

Q. Fair enough.

You don't dispute that Cabometyx can extend a patient's life while maintaining quality of life, at least in some circumstances; correct?

A. Yes, I agree.

MS. WIGMORE: Thank you. No further questions.

THE COURT: All right. Anything more, Mr. Cooper?

MR. COOPER: No, thank you.

THE COURT: All right. Dr. Mega, thank you. Watch your step stepping down.

MR. BOYLE: Good afternoon, Your Honor. Kevin Boyle on behalf of Defendant, MSN. Defendants call their next witness, Dr. DeForest McDuff.

THE COURT: All right. Thank you.

MR. BOYLE: And we have some binders, as well, to bring up.

DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: Robert DeForest McDuff. R-O-B-E-R-T. D-E, capital F, O-R-E-S-T. M-C, capital D, U-F-F.

ROBERT DeFOREST McDUFF, the witness herein,

after having been affirmed, was examined and testified as follows:

THE WITNESS: Yes, I do.

DIRECT EXAMINATION

BY MR. BOYLE:

Q. Good afternoon, Dr. McDuff. Could you please introduce yourself?

A. Good afternoon. My name is DeForest McDuff, and I'm an economist.

Q. Have you prepared slides to assist with your testimony today?

A. Yes. They're on the screen.

Q. All right. Dr. McDuff, I briefly want to talk about your professional background.

MR. BOYLE: Can we pull up DTX-530?

BY MR. BOYLE:

Q. Dr. McDuff, what is DTX-530?

A. This is a copy of my professional CV.

Q. And does it accurately reflect your professional qualifications?

A. Yes, it does.

MR. BOYLE: Can we go to DDX-2?

BY MR. BOYLE:

Q. Dr. McDuff, can you please provide the Court with a brief description of your educational background?

A. Sure. I have bachelor degrees in economics and mathematics from the University of Maryland and I have a master's degree and Ph.D. in economics from Princeton.

Q. And can you also describe your professional background?

A. Yes. I work as an economic consultant at a firm called Insight Economics, which I founded in 2017. And I'm an assistant teaching professor in the Department of Economics at UNC, Chapel Hill.

Q. And can you provide a summary of your experience evaluating economics of the pharmaceutical industry?

A. Yes. I worked on more than 75 cases on topics of commercial success, irreparable harm, damages, product launches, and other issues.

Q. And have you previously testified in this Court?

A. Yes.

MR. BOYLE: Your Honor, Defendants proffer Dr. DeForest McDuff as an expert in economics and commercial success.

MS. PIROZZOLO: No objection.

THE COURT: All right. You may proceed.

BY MR. BOYLE:

Q. Dr. McDuff, were you here in the courtroom for Mr. Tate's testimony?

A. Yes, I was.

04:24:15 Q. And did you prepare a slide summarizing the testimony
04:24:19 you plan to offer today?
04:24:21 A. Yes.
04:24:22 MR. BOYLE: Can we go to DDX-3?
04:24:22 BY MR. BOYLE:
04:24:26 Q. Having listened to Mr. Tate's testimony, can you
04:24:28 please provide an overview of the opinions that you'll be
04:24:31 offering?
04:24:32 A. Sure. I have three main opinions. The first is that
04:24:35 there's no commercial success due to blocking disincentives.
04:24:38 The second is that there's -- he has performed no analysis
04:24:41 of other patents which pertains to nexus. And the third is
04:24:43 that his analysis of the product success itself is
04:24:46 incomplete.
04:24:48 Q. All right. Let's start with that first point, no
04:24:51 commercial success due to blocking disincentives.
04:24:55 Could you please explain the idea behind
04:24:58 blocking and market exclusivity as it relates to commercial
04:25:01 success?
04:25:02 A. Sure. Blocking via earlier patents or FDA
04:25:06 exclusivity deters other from pursuing the claimed subject
04:25:10 matter, even if it's obvious. And so the inference about
04:25:13 obviousness from commercial success is no longer present if
04:25:16 there's a blocking patent or exclusivity.
04:25:19 Q. And is that -- has that kind of deterrence been

04:25:23 present in this case?
04:25:23 A. Yes.
04:25:26 MR. BOYLE: Let's pull up DTX-013.
04:25:26 BY MR. BOYLE:
04:25:31 Q. Dr. McDuff, what is DTX-013?
04:25:34 A. This is the '473 patent, which relates to the
04:25:37 cabozantinib compound. We heard about this in testimony
04:25:40 this week.
04:25:41 Q. And is this one of the patents at issue in the first
04:25:43 case?
04:25:43 A. Yes.
04:25:46 MR. BOYLE: Let's pull up DTX-192.
04:25:46 BY MR. BOYLE:
04:25:50 Q. Dr. McDuff, what is DTX-192?
04:25:53 A. This is the international publication date of the
04:25:57 application ending in 140A-2. We also heard about this this
04:26:01 week relating to the cabozantinib compound where the
04:26:05 publication leading to the '473 was published in April 2005.
04:26:10 Q. So, this is the earlier application that eventually
04:26:14 led to the '473?
04:26:16 A. Yes.
04:26:19 MR. BOYLE: Can we pull up DDX-4.
04:26:19 BY MR. BOYLE:
04:26:21 Q. Let's start at the top here of DDX-4.
04:26:25 Dr. McDuff, can you please explain what you're

04:26:27 showing in the first red line?
04:26:29 A. Yes. This is a timeline of the relevant events,
04:26:33 which I think helps illustrate the blocking analysis.
04:26:36 From 2002 to 2010, at the top, you can see
04:26:39 collaborations that Exelixis had with GlaxoSmithKline and
04:26:44 Bristol Myers Squibb. Those were exclusive collaborations
04:26:48 that were announced in Exelixis' SEC filings.
04:26:51 Q. And that collaboration started in October 2002?
04:26:55 A. Yes.
04:26:57 Q. And let's go to the second red line.
04:26:59 What are you showing in the second red line?
04:27:01 A. This is the timeline for the '473 patent in the
04:27:06 cabozantinib compound claiming priority in September 2003
04:27:10 and the publication date we just talked about in April 2005.
04:27:15 Q. All right. And in blue, what are you showing in
04:27:18 blue?
04:27:18 A. These are the patents-in-suits in the current case,
04:27:21 the malate salt patents with priority in -- claimed in 2009.
04:27:25 And the '349 patent with priority claimed in 2011.
04:27:29 Q. And in green, what are you showing in green?
04:27:32 A. The green are the sales of the products that were
04:27:35 discussed by Mr. Tate, Cabometyx and Cometriq.
04:27:38 Q. So, what does this timeline show about blocking and
04:27:42 exclusivity as it relates to commercial success in this
04:27:45 case?

04:27:46 A. Because of the earlier development and the earlier
04:27:50 intellectual property, even if the sales were successful
04:27:54 there's no inference to be made about whether others would
04:27:57 have developed the malate salt patents or the '349 patent
04:28:00 had they been obvious. There's just no inference one way or
04:28:03 the other because of the earlier intellectual property and
04:28:05 collaborations.
04:28:07 Q. So looking at the time between April 2005 and
04:28:12 August 2009, which is the time between the publication of
04:28:15 the application, which is DTX-192, and the issuance of the
04:28:21 '473 patent, would other entities have been aware that
04:28:25 Exelixis was seeking patent protection related to
04:28:28 cabozantinib?
04:28:28 A. Yes. And that would have provided a deterrence based
04:28:33 on the patent issuing at a future point in time.
04:28:35 Q. And does the priority date of both the malate salt
04:28:39 patents and the '349 patent fall within this blocking period
04:28:43 that you described?
04:28:43 A. Yes, that's right.
04:28:47 Q. And how do you evaluate the strength of the economic
04:28:52 deterrence that this blocking period would provide?
04:28:56 A. I evaluated economic factors that come from the
04:28:59 *Acorda* case from the Federal Circuit.
04:29:02 MR. BOYLE: All right. Let's turn to the next
04:29:03 slide, DDX-5.

04:29:06 Q. Dr. McDuff, what are the *Acorda* factors?
04:29:09 A. The *Acorda* factors are economic factors that are
04:29:12 outlined in the -- in the case opinion which relate to how
04:29:17 strong the disincentives are -- how strong are the
04:29:19 disincentives for others to be deterred from that
04:29:22 development.
04:29:22 Q. Can you please briefly explain the role that each of
04:29:26 these factors played in this case?
04:29:27 A. Yes. Number one, there's been no successful
04:29:30 challenge of the '473 patent that's been asserted against
04:29:33 entities like MSN.
04:29:34 Number two, there's been no development of
04:29:36 others in the 2009 to 2011 time frame that I've seen.
04:29:41 Number three, the invention race with Exelixis
04:29:44 is important because the holder of the patent is also
04:29:47 pursuing the product. So, a third-party developer would be
04:29:51 concerned that even if they were going to pursue this
04:29:53 development, they would lose the invention race to Exelixis
04:29:56 and its partners.
04:29:57 Number four on licensing. There's no evidence
04:29:59 that there's a good licensing opportunity here, not with the
04:30:02 exclusive collaborations with GSK and BMS.
04:30:06 And overall, number five, there's low economic
04:30:09 opportunity for others in light of the blocking patent.
04:30:12 Q. So after evaluating these five *Acorda* factors, what

did you conclude with respect to the blocking deterrence here?

A. There's a strong deterrence here.

Q. And how does that relate to commercial success?

A. As a result, commercial success, even if it's true for the product, doesn't provide an inference of nonobviousness for the patents.

MR. BOYLE: All right. We can take that down for a moment.

BY MR. BOYLE:

Q. Let's talk about your second opinion, no nexus analysis.

Dr. McDuff, can you briefly explain what does it mean to analyze nexus as it relates to commercial success?

A. Sure. Nexus is about the degree of connection between what is the claimed subject matter and the product performance.

Q. And do you think Mr. Tate has provided an adequate evaluation of nexus in this case?

A. No, not in my opinion.

Q. And why not?

A. Because he's only analyzed the patents at issue in this case. He doesn't weigh them against the other patents that are listed in the FDA Orange Book for the products at issue.

04:31:13 Q. All right. Let's take a look at those patents.

04:31:15 MR. BOYLE: Can we pull up DDX-6?

04:31:15 BY MR. BOYLE:

04:31:20 Q. And are these the patents listed in the Orange Book that you're referring to?

04:31:24 A. Yes, that's right.

04:31:25 Q. And these refer to the Cabometyx product?

04:31:28 A. Yes. These are the patents listed for Cabometyx in the FDA Orange Book. You'll see there are 11 here; there are four non-asserted patents, there are three patents from the prior case, and there are four patents asserted in the current case.

04:31:40 Q. And did Mr. Tate's analysis of nexus evaluate all of these patents?

04:31:45 A. No, not at all.

04:31:47 Q. And why is that a problem?

04:31:48 A. Because we're trying to figure out if there is some degree of market success what inference of obviousness to draw on the patents-in-suit or some other patents.

04:31:59 So, without evaluating the contributions of the claimed subject matter compared to what else covers the product, there's no way to draw a nexus or an inference that others would have developed the claimed subject matter sooner.

04:32:11 Q. And did you testify last year in the first trial, the

04:32:14 MSN 1 trial?
04:32:15 A. Yes.
04:32:16 Q. And how did Mr. Tate's nexus analysis from that trial
04:32:20 regarding the '473 patent compare to his nexus analysis
04:32:23 here?
04:32:23 A. It was exactly the same. The product analysis was
04:32:27 exactly the same, the nexus analysis was the same, and I
04:32:29 think it shows a lack of differentiation for which patents
04:32:33 we're drawing an inference to.
04:32:36 Q. For the '349 patent at issue in this case, what's
04:32:39 your understanding of the opinions offered by MSN's experts?
04:32:44 A. My understanding from Dr. Donovan is that a
04:32:48 formulation could be created without the glidant as part of
04:32:51 the '349 patent. And so as a result, it's not necessary for
04:32:54 the formulation that's claimed.
04:32:56 Q. So, why does that matter for nexus, that the
04:32:59 '349 patent is not necessary?
04:33:02 A. Because if you could get similar chemical performance
04:33:06 or clinical performance, and then ultimately market
04:33:09 performance without the '349 patent, then that's a lack of
04:33:11 nexus.
04:33:12 MR. BOYLE: All right. Let's go to DDX-7.
04:33:12 BY MR. BOYLE:
04:33:16 Q. And are you showing the same thing with respect to
04:33:19 the patents listed in the Orange Book for Cometriq?

04:33:22 A. Yes, that's right. There are seven of them.
04:33:24 Q. And is there the same lack of nexus issue for
04:33:27 Cometriq?
04:33:28 A. Yes. It's basically unevaluated by Plaintiff's
04:33:31 commercial success analysis.
04:33:33 Q. And could you explain again why that is a problem?
04:33:35 A. Because you risk drawing an inference to patents that
04:33:39 are not relevant. There needs to be some sort of weighing
04:33:42 of the importance of these various patents in driving the
04:33:44 commercial performance.
04:33:47 Q. So, overall, what did you conclude about Mr. Tate's
04:33:50 nexus analysis?
04:33:51 A. It's not sufficient to conclude nexus, in my opinion.
04:33:55 Q. All right. Let's talk about your third opinion, the
04:33:58 product performance.
04:34:00 MR. BOYLE: Can we go to DDX-8?
04:34:00 BY MR. BOYLE:
04:34:04 Q. What is your view of Mr. Tate's market analysis of
04:34:10 Cabometyx and the Cometriq product performance?
04:34:12 A. That it's very high level and incomplete. As you can
04:34:16 see, I've got three opinions here relating to definition of
04:34:19 success, development costs, and the market shares.
04:34:21 Q. All right. Let's take those one at a time. What do
04:34:23 you mean by no definition of success?
04:34:25 A. Here, I'm referring to the sales being presented in

isolation. We saw a bar chart of the sales over time, but there's no comparison to know whether those are high, average, low for this kind of product.

Same thing with number of patients. We heard 55,000 patients, but I don't know if that's high, I don't know if that's low. There's no definition of what constitutes success here. And, ultimately, no evaluation of whether others would have developed this product sooner.

THE COURT: I'm sorry, when you are saying high or low, high or low relevant to what?

THE WITNESS: That's the point. There's no bar or benchmark or comparison to say this level of sales or this level of patients would motivate others to pursue this product.

THE COURT: All right.

BY MR. BOYLE:

Q. And turning to your second point, no development cost. What do you mean by no development costs?

A. Here, I'm talking about the investment to bring the product to market. In pharmaceuticals, it's -- for evaluating success, it's really a weighing of the many years of investment, clinical trials, with the sales and profits.

But in Mr. Tate's analysis, there was no evaluation of profits in comparison with the investment required to bring this product to market. So there's no

04:35:43 evaluation of a return on investment or whether it's
04:35:45 successful or not.
04:35:47 Q. And third, wide range of market shares, could you
04:35:52 explain what that means?
04:35:53 A. Yes. So in Mr. Tate's report, he had many market
04:35:56 definitions and market shares. He presented two or three of
04:35:59 them today, but there were over 20 in his expert report,
04:36:03 some are very high, some are very low, in the single digits.
04:36:06 Here, again, there's no explanation or
04:36:09 definition of what constitutes success for this kind of
04:36:12 product.
04:36:14 Q. So, taken together, what's your opinion of Mr. Tate's
04:36:18 product analysis?
04:36:19 A. In my view, it's incomplete, it's not enough to draw
04:36:22 a conclusion on commercial success one way or the other.
04:36:25 Q. All right.
04:36:26 MR. BOYLE: Let's go to DDX-9.
04:36:26 BY MR. BOYLE:
04:36:28 Q. Can you please re-summarize for the Court your three
04:36:31 main points again?
04:36:32 A. Yeah. Primarily, there's no inference of commercial
04:36:35 success due to the blocking disincentives, I think that's
04:36:38 the main point, due to the earlier IP. In my opinion,
04:36:41 plaintiffs also have not shown that there's a nexus or that
04:36:44 the product itself has been successful.

04:36:46 Q. And what conclusion should be drawn from these three
04:36:49 points?
04:36:49 A. No commercial success, in my view.
04:36:53 MR. BOYLE: Thank you, Dr. McDuff. I pass the
04:36:57 witness, but first defendants would like to introduce
04:37:00 DTX-530.
04:37:02 THE COURT: All right. Admitted without
04:37:03 objection?
04:37:05 MS. PIROZZOLO: No objection, Your Honor.
04:37:06 THE COURT: All right.
04:37:06 (DTX Exhibit No. 530 was admitted into
04:37:07 evidence.)
04:37:07 THE COURT: Actually, Dr. McDuff, the point you
04:37:12 were making about the nexus and the glidant and the -- I
04:37:16 think it's the '439 patent, but the one with the essentially
04:37:20 free, can you just try running that one by me again?
04:37:25 THE WITNESS: Sure. As I understand it from
04:37:28 Dr. Donovan, technically you could have a formulation or a
04:37:32 process that produces a formulation with or without the
04:37:35 glidant, one of the claimed elements, as I understand it.
04:37:38 So, if that's true, you don't need to practice
04:37:41 the patent to get the same chemical, clinical, and market
04:37:44 performance, then there's no nexus to the patent.
04:37:48 THE COURT: And so, does that depend because, of
04:37:51 course -- well, maybe this is -- "of course" is the wrong

words.

Dr. Donovan's opinion is there isn't a glidant in the MSN product. Exelixis' opinion is there is. Your opinion on that depends on Dr. Donovan being right rather than Exelixis' technical experts?

THE WITNESS: I think that's right. It depends on whether you could have a similarly performing product without the '349 patent.

THE COURT: All right.

All right. Ms. Pirozzolo, you've got two minutes max.

MS. PIROZZOLO: Thank you, Your Honor.

CROSS-EXAMINATION

BY MS. PIROZZOLO:

Q. Dr. McDuff, you're not disputing that Exelixis' product, Cabometyx, practices the asserted patents; correct?

A. I'm not assessing that one way or the other.

Q. You don't dispute that tens of thousands of patients have taken Cabometyx and Cometriq instead of many other drugs approved for treatment of cancer; correct?

A. I'm not disputing the numbers, no.

Q. Okay. You agree that revenues reflect physicians' decisions to prescribe a drug to patients; correct?

A. Yes. Downstream, first it's prescriptions and then that's realized in revenues.

04:39:23 Q. And you don't dispute Mr. Tate's summary of the
04:39:26 revenues for Cabometyx; correct?
04:39:28 A. I'm not disputing the figures, no.
04:39:30 Q. Okay. Now, your blocking analysis pertains to the
04:39:34 effect of the '473 on the patents-in-suit; correct?
04:39:39 A. Yes.
04:39:40 Q. Okay. You understand that MSN's defense is
04:39:45 obviousness-type double patenting, not obviousness, for the
04:39:48 malate salt patents; correct?
04:39:50 A. I understand that's one defense, yes.
04:39:53 Q. Okay. And you understand that the '473 is not prior
04:39:58 art to the crystalline malate salt patents; correct?
04:40:00 A. I'm not sure.
04:40:03 MS. PIROZZOLO: I have no further questions,
04:40:05 Your Honor.
04:40:05 THE COURT: All right. Thank you. Any
04:40:06 redirect.
04:40:07 MR. BOYLE: No redirect, Your Honor.
04:40:08 THE COURT: All right. Dr. McDuff, you can step
04:40:10 down. Watch your step. Okay.
04:40:12 THE WITNESS: Thank you, Your Honor.
04:40:14 THE COURT: All right. I guess we're done.
04:40:16 MR. COOPER: Yeah, Your Honor, can I move in
04:40:22 from Dr. Mega's examination DTX-536.
04:40:27 MS. WIGMORE: No objection.

04:40:28 THE COURT: All right.

04:40:29 MR. COOPER: And defendants rest their case.

04:40:31 Thank you.

04:40:32 THE COURT: All right. So that's admitted

04:40:34 without objection.

04:40:34 (DTX Exhibit No. 536 was admitted into

04:40:34 evidence.)

04:40:36 THE COURT: I'm not entirely sure, but I think

04:40:38 I've been admitting some of these things multiple times

04:40:41 without objection.

04:40:42 Okay. So, in any event, we're done with the

04:40:45 testimony; right?

04:40:47 MR. COOPER: Yes, Your Honor.

04:40:47 MS. PIROZZOLO: Yes, Your Honor.

04:40:48 THE COURT: Okay. So, we've got closing

04:40:53 arguments tomorrow morning at 9:30, and I want to talk about

04:40:57 that in a minute.

04:40:59 I can't recall in terms of the briefing to

04:41:05 follow, is that something that has been worked out or is

04:41:09 that something that's still to be determined?

04:41:13 MR. PRUSSIA: I think, Your Honor, we have been

04:41:15 so caught up in the trial that we haven't had a chance to

04:41:17 discuss that. I think myself and Mr. Cooper and the others

04:41:19 can probably caucus on it this evening and come to you

04:41:23 tomorrow.

04:41:24 THE COURT: Yeah, so that would be better. I'd rather have you caucus first. All right. In terms of closing argument. So, how much -- as I recall, at least it's partly because it's what I usually do. When we talk about closing argument, I said maybe 30 minutes, maybe 45 minutes, maybe somewhere in between. At least I would expect that I said that.

What do you-all think.

MR. PRUSSIA: Your Honor, we would request 45 minutes, if that works for the Court.

MR. LOMBARDI: And that's fine with us, too, Your Honor.

THE COURT: All right. Well, so I'm willing to do 45 minutes a side. But one of the things that I want to make sure that I'm not getting is an argument that's really as though somebody is just reading a brief to me. So, I've been trying to think. You know, earlier I tried to take care of that concern by limiting the number of slides, but that didn't really seem to necessarily achieve my objective.

So, I don't want you to read your arguments to me. I certainly expect you to have notes, topics, things to remind you of, you know, what it is you want to talk about, but I want to see your eyes looking at me for most of the time, okay?

And I don't mind if you have -- I don't require

that you have any slides. But particularly -- and I'm not sure how actually important it is in this case. But particularly, if, you know, you want to be making arguments about text, I don't object to having the text up there, and I leave it to your judgment if you think there's a few slides I really need to see.

But I -- again, I want to be looking mostly at you at the podium. And I can't look at the slide at the same time. So, if you need to -- if you need slides, yeah, use slides in moderation.

And so partly -- partly I thought that maybe -- maybe I was shooting myself in the foot earlier because I said, okay, 30 minutes. And then you just felt like there was so much stuff. And by -- when I say you, I don't mean any of you personally, but that lawyers thought there was so much important stuff they had to tell me that they then, you know, write down 45 minutes worth of stuff and deliver it in 30 minutes. So, by giving you 45 minutes, hoping that won't happen.

In any event, that's my hopes about that.

Is there anything else we need to discuss right now or otherwise I'll let you go and get ready for tomorrow and do whatever else you need to do. And we can talk about the briefing after you've done the arguments.

MR. PRUSSIA: Nothing for Plaintiffs,

Your Honor.

MR. LOMBARDI: Nothing for Defendants, Your Honor.

THE COURT: Okay. All right. Well, thank you very much. And I will see you tomorrow.

DEPUTY CLERK: All rise.

(Court was recessed at 4:45 p.m.)

I hereby certify the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Heather M. Triozzi
Certified Merit and Real-Time Reporter
U.S. District Court.

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'015 [1] - 843:19
'081 [2] - 732:12, 734:14
'349 [34] - 707:14, 710:1, 712:2, 712:3, 712:6, 712:16, 723:11, 723:14, 728:7, 729:4, 734:17, 738:21, 740:1, 740:17, 740:20, 740:23, 740:24, 742:18, 744:6, 774:1, 787:3, 787:4, 796:5, 796:14, 797:18, 959:21, 1016:19, 1017:4, 1017:17, 1021:10, 1021:14, 1021:17, 1021:20, 1026:8
'394 [2] - 786:25, 787:1
'439 [5] - 843:18, 847:6, 899:1, 902:5, 1025:15
'440 [1] - 843:18
'473 [41] - 867:24, 868:3, 868:24, 868:25, 869:2, 869:16, 870:3, 870:10, 870:12, 870:15, 870:21, 870:22, 870:25, 871:3, 871:6, 871:8, 871:13, 871:16, 871:22, 872:6, 872:18, 872:22, 873:10, 874:24, 875:8, 887:21, 899:15, 960:12, 988:4, 988:8, 988:13, 988:17, 1015:6, 1015:18, 1015:20, 1016:12, 1017:11, 1018:10, 1021:4, 1027:5, 1027:11
'549 [1] - 855:14
'776 [1] - 855:13
'928 [2] - 892:16, 892:19

/

/s [1] - 1031:11

0

0 [2] - 813:22, 876:20
0.02 [3] - 711:12, 711:14, 735:11
0.06 [1] - 716:10
0.26 [1] - 821:13
0.36 [2] - 717:14, 785:16
0.4 [1] - 822:19
0.54 [1] - 795:23
0.87 [1] - 795:22
06 [2] - 716:11, 785:8

1

1 [60] - 709:24, 715:5, 715:9, 715:24, 717:24, 718:2, 718:4, 724:3, 726:1, 778:6, 779:8, 779:15, 779:16, 786:4, 786:5, 788:18, 788:24, 789:7, 790:5, 791:6, 791:22, 793:1, 793:5, 795:14, 795:16, 814:7, 819:22, 820:1, 820:3, 820:9, 820:14, 820:15, 821:15, 834:24, 835:2, 842:18, 847:7, 847:17, 850:17, 850:18, 850:19, 850:25, 851:7, 855:11, 895:11, 899:17, 900:9, 900:11, 900:18, 941:3, 944:9, 969:11, 978:6, 984:2, 988:1, 988:2, 1021:1
1,300 [1] - 822:6
1-1 [93] - 707:17, 707:22, 708:1, 708:14, 708:18, 708:21, 708:24, 709:9, 709:13, 709:16, 710:17, 711:3, 711:5, 711:9, 711:11, 711:12, 711:14, 711:18, 711:20, 712:5, 712:7, 712:9, 712:17, 712:19, 712:20, 712:24, 713:2, 713:3, 713:8, 713:11, 715:15, 715:19, 715:22, 716:7, 717:21, 719:11, 719:16, 721:7, 721:13, 721:23, 722:3, 722:9, 722:18, 723:13, 724:13, 725:2, 726:18, 727:15, 727:17, 727:20, 728:2, 730:17, 735:1, 735:11, 736:17, 737:8, 737:12, 737:14, 738:3, 738:10, 738:17, 738:19, 738:25, 739:4, 739:5, 739:13, 740:3, 740:9, 741:1, 741:3, 741:20, 743:24, 745:10, 751:13, 752:4, 752:14, 752:16, 753:10, 759:8, 762:3, 764:15, 769:4, 769:14, 771:10, 771:18, 773:13, 779:16, 784:14, 784:21, 789:9, 789:12, 796:12
1-1's [1] - 769:5
1-2 [2] - 710:7, 710:8
1-3 [2] - 710:7
1-4 [1] - 710:8
1.4 [1] - 985:17
10 [12] - 708:4, 714:4, 714:5, 731:6, 745:19, 802:15, 848:18, 886:3, 886:9, 895:6, 895:11, 983:19
10.6 [1] - 953:9
10.8 [1] - 953:10
100 [3] - 711:15, 711:16, 767:21
100-milligram [1] - 720:22
103 [2] - 935:24, 936:5
108 [1] - 913:15
11 [4] - 714:24, 783:25, 795:13, 1020:9
111 [1] - 863:21
113 [9] - 821:1, 821:3, 821:5, 823:12, 873:6, 873:7, 873:15, 873:17, 887:16
12 [10] - 744:4, 745:20, 746:7, 746:9, 746:12, 796:12, 914:9, 915:6, 916:4
13 [5] - 707:9, 723:7, 811:5, 858:24, 983:8
14 [5] - 719:21, 719:23, 724:21, 890:10, 907:21
140A-2 [1] - 1015:16
15 [16] - 712:13, 725:14, 808:5, 872:2, 872:7, 872:8, 890:22, 891:8, 891:19, 893:5, 947:11, 947:18, 966:9, 983:19, 983:21, 997:14
15-minute [1] - 795:2
16 [13] - 718:23, 724:5, 724:6, 724:9, 724:10, 778:24, 798:2, 808:5, 849:5, 876:3, 966:9, 983:8, 1002:23
16-20 [1] - 892:12
1680 [1] - 947:12
16th [2] - 844:8, 869:13
17 [7] - 724:6, 724:7, 724:10, 734:21, 738:14, 891:20
18 [2] - 706:22, 726:25
185 [1] - 849:9
186 [1] - 925:21
187 [1] - 925:21
19 [3] - 706:22, 847:7, 892:11
1970s [1] - 831:17
1977 [2] - 886:15
1993 [1] - 819:24
1996 [1] - 841:3
1998 [1] - 940:2

2

2 [38] - 709:21, 715:6, 715:9, 718:23, 744:4, 745:20, 746:9, 779:1, 785:24, 796:12, 804:24, 805:5, 805:7, 805:9, 805:17, 805:19, 806:1, 822:8, 822:10, 822:16, 822:21, 834:15, 835:3, 835:6, 835:7, 843:24, 843:25, 844:2, 847:5, 876:13, 890:11, 895:11, 895:20, 944:4, 977:10, 979:21, 985:3, 990:9
20 [15] - 722:16, 722:21, 774:1, 774:9, 802:15, 869:25, 890:23, 895:20, 943:11, 965:18, 983:21, 984:21, 991:7, 991:10, 1024:7
200 [28] - 712:19, 713:18, 714:22, 715:15, 715:19, 715:21, 716:8, 716:9, 716:10, 718:17, 719:8, 735:11, 739:6, 744:16, 746:7, 746:8, 746:10, 780:1, 780:11, 781:8, 783:3, 784:23, 784:25, 785:5, 790:2, 792:3, 876:9
2000s [3] - 927:6, 932:1, 932:2
2001 [1] - 993:12
2002 [3] - 822:22, 1016:4, 1016:8
2003 [1] - 1016:13
2004 [1] - 869:10
2005 [3] - 1015:18, 1016:14, 1017:8
2006 [2] - 822:22, 876:12
2009 [38] - 798:2, 801:5, 803:21, 804:6, 806:9, 809:11, 809:24, 823:9, 825:2, 827:7, 827:11, 827:14, 827:17, 827:20, 828:20, 829:6, 830:5, 830:8, 830:15, 830:23, 831:13, 832:11, 832:15, 835:17, 844:8, 869:1, 869:13, 955:9, 962:17, 962:18, 963:17, 964:6, 965:4, 994:12, 996:23, 1016:18, 1017:9, 1018:13
2010 [1] - 1016:4
2011 [7] - 726:17, 727:14, 730:21, 730:24, 955:6, 1016:19, 1018:13
2015 [1] - 965:22
2016 [5] - 944:3,

949:9, 982:14, 985:14, 985:18
2017 [3] - 965:17, 965:22, 1013:7
2019 [2] - 965:20, 983:11
2020 [1] - 981:22
2021 [2] - 892:11, 940:22
2022 [7] - 981:25, 982:2, 983:11, 984:9, 985:16, 985:17, 985:19
2023 [5] - 705:12, 947:4, 980:5, 982:2, 990:5
208 [1] - 893:15
21 [7] - 735:25, 775:11, 775:20, 775:21, 849:16, 873:25, 947:4
213 [2] - 713:21, 714:5
21st [1] - 876:12
22 [1] - 737:17
22-228-RGA [1] - 705:5
225 [2] - 895:6, 895:13
23 [1] - 720:2
24 [1] - 872:16
25 [9] - 705:12, 720:22, 840:24, 851:23, 872:3, 930:25, 940:8, 940:14, 976:9
252 [2] - 895:6, 895:13
258 [2] - 895:6, 895:13
25th [1] - 869:1
26 [3] - 850:4, 882:9, 981:23
27 [3] - 786:6, 806:2, 936:23
270 [1] - 872:2
272 [3] - 724:19, 724:23, 724:25
277 [3] - 921:1, 921:4, 935:9
283 [1] - 895:13
287 [1] - 826:18
291 [4] - 708:5, 713:21, 727:1, 731:4
299 [2] - 725:13, 797:5

3

3 [34] - 726:2, 728:7, 729:3, 729:8, 733:16, 734:17, 736:3, 740:16, 740:20, 742:18, 744:6, 744:11, 746:14, 747:21, 756:25, 777:7, 810:16, 822:23, 843:24, 843:25, 844:2, 862:22, 893:11, 895:11, 941:24, 946:21, 951:18, 952:11, 959:21, 969:8, 979:7, 981:22, 1003:12
3.10 [2] - 736:6, 736:9
3.40 [1] - 811:23
3.9 [1] - 933:15
30 [6] - 776:20, 966:4, 990:15, 1029:5, 1030:13, 1030:18
304 [3] - 737:17, 737:20, 737:22
31 [1] - 850:4
313 [2] - 913:5, 913:15
315 [1] - 914:24
327 [2] - 895:6, 895:13
33 [1] - 834:18
333 [2] - 929:22, 929:23
334 [3] - 834:19, 834:25, 835:24
335 [2] - 732:1, 732:13
336 [6] - 834:15, 834:16, 834:19, 834:22, 835:3, 835:6
338 [1] - 835:4
34 [2] - 783:2, 850:10
35 [6] - 718:22, 719:6, 732:13, 779:23, 783:2, 984:22
350 [1] - 783:2
36 [1] - 822:23
363 [1] - 961:15
366 [1] - 961:15
367 [1] - 961:15
37 [3] - 775:11, 775:21, 775:22
373 [2] - 826:16, 891:25
374 [1] - 892:4
38 [11] - 714:24, 715:6, 715:25, 719:24, 720:1, 720:4, 720:6, 720:8, 795:12, 796:25, 797:5
39 [4] - 787:1, 850:10, 982:1, 982:7

4

4 [14] - 777:8, 813:13, 813:22, 819:15, 843:24, 844:2, 900:7, 900:13, 949:22, 950:4, 980:19, 983:11, 984:2
4.10 [1] - 758:3
4.4 [1] - 751:2
4.9 [1] - 985:21
4.90 [1] - 811:13
40 [6] - 735:18, 774:14, 877:2, 940:11, 943:11, 965:24
411 [8] - 719:7, 719:15, 779:23, 780:1, 780:18, 781:3, 781:7, 783:2
412 [1] - 869:15
421 [2] - 895:6, 895:13
45 [6] - 876:20, 1029:6, 1029:10, 1029:14, 1030:17, 1030:18
453 [1] - 819:18
454 [1] - 819:25
455 [1] - 819:25
470 [1] - 961:15
480 [4] - 813:18, 813:20, 813:21, 814:2
481 [2] - 814:9, 816:19
486 [1] - 815:21
494 [3] - 735:25, 736:2, 797:5
4:00 [1] - 976:9
4:45 [1] - 1031:7

5

5 [20] - 820:11, 847:11, 867:23, 868:3, 869:14, 869:18, 869:22, 870:2, 870:10, 870:11, 870:14, 870:18, 871:18, 873:9, 895:11, 950:19, 984:3, 985:3, 988:13, 988:17
5.10 [1] - 809:22
5.12 [1] - 813:4
5.13 [1] - 817:14
5.8 [1] - 808:17
5.9 [1] - 933:10
50 [4] - 847:12, 873:4, 965:25, 991:6
528 [1] - 961:15
530 [1] - 1025:11
536 [1] - 1028:6
55,000 [2] - 980:6, 1023:5
553A [1] - 732:25
56 [2] - 847:25, 854:6
59 [1] - 848:7

6

6 [12] - 736:7, 805:4, 810:24, 811:2, 821:18, 847:24, 854:5, 868:21, 895:5, 895:11, 951:15, 985:3
60 [1] - 943:10
600 [5] - 716:10, 716:12, 785:8, 790:2, 790:3
625 [2] - 895:6, 895:14
65 [1] - 767:25
6667 [1] - 822:7
68 [1] - 787:16

7

7 [7] - 811:17, 823:13, 848:15, 850:4, 895:5, 895:11, 952:5
70 [3] - 767:24, 767:25, 787:15
700 [1] - 706:22
75 [2] - 947:16, 1013:12
76 [1] - 733:15
773 [2] - 796:25, 797:5
774 [2] - 895:6, 895:14
775 [1] - 961:16
778 [4] - 978:6, 978:7, 986:25, 987:6
782 [1] - 826:16
783 [2] - 895:6, 895:14
791 [2] - 987:1, 987:6

8

8 [8] - 797:1, 797:7, 813:22, 850:9, 850:20, 851:21, 977:10, 984:3
8.3 [1] - 979:8
8.4 [1] - 983:1
8.5 [1] - 984:11
8.6 [1] - 985:9
8.95 [1] - 824:10
80 [1] - 947:16
802 [2] - 987:2, 987:6
82 [4] - 731:3, 731:7, 731:10, 731:13
823 [4] - 980:19, 981:16, 987:1, 987:6
824 [4] - 979:21, 979:23, 986:25, 987:6
844 [1] - 705:10
853 [2] - 987:2, 987:6
8:30 [1] - 705:12

9

9 [7] - 720:16, 720:18, 720:19, 720:23, 721:1, 895:5, 895:11
90 [2] - 945:10, 954:15
91 [2] - 727:2, 727:4
92 [1] - 980:15
93 [1] - 980:15
95 [1] - 978:22
97 [2] - 710:12, 710:15
98 [2] - 709:9, 821:17
99.98 [1] - 711:16
9:30 [1] - 1028:16
9ER [2] - 951:18, 1002:12

A

A-1 [1] - 743:14
A-2 [14] - 716:4, 716:23, 719:6, 719:15, 743:17, 779:7, 781:10, 781:15, 781:16, 782:21, 782:22, 782:24, 783:14, 795:24
a.m [1] - 705:12
ability [3] - 734:7, 1006:14, 1010:13
able [16] - 758:17, 809:25, 815:19, 817:1, 828:14, 828:20, 830:15, 838:18, 856:12, 902:20, 933:3, 948:25, 949:16, 956:19, 982:12, 982:18
absence [1] - 906:24
absolute [1] - 880:15
absolutely [12] - 881:8, 921:9, 954:10, 955:8, 957:1, 957:4, 963:2, 970:24, 973:24, 974:4, 993:7, 996:4
absorbed [5] - 875:24, 875:25, 877:22, 1008:4, 1008:5
absorption [6] - 898:22, 959:2, 1007:18, 1007:22, 1007:24, 1008:2

abstracts [1] - 991:7
accelerate [1] - 946:10
accelerated [1] - 975:1
acceptable [22] - 774:22, 806:4, 821:5, 823:11, 829:15, 831:11, 869:21, 869:22, 871:20, 871:23, 871:25, 872:1, 872:8, 872:11, 872:19, 873:11, 873:18, 873:21, 887:17, 888:5, 927:6, 933:14
accomplished [1] - 746:3
accomplishing [1] - 744:19
according [5] - 716:22, 775:25, 776:4, 777:8, 903:6
account [5] - 832:10, 832:12, 881:15, 933:1, 971:24
accounting [1] - 986:2
accumulated [1] - 931:4
accuracy [1] - 906:7
accurate [12] - 718:12, 767:20, 767:21, 767:23, 789:16, 838:17, 842:21, 906:6, 934:25, 941:8, 978:9, 1031:9
accurately [2] - 990:6, 1012:19
acetate [1] - 818:7
acetone [1] - 806:5
achieve [8] - 733:23, 734:1, 735:1, 735:16, 735:22, 738:2, 982:13, 1029:19
achieved [1] - 982:4
achieving [1] - 738:23
acid [77] - 799:20, 801:25, 803:6, 803:12, 803:14, 808:23, 808:25, 809:2, 809:3, 810:1, 810:13, 810:14, 811:20, 811:22, 811:25, 812:1, 812:11, 812:12, 812:18, 813:6, 814:18, 814:23, 815:3, 815:4, 815:12, 817:5, 817:6, 817:7, 818:8, 818:10, 818:13, 819:2, 820:7, 822:15, 823:21, 827:9, 829:11, 831:24, 837:11, 837:23, 847:15, 847:20, 847:22, 868:11, 868:14, 872:9, 872:11, 872:18, 872:19, 879:25, 880:4, 880:13, 880:16, 881:4, 881:9, 881:21, 881:22, 882:2, 882:3, 882:6, 882:8, 882:18, 883:7, 883:9, 889:10, 926:25, 927:2, 927:17, 928:11, 932:23
acidity [2] - 881:24, 889:8
Acids [1] - 835:9
acids [42] - 809:1, 811:4, 813:8, 815:5, 815:6, 815:7, 815:10, 815:15, 815:17, 816:3, 816:21, 816:24, 817:2, 817:8, 817:13, 817:16, 817:21, 818:2, 818:5, 818:11, 818:14, 819:5, 823:7, 823:9, 824:16, 829:14, 835:7, 835:11, 837:15, 871:25, 872:13, 872:21, 872:24, 873:5, 931:5, 931:11, 933:14, 934:21
acknowledge [1] - 829:24
acknowledgment [1] - 993:15
Acorda [4] - 1017:23, 1018:1, 1018:2, 1018:25
acronym [1] - 981:3
act [1] - 737:13
action [1] - 892:3
activated [1] - 998:23
activates [1] - 952:19
activation [1] - 993:2
active [17] - 733:22, 736:24, 737:23, 762:11, 800:18, 800:19, 802:25, 803:23, 804:9, 808:5, 818:25, 820:6, 823:22, 825:14, 943:18, 958:21, 1002:2
activity [2] - 800:20, 1002:3
actual [13] - 755:17, 757:8, 787:13, 824:3, 846:12, 858:20, 866:6, 866:20, 906:5, 906:8, 907:15, 973:20
add [4] - 729:1, 738:2, 817:25, 984:6
added [1] - 734:24
adding [3] - 796:16, 1002:8, 1003:3
addition [16] - 710:8, 716:25, 717:20, 730:19, 737:11, 852:13, 860:2, 872:9, 872:11, 872:19, 882:2, 882:4, 914:15, 915:8, 919:24, 1002:5
additional [21] - 713:2, 721:20, 724:7, 737:14, 755:8, 766:6, 773:12, 855:23, 873:24, 880:11, 880:12, 905:14, 914:7, 916:16, 920:17, 922:14, 937:7, 956:24, 1004:10, 1004:15
Additives [1] - 834:8
additives [4] - 818:22, 832:7, 910:3, 910:6
address [8] - 797:20, 798:23, 939:7, 939:8, 947:19, 948:3, 955:11, 977:6
addressed [5] - 819:21, 829:23, 848:18, 887:25, 1005:19
addressing [6] - 798:17, 800:16, 816:9, 843:9, 935:12, 936:14
adequate [1] - 1019:18
ADI [2] - 836:2, 836:9
adjective [1] - 904:22
adjustments [1] - 807:14
administer [1] - 1008:12
administered [1] - 816:11
administration [2] - 977:14, 977:18
Administration [1] - 944:2
admissibility [1] - 805:25
admission [1] - 796:24
admit [4] - 791:5, 826:12, 895:9, 961:11
admitted [16] - 797:3, 797:6, 797:7, 826:15, 826:16, 826:18, 895:12, 895:14, 961:14, 961:16, 987:4, 987:7, 1025:7, 1025:11, 1028:4, 1028:6
admitting [1] - 1028:9
adopted [1] - 845:7
advance [5] - 806:14, 828:11, 885:16, 905:24, 921:11
advanced [21] - 943:9, 945:1, 945:4, 945:5, 945:15, 946:15, 950:5, 950:18, 950:25, 951:5, 951:20, 952:4, 995:24, 995:25, 996:5, 1000:2, 1004:20, 1004:22, 1006:7, 1006:21, 1009:11
advancement [2] - 993:16, 1006:12
Advances [1] - 725:18
advances [1] - 725:19
advantages [1] - 893:24
advent [2] - 994:13, 997:7
advisory [1] - 842:10
advocacy [1] - 941:1
affect [10] - 722:11, 802:25, 804:12, 804:18, 806:21, 807:4, 897:2, 908:3, 923:21, 994:25
affected [4] - 740:3, 910:9, 921:18, 995:2
affecting [2] - 919:25, 1002:7
affects [1] - 995:5
affinity [1] - 736:21
affirmed [2] - 976:22, 1012:1
affordability [1] - 998:6
afternoon [12] - 896:7, 896:8, 938:25, 961:21, 977:1, 977:2, 987:14, 987:15, 1006:20, 1011:14, 1012:6, 1012:8
agencies [1] - 975:21
agent [6] - 948:13, 954:6, 969:14, 994:5, 996:24, 1001:16
agents [9] - 969:9, 994:24, 995:1, 996:25, 998:20, 1004:25, 1005:13, 1008:22, 1010:17
agitated [1] - 807:1
agitation [2] - 909:23, 921:20
ago [8] - 834:1, 834:13, 879:15, 880:7, 889:19, 916:7, 931:1, 954:7
agree [65] - 706:22, 709:3, 710:18, 710:25, 713:16, 715:13, 715:17, 715:20, 716:16, 716:25, 718:18, 721:8, 721:16, 722:7, 722:19, 729:9, 733:8, 734:2, 735:4, 745:15, 746:9, 759:2, 759:20, 759:23, 761:18, 763:5, 763:23, 771:5, 786:19, 788:16, 789:5, 792:2, 793:16, 807:15, 819:7, 819:9, 829:5, 829:13, 831:10, 831:13, 832:14, 837:3, 837:4, 837:6, 880:8, 882:16, 884:24, 912:8, 917:4, 918:1, 921:14, 932:10, 932:14, 932:18, 956:3, 956:5, 962:3, 972:20, 973:25, 974:22, 975:13, 1004:18, 1007:1, 1011:7, 1026:22

agreed [4] - 834:10, 918:3, 966:15, 966:16
agrees [1] - 864:18
ahead [8] - 749:6, 769:3, 779:11, 826:25, 882:22, 890:2, 1002:24, 1006:17
aid [1] - 814:7
aim [1] - 1004:6
al [1] - 705:7
albeit [1] - 1000:6
alert [2] - 767:16, 770:10
alerting [1] - 767:15
alerts [9] - 767:2, 767:4, 767:7, 767:9, 767:12, 767:16, 767:19, 768:2, 768:24
allow [3] - 739:8, 866:25, 992:21
allowed [4] - 741:2, 893:3, 937:4, 957:12
allowing [1] - 778:6
allows [5] - 718:2, 803:13, 894:24, 894:25, 974:25
almost [1] - 1002:2
alone [8] - 948:24, 948:25, 953:22, 971:18, 971:21, 983:17, 984:23, 1001:21
aloud [1] - 790:21
alpha [1] - 996:25
alphabetically [1] - 820:15
altogether [1] - 851:9
American [1] - 940:22
Ames [17] - 724:10, 765:7, 767:13, 768:2, 768:4, 768:6, 768:9, 770:13, 770:15, 770:18, 770:20, 770:25, 771:3, 771:7, 771:21, 771:23
AMES [3] - 724:17, 768:12, 770:15
ammunition [1] - 993:16
amorphous [26] - 801:3, 846:14, 846:15, 846:18, 853:14, 856:10, 856:13, 856:21, 856:24, 857:10, 857:12, 858:22, 865:10, 865:12, 866:18, 879:16, 884:15, 888:25, 889:16, 890:20, 890:23, 891:5, 893:16, 893:21, 893:25
amount [7] - 709:13, 717:9, 717:19, 743:9, 745:21, 839:7, 979:17
amounts [6] - 716:7, 721:22, 739:4, 743:24, 748:9, 789:8
AMY [1] - 705:21
analyses [3] - 978:1, 979:5, 979:12
analysis [31] - 715:4, 747:19, 749:15, 749:22, 750:4, 752:23, 857:17, 897:19, 901:7, 915:14, 916:7, 916:13, 978:13, 978:19, 979:11, 982:15, 1014:11, 1014:13, 1016:3, 1019:12, 1020:13, 1021:3, 1021:4, 1021:6, 1021:7, 1022:5, 1022:12, 1022:18, 1023:23, 1024:13, 1027:4
analytical [4] - 758:21, 839:7, 844:23, 849:7
analyze [2] - 839:8, 1019:14
analyzed [3] - 820:9, 979:14, 1019:22
ANDA [1] - 937:19
Andrews [1] - 706:14
ANDREWS [1] - 705:14
anesthetics [1] - 726:5
angiogenesis [1] - 1002:7
angiogenic [1] - 996:24
anionic [7] - 820:4, 820:5, 820:16, 820:24, 821:12, 822:13, 873:18
anions [2] - 819:4, 821:15
Anions [1] - 822:11
announced [1] - 1016:7
annual [1] - 985:12
answer [13] - 749:3, 749:5, 834:1, 864:9, 864:10, 902:21, 908:18, 909:7, 918:10, 953:15, 953:18, 1003:24, 1011:2
answered [1] - 953:17
ANTHONY [3] - 705:17, 989:9, 989:10
Anthony [5] - 942:22, 989:5, 989:8, 989:19, 991:12
anti [4] - 726:5, 726:6, 965:5, 965:9
anti-cancers [1] - 726:5
anti-tubercular [1] - 726:6
anti-VEGFR [2] - 965:5, 965:9
antibacterials [1] - 726:5
antibody [2] - 945:21, 952:18
antihypertensive [1] - 959:16
antimalarials [1] - 726:4
anyhow [1] - 895:16
apart [1] - 728:22
API [47] - 712:19, 712:25, 718:17, 719:14, 721:14, 729:14, 730:8, 730:19, 732:21, 733:14, 734:6, 735:1, 735:12, 737:8, 737:12, 738:18, 739:4, 741:19, 742:16, 746:1, 746:9, 753:11, 753:19, 753:24, 754:14, 757:19, 757:25, 758:11, 759:22, 760:2, 763:4, 763:13, 763:19, 771:11, 773:1, 773:6, 773:11, 793:6, 800:19, 807:21, 817:25, 822:14, 837:13, 860:25, 894:12, 894:20
APIs [5] - 732:10, 732:18, 732:19, 822:5, 822:11
apologize [7] - 771:16, 788:21, 899:15, 904:8, 905:16, 1001:2
appear [1] - 788:15
APPEARANCES [2] - 705:16, 706:1
appended [1] - 714:17
applicable [2] - 727:22, 818:23
applicant [1] - 757:7
application [16] - 732:1, 732:4, 732:6, 732:9, 732:12, 734:14, 749:22, 749:23, 759:3, 892:16, 892:19, 937:12, 937:25, 1015:16, 1015:19, 1017:10
applied [2] - 800:14, 859:21
applies [1] - 772:22
apply [3] - 800:7, 844:25, 946:13
approach [10] - 766:8, 800:22, 801:15, 813:9, 813:10, 813:11, 814:17, 815:1, 816:20, 921:23
approaches [6] - 727:11, 800:25, 801:1, 801:3, 809:1, 813:8
appropriate [4] - 734:9, 886:19, 886:21, 999:3
approval [7] - 930:25, 946:9, 946:10, 947:9, 965:5, 982:12, 996:17
approved [27] - 757:15, 822:23, 831:14, 831:16, 831:19, 944:1, 944:21, 945:25, 946:2, 949:5, 955:21, 962:4, 962:9, 962:19, 962:25, 964:5, 965:9, 965:24, 966:3, 970:12, 970:15, 982:10, 993:10, 994:12, 994:15, 997:2, 1026:20
April [4] - 980:5, 1015:18, 1016:14, 1017:8
aqueous [4] - 809:12, 817:22, 877:11, 877:25
area [3] - 841:11, 981:20, 1008:13
areas [2] - 735:18, 981:18
arguing [1] - 935:20
argument [3] - 1029:3, 1029:5, 1029:15
arguments [5] - 936:15, 1028:16, 1029:20, 1030:3, 1030:24
arise [3] - 757:9, 758:10, 896:24
arm [1] - 1000:17
arms [1] - 953:11
arose [1] - 901:6
arranged [1] - 820:20
arrive [1] - 935:17
ARSHT [1] - 705:17
art [93] - 714:16, 720:23, 720:25, 724:12, 727:20, 730:22, 730:25, 739:11, 739:23, 741:15, 748:11, 748:15, 749:23, 750:5, 750:11, 750:12, 751:8, 751:16, 751:17, 752:20, 754:18, 755:14, 757:16, 758:17, 758:22, 759:16, 760:10, 761:7, 761:20, 763:6, 763:22, 764:17, 766:13, 766:16, 766:21, 767:5, 768:5, 769:17, 769:25, 770:6, 770:12, 770:25, 771:3, 771:6, 771:9, 771:17, 773:16, 777:9, 777:13, 794:12, 800:6, 800:10, 804:6, 805:16, 808:20, 809:14, 809:19, 813:5, 828:13, 829:6, 829:7, 835:16, 835:19, 844:10, 845:10, 850:14, 857:2, 868:10, 868:12, 869:3, 869:6, 874:15, 874:21, 897:9, 905:5, 905:10, 905:13, 906:3, 920:12,

921:24, 922:10, 927:10, 931:20, 932:3, 932:6, 932:14, 932:23, 933:3, 933:6, 936:1, 936:8, 937:4, 1027:12
article [11] - 725:14, 725:17, 725:18, 886:6, 886:7, 928:19, 928:24, 929:2, 929:3, 929:11, 929:16
articles [5] - 928:6, 928:21, 928:23, 991:4, 991:7
artisan [40] - 708:24, 709:15, 721:12, 722:1, 722:14, 726:17, 727:15, 729:7, 731:20, 733:4, 734:24, 737:6, 738:1, 738:22, 776:5, 801:13, 803:21, 806:10, 806:13, 807:9, 809:11, 809:25, 810:12, 811:24, 814:18, 814:20, 815:2, 815:14, 816:3, 816:20, 816:23, 823:10, 823:21, 825:8, 825:9, 825:17, 867:1, 882:14, 885:11, 887:5
aside [1] - 838:23
aspect [16] - 775:15, 775:18, 775:22, 775:24, 842:10, 851:24, 852:9, 852:10, 852:14, 852:19, 852:21, 852:24, 852:25, 891:17, 892:11, 970:22
aspects [3] - 841:8, 842:8, 986:20
assay [1] - 849:3
asserted [35] - 712:16, 799:25, 843:17, 846:23, 847:1, 853:9, 855:5, 855:12, 855:15, 856:7, 867:23, 869:3, 869:7, 869:11, 869:12, 870:3, 870:13, 889:24, 894:17, 900:7, 902:4, 936:13, 941:18, 941:20, 942:3, 942:12, 957:23, 979:1, 986:5, 991:22, 992:3, 1018:10, 1020:10, 1020:11, 1026:16
assess [5] - 766:8, 803:5, 805:11, 828:14, 839:7
assessed [1] - 837:21
assessing [3] - 801:16, 978:2, 1026:17
assessment [4] - 803:1, 803:2, 803:6, 808:4
assist [2] - 989:20, 1012:10
assistant [1] - 1013:8
associate [1] - 990:18
associated [9] - 798:18, 801:18, 816:9, 827:7, 939:9, 953:12, 957:7, 959:17, 961:6
Associates [3] - 977:21, 977:22, 977:24
Association [2] - 940:24, 940:25
assume [4] - 825:8, 859:15, 900:17, 921:13
assumed [1] - 750:4
assumes [1] - 761:6
assuming [3] - 750:12, 905:17, 910:23
assumption [4] - 750:16, 753:14, 879:2, 883:10
atezolizumab [5] - 952:12, 952:16, 952:17, 953:5, 953:8
atom [1] - 882:16
atoms [1] - 846:10
attach [2] - 852:10, 852:21
attained [1] - 921:10
attempting [1] - 823:10
attention [15] - 802:24, 804:11, 804:23, 810:10, 811:7, 811:17, 813:23, 815:23, 819:14, 819:20, 821:8, 821:9, 824:6, 952:25, 980:20
attributable [2] - 988:10, 988:13
attributed [4] - 800:20, 848:11, 849:11, 849:23
attributes [3] - 804:5, 824:3, 824:5
August [2] - 869:1, 1017:9
author [1] - 893:13
authors [1] - 930:24
autoimmune [1] - 967:18
available [21] - 776:5, 799:8, 806:9, 812:15, 830:23, 831:4, 835:16, 876:23, 888:3, 897:8, 949:10, 961:25, 962:4, 962:5, 962:6, 962:11, 967:9, 996:16, 1005:10, 1009:9, 1009:20
avelumab [1] - 971:20
average [2] - 877:2, 1023:3
avoid [1] - 975:14
awarded [1] - 940:20
awards [1] - 941:9
aware [15] - 727:17, 791:12, 812:5, 812:6, 812:8, 813:7, 829:25, 830:1, 830:4, 830:7, 926:13, 931:21, 932:4, 959:15, 1017:11
axis [3] - 862:12, 862:15, 876:17
axitinib [7] - 964:10, 966:17, 971:17, 971:20, 998:15, 1001:6, 1001:7

B

B-1 [1] - 743:19
B-2 [8] - 743:21, 743:23, 745:4, 745:7, 745:17, 746:3, 796:10, 796:13
bachelor [2] - 977:13, 1013:1
bachelor's [1] - 844:17
background [7] - 840:25, 845:14, 977:12, 992:7, 1012:14, 1012:25, 1013:5
bacterial [1] - 765:7
Bairy [1] - 706:10
balance [1] - 733:21
ballpark [3] - 747:4, 907:22, 908:2
Bannen [2] - 892:14, 892:16
bar [6] - 980:3, 980:6, 981:21, 981:22, 1023:1, 1023:11
bars [1] - 981:18
base [22] - 801:2, 801:25, 803:6, 805:12, 809:10, 810:1, 811:15, 820:7, 824:14, 827:9, 837:14, 838:4, 838:13, 839:1, 862:22, 863:3, 869:21, 928:13, 928:16, 932:8, 954:19
based [42] - 733:14, 737:9, 744:24, 750:6, 768:24, 770:6, 771:11, 803:22, 804:7, 808:24, 809:12, 810:1, 812:15, 814:17, 815:1, 816:3, 822:25, 824:2, 824:3, 862:19, 862:20, 862:21, 868:10, 868:12, 882:21, 889:20, 889:23, 892:12, 892:25, 905:6, 905:14, 906:13, 930:21, 932:8, 942:19, 950:15, 955:22, 969:6, 979:5, 981:15, 983:5, 1017:14
bases [3] - 811:4, 931:5, 931:11
basic [4] - 810:5, 822:14, 827:7, 862:11
basis [4] - 716:18, 828:19, 854:2, 883:14
batch [19] - 715:4, 716:9, 716:14, 717:12, 717:13, 717:15, 718:5, 783:3, 783:15, 786:16, 787:9, 787:11, 787:12, 787:18, 787:21, 791:24, 911:17, 911:18
batches [15] - 716:21, 717:13, 717:16, 718:6, 718:7, 718:16, 719:6, 719:7, 780:22, 781:10, 783:15, 789:11, 789:14, 795:18, 795:21
Bates [2] - 834:18, 947:12
BBA [1] - 977:13
bear [3] - 825:24, 855:20, 954:11
became [2] - 949:10, 984:9
become [1] - 982:19
BEFORE [1] - 705:14
beforehand [1] - 812:21
begin [1] - 1006:4
beginning [9] - 709:10, 811:1, 848:18, 849:16, 851:22, 887:3, 921:6, 953:1, 982:1
begins [5] - 733:18, 775:14, 834:15, 847:7, 915:1
begun [2] - 814:18, 814:21
behalf [4] - 797:12, 913:18, 1011:15
behavior [1] - 887:9
behind [1] - 1014:17
beholden [1] - 829:7
below [10] - 716:8, 716:10, 735:10, 739:6, 784:13, 784:23, 784:25, 793:4, 796:12, 851:21
Bench [1] - 705:13
benchmark [1] - 1023:12
beneficial [3] - 808:10, 815:20, 1004:2
benefit [17] - 740:1, 936:2, 936:4, 936:9, 936:10, 936:12, 951:11, 954:23, 955:23, 956:13, 996:4, 1000:10, 1000:11, 1004:6, 1004:8, 1005:11,

1005:12
benefited [2] - 996:2, 996:6
benefits [13] - 741:15, 741:17, 894:22, 894:24, 952:1, 956:22, 957:23, 963:18, 986:11, 986:12, 986:14, 1010:18
Berge [11] - 886:7, 886:18, 887:5, 887:7, 892:14, 892:17, 892:20, 930:7, 930:10, 930:13
Berkeley [1] - 841:3
Bernhardt [3] - 839:16, 839:20, 840:6
BERNHARDT [2] - 839:21, 839:22
best [17] - 754:20, 799:12, 825:11, 851:18, 851:19, 885:19, 888:19, 889:3, 889:7, 889:20, 916:5, 916:11, 926:6, 926:11, 955:16, 1009:13, 1009:14
better [13] - 789:17, 808:9, 888:24, 889:15, 947:23, 954:5, 972:9, 994:9, 999:9, 1000:18, 1001:21, 1002:10, 1029:1
between [46] - 712:2, 723:19, 723:23, 724:6, 740:19, 740:22, 760:5, 760:9, 762:3, 762:10, 763:25, 795:22, 797:24, 798:9, 801:25, 803:23, 804:8, 822:22, 847:21, 853:21, 856:12, 856:21, 857:9, 868:9, 870:2, 893:20, 934:14, 939:9, 942:11, 957:22, 969:9, 970:6, 972:17, 983:19, 984:2, 984:21, 985:3, 985:18, 986:4, 986:19, 988:7, 992:16, 1017:8, 1017:9, 1019:16, 1029:6
bevacizumab [1] - 996:24
beyond [7] - 878:14, 902:17, 912:8, 912:12, 961:25, 962:5, 962:10
Bighley [22] - 813:17, 813:18, 813:19, 814:2, 814:9, 814:14, 814:17, 815:1, 815:21, 816:4, 816:20, 819:15, 819:22, 823:1, 823:12, 829:2, 829:16, 873:5, 930:13, 930:17, 930:21
billion [2] - 985:17, 985:21
bind [1] - 992:11
Binder [1] - 899:17
binder [36] - 708:4, 714:23, 720:2, 723:7, 724:21, 731:6, 735:25, 737:17, 756:7, 756:11, 774:2, 774:6, 774:7, 778:13, 783:25, 804:24, 813:13, 823:13, 826:21, 833:10, 842:17, 843:24, 847:6, 868:21, 899:8, 899:9, 941:3, 944:4, 946:22, 949:22, 950:19, 951:15, 952:6, 978:6, 979:21, 980:19
binders [11] - 742:24, 833:15, 876:3, 886:3, 886:9, 890:10, 891:21, 893:5, 896:3, 987:9, 1011:18
binding [1] - 883:2
bio [5] - 877:12, 877:14, 877:24, 878:2, 878:22
bio-relevant [4] - 877:14, 877:24, 878:2, 878:22
bioavailability [14] - 825:4, 825:22, 874:17, 875:3, 875:9, 875:18, 875:20, 876:1, 877:10, 877:13, 877:16, 877:20, 920:6, 923:21
bioavailable [1] - 877:5
bioequivalent [3] - 911:14, 911:18, 938:4
biology [1] - 956:10
Biopharmaceutical [1] - 876:8
biorelevant [1] - 825:21
bit [14] - 761:23, 777:1, 778:5, 783:8, 784:14, 815:22, 829:20, 838:7, 842:4, 888:22, 928:5, 980:14, 988:4, 988:15
bladder [1] - 939:20
blend [1] - 776:14
blending [3] - 712:22, 776:9, 776:14
blends [1] - 734:11
block [5] - 958:23, 958:25, 964:21, 993:2, 994:1
blocking [15] - 959:2, 1002:7, 1014:10, 1014:16, 1014:18, 1014:20, 1014:24, 1016:3, 1016:23, 1017:17, 1017:21, 1018:24, 1019:1, 1024:22, 1027:4
blood [2] - 959:1, 959:2
blue [7] - 810:4, 862:20, 870:11, 981:18, 981:20, 1016:15, 1016:16
BLUMENFELD [1] - 705:18
BMS [3] - 913:25, 914:2, 1018:22
board [3] - 842:10, 990:11, 990:12
body [7] - 728:17, 816:12, 875:24, 878:3, 958:25, 959:9, 1008:3
body's [1] - 998:21
Boggs [1] - 705:10
boiling [1] - 805:24
bona [1] - 912:15
bonded [1] - 882:17
bonds [1] - 882:13
Book [5] - 822:6, 1019:24, 1020:4, 1020:9, 1021:25
book [1] - 736:5
bottom [19] - 717:12, 724:8, 776:24, 785:16, 811:17, 811:18, 821:8, 834:21, 850:23, 862:12, 886:20, 893:19, 929:25, 950:9, 981:17, 983:23, 984:25, 989:24
box [2] - 967:5, 967:7
Boyle [1] - 1011:15
BOYLE [32] - 706:7, 1011:14, 1011:18, 1012:5, 1012:15, 1012:16, 1012:22, 1012:23, 1013:17, 1013:22, 1014:4, 1014:5, 1015:3, 1015:4, 1015:12, 1015:13, 1015:22, 1015:23, 1017:24, 1019:8, 1019:10, 1020:2, 1020:3, 1021:22, 1021:23, 1022:16, 1022:17, 1023:16, 1024:17, 1024:18, 1025:4, 1027:18
brand [2] - 894:18, 993:11
break [7] - 728:22, 734:8, 795:2, 795:3, 895:16, 895:17, 976:8
breaking [1] - 1002:3
breakthrough [6] - 946:4, 946:12, 946:14, 974:12, 974:18, 974:24
breast [1] - 963:19
BRIAN [1] - 706:7
bridge [1] - 957:18
brief [3] - 992:7, 1012:25, 1029:16
briefing [2] - 1028:18, 1030:24
briefly [13] - 800:17, 844:1, 845:14, 935:5, 942:7, 958:14, 974:11, 990:16, 992:9, 1003:11, 1012:13, 1018:7, 1019:13
bring [3] - 1011:19, 1023:19, 1023:25
Bristol [2] - 914:5, 1016:6
Bristol-Myers-Squibb [1] - 914:5
Britain [1] - 876:10
broad [5] - 799:3, 865:9, 865:10, 906:16, 908:5
broader [1] - 982:22
broadly [2] - 867:14, 896:22
bromide [1] - 815:11
brought [3] - 760:20, 791:3, 1010:18
Brown [70] - 708:4, 708:11, 708:14, 708:18, 708:21, 708:25, 709:15, 709:20, 709:24, 710:6, 710:13, 710:15, 711:19, 712:2, 712:9, 713:17, 713:20, 713:23, 714:7, 714:20, 715:18, 715:20, 716:15, 716:23, 717:2, 717:24, 718:2, 719:9, 721:3, 721:5, 721:14, 722:2, 726:21, 731:4, 731:7, 731:10, 734:14, 734:25, 738:2, 738:10, 738:22, 739:3, 749:22, 750:1, 750:6, 750:13, 750:15, 753:17, 758:24, 759:3, 778:6, 779:7, 782:14, 785:24, 786:1, 786:4, 786:5, 788:18, 788:19, 788:24, 790:5, 790:12, 791:6, 791:22, 796:17, 990:18, 990:20
Bruce [1] - 770:18
BRYCE [1] - 706:5
Bryce [1] - 967:11
build [1] - 1004:19
bulk [2] - 774:23, 817:25
bullet [2] - 752:7, 753:8
bunch [2] - 833:14, 870:5
business [5] - 916:14, 977:14, 977:22, 979:25, 980:25
but.. [4] - 918:16, 926:25, 933:13, 933:17

BY [207] - 705:17, 705:18, 705:20, 705:21, 705:21, 705:22, 705:22, 706:2, 706:5, 706:5, 706:6, 706:7, 707:4, 707:11, 708:7, 710:14, 711:25, 712:14, 713:22, 715:1, 715:8, 716:1, 718:25, 719:22, 720:3, 720:17, 722:17, 722:22, 724:20, 727:3, 729:5, 731:5, 732:2, 733:17, 734:22, 736:1, 736:8, 737:18, 738:15, 743:3, 749:8, 750:21, 751:4, 752:2, 757:2, 758:5, 759:7, 762:2, 772:20, 774:3, 774:16, 776:21, 777:3, 777:23, 778:11, 779:3, 779:14, 783:23, 792:12, 795:11, 797:14, 797:23, 799:16, 800:3, 801:22, 802:17, 804:25, 805:6, 806:19, 808:18, 809:8, 809:23, 810:11, 810:17, 810:25, 811:6, 811:19, 821:4, 827:4, 833:3, 833:17, 834:17, 836:1, 836:23, 840:3, 840:16, 843:5, 843:8, 843:15, 844:14, 845:18, 846:3, 846:21, 847:8, 847:13, 847:18, 848:1, 848:16, 850:11, 850:21, 854:7, 854:13, 855:3, 855:9, 856:5, 856:16, 858:9, 858:25, 861:15, 861:25, 863:24, 864:15, 864:25, 866:9, 866:15, 868:5, 868:22, 869:17, 870:1, 872:4, 872:17, 874:2, 874:11, 875:12, 876:4, 876:14, 879:6, 879:21, 880:2, 880:10, 881:19, 882:11, 883:13, 883:25, 884:9, 885:10, 885:18, 886:5, 887:15, 888:9, 888:15, 890:6, 890:12, 891:22, 892:1, 892:5, 893:6, 893:12, 893:18, 894:5, 896:6, 899:2, 913:8, 929:6, 929:24, 933:24, 935:7, 938:24, 939:12, 940:16, 941:5, 941:16, 942:6, 942:16, 943:6, 946:24, 947:13, 952:8, 952:24, 955:1, 957:21, 961:20, 966:10, 970:14, 976:25, 977:11, 978:17, 979:9, 979:22, 980:23, 983:2, 984:12, 985:10, 987:13, 989:16, 990:3, 990:10, 991:17, 993:9, 995:16, 997:15, 1006:19, 1012:5, 1012:16, 1012:23, 1013:22, 1014:5, 1015:4, 1015:13, 1015:23, 1019:10, 1020:3, 1021:23, 1022:17, 1023:16, 1024:18, 1026:14

byproducts [1] - 728:2

C

C-2 [2] - 914:14, 915:7

C-5 [2] - 914:14, 915:8

c-Met [1] - 995:6

C.A [1] - 705:5

cabo [2] - 926:8, 1009:25

Cabo [2] - 913:4, 915:25

Cabometyx [131] - 740:18, 741:15, 741:23, 816:16, 894:9, 894:18, 894:20, 937:22, 938:1, 939:9, 941:22, 941:25, 942:8, 942:10, 943:7, 943:8, 943:16, 943:18, 943:20, 943:24, 944:1, 944:12, 944:22, 945:25, 946:13, 946:14, 946:17, 948:3, 948:5, 948:7, 948:14, 948:17, 949:5, 949:7, 949:10, 950:2, 954:3, 954:9, 954:12, 954:13, 954:16, 955:4, 955:11, 955:23, 956:1, 957:2, 957:11, 957:24, 958:2, 958:3, 958:17, 958:22, 959:22, 959:23, 960:13, 960:18, 961:1, 962:4, 962:8, 965:2, 965:16, 965:23, 966:3, 969:2, 969:22, 970:6, 970:8, 970:12, 970:19, 972:17, 973:7, 974:5, 974:8, 974:11, 977:8, 978:20, 978:21, 978:25, 979:6, 979:15, 980:9, 980:12, 981:8, 981:9, 981:11, 981:15, 981:20, 982:4, 982:6, 982:9, 982:18, 982:20, 983:12, 983:16, 983:24, 984:4, 984:9, 984:20, 984:22, 985:1, 985:4, 985:6, 985:13, 985:22, 986:1, 986:4, 987:22, 988:8, 988:12, 988:18, 996:13, 996:23, 1005:20, 1006:10, 1006:11, 1006:21, 1006:24, 1007:2, 1007:5, 1009:23, 1009:25, 1010:3, 1010:9, 1011:4, 1016:22, 1020:7, 1020:8, 1022:19, 1026:16, 1026:19, 1027:2

Cabometyx's [3] - 965:4, 981:22, 982:22

CABOSUN [9] - 950:23, 968:16, 970:1, 999:24, 999:25, 1000:12, 1000:13, 1000:15, 1000:19

cabozantinib [248] - 707:13, 707:18, 707:25, 708:12, 708:15, 709:25, 710:16, 711:20, 712:8, 714:21, 715:10, 717:15, 719:10, 720:11, 720:22, 721:21, 722:25, 723:3, 728:3, 729:7, 730:12, 730:16, 730:22, 730:24, 731:11, 731:23, 732:6, 732:13, 733:5, 734:16, 735:8, 735:12, 736:15, 736:16, 737:7, 738:3, 738:18, 738:24, 739:10, 739:12, 740:2, 740:25, 741:12, 743:11, 749:19, 750:6, 751:8, 751:15, 753:15, 754:1, 757:14, 759:9, 759:18, 759:21, 761:2, 761:12, 761:22, 762:4, 764:1, 768:23, 769:5, 769:12, 771:13, 771:14, 796:11, 796:18, 799:21, 805:12, 809:6, 809:10, 809:12, 809:16, 810:1, 810:7, 812:19, 820:8, 824:12, 824:14, 825:18, 825:20, 826:5, 830:22, 831:2, 831:7, 844:6, 847:3, 847:10, 848:8, 848:9, 848:20, 848:21, 849:2, 849:13, 850:7, 850:8, 850:13, 851:1, 851:11, 852:14, 853:2, 853:24, 854:25, 855:13, 855:15, 858:2, 858:5, 858:21, 860:8, 862:23, 862:25, 864:19, 866:7, 866:19, 867:2, 867:14, 869:19, 870:21, 870:23, 870:25, 871:3, 871:5, 871:10, 871:13, 871:16, 872:23, 873:12, 874:15, 874:22, 874:25, 875:15, 877:16, 877:18, 877:20, 877:22, 878:12, 878:22, 879:1, 879:8, 879:10, 881:5, 881:13, 883:21, 884:11, 884:12, 887:22, 888:1, 888:6, 888:24, 888:25, 894:11, 894:21, 894:22, 901:13, 904:25, 912:17, 914:9, 921:25, 928:3, 933:10, 934:15, 937:1, 937:7, 937:21, 943:15, 943:21, 943:22, 944:6, 948:7, 948:20, 948:24, 949:4, 950:4, 950:13, 950:16, 950:24, 951:10, 951:20, 952:1, 952:13, 953:4, 953:5, 953:8, 953:9, 953:18, 953:22, 960:2, 960:12, 960:16, 960:21, 962:19, 964:20, 964:24, 965:13, 966:14, 967:5, 967:8, 967:14, 967:19, 967:22, 968:6, 968:17, 968:24, 969:13, 972:8, 972:10, 973:2, 973:3, 973:22, 974:1, 977:8, 978:23, 979:14, 980:2, 980:7, 993:4, 993:6, 995:5, 995:22, 996:2, 996:17, 997:2, 998:10, 998:15, 999:7, 999:15, 999:17, 1000:1, 1000:7, 1000:20, 1001:20, 1002:14, 1003:9, 1003:16, 1003:18, 1004:5,

1005:2, 1005:8, 1005:9, 1005:12, 1005:15, 1015:7, 1015:17, 1016:13, 1017:13
Cabozantinib [1] - 988:1
cabozantinib's [6] - 809:18, 875:3, 875:6, 875:8, 878:7, 1004:23
Caleb [1] - 705:10
California [1] - 841:2
calorimetry [4] - 898:18, 903:13, 903:16, 903:17
Cancer [6] - 940:24, 940:25, 947:1, 947:2, 990:19, 990:24
cancer [63] - 741:13, 870:12, 870:13, 871:15, 927:21, 939:20, 940:13, 941:2, 941:12, 942:9, 943:9, 943:17, 945:10, 945:24, 946:3, 946:20, 949:5, 949:21, 955:7, 956:11, 956:12, 956:24, 957:7, 957:14, 958:24, 959:10, 959:19, 962:19, 963:1, 963:2, 963:19, 964:3, 964:6, 969:10, 974:22, 974:24, 975:18, 991:2, 992:17, 993:5, 993:10, 993:16, 993:20, 994:9, 994:12, 995:23, 995:24, 995:25, 997:10, 998:22, 998:23, 1007:23, 1008:1, 1008:6, 1008:16, 1010:14, 1026:20
cancerous [1] - 992:25
cancers [5] - 726:5, 939:20, 945:10, 945:11, 946:1
cannot [5] - 905:13, 923:1, 974:5, 1009:23, 1010:4
capability [1] - 828:17
capital [2] - 1011:23
capsule [5] - 728:22, 776:13, 776:15, 777:7, 943:15
capsules [11] - 713:14, 715:4, 720:13, 720:22, 720:25, 721:1, 728:21, 729:1, 729:2, 740:18, 741:13
carbon [1] - 815:8
carcinogenic [4] - 727:10, 755:23, 765:18, 766:3
carcinogens [1] - 766:9
carcinoma [32] - 941:13, 945:2, 945:5, 945:6, 945:8, 945:9, 945:15, 946:2, 946:16, 947:16, 950:6, 950:18, 950:25, 951:6, 951:14, 951:21, 952:4, 952:14, 953:24, 962:25, 980:10, 980:13, 982:10, 982:23, 996:5, 1000:2, 1002:2, 1004:22, 1006:7, 1006:13, 1006:22, 1009:11
carcinomas [1] - 947:17
care [11] - 707:1, 896:2, 950:17, 951:4, 951:12, 954:2, 965:5, 993:22, 999:1, 999:2, 1029:18
career [7] - 798:17, 798:22, 801:12, 991:5, 993:14, 993:22, 1006:8
careful [1] - 865:17
carefully [1] - 969:20
carried [1] - 802:7
carriers [2] - 774:17, 774:21
carries [1] - 900:13
carry [2] - 709:6, 709:14
carrying [1] - 729:25
cartoon [1] - 846:9
case [68] - 725:15, 725:22, 726:9, 740:13, 741:10, 754:1, 757:23, 762:19, 764:21, 766:2, 773:19, 786:12, 787:10, 788:17, 800:6, 812:5, 819:2, 840:8, 840:10, 841:17, 845:1, 845:25, 855:21, 886:25, 887:11, 912:17, 912:19, 913:19, 915:14, 915:25, 920:21, 924:1, 926:16, 926:23, 935:9, 936:14, 939:4, 941:18, 943:1, 955:3, 957:23, 958:17, 958:22, 961:24, 969:19, 977:4, 986:10, 987:18, 987:23, 987:25, 988:1, 988:5, 988:7, 991:19, 1015:1, 1015:10, 1016:17, 1016:25, 1017:23, 1018:3, 1018:8, 1019:19, 1019:23, 1020:11, 1020:12, 1021:10, 1028:2, 1030:2
cases [5] - 735:19, 739:5, 799:5, 978:3, 1013:12
categories [8] - 746:18, 749:12, 749:18, 876:21, 947:22, 948:10, 996:22, 998:13
category [13] - 877:1, 948:13, 968:12, 968:13, 996:20, 998:1, 999:9, 1002:15, 1002:19, 1003:4, 1009:16, 1009:17
Category [4] - 822:11, 822:12, 948:8, 948:11
caucus [2] - 1028:24, 1029:2
caught [1] - 1028:22
causing [1] - 959:10
cell [38] - 941:13, 945:1, 945:4, 945:6, 945:8, 945:9, 945:15, 946:16, 947:14, 947:15, 947:16, 947:17, 950:5, 950:18, 950:25, 951:5, 951:14, 951:21, 952:4, 952:14, 953:24, 962:25, 980:10, 980:13, 982:10, 982:22, 992:11, 992:14, 992:23, 996:5, 1000:2, 1002:2, 1004:22, 1006:7, 1006:13, 1006:21, 1009:11
cells [6] - 765:3, 959:9, 992:13, 992:19, 998:22, 998:23
cellular [1] - 995:12
Celsius [1] - 849:9
certain [12] - 728:7, 730:18, 762:4, 764:24, 804:18, 810:3, 974:16, 981:10, 992:3, 992:19, 997:23, 1007:3
certainly [14] - 713:7, 718:19, 729:23, 789:9, 789:18, 794:14, 851:24, 852:18, 859:13, 865:13, 881:15, 994:3, 996:6, 1029:21
certified [2] - 990:11, 990:12
Certified [1] - 1031:11
certify [1] - 1031:8
cetera [1] - 837:19
Chair [1] - 940:20
chair [1] - 940:23
challenge [1] - 1018:10
challenges [1] - 959:11
chance [2] - 896:9, 1028:22
chances [1] - 975:18
change [7] - 760:20, 800:13, 807:7, 845:6, 849:3, 859:20, 957:2
changed [4] - 949:10, 949:20, 957:11, 1004:2
changes [9] - 710:8, 710:10, 710:11, 714:16, 828:19, 896:25, 919:18, 919:20, 919:22
changing [3] - 926:19, 1009:16, 1009:17
Chapel [1] - 1013:9
Chapter [1] - 736:3
chapter [2] - 893:9, 893:10
characteristic [1] - 898:6
characteristics [6] - 753:18, 753:24, 804:21, 896:24, 1007:11, 1007:14
characterization [3] - 898:15, 898:16, 903:11
characterize [3] - 898:12, 925:23, 937:6
characterized [4] - 889:6, 897:6, 925:10, 925:17
charge [1] - 729:25
Charles [3] - 977:21, 977:23
chart [28] - 762:5, 784:6, 784:9, 821:15, 876:15, 928:22, 930:21, 934:1, 934:14, 934:20, 934:21, 968:5, 981:17, 983:3, 983:6, 983:9, 983:12, 983:15, 983:24, 984:3, 984:13, 984:14, 984:25, 985:12, 997:14, 997:17, 998:11, 1023:1
charts [2] - 966:8, 983:4
check [2] - 1001:1, 1001:2
checked [1] - 769:2
checkmarks [1] - 805:13
CheckMate [9] - 951:18, 970:18, 971:11, 971:12, 1000:22, 1001:1, 1001:2, 1001:21, 1002:12
checkpoint [22] - 945:23, 952:15, 952:17, 953:16, 953:25, 996:1, 997:7, 998:16, 998:18, 998:19, 999:4, 1000:25, 1001:3, 1001:17, 1001:18, 1002:1, 1002:9, 1003:2, 1003:3, 1003:25, 1004:4, 1004:7
chemical [43] - 730:4,

730:7, 730:13, 730:21, 734:7, 739:15, 752:14, 760:2, 760:20, 762:3, 762:10, 763:25, 769:9, 769:11, 770:3, 800:20, 803:7, 809:10, 824:4, 824:11, 825:5, 840:21, 840:22, 841:3, 841:7, 841:15, 841:20, 844:17, 847:3, 851:5, 858:20, 860:20, 866:20, 893:24, 896:24, 917:19, 918:4, 918:11, 918:21, 919:19, 958:16, 1021:18, 1025:22
chemically [2] - 763:18, 822:4
chemist [1] - 760:6
Chemistry [1] - 810:21
chemistry [4] - 725:19, 817:23, 844:17, 844:20
chemists [2] - 844:22, 844:23
chemotherapy [1] - 994:10
chloride [6] - 724:7, 814:19, 814:21, 814:24, 815:2, 815:19
choice [6] - 804:17, 804:20, 824:16, 881:16, 910:1, 969:15
choose [2] - 932:24, 947:9
choosing [2] - 886:18, 886:21
chose [3] - 808:4, 808:5, 916:19
chosen [2] - 814:5, 884:10
chromosomal [2] - 765:3, 765:17
chronic [3] - 963:20, 993:17, 993:23
Cipla [2] - 865:24, 937:14
circle [1] - 846:9
circles [2] - 736:13, 736:17
Circuit [1] - 1017:23
circumstances [6] - 816:23, 958:9, 997:23, 1010:15, 1010:16, 1011:6
CISVL [2] - 981:2, 981:3
cite [1] - 937:11
cited [4] - 793:9, 928:18, 928:21, 929:19
cites [1] - 775:5
citrate [1] - 818:6
claim [35] - 712:16, 744:20, 744:21, 744:23, 744:24, 745:6, 745:15, 745:17, 745:21, 746:1, 746:2, 747:20, 747:24, 748:3, 748:7, 748:23, 749:1, 749:4, 749:10, 749:11, 749:16, 757:23, 758:9, 761:1, 761:11, 763:24, 772:4, 773:7, 794:18, 794:21, 859:16, 900:6, 900:7
Claim [30] - 728:7, 729:3, 729:8, 734:17, 740:16, 740:20, 742:18, 744:6, 744:11, 746:14, 747:21, 855:11, 867:23, 868:3, 869:14, 869:18, 869:22, 870:2, 870:10, 870:11, 870:14, 870:18, 871:18, 873:9, 900:13, 900:18, 941:24, 959:21, 988:13, 988:17
claimed [19] - 734:17, 738:24, 741:14, 745:10, 745:13, 772:9, 796:18, 855:25, 857:23, 857:25, 987:17, 1014:21, 1016:18, 1016:19, 1019:16, 1020:21, 1020:23, 1021:15, 1025:20
claiming [1] - 1016:13
claims [43] - 714:17, 757:22, 772:10, 846:23, 847:1, 853:4, 853:9, 854:14, 854:18, 854:23, 855:1, 855:5, 855:17, 856:3, 856:7, 859:20, 867:17, 867:23, 868:9, 869:3, 869:7, 869:11, 869:12, 870:3, 870:16, 870:17, 888:10, 893:2, 893:3, 899:5, 899:14, 899:24, 902:4, 941:17, 941:21, 942:3, 942:12, 957:23, 986:5, 986:20, 991:21, 992:3
Claims [1] - 892:12
clarify [1] - 897:24
clarity [2] - 714:10, 916:8
class [4] - 731:12, 998:19, 1002:1, 1004:25
classes [4] - 728:7, 728:11, 729:17, 733:10
Classification [1] - 876:9
classified [1] - 918:19
classroom [1] - 841:10
clean [1] - 788:22
clear [21] - 782:24, 783:7, 831:10, 855:4, 861:21, 865:13, 865:24, 866:22, 870:10, 878:6, 881:10, 905:17, 914:8, 922:25, 925:13, 934:8, 947:14, 947:15, 984:22, 985:4, 1001:13
clearly [3] - 723:1, 791:19, 916:17
CLERK [13] - 706:13, 795:4, 795:6, 839:18, 895:22, 895:24, 938:13, 976:11, 976:13, 976:17, 989:6, 1011:20, 1031:6
client [1] - 807:25
clinic [3] - 943:9, 958:2, 959:17
Clinical [2] - 940:22, 950:22
clinical [46] - 741:23, 741:25, 742:1, 786:3, 810:4, 894:7, 894:14, 939:8, 939:10, 940:3, 940:18, 942:9, 942:11, 942:20, 946:23, 948:19, 951:10, 953:14, 954:11, 954:21, 954:23, 955:4, 955:16, 956:21, 957:23, 958:5, 959:21, 960:17, 961:6, 963:18, 973:7, 973:11, 973:14, 973:22, 986:11, 986:13, 986:14, 990:19, 992:5, 996:8, 1005:4, 1006:24, 1007:12, 1021:19, 1023:22, 1025:22
clinically [2] - 819:23, 954:9
clinician [1] - 954:8
clinicians [3] - 844:24, 947:5, 947:6
clinics [1] - 990:23
clock [1] - 895:20
close [2] - 783:4, 934:10
closely [1] - 708:3
closest [1] - 874:8
closing [3] - 1028:15, 1029:3, 1029:5
collaboration [1] - 1016:8
collaborations [4] - 1016:5, 1016:6, 1017:7, 1018:22
colleagues [1] - 942:21
color [1] - 919:16
colors [2] - 870:6, 876:21
Column [17] - 774:1, 774:9, 775:11, 775:20, 775:21, 776:20, 847:7, 847:11, 847:24, 848:15, 850:4, 850:9, 850:20, 851:21, 854:5, 869:15, 872:2
column [13] - 779:15, 779:18, 785:2, 805:13, 806:3, 811:8, 822:16, 822:21, 835:12, 847:16, 934:1, 947:25
columns [2] - 795:18, 850:19
combination [45] - 733:23, 812:18, 818:24, 837:13, 848:22, 851:10, 851:20, 862:12, 926:11, 945:7, 948:7, 948:11, 948:14, 948:18, 948:19, 948:23, 949:1, 951:19, 952:12, 953:5, 953:8, 953:12, 953:20, 961:1, 967:1, 970:15, 970:22, 971:1, 971:5, 983:25, 984:7, 985:1, 988:19, 995:25, 998:15, 999:3, 999:6, 999:8, 999:13, 1000:20, 1001:3, 1001:10, 1001:20, 1002:10
combinations [2] - 920:13, 922:12
combining [2] - 776:9, 776:13
combo [4] - 966:17, 966:21, 971:13, 973:2
Cometriq [12] - 718:22, 740:18, 943:12, 943:14, 943:15, 943:19, 978:20, 1016:22, 1021:25, 1022:3, 1022:19, 1026:19
coming [3] - 773:8, 821:14, 959:25
commercial [34] - 742:6, 742:7, 742:14, 894:8, 894:10, 894:14, 894:16, 977:7, 978:2, 978:14, 978:19, 979:4, 979:6, 982:16, 982:17, 986:4, 987:22, 988:12, 1013:13, 1013:18, 1014:10, 1014:16, 1014:18, 1014:23, 1016:24, 1019:4, 1019:5, 1019:14, 1022:5, 1022:10, 1024:15, 1024:21, 1025:3
commercialized [1] - 924:13
commercially [2] -

742:10, 819:24
Committee [1] - 940:23
committees [1] - 841:12
common [16] - 736:24, 747:5, 747:6, 797:25, 798:11, 814:23, 818:4, 818:11, 819:4, 846:25, 860:5, 866:12, 866:16, 937:3, 945:9, 947:15
commonly [5] - 809:1, 813:8, 819:8, 883:4, 883:6
compacting [1] - 776:9
companies [6] - 737:2, 842:6, 842:11, 842:12, 842:14
company [4] - 799:11, 911:20, 914:3, 914:4
comparable [1] - 1000:16
comparatively [1] - 994:10
compare [10] - 803:13, 814:14, 823:3, 824:11, 851:6, 993:19, 1003:15, 1004:23, 1005:9, 1021:4
compared [7] - 950:3, 950:15, 968:17, 970:19, 971:12, 1000:13, 1020:21
compares [1] - 823:4
comparing [6] - 950:4, 951:19, 952:12, 968:22, 1001:3, 1003:13
comparison [8] - 870:16, 950:23, 952:11, 956:2, 982:20, 1023:2, 1023:12, 1023:24
compatibility [8] - 713:8, 739:7, 739:18, 762:14, 762:16, 762:25, 763:5, 763:8
compatible [2] - 763:13, 763:19
compensated [1] - 840:10
compensation [1] - 840:12
competition [1] - 982:13
complete [2] - 909:4, 949:18
completely [2] - 732:20, 891:18
complex [2] - 807:20, 824:21
complexation [1] - 801:4
complexity [2] - 882:4, 884:5
complicate [1] - 817:23
complicated [1] - 1011:2
complications [1] - 958:20
component [3] - 772:2, 794:4, 994:3
components [3] - 776:9, 776:14, 994:4
composition [36] - 712:18, 712:20, 721:6, 731:23, 738:19, 738:24, 746:1, 746:8, 749:18, 764:19, 772:17, 772:23, 773:2, 773:5, 773:8, 773:15, 773:17, 773:18, 773:19, 773:21, 773:23, 775:25, 777:7, 782:15, 823:18, 849:21, 850:1, 861:2, 870:9, 918:4, 918:12, 918:22, 922:21, 923:3, 924:11, 924:25
compositions [12] - 711:19, 728:10, 774:12, 774:19, 774:22, 774:25, 776:4, 776:10, 776:13, 777:4, 871:12, 926:22
Compound [10] - 724:5, 724:7, 847:9, 847:10, 848:21, 849:2, 849:8, 851:25, 852:1, 852:18
compound [43] - 707:22, 708:21, 723:10, 723:13, 725:3, 743:11, 753:6, 757:17, 764:19, 803:3, 812:14, 814:25, 830:11, 835:20, 850:16, 867:24, 877:4, 877:9, 886:23, 887:9, 905:25, 906:13, 907:3, 907:14, 910:9, 919:19, 920:2, 920:4, 921:12, 921:17, 923:2, 924:7, 924:17, 924:18, 924:24, 932:17, 958:17, 960:12, 960:16, 1008:6, 1015:7, 1015:17, 1016:13
compounds [11] - 766:9, 767:12, 798:14, 799:9, 800:23, 801:8, 808:1, 819:8, 822:2, 827:12, 927:9
Comprehensive [1] - 947:1
comprehensive [1] - 930:6
compressibility [1] - 730:1
comprising [1] - 823:18
concedes [2] - 913:22, 913:25
concentration [3] - 806:24, 909:19, 921:19
concept [1] - 946:4
concepts [2] - 800:16, 845:14
concern [2] - 924:1, 1029:18
concerned [4] - 754:19, 765:9, 835:23, 1018:17
concerning [10] - 742:18, 765:24, 766:18, 766:22, 767:1, 850:25, 859:19, 866:2, 928:19, 960:11
concerns [1] - 809:15
conclude [4] - 979:3, 1019:1, 1022:11, 1022:13
concluded [2] - 893:1, 988:11
conclusion [8] - 742:17, 861:20, 865:24, 951:7, 951:8, 951:24, 1024:15, 1025:1
conclusions [6] - 822:25, 862:24, 865:6, 881:3, 891:1, 951:22
concomitant [1] - 958:7
condition [2] - 974:20, 974:23
conditions [13] - 739:16, 740:8, 787:14, 802:3, 806:20, 806:21, 806:22, 807:4, 807:10, 828:15, 838:15, 849:1, 920:13
conduct [1] - 828:15
conducted [2] - 804:15, 838:15
confidence [1] - 960:2
confirm [1] - 915:21
confirms [2] - 868:16, 888:12
confusing [1] - 916:23
confusion [1] - 932:13
connecting [1] - 746:5
connection [3] - 830:19, 845:1, 1019:15
consensus [4] - 948:1, 997:19, 998:3, 999:11
consequence [1] - 856:23
consequences [1] - 824:15
conservative [1] - 766:8
consider [16] - 717:4, 740:12, 740:19, 741:6, 742:3, 742:5, 754:16, 808:2, 816:7, 817:18, 824:17, 832:17, 888:17, 932:23, 942:17, 975:7
considerably [2] - 745:22, 746:2
consideration [8] - 801:19, 804:3, 818:24, 832:9, 832:22, 932:19, 998:4, 998:8
considerations [5] - 799:23, 802:4, 804:4, 824:22, 824:25
considered [25] - 725:14, 751:12, 802:22, 803:20, 815:15, 816:21, 816:24, 817:9, 818:17, 823:5, 823:10, 824:14, 825:1, 827:25, 836:25, 837:15, 861:7, 877:23, 925:24, 950:16, 957:22, 979:10, 997:24, 1010:2
consistency [1] - 1007:24
consistent [10] - 764:11, 780:23, 808:13, 814:16, 853:14, 887:1, 887:12, 1007:16, 1007:18, 1007:20
consistently [1] - 796:10
constant [2] - 805:24, 838:12
constants [1] - 811:3
constitutes [2] - 1023:7, 1024:10
consultant [2] - 842:5, 1013:6
consulted [1] - 799:11
consulting [3] - 842:7, 842:9, 977:22
contact [1] - 713:9
Contact-03 [1] - 952:10
CONTACT-03 [3] - 972:25, 1003:21, 1003:23
contain [5] - 842:21, 846:16, 853:4, 855:6, 855:17
containing [2] - 720:13, 812:14
contaminants [1] - 728:3
context [7] - 735:8, 778:7, 816:8, 853:9, 954:2, 958:4, 1009:16
continuation [1] - 1004:3
continue [10] - 706:16, 801:11, 805:15, 838:18, 864:23, 896:1, 954:17, 1004:19, 1007:5, 1007:8
Continued [1] - 707:3
CONTINUED [1] - 706:1
continued [5] - 741:3, 878:20, 940:4, 997:5
continuing [6] - 849:5,

953:16, 1003:25, 1004:7, 1004:8
continuous [1] - 709:8
continuously [1] - 801:11
contrary [1] - 766:10
contrast [3] - 853:13, 865:8, 890:22
contribute [4] - 948:17, 986:12, 1007:11, 1007:15
contributed [1] - 960:13
contributions [1] - 1020:20
control [15] - 708:24, 721:13, 721:23, 722:12, 722:18, 724:13, 726:18, 727:15, 757:4, 764:22, 764:24, 773:12, 949:18, 1000:17, 1003:13
controlled [2] - 728:18, 958:5
controlled-release [1] - 728:18
controlling [4] - 738:17, 738:18, 745:9, 768:21
controls [1] - 773:8
Conventional [1] - 793:12
conventional [1] - 793:16
conversations [1] - 942:20
convey [2] - 850:4, 953:4
conveys [1] - 857:22
Cooper [2] - 1011:10, 1028:23
COOPER [31] - 706:5, 941:14, 961:13, 961:17, 961:20, 966:8, 966:10, 970:13, 970:14, 976:4, 989:5, 989:14, 989:16, 990:1, 990:3, 990:9, 990:10, 991:11, 991:16, 991:17, 993:8, 993:9, 995:15, 995:16, 997:13, 997:15, 1006:2, 1011:11, 1027:23, 1028:2, 1028:13
copy [2] - 833:11, 1012:18
corner [1] - 989:24
Correct [1] - 762:6
correct [385] - 708:9, 708:21, 709:22, 709:23, 716:13, 719:24, 726:22, 728:8, 728:9, 733:19, 733:21, 743:13, 743:21, 743:22, 743:25, 744:10, 744:17, 744:20, 745:5, 746:15, 746:16, 746:19, 746:22, 746:25, 747:13, 747:23, 748:2, 748:10, 748:13, 748:16, 749:13, 749:24, 749:25, 750:2, 750:3, 750:7, 750:9, 751:18, 753:20, 753:21, 753:25, 754:2, 754:6, 754:9, 754:12, 754:15, 754:22, 755:4, 755:10, 756:1, 757:15, 758:14, 758:15, 758:19, 758:23, 759:3, 759:14, 760:13, 760:17, 761:3, 761:4, 761:24, 762:13, 762:18, 762:20, 763:15, 764:2, 764:3, 764:19, 765:19, 765:23, 766:4, 766:19, 766:24, 767:10, 768:17, 769:4, 770:8, 770:11, 770:14, 770:15, 772:3, 772:6, 772:8, 772:24, 773:3, 773:4, 773:24, 774:20, 775:4, 775:8, 775:10, 777:25, 778:4, 778:22, 778:23, 779:9, 779:21, 779:22, 779:24, 779:25, 780:1, 780:2, 780:6, 781:14, 781:18, 781:21, 782:5, 782:7, 782:17, 784:11, 784:19, 785:1, 785:4, 785:6, 785:7, 785:10, 785:17, 787:24, 788:8, 789:1, 789:4, 790:1, 790:11, 790:12, 791:10, 791:15, 791:23, 792:5, 792:7, 792:8, 793:15, 793:18, 793:21, 794:20, 794:23, 795:16, 796:15, 797:18, 797:19, 827:19, 828:9, 828:12, 829:4, 829:9, 829:12, 829:19, 830:6, 830:20, 830:23, 831:4, 831:8, 859:10, 873:19, 878:17, 882:23, 883:3, 889:24, 897:3, 897:4, 897:9, 897:11, 897:15, 897:22, 897:23, 898:6, 898:9, 898:10, 900:10, 900:14, 901:11, 902:2, 902:9, 902:13, 902:17, 902:18, 902:23, 903:7, 903:8, 903:9, 903:11, 903:13, 903:19, 903:22, 904:1, 904:2, 904:4, 904:5, 904:7, 904:15, 904:17, 904:18, 904:21, 904:22, 905:1, 905:12, 905:15, 905:16, 906:1, 906:6, 906:7, 906:10, 906:13, 906:14, 906:18, 906:23, 907:10, 907:16, 907:17, 907:25, 908:4, 908:25, 909:14, 909:17, 910:10, 910:12, 910:13, 910:18, 910:22, 911:7, 911:10, 911:14, 911:23, 911:24, 912:5, 912:6, 912:10, 912:12, 912:17, 912:20, 912:24, 913:1, 913:19, 913:20, 914:20, 915:12, 916:2, 917:3, 917:19, 918:2, 918:6, 918:13, 918:19, 918:22, 919:6, 919:8, 919:10, 919:12, 919:14, 919:16, 919:17, 920:8, 920:18, 920:22, 921:9, 923:8, 923:19, 923:23, 924:3, 924:7, 924:12, 924:18, 924:21, 925:17, 925:18, 925:21, 925:22, 926:5, 927:12, 927:18, 928:1, 928:2, 928:7, 928:15, 928:20, 928:23, 929:17, 929:20, 930:3, 931:24, 932:4, 932:9, 932:24, 934:2, 934:5, 936:17, 962:1, 962:6, 962:11, 962:15, 962:20, 963:15, 963:20, 963:24, 963:25, 964:3, 964:4, 964:7, 964:10, 964:14, 964:24, 965:6, 965:14, 965:25, 966:23, 967:1, 967:15, 967:23, 967:24, 968:3, 968:7, 968:10, 968:14, 968:19, 968:25, 970:3, 970:4, 970:7, 970:10, 970:16, 970:17, 970:20, 970:21, 971:2, 971:21, 972:6, 972:12, 972:18, 972:22, 973:23, 974:1, 974:9, 974:20, 975:1, 975:5, 975:15, 975:19, 976:2, 980:11, 987:19, 987:21, 988:2, 988:6, 988:8, 988:13, 988:14, 988:18, 988:19, 988:20, 1006:22, 1006:25, 1007:3, 1007:6, 1007:9, 1007:12, 1007:17, 1007:20, 1007:23, 1007:25, 1008:3, 1008:8, 1008:12, 1008:17, 1008:20, 1008:25, 1009:1, 1009:3, 1009:7, 1009:11, 1009:12, 1009:14, 1009:15, 1009:20, 1009:24, 1010:5, 1010:15, 1010:22, 1011:6, 1026:16, 1026:20, 1026:23, 1027:2, 1027:5, 1027:9, 1027:12
correctly [1] - 823:4
correlate [1] - 891:12
correlation [2] - 723:19, 723:23
corresponding [3] - 804:17, 819:5, 820:7
cost [1] - 1023:18
costs [2] - 1022:22, 1023:18
counsel [6] - 864:13, 885:4, 913:6, 916:5, 930:17, 987:16
Counsel [7] - 881:1, 886:7, 897:24, 899:15, 901:12, 909:3, 932:10
counterion [14] - 799:21, 803:23, 804:8, 804:17, 808:24, 814:24, 818:18, 818:24, 819:2, 820:7, 822:15, 872:23, 881:4, 932:7
counterions [17] - 802:10, 808:5, 812:9, 817:17, 824:2, 832:12, 832:17, 835:21, 881:12, 881:17, 883:2, 883:5, 928:6, 928:10, 928:20, 932:15, 933:14
countries [1] - 876:22
couple [9] - 775:5, 777:17, 792:10, 802:14, 829:17, 838:24, 839:5, 852:3, 891:3
coupled [1] - 937:3
course [29] - 709:6, 728:24, 733:10, 737:11, 741:25, 744:24, 744:25, 745:24, 752:24, 754:22, 763:15, 765:7, 766:17, 769:19, 785:24, 789:15, 790:14, 793:23, 803:9, 806:22, 807:25,

825:2, 854:25, 873:6, 962:3, 980:7, 991:4, 1025:25
courses [2] - 841:16, 841:22
COURT [81] - 705:1, 706:15, 706:20, 706:24, 718:15, 718:20, 742:22, 742:25, 749:4, 751:22, 795:1, 795:7, 796:22, 797:3, 797:8, 826:15, 826:22, 833:8, 833:13, 838:2, 838:4, 838:20, 838:25, 839:10, 839:12, 839:17, 843:4, 862:9, 863:16, 863:20, 864:8, 864:22, 889:18, 890:1, 895:9, 895:15, 895:25, 896:4, 933:22, 935:4, 938:7, 938:12, 938:22, 941:15, 961:14, 961:18, 976:6, 976:14, 976:16, 978:16, 987:4, 987:8, 987:11, 988:23, 989:2, 989:4, 991:15, 1006:4, 1006:9, 1006:17, 1011:9, 1011:12, 1011:17, 1013:21, 1023:9, 1023:15, 1025:7, 1025:10, 1025:13, 1025:24, 1026:9, 1027:16, 1027:19, 1027:22, 1028:1, 1028:4, 1028:8, 1028:15, 1029:1, 1029:13, 1031:4
Court [37] - 706:13, 780:21, 781:6, 790:9, 790:18, 790:20, 791:3, 797:11, 801:23, 840:5, 851:13, 856:17, 856:20, 857:18, 860:3, 861:7, 862:2, 864:4, 865:4, 883:8, 886:4, 890:14, 892:21, 916:16, 925:14, 933:9, 988:16, 989:14, 989:18, 991:24, 995:20, 1012:24, 1013:15, 1024:19, 1029:10, 1031:7, 1031:12
court [2] - 706:25, 790:15
Court's [1] - 894:9
Courthouse [1] - 705:10
courtroom [3] - 786:22, 833:23, 1013:23
cover [13] - 843:17, 843:19, 845:14, 893:8, 900:21, 900:25, 901:10, 901:15, 901:17, 901:19, 901:21, 901:23, 941:21
covers [4] - 901:13, 902:9, 941:25, 1020:21
COX [1] - 705:22
CRC [1] - 810:21
create [6] - 798:7, 814:3, 818:1, 882:3, 897:16, 897:21
created [7] - 910:25, 911:4, 911:6, 914:14, 915:7, 949:11, 1021:13
creation [1] - 743:11
credentials [1] - 990:7
criteria [2] - 997:25, 998:7
critical [2] - 1007:16, 1007:22
critically [1] - 921:16
CROSS [7] - 743:2, 827:3, 896:5, 961:19, 987:12, 1006:18, 1026:13
cross [6] - 790:8, 826:20, 833:10, 895:17, 896:3, 987:9
cross-examination [1] - 895:17
CROSS-EXAMINATION [7] - 743:2, 827:3, 896:5, 961:19, 987:12, 1006:18, 1026:13
cross-examined [1] - 790:8
crucial [1] - 740:24
crystal [12] - 729:24, 739:20, 846:12, 852:7, 853:17, 917:18, 918:5, 918:22, 920:13, 922:12
crystalline [176] - 708:13, 710:22, 710:23, 711:14, 735:15, 736:18, 750:6, 751:8, 797:21, 798:10, 842:2, 843:18, 844:5, 846:8, 846:11, 846:23, 847:3, 849:11, 849:13, 850:13, 850:15, 850:16, 851:3, 851:25, 852:1, 852:4, 852:5, 852:6, 852:13, 852:15, 853:1, 853:2, 853:3, 853:4, 853:7, 853:8, 853:11, 853:24, 854:15, 854:18, 854:25, 855:12, 855:15, 856:3, 856:6, 856:8, 856:9, 856:12, 856:21, 856:22, 857:2, 857:7, 857:10, 857:12, 858:7, 858:10, 858:21, 859:3, 859:8, 859:14, 859:17, 860:1, 860:19, 861:6, 862:13, 862:25, 863:15, 865:11, 865:16, 865:18, 866:7, 866:18, 866:24, 867:1, 867:13, 870:11, 870:14, 870:17, 871:5, 871:9, 879:18, 883:19, 883:21, 884:12, 884:15, 884:18, 885:8, 885:14, 888:24, 889:15, 890:21, 891:6, 891:7, 893:21, 893:23, 894:11, 894:17, 894:21, 894:22, 896:13, 896:15, 896:16, 896:20, 896:25, 897:5, 897:21, 897:25, 898:2, 898:8, 898:11, 898:12, 898:16, 900:11, 900:18, 900:21, 901:1, 901:2, 901:10, 901:14, 902:24, 904:9, 904:14, 904:21, 904:22, 904:25, 905:2, 905:6, 905:20, 905:23, 905:25, 906:23, 907:3, 907:9, 907:19, 908:4, 910:21, 912:5, 912:9, 912:23, 917:10, 917:13, 917:22, 918:4, 918:9, 918:11, 918:12, 918:15, 918:17, 918:23, 921:10, 921:12, 922:7, 922:18, 923:1, 923:18, 926:7, 926:11, 927:18, 936:3, 936:25, 937:7, 937:11, 937:18, 937:21, 941:21, 943:20, 943:22, 960:1, 960:22, 1027:12
crystallinity [1] - 860:19
crystallization [18] - 735:18, 736:24, 738:9, 792:13, 792:17, 792:23, 793:13, 793:25, 794:7, 794:13, 794:22, 843:1, 906:18, 906:22, 907:6, 908:25, 909:17, 910:18
Crystallization [1] - 736:4
crystallizations [1] - 735:13
crystallize [1] - 936:11
cumulative [1] - 980:1
current [7] - 820:22, 820:23, 940:5, 978:8, 990:16, 1016:17, 1020:12
curriculum [1] - 990:5
curtain [1] - 998:22
curve [4] - 862:20, 862:21, 890:19, 890:23
CV [4] - 842:20, 941:7, 978:8, 1012:18
cycle [1] - 980:8
cyclodextrin [1] - 801:3
cytokine [2] - 965:11, 996:25

D

D)-malate [6] - 848:8, 850:6, 850:13, 850:15, 854:1, 871:3
D)-malic [2] - 847:20, 847:22
daily [1] - 727:12
damage [1] - 765:17
damages [3] - 765:17, 978:2, 1013:13
damaging [1] - 958:18
Dana [1] - 940:2
Dana-Farber [1] - 940:2
Daniel [4] - 938:11, 938:15, 939:2, 941:11
DANIEL [2] - 938:16, 938:17
dasatinib [2] - 963:11, 994:16
dashed [2] - 983:23, 984:25
data [20] - 780:7, 780:9, 789:16, 820:14, 828:18, 862:19, 862:20, 862:22, 882:21, 891:2, 936:23, 948:20, 955:15, 955:16, 956:21, 961:6, 969:13, 981:15, 985:19, 998:5
date [33] - 797:25, 798:1, 831:20, 837:24, 844:7, 844:8, 844:11, 845:9, 856:11, 857:1, 868:25, 869:11, 869:12, 873:22, 874:20, 875:2, 875:5, 876:11, 876:12, 876:16, 878:6, 879:12, 886:13, 887:18, 887:24, 915:22, 915:23, 921:11, 926:22, 947:3, 1015:15, 1016:14, 1017:16
dated [1] - 990:5
David [1] - 810:22
days [1] - 838:22
DDX [3] - 858:24, 989:24, 990:9
DDX-2 [1] - 1012:22
DDX-3 [2] - 993:8, 1014:4

DDX-4 [2] - 1015:22, 1015:24
DDX-5 [1] - 1017:25
DDX-6 [1] - 1020:2
DDX-7 [1] - 1021:22
DDX-8 [1] - 1022:16
DDX-9 [1] - 1024:17
de [3] - 709:14, 759:8, 923:9
DE [1] - 1011:23
dealing [4] - 767:10, 793:19, 793:20, 958:6
death [2] - 957:7, 992:14
debate [1] - 930:9
decade [1] - 831:20
decide [1] - 729:17
decided [1] - 911:20
decision [10] - 814:3, 814:7, 814:11, 814:13, 815:16, 816:18, 817:9, 829:3, 829:7, 954:11
decisions [2] - 954:19, 1026:23
declaration [5] - 890:8, 892:7, 892:10, 892:24, 892:25
Declaration [1] - 892:9
decompose [2] - 730:8, 730:17
decomposed [1] - 739:16
decomposition [3] - 737:12, 738:11, 763:16
decreasing [1] - 1003:1
deemed [3] - 806:4, 806:7, 931:10
deeper [2] - 915:14, 916:7
Defendant [2] - 989:4, 1011:15
Defendants [5] - 705:8, 706:8, 1011:15, 1013:17, 1031:2
defendants [3] - 991:11, 1025:5, 1028:2
Defendants' [19] - 708:5, 713:20, 719:23, 720:4, 720:6, 720:8, 720:23, 724:18, 724:22, 724:25, 727:1, 727:4, 731:4, 731:25, 732:13, 737:16, 737:19, 737:22
defendants' [1] - 942:22
defense [2] - 1027:7, 1027:10
defenses [1] - 998:21
defined [2] - 802:12, 822:5
defining [1] - 856:9
definition [15] - 800:7, 800:14, 844:25, 845:7, 845:11, 871:24, 872:9, 872:11, 872:14, 873:10, 974:18, 1022:21, 1022:24, 1023:6, 1024:10
definitions [3] - 800:5, 800:11, 1024:6
definitive [1] - 832:24
definitively [1] - 953:17
deForest [1] - 1011:16
DeForest [4] - 1011:22, 1011:25, 1012:8, 1013:18
degra [1] - 759:8
degradated [1] - 958:16
degradation [28] - 707:18, 709:16, 722:3, 722:9, 740:10, 752:7, 752:10, 752:25, 753:2, 753:10, 754:13, 754:19, 754:23, 755:2, 755:9, 755:14, 757:18, 757:24, 758:10, 758:18, 759:9, 759:17, 760:18, 761:2, 761:12, 761:17, 761:21, 1008:11
degree [13] - 841:1, 841:2, 844:17, 875:24, 956:2, 977:14, 977:18, 996:11, 1005:25, 1010:10, 1013:3, 1019:15, 1020:18
degrees [4] - 787:15, 787:16, 849:9, 1013:1
DELAWARE [1] - 705:2
Delaware [1] - 705:11
delay [3] - 948:22, 955:22, 955:24
delayed [2] - 950:14, 957:8
delays [1] - 958:7
deliver [1] - 1030:17
demonstrate [2] - 916:15, 936:25
demonstrated [7] - 948:21, 951:10, 953:7, 955:24, 956:18, 963:17, 969:9
demonstrates [1] - 717:18
demonstrating [2] - 954:23, 956:22
demonstrative [4] - 772:19, 809:22, 810:8, 817:15
Demonstrative [6] - 740:16, 977:10, 979:8, 983:1, 984:11, 985:9
demonstratives [1] - 806:18
densities [2] - 805:24, 918:24
Department [1] - 1013:8
department [1] - 841:11
dependent [1] - 900:8
deposition [9] - 754:24, 786:15, 790:13, 790:20, 790:23, 934:13, 934:18, 934:24, 972:10
depth [2] - 916:15, 916:16
DEPUTY [11] - 706:13, 795:6, 839:18, 895:22, 938:13, 976:11, 976:13, 976:17, 989:6, 1011:20, 1031:6
Deputy [1] - 895:24
derivatives [1] - 725:11
describe [24] - 707:25, 710:3, 720:8, 723:19, 727:7, 728:2, 739:7, 786:2, 801:23, 802:20, 803:10, 808:19, 808:21, 811:1, 817:19, 858:20, 942:7, 979:23, 985:11, 990:16, 992:9, 997:19, 998:17, 1013:4
described [16] - 714:9, 716:3, 762:13, 762:15, 779:5, 796:13, 813:11, 816:20, 848:25, 849:6, 849:18, 852:2, 904:19, 905:4, 927:25, 1017:18
describes [5] - 710:16, 720:9, 725:17, 762:8, 807:20
description [11] - 714:18, 843:12, 857:6, 857:21, 859:20, 902:21, 903:2, 904:13, 936:16, 936:20, 1012:25
descriptions [1] - 903:22
Design [1] - 821:25
design [1] - 841:20
designated [3] - 819:5, 832:24, 974:12
designation [9] - 818:17, 818:21, 832:19, 946:5, 946:12, 946:14, 946:17, 974:15, 974:19
designed [5] - 712:4, 728:19, 953:14, 960:24, 1000:10
desirable [1] - 817:3
desired [2] - 733:23, 887:21
despite [4] - 851:17, 888:20, 889:7, 891:18
detail [7] - 714:9, 779:5, 861:18, 865:21, 936:22, 936:23, 942:13
detailed [1] - 857:17
detect [1] - 998:21
detectable [1] - 721:22
detected [3] - 716:6, 784:21, 789:14
detection [2] - 716:7, 784:24
determination [8] - 748:12, 761:8, 761:21, 764:8, 765:21, 768:10, 923:15, 998:3
determinations [1] - 766:14
determinative [5] - 874:17, 875:17, 877:12, 881:16, 894:24
determine [16] - 730:7, 754:7, 754:10, 755:1, 756:4, 759:17, 764:18, 766:18, 767:14, 769:23, 771:10, 773:20, 906:9, 933:4, 933:25
determined [11] - 755:21, 758:21, 763:9, 763:12, 805:13, 830:11, 934:13, 979:5, 979:13, 979:17, 1028:20
determines [1] - 763:6
determining [16] - 744:21, 761:2, 761:12, 762:10, 763:25, 769:25, 772:5, 772:10, 806:23, 835:21, 838:5, 899:6, 932:23, 936:19, 978:2, 997:25
deterred [1] - 1018:5
deterrence [5] - 1014:25, 1017:14, 1017:21, 1019:1, 1019:3
deters [1] - 1014:21
develop [3] - 733:13, 754:7, 973:25
developed [7] - 743:10, 894:25, 993:5, 1009:7, 1017:4, 1020:23, 1023:8
developer [1] - 1018:16
developing [4] - 754:23, 796:10, 816:25, 975:25
development [40] - 733:13, 753:1, 753:4, 753:19, 753:22, 754:4, 755:1, 760:3, 760:17, 762:17, 762:19, 764:20, 766:23, 798:4, 799:22, 801:20, 808:2, 824:21,

825:1, 825:2, 832:18, 841:25, 842:25, 844:20, 848:23, 849:15, 851:10, 860:16, 883:23, 885:15, 974:16, 992:17, 1008:20, 1017:1, 1018:6, 1018:12, 1018:18, 1022:22, 1023:17, 1023:18
deviation [2] - 718:3, 791:20
deviations [23] - 717:1, 717:3, 717:4, 717:6, 717:8, 717:15, 717:18, 717:20, 717:22, 790:4, 790:8, 790:10, 790:12, 790:16, 791:5, 791:6, 791:9, 791:14, 791:17, 791:20, 791:21, 791:25
diarrhea [1] - 959:1
died [1] - 957:13
dielectric [1] - 805:24
differ [7] - 767:22, 917:7, 917:8, 917:11, 917:15, 917:16, 919:5
difference [26] - 710:6, 712:3, 724:6, 785:12, 792:6, 812:23, 813:1, 824:15, 847:21, 853:21, 897:2, 912:4, 912:5, 920:1, 956:2, 969:9, 994:2, 996:9, 996:11, 1000:6, 1005:25, 1010:10, 1010:14, 1010:19
differences [18] - 710:4, 710:5, 712:2, 803:15, 803:23, 804:2, 804:8, 812:7, 812:8, 868:9, 870:2, 870:4, 870:7, 896:23, 919:25, 923:12, 925:8, 971:25
different [88] - 709:25, 710:2, 712:4, 713:9, 720:10, 732:18, 732:19, 732:21, 732:23, 735:21, 735:22, 747:11, 747:12, 747:14, 747:15, 747:18, 755:11, 780:14, 789:6, 789:8, 789:10, 789:19, 791:25, 792:2, 795:20, 802:19, 804:4, 820:18, 824:17, 824:18, 845:4, 846:4, 846:5, 846:19, 849:1, 853:16, 855:12, 856:25, 859:3, 870:6, 876:21, 896:16, 896:20, 897:5, 897:16, 897:17, 897:21, 897:22, 898:1, 910:25, 911:1, 911:6, 912:1, 912:9, 917:18, 917:19, 917:21, 917:24, 918:5, 918:8, 918:12, 918:14, 918:22, 918:24, 919:1, 919:3, 919:8, 919:10, 919:12, 919:14, 919:16, 925:6, 928:2, 931:1, 956:6, 959:4, 979:12, 995:8, 1003:6, 1005:20, 1005:23
differential [3] - 898:18, 903:13, 903:16
differentiate [2] - 904:9, 992:14
differentiated [2] - 946:3, 946:20
differentiation [1] - 1021:8
differently [4] - 783:11, 785:18, 790:23, 911:23
differing [1] - 767:23
differs [1] - 911:25
difficult [4] - 735:8, 735:15, 737:3, 886:22
diffraction [1] - 857:18
diffractogram [2] - 865:5, 897:20
diffractograms [4] - 862:5, 865:9, 897:17, 897:22
dig [1] - 809:4
digits [2] - 745:18, 1024:8
dimensions [4] - 846:11, 853:12, 853:13, 853:18
Diovan [1] - 959:16
DIRECT [7] - 707:3, 797:13, 840:2, 938:23, 976:24, 989:15, 1012:4
direct [20] - 778:21, 783:25, 804:23, 811:7, 811:16, 813:23, 815:23, 819:14, 821:8, 824:6, 829:21, 832:5, 935:21, 936:21, 942:11, 952:25, 980:20, 986:19, 988:16, 990:22
directed [4] - 708:11, 708:12, 869:18, 869:19
directing [1] - 802:24
directly [4] - 710:8, 807:6, 816:11, 818:23
director [1] - 990:21
disagree [7] - 716:2, 722:23, 791:16, 807:18, 819:10, 824:1, 838:11
disagreeing [1] - 721:11
disagreement [1] - 716:18
discipline [1] - 844:18
disclose [22] - 711:3, 711:4, 711:8, 711:19, 712:9, 720:25, 723:13, 727:20, 844:4, 844:5, 850:12, 850:25, 858:10, 861:10, 861:12, 871:9, 874:24, 875:8, 876:15, 886:18, 887:5, 893:20
disclosed [24] - 707:14, 710:1, 740:25, 749:23, 774:25, 809:19, 848:5, 851:7, 854:3, 858:13, 858:16, 859:16, 860:2, 860:6, 860:11, 861:19, 866:12, 870:24, 871:2, 871:22, 874:21, 887:20, 887:25, 889:23
discloses [7] - 708:13, 712:6, 750:15, 851:2, 858:1, 858:4, 893:22
disclosing [1] - 773:10
disclosure [16] - 714:9, 775:24, 848:2, 849:23, 851:24, 852:11, 852:15, 852:19, 852:22, 852:25, 854:9, 854:12, 886:24, 887:10, 903:3, 905:7
disclosures [2] - 849:11, 870:20
discontinuations [1] - 958:8
discover [2] - 753:1, 907:11
discovered [4] - 752:6, 752:10, 752:13, 752:16
discoveries [6] - 751:12, 752:3, 752:19, 752:20, 759:13, 762:5
discovery [3] - 764:14, 914:8, 914:18
discuss [10] - 712:10, 723:10, 724:22, 725:2, 737:19, 806:20, 977:7, 997:16, 1028:23, 1030:21
discussed [32] - 707:12, 707:16, 707:21, 707:24, 709:20, 709:24, 717:4, 718:11, 719:17, 723:8, 727:5, 727:25, 732:25, 787:10, 800:21, 804:14, 807:19, 810:2, 819:16, 821:20, 822:14, 826:7, 833:6, 857:19, 860:18, 867:12, 915:2, 915:5, 930:17, 931:17, 997:9, 1016:22
discussing [5] - 732:3, 778:18, 935:25, 982:20, 997:16
discussion [7] - 750:17, 778:2, 831:23, 856:25, 880:24, 992:8, 1010:23
discussions [1] - 928:19
disease [9] - 750:14, 948:22, 949:18, 950:14, 955:23, 955:24, 955:25, 957:10, 993:24
diseases [1] - 967:18
disfavored [1] - 816:3
disincentives [5] - 1014:10, 1014:16, 1018:4, 1018:5, 1024:22
disintegrant [6] - 728:18, 728:20, 728:21, 732:14, 748:1, 748:5
disintegrants [7] - 733:6, 746:20, 747:8, 747:10, 747:11, 748:4, 748:19
dispersion [1] - 801:3
display [1] - 815:20
displayed [2] - 817:15, 900:3
dispute [7] - 718:10, 858:1, 858:4, 1006:24, 1011:4, 1026:18, 1027:1
disputing [5] - 831:6, 837:22, 1026:15, 1026:21, 1027:3
dissociation [1] - 811:3
dissolution [11] - 734:9, 825:5, 849:4, 888:25, 889:16, 890:15, 890:16, 891:13, 893:21, 894:1, 923:21
dissolve [3] - 728:17, 728:19, 891:5
dissolved [1] - 839:8
dissolves [5] - 890:21, 890:23, 890:24, 891:8, 891:18
distill [1] - 961:3
distinct [8] - 860:4, 861:21, 861:22, 865:25, 867:23, 868:3, 870:18, 995:10
distinction [2] - 760:5, 946:8
distinguish [3] - 856:12, 856:21,

857:9
Distinguished [1] - 940:20
distribution [2] - 729:24, 822:11
DISTRICT [2] - 705:1, 705:2
District [1] - 1031:12
divide [1] - 918:20
DL)-malate [2] - 848:9, 854:1
DNA [4] - 765:6, 765:10, 765:11, 958:18
doc [1] - 778:20
doctor [4] - 749:21, 750:22, 753:10, 973:6
Doctor [35] - 746:7, 746:14, 748:6, 748:24, 749:9, 756:17, 757:5, 762:9, 766:8, 772:14, 772:16, 772:21, 774:9, 775:12, 776:22, 777:17, 777:24, 784:7, 784:18, 792:10, 899:25, 900:17, 902:12, 906:20, 908:16, 910:16, 913:13, 915:1, 915:17, 916:18, 926:20, 929:25, 961:23, 969:18, 1006:4
Doctor's [2] - 750:19, 772:19
doctoral [1] - 841:4
document [50] - 715:2, 715:3, 720:5, 720:6, 720:21, 778:12, 778:15, 778:17, 778:21, 780:3, 780:21, 781:9, 781:11, 781:12, 783:1, 783:21, 790:6, 790:7, 790:9, 790:14, 790:16, 791:19, 805:1, 805:5, 810:20, 813:16, 820:13, 821:21, 823:15, 833:9, 834:20, 834:25, 868:23, 868:24, 876:5, 890:7, 891:23, 893:7, 893:11, 926:15, 941:6, 944:5, 947:3, 947:5, 949:24, 950:21, 951:8, 951:16, 952:9, 986:2
Document [1] - 834:19
documents [7] - 781:3, 782:6, 782:10, 783:13, 914:8, 915:16, 916:9
DOMINICK [1] - 706:2
done [20] - 717:20, 720:19, 749:5, 759:21, 760:1, 760:4, 760:16, 764:3, 787:6, 787:17, 839:13, 856:18, 857:13, 862:16, 934:12, 953:24, 957:11, 1027:22, 1028:11, 1030:24
Donovan [18] - 707:7, 707:12, 707:16, 707:21, 707:24, 708:8, 726:13, 727:25, 729:6, 731:7, 731:14, 731:20, 732:3, 732:25, 733:3, 1021:12, 1025:18, 1026:4
Donovan's [2] - 733:8, 1026:2
door [1] - 994:14
dosage [7] - 729:13, 733:2, 774:24, 816:13, 885:25, 1007:16, 1007:19
dose [4] - 729:14, 763:9, 886:1, 1007:20
double [7] - 843:12, 867:21, 879:23, 888:11, 926:18, 926:20, 1027:8
doubly [1] - 882:3
down [30] - 774:12, 775:11, 777:1, 785:16, 792:11, 796:23, 815:3, 821:24, 853:17, 887:14, 895:25, 900:13, 913:21, 914:23, 914:25, 930:23, 938:8, 957:8, 961:3, 967:6, 970:13, 976:7, 983:15, 988:24, 991:16, 995:15, 1011:13, 1019:8, 1027:20, 1030:17
downstream [1] - 1026:24
Dr [235] - 706:10, 706:21, 707:5, 707:7, 708:23, 709:8, 709:18, 709:24, 710:15, 712:11, 713:16, 714:20, 715:13, 715:17, 715:20, 716:14, 716:19, 717:4, 717:23, 718:6, 718:11, 719:17, 719:20, 719:23, 720:12, 720:16, 721:3, 721:8, 721:11, 721:12, 722:1, 722:7, 722:8, 722:14, 722:23, 723:8, 724:22, 726:13, 726:21, 727:4, 729:6, 731:7, 731:14, 731:20, 732:3, 732:25, 733:3, 733:8, 733:20, 734:23, 737:19, 741:6, 741:8, 741:11, 741:16, 741:22, 742:17, 742:20, 743:4, 790:8, 791:12, 795:13, 796:22, 797:8, 797:15, 800:21, 803:15, 807:15, 812:2, 816:2, 818:13, 819:7, 823:20, 825:17, 826:3, 826:10, 827:5, 829:5, 829:24, 830:10, 831:10, 833:4, 833:19, 833:23, 834:12, 836:17, 838:2, 839:12, 839:16, 840:7, 842:25, 843:11, 851:14, 853:15, 853:16, 854:14, 859:1, 859:20, 861:19, 863:5, 863:11, 863:13, 864:2, 864:3, 864:7, 864:16, 865:3, 865:20, 866:2, 867:12, 867:18, 869:9, 872:25, 873:4, 873:17, 874:4, 877:17, 877:21, 878:10, 879:14, 880:3, 880:6, 880:12, 880:19, 880:20, 881:20, 881:24, 882:12, 882:19, 882:23, 883:1, 883:7, 884:1, 884:4, 884:20, 885:6, 888:23, 889:13, 889:19, 890:8, 891:11, 891:15, 892:20, 894:2, 894:6, 894:13, 895:3, 896:7, 896:13, 913:22, 913:25, 914:19, 915:13, 916:7, 930:18, 933:12, 935:8, 935:16, 935:20, 938:7, 938:11, 938:15, 938:25, 939:2, 940:17, 941:11, 941:17, 941:20, 942:21, 942:22, 954:8, 956:1, 961:9, 961:21, 975:4, 976:6, 984:16, 986:13, 986:14, 989:5, 989:20, 990:4, 990:11, 991:12, 991:18, 991:25, 992:4, 992:8, 993:4, 994:20, 995:5, 995:17, 996:13, 997:9, 997:12, 997:16, 998:10, 999:6, 999:22, 1000:21, 1002:14, 1003:8, 1003:21, 1004:9, 1004:18, 1005:3, 1006:2, 1006:20, 1011:12, 1011:16, 1012:6, 1012:13, 1012:17, 1012:24, 1013:18, 1013:23, 1015:5, 1015:14, 1015:25, 1018:1, 1019:13, 1021:12, 1025:4, 1025:13, 1025:18, 1026:2, 1026:4, 1026:15, 1027:19, 1027:24
draw [3] - 1020:19, 1020:22, 1024:14
drawing [3] - 770:5, 1021:9, 1022:7
drawn [1] - 1025:1
draws [1] - 998:22
drive [2] - 804:18, 986:14
driving [1] - 1022:9
Drs [6] - 707:12, 707:16, 707:21, 707:24, 708:8, 727:25
Drug [2] - 876:9, 944:1
drug [97] - 712:23, 713:1, 713:4, 720:9, 720:21, 727:10, 727:13, 727:16, 729:12, 739:8, 741:2, 741:25, 742:2, 742:9, 742:16, 753:19, 753:22, 754:3, 754:20, 754:21, 754:23, 755:18, 756:18, 757:10, 757:13, 760:20, 760:21, 760:25, 763:9, 773:5, 798:6, 798:7, 798:24, 799:13, 800:17, 816:16, 822:5, 837:20, 861:3, 875:22, 879:10, 885:25, 897:3, 923:22, 930:25, 949:16, 949:19, 954:17, 954:21, 954:23, 956:6, 956:21, 958:10, 958:11, 959:12, 959:15, 959:16, 960:9, 960:10, 960:25, 961:24, 964:2, 968:24, 970:25, 973:15, 973:24, 974:19, 975:1, 975:13, 975:23, 975:25, 976:1, 993:10, 996:4, 1000:24, 1001:3, 1001:4, 1007:12, 1007:19, 1007:21, 1007:22, 1008:2, 1008:4, 1008:7, 1008:11, 1008:12, 1008:15, 1008:20, 1008:23, 1009:7, 1009:16, 1009:17, 1026:23
drugs [31] - 722:24, 723:1, 726:1, 726:3, 726:6, 726:7, 726:12, 769:20,

798:19, 816:10, 816:14, 822:23, 831:14, 831:16, 831:20, 876:18, 876:19, 877:3, 946:8, 949:1, 957:17, 958:7, 962:3, 964:12, 968:1, 974:16, 993:5, 994:19, 996:22, 1009:23, 1026:20
DSC/TGA [1] - 849:7
DTX [4] - 826:18, 882:9, 1025:11, 1028:6
DTX-013 [2] - 1015:3, 1015:5
DTX-167 [2] - 813:14, 819:15
DTX-177 [1] - 821:20
DTX-192 [3] - 1015:12, 1015:14, 1017:10
DTX-274 [2] - 756:7, 756:12
DTX-287 [3] - 823:14, 824:7, 826:13
DTX-530 [3] - 1012:15, 1012:17, 1025:6
DTX-536 [2] - 990:1, 1027:24
due [9] - 713:1, 730:8, 742:15, 752:13, 762:3, 1014:10, 1014:16, 1024:22, 1024:23
Duke [4] - 939:17, 939:18, 940:4, 940:19
duly [4] - 839:23, 938:18, 976:22, 989:11
durable [2] - 1002:4, 1006:15
duration [1] - 1008:24
during [22] - 709:16, 713:4, 721:13, 722:13, 752:9, 753:11, 757:9, 757:18, 758:10, 791:12, 814:22, 819:12, 822:24, 829:21, 892:20, 892:24, 930:16, 934:18, 983:18, 984:17, 988:4, 1008:7
dying [3] - 957:6, 957:9, 1011:1
dysregulated [1] - 992:23

E

early [6] - 750:23, 927:6, 932:1, 932:2, 940:2, 940:3
ease [1] - 885:21
easier [4] - 714:1, 783:24, 908:16, 913:7
Easley [1] - 940:20
economic [8] - 977:22, 978:1, 978:13, 1013:6, 1017:20, 1017:22, 1018:2, 1018:23
economics [4] - 1013:1, 1013:3, 1013:11, 1013:18
Economics [2] - 1013:7, 1013:9
economist [1] - 1012:9
edited [3] - 736:5, 810:22, 893:8
edition [1] - 736:4
education [5] - 841:9, 842:22, 939:15, 978:10, 990:7
educational [3] - 840:25, 977:12, 1012:25
effect [18] - 717:6, 740:7, 760:22, 908:9, 908:11, 908:19, 909:5, 909:7, 909:12, 909:14, 910:3, 910:7, 923:25, 959:4, 994:10, 996:8, 1002:7, 1027:5
effective [11] - 733:24, 734:13, 895:1, 953:19, 958:10, 969:3, 969:23, 971:17, 971:21, 1007:9, 1008:15
effectively [1] - 994:9
effectiveness [1] - 953:11
effects [9] - 759:22, 953:12, 958:19, 958:20, 958:23, 958:24, 959:6, 960:5, 1005:2
efficacy [5] - 963:18, 993:21, 994:3, 998:4, 998:8
efficient [1] - 814:5
effort [1] - 838:5
EGFR [1] - 995:1
EGFR-specific [1] - 995:1
eight [5] - 811:18, 882:16, 962:18, 963:22, 1000:8
either [13] - 721:25, 730:8, 800:10, 807:6, 815:18, 817:2, 833:21, 845:11, 881:11, 948:24, 954:14, 992:13, 999:13
elaborate [1] - 912:14
elaborated [1] - 915:15
Eleanor [1] - 940:20
elected [1] - 940:23
electric [1] - 729:25
elements [4] - 749:16, 825:4, 846:25, 1025:20
eligible [1] - 967:17
eliminated [1] - 710:7
ELIZABETH [1] - 706:6
emblematic [1] - 846:9
embodied [1] - 741:14
embodiment [2] - 775:17, 894:16
emerged [1] - 925:2
Emmanuel [1] - 989:8
EMMANUEL [1] - 989:9
employ [1] - 729:17
employed [4] - 774:24, 893:16, 939:16, 990:20
employment [2] - 990:6, 990:17
enables [1] - 905:9
encompasses [1] - 711:16
encompassing [1] - 799:4
end [11] - 709:12, 711:1, 712:25, 873:1, 876:23, 876:24, 876:25, 885:7, 899:25, 975:10, 980:5
ended [1] - 743:24
ending [2] - 892:16, 1015:16
ends [1] - 947:12
ENERIO [1] - 706:2
engaged [1] - 992:2
engineering [6] - 840:21, 840:23, 841:3, 841:7, 841:15, 844:17
England [1] - 951:17
entered [4] - 965:13, 977:15, 977:16, 997:4
entire [9] - 748:4, 748:23, 749:4, 773:2, 801:19, 816:8, 873:20, 888:4, 991:24
entirely [1] - 1028:8
entities [2] - 1017:11, 1018:11
entity [1] - 782:21
entries [1] - 812:11
entry [3] - 822:17, 830:18, 830:21
environment [1] - 958:5
envisioned [1] - 873:12
enzyme [1] - 992:10
EPA [3] - 725:1, 725:2, 725:5
equal [1] - 999:12
equipped [1] - 838:21
equivalent [1] - 911:9
erlotinib [4] - 963:5, 963:23, 964:15, 994:16
error [1] - 828:19
ESQUIRE [13] - 705:17, 705:18, 705:20, 705:21, 705:21, 705:22, 706:2, 706:5, 706:5, 706:6, 706:6, 706:7, 706:7
essentially [34] - 708:1, 710:16, 711:3, 711:5, 711:9, 711:12, 711:17, 711:20, 712:7, 712:8, 712:16, 712:25, 713:1, 721:4, 721:6, 721:18, 728:6, 735:1, 737:8, 737:15, 738:3, 739:9, 739:12, 741:20, 744:15, 749:19, 772:22, 773:1, 782:15, 782:16, 953:10, 998:20, 1025:15
estimate [1] - 838:18
et [2] - 705:7, 837:19
ethical [1] - 1010:23
evaluate [5] - 802:4, 826:7, 857:14, 1017:20, 1020:13
evaluated [6] - 769:19, 798:23, 801:13, 805:11, 819:23, 1017:22
evaluating [4] - 1013:11, 1018:25, 1020:20, 1023:21
evaluation [4] - 1019:19, 1023:7, 1023:24, 1024:1
evaporation [2] - 908:9, 909:2
evening [1] - 1028:24
event [3] - 917:4, 1028:11, 1030:20
events [1] - 1016:2
eventually [3] - 756:3, 900:9, 1015:19
everolimus [8] - 950:5, 950:15, 955:14, 955:21, 972:9, 972:10, 972:16, 1003:17
evidence [27] - 766:10, 796:16, 797:6, 797:7, 821:23, 826:17, 826:19, 855:23, 861:21, 865:24, 865:25, 866:6, 868:16, 888:12, 892:6, 893:1, 895:12, 895:14, 961:16, 969:12, 973:12, 986:24, 987:7, 1001:24, 1018:20, 1025:12, 1028:7
evident [1] - 1002:11
exact [4] - 907:21, 915:22, 934:23, 964:18
exactly [17] - 746:6, 756:1, 778:10, 780:24, 785:21, 785:23, 787:6, 788:11, 796:2, 857:7, 928:4, 928:25, 930:5, 956:13, 998:17, 1021:6, 1021:7
examination [3] - 778:21, 895:17, 1027:24
EXAMINATION [16] - 707:3, 743:2,

795:10, 797:13, 827:3, 840:2, 896:5, 935:6, 938:23, 961:19, 976:24, 987:12, 989:15, 1006:18, 1012:4, 1026:13
examined [6] - 790:8, 839:23, 938:18, 976:22, 989:11, 1012:1
examiner [2] - 892:6, 893:1
example [27] - 724:5, 728:15, 728:24, 776:8, 782:14, 785:21, 786:14, 807:22, 815:9, 817:4, 841:18, 842:9, 856:19, 857:8, 857:17, 870:8, 878:4, 879:16, 879:18, 885:25, 904:19, 911:3, 924:16, 924:21, 927:16, 959:14, 992:21
Example [16] - 709:24, 717:24, 718:2, 718:4, 778:6, 779:8, 785:24, 786:4, 786:5, 788:18, 788:24, 790:5, 790:12, 791:6, 791:22
examples [21] - 714:10, 726:3, 726:6, 748:16, 815:11, 817:10, 824:25, 858:15, 858:17, 858:18, 858:19, 858:22, 885:7, 904:16, 904:20, 904:24, 910:24, 924:5, 927:4, 939:25
exceedingly [1] - 1002:25
except [3] - 963:22, 964:15, 984:14
exception [1] - 994:25
exceptionally [3] - 741:1, 773:11, 796:11
excerpt [2] - 814:14, 816:4
excipient [12] - 713:7, 731:15, 733:21, 739:7, 739:18, 748:8, 748:25, 762:14, 762:16, 762:25, 763:4, 763:8
excipients [28] - 712:23, 713:10, 728:8, 728:11, 729:17, 730:9, 730:18, 731:12, 733:11, 734:11, 738:25, 740:8, 746:15, 746:17, 746:18, 746:23, 748:8, 748:9, 749:12, 762:4, 762:11, 763:7, 763:10, 763:12, 763:18, 764:1, 773:4, 773:6
exclude [1] - 934:24
excluded [1] - 881:9
exclusive [4] - 932:20, 933:1, 1016:6, 1018:22
exclusivity [4] - 1014:18, 1014:21, 1014:24, 1016:24
excuse [6] - 748:5, 759:8, 827:24, 889:18, 899:19, 914:23
executed [3] - 798:22, 799:3, 808:6
EXEL-7184 [1] - 805:3
EXELIXIS [1] - 705:4
Exelixis [45] - 709:21, 713:10, 715:3, 716:20, 720:5, 720:20, 743:11, 751:13, 752:6, 759:3, 778:20, 786:2, 787:20, 796:7, 796:9, 797:12, 800:6, 826:12, 840:7, 851:16, 902:12, 902:16, 902:22, 913:18, 924:12, 924:13, 926:13, 930:17, 938:10, 939:3, 959:25, 977:3, 978:12, 978:23, 979:18, 979:25, 980:25, 981:8, 985:22, 991:21, 1016:5, 1017:12, 1018:14, 1018:18
Exelixis' [15] - 713:3, 752:3, 778:18, 800:8, 862:22, 915:18, 916:3, 916:10, 916:13, 986:2, 991:25, 1016:7, 1026:3, 1026:5, 1026:15
exemplified [4] - 870:22, 871:5, 871:13, 871:16
exhibit [11] - 789:20, 789:22, 810:23, 811:17, 834:15, 835:25, 860:15, 978:9, 980:20, 981:15, 990:4
Exhibit [66] - 708:5, 713:21, 714:24, 715:6, 715:25, 718:14, 718:22, 719:24, 720:1, 720:4, 720:6, 720:8, 720:16, 720:18, 720:19, 720:23, 721:1, 724:19, 724:23, 724:25, 725:13, 727:1, 727:2, 727:4, 731:4, 732:1, 732:13, 732:25, 735:25, 736:2, 737:17, 737:20, 737:22, 795:12, 796:25, 797:1, 797:5, 797:7, 826:16, 826:18, 834:19, 835:2, 835:4, 895:11, 895:13, 929:22, 961:15, 977:10, 978:5, 978:7, 979:21, 979:23, 980:19, 981:16, 984:11, 985:9, 986:25, 987:1, 987:2, 987:6, 1025:11, 1028:6
exhibited [1] - 805:14
exhibits [2] - 895:5, 986:24
exist [4] - 853:24, 896:16, 901:21, 912:8
existed [3] - 879:13, 905:6, 982:14
existential [1] - 1010:25
existing [1] - 956:3
expect [11] - 709:13, 709:14, 721:22, 761:19, 768:15, 787:2, 891:12, 893:23, 954:3, 1029:7, 1029:21
Expectation [1] - 734:21
expectation [26] - 737:6, 737:10, 738:1, 738:17, 738:23, 806:14, 807:12, 825:10, 825:25, 826:2, 826:8, 868:14, 883:12, 883:15, 883:17, 883:18, 883:22, 884:2, 884:14, 884:18, 884:22, 885:12, 885:14, 922:4, 922:6, 937:6
expectations [2] - 807:9, 884:11
expected [9] - 709:19, 717:21, 722:3, 722:9, 812:21, 814:24, 886:1, 936:9, 1002:9
expenditure [1] - 814:6
experience [32] - 734:10, 736:23, 794:7, 798:4, 798:12, 798:13, 798:16, 798:20, 798:25, 799:2, 801:10, 802:14, 807:22, 814:14, 823:3, 825:13, 842:2, 842:4, 842:22, 844:19, 931:4, 939:15, 941:9, 942:20, 954:21, 954:22, 958:21, 969:6, 978:10, 1005:7, 1005:8, 1013:10
experiencing [1] - 1005:1
experiment [7] - 799:6, 805:15, 806:10, 828:18, 832:20, 862:6, 910:13
experimental [7] - 766:10, 767:13, 806:20, 806:21, 806:22, 807:3, 936:22
experimentally [4] - 767:8, 878:12, 878:18, 878:20
experimentation [6] - 799:4, 807:14, 807:16, 831:5, 838:11, 838:17
experiments [4] - 802:3, 807:21, 808:12, 940:2
expert [24] - 764:12, 793:9, 840:8, 842:25, 845:3, 912:19, 912:22, 913:2, 913:18, 916:1, 920:21, 928:19, 931:15, 939:4, 941:12, 942:22, 975:4, 977:4, 978:13, 991:9, 991:12, 991:25, 1013:18, 1024:7
expertise [1] - 1008:14
experts [4] - 843:10, 986:10, 1021:11, 1026:5
explain [33] - 709:5, 710:20, 711:7, 713:6, 716:2, 716:18, 718:1, 719:4, 719:13, 723:22, 724:1, 725:9, 725:17, 725:24, 729:11, 732:17, 734:4, 736:13, 738:6, 739:2, 740:6, 856:17, 859:12, 949:7, 979:10, 984:13, 984:17, 1014:17, 1015:25, 1018:7, 1019:13, 1022:6, 1024:4
explained [4] - 908:2, 914:7, 921:16, 936:21
explaining [3] - 857:8, 862:2, 884:5
explanation [3] - 726:14, 851:16, 1024:9
explicitly [3] - 860:10, 865:3, 926:2
exposed [8] - 713:11, 730:17, 752:11, 759:10, 759:18, 761:3, 761:13, 761:22
express [2] - 786:11, 786:13
extend [2] - 1010:13, 1011:4
extended [4] - 949:12, 949:17, 962:4,

962:10
extending [1] - 949:14
extends [1] - 961:24
extensive [3] - 902:21, 903:2, 942:20
extensively [1] - 932:11
extent [3] - 867:13, 956:1, 1002:2
extraordinary [1] - 993:21
extrapolate [2] - 969:12
extreme [1] - 907:21
eye [1] - 801:17
eyes [1] - 1029:23

F

face [1] - 781:12
facets [2] - 846:13, 856:22
facilitate [1] - 807:7
fact [29] - 711:15, 717:11, 718:18, 725:25, 726:11, 734:10, 740:9, 755:1, 758:13, 758:20, 768:3, 786:7, 787:5, 789:2, 829:10, 855:25, 879:3, 889:10, 889:14, 891:7, 896:23, 903:6, 923:14, 925:6, 958:11, 960:16, 969:6, 988:11, 1001:20
facto [1] - 923:9
factors [21] - 803:19, 825:1, 906:17, 906:21, 907:6, 908:3, 908:6, 908:24, 909:2, 909:16, 910:17, 921:19, 979:10, 997:24, 1010:24, 1017:22, 1018:1, 1018:2, 1018:8, 1018:25
factual [4] - 790:16, 791:2, 902:11, 902:13
failed [2] - 953:13, 1004:1
fair [10] - 743:9, 748:24, 749:20, 784:25, 788:3, 829:16, 931:25, 969:24, 1011:3
fall [4] - 717:2, 831:3, 902:1, 1017:17
fallen [1] - 831:1
falls [3] - 718:3, 831:7, 998:10
false [1] - 814:5
familiar [15] - 784:8, 793:8, 805:17, 842:15, 845:22, 857:18, 862:3, 880:25, 881:1, 941:17, 942:22, 943:12, 944:21, 946:4, 975:4
family [2] - 855:15, 855:23
famous [1] - 770:21
far [10] - 783:12, 785:2, 822:21, 831:18, 835:12, 876:24, 876:25, 882:20, 910:21, 947:21
Farber [1] - 940:2
faster [1] - 894:1
favor [1] - 809:1
favorable [6] - 825:9, 882:4, 947:23, 948:6, 966:22, 970:7
favored [2] - 813:8, 818:14
FDA [29] - 716:21, 719:5, 755:15, 755:24, 760:15, 760:18, 783:14, 792:23, 822:6, 831:14, 831:16, 831:19, 923:7, 937:25, 938:3, 946:8, 950:2, 974:12, 974:13, 974:15, 975:1, 975:22, 976:1, 994:12, 996:17, 997:2, 1014:20, 1019:24, 1020:9
FDA-approved [3] - 831:14, 831:16, 831:19
feature [2] - 741:21, 742:1
featured [2] - 888:19, 889:7
features [10] - 860:6, 865:10, 866:12, 866:16, 866:25, 867:4, 867:11, 889:20, 947:24, 960:17
February [1] - 876:12
Federal [1] - 1017:23
fellow [1] - 940:21
fellowship [1] - 940:1
felt [11] - 942:10, 955:4, 957:3, 962:1, 992:4, 995:18, 995:22, 1004:10, 1004:14, 1006:5, 1030:13
few [16] - 728:1, 802:13, 814:5, 858:13, 870:4, 885:21, 894:2, 916:7, 926:18, 953:25, 957:16, 964:9, 964:10, 975:10, 994:8, 1030:5
fewer [1] - 821:15
fide [1] - 912:15
field [6] - 764:12, 975:8, 978:13, 990:13, 991:9, 991:12
fifth [2] - 709:12, 888:10
Figure [6] - 726:1, 736:6, 736:9, 814:7, 876:13, 890:11
figure [7] - 736:10, 736:14, 753:23, 890:13, 890:14, 891:18, 1020:17
figures [6] - 861:6, 861:8, 861:10, 861:12, 936:23, 1027:3
file [3] - 843:20, 843:21, 891:24
filed [2] - 892:11, 916:1
filings [1] - 1016:7
filled [1] - 986:17
filler [3] - 732:14, 747:21, 747:25
fillers [7] - 729:2, 733:5, 746:20, 747:1, 747:6, 748:19
fills [1] - 967:19
final [5] - 709:7, 773:5, 793:4, 793:5, 824:24
finally [2] - 860:5, 868:16
finance [1] - 977:13
financial [1] - 978:1
findings [1] - 952:23
fine [10] - 756:12, 759:1, 790:20, 838:19, 930:11, 933:20, 933:23, 934:9, 1029:11
fingerprints [1] - 898:8
finish [1] - 749:2
finishing [1] - 940:1
firm [2] - 977:22, 1013:6
first [140] - 709:10, 712:3, 712:15, 713:7, 716:20, 721:18, 729:12, 730:13, 734:23, 738:10, 739:3, 739:14, 743:15, 751:21, 752:7, 753:8, 757:7, 762:21, 762:24, 763:20, 770:2, 771:10, 774:18, 786:20, 799:3, 799:7, 803:1, 804:2, 804:14, 805:10, 806:22, 808:24, 810:12, 813:24, 814:2, 815:17, 821:24, 822:16, 824:7, 824:16, 826:6, 846:6, 847:2, 848:17, 851:22, 852:3, 852:5, 854:22, 859:6, 860:7, 868:8, 868:19, 874:3, 874:14, 880:18, 884:1, 886:16, 889:1, 899:9, 899:15, 912:17, 912:19, 920:23, 926:10, 930:4, 930:5, 935:9, 944:1, 944:17, 945:1, 945:4, 945:6, 945:12, 945:13, 945:18, 946:15, 946:22, 949:10, 949:12, 949:17, 950:2, 950:9, 950:11, 951:5, 951:8, 951:12, 951:24, 954:14, 955:19, 956:6, 956:13, 965:9, 965:16, 965:18, 965:19, 965:23, 966:14, 966:22, 967:14, 967:22, 968:2, 968:18, 969:4, 969:23, 970:16, 971:5, 971:12, 979:12, 982:2, 982:9, 983:18, 984:1, 993:10, 993:11, 993:21, 995:19, 997:2, 999:18, 999:19, 999:21, 1000:2, 1001:2, 1001:24, 1004:11, 1004:16, 1009:24, 1014:9, 1014:15, 1015:9, 1016:1, 1020:25, 1025:5, 1026:24, 1029:2
first-line [24] - 945:6, 945:12, 945:13, 945:18, 949:17, 951:5, 951:12, 965:16, 965:18, 966:14, 966:22, 967:14, 967:22, 968:2, 968:18, 969:4, 969:23, 970:16, 971:5, 999:18, 999:19, 999:21, 1000:2, 1009:24
fit [2] - 908:22, 934:19
five [9] - 715:10, 716:3, 796:4, 818:10, 895:16, 993:25, 1000:8, 1018:23, 1018:25
five-step [1] - 796:4
five-year [1] - 993:25
flag [1] - 769:16
floor [1] - 826:24
flow [1] - 734:7
flowability [5] - 730:1, 730:14, 730:24, 739:20, 885:24
flowing [3] - 728:25, 730:19, 730:20
fluid [2] - 878:4, 878:5
focus [23] - 710:24, 821:9, 841:13, 841:23, 841:25, 850:19, 862:11, 870:20, 871:19, 874:16, 875:16, 880:18, 892:15, 943:24, 944:16, 945:24, 978:18, 978:21, 980:3, 981:17, 983:22, 984:18, 984:24
focused [2] - 710:22, 772:21
focusing [11] - 728:6, 795:18, 806:3, 820:24, 822:16,

878:17, 884:1, 887:2, 889:11, 893:19, 944:24
follow [6] - 768:3, 768:6, 768:9, 881:8, 881:11, 1028:19
followed [3] - 785:24, 786:1, 881:2
following [6] - 751:20, 814:7, 829:7, 881:7, 895:5, 986:23
follows [5] - 839:24, 938:19, 976:23, 989:12, 1012:2
food [3] - 818:22, 832:7, 837:1
Food [2] - 834:8, 944:1
foods [1] - 832:8
foot [1] - 1030:12
footing [1] - 999:12
FOR [1] - 705:2
force [1] - 713:13
foregoing [2] - 714:8, 1031:8
forget [1] - 863:16
forgive [2] - 870:4, 870:5
form [171] - 710:22, 710:23, 711:14, 713:4, 722:3, 722:9, 722:13, 729:13, 751:8, 752:14, 753:10, 759:8, 759:9, 762:3, 803:3, 807:4, 808:7, 812:24, 813:2, 814:4, 815:19, 820:5, 823:10, 823:22, 825:14, 828:8, 850:15, 850:16, 852:1, 852:4, 852:5, 852:6, 852:18, 853:14, 854:22, 855:6, 855:18, 857:3, 857:15, 859:15, 860:24, 862:14, 862:21, 862:24, 862:25, 863:2, 863:3, 863:5, 863:6, 863:8, 863:14, 863:15, 863:17, 863:18, 864:4, 864:17, 864:18, 864:19, 865:3, 865:6, 865:7, 865:14, 865:16, 865:18, 865:19, 867:5, 867:7, 867:9, 872:1, 874:5, 874:21, 874:25, 878:25, 882:6, 883:6, 883:9, 883:20, 885:13, 885:25, 889:9, 896:25, 898:9, 898:16, 900:18, 901:2, 901:4, 901:15, 901:17, 901:19, 901:21, 901:23, 902:9, 902:12, 904:4, 904:6, 904:9, 904:10, 904:14, 905:18, 905:19, 905:20, 905:23, 906:23, 907:10, 907:11, 910:21, 911:4, 911:6, 911:9, 911:22, 911:23, 912:8, 912:9, 914:1, 914:13, 914:15, 915:6, 915:8, 916:19, 916:22, 916:23, 916:24, 916:25, 919:18, 919:22, 919:25, 921:10, 921:12, 922:4, 922:5, 922:7, 922:18, 923:2, 923:18, 924:12, 924:14, 925:6, 925:9, 925:11, 925:16, 925:18, 925:25, 926:1, 926:6, 926:14, 928:12, 928:16, 935:18, 937:12, 937:16, 937:18, 937:20, 937:21, 937:23, 938:3, 938:4, 943:15, 945:9, 947:16, 949:4, 959:24, 960:1, 960:22
Form [3] - 862:22, 863:3, 914:13
formation [23] - 710:9, 713:2, 740:9, 752:7, 798:23, 802:18, 802:25, 803:5, 803:22, 804:12, 806:10, 806:18, 806:21, 807:11, 827:8, 851:4, 883:17, 883:19, 884:5, 885:22, 908:4, 908:19, 909:14
formed [9] - 801:23, 802:5, 806:13, 808:8, 808:10, 867:22, 883:20, 973:10
formers [1] - 883:5
forming [8] - 825:19, 845:1, 885:7, 888:1, 921:25, 931:11, 942:17, 961:23
forms [110] - 708:13, 709:16, 710:24, 733:2, 774:24, 816:14, 819:23, 820:4, 827:12, 827:13, 851:25, 852:16, 853:1, 853:5, 854:15, 854:19, 855:25, 857:1, 859:2, 859:3, 859:17, 860:2, 860:3, 860:4, 860:8, 860:10, 860:12, 860:13, 861:11, 861:17, 861:18, 861:20, 861:21, 861:22, 864:21, 865:20, 865:23, 865:25, 867:12, 896:17, 897:5, 897:16, 897:21, 897:25, 898:2, 898:11, 898:13, 900:21, 900:24, 900:25, 901:1, 901:4, 901:6, 901:10, 902:5, 902:17, 902:18, 902:22, 902:24, 903:4, 904:19, 904:20, 904:21, 904:23, 904:25, 905:1, 905:2, 905:3, 905:6, 905:11, 905:14, 905:25, 906:9, 907:3, 908:4, 909:25, 910:9, 912:7, 912:12, 912:15, 912:23, 914:9, 914:14, 914:15, 915:6, 915:7, 915:8, 916:4, 916:12, 916:16, 916:17, 917:13, 917:18, 918:21, 918:23, 921:12, 921:17, 923:8, 923:16, 923:18, 923:20, 925:6, 926:8, 964:3, 964:6
formula [2] - 847:3, 866:18
formulate [9] - 729:7, 729:15, 732:21, 733:4, 734:16, 739:8, 739:12, 768:19, 801:7
formulated [8] - 712:20, 730:12, 732:14, 741:2, 741:12, 742:2, 768:22, 894:25
formulating [6] - 731:11, 739:19, 774:21, 800:22, 818:1, 975:13
formulation [45] - 707:25, 712:6, 712:8, 712:10, 721:1, 728:5, 728:14, 728:25, 729:12, 729:22, 732:20, 733:10, 733:12, 733:13, 733:23, 734:5, 734:13, 740:4, 741:17, 741:19, 741:20, 742:15, 754:4, 754:11, 755:3, 755:7, 759:24, 760:7, 762:19, 763:14, 764:23, 772:1, 788:18, 788:20, 798:4, 801:2, 844:23, 895:1, 927:17, 959:20, 1021:13, 1021:15, 1025:18, 1025:19
formulations [7] - 712:10, 728:24, 763:11, 776:8, 787:24, 788:2, 943:10
formulator [1] - 762:24
formulator's [1] - 827:21
formulators [2] - 762:22, 763:2
forth [3] - 729:8, 752:3, 783:8
forward [3] - 751:11, 822:7, 835:3
founded [1] - 1013:7
four [22] - 716:4, 728:11, 746:18, 748:3, 748:4, 748:8, 749:17, 751:11, 779:4, 780:22, 783:13, 787:21, 817:17, 872:15, 914:25, 978:25, 985:19, 991:18, 1003:6, 1018:20, 1020:10, 1020:11
four-year [1] - 985:19
fourth [3] - 913:21, 982:2, 982:11
fraction [2] - 862:6, 890:24
fractional [1] - 793:12
frame [10] - 915:20, 915:22, 932:4, 965:23, 966:2, 981:25, 983:7, 985:5, 985:20, 1018:13
frankly [1] - 874:6
free [45] - 708:1, 710:16, 711:5, 711:9, 711:12, 711:17, 711:20, 712:7, 712:9, 712:17, 712:20, 712:25, 713:1, 719:11, 721:4, 721:6, 728:6, 735:1, 737:8, 737:15, 738:3, 738:25, 739:9, 739:12, 741:20, 744:15, 749:19, 772:22, 773:1, 782:16, 805:12, 808:7, 825:14, 862:22, 863:3, 869:21, 890:4, 951:11, 952:2, 953:7, 968:23, 1000:7, 1000:18, 1025:16
French [1] - 930:12
frequency [1] - 820:17
frequent [2] - 820:23
frequently [1] - 787:25
front [8] - 756:22, 899:4, 948:20, 956:17, 962:14, 965:10, 969:16, 972:23
front-line [3] - 948:20, 969:16, 972:23
fulfilled [1] - 957:3
full [7] - 839:18, 867:17, 886:16, 938:13, 976:17, 989:6, 1011:20
fully [5] - 838:21, 865:12, 891:8, 906:14, 907:16
function [1] - 890:17
functional [2] - 810:3,

817:23
functionality [3] - 803:4, 838:8, 838:10
functionalized [1] - 725:20
functioning [1] - 992:19
furtherly [1] - 769:19
furthermore [1] - 880:16
future [3] - 901:6, 901:24, 1017:15

G

G-E-O-R-G-E [1] - 938:16
gas [1] - 845:24
GATTUSO [2] - 706:2, 706:2
gears [2] - 879:19, 926:19
Gefitinib [4] - 963:3, 963:23, 964:15, 994:16
gelatin [1] - 776:15
general [11] - 732:8, 733:9, 793:25, 794:2, 802:2, 849:14, 851:19, 883:9, 891:4, 917:8, 922:23
generally [36] - 726:10, 729:1, 764:24, 794:9, 802:2, 803:12, 812:6, 812:8, 818:15, 831:2, 832:2, 832:14, 841:6, 841:8, 842:12, 842:14, 844:4, 844:5, 860:22, 865:19, 879:12, 884:16, 897:23, 898:7, 898:10, 905:16, 934:4, 934:6, 939:6, 945:25, 947:18, 964:17, 999:19, 999:24, 1009:15
generate [2] - 858:20, 986:17
generated [4] - 978:23, 979:18, 985:21, 986:21
generates [1] - 858:22
generation [3] - 920:18, 922:15, 988:17
generic [2] - 807:20, 937:25
genetic [1] - 765:16
genitourinary [3] - 939:20, 990:22, 990:23
genotoxic [58] - 707:22, 721:25, 723:2, 723:5, 723:17, 724:15, 724:16, 725:7, 726:11, 726:14, 727:9, 727:18, 727:20, 727:23, 752:16, 755:22, 756:5, 764:15, 764:19, 764:23, 764:25, 765:1, 765:2, 765:5, 765:9, 765:10, 765:16, 765:21, 765:24, 766:5, 766:9, 766:15, 766:19, 768:10, 768:13, 768:15, 768:18, 768:24, 769:21, 771:11, 771:19, 772:11, 793:20, 796:6, 958:12, 958:14, 959:4, 959:6, 959:11, 959:18, 975:14, 975:17, 975:22, 1008:16, 1008:19, 1008:24
genotoxicity [7] - 723:20, 723:24, 767:14, 767:17, 767:21, 772:5, 975:11
genotoxins [1] - 958:19
genus [7] - 854:15, 854:18, 854:23, 873:12, 873:15, 873:20, 888:4
GEORGE [2] - 706:5, 938:17
George [40] - 741:6, 741:8, 741:11, 741:16, 741:22, 743:6, 896:9, 938:11, 938:15, 938:25, 939:2, 940:17, 941:12, 941:17, 954:8, 961:9, 961:21, 961:23, 976:6, 984:16, 986:13, 986:14, 991:25, 992:4, 993:4, 994:20, 995:5, 996:13, 997:9, 997:12, 997:16, 998:10, 999:6, 999:22, 1002:14, 1003:8, 1003:21, 1004:18, 1005:3
George's [2] - 894:13, 1000:21
German [1] - 930:12
Germany [1] - 841:5
GI [1] - 875:23
Girindus [28] - 716:5, 716:9, 716:14, 716:22, 716:25, 717:6, 717:13, 717:23, 718:5, 781:22, 781:23, 781:24, 781:25, 782:3, 782:4, 783:15, 783:20, 785:3, 785:5, 785:18, 789:6, 789:10, 789:12, 789:24, 791:6, 791:9, 791:19, 791:21
given [14] - 741:4, 750:16, 751:7, 751:15, 803:12, 807:21, 852:7, 857:25, 891:7, 906:23, 907:9, 910:20, 982:18, 991:8
GlaxoSmithKline [1] - 1016:5
Gleevec [1] - 993:11
glidant [11] - 729:1, 731:11, 731:12, 731:17, 731:21, 731:22, 732:15, 1021:13, 1025:14, 1025:20, 1026:2
glidants [5] - 728:25, 733:6, 746:20, 747:12, 748:19
goal [1] - 733:25
graduate [2] - 841:19, 841:21
graduating [1] - 977:15
granted [1] - 946:11
graph [1] - 981:10
GRAS [29] - 818:17, 818:21, 819:5, 831:24, 832:2, 832:6, 832:8, 832:12, 832:16, 832:19, 832:21, 832:24, 834:2, 835:13, 835:21, 835:23, 836:2, 836:9, 836:12, 836:17, 837:9, 837:16, 837:23, 934:2, 934:4, 934:14, 934:16, 934:20
GRDEN [6] - 706:6, 978:15, 987:3, 987:9, 987:13, 988:21
great [2] - 764:5, 906:6
Great [1] - 876:10
greater [9] - 739:5, 746:7, 746:10, 813:1, 825:23, 953:11, 955:24, 980:15
green [4] - 870:13, 1016:20, 1016:21
grew [2] - 981:24, 983:20
grinding [1] - 909:5
ground [1] - 1002:3
ground-breaking [1] - 1002:3
group [12] - 748:4, 748:7, 760:9, 810:4, 883:7, 883:9, 941:1, 963:17, 986:16, 990:22, 999:16
groups [4] - 810:3, 817:23, 882:3, 889:10
grow [1] - 982:18
growth [11] - 920:13, 922:12, 985:15, 985:18, 992:11, 992:15, 992:24, 995:9, 995:12, 997:5, 1005:24
GSK [1] - 1018:22
GTI [14] - 718:6, 718:9, 718:10, 718:12, 780:10, 780:13, 780:22, 781:6, 781:9, 782:9, 782:10, 782:25, 789:16
guarantee [5] - 828:4, 828:8, 828:10, 920:16, 922:14
guess [6] - 749:15, 780:16, 855:23, 863:12, 920:6, 1027:22
guidance [7] - 727:4, 727:8, 727:9, 737:23, 755:17, 756:17, 937:2
guidances [1] - 726:22
guide [2] - 750:17, 947:7
guideline [4] - 880:15, 880:22, 881:8, 885:5
guidelines [17] - 727:14, 727:22, 728:1, 881:14, 923:9, 923:10, 923:11, 923:14, 966:6, 975:22, 997:9, 997:20, 998:2, 1002:20, 1009:22, 1010:6
Guidelines [2] - 947:2, 947:19
Guillory [4] - 893:9, 893:14, 893:20, 893:22

H

half [8] - 890:25, 907:18, 983:18, 983:20, 984:1, 984:3, 1000:8
halfway [3] - 774:11, 899:19, 983:15
halo [1] - 865:9
hand [15] - 811:8, 822:20, 826:20, 833:11, 835:12, 846:14, 850:20, 858:16, 905:24, 944:17, 980:3, 980:21, 981:21, 981:22, 989:24
Handbook [5] - 736:3, 810:21, 834:6, 834:8, 836:13
handful [2] - 907:20, 955:13
handled [1] - 790:22
handy [1] - 827:1
hard [2] - 736:21, 864:9
harder [1] - 737:15
hardly [1] - 890:23
hardness [1] - 734:9
harm [3] - 765:10, 765:11, 1013:13
harmful [4] - 708:18, 769:24, 958:18
head [13] - 764:13, 968:22, 969:8, 969:12, 970:5,

972:17, 1003:18
head-to-head [5] - 968:22, 969:8, 969:12, 970:5, 972:17
heading [4] - 774:11, 774:18, 776:25, 892:8
hear [15] - 723:12, 724:22, 733:3, 737:19, 742:8, 761:5, 818:13, 864:10, 874:4, 891:10, 910:5, 920:23, 991:24, 1000:21, 1005:5
heard [42] - 709:7, 709:18, 722:8, 729:6, 729:18, 734:23, 762:13, 786:6, 786:23, 800:18, 803:9, 814:22, 825:3, 829:24, 846:6, 853:14, 856:25, 860:3, 861:1, 862:4, 869:9, 872:25, 873:5, 873:17, 877:21, 878:10, 880:14, 880:24, 888:23, 894:9, 927:3, 927:11, 933:9, 984:16, 986:13, 988:4, 992:8, 993:4, 994:18, 1015:7, 1015:16, 1023:4
hearing [2] - 864:9, 874:6
heat [13] - 713:12, 730:18, 740:8, 752:11, 759:10, 759:18, 759:22, 761:3, 761:13, 761:22, 787:15, 787:16
Heather [1] - 1031:11
heavy [1] - 881:25
help [8] - 742:2, 750:17, 758:7, 758:8, 781:3, 783:16, 927:8, 933:19
helpful [5] - 862:7, 899:8, 947:6, 1009:19, 1009:21
helping [2] - 841:11, 842:11
helps [5] - 754:7, 899:5, 947:7, 947:9, 1016:3
hence [1] - 814:3
hepatocellular [1] - 946:2
hereby [1] - 1031:8
herein [7] - 774:25, 839:22, 852:2, 938:17, 976:21, 989:10, 1011:25
HEYMAN [1] - 706:2
Hi [1] - 939:2
hierarchical [6] - 808:25, 813:7, 813:9, 816:19, 828:23, 829:8
high [22] - 719:15, 798:3, 803:10, 808:19, 845:20, 859:23, 868:6, 874:12, 877:8, 877:18, 883:14, 888:16, 889:8, 902:3, 959:1, 979:3, 1022:20, 1023:2, 1023:5, 1023:9, 1023:10, 1024:8
high-level [1] - 845:20
higher [4] - 745:22, 746:3, 817:20, 842:9
higher-level [1] - 842:9
highest [2] - 800:18, 948:9
highlight [5] - 774:15, 779:12, 784:15, 854:9, 915:1
highlighted [9] - 779:7, 784:17, 798:2, 810:4, 821:13, 829:17, 847:2, 967:4, 998:10
highlighting [2] - 892:9, 967:7
highly [6] - 733:24, 877:22, 877:23, 906:23, 907:10, 910:21
highways [1] - 995:13
Hill [1] - 1013:9
himself [2] - 880:20, 882:20
hindsight [1] - 752:23
HIRZEL [1] - 706:2
histogram [1] - 876:17
histology [2] - 947:14, 947:15
histories [2] - 843:20, 843:21
history [2] - 891:24, 892:2
holder [1] - 1018:15
holistic [1] - 801:15
Honor [54] - 706:17, 707:2, 742:23, 749:2, 752:1, 794:25, 795:9, 797:2, 826:12, 826:14, 826:20, 833:7, 833:11, 839:11, 839:15, 842:24, 845:20, 862:3, 863:10, 863:22, 864:6, 870:5, 884:5, 889:23, 890:4, 895:4, 896:2, 935:3, 935:5, 938:10, 938:21, 941:11, 976:5, 978:12, 981:3, 986:23, 987:10, 989:1, 991:11, 1011:14, 1013:17, 1025:9, 1026:12, 1027:15, 1027:18, 1027:21, 1027:23, 1028:13, 1028:14, 1028:21, 1029:9, 1029:12, 1031:1, 1031:3
Honor's [1] - 846:6
HONORABLE [1] - 705:14
Honorable [1] - 706:14
honors [2] - 940:17, 941:9
hope [2] - 949:15, 957:18
hopefully [2] - 928:14, 928:16
hopes [1] - 1030:20
hoping [1] - 1030:18
host [6] - 801:1, 841:22, 936:22, 998:21, 1006:14, 1008:22
hour [2] - 890:24, 895:19
housekeeping [1] - 706:18
Houston [1] - 977:15
HPLC [3] - 757:20, 784:10, 789:15
humans [1] - 819:24
humidity [1] - 849:2
hundred [3] - 890:16, 890:17, 890:20
hydrate [1] - 851:4
hydrogen [8] - 814:19, 814:21, 815:2, 815:11, 815:19, 882:13, 882:17, 883:1
hydrogen-bonded [1] - 882:17
hygroscopic [3] - 925:9, 925:10, 925:16
hygroscopicity [3] - 729:25, 885:24, 919:8
hypothetical [3] - 900:17, 901:3, 901:8

I

i.e [1] - 733:24
idea [5] - 765:8, 803:6, 838:9, 838:10, 1014:17
identical [2] - 724:9, 786:3
identified [20] - 721:24, 731:19, 766:5, 796:6, 818:15, 861:17, 861:19, 865:20, 872:5, 872:20, 872:24, 878:11, 878:18, 898:5, 903:6, 914:8, 937:2, 979:14, 999:6, 1002:14
identify [30] - 755:19, 756:2, 757:21, 767:12, 805:1, 810:4, 810:20, 813:16, 820:13, 821:21, 823:14, 827:13, 838:12, 842:19, 844:1, 857:2, 867:1, 872:18, 878:20, 886:3, 886:6, 888:4, 896:20, 898:11, 903:4, 903:25, 906:25, 907:2, 978:7, 990:4
identifying [13] - 799:12, 799:22, 818:18, 824:23, 827:12, 860:23, 881:12, 883:2, 885:19, 906:22, 907:3, 907:9, 910:20
II [2] - 929:7, 999:25
III [2] - 705:6, 863:3
illustrate [1] - 1016:3
illustrating [1] - 736:10
illustration [1] - 714:10
illustrative [1] - 714:19
images [1] - 847:23
imatinib [6] - 962:22, 962:24, 962:25, 993:11, 993:19, 994:13
immediate [3] - 728:16, 876:18, 877:2
immediate-release [2] - 876:18, 877:2
immediately [2] - 728:17, 873:11
immune [23] - 952:15, 952:17, 953:16, 953:25, 954:1, 996:1, 997:7, 998:16, 998:17, 998:19, 998:20, 998:23, 999:4, 1000:25, 1001:25, 1002:8, 1003:2, 1003:3, 1003:5, 1003:25, 1004:4, 1004:7
immuno [4] - 945:23, 1001:16, 1009:23, 1010:5
immuno-oncology [2] - 1009:23, 1010:5
immunotherapeutics [1] - 1006:13
immunotherapy [3] - 945:21, 967:17, 969:17
impact [7] - 724:11, 803:16, 804:20, 807:6, 825:19, 919:19, 982:15
impacted [2] - 802:19, 949:7
impacts [1] - 960:16
imparts [1] - 886:22
impeach [1] - 790:19
implicated [1] - 964:3
importance [1] - 1022:9
important [35] - 729:21, 730:4, 730:11, 730:15, 753:19, 754:13, 754:16, 760:24, 832:22, 845:23, 860:25, 876:24, 885:22, 885:23, 896:19, 897:24, 904:8, 905:21,

920:7, 920:10, 956:11, 961:2, 967:19, 970:23, 1003:24, 1007:24, 1008:10, 1008:14, 1008:19, 1008:21, 1009:10, 1009:24, 1018:15, 1030:2, 1030:16
improve [13] - 794:1, 794:2, 794:3, 794:9, 825:19, 838:18, 874:18, 874:19, 879:9, 879:11, 962:13, 973:22, 1007:2
improved [5] - 825:14, 950:14, 955:6, 1004:10, 1004:15
improvement [2] - 948:21, 996:10
improves [1] - 794:7
improving [1] - 971:1
impurities [54] - 711:8, 712:17, 715:12, 717:10, 717:11, 717:19, 727:10, 727:12, 735:20, 736:12, 736:20, 745:23, 754:25, 755:18, 755:19, 755:20, 755:21, 755:24, 755:25, 756:3, 756:18, 757:4, 757:8, 758:20, 758:21, 760:19, 764:18, 764:23, 764:25, 765:1, 765:21, 766:15, 773:9, 779:18, 785:12, 785:15, 793:1, 793:21, 794:5, 795:19, 795:20, 910:3, 910:6, 958:12, 958:14, 959:11, 959:18, 975:15, 975:17, 975:23, 1008:19, 1008:24
impurity [96] - 707:17, 708:1, 708:14, 708:19, 709:16, 710:17, 711:3, 711:6, 711:10, 711:11, 711:13, 711:18, 711:21, 712:5, 712:7, 712:9, 712:21, 712:24, 713:3, 713:11, 714:22, 715:15, 715:22, 716:7, 717:14, 717:21, 719:11, 719:16, 721:7, 721:23, 721:25, 722:3, 722:9, 724:13, 727:16, 727:17, 727:20, 727:22, 730:17, 735:1, 735:10, 735:11, 735:14, 735:15, 736:17, 736:19, 736:24, 737:3, 737:8, 737:12, 737:14, 738:4, 738:11, 738:25, 739:4, 739:5, 739:13, 740:3, 740:9, 741:1, 741:3, 741:21, 743:25, 744:19, 745:10, 751:13, 752:4, 752:16, 764:15, 765:5, 765:9, 765:16, 765:24, 766:5, 767:10, 768:10, 768:15, 768:18, 768:22, 771:10, 771:18, 772:11, 773:1, 779:16, 782:15, 782:16, 784:14, 784:21, 789:9, 794:10, 794:11, 796:3, 796:6, 796:12, 941:25, 1008:16
IN [1] - 705:1
inadvertently [1] - 706:18
Inc [1] - 939:3
INC [1] - 705:4
include [16] - 731:20, 731:22, 773:4, 790:12, 796:5, 806:23, 815:8, 815:11, 817:22, 825:4, 835:21, 851:25, 868:11, 879:25, 908:6, 921:18
included [6] - 780:23, 818:10, 823:6, 844:22, 880:4, 1000:13
includes [5] - 773:6, 836:17, 837:13, 999:7, 1005:2
including [14] - 739:4, 739:18, 801:1, 804:4, 843:1, 870:5, 916:6, 917:2, 936:22, 936:24, 941:12, 963:19, 1005:15, 1010:24
incompetent [1] - 759:23
incomplete [3] - 1014:14, 1022:20, 1024:14
incorporate [1] - 901:4
incorporated [1] - 894:12
Incorporated [1] - 990:20
incorporating [1] - 934:25
increase [5] - 712:24, 713:9, 713:11, 975:18, 992:14
increased [3] - 950:13, 984:2, 1010:21
increasing [4] - 717:9, 835:8, 835:9, 959:19
increasingly [1] - 993:14
incremental [2] - 996:10, 1005:24
IND [1] - 786:2
indeed [1] - 868:2
indicate [1] - 716:8
indicated [3] - 811:24, 834:2, 993:12
indicates [1] - 934:2
indicating [3] - 719:5, 719:7, 809:14
indication [13] - 767:9, 768:2, 824:2, 824:3, 851:3, 862:13, 946:9, 946:15, 946:18, 950:2, 965:16, 981:13, 996:18
Indications [1] - 944:17
indications [6] - 944:21, 944:24, 945:3, 980:9, 981:11, 996:13
indicative [1] - 865:9
indicator [1] - 982:17
indicia [8] - 740:12, 740:20, 740:23, 888:16, 973:6, 973:20, 992:3, 1005:19
individual [4] - 763:10, 794:4, 996:2, 996:6
individualized [1] - 807:21
individually [2] - 961:8, 1005:11
individuals [1] - 1009:10
industrial [1] - 977:18
Industrial [1] - 736:3
industry [5] - 727:9, 737:23, 756:18, 896:19, 1013:11
ineffective [1] - 738:12
inference [9] - 1014:22, 1017:3, 1017:5, 1019:6, 1020:18, 1020:22, 1021:9, 1022:7, 1024:21
infinite [2] - 920:14, 922:13
influence [8] - 887:8, 906:17, 906:21, 907:6, 908:25, 909:17, 910:17, 995:12
inform [7] - 719:1, 719:9, 725:21, 732:20, 741:9, 741:24, 748:17
information [39] - 719:1, 720:9, 738:21, 739:7, 740:7, 740:11, 805:9, 809:14, 809:18, 809:24, 811:1, 812:12, 812:15, 819:11, 819:21, 835:15, 835:20, 850:25, 870:24, 871:2, 871:8, 871:22, 874:20, 878:7, 887:20, 887:24, 888:3, 903:25, 906:2, 906:24, 910:14, 910:23, 922:3, 923:6, 923:8, 931:15, 936:24, 942:17, 944:12
informed [1] - 882:13
infringe [1] - 745:6
infringement [2] - 797:18, 978:3
ingestion [1] - 727:12
ingredient [14] - 733:22, 762:11, 800:19, 802:25, 803:24, 804:9, 808:6, 818:25, 820:6, 823:22, 825:15, 943:18, 958:22
ingredients [3] - 736:25, 737:24, 777:8
inherency [5] - 712:11, 719:2, 777:25, 778:3, 778:6
inherently [8] - 713:17, 714:21, 715:14, 715:18, 715:21, 719:11, 721:4, 782:14
inhibit [1] - 807:7
inhibition [1] - 964:13
inhibitor [32] - 945:23, 948:12, 951:4, 952:15, 953:16, 953:25, 956:7, 956:9, 956:19, 982:9, 996:1, 998:16, 998:18, 998:19, 999:4, 999:5, 1001:4, 1001:17, 1001:18, 1002:6, 1002:9, 1003:2, 1003:3, 1003:14, 1003:15, 1003:16, 1003:17, 1004:1, 1004:3, 1004:4, 1004:7
inhibitors [21] - 732:11, 939:23, 940:4, 940:7, 950:7, 955:13, 965:14, 981:7, 982:21, 993:1, 993:2, 995:4, 996:21, 997:1, 997:6, 997:7, 1000:25, 1002:1, 1005:10, 1008:22, 1010:1
inhibits [2] - 964:2, 965:2
initial [2] - 765:6, 950:24
injectable [4] - 816:10, 816:14, 816:16, 817:1
injected [1] - 816:11
innocuous [1] - 931:6
inorganic [7] - 815:6, 815:7, 815:10, 815:15, 816:3, 817:2, 817:21
insert [2] - 846:11, 944:14

insidiously [1] - 959:8
Insight [1] - 1013:7
insoluble [2] - 876:25, 877:1
instance [13] - 745:4, 747:2, 781:12, 781:20, 803:6, 805:25, 807:1, 815:12, 817:7, 911:13, 912:2, 966:17, 969:4
instead [1] - 1026:19
Institute [4] - 840:18, 841:5, 990:20, 990:25
institute [1] - 841:12
instructed [1] - 973:19
instruction [1] - 973:11
instrumental [1] - 971:1
intellectual [3] - 977:20, 1017:2, 1017:6
intended [2] - 714:19, 767:16
intentionally [1] - 956:8
interact [1] - 765:6
interaction [2] - 730:8, 763:25
interactions [3] - 752:14, 762:3, 762:10
interconversion [1] - 909:25
interest [4] - 915:18, 916:3, 916:11, 916:14
interested [5] - 730:2, 765:20, 782:13, 793:23, 799:5
interesting [1] - 819:3
interferon [1] - 996:25
interleukin [1] - 997:1
intermediate [9] - 947:24, 948:10, 951:13, 956:16, 966:23, 967:7, 970:2, 999:9, 999:16
internal [3] - 979:25, 980:25, 986:2
international [1] - 1015:15
interpret [1] - 830:15
interpretation [1] - 867:18
Interpretation [1] - 950:9
interprets [1] - 744:24
interrupt [1] - 925:12
interstate [1] - 995:13
intestinal [1] - 878:5
intrinsic [1] - 859:3
introduce [7] - 800:16, 840:4, 939:1, 977:1, 989:17, 1012:7, 1025:5
invalid [1] - 888:11
invent [2] - 902:12, 902:16
invented [1] - 902:22
invention [12] - 714:15, 741:14, 796:5, 800:9, 852:25, 857:23, 857:25, 894:23, 936:20, 987:18, 1018:14, 1018:18
inventor [1] - 936:19
inventors [13] - 757:23, 758:9, 758:13, 852:13, 855:22, 855:24, 857:22, 857:25, 867:17, 902:15, 902:16, 903:24, 936:25
investigation [1] - 766:6
investment [4] - 1023:19, 1023:22, 1023:24, 1024:1
involved [6] - 827:17, 912:16, 915:25, 939:22, 968:20, 972:5
involves [3] - 807:16, 940:9, 977:25
involving [3] - 751:13, 912:17, 939:22
IO [5] - 968:7, 970:25, 971:13, 1001:10, 1001:14
ionizable [1] - 882:3
ionization [1] - 838:12
ionized [2] - 928:12, 928:17
IP [1] - 1024:23
irregardless [1] - 793:4
irrelevant [2] - 863:12, 864:23
irreparable [1] - 1013:13
isolate [1] - 896:20
isolation [2] - 883:18, 1023:1
issuance [1] - 1017:10
issue [24] - 723:10, 723:14, 737:3, 748:18, 748:20, 748:21, 749:9, 749:11, 797:17, 816:9, 838:14, 868:25, 879:3, 900:6, 935:12, 935:24, 936:14, 988:3, 1015:9, 1019:22, 1019:25, 1021:10, 1022:2
issues [10] - 798:18, 818:1, 841:17, 843:9, 889:8, 939:6, 958:9, 977:6, 1004:25, 1013:14
issuing [1] - 1017:15
it'll [1] - 758:6
iterations [1] - 734:11
itself [13] - 744:20, 744:21, 744:23, 869:14, 871:18, 875:17, 885:7, 906:13, 948:13, 967:8, 982:1, 1014:13, 1024:25

J

JACK [1] - 705:18
James [1] - 938:15
JAMES [2] - 938:16, 938:17
January [4] - 798:2, 844:8, 869:13, 886:15
Japan [1] - 876:10
JCO [1] - 950:22
job [1] - 841:6
Joint [1] - 797:1
JONATHAN [1] - 705:22
Journal [2] - 950:22, 951:17
journal [1] - 952:11
journey [1] - 954:16
JTX [2] - 797:7, 895:11
JTX-1 [5] - 843:25, 847:5, 895:5, 898:25, 899:21
JTX-2 [1] - 895:5
JTX-3 [1] - 895:5
JTX-4 [2] - 774:1, 774:4
JTX-5 [3] - 891:20, 891:25, 895:5
judge [2] - 916:19, 917:1
judgment [1] - 1030:5
June [2] - 947:4, 990:5
jurisdictions [1] - 876:22
justify [1] - 947:8

K

keep [3] - 783:5, 826:25, 879:17
Keith [1] - 893:14
KEVIN [3] - 705:20, 705:22, 706:7
Kevin [2] - 797:11, 1011:14
key [14] - 710:4, 710:5, 712:1, 712:3, 740:10, 741:21, 742:1, 803:1, 803:7, 803:8, 804:13, 825:7, 885:21, 981:4
keynote [1] - 1001:6
Khalid [3] - 851:14, 892:9, 892:10
kidney [23] - 870:13, 871:15, 939:20, 940:13, 941:2, 942:9, 943:9, 945:10, 945:11, 945:24, 949:5, 949:20, 955:6, 956:11, 956:12, 956:24, 957:7, 957:14, 963:19, 995:24, 995:25, 997:9
Kidney [3] - 940:24, 940:25, 947:2
kill [1] - 998:22
kinase [30] - 732:11, 939:23, 940:3, 940:7, 948:12, 950:7, 951:3, 956:19, 981:7, 982:9, 982:21, 992:9, 992:10, 993:1, 993:2, 994:1, 994:24, 996:20, 997:6, 999:4, 1001:8, 1002:5, 1003:6, 1003:7, 1003:14, 1003:16, 1004:3, 1005:10, 1008:22, 1009:25
kinases [6] - 964:2, 992:16, 992:18, 992:20, 993:3, 995:2
kind [24] - 736:23, 752:23, 761:8, 764:8, 767:22, 769:8, 769:11, 822:2, 842:8, 842:11, 865:11, 878:3, 934:13, 955:12, 996:9, 1005:20, 1005:23, 1006:1, 1010:10, 1010:14, 1010:20, 1014:25, 1023:3, 1024:10
kinds [4] - 730:10, 737:4, 777:13, 909:13
kinetics [1] - 841:20
King [1] - 705:10
knowing [4] - 739:25, 857:2, 857:10, 857:11
knowledge [6] - 751:7, 751:15, 905:14, 931:4, 937:3, 1008:9
known [54] - 730:22, 730:25, 739:22, 750:5, 750:8, 750:11, 750:13, 751:16, 753:15, 753:16, 754:25, 758:13, 758:22, 761:8, 761:15, 761:17, 764:3, 764:7, 766:9, 767:4, 768:23, 772:7, 773:16, 773:19, 773:20, 774:22, 775:6, 777:9, 794:12, 794:15, 801:5, 809:11, 823:9, 827:11, 827:14, 836:16, 837:23, 838:8, 850:14, 873:21, 875:2, 875:5, 877:15, 877:19, 882:22, 887:17, 889:25, 912:15, 926:21, 927:5, 931:24, 932:1, 957:13, 963:23
knows [2] - 763:17, 957:15
Koleng [15] - 797:8, 797:15, 826:10, 827:5, 829:5, 830:10, 831:10, 833:4, 833:19, 836:17, 838:2, 839:12, 879:14, 881:24, 884:4
Koleng's [5] - 873:17, 880:3, 880:6, 881:20, 884:1

Kondal [1] - 706:10
Krannert [1] - 977:16
KREIGER [1] - 705:21
KURT [1] - 706:6

L

L)-malate [87] - 707:14, 707:19, 707:25, 708:16, 710:1, 710:16, 711:20, 712:8, 714:21, 715:10, 717:16, 719:10, 720:22, 721:21, 728:3, 729:8, 730:12, 730:16, 730:22, 730:25, 731:23, 732:14, 733:5, 734:17, 735:9, 735:12, 736:15, 736:16, 737:7, 738:3, 738:18, 738:24, 739:10, 739:12, 740:2, 741:1, 759:10, 759:18, 759:21, 761:3, 762:4, 796:11, 796:19, 797:21, 798:10, 820:8, 826:5, 847:10, 848:8, 848:22, 849:3, 849:13, 849:17, 849:19, 850:5, 850:7, 850:17, 850:22, 851:1, 851:6, 851:17, 852:14, 853:2, 853:25, 858:21, 862:23, 864:19, 866:7, 867:14, 870:25, 883:21, 894:11, 894:21, 894:23, 900:22, 904:25, 914:9, 915:6, 921:25, 926:11, 927:5, 927:25, 937:8, 943:20, 943:22, 960:2, 960:21
L)-malic [2] - 799:20, 847:15
L1 [1] - 952:18
lab [6] - 780:17, 780:19, 783:16, 838:21, 841:9, 842:4
label [3] - 823:16, 927:24, 944:13
LABORATORIES [1] - 705:7
laboratory [3] - 765:13, 841:22, 960:23
Lachman [7] - 732:24, 733:1, 733:4, 733:9, 733:16, 734:2, 734:15
lack [3] - 1021:8, 1021:20, 1022:2
Lancet [2] - 949:25, 952:11
landscape [3] - 949:11, 953:23, 957:12
language [2] - 786:2, 871:19
lapatinib [1] - 994:17
large [7] - 799:4, 846:9, 853:13, 873:15, 909:16, 969:8, 1005:15
larger [4] - 817:25, 842:14, 882:7, 1003:4
largest [1] - 980:17
laser [1] - 862:8
last [11] - 744:14, 764:14, 813:23, 814:1, 819:20, 850:3, 956:10, 980:3, 987:16, 1006:16, 1020:25
lastly [1] - 979:17
latter [3] - 983:20, 984:3, 984:8
lattice [3] - 735:15, 736:19, 736:21
launch [3] - 982:14, 985:14, 985:18
launched [1] - 993:12
launches [1] - 1013:14
lawyers [1] - 1030:15
lead [3] - 992:24, 1001:23, 1008:16
lead-in [1] - 1001:23
leader [4] - 982:19, 984:9, 984:22, 985:4
leadership [1] - 982:4
leading [3] - 831:20, 995:13, 1015:18
leads [1] - 912:4
learn [1] - 981:14
learned [4] - 790:20, 804:19, 825:21, 878:25
least [28] - 719:7, 768:13, 783:3, 789:12, 789:13, 812:16, 820:23, 823:12, 831:17, 844:16, 861:21, 873:16, 877:3, 890:24, 901:4, 902:1, 914:9, 915:5, 916:17, 932:8, 932:16, 933:11, 1003:13, 1011:5, 1029:3, 1029:6
leave [2] - 748:11, 1030:5
led [8] - 752:21, 807:23, 880:17, 882:17, 931:4, 950:1, 994:1, 1015:20
Lee [1] - 821:2
left [12] - 724:8, 802:24, 811:8, 821:9, 846:8, 855:11, 855:13, 876:20, 944:17, 947:22, 981:21, 981:22
left-hand [4] - 811:8, 944:17, 981:21, 981:22
legal [2] - 892:11, 892:13
lengthy [1] - 993:14
lenvatinib [4] - 964:9, 966:25, 998:15, 1001:8
Lepore [40] - 707:7, 707:13, 707:17, 707:22, 707:25, 708:8, 708:23, 709:24, 710:15, 713:16, 714:20, 715:13, 715:17, 715:20, 716:14, 716:19, 717:4, 717:23, 718:11, 719:17, 720:12, 720:16, 721:3, 721:8, 721:11, 721:12, 722:1, 722:7, 722:14, 722:23, 723:8, 724:22, 726:13, 726:21, 727:4, 727:25, 734:23, 737:19, 790:8, 791:12
Lepore' [1] - 719:23
Lepore's [3] - 712:11, 718:6, 719:20
less [17] - 712:19, 713:17, 714:21, 715:15, 715:18, 715:21, 718:17, 744:4, 744:16, 745:20, 746:8, 747:6, 812:23, 882:4, 920:17, 922:15, 933:17
lesser [1] - 926:14
lethal [1] - 993:24
leukemia [5] - 963:20, 993:18, 993:23, 994:3, 994:7
level [29] - 732:8, 735:16, 735:22, 744:19, 746:3, 748:14, 766:15, 768:21, 798:3, 800:18, 803:11, 808:19, 841:19, 841:21, 842:9, 845:20, 859:23, 868:6, 874:12, 877:8, 883:14, 888:16, 902:3, 933:6, 953:6, 979:3, 1022:20, 1023:12, 1023:13
Level [1] - 969:11
levels [9] - 712:5, 735:20, 736:22, 737:4, 740:3, 741:1, 741:3, 796:11, 796:18
liability [1] - 803:7
licensing [2] - 1018:20, 1018:21
Lide [2] - 810:22, 812:10
life [9] - 949:14, 949:20, 958:5, 974:20, 974:23, 980:8, 1010:25, 1011:5
life-threatening [2] - 974:20, 974:23
Lifespan [2] - 990:19, 990:24
lifetime [2] - 861:2, 975:18
ligands [1] - 992:12
light [2] - 760:22, 1018:24
likelihood [1] - 952:3
likely [2] - 757:9, 824:18
limit [3] - 716:7, 745:22, 784:24
limitation [4] - 721:4, 728:6, 772:22, 858:8
limitations [3] - 801:17, 817:16, 817:19
LIMITED [1] - 705:7
limited [3] - 747:17, 902:5, 1008:9
limiting [2] - 728:2, 1029:18
limits [4] - 727:12, 764:25, 975:22, 976:1
line [67] - 782:11, 795:19, 848:20, 913:21, 930:23, 931:9, 945:6, 945:12, 945:13, 945:16, 945:17, 945:18, 948:20, 949:17, 951:5, 951:12, 953:17, 954:4, 954:14, 955:19, 956:17, 962:14, 965:10, 965:16, 965:18, 965:19, 966:14, 966:22, 967:14, 967:22, 968:2, 968:5, 968:18, 969:4, 969:16, 969:23, 970:16, 971:5, 972:12, 972:14, 972:18, 972:23, 983:14, 983:16, 983:23, 984:16, 984:17, 984:19, 984:25, 985:4, 999:18, 999:19, 999:21, 1000:2, 1002:13, 1003:9, 1003:19, 1004:12, 1009:9, 1009:24, 1016:1, 1016:10, 1016:11
Line [14] - 774:14, 775:11, 775:21, 847:12, 847:17, 847:25, 848:7, 848:18, 849:5, 849:16, 851:23, 854:6, 872:7, 872:8
Lines [4] - 706:22, 850:4, 850:10, 872:2
lines [6] - 706:25, 811:18, 914:25, 949:13, 984:18, 1004:17
link [1] - 986:19
lipid [1] - 801:2
liquid [1] - 845:24
LISA [1] - 705:21

list [15] - 739:17, 747:7, 805:10, 806:11, 817:17, 818:10, 835:7, 835:11, 858:13, 872:20, 872:24, 873:6, 909:4, 931:11, 967:20
listed [25] - 716:5, 731:13, 731:17, 731:18, 755:20, 756:3, 791:19, 819:4, 820:25, 858:19, 872:5, 872:13, 928:6, 948:7, 948:9, 948:12, 968:2, 981:4, 994:15, 997:21, 1005:13, 1019:24, 1020:4, 1020:8, 1021:25
listen [1] - 969:19
listened [1] - 1014:6
lists [2] - 823:12, 928:6
literally [2] - 902:1, 949:19
literature [7] - 812:16, 813:11, 832:16, 832:20, 833:1, 942:19, 954:20
litigation [5] - 915:11, 915:13, 916:10, 935:16, 935:20
live [1] - 957:12
lives [3] - 961:24, 962:5, 962:10
living [3] - 957:9, 958:10, 960:9
LLP [3] - 705:17, 706:2, 706:4
local [1] - 726:5
locate [1] - 758:18
LOMBARDI [65] - 706:5, 742:23, 743:1, 743:3, 749:7, 749:8, 750:19, 750:21, 751:2, 751:4, 751:25, 752:2, 756:25, 757:2, 758:2, 758:5, 759:6, 759:7, 762:1, 762:2, 772:18, 772:20, 773:25, 774:3, 774:14, 774:16, 776:20, 776:21, 777:1, 777:3, 777:21, 777:23, 778:9, 778:11, 778:24, 779:3, 779:11, 779:14, 783:22, 783:23, 792:11, 792:12, 794:25, 797:2, 843:3, 863:10, 863:18, 864:6, 895:8, 896:2, 896:6, 898:24, 899:2, 913:4, 913:8, 920:25, 929:3, 929:6, 929:22, 929:24, 933:23, 933:24, 935:3, 1029:11, 1031:2
Lombardi [4] - 706:22, 742:22, 743:6, 896:9
long-felt [7] - 942:10, 992:4, 995:18, 995:22, 1004:10, 1004:14, 1006:5
long-range [1] - 846:16
look [60] - 708:3, 710:21, 717:11, 717:20, 718:23, 720:1, 724:2, 724:5, 724:6, 724:14, 728:15, 740:15, 747:7, 756:11, 757:22, 759:22, 761:17, 766:17, 766:21, 771:17, 773:25, 778:14, 781:5, 784:8, 785:11, 810:2, 810:3, 815:3, 821:14, 821:19, 821:24, 822:20, 832:25, 836:21, 842:17, 843:24, 847:24, 850:3, 850:18, 855:1, 869:14, 892:8, 902:19, 902:20, 915:23, 921:2, 929:7, 955:14, 981:21, 982:21, 983:15, 984:23, 985:6, 986:9, 1000:16, 1002:20, 1004:6, 1020:1, 1030:8
looked [7] - 778:25, 784:13, 789:18, 835:8, 978:20, 979:16, 1000:1
looking [41] - 709:15, 712:15, 733:18, 738:22, 744:22, 749:15, 754:23, 754:25, 755:6, 755:9, 756:17, 757:24, 758:10, 760:18, 760:19, 763:15, 770:3, 778:16, 779:4, 782:23, 783:1, 784:6, 799:17, 804:3, 812:9, 817:12, 822:17, 834:20, 856:3, 856:22, 872:21, 921:1, 944:7, 965:22, 967:25, 984:6, 984:15, 985:5, 1017:8, 1029:23, 1030:7
looks [3] - 715:11, 744:23, 846:19
lose [1] - 1018:18
loss [1] - 986:1
lost [1] - 718:15
low [25] - 712:5, 735:20, 736:22, 741:1, 741:3, 773:11, 796:11, 800:22, 801:8, 851:17, 851:19, 889:8, 891:7, 891:10, 891:12, 891:18, 925:18, 926:2, 941:24, 1018:23, 1023:3, 1023:6, 1023:10, 1024:8
lower [8] - 784:14, 890:23, 925:20, 925:24, 926:1, 926:14, 932:8, 932:16
lowest [2] - 743:24, 876:25
lubricant [2] - 731:18, 732:15
lubricants [5] - 733:6, 746:20, 747:15, 747:17, 748:20
lunch [2] - 895:16, 895:17
lung [1] - 963:19

M

M-1 [8] - 865:3, 865:6, 865:20, 914:14, 915:7, 916:24, 916:25, 917:2
M-4 [2] - 914:14, 915:7
M-E-G-A [1] - 989:9
M.D [1] - 989:19
MacMillan [3] - 709:8, 709:18, 722:8
magazine [1] - 993:14
main [5] - 730:2, 735:18, 1014:9, 1024:20, 1024:23
maintain [1] - 982:19
maintained [2] - 741:20, 982:1
maintaining [1] - 1011:5
major [1] - 1006:12
majority [1] - 949:13
makeup [1] - 765:3
malate [78] - 708:12, 708:13, 750:6, 750:8, 819:7, 821:9, 821:11, 822:17, 822:22, 823:2, 823:19, 823:22, 824:9, 825:18, 825:19, 831:10, 831:13, 831:19, 843:18, 844:6, 846:24, 847:4, 848:11, 848:13, 848:18, 849:12, 851:11, 853:3, 854:12, 854:15, 854:18, 854:25, 855:12, 855:15, 856:3, 858:5, 861:6, 862:25, 863:4, 866:20, 867:14, 870:8, 870:14, 870:17, 873:12, 880:17, 884:13, 888:19, 888:21, 888:24, 888:25, 889:2, 889:6, 889:19, 894:17, 900:22, 900:23, 901:1, 901:13, 912:23, 926:8, 926:21, 927:1, 927:18, 927:19, 936:3, 936:11, 937:1, 937:11, 937:18, 937:21, 941:21, 1016:18, 1017:4, 1017:16, 1027:9, 1027:12
maleate [1] - 818:6
maleic [1] - 817:6
malic [42] - 808:23, 808:25, 809:2, 810:13, 810:14, 811:20, 811:22, 811:25, 812:11, 812:12, 812:14, 812:18, 813:6, 818:8, 818:10, 818:13, 823:6, 823:21, 829:10, 831:23, 837:23, 848:3, 848:5, 868:11, 868:14, 872:18, 879:25, 880:4, 880:13, 880:16, 881:4, 881:8, 881:21, 881:22, 882:2, 882:6, 882:8, 882:18, 926:25, 927:2, 927:17, 928:11
malignancies [1] - 1006:14
malignant [1] - 992:24
manage [2] - 960:6, 1009:18
Management [1] - 977:16
manner [2] - 734:17, 814:5
manufacturability [4] - 825:7, 849:25, 885:22, 897:2
manufacture [5] - 760:21, 782:19, 787:11, 793:6, 908:7
manufactured [10] - 715:11, 782:22, 783:9, 783:12, 783:13, 786:3, 849:25, 894:25, 911:23
manufacturer [1] - 923:15
manufacturers [1] - 923:7
manufacturing [14] - 713:4, 713:13, 730:9, 737:23, 741:4, 760:25, 778:19, 842:1, 843:1, 911:1, 912:1, 1008:7, 1008:9, 1008:13
March [1] - 892:11
marked [2] - 810:20, 989:23
market [36] - 937:25, 965:13, 979:16, 981:1, 981:8, 981:14, 981:19, 981:23, 982:4, 982:8, 982:19, 982:22, 983:4, 983:10, 983:17,

983:24, 984:9, 984:15, 984:16, 984:22, 985:4, 985:21, 986:18, 997:4, 1014:18, 1020:18, 1021:19, 1022:18, 1022:22, 1023:20, 1023:25, 1024:3, 1024:5, 1024:6, 1025:22
marketed [4] - 726:3, 726:7, 819:24, 894:10
marketplace [15] - 742:10, 979:19, 980:16, 981:5, 981:6, 981:13, 982:6, 982:7, 982:12, 982:14, 983:7, 983:8, 984:5, 985:16, 1010:18
markets [2] - 979:15, 979:16
Maryland [1] - 1013:2
Massachusetts [1] - 840:18
master [1] - 977:17
master's [2] - 841:1, 1013:3
match [2] - 782:11, 863:2
material [30] - 708:25, 709:9, 721:15, 721:18, 760:8, 786:3, 794:8, 802:6, 804:5, 804:16, 804:21, 846:11, 846:14, 846:16, 846:19, 853:11, 856:12, 856:13, 857:12, 858:23, 865:10, 865:11, 865:13, 879:16, 884:18, 889:15, 889:16, 891:5, 891:6, 891:7
materials [13] - 709:6, 733:22, 735:14, 801:18, 804:19, 806:24, 810:15, 818:22, 819:15, 820:11, 821:18, 893:17, 907:19
MATHAS [17] - 706:6, 826:14, 826:20, 826:25, 827:4, 833:2, 833:3, 833:11, 833:14, 833:17, 834:14, 834:17, 835:24, 836:1, 836:22, 836:23, 838:1
mathematics [1] - 1013:2
matter [12] - 706:18, 773:15, 845:23, 858:21, 902:11, 902:13, 957:15, 1014:22, 1019:16, 1020:21, 1020:23, 1021:16
matters [6] - 832:7, 957:13, 957:15, 957:16, 958:12, 1010:21
maturation [2] - 998:4, 998:5
max [1] - 1026:11
Max [1] - 841:5
Max-Planck [1] - 841:5
MBA [1] - 977:18
MC [1] - 1011:23
McDuff [19] - 1011:16, 1011:22, 1011:25, 1012:6, 1012:8, 1012:13, 1012:17, 1012:24, 1013:18, 1013:23, 1015:5, 1015:14, 1015:25, 1018:1, 1019:13, 1025:4, 1025:13, 1026:15, 1027:19
mean [50] - 716:23, 722:24, 738:7, 745:12, 747:5, 749:14, 765:1, 766:13, 769:5, 771:13, 781:5, 785:23, 789:8, 812:23, 813:1, 858:18, 873:4, 876:21, 905:18, 905:19, 906:24, 906:25, 907:11, 907:12, 908:8, 908:12, 910:1, 915:18, 918:7, 918:8, 918:16, 920:4, 922:23, 923:9, 924:10, 925:11, 926:24, 928:24, 933:17, 940:19, 953:13, 953:14, 960:17, 960:22, 1009:15, 1019:14, 1022:24, 1023:18, 1030:14
meaning [12] - 789:10, 841:9, 853:8, 853:22, 856:8, 859:7, 859:14, 866:17, 898:1, 904:11, 919:20, 958:23
meaningful [1] - 853:21
means [6] - 711:12, 744:16, 767:23, 786:6, 994:22, 1024:4
meant [1] - 984:17
measure [1] - 960:8
measures [1] - 979:16
mechanism [3] - 737:9, 993:17, 993:25
media [6] - 825:21, 877:14, 877:24, 878:2, 878:22
median [4] - 953:1, 953:7, 955:15, 955:16
medical [7] - 939:19, 958:8, 990:12, 990:14, 990:21, 991:9, 991:12
Medical [1] - 940:23
Medicare [1] - 955:14
medications [1] - 958:6
medicine [2] - 939:21, 990:18
Medicine [2] - 940:21, 951:17
medium [1] - 842:15
medullary [1] - 943:17
meet [9] - 743:7, 743:8, 845:9, 896:10, 896:11, 896:12, 995:22, 1006:10, 1006:11
meeting [1] - 961:25
MEGA [1] - 989:10
Mega [18] - 942:23, 956:1, 975:4, 989:5, 989:8, 989:19, 989:20, 989:24, 990:4, 990:11, 991:12, 991:18, 992:8, 995:17, 1004:9, 1006:2, 1006:20, 1011:12
Mega's [1] - 1027:24
melting [12] - 805:23, 908:11, 908:19, 908:21, 909:2, 909:5, 919:1, 925:18, 925:20, 925:25, 926:1, 926:2
memorized [1] - 912:3
memory [1] - 935:18
mentioned [24] - 707:7, 716:11, 717:3, 739:17, 739:22, 783:20, 841:13, 841:23, 860:22, 874:7, 874:8, 880:23, 891:10, 898:21, 958:14, 963:22, 964:21, 965:1, 968:16, 970:1, 970:18, 974:11, 975:10, 995:5
mentions [1] - 738:8
merge [1] - 995:11
Merit [1] - 1031:11
mesylate [1] - 818:6
MET [3] - 956:8, 956:10, 964:21
met [3] - 711:13, 743:6, 955:23
Met [1] - 995:6
metastatic [2] - 951:13, 957:14
METEOR [6] - 950:1, 953:24, 954:5, 972:2, 1003:8, 1003:12
methane [1] - 817:7
method [27] - 707:13, 745:9, 758:12, 780:10, 780:22, 781:13, 781:15, 781:16, 782:19, 782:25, 784:22, 785:21, 789:15, 789:17, 790:3, 791:22, 793:19, 793:20, 794:18, 794:21, 856:20, 857:8, 870:12, 897:11, 898:20, 903:18
methodology [1] - 839:7
Methods [1] - 893:16
methods [16] - 728:2, 757:23, 758:9, 764:3, 764:7, 776:4, 780:11, 780:14, 784:10, 849:8, 871:15, 874:18, 879:11, 879:13, 906:25, 909:13
Michael [2] - 976:15, 976:19
MICHAEL [2] - 976:19, 976:21
micronization [1] - 801:2
microscope [1] - 846:18
microscopy [1] - 856:19
middle [4] - 774:6, 834:21, 929:25, 930:24
might [27] - 734:6, 735:8, 753:1, 755:1, 756:4, 758:8, 767:17, 783:24, 787:16, 794:10, 834:2, 857:18, 862:6, 873:4, 905:25, 909:7, 909:12, 910:11, 917:16, 922:24, 924:1, 926:5, 928:20, 944:7, 1009:13
Mike [1] - 977:2
milligrams [3] - 943:10, 943:11
million [10] - 716:12, 718:18, 719:7, 719:8, 744:2, 745:19, 779:23, 785:8, 792:4, 796:12
mimic [1] - 878:3
mind [2] - 913:7, 1029:25
mineral [6] - 815:3, 815:4, 815:5, 815:10, 815:15
minimis [1] - 709:14
minimize [4] - 712:5, 763:16, 772:2, 975:14
minimized [1] - 708:15
minimum [1] - 814:6
minute [2] - 889:19, 1028:17
minutes [16] - 890:18, 890:22, 891:8, 891:19, 895:16, 895:20, 976:9, 1026:11, 1029:5, 1029:6, 1029:10, 1029:14, 1030:13, 1030:17, 1030:18
mirror [1] - 847:23
misplaced [1] - 816:7
misspeaking [1] - 782:20
mistake [3] - 863:13, 899:19, 899:20
MIT [5] - 840:18,

840:20, 841:2, 841:7, 842:5
mixing [1] - 777:8
mixture [1] - 710:23
moderation [1] - 1030:10
modest [2] - 955:22, 1000:6
modifications [2] - 714:14, 714:16
modifier [1] - 898:1
modify [4] - 721:5, 722:2, 726:21, 738:10
modulation [1] - 1002:8
moisture [6] - 713:12, 730:17, 740:8, 849:3, 898:22, 903:19
molecular [4] - 817:25, 869:20, 881:25, 889:8
molecule [4] - 882:7, 910:18, 928:2, 960:23
molecules [2] - 846:10, 882:5
moment [11] - 772:21, 792:10, 798:8, 798:13, 809:5, 834:1, 834:13, 906:20, 910:16, 993:13, 1019:9
momentarily [1] - 942:13
momentous [1] - 993:13
monitor [1] - 722:15
monitors [1] - 981:8
Monkhouse [1] - 930:13
monoclonal [1] - 952:18
monotherapy [21] - 948:13, 952:13, 953:9, 953:19, 967:6, 967:8, 967:14, 967:22, 970:9, 970:10, 971:13, 973:4, 983:17, 984:4, 984:7, 984:20, 984:23, 999:15, 999:18, 999:19, 1004:5
month [1] - 1010:21
months [7] - 838:22, 916:7, 953:9, 953:10, 957:16, 1000:8, 1000:9
morning [19] - 706:15, 707:5, 707:6, 743:4, 743:5, 750:2, 795:2, 797:15, 797:16, 827:5, 827:6, 840:4, 840:6, 897:13, 916:19, 917:1, 927:3, 989:17, 1028:16
MORRIS [1] - 705:17
most [21] - 757:8, 770:20, 798:17, 818:4, 818:10, 819:4, 820:22, 820:23, 851:9, 851:11, 860:12, 907:19, 945:9, 947:15, 948:19, 967:13, 967:21, 974:2, 977:25, 985:19, 1029:23
mostly [1] - 1030:7
motifs [1] - 725:20
motivate [4] - 731:20, 737:25, 738:9, 1023:13
motivated [32] - 708:24, 721:5, 721:13, 722:2, 722:12, 722:15, 724:12, 726:17, 729:7, 733:4, 751:18, 752:21, 752:24, 753:3, 753:23, 755:14, 757:17, 759:17, 764:18, 810:13, 813:5, 823:21, 825:18, 826:7, 874:13, 875:14, 879:8, 881:11, 932:7, 932:15, 975:14, 976:1
motivation [11] - 721:23, 722:11, 726:20, 727:15, 734:16, 868:9, 868:11, 874:1, 874:5, 874:8, 879:25
mouth [1] - 875:23
move [19] - 738:18, 772:14, 772:15, 777:16, 796:24, 826:12, 843:6, 845:13, 845:17, 850:9, 866:10, 867:20, 879:19, 883:12, 884:7, 946:22, 961:11, 986:23, 1027:23
moved [1] - 940:4
moving [1] - 845:13
MR [322] - 742:23, 743:1, 743:3, 749:7, 749:8, 750:19, 750:21, 751:2, 751:4, 751:25, 752:2, 756:25, 757:2, 758:2, 758:5, 759:6, 759:7, 762:1, 762:2, 772:18, 772:20, 773:25, 774:3, 774:14, 774:16, 776:20, 776:21, 777:1, 777:3, 777:21, 777:23, 778:9, 778:11, 778:24, 779:3, 779:11, 779:14, 783:22, 783:23, 792:11, 792:12, 794:25, 797:2, 797:11, 797:14, 797:22, 797:23, 799:15, 799:16, 800:2, 800:3, 801:21, 801:22, 802:16, 802:17, 804:23, 804:25, 805:4, 805:6, 806:17, 806:19, 808:17, 808:18, 809:7, 809:8, 809:21, 809:23, 810:9, 810:11, 810:15, 810:17, 810:23, 810:25, 811:5, 811:6, 811:16, 811:19, 821:2, 821:4, 826:10, 826:14, 826:20, 826:25, 827:4, 833:2, 833:3, 833:7, 833:9, 833:11, 833:14, 833:17, 834:14, 834:17, 835:24, 836:1, 836:22, 836:23, 838:1, 839:11, 839:15, 840:1, 840:3, 840:15, 840:16, 842:24, 843:3, 843:5, 843:7, 843:8, 843:13, 843:15, 844:13, 844:14, 845:17, 845:18, 846:2, 846:3, 846:20, 846:21, 847:5, 847:8, 847:11, 847:13, 847:16, 847:18, 847:24, 848:1, 848:15, 848:16, 850:9, 850:11, 850:18, 850:21, 854:5, 854:7, 854:9, 854:13, 855:1, 855:3, 855:8, 855:9, 856:2, 856:5, 856:15, 856:16, 858:7, 858:9, 858:24, 858:25, 861:14, 861:15, 861:23, 861:25, 863:10, 863:18, 863:22, 863:24, 864:6, 864:15, 864:20, 864:24, 864:25, 866:8, 866:9, 866:14, 866:15, 868:4, 868:5, 868:20, 868:22, 869:15, 869:17, 869:25, 870:1, 872:2, 872:4, 872:16, 872:17, 873:25, 874:2, 874:9, 874:11, 875:11, 875:12, 876:2, 876:4, 876:13, 876:14, 879:5, 879:6, 879:19, 879:21, 880:1, 880:2, 880:9, 880:10, 881:18, 881:19, 882:9, 882:11, 883:11, 883:13, 883:24, 883:25, 884:7, 884:9, 885:9, 885:10, 885:17, 885:18, 886:2, 886:5, 887:14, 887:15, 888:8, 888:9, 888:14, 888:15, 889:17, 890:3, 890:6, 890:10, 890:12, 891:20, 891:22, 891:25, 892:1, 892:4, 892:5, 893:4, 893:6, 893:10, 893:12, 893:15, 893:18, 894:3, 894:5, 895:3, 895:8, 896:2, 896:6, 898:24, 899:2, 913:4, 913:8, 920:25, 929:3, 929:6, 929:22, 929:24, 933:23, 933:24, 935:3, 935:5, 935:7, 938:6, 941:14, 961:13, 961:17, 961:20, 966:8, 966:10, 970:13, 970:14, 976:4, 989:5, 989:14, 989:16, 990:1, 990:3, 990:9, 990:10, 991:11, 991:16, 991:17, 993:8, 993:9, 995:15, 995:16, 997:13, 997:15, 1006:2, 1011:11, 1011:14, 1011:18, 1012:5, 1012:15, 1012:16, 1012:22, 1012:23, 1013:17, 1013:22, 1014:4, 1014:5, 1015:3, 1015:4, 1015:12, 1015:13, 1015:22, 1015:23, 1017:24, 1019:8, 1019:10, 1020:2, 1020:3, 1021:22, 1021:23, 1022:16, 1022:17, 1023:16, 1024:17, 1024:18, 1025:4, 1027:18, 1027:23, 1028:2, 1028:13, 1028:21, 1029:9, 1029:11, 1030:25, 1031:2
MS [131] - 706:17, 706:21, 707:2, 707:4, 707:9, 707:11, 708:3, 708:7, 710:12, 710:14, 711:23, 711:25, 712:13, 712:14, 713:20, 713:22, 714:23, 715:1, 715:5, 715:8, 715:24, 716:1, 718:13, 718:21, 718:25, 719:20, 719:22, 720:1, 720:3, 720:15, 720:17, 722:16, 722:17, 722:21, 722:22, 724:18, 724:20, 726:25, 727:3, 729:3, 729:5, 731:3, 731:5, 731:25, 732:2, 733:15, 733:17, 734:20, 734:22,

735:24, 736:1, 736:6, 736:8, 737:16, 737:18, 738:14, 738:15, 742:20, 749:2, 795:9, 795:11, 795:14, 796:21, 796:24, 938:10, 938:21, 938:24, 939:11, 939:12, 940:15, 940:16, 941:4, 941:5, 941:11, 941:16, 942:5, 942:6, 942:14, 942:16, 943:5, 943:6, 946:21, 946:24, 947:11, 947:13, 952:5, 952:8, 952:23, 952:24, 954:25, 955:1, 957:20, 957:21, 961:9, 976:5, 976:15, 976:25, 977:9, 977:11, 978:5, 978:12, 978:15, 978:17, 979:7, 979:9, 979:20, 979:22, 980:18, 980:23, 982:25, 983:2, 984:10, 984:12, 985:8, 985:10, 986:22, 987:3, 987:9, 987:13, 988:21, 989:1, 991:14, 1006:19, 1011:8, 1013:20, 1025:9, 1026:12, 1026:14, 1027:14, 1027:25, 1028:14

MSN [24] - 705:7, 800:6, 845:3, 914:13, 915:7, 916:23, 926:16, 935:9, 935:16, 935:20, 937:11, 937:19, 937:20, 937:24, 938:3, 960:11, 988:2, 989:5, 991:22, 992:2, 1011:15, 1018:11, 1021:1, 1026:3

MSN's [10] - 843:10, 862:20, 863:2, 867:9, 902:9, 911:22, 925:14, 975:4, 1021:11, 1027:7

mTOR [3] - 955:13, 997:1, 1003:17

multidisciplinary [1] - 990:23

multiple [20] - 709:8, 709:11, 710:5, 721:19, 794:4, 817:22, 865:22, 874:18, 879:11, 896:16, 923:16, 923:20, 964:2, 994:23, 995:1, 1007:11, 1007:13, 1007:14, 1009:19, 1028:9

multiplier [1] - 789:17

multitude [1] - 908:24

must [2] - 712:16, 923:15

mutation [1] - 992:22

mutations [1] - 992:20

my.. [1] - 713:24

myelogenous [2] - 993:17, 993:23

Myers [2] - 914:5, 1016:6

Myerson [10] - 706:21, 707:5, 715:13, 733:20, 742:17, 742:20, 743:4, 795:13, 796:22, 942:21

Mylan [6] - 865:2, 865:23, 916:21, 916:24, 916:25, 937:14

N

N-.2 [1] - 926:2

N-1 [37] - 852:1, 852:16, 853:1, 853:4, 860:10, 860:13, 861:11, 867:5, 901:5, 901:17, 902:5, 902:17, 903:4, 903:7, 903:22, 903:25, 904:7, 904:14, 904:17, 904:20, 904:21, 905:1, 905:3, 905:15, 911:4, 911:9, 911:14, 911:18, 912:10, 914:1, 914:15, 915:8, 924:11, 924:12, 925:7, 925:25, 926:1

N-2 [44] - 852:1, 852:16, 853:1, 853:4, 860:10, 860:13, 861:11, 867:7, 901:5, 901:19, 902:5, 902:17, 903:4, 903:7, 903:22, 903:25, 904:7, 904:14, 904:17, 904:20, 904:21, 905:1, 905:4, 905:15, 911:6, 911:9, 911:13, 911:17, 911:21, 911:23, 912:10, 914:15, 915:8, 922:7, 924:14, 925:7, 925:11, 925:16, 925:25, 926:6, 926:14, 935:18, 937:23, 938:4

N-5 [1] - 914:1

Nagao [7] - 723:8, 723:10, 723:13, 723:16, 723:19, 723:24, 724:2

name [16] - 743:6, 805:7, 820:3, 839:19, 840:6, 866:20, 872:13, 894:19, 938:14, 976:18, 977:2, 989:7, 993:11, 1011:21, 1012:8

named [2] - 770:16, 858:19

namely [2] - 992:4, 1004:4

nanomilling [1] - 801:2

National [1] - 947:1

nature [3] - 767:9, 817:24, 977:23

NCCN [8] - 947:1, 947:19, 966:6, 997:9, 998:1, 1002:20, 1009:22, 1010:6

ND [1] - 784:25

NDA [3] - 715:3, 718:22, 778:18

near [1] - 949:18

nearly [1] - 990:15

necessarily [7] - 712:20, 719:10, 728:20, 757:21, 794:3, 1009:14, 1029:19

necessary [6] - 763:7, 807:10, 828:19, 1008:12, 1021:14, 1021:17

need [35] - 772:2, 782:6, 795:1, 803:19, 814:3, 817:17, 878:25, 942:10, 955:5, 955:6, 955:11, 955:23, 956:24, 957:3, 961:5, 962:1, 962:13, 967:19, 983:22, 992:4, 995:18, 995:23, 1004:10, 1004:15, 1004:18, 1004:21, 1005:23, 1006:5, 1008:4, 1025:21, 1030:6, 1030:9, 1030:21, 1030:23

needed [3] - 739:11, 887:25, 955:19

needs [3] - 861:2, 956:22, 1022:8

negative [2] - 724:10, 922:24

net [2] - 985:13, 985:15

Network [1] - 947:2

never [10] - 787:6, 787:18, 787:21, 796:2, 863:19, 933:12, 968:22, 970:5, 972:16, 1009:5

New [1] - 951:17

new [24] - 734:6, 756:18, 757:10, 757:13, 757:23, 758:9, 758:12, 760:21, 763:4, 865:14, 865:16, 865:18, 865:25, 907:11, 916:17, 946:8, 950:16, 953:23, 954:1, 962:9, 983:5, 993:16, 997:3, 1001:19

newer [1] - 997:6

next [23] - 726:20, 752:11, 768:1, 782:8, 787:13, 809:21, 814:9, 843:13, 847:16, 849:5, 852:17, 861:23, 863:22, 876:25, 879:22, 887:2, 892:4, 897:18, 914:22, 938:11, 947:25, 1011:16, 1017:24

nexus [27] - 740:19, 740:22, 939:9, 942:11, 957:22, 986:4, 986:9, 987:17, 988:7, 1014:12, 1019:11, 1019:14, 1019:15, 1019:19, 1020:13, 1020:22, 1021:3, 1021:4, 1021:7, 1021:16, 1021:21, 1022:2, 1022:12, 1022:13, 1024:24, 1025:14, 1025:23

nice [5] - 743:7, 743:8, 896:11, 896:12, 987:14

NICHOLS [1] - 705:17

Nilotinib [1] - 963:13

nilotinib [1] - 994:17

nine [3] - 934:21, 983:6, 983:9

nitric [1] - 815:12

nivolumab [19] - 945:7, 945:20, 945:21, 948:8, 948:11, 948:15, 948:20, 948:25, 951:19, 952:1, 952:22, 970:8, 970:16, 970:19, 971:5, 1000:21, 1000:24, 1001:7, 1001:20

nominated [2] - 808:7, 808:11

non [7] - 716:6, 819:5, 868:17, 888:13, 941:1, 973:12, 1020:10

non-asserted [1] - 1020:10

non-detected [1] - 716:6

non-GRAS [1] - 819:5

non-obviousness [3] - 868:17, 888:13, 973:12

non-profit [1] - 941:1

none [9] - 809:20, 823:8, 870:23, 871:7, 871:14, 871:17, 888:2, 964:18, 964:21

nonetheless [2] - 877:5, 877:9

nonhygroscopic [3] - 851:3, 860:20, 925:14

nonionized [1] - 928:16
nonobviousness [1] - 1019:7
normal [4] - 754:3, 762:17, 992:18, 992:19
North [1] - 705:10
Norvir [3] - 924:20, 924:23, 925:5
Nos [5] - 797:5, 895:11, 895:13, 961:15, 987:6
note [4] - 738:11, 819:4, 822:4, 913:17
notebooks [3] - 780:17, 780:19, 783:16
noted [8] - 721:17, 779:10, 779:15, 784:20, 785:2, 786:15, 793:23, 997:12
notes [2] - 1029:21, 1031:9
noteworthy [1] - 1010:16
nothing [16] - 758:16, 772:9, 780:3, 871:1, 871:4, 871:11, 874:23, 875:4, 875:7, 887:23, 888:7, 905:9, 938:6, 988:25, 1030:25, 1031:2
noticed [1] - 999:15
novel [8] - 761:1, 761:11, 763:24, 772:5, 772:10, 773:7, 794:18, 794:21
Number [4] - 892:16, 947:12, 1018:9, 1018:20
number [47] - 713:9, 746:10, 746:12, 747:11, 747:12, 747:14, 747:15, 747:18, 756:20, 777:21, 780:11, 781:2, 791:8, 802:12, 803:12, 817:1, 821:3, 829:14, 829:16, 831:15, 834:21, 899:21, 907:21, 907:22, 909:16, 912:23, 916:11, 927:3, 931:5, 933:12, 934:23, 935:1, 979:12, 979:13, 980:1, 980:4, 982:5, 989:25, 998:14, 1003:1, 1005:13, 1005:15, 1018:12, 1018:14, 1018:23, 1023:4, 1029:18
numbers [7] - 755:17, 780:14, 780:15, 780:23, 789:2, 831:22, 1026:21
numeric [1] - 803:12
numerous [1] - 996:19

O

O'GARA [1] - 706:7
O-R-E-S-T [1] - 1011:23
oath [4] - 839:23, 938:18, 976:22, 989:11
object [3] - 833:9, 863:11, 1030:4
objection [19] - 797:2, 797:4, 826:14, 826:15, 843:3, 895:10, 941:14, 961:13, 961:14, 978:15, 987:3, 987:5, 991:14, 1013:20, 1025:8, 1025:9, 1027:25, 1028:5, 1028:10
objections [1] - 895:8
objective [14] - 740:12, 740:20, 740:23, 868:16, 888:12, 888:16, 950:15, 973:6, 973:12, 973:20, 992:3, 1003:22, 1005:18, 1029:19
observed [1] - 1007:2
obtain [6] - 721:6, 737:7, 817:1, 893:16, 905:25, 937:6
obtained [5] - 717:16, 817:3, 906:4, 907:14, 922:6
obtaining [3] - 884:12, 884:18, 935:21
obvious [12] - 714:15, 742:18, 742:19, 744:9, 748:19, 749:5, 749:10, 749:12, 749:15, 826:4, 1014:22, 1017:5
obviously [4] - 766:13, 766:14, 832:23, 947:23
obviousness [20] - 707:8, 742:12, 744:22, 744:23, 749:22, 750:4, 843:12, 867:20, 868:17, 879:23, 888:11, 888:13, 926:18, 926:20, 935:13, 973:12, 1014:23, 1020:18, 1027:8
obviousness-type [7] - 843:12, 867:20, 879:23, 888:11, 926:18, 926:20, 1027:8
occasionally [1] - 893:25
occur [3] - 795:24, 803:22, 992:20
occurrence [2] - 820:17, 820:22
occurs [1] - 1009:2
October [2] - 705:12, 1016:8
OF [1] - 705:2
offer [4] - 799:17, 893:24, 941:11, 1014:2
offered [9] - 708:23, 741:22, 844:9, 845:4, 859:1, 869:2, 942:25, 956:2, 1021:11
offering [10] - 707:8, 799:24, 824:20, 935:16, 942:2, 955:2, 969:2, 969:19, 969:22, 1014:8
offers [2] - 978:12, 1010:9
office [1] - 892:3
often [13] - 728:21, 735:13, 737:2, 754:24, 794:6, 815:6, 821:11, 822:17, 822:22, 969:10, 992:24, 995:11
oily [1] - 884:15
old [1] - 780:11
older [2] - 784:10
once [2] - 822:23, 948:10
oncologist [3] - 939:19, 954:17, 990:24
oncologists [3] - 954:19, 986:14, 1009:19
oncology [12] - 975:8, 990:12, 990:14, 990:22, 990:23, 991:9, 991:13, 1001:16, 1003:5, 1007:8, 1009:23, 1010:5
Oncology [3] - 940:22, 949:25, 950:22
one [142] - 706:17, 708:14, 710:23, 714:15, 728:23, 733:5, 735:18, 743:15, 743:23, 748:7, 750:22, 750:23, 751:21, 752:11, 753:8, 759:6, 759:13, 762:1, 762:21, 762:24, 764:14, 764:15, 769:3, 770:20, 772:22, 776:18, 777:19, 783:3, 783:5, 783:15, 783:24, 784:10, 784:17, 787:9, 792:9, 792:10, 793:19, 793:20, 798:23, 799:7, 801:16, 803:19, 804:3, 807:25, 808:9, 814:24, 816:25, 823:4, 824:16, 827:1, 830:3, 831:18, 832:22, 834:11, 841:8, 842:8, 856:20, 858:22, 859:2, 862:12, 864:13, 868:18, 873:23, 874:15, 874:17, 875:16, 876:24, 877:1, 879:15, 879:24, 880:14, 880:18, 881:22, 882:6, 885:5, 885:16, 891:3, 897:11, 898:22, 899:9, 899:15, 901:7, 905:23, 906:8, 906:20, 907:19, 908:18, 910:16, 911:4, 911:18, 913:21, 916:23, 924:16, 924:17, 924:18, 924:23, 928:18, 928:23, 929:19, 931:14, 935:16, 942:8, 945:1, 947:7, 950:6, 956:8, 959:15, 965:1, 966:18, 968:6, 972:8, 972:15, 973:6, 980:9, 981:4, 981:7, 981:18, 983:14, 984:18, 988:3, 992:21, 994:4, 994:8, 995:6, 999:6, 1000:25, 1003:14, 1009:13, 1015:9, 1017:5, 1018:9, 1022:23, 1024:15, 1025:15, 1025:16, 1025:20, 1026:17, 1027:10, 1029:14
ones [11] - 730:2, 747:14, 747:18, 817:10, 873:24, 877:3, 883:6, 912:25, 964:15, 964:21, 1003:4
Oops [1] - 906:20
Opdivo [2] - 983:25, 985:1
opened [1] - 994:14
opine [1] - 987:20
opined [1] - 987:22
opinion [90] - 708:23, 709:3, 712:12, 713:6, 717:2, 717:7, 717:17, 717:22, 719:2, 719:9, 724:11, 725:5, 731:10, 733:8, 734:16, 735:6, 737:5, 737:25, 738:6, 742:7, 742:12, 742:19, 786:11, 786:13, 799:24, 804:1, 824:19, 825:24, 844:9, 845:4, 854:2, 857:21, 857:24, 859:1, 859:7, 859:10, 859:19, 859:24, 865:19, 867:16, 867:19, 867:22, 868:1, 868:2, 868:7, 869:2, 869:5, 869:7, 870:17, 875:21, 878:19, 879:22,

880:3, 880:19, 881:10, 914:19, 921:21, 922:8, 922:16, 935:17, 942:2, 942:4, 946:23, 955:2, 957:2, 958:1, 969:2, 969:22, 973:10, 995:17, 996:8, 999:7, 1004:9, 1004:14, 1005:3, 1005:19, 1005:22, 1006:5, 1006:9, 1010:9, 1018:3, 1019:11, 1019:20, 1022:13, 1022:14, 1024:12, 1024:23, 1026:2, 1026:3, 1026:4
opinions [62] - 707:8, 712:1, 725:15, 725:21, 726:8, 740:13, 741:6, 741:9, 741:22, 741:24, 742:3, 742:5, 742:11, 751:3, 799:17, 800:13, 809:4, 810:7, 827:23, 840:13, 843:6, 845:1, 845:6, 845:14, 855:20, 857:5, 857:20, 864:5, 874:1, 874:4, 874:6, 874:10, 880:3, 880:6, 880:8, 880:13, 881:20, 883:12, 884:2, 886:24, 887:1, 887:10, 891:16, 891:17, 894:7, 921:7, 942:7, 942:8, 942:18, 942:25, 961:23, 969:18, 973:6, 975:11, 992:2, 995:20, 1005:18, 1014:7, 1014:9, 1021:11, 1022:21
opportunity [2] - 1018:21, 1018:24
opposed [1] - 866:18
opposite [1] - 935:21
optimized [1] - 1007:21
option [7] - 949:11, 950:17, 1002:14, 1003:2, 1009:10, 1009:24, 1010:3
options [10] - 996:16, 996:20, 998:12, 998:14, 1002:18, 1004:11, 1004:16, 1004:20, 1010:1, 1010:2
or.. [1] - 774:2
Oral [1] - 876:9
oral [12] - 816:13, 874:17, 875:17, 875:20, 875:22, 876:18, 877:3, 877:12, 877:20, 994:5, 994:7, 994:8
orange [2] - 824:9, 862:21
Orange [5] - 822:6, 1019:24, 1020:4, 1020:9, 1021:25
order [9] - 820:22, 828:23, 829:8, 839:5, 839:7, 844:3, 846:16, 1002:19, 1008:12
ordinary [21] - 709:19, 721:5, 724:12, 761:7, 800:5, 805:16, 828:13, 829:6, 832:11, 835:16, 835:19, 838:21, 844:10, 845:10, 853:8, 853:22, 859:7, 859:14, 936:1, 936:8, 937:4
organic [14] - 811:4, 815:24, 816:21, 816:24, 817:5, 817:8, 817:16, 818:2, 818:5, 818:9, 818:11, 829:14, 844:22, 883:9
originally [2] - 863:7, 960:24
originate [1] - 945:11
otherwise [5] - 724:8, 826:24, 861:3, 951:2, 1030:22
outcome [2] - 807:8, 840:12
outcomes [6] - 824:18, 971:2, 971:25, 973:23, 994:2, 1007:2
outlined [2] - 865:22, 1018:3
outperformed [1] - 948:24
outside [1] - 717:23
overall [26] - 715:12, 717:19, 789:10, 792:6, 794:3, 794:7, 794:9, 822:18, 826:3, 874:14, 926:10, 940:19, 948:22, 950:13, 951:11, 952:3, 968:23, 983:4, 983:16, 984:15, 1000:9, 1010:13, 1018:23, 1022:11
overcome [2] - 892:12, 893:2
overlap [1] - 934:14
overlapping [3] - 953:10, 964:19, 964:22
overlay [4] - 862:1, 862:14, 862:17, 863:1
overview [1] - 1014:7
own [10] - 713:3, 734:10, 807:22, 842:4, 916:14, 954:20, 964:13, 969:6, 998:21, 998:23

P

p.m [1] - 1031:7
pace [1] - 997:5
package [1] - 944:14
packaged [1] - 1008:2
page [30] - 756:16, 770:5, 782:2, 784:5, 784:6, 784:13, 795:14, 814:9, 819:21, 819:25, 821:24, 824:7, 834:18, 834:20, 834:21, 836:5, 843:17, 843:19, 892:4, 893:8, 893:19, 914:22, 930:2, 944:17, 950:9, 951:8, 980:20, 980:24, 990:2
Page [37] - 706:22, 715:6, 718:23, 726:2, 733:15, 733:16, 736:7, 756:25, 778:24, 805:4, 810:24, 811:2, 811:5, 811:17, 813:18, 813:20, 814:2, 815:21, 816:19, 819:18, 822:7, 834:15, 834:19, 835:3, 835:4, 835:24, 891:25, 893:11, 893:15, 913:15, 929:22, 929:23, 947:11, 947:18, 997:14, 1002:23
Pages [2] - 819:25, 966:8
pages [3] - 822:7, 865:22, 916:15
pain [1] - 1010:25
pair [1] - 881:13
panel [2] - 947:21, 948:1
paper [9] - 723:8, 723:10, 723:13, 723:24, 724:2, 725:21, 726:1, 726:8, 885:7
papers [1] - 947:10
Paragraph [6] - 710:12, 710:15, 913:5, 913:15, 914:24, 921:1
paragraph [34] - 710:21, 713:21, 713:23, 714:5, 714:7, 731:3, 731:7, 731:10, 731:13, 731:14, 731:17, 733:11, 744:14, 775:14, 776:25, 813:24, 814:2, 815:23, 816:8, 819:21, 824:6, 824:8, 847:25, 848:5, 848:17, 849:17, 850:3, 851:21, 886:16, 887:2, 914:22, 914:23, 935:9, 950:12
paragraphs [1] - 914:23
parameters [3] - 788:9, 908:13, 921:24
parent [2] - 886:23, 887:9
part [27] - 742:14, 748:25, 749:10, 749:11, 749:21, 755:1, 762:11, 762:17, 777:24, 808:2, 816:19, 819:11, 826:5, 844:21, 846:6, 891:24, 897:18, 912:1, 920:23, 970:25, 988:9, 990:21, 991:1, 997:10, 997:11, 1021:13
particle [1] - 879:17
particular [34] - 727:8, 744:18, 746:23, 747:21, 747:25, 748:1, 748:4, 763:13, 769:23, 781:14, 784:22, 784:24, 799:13, 825:6, 843:11, 850:2, 852:6, 852:7, 854:23, 857:14, 865:4, 871:25, 887:8, 898:7, 907:14, 917:18, 923:2, 977:8, 978:18, 981:5, 981:23, 982:3, 1008:23, 1009:3
particularly [13] - 721:24, 756:4, 765:20, 765:24, 819:3, 848:21, 956:12, 958:18, 960:8, 971:23, 1030:1, 1030:3
partly [3] - 1029:4, 1030:11
partner [1] - 1004:2
partners [1] - 1018:19
parts [12] - 716:12, 718:17, 719:7, 719:8, 744:2, 745:19, 779:23, 785:8, 786:15, 792:3, 796:12, 814:25
party [1] - 1018:16
pass [5] - 742:23, 895:7, 987:9, 1006:2, 1025:4
passage [4] - 764:9, 814:12, 850:12, 854:8
past [1] - 927:4
patent [128] - 707:14, 710:1, 712:2, 712:4, 712:16, 723:11, 723:14, 728:7, 729:4, 732:1, 732:3, 732:6, 732:8, 734:18, 738:21, 740:1, 740:17, 740:20, 740:23, 740:24, 742:18, 744:6, 744:16, 745:10, 748:16,

758:16, 759:3, 761:1, 761:6, 761:11, 761:19, 763:24, 764:7, 772:4, 772:9, 773:7, 773:14, 774:1, 774:4, 774:17, 775:3, 776:18, 777:12, 786:15, 786:25, 787:1, 796:5, 796:14, 797:18, 847:6, 847:12, 848:13, 849:12, 849:23, 850:19, 851:8, 854:4, 855:13, 855:14, 858:12, 858:19, 867:24, 868:3, 868:24, 868:25, 869:3, 869:16, 870:3, 870:21, 870:22, 870:25, 871:3, 871:6, 871:8, 871:13, 871:16, 871:22, 872:1, 872:6, 872:10, 872:18, 872:22, 873:10, 887:21, 892:16, 892:19, 892:25, 893:3, 898:25, 899:1, 902:4, 902:5, 936:3, 937:12, 941:17, 941:25, 944:6, 959:21, 960:12, 973:13, 978:3, 986:20, 988:4, 988:8, 988:10, 988:13, 988:17, 1014:24, 1015:6, 1016:12, 1016:19, 1017:4, 1017:11, 1017:12, 1017:15, 1017:17, 1018:10, 1018:15, 1018:24, 1021:4, 1021:10, 1021:14, 1021:17, 1021:20, 1025:15, 1025:22, 1025:23, 1026:8

patent's [1] - 848:11

patentably [3] - 867:23, 868:2, 870:18

patenting [7] - 843:12, 867:21, 879:23, 888:11, 926:19, 926:20, 1027:8

patents [66] - 794:18, 797:20, 797:21, 797:24, 798:9, 799:25, 843:18, 843:22, 844:3, 844:4, 844:7, 844:11, 845:22, 846:24, 848:6, 848:19, 853:3, 855:12, 855:13, 855:16, 855:17, 856:4, 859:16, 861:6, 870:14, 870:18, 889:24, 894:17, 936:11, 936:12, 936:13, 937:11, 939:10, 941:21, 979:1, 987:18, 988:3, 988:19, 991:18, 1014:12, 1014:20, 1015:9, 1016:17, 1016:18, 1017:4, 1017:17, 1019:7, 1019:22, 1019:23, 1020:1, 1020:4, 1020:8, 1020:10, 1020:11, 1020:14, 1020:19, 1021:8, 1021:25, 1022:7, 1022:9, 1026:16, 1027:5, 1027:9, 1027:12

patents' [1] - 852:21

patents-in-suit [3] - 991:18, 1020:19, 1027:5

patents-in-suits [1] - 1016:17

pathway [3] - 952:20, 952:21, 995:8

pathways [8] - 993:3, 994:1, 994:24, 995:2, 995:6, 995:10, 995:11

patient [12] - 956:13, 971:2, 983:5, 986:15, 986:16, 998:12, 1007:16, 1008:23, 1009:2, 1009:13, 1010:14, 1010:22

patient's [2] - 1008:3, 1011:5

patients [111] - 741:5, 741:18, 895:2, 940:10, 940:12, 941:1, 942:10, 943:9, 945:4, 945:5, 945:14, 945:18, 947:9, 947:23, 947:24, 948:23, 949:8, 949:9, 949:11, 949:12, 949:13, 949:14, 949:19, 949:20, 950:5, 950:17, 950:18, 950:25, 951:5, 951:13, 951:20, 952:3, 952:13, 953:25, 954:3, 954:14, 954:15, 954:22, 955:16, 955:18, 956:16, 957:6, 957:12, 957:19, 958:3, 958:13, 958:21, 959:6, 959:23, 960:3, 960:9, 960:25, 961:2, 961:6, 961:7, 961:25, 962:5, 962:10, 965:25, 966:4, 966:23, 967:13, 967:16, 967:17, 967:21, 968:7, 968:12, 968:13, 969:16, 970:3, 970:6, 972:22, 973:23, 973:25, 974:5, 979:13, 980:1, 980:4, 980:6, 980:15, 986:16, 991:2, 993:22, 996:3, 996:5, 996:6, 999:3, 1000:3, 1002:15, 1002:19, 1003:13, 1004:11, 1004:16, 1005:1, 1005:8, 1005:11, 1005:16, 1005:17, 1006:21, 1006:25, 1007:3, 1009:6, 1009:20, 1010:4, 1023:4, 1023:5, 1023:13, 1026:18, 1026:23

pattern [5] - 846:10, 852:7, 853:12, 856:23, 865:2

Paulekuhn [3] - 821:22, 822:2, 823:1

pazopanib [9] - 963:15, 965:8, 966:3, 968:1, 969:3, 969:7, 969:23, 971:5

PD [1] - 952:18

PD-1 [1] - 945:22

PD-L1 [1] - 952:18

PD1 [1] - 952:19

PDF [1] - 733:16

PDX [9] - 751:2, 758:3, 808:17, 809:22, 813:4, 817:14, 869:25, 873:25, 889:17

PDX-10 [1] - 856:15

PDX-11 [1] - 858:8

PDX-12 [1] - 859:23

PDX-13 [1] - 860:7

PDX-14 [1] - 861:14

PDX-15 [1] - 861:24

PDX-16 [1] - 864:24

PDX-17 [1] - 866:8

PDX-18 [1] - 866:14

PDX-19 [1] - 868:4

PDX-2 [1] - 840:15

PDX-22 [1] - 874:9

PDX-23 [1] - 875:11

PDX-24 [1] - 877:7

PDX-25 [1] - 879:5

PDX-26 [1] - 879:20

PDX-27 [1] - 880:1

PDX-28 [1] - 880:9

PDX-29 [1] - 881:18

PDX-3 [1] - 843:7

PDX-32 [1] - 883:11

PDX-33 [1] - 883:24

PDX-34 [1] - 884:7

PDX-35 [1] - 885:9

PDX-36 [1] - 885:17

PDX-37 [1] - 888:8

PDX-38 [1] - 888:14

PDX-39 [1] - 894:3

PDX-4 [1] - 843:14

PDX-4.10 [1] - 750:20

PDX-4.15 [2] - 772:19, 777:21

PDX-5 [1] - 844:13

PDX-5.11 [1] - 810:10

PDX-5.14 [2] - 818:4, 818:11

PDX-5.15 [1] - 819:6

PDX-5.16 [1] - 824:19

PDX-5.2 [1] - 797:22

PDX-5.3 [1] - 799:15

PDX-5.4 [1] - 800:2

PDX-5.5 [1] - 801:21

PDX-5.6 [1] - 802:16

PDX-5.9 [1] - 809:7

PDX-6 [1] - 845:17

PDX-7 [1] - 846:2

PDX-7.2 [1] - 939:11

PDX-7.3 [1] - 940:15

PDX-7.4 [1] - 942:5

PDX-7.5 [1] - 942:15

PDX-7.6 [1] - 943:5

PDX-7.7 [1] - 954:25

PDX-7.8 [1] - 957:20

PDX-8 [3] - 846:20, 855:2, 856:2

PDX-8.6 [1] - 985:24

PDX-9 [1] - 855:8

peaks [5] - 862:11, 862:12, 863:2, 897:14, 898:6

peer [1] - 991:6

peer-reviewed [1] - 991:6

pembrolizumab [6] - 966:17, 966:25, 967:2, 971:16, 1001:6, 1001:9

pen [1] - 787:13

people [10] - 742:2, 755:6, 755:7, 765:11, 773:15, 957:9, 994:2, 1003:1, 1003:4, 1009:23

per [13] - 716:12, 718:17, 719:7, 719:8, 744:2, 745:19, 779:23, 785:8, 792:3, 796:12, 808:5, 878:1, 879:4

percent [44] - 709:9, 711:12, 711:14, 711:15, 711:16, 716:10, 716:11, 717:14, 735:11, 767:21, 767:24, 767:25, 793:1, 793:5, 795:22, 795:23, 821:13, 821:15, 822:19, 822:23, 876:20, 877:2, 890:20, 890:23, 940:11, 945:10, 947:16, 954:15, 965:25, 966:4, 978:22, 980:15, 981:23, 982:1, 982:7, 983:19, 983:21, 984:2, 984:3, 984:21, 984:22, 985:3

percentage [3] - 876:18, 890:15, 980:12

percentages [1] - 961:4

perfect [1] - 899:11

perform [6] - 794:13, 794:15, 830:15, 884:10, 937:5, 1000:12

performance [11] -

798:18, 897:3, 981:9, 1019:17, 1021:18, 1021:19, 1021:20, 1022:10, 1022:15, 1022:19, 1025:23
performed [4] - 970:2, 973:3, 1001:21, 1014:11
performers [1] - 983:9
performing [4] - 802:22, 830:12, 954:21, 1026:7
perhaps [3] - 745:19, 760:5, 920:6
period [12] - 822:24, 980:14, 983:18, 983:20, 984:1, 984:8, 984:9, 993:25, 1006:6, 1008:25, 1017:17, 1017:21
periods [1] - 949:18
permeability [5] - 729:23, 877:13, 877:19, 878:8, 878:21
permeable [1] - 877:23
permission [1] - 987:10
person [113] - 709:19, 721:4, 724:12, 738:9, 740:2, 748:11, 750:5, 750:11, 750:12, 751:7, 751:17, 752:20, 754:18, 755:13, 757:16, 758:17, 759:16, 761:7, 761:19, 763:6, 764:17, 766:13, 766:20, 768:5, 769:16, 769:25, 770:12, 770:16, 771:9, 771:17, 777:13, 794:12, 800:5, 800:10, 804:6, 805:16, 808:20, 813:5, 828:13, 829:6, 835:16, 838:21, 844:10, 844:15, 844:16, 844:25, 845:10, 848:10, 849:10, 849:22, 850:5, 852:9, 852:12, 852:20, 856:11, 856:18, 857:1, 857:9, 857:13, 857:14, 857:16, 868:13, 872:21, 873:9, 873:11, 874:13, 875:13, 876:15, 878:11, 878:18, 878:24, 879:7, 879:9, 880:4, 881:2, 881:3, 881:7, 881:8, 881:11, 881:14, 882:8, 882:17, 883:15, 883:19, 883:20, 884:10, 884:17, 884:21, 885:13, 891:4, 891:11, 893:23, 897:9, 905:5, 905:10, 905:13, 906:3, 927:10, 931:20, 932:3, 932:6, 932:14, 932:22, 932:25, 933:3, 933:8, 933:25, 934:24, 936:1, 936:4, 936:8, 937:3, 937:5
personal [2] - 814:14, 1005:7
personally [1] - 1030:15
persons [8] - 760:10, 763:21, 770:25, 771:3, 771:6, 773:15, 832:11, 835:19
perspective [1] - 954:8
pertain [1] - 981:10
pertains [3] - 978:14, 1014:12, 1027:4
pH [3] - 760:22, 921:20, 932:16
Ph.D [3] - 705:22, 841:2, 1013:3
Pharmaceutical [4] - 774:12, 774:18, 834:6, 836:13
pharmaceutical [88] - 711:19, 712:18, 721:6, 728:10, 733:2, 736:24, 737:24, 738:19, 746:1, 746:8, 749:18, 751:9, 751:16, 762:17, 772:17, 772:23, 773:2, 773:5, 773:18, 773:21, 773:22, 774:25, 775:25, 777:4, 777:7, 787:24, 798:5, 798:21, 799:11, 799:19, 799:22, 800:19, 814:23, 818:2, 819:8, 820:4, 820:5, 821:12, 821:16, 822:14, 823:18, 824:21, 824:23, 835:12, 836:16, 837:8, 837:11, 841:25, 842:3, 842:5, 842:25, 843:2, 844:18, 844:19, 848:23, 849:14, 849:21, 850:1, 851:10, 860:16, 861:1, 870:9, 871:12, 883:23, 885:15, 889:5, 894:10, 896:19, 919:18, 920:7, 920:10, 922:21, 923:2, 924:6, 924:11, 924:24, 924:25, 926:22, 927:14, 927:16, 927:25, 930:3, 930:7, 958:21, 1013:11
pharmaceutically [22] - 774:22, 821:5, 823:11, 829:15, 831:11, 860:12, 860:23, 869:21, 869:22, 871:19, 871:23, 871:24, 872:1, 872:8, 872:11, 872:19, 873:10, 873:18, 873:21, 887:17, 888:4, 927:6
pharmaceuticals [2] - 818:23, 1023:20
Pharmorphix [2] - 805:2, 808:3
Phase [6] - 950:4, 951:18, 952:11, 969:8, 999:25, 1003:12
phosphoric [1] - 815:12
phosphorylation [1] - 993:3
phrase [4] - 767:11, 783:11, 848:2, 852:8
phrasing [1] - 751:20
physical [7] - 713:13, 802:5, 825:5, 851:5, 860:21, 896:24, 917:10
physically [1] - 763:18
physician [1] - 990:11
physicians [2] - 999:17, 1002:18
Physicians [1] - 990:20
physicians' [1] - 1026:22
physicochemical [6] - 729:14, 729:18, 729:21, 730:10, 732:22, 739:17
Physics [1] - 810:22
physiochemical [2] - 753:18, 753:23
pick [1] - 969:11
picture [4] - 846:12, 846:17, 846:18, 939:14
pictured [1] - 983:6
piece [1] - 740:10
pieces [2] - 734:8, 961:3
PIROZZOLO [92] - 705:21, 706:17, 706:21, 707:2, 707:4, 707:9, 707:11, 708:3, 708:7, 710:12, 710:14, 711:23, 711:25, 712:13, 712:14, 713:20, 713:22, 714:23, 715:1, 715:5, 715:8, 715:24, 716:1, 718:13, 718:21, 718:25, 719:20, 719:22, 720:1, 720:3, 720:15, 720:17, 722:16, 722:17, 722:21, 722:22, 724:18, 724:20, 726:25, 727:3, 729:3, 729:5, 731:3, 731:5, 731:25, 732:2, 733:15, 733:17, 734:20, 734:22, 735:24, 736:1, 736:6, 736:8, 737:16, 737:18, 738:14, 738:15, 742:20, 749:2, 795:9, 795:11, 795:14, 796:21, 796:24, 976:15, 976:25, 977:9, 977:11, 978:5, 978:12, 978:17, 979:7, 979:9, 979:20, 979:22, 980:18, 980:23, 982:25, 983:2, 984:10, 984:12, 985:8, 985:10, 986:22, 989:1, 1013:20, 1025:9, 1026:12, 1026:14, 1027:14, 1028:14
Pirozzolo [1] - 1026:10
pivotal [1] - 950:1
PK [1] - 825:5
pKa [30] - 803:10, 803:16, 803:23, 804:8, 809:18, 811:12, 811:22, 811:23, 812:7, 812:11, 812:23, 813:1, 824:10, 824:13, 829:21, 830:1, 830:11, 830:19, 830:21, 831:1, 835:8, 835:9, 838:5, 838:12, 932:8, 932:16, 933:4, 933:10, 933:15
pKas [1] - 817:20
place [4] - 775:19, 777:20, 899:7, 983:22
placed [1] - 998:1
places [7] - 777:12, 788:12, 788:14, 858:12, 878:3, 983:12, 983:13
placing [1] - 776:14
plain [4] - 853:8, 853:22, 859:7, 859:13
plainly [2] - 857:11, 914:18
Plaintiff [2] - 705:5, 705:23
Plaintiff's [31] - 714:24, 715:6, 715:25, 718:13, 718:21, 720:15, 725:13, 732:25, 735:24, 740:15, 795:12, 796:25, 977:9, 978:5, 979:8, 979:20, 979:23, 980:18, 981:15, 982:25, 984:10, 985:8, 986:24, 986:25, 987:1,

987:2, 989:1, 1022:4
plaintiffs [1] - 1024:24
Plaintiffs [4] - 839:15, 895:4, 976:15, 1030:25
plan [1] - 1014:2
Planck [1] - 841:5
planned [9] - 717:1, 717:14, 791:8, 791:17, 791:20, 791:21, 791:24, 791:25
play [6] - 860:23, 936:18, 959:21, 961:7, 995:8, 1010:24
played [1] - 1018:8
playing [1] - 961:2
plays [3] - 877:16, 877:20, 1011:1
plus [10] - 773:6, 951:19, 952:1, 952:12, 970:19, 971:16, 999:4, 1001:6, 1001:7, 1001:20
podium [1] - 1030:8
point [49] - 712:15, 713:15, 734:23, 736:11, 753:8, 759:20, 760:2, 760:17, 766:23, 770:14, 790:7, 791:1, 805:24, 808:23, 845:21, 845:22, 863:5, 863:23, 866:10, 870:7, 874:10, 880:21, 883:8, 884:1, 884:8, 889:1, 889:11, 889:12, 899:7, 925:18, 925:20, 925:25, 926:1, 926:3, 929:5, 954:16, 970:11, 993:22, 1001:1, 1001:2, 1014:15, 1017:15, 1023:11, 1023:17, 1024:23, 1025:13
pointed [7] - 731:14, 744:15, 779:21, 780:1, 785:11, 949:3, 967:5
pointer [1] - 862:8
pointing [1] - 785:16
points [3] - 919:1, 1024:20, 1025:2
polymorph [13] - 852:6, 857:14, 898:7, 906:4, 907:19, 912:7, 914:3, 922:18, 923:25, 924:16, 924:23, 925:2, 937:5
polymorphic [21] - 852:15, 853:1, 857:15, 862:13, 864:21, 865:16, 865:18, 896:17, 900:24, 902:18, 902:24, 904:23, 905:14, 905:19, 906:9, 912:9, 917:13, 919:18, 919:22, 919:25, 923:8
polymorphs [26] - 854:24, 860:14, 871:9, 896:20, 906:12, 907:13, 908:20, 909:14, 910:25, 917:6, 917:12, 918:9, 918:15, 918:19, 918:20, 920:17, 922:14, 924:5, 924:6, 924:17, 926:7, 935:21, 937:7, 937:9
poor [11] - 877:4, 877:9, 877:11, 947:24, 948:10, 951:13, 956:16, 966:23, 970:2, 999:9, 999:16
poorly [4] - 730:19, 798:13, 798:19
population [3] - 956:14, 956:15, 970:3
portion [4] - 872:5, 892:2, 935:13, 940:9
POSA [30] - 744:24, 745:7, 748:17, 754:4, 754:7, 754:16, 761:7, 761:15, 763:17, 764:22, 765:20, 768:23, 803:1, 809:2, 810:2, 812:13, 812:15, 813:7, 816:8, 817:17, 824:2, 826:1, 830:7, 830:11, 832:23, 836:16, 844:21, 878:19, 880:17, 922:3
POSAs [1] - 830:14
position [2] - 840:20, 982:5
positive [3] - 724:10, 768:12, 771:24
possess [1] - 857:25
possessed [3] - 857:23, 867:17, 936:25
possession [1] - 936:19
possibility [1] - 920:3
possible [4] - 712:24, 798:23, 975:15, 976:2
post [1] - 841:4
post-doctoral [1] - 841:4
potency [7] - 877:13, 877:15, 877:18, 878:8, 878:21, 920:2, 920:4
potential [16] - 725:20, 727:12, 757:8, 766:9, 799:5, 801:17, 818:14, 872:23, 873:16, 881:4, 881:16, 882:16, 883:5, 889:8, 928:6, 1002:4
potentially [12] - 713:12, 765:11, 768:24, 771:11, 771:19, 799:7, 807:7, 816:22, 825:6, 830:13, 881:13, 960:9
powder [2] - 824:9, 857:17
powdered [1] - 862:6
powered [1] - 1000:11
PPM [24] - 712:19, 713:18, 714:22, 715:15, 715:19, 715:21, 716:8, 716:9, 716:10, 735:11, 739:6, 744:4, 744:16, 755:19, 755:20, 756:2, 756:3, 783:2, 783:3, 784:23
ppms [1] - 719:15
practically [2] - 876:25, 877:1
Practice [1] - 947:2
practice [13] - 733:25, 740:16, 869:8, 869:10, 947:7, 977:21, 978:25, 990:19, 990:21, 997:10, 997:11, 1009:6, 1025:21
practiced [1] - 714:17
practices [1] - 1026:16
practicing [2] - 990:13, 990:24
pre [1] - 754:4
pre-formulation [1] - 754:4
precise [6] - 788:6, 788:9, 788:12, 788:15, 789:2, 918:14
predict [7] - 828:4, 889:4, 905:10, 905:13, 905:24, 906:4, 921:11
predictable [2] - 808:15, 935:17
predicted [4] - 740:2, 803:21, 804:7, 885:16
predicting [2] - 767:20, 887:8
predictive [2] - 825:22, 884:19
prefer [3] - 778:13, 778:14, 782:1
preferable [1] - 1009:17
preferred [16] - 848:22, 893:25, 947:25, 948:6, 966:15, 966:18, 967:6, 967:9, 967:21, 997:22, 998:11, 998:25, 999:8, 999:13, 999:16, 1010:3
preformulation [2] - 762:7, 762:12
prep [1] - 839:6
preparation [8] - 720:11, 774:23, 798:20, 799:19, 815:23, 920:16, 922:14, 977:25
preparative [3] - 858:15, 858:17, 858:18
prepare [6] - 826:4, 839:8, 903:22, 976:1, 985:23, 1014:1
prepared [10] - 776:4, 776:8, 776:13, 777:8, 862:17, 910:10, 921:18, 943:3, 989:20, 1012:10
preparing [1] - 922:6
prescribe [12] - 943:8, 954:12, 954:13, 954:17, 958:3, 967:14, 967:22, 968:12, 986:15, 1007:5, 1007:8, 1026:23
prescribed [6] - 943:16, 965:24, 966:3, 966:21, 973:23, 1006:20
prescribing [4] - 944:12, 960:3, 961:5, 999:17
prescriptions [4] - 980:12, 982:6, 986:17, 1026:24
presence [4] - 730:18, 758:20, 910:3, 910:6
Present [1] - 706:9
present [15] - 710:23, 711:2, 863:11, 863:14, 863:21, 864:3, 867:5, 867:7, 867:9, 867:12, 867:15, 931:1, 991:24, 1014:23, 1015:1
present-day [1] - 931:1
presentation [1] - 707:10
presented [8] - 820:15, 863:19, 864:4, 930:24, 959:11, 986:19, 1022:25, 1024:6
presents [1] - 845:21
president [1] - 977:20
presiding [1] - 706:14
press [1] - 734:12
pressure [2] - 919:14, 959:2
pressures [1] - 734:12
presume [1] - 882:20
pretty [4] - 767:20, 767:21, 767:23, 985:17
prevented [1] - 1008:2
preventing [1] - 1008:11
previous [5] - 852:23, 865:8, 952:14, 960:11, 993:19
previously [9] - 805:3, 810:2, 950:17, 952:4, 961:25, 962:10, 1000:3, 1013:15

primarily [2] - 865:12, 1024:21
primary [1] - 841:13
Princeton [1] - 1013:3
principally [1] - 998:14
principle [2] - 829:25, 830:1
principles [1] - 827:7
priority [26] - 797:25, 798:1, 831:20, 837:24, 844:7, 844:8, 845:9, 856:11, 857:1, 869:11, 869:12, 873:22, 874:20, 875:2, 875:5, 876:16, 878:6, 879:12, 887:18, 887:24, 921:11, 926:22, 1016:13, 1016:18, 1016:19, 1017:16
PRIVATE [1] - 705:7
problem [8] - 734:6, 737:1, 794:10, 796:6, 796:9, 801:16, 1020:16, 1022:6
problematic [1] - 723:2
problems [5] - 734:7, 798:24, 842:11, 874:15, 887:25
procedure [2] - 787:12, 807:3
proceed [8] - 840:1, 843:4, 938:21, 941:15, 961:17, 978:16, 991:15, 1013:21
proceeding [2] - 828:24, 1031:10
PROCEEDINGS [1] - 706:11
Process [1] - 743:14
process [78] - 707:17, 707:18, 709:8, 709:16, 709:20, 709:21, 710:6, 711:1, 711:8, 712:4, 712:22, 713:17, 714:20, 715:14, 715:18, 715:21, 716:4, 716:15, 716:23, 716:24, 719:6, 719:10, 719:15, 719:18, 722:13, 730:9, 734:25, 735:21, 735:22, 738:2, 738:13, 739:3, 740:25, 744:25, 745:3, 753:17, 753:20, 754:4, 755:1, 755:7, 760:3, 762:17, 764:20, 766:23, 773:10, 782:21, 782:24, 783:14, 785:25, 787:7, 789:5, 789:6, 790:4, 790:11, 791:6, 795:25, 796:4, 796:10, 796:13, 796:17, 814:4, 824:21, 841:21, 844:23, 906:22, 907:6, 907:9, 908:6, 908:12, 910:20, 912:1, 946:10, 947:10, 1008:7, 1008:13, 1025:19
processes [18] - 709:11, 709:12, 716:22, 743:10, 777:9, 778:19, 779:5, 786:7, 786:16, 787:5, 787:17, 787:22, 788:1, 793:12, 793:16, 796:2, 858:20, 911:1
processing [3] - 740:8, 758:21, 837:1
produce [5] - 717:21, 719:10, 737:14, 740:25, 949:1
produced [1] - 804:7
produces [3] - 714:21, 782:15, 1025:19
producing [1] - 718:17
product [80] - 709:7, 712:23, 713:1, 713:4, 720:21, 722:4, 722:10, 729:13, 733:25, 737:12, 738:11, 739:9, 740:10, 741:2, 741:15, 742:2, 742:16, 752:7, 752:10, 752:25, 753:2, 753:11, 754:8, 759:9, 760:21, 761:2, 763:9, 768:19, 768:22, 773:5, 801:19, 817:1, 823:16, 885:25, 897:3, 925:15, 926:17, 927:14, 927:16, 927:25, 937:19, 943:8, 960:25, 975:13, 976:1, 978:18, 979:6, 979:18, 980:2, 982:11, 983:25, 984:8, 985:13, 986:12, 986:15, 1007:12, 1007:21, 1008:2, 1013:13, 1014:13, 1018:16, 1019:6, 1019:16, 1020:7, 1020:22, 1021:6, 1022:15, 1022:19, 1023:3, 1023:8, 1023:14, 1023:20, 1023:25, 1024:11, 1024:13, 1024:25, 1026:3, 1026:7, 1026:16
production [2] - 733:24, 774:24
Products [1] - 876:9
products [43] - 727:13, 727:16, 740:15, 740:16, 742:9, 754:13, 754:19, 754:23, 755:2, 755:10, 755:15, 755:18, 757:18, 757:24, 758:10, 758:18, 759:17, 760:19, 761:12, 761:18, 761:21, 798:7, 818:1, 824:24, 862:5, 958:16, 959:12, 975:23, 977:8, 978:20, 978:24, 979:14, 980:7, 981:4, 981:5, 981:6, 982:13, 983:6, 983:8, 983:11, 1016:21, 1019:24
products' [1] - 980:8
professional [6] - 842:22, 978:10, 1012:14, 1012:18, 1012:19, 1013:4
professor [6] - 840:21, 840:22, 841:7, 939:21, 990:18, 1013:8
proffer [3] - 895:4, 991:11, 1013:17
proffered [1] - 800:6
profile [5] - 796:3, 964:13, 974:8, 994:10, 1004:23
profit [2] - 941:1, 986:1
profits [2] - 1023:22, 1023:24
profound [3] - 993:15, 994:1, 1010:23
profusely [1] - 836:25
prognostic [1] - 947:22
program [2] - 801:20, 992:14
programs [1] - 798:22
progressing [2] - 955:18, 956:17
progression [13] - 754:3, 808:11, 948:22, 950:14, 951:11, 952:2, 952:14, 953:7, 955:22, 955:25, 968:23, 1000:7, 1000:18
progression-free [3] - 968:23, 1000:7, 1000:18
project [2] - 733:13, 753:22
projects [1] - 823:6
proliferate [1] - 992:13
proliferation [1] - 995:12
prolonging [1] - 957:15
prominent [1] - 995:11
promote [1] - 1007:21
properly [1] - 918:8
properties [72] - 720:10, 729:14, 729:19, 729:21, 730:11, 732:19, 732:22, 733:14, 734:10, 739:10, 739:17, 739:22, 739:25, 802:5, 804:7, 804:18, 805:20, 805:22, 805:23, 808:9, 808:10, 809:5, 810:6, 815:20, 817:3, 824:11, 828:10, 848:23, 848:25, 849:6, 849:15, 849:18, 850:1, 850:7, 850:12, 850:16, 851:6, 851:7, 851:8, 851:10, 851:20, 859:3, 860:15, 860:17, 860:18, 880:16, 881:21, 881:23, 883:22, 885:15, 885:16, 885:19, 885:21, 886:22, 887:21, 888:20, 888:21, 888:25, 889:3, 889:5, 889:7, 889:16, 889:20, 911:12, 917:6, 917:10, 917:15, 917:19, 918:6, 919:5, 919:25, 926:12
property [5] - 854:24, 901:14, 977:20, 1017:2, 1017:6
proposed [1] - 814:7
prosecution [2] - 892:2, 892:24
prostate [1] - 939:20
protection [1] - 1017:12
protein [3] - 945:22, 952:18, 952:19
proteins [1] - 992:12
prototype [1] - 814:4
provide [15] - 726:13, 734:16, 741:15, 815:9, 817:4, 894:23, 923:8, 975:22, 978:9, 992:2, 1012:24, 1013:10, 1014:7, 1017:21, 1019:6
provided [11] - 727:14, 738:21, 805:9, 851:16, 889:3, 903:25, 912:19, 997:20, 1005:3, 1017:14, 1019:18
provides [5] - 726:21, 775:25, 805:10, 954:2, 986:12
providing [3] - 806:7, 884:21, 913:18
Provisional [1] - 876:8
proviso [1] - 905:18
PRUSSIA [142] - 705:20, 839:15, 840:1, 840:3, 840:15, 840:16, 842:24, 843:5, 843:7, 843:8, 843:13, 843:15, 844:13, 844:14,

845:17, 845:18, 846:2, 846:3, 846:20, 846:21, 847:5, 847:8, 847:11, 847:13, 847:16, 847:18, 847:24, 848:1, 848:15, 848:16, 850:9, 850:11, 850:18, 850:21, 854:5, 854:7, 854:9, 854:13, 855:1, 855:3, 855:8, 855:9, 856:2, 856:5, 856:15, 856:16, 858:7, 858:9, 858:24, 858:25, 861:14, 861:15, 861:23, 861:25, 863:22, 863:24, 864:15, 864:20, 864:24, 864:25, 866:8, 866:9, 866:14, 866:15, 868:4, 868:5, 868:20, 868:22, 869:15, 869:17, 869:25, 870:1, 872:2, 872:4, 872:16, 872:17, 873:25, 874:2, 874:9, 874:11, 875:11, 875:12, 876:2, 876:4, 876:13, 876:14, 879:5, 879:6, 879:19, 879:21, 880:1, 880:2, 880:9, 880:10, 881:18, 881:19, 882:9, 882:11, 883:11, 883:13, 883:24, 883:25, 884:7, 884:9, 885:9, 885:10, 885:17, 885:18, 886:2, 886:5, 887:14, 887:15, 888:8, 888:9, 888:14, 888:15, 889:17, 890:3, 890:6, 890:10, 890:12, 891:20, 891:22, 891:25, 892:1, 892:4, 892:5, 893:4, 893:6, 893:10, 893:12, 893:15, 893:18, 894:3, 894:5, 895:3, 935:5, 935:7, 938:6, 1028:21, 1029:9, 1030:25

Prussia [1] - 889:18

pseudodimerism [2] - 882:5, 889:9

PTX [7] - 797:5, 826:16, 895:13, 929:11, 944:10, 961:15, 987:6

PTX-0035 [1] - 778:12

PTX-0087 [1] - 804:24

PTX-1 [2] - 944:4, 944:8

PTX-16 [1] - 864:20

PTX-225 [1] - 890:5

PTX-252 [1] - 868:20

PTX-283 [1] - 895:6

PTX-299 [1] - 796:25

PTX-327 [1] - 886:2

PTX-35 [1] - 778:8

PTX-363 [2] - 949:23, 961:11

PTX-366 [2] - 950:20, 961:12

PTX-367 [2] - 951:15, 961:12

PTX-373 [2] - 810:20, 826:13

PTX-38 [1] - 783:22

PTX-421 [1] - 893:5

PTX-470 [2] - 952:6, 961:12

PTX-494 [1] - 797:1

PTX-528 [6] - 946:22, 946:25, 961:11, 966:7, 997:13, 1002:23

PTX-610 [3] - 833:2, 929:4, 929:12

PTX-625 [1] - 876:2

PTX-774 [1] - 842:18

PTX-775 [2] - 941:4, 961:11

PTX-782 [5] - 820:12, 820:21, 820:24, 821:3, 826:13

PTX-802 [1] - 985:25

publication [8] - 949:25, 950:23, 951:18, 952:10, 1015:15, 1015:18, 1016:14, 1017:9

publications [1] - 941:9

published [4] - 749:23, 991:4, 991:6, 1015:18

pull [25] - 713:20, 719:20, 720:15, 731:25, 795:12, 797:22, 809:7, 812:10, 833:2, 854:5, 868:20, 887:14, 898:25, 899:4, 941:4, 966:7, 966:8, 979:7, 990:1, 997:13, 1012:15, 1015:3, 1015:12, 1015:22, 1020:2

pulled [4] - 791:13, 791:17, 829:2, 959:17

Purdue [1] - 977:16

pure [2] - 818:22, 870:16

purer [3] - 717:15, 785:20, 789:11

purest [1] - 717:12

purification [10] - 709:11, 709:12, 721:19, 721:20, 735:16, 738:7, 757:9, 793:4, 793:6

purify [1] - 738:8

purities [2] - 711:1, 711:14

purity [14] - 710:22, 711:15, 715:12, 735:23, 789:10, 792:6, 794:1, 794:3, 794:4, 794:7, 796:3, 796:18, 849:3, 849:20

purported [8] - 860:3, 861:17, 861:20, 862:21, 863:2, 863:5, 865:2, 867:12

purpose [5] - 717:9, 728:15, 799:12, 943:23, 978:1

purposes [8] - 714:10, 747:19, 751:17, 755:11, 924:6, 924:24, 928:9, 978:21

pursue [15] - 801:14, 810:13, 812:14, 825:18, 868:10, 868:13, 874:1, 874:13, 875:14, 879:8, 879:24, 881:22, 911:20, 1018:17, 1023:13

pursued [1] - 851:17

pursuing [3] - 799:5, 1014:21, 1018:16

put [45] - 706:18, 707:9, 708:5, 722:16, 722:21, 723:7, 726:25, 729:3, 731:3, 750:16, 750:19, 751:11, 755:17, 756:6, 756:7, 756:8, 758:2, 770:13, 772:18, 778:8, 778:9, 780:20, 781:6, 783:21, 789:7, 819:12, 826:24, 832:20, 833:4, 858:24, 862:14, 899:3, 913:3, 922:24, 929:3, 931:10, 961:3, 970:18, 977:9, 978:5, 980:18, 982:25, 983:8, 984:10, 985:8

putative [1] - 916:16

putting [1] - 930:21

Q

Q3A [1] - 756:18

qualifications [4] - 844:10, 844:15, 845:10, 1012:20

qualified [3] - 763:22, 800:10, 818:25

quality [3] - 897:3, 1010:25, 1011:5

quantities [8] - 747:21, 747:24, 748:1, 788:5, 788:7, 788:13, 788:25, 789:3

quarter [7] - 980:2, 981:24, 981:25, 982:2, 984:6, 984:21, 985:3

Quarter [3] - 981:22, 983:11

quarterly [2] - 981:19

quarters [1] - 982:2

questioning [1] - 934:13

questions [20] - 742:21, 792:10, 794:25, 795:16, 796:21, 826:11, 838:1, 859:6, 890:4, 894:2, 926:18, 935:3, 935:8, 937:16, 961:10, 975:3, 976:4, 988:22, 1011:8, 1027:14

quick [3] - 821:19, 970:19, 972:24

quickly [2] - 890:21, 891:5

quinoline [35] - 722:18, 722:24, 723:1, 723:3, 723:16, 723:23, 724:13, 725:1, 725:6, 725:7, 725:10, 725:11, 725:20, 726:14, 726:18, 769:1, 769:4, 769:5, 769:6, 769:8, 769:23, 770:1, 770:3, 770:6, 770:9, 770:13, 771:11, 771:19, 811:10, 811:12, 811:14, 812:11, 812:12, 812:14

quinoline-containing [1] - 812:14

quinolines [12] - 722:25, 723:1, 723:20, 725:25, 726:4, 726:7, 726:11, 769:20, 769:21, 830:18, 830:25, 831:2

quite [13] - 737:1, 737:2, 761:23, 803:1, 804:13, 838:7, 842:4, 857:11, 858:13, 870:4, 875:22, 884:4, 908:22

quote [3] - 758:24, 786:14, 922:11

quote/unquote [1] - 973:11

quoted [1] - 920:20

quotes [1] - 872:10

quoting [1] - 790:13

R

R-O-B-E-R-T [1] - 1011:23

race [2] - 1018:14, 1018:18

randomized [3] - 999:25, 1003:12, 1003:15

randomness [1] - 846:17

range [11] - 779:18, 779:23, 788:10, 799:23, 824:22, 846:16, 920:12, 922:12, 983:21, 984:3, 1024:3

ranked [2] - 820:17,

984:5
rapid [2] - 890:22, 891:19
rapidly [1] - 956:17
rarely [3] - 809:3, 819:13, 823:2
rate [6] - 882:21, 891:13, 893:21, 894:1, 951:12, 957:7
rates [2] - 1000:18, 1002:10
rather [3] - 1005:25, 1026:4, 1029:2
Rationale [1] - 757:3
rationale [1] - 882:24
RAUCCI [1] - 705:17
ray [2] - 857:17, 862:5
RCC [39] - 945:8, 962:5, 962:10, 962:13, 962:15, 965:6, 965:10, 965:16, 965:25, 966:4, 966:14, 967:13, 968:18, 969:4, 969:24, 970:6, 970:16, 971:6, 972:18, 972:21, 973:25, 980:16, 981:12, 983:4, 983:16, 996:2, 996:9, 996:16, 996:23, 997:2, 998:12, 999:1, 999:21, 1002:13, 1003:9, 1003:19, 1004:11, 1004:16, 1005:21
re [2] - 864:12, 1024:19
re-asked [1] - 864:12
re-summarize [1] - 1024:19
reach [5] - 822:25, 862:24, 865:6, 875:25, 891:1
reached [1] - 881:3
react [4] - 814:25, 828:18, 882:6, 928:13
reacted [1] - 807:2
reaction [3] - 758:20, 801:25, 804:14
reactions [4] - 806:25, 817:24, 827:8, 827:9
reactor [1] - 841:20
reacts [1] - 928:16
read [18] - 714:1, 813:19, 814:1, 814:12, 824:7, 851:22, 852:17, 859:15, 892:11, 894:13, 901:3, 901:8, 901:9, 912:3, 913:7, 950:11, 951:8, 1029:20
readily [1] - 814:25
reading [4] - 758:7, 775:18, 873:9, 1029:16
ready [4] - 777:16, 913:13, 913:14, 1030:22
Real [1] - 1031:11
real [5] - 910:24, 958:5, 970:19, 972:24, 973:17
Real-Time [1] - 1031:11
real-world [1] - 910:24
realized [1] - 1026:25
really [31] - 710:21, 725:10, 728:14, 732:19, 747:5, 770:20, 818:23, 934:25, 947:7, 948:25, 949:10, 949:14, 951:4, 953:19, 954:2, 955:12, 956:21, 957:19, 967:16, 967:19, 993:13, 993:15, 994:1, 1000:10, 1004:6, 1005:25, 1023:21, 1029:15, 1029:19, 1030:6
reason [19] - 737:11, 755:22, 780:10, 787:10, 810:12, 813:4, 815:18, 859:15, 860:8, 861:16, 875:13, 875:20, 879:7, 879:22, 885:11, 888:10, 956:9, 956:11, 973:18
Reasonable [1] - 734:20
reasonable [18] - 737:6, 737:10, 738:1, 738:17, 738:23, 803:2, 806:13, 825:10, 825:25, 826:2, 826:8, 868:14, 873:8, 883:15, 884:2, 885:12, 922:4, 922:6
reasonably [2] - 812:21, 827:9
reasoning [2] - 868:19, 884:17
reasons [25] - 721:10, 728:23, 735:7, 804:1, 807:18, 808:24, 814:20, 815:14, 818:20, 819:10, 857:24, 859:24, 868:6, 873:14, 874:12, 874:21, 874:24, 875:19, 877:8, 880:11, 885:1, 889:2, 891:3, 931:14, 956:5
rebuttal [3] - 913:4, 913:9, 920:25
recap [1] - 867:16
receive [3] - 946:17, 969:16, 999:3
received [14] - 780:18, 940:17, 945:14, 945:18, 946:14, 965:16, 973:11, 974:12, 977:17, 982:12, 996:17, 1003:1, 1003:5, 1003:13
receiving [3] - 945:18, 954:3, 954:15
recent [3] - 725:19, 948:19, 985:19
recently [1] - 940:20
receptor [2] - 952:19, 958:24
recess [1] - 895:21
Recess [3] - 795:5, 895:23, 976:12
recessed [1] - 1031:7
recognize [3] - 810:5, 816:8, 867:1
recognized [6] - 818:15, 832:2, 837:23, 916:4, 934:6, 940:21
recommend [1] - 967:25
recommendation [2] - 948:8, 948:9
recommendations [7] - 812:7, 947:21, 948:1, 948:2, 948:6, 997:20, 997:21
recommended [12] - 727:11, 792:23, 793:3, 966:12, 968:6, 997:22, 998:11, 999:14, 1002:18, 1003:7, 1010:1
record [16] - 751:2, 787:9, 787:12, 787:18, 787:21, 831:10, 839:19, 938:14, 951:9, 976:18, 980:1, 981:1, 989:7, 989:23, 1001:13, 1011:21
recover [1] - 804:22
recrystallization [11] - 734:25, 735:7, 738:2, 738:12, 792:14, 792:17, 793:13, 793:21, 794:16, 794:19, 796:17
recrystallize [1] - 737:14
recrystallizing [2] - 736:14, 737:7
red [10] - 769:16, 870:9, 983:14, 983:16, 983:23, 984:19, 984:25, 1016:1, 1016:10, 1016:11
Reddy [1] - 706:10
redirect [6] - 795:7, 839:11, 935:4, 976:5, 1027:17, 1027:18
REDIRECT [2] - 795:10, 935:6
redissolving [1] - 737:13
reduce [6] - 717:19, 735:10, 735:19, 736:21, 879:17, 1008:19
reduced [3] - 817:21, 869:8, 869:10
reducing [1] - 717:9
reduction [1] - 931:5
refer [6] - 728:1, 813:9, 837:11, 877:24, 958:20, 1020:7
reference [56] - 708:4, 708:8, 731:4, 731:19, 732:24, 733:1, 733:2, 733:9, 734:15, 736:13, 737:25, 738:22, 744:14, 746:14, 746:17, 766:25, 793:9, 793:11, 811:3, 811:10, 812:10, 813:17, 815:22, 816:4, 819:16, 821:19, 821:22, 821:25, 822:3, 826:23, 829:2, 833:5, 833:18, 834:5, 835:18, 850:22, 852:4, 858:15, 862:1, 866:22, 873:5, 873:23, 876:6, 882:19, 886:3, 886:6, 886:14, 892:15, 892:17, 892:20, 904:3, 904:6, 921:17, 932:4, 934:8, 947:8
referenced [5] - 706:21, 717:22, 814:11, 834:1, 933:13
references [7] - 707:8, 707:12, 707:16, 707:21, 707:24, 728:5, 823:1
referred [11] - 708:9, 709:21, 720:16, 731:7, 782:7, 944:13, 945:22, 948:14, 951:2, 996:13, 1001:15
referring [7] - 733:19, 780:16, 834:12, 854:8, 866:23, 1020:5, 1022:25
refers [16] - 708:21, 709:20, 711:7, 719:23, 765:2, 914:2, 923:18, 930:2, 945:9, 945:13, 945:17, 947:15, 947:22, 949:3, 958:16, 964:1
reflect [4] - 873:20, 990:6, 1012:19, 1026:22
reflected [2] - 983:13, 983:19
reflects [4] - 983:4, 983:10, 985:1, 985:12
refractory [1] - 1009:5
refresh [1] - 935:18
refutes [1] - 914:18
reg [1] - 999:12
regard [1] - 979:3
regarded [3] - 931:5, 934:4, 934:8
regarding [36] - 752:4, 807:10, 825:25, 844:9, 850:5, 857:5,

857:20, 857:21, 861:10, 861:17, 865:19, 867:16, 870:25, 871:3, 871:19, 871:23, 874:1, 874:4, 874:21, 874:24, 880:13, 880:19, 881:4, 881:21, 882:12, 883:12, 884:20, 887:21, 887:25, 891:1, 891:16, 893:20, 921:24, 946:23, 995:17, 1021:4
regardless [1] - 845:6
regards [4] - 994:2, 997:6, 999:12, 999:21
regimen [5] - 966:15, 998:1, 999:16, 1001:3, 1004:1
regimens [19] - 947:25, 948:7, 962:9, 966:12, 966:18, 967:9, 967:21, 967:25, 968:6, 968:10, 968:13, 997:22, 999:8, 999:13, 999:14, 1001:10
Regis [25] - 716:5, 716:6, 716:22, 717:16, 718:5, 718:16, 719:18, 720:6, 781:19, 783:15, 785:18, 785:20, 785:21, 789:5, 789:6, 789:11, 789:14, 789:24, 790:4, 790:11, 795:18, 795:21, 795:24
regular [2] - 853:12, 856:23
regularly [2] - 853:18, 943:9
regulate [1] - 992:19
regulates [1] - 992:10
regulations [1] - 818:21
regulators [2] - 768:14
regulatory [5] - 726:22, 946:9, 946:10, 974:15, 975:21
reinforces [1] - 852:23
rejection [2] - 892:12, 893:2
relate [16] - 732:6, 732:9, 737:5, 742:11, 798:10, 857:5, 880:3, 881:20, 884:2, 886:24, 887:10, 891:15, 904:16, 1018:3, 1019:4
related [10] - 764:9, 808:1, 812:6, 812:7, 818:22, 844:18, 854:10, 992:3, 998:7, 1017:12
relates [9] - 732:10, 848:2, 851:25, 852:15, 981:12, 1014:18, 1015:6, 1016:24, 1019:14
relating [2] - 1015:17, 1022:21
relationship [4] - 797:24, 798:9, 893:20, 992:16
relative [4] - 824:14, 825:14, 849:2, 982:7
relatively [3] - 803:13, 907:23, 999:11
release [4] - 728:16, 728:18, 876:18, 877:2
relevant [29] - 717:17, 726:8, 736:14, 741:18, 811:22, 811:23, 832:6, 841:17, 845:25, 859:7, 859:14, 860:12, 860:24, 863:20, 875:21, 875:22, 876:19, 877:14, 877:24, 878:2, 878:22, 893:9, 954:6, 979:15, 986:15, 986:16, 1016:2, 1022:8, 1023:10
reliable [3] - 733:25, 734:13, 887:8
reliance [2] - 863:8, 880:19
relied [3] - 741:11, 863:25, 892:20
relies [1] - 864:17
relying [3] - 741:16, 742:13, 986:10
remain [1] - 1004:14
remaining [1] - 714:14
remains [3] - 1004:18, 1005:23, 1008:7
remember [16] - 706:20, 764:9, 778:12, 778:15, 781:8, 853:19, 854:16, 878:15, 925:4, 926:15, 930:19, 930:21, 934:22, 934:23, 935:13, 967:9
remember.. [1] - 934:22
remind [8] - 798:3, 802:1, 822:12, 958:15, 994:22, 1003:11, 1003:22, 1029:22
Remington [1] - 775:6
removed [1] - 735:20
removing [1] - 793:20
renal [33] - 941:13, 945:1, 945:4, 945:6, 945:8, 945:9, 945:15, 946:15, 947:16, 947:17, 950:5, 950:18, 950:25, 951:5, 951:13, 951:21, 952:4, 952:14, 953:23, 962:25, 980:9, 980:13, 982:10, 982:22, 995:24, 996:5, 1000:2, 1002:2, 1004:22, 1006:7, 1006:13, 1006:21, 1009:11
rendering [2] - 725:14, 740:13
repeat [5] - 715:16, 772:12, 880:7, 920:19, 934:11
repeated [1] - 853:18
repeating [5] - 772:13, 846:10, 852:7, 853:12, 856:23
rephrase [1] - 751:23
report [30] - 793:9, 793:20, 805:2, 861:20, 865:22, 894:13, 894:14, 912:20, 912:22, 913:2, 913:5, 913:9, 913:18, 915:19, 916:1, 916:5, 920:21, 920:25, 921:1, 921:7, 928:19, 929:10, 929:19, 931:15, 931:17, 935:9, 935:13, 935:25, 1024:5, 1024:7
reported [9] - 723:16, 780:15, 874:14, 912:23, 914:9, 915:6, 916:4, 1001:5, 1002:12
reporter [1] - 706:25
Reporter [1] - 1031:11
reporting [1] - 757:3
reports [3] - 792:17, 914:1, 915:15
represent [4] - 822:6, 996:8, 1005:22, 1010:19
representation [1] - 941:8
representative [7] - 716:15, 859:2, 859:16, 860:1, 860:8, 860:13, 911:12
represented [3] - 716:21, 938:3, 993:15
represents [8] - 914:14, 915:7, 978:22, 980:4, 981:19, 996:11, 1005:20, 1005:24
request [2] - 946:11, 1029:9
require [6] - 854:15, 854:18, 854:23, 854:24, 869:22, 1029:25
required [1] - 1023:25
requirement [1] - 804:15
requirements [2] - 801:19, 923:10
requires [6] - 728:7, 729:13, 755:15, 760:15, 923:7, 1008:6
research [9] - 841:4, 841:9, 841:23, 841:24, 842:1, 939:21, 975:14, 975:25
researcher [1] - 975:7
researching [1] - 940:6
reserve [1] - 864:10
resistance [4] - 974:1, 1009:2, 1009:4, 1009:7
resistant [1] - 956:12
resources [1] - 814:6
respect [14] - 748:25, 768:14, 788:25, 799:25, 843:1, 843:11, 878:25, 883:1, 934:15, 936:15, 952:2, 1005:18, 1019:1, 1021:24
respected [1] - 975:7
respective [1] - 843:19
respectively [1] - 844:2
respond [2] - 892:6, 943:3
responding [5] - 843:10, 936:15, 1009:3, 1009:5
response [14] - 733:24, 803:18, 816:6, 823:25, 826:3, 861:16, 866:5, 872:25, 873:3, 950:15, 951:11, 952:3, 955:25, 1002:10
responses [4] - 880:12, 949:18, 1002:4, 1006:15
responsibilities [1] - 841:6
responsible [1] - 798:6
rest [2] - 989:1, 1028:2
restate [1] - 933:21
restrictive [1] - 714:19
result [18] - 712:23, 713:17, 715:14, 715:18, 716:9, 760:20, 780:17, 780:18, 780:22, 781:6, 782:10, 825:13, 883:3, 897:18, 910:1, 920:1, 1019:5, 1021:14
resulted [3] - 717:15, 796:18, 888:5
resulting [3] - 815:20, 825:6, 837:20
results [29] - 715:11, 715:21, 718:10, 771:7, 781:10, 782:8, 789:6, 791:25, 792:2, 792:3, 806:3, 806:6, 807:24, 808:12, 828:5, 839:9, 888:18, 891:16, 908:1, 927:1, 930:24, 948:23, 949:2, 950:16, 953:6, 953:10, 954:4, 1000:4, 1000:5

retained [3] - 840:7, 939:3, 977:3
retrospective [1] - 882:21
return [2] - 895:18, 1024:1
returning [1] - 856:2
reveal [1] - 953:21
revenue [10] - 978:22, 979:17, 985:6, 985:13, 985:15, 985:17, 985:21, 985:24, 986:21, 988:17
revenues [4] - 986:17, 1026:22, 1026:25, 1027:2
review [10] - 725:1, 725:2, 725:5, 725:20, 822:25, 942:19, 946:9, 946:15, 946:19, 975:1
reviewed [7] - 820:15, 843:21, 942:25, 954:20, 991:6, 991:18, 991:21
reviews [2] - 930:2, 930:6
revised [1] - 931:11
Richard [1] - 706:14
RICHARD [1] - 705:14
right-hand [7] - 822:20, 835:12, 850:20, 858:16, 980:3, 980:21, 989:24
ring [1] - 882:17
rise [8] - 706:13, 795:4, 795:6, 895:22, 895:24, 976:11, 976:13, 1031:6
risk [19] - 947:22, 947:23, 947:24, 948:6, 948:10, 951:13, 956:16, 958:11, 959:9, 959:19, 966:22, 966:23, 970:2, 970:7, 998:12, 999:16, 1008:24, 1010:4, 1022:7
risks [1] - 975:18
River [3] - 977:21, 977:23
road [1] - 799:7
roadmap [1] - 988:16
roads [1] - 995:13
Robert [1] - 1011:22
ROBERT [1] - 1011:25
Robinson [2] - 793:9, 793:11
role [8] - 860:23, 877:15, 877:19, 883:2, 936:18, 959:20, 995:8, 1018:7
room [1] - 841:10
roughly [2] - 822:23, 966:5
route [1] - 720:11
routine [8] - 759:24, 807:16, 830:14, 910:21, 935:17, 937:6, 937:9
routinely [2] - 771:4, 954:13
row [3] - 805:12, 811:7, 850:23
RSC [1] - 725:18
rule [7] - 793:25, 794:2, 880:15, 931:24, 932:9, 933:15, 934:19
Rule-of-2 [17] - 812:3, 812:5, 812:13, 812:17, 812:19, 829:21, 829:24, 831:1, 831:3, 831:7, 880:14, 880:19, 880:22, 881:12, 884:21, 931:21, 934:14
Rule-of-3 [4] - 880:24, 881:3, 881:7, 881:12
rules [3] - 812:6, 880:22, 880:23
run [4] - 734:6, 806:25, 838:11, 841:9
running [1] - 1025:16

S

safe [9] - 733:24, 734:13, 818:15, 832:2, 895:1, 934:5, 934:6, 958:11, 960:4
safety [2] - 819:1, 998:8
sale [3] - 978:23, 979:18, 985:22
sales [6] - 1016:21, 1017:2, 1022:25, 1023:1, 1023:12, 1023:22
salt [238] - 708:12, 708:13, 710:9, 750:6, 750:8, 797:21, 798:23, 798:25, 799:3, 799:6, 799:12, 799:22, 800:21, 801:23, 802:1, 802:2, 802:4, 802:7, 802:10, 802:18, 802:22, 802:25, 803:3, 803:4, 803:16, 803:20, 803:22, 804:7, 804:12, 804:13, 805:3, 805:15, 806:10, 806:18, 806:21, 807:4, 807:10, 807:15, 807:19, 807:23, 808:2, 808:12, 812:14, 812:24, 813:2, 813:6, 814:4, 814:15, 815:19, 815:20, 816:10, 817:2, 818:18, 819:1, 819:23, 820:4, 820:5, 820:6, 820:16, 821:10, 821:11, 822:17, 822:22, 823:2, 823:6, 823:11, 823:23, 824:23, 825:2, 825:6, 825:9, 825:10, 825:13, 825:18, 825:19, 826:5, 827:8, 827:11, 827:12, 827:13, 827:18, 827:20, 827:25, 828:3, 828:5, 828:8, 828:11, 828:16, 828:24, 829:8, 830:2, 831:11, 831:13, 831:19, 832:13, 832:21, 835:22, 837:11, 837:14, 837:16, 837:19, 843:18, 846:24, 848:8, 848:9, 849:12, 849:18, 849:19, 850:6, 850:8, 850:15, 850:17, 850:22, 851:1, 851:6, 851:11, 851:17, 852:14, 853:3, 854:15, 854:19, 856:3, 857:2, 857:3, 859:3, 861:6, 862:25, 863:3, 863:4, 864:19, 868:10, 868:11, 868:13, 869:21, 869:23, 870:8, 870:14, 870:17, 870:25, 871:3, 871:10, 871:20, 871:23, 872:9, 872:19, 873:11, 873:12, 874:1, 874:5, 874:13, 874:22, 874:25, 875:14, 879:1, 879:8, 879:24, 879:25, 880:5, 881:13, 881:23, 882:13, 882:18, 883:5, 883:17, 883:19, 883:20, 883:21, 883:22, 884:5, 884:10, 884:13, 885:8, 885:14, 885:19, 885:20, 886:22, 887:6, 887:9, 887:22, 888:1, 888:5, 889:3, 889:5, 889:7, 889:21, 889:23, 894:17, 896:21, 897:5, 900:18, 900:22, 900:23, 901:1, 901:9, 904:9, 905:18, 908:25, 909:17, 909:19, 910:9, 912:23, 914:10, 915:6, 917:11, 917:18, 921:18, 921:25, 926:8, 926:21, 927:1, 927:5, 927:6, 927:18, 927:19, 928:1, 928:14, 928:17, 931:11, 932:7, 932:24, 936:3, 936:11, 937:11, 941:21, 1016:18, 1017:4, 1017:16, 1027:9, 1027:12
salt-forming [1] - 931:11
salts [67] - 798:21, 799:19, 804:20, 808:8, 814:23, 815:3, 815:4, 815:5, 815:24, 817:2, 818:2, 819:7, 820:9, 820:16, 820:20, 820:24, 820:25, 821:5, 821:6, 821:12, 821:16, 822:14, 829:15, 830:2, 832:13, 832:17, 835:12, 836:16, 837:8, 842:3, 843:2, 848:3, 848:5, 848:12, 848:14, 848:18, 848:20, 850:5, 851:7, 853:24, 854:12, 858:5, 858:10, 860:9, 867:2, 870:21, 870:23, 871:25, 872:1, 872:12, 873:16, 873:18, 873:21, 880:17, 883:18, 886:19, 886:21, 887:17, 888:5, 896:14, 896:15, 896:16, 928:7, 930:3, 930:7, 930:25
Salts [2] - 834:6, 836:13
sample [3] - 822:18, 906:25, 907:2
samples [4] - 806:25, 839:6, 839:8
sat [1] - 786:22
satisfied [2] - 812:16, 955:4
satisfies [1] - 942:10
satisfy [1] - 812:19
saw [12] - 713:7, 733:11, 790:18, 791:2, 791:3, 793:11, 884:6, 890:15, 930:17, 954:5, 986:18, 1023:1
scale [2] - 862:15, 880:21
scanning [3] - 898:18, 903:13, 903:16
Scheme [1] - 847:7
scheme [1] - 709:25
School [2] - 940:21, 977:16
science [3] - 760:9, 916:5, 977:17
sciences [1] - 844:18
scientific [3] - 726:13, 842:10, 916:13
scientifically [1] - 1002:6
scientist [1] - 798:5
scientists [7] - 729:22, 755:3, 759:24, 762:22, 763:14, 844:23, 844:24
scope [6] - 714:15,

714:17, 717:2, 717:23, 718:4, 867:17
screen [62] - 713:25, 744:12, 750:17, 756:8, 756:10, 778:9, 799:3, 799:6, 802:1, 802:2, 802:7, 802:11, 802:23, 804:13, 805:3, 805:8, 807:23, 808:20, 808:21, 813:6, 818:18, 823:6, 826:5, 827:20, 827:25, 828:5, 828:16, 828:24, 829:8, 830:2, 833:4, 835:22, 837:16, 837:19, 866:19, 868:12, 868:14, 869:20, 872:16, 879:25, 880:5, 881:13, 881:23, 882:18, 884:11, 885:20, 889:21, 889:23, 899:3, 900:3, 914:3, 915:19, 929:4, 937:5, 937:10, 944:11, 977:10, 978:6, 980:19, 989:23, 1012:12
screened [1] - 932:17
screening [15] - 798:25, 800:21, 800:22, 807:16, 807:19, 808:2, 808:12, 814:15, 827:11, 827:18, 828:3, 832:13, 839:3, 932:7, 932:16
screenings [1] - 839:4
se [2] - 878:1, 879:4
seated [2] - 795:8, 976:14
SEC [1] - 1016:7
second [43] - 713:15, 730:13, 736:4, 759:6, 777:24, 783:5, 784:5, 784:6, 808:22, 813:4, 819:20, 824:6, 836:21, 848:24, 859:10, 861:16, 875:13, 884:8, 886:20, 889:11, 889:18, 891:17, 913:10, 945:5, 955:2, 972:12, 980:20, 983:22, 984:5, 984:16, 984:17, 985:4, 990:2, 1002:13, 1003:19, 1004:12, 1009:9, 1014:11, 1016:10, 1016:11, 1019:11, 1023:17
second-line [6] - 972:12, 984:17, 985:4, 1002:13, 1003:19, 1004:12
second-to-last [1] - 819:20
secondary [3] - 975:18, 995:13, 1008:16
secondly [3] - 712:6, 713:10, 891:6
section [14] - 803:16, 815:25, 821:25, 836:2, 836:9, 836:12, 836:17, 872:9, 893:16, 921:17, 944:16, 950:8, 951:7, 951:22
see [106] - 711:16, 713:10, 717:12, 723:22, 723:23, 726:4, 744:11, 752:17, 753:12, 757:5, 757:11, 757:20, 759:11, 764:10, 764:15, 774:11, 774:17, 775:1, 775:14, 775:16, 776:2, 776:6, 776:11, 776:16, 777:5, 777:10, 778:10, 779:19, 782:6, 782:11, 784:15, 785:12, 811:10, 815:25, 821:25, 835:14, 836:2, 837:4, 846:9, 846:12, 846:15, 846:17, 847:2, 848:2, 850:22, 856:20, 857:10, 858:13, 863:1, 865:8, 866:19, 876:17, 877:1, 890:19, 892:17, 900:11, 913:22, 913:23, 914:11, 914:16, 914:25, 915:3, 915:9, 921:4, 930:14, 931:2, 931:7, 931:12, 944:19, 947:21, 948:6, 948:9, 953:2, 961:21, 961:22, 968:6, 980:5, 981:4, 981:18, 981:20, 981:22, 982:3, 983:9, 983:15, 983:18, 984:1, 984:4, 984:20, 985:2, 985:15, 985:16, 987:14, 991:1, 997:21, 998:14, 1002:22, 1002:25, 1003:5, 1007:15, 1009:6, 1016:4, 1020:9, 1022:21, 1029:23, 1030:6, 1031:5
seeding [1] - 909:23
seeing [3] - 852:4, 949:17, 961:7
seek [1] - 880:17
seeking [1] - 1017:12
seem [1] - 1029:19
segment [5] - 980:16, 980:17, 981:23, 982:3, 984:16
select [7] - 813:6, 824:2, 828:15, 839:6, 882:18, 932:7, 932:15
selected [7] - 799:21, 808:23, 824:23, 931:14, 931:16, 956:8, 960:24
selecting [6] - 763:10, 799:7, 830:2, 832:13, 832:17, 836:16
selection [10] - 733:19, 733:21, 803:4, 803:20, 814:8, 816:10, 818:18, 882:13, 887:6, 903:19
selective [7] - 951:3, 963:23, 964:1, 964:7, 964:12, 994:19, 994:23
sense [1] - 751:24
sentence [24] - 714:12, 733:18, 757:7, 824:8, 836:21, 848:17, 848:24, 849:5, 849:16, 850:3, 850:4, 850:6, 851:22, 852:3, 852:8, 852:17, 852:24, 886:20, 887:3, 930:4, 930:5, 951:24, 952:25, 953:4
sentences [3] - 813:24, 814:1, 950:11
separate [6] - 852:13, 852:18, 852:21, 852:24, 852:25, 853:2
separately [1] - 755:7
separation [1] - 735:21
September [1] - 1016:13
sequence [1] - 994:14
serious [2] - 974:20, 974:22
serve [1] - 973:12
service [1] - 841:11
services [1] - 799:9
serving [1] - 842:9
session [1] - 706:14
set [9] - 729:8, 747:17, 752:3, 799:4, 802:2, 802:3, 807:21, 828:18, 838:22
setting [10] - 827:25, 829:8, 948:21, 949:17, 953:20, 956:18, 960:9, 969:14, 969:16, 972:23
seven [2] - 954:6, 1022:1
several [12] - 707:7, 732:10, 801:24, 802:13, 825:3, 844:19, 914:1, 925:7, 928:21, 948:5, 963:18, 996:20
severe [1] - 967:18
shaded [2] - 981:18, 981:20
Shah [12] - 851:14, 869:9, 877:17, 877:21, 888:23, 890:8, 892:7, 892:9, 892:10, 892:23, 892:25
Shah's [1] - 889:13
shape [2] - 729:24, 739:20
share [19] - 797:25, 798:11, 805:19, 979:16, 981:1, 981:14, 981:23, 981:24, 982:7, 982:19, 982:22, 983:5, 983:16, 983:19, 983:20, 983:24, 984:1, 984:21, 985:2
shared [1] - 805:3
shares [7] - 981:19, 982:13, 983:10, 986:18, 1022:22, 1024:3, 1024:6
sheer [1] - 891:6
shelf [1] - 760:25
shift [2] - 867:20, 879:19
shifting [2] - 975:3, 1002:13
shooting [1] - 1030:12
short [2] - 904:11, 910:17
shortcut [2] - 904:12
show [28] - 713:3, 715:2, 715:9, 716:6, 736:9, 766:2, 782:10, 830:21, 843:16, 851:9, 861:7, 865:1, 865:4, 865:11, 890:13, 916:19, 920:24, 948:25, 951:25, 956:13, 956:19, 980:24, 983:3, 999:24, 1000:4, 1000:11, 1010:18, 1016:23
showed [19] - 713:8, 713:11, 716:9, 808:10, 830:18, 831:22, 834:12, 849:3, 849:8, 881:6, 916:18, 916:25, 917:2, 966:6, 972:24, 1000:5, 1000:19, 1003:8, 1003:11
showing [6] - 899:5, 1016:1, 1016:11, 1016:15, 1016:20, 1021:24
shown [24] - 765:2, 790:9, 800:4, 809:9, 811:13, 814:10, 814:17, 815:1, 818:6, 836:20, 845:19, 846:22, 855:10, 939:13, 943:10, 956:23, 969:3, 969:23, 971:17, 971:20, 972:21, 985:11, 1001:10, 1024:24
shows [16] - 715:10,

726:10, 779:18, 819:12, 820:16, 829:16, 843:17, 848:13, 855:23, 876:22, 979:24, 980:1, 981:1, 982:17, 984:13, 1021:8
side [18] - 817:24, 822:20, 846:15, 850:20, 858:16, 876:20, 944:17, 953:11, 958:19, 958:20, 959:4, 959:6, 960:5, 980:3, 980:21, 994:10, 1005:1, 1029:14
side's [1] - 845:11
signal [2] - 992:11, 992:13
significance [5] - 848:10, 849:10, 849:22, 852:9, 852:20
significant [13] - 709:13, 710:10, 829:13, 868:8, 896:23, 917:9, 923:12, 948:21, 951:10, 952:1, 985:18, 1000:6, 1005:16
significantly [6] - 710:2, 795:22, 917:17, 917:21, 917:24, 1005:12
silent [1] - 959:6
similar [17] - 724:15, 735:12, 735:14, 736:18, 808:4, 824:1, 911:11, 943:15, 952:19, 952:21, 974:8, 977:18, 984:14, 995:12, 997:11, 1007:4, 1021:18
similarities [1] - 925:8
similarly [1] - 1026:7
simple [1] - 733:25
simply [3] - 726:18, 734:24, 906:13
simulated [2] - 878:4
simultaneously [2] - 964:2, 1001:7
single [5] - 745:18, 948:13, 1002:1, 1010:21, 1024:8
single-class [1] - 1002:1
sit [1] - 895:25
site [1] - 875:25
sitting [1] - 790:14
situation [6] - 923:4, 924:23, 931:1, 954:1, 992:23, 993:23
situations [1] - 992:25
six [2] - 885:7, 962:9
size [4] - 729:24, 739:20, 842:15, 879:17
skill [81] - 709:19, 714:16, 721:5, 724:12, 740:2, 748:11, 748:14, 750:5, 750:11, 750:12, 751:7, 751:17, 752:20, 754:18, 755:13, 757:16, 758:17, 759:16, 760:10, 761:7, 761:20, 763:6, 763:21, 764:17, 766:13, 766:15, 766:20, 768:5, 769:16, 769:25, 770:5, 770:12, 770:25, 771:3, 771:6, 771:9, 771:17, 773:15, 777:13, 794:12, 800:6, 800:10, 804:6, 805:16, 808:20, 813:5, 828:13, 829:6, 832:11, 835:16, 835:19, 838:22, 844:10, 845:1, 845:10, 849:23, 857:2, 876:15, 881:11, 882:17, 884:17, 884:21, 891:11, 897:9, 905:5, 905:10, 905:13, 906:3, 927:10, 931:20, 932:3, 932:6, 932:14, 932:23, 933:3, 933:6, 936:1, 936:8, 937:4, 937:5
skilled [74] - 708:23, 709:15, 721:12, 722:1, 722:14, 726:17, 727:15, 729:6, 731:20, 733:3, 734:24, 737:6, 738:1, 738:22, 776:5, 801:13, 803:21, 806:10, 806:13, 807:9, 809:11, 809:24, 810:12, 811:24, 814:18, 814:20, 815:2, 815:14, 816:2, 816:20, 816:23, 823:10, 823:20, 825:8, 825:9, 825:17, 848:10, 849:10, 850:5, 852:9, 852:12, 852:20, 856:11, 856:17, 857:9, 857:13, 866:25, 868:13, 872:21, 873:9, 874:12, 875:13, 878:11, 878:18, 878:24, 879:7, 879:9, 880:4, 881:2, 881:6, 881:14, 882:8, 882:14, 883:14, 883:19, 883:20, 884:10, 885:11, 885:13, 887:5, 891:4, 893:22, 932:25, 934:24
skip [1] - 714:12
skipping [2] - 755:5, 931:9
slide [27] - 706:19, 711:23, 712:13, 712:15, 750:20, 751:11, 752:3, 758:2, 758:7, 777:21, 777:24, 799:17, 801:24, 802:20, 843:13, 843:16, 845:19, 845:20, 853:10, 861:23, 862:16, 865:1, 939:13, 989:25, 1014:1, 1017:25, 1030:8
Slide [11] - 707:9, 719:21, 719:23, 722:16, 722:21, 734:21, 738:14, 740:16, 977:10, 979:7, 990:9
slides [13] - 734:21, 750:22, 750:23, 777:19, 986:18, 989:20, 989:23, 1012:10, 1029:18, 1030:1, 1030:6, 1030:9, 1030:10
slightly [3] - 780:14, 783:11, 853:16
slow [1] - 891:13
small [7] - 721:22, 827:1, 831:15, 831:22, 890:24, 907:23, 927:3
smaller [4] - 842:15, 846:11, 916:11, 1010:18
so.. [1] - 899:5
Society [1] - 940:22
sold [2] - 741:4, 985:13
solid [19] - 801:3, 804:21, 844:20, 845:24, 846:1, 846:8, 853:11, 856:8, 909:25, 910:9, 921:17, 922:4, 922:5, 923:16, 923:17, 923:20, 983:14, 983:15, 984:19
solid-state [1] - 844:20
solids [9] - 846:4, 846:5, 893:21, 893:23, 893:25, 917:22, 918:4, 918:11, 918:17
solubilities [1] - 919:3
solubility [53] - 729:23, 800:22, 801:8, 805:11, 805:14, 806:8, 809:12, 809:15, 817:22, 825:4, 825:9, 825:11, 825:14, 825:19, 825:20, 825:21, 849:20, 850:2, 851:2, 851:4, 851:17, 851:18, 851:19, 874:7, 874:16, 874:18, 874:19, 875:6, 875:9, 875:16, 875:17, 877:4, 877:9, 877:12, 877:14, 877:24, 878:1, 878:2, 878:7, 878:12, 878:19, 878:21, 879:4, 879:10, 879:11, 885:23, 891:8, 891:10, 891:12, 891:18, 919:10
soluble [4] - 798:13, 798:19, 851:11, 876:22
solution [3] - 804:15, 804:16, 909:19
solutions [1] - 816:11
solvates [2] - 866:3, 866:7
solve [3] - 796:9, 801:16, 842:11
solvent [10] - 710:9, 804:12, 804:17, 805:8, 838:25, 839:2, 839:3, 839:4, 839:6, 909:21
solvents [14] - 804:11, 804:13, 805:8, 805:11, 805:14, 805:17, 805:19, 805:22, 806:1, 806:4, 806:6, 806:9, 806:14, 921:19
solving [1] - 796:5
something's [3] - 766:3, 770:1, 770:2
sometimes [5] - 728:23, 760:8, 767:1, 944:13, 1009:15
somewhere [3] - 764:20, 932:2, 1029:6
sooner [2] - 1020:24, 1023:8
sorafenib [5] - 963:7, 965:8, 965:11, 972:21, 994:16
sorry [41] - 712:7, 714:3, 715:16, 718:15, 723:12, 727:1, 745:13, 751:19, 758:1, 761:5, 761:10, 764:4, 771:14, 772:13, 773:17, 773:20, 781:15, 786:10, 787:3, 836:5, 836:8, 836:19, 864:11, 876:24, 885:2, 886:7, 886:11, 890:2, 894:6, 917:12, 922:5, 925:11, 925:13, 929:7, 943:22, 944:9, 962:23, 963:2, 994:6, 1023:9
Sorry [1] - 944:11
sort [4] - 947:20, 997:21, 1001:7, 1022:8
sorted [2] - 835:7, 835:9
sorts [2] - 822:13, 879:12

sounds [1] - 925:5
source [2] - 775:6, 985:25
sources [2] - 775:5, 985:23
space [1] - 997:8
Spain [1] - 876:10
spans [1] - 850:19
spatial [1] - 853:13
speaking [10] - 896:22, 902:18, 939:6, 945:25, 947:18, 999:19, 1002:3, 1007:14, 1007:18, 1010:6
spec [1] - 745:3
specialize [1] - 939:19
species [2] - 859:17, 887:9
specific [30] - 712:10, 718:9, 718:10, 745:12, 747:20, 747:21, 747:24, 747:25, 780:10, 780:13, 780:22, 781:6, 781:10, 782:25, 794:10, 802:3, 804:4, 832:8, 852:15, 853:1, 854:24, 857:3, 857:11, 862:13, 903:21, 926:15, 927:9, 945:3, 995:1
specifically [16] - 714:8, 719:14, 744:8, 745:10, 745:12, 745:15, 760:19, 775:5, 778:25, 816:9, 829:23, 841:10, 925:5, 948:4, 995:23, 996:17
specification [37] - 744:24, 744:25, 797:25, 798:11, 855:16, 857:22, 858:1, 858:4, 858:10, 858:12, 860:2, 860:6, 860:11, 861:5, 866:13, 866:21, 870:21, 872:6, 872:22, 902:19, 902:23, 903:3, 903:21, 904:3, 904:6, 904:13, 904:16, 904:20, 904:24, 905:4, 905:7, 905:9, 936:2, 936:11, 936:18, 936:22, 937:3
specifies [1] - 748:8
specify [2] - 744:18, 746:23
spectrum [7] - 951:3, 963:23, 964:1, 964:6, 964:12, 994:19, 994:23
spectrum-selective [1] - 964:12
spell [5] - 839:18, 938:13, 976:17, 989:6, 1011:20
spent [1] - 743:9
spirit [1] - 714:14
spite [1] - 982:13
sponsor [1] - 946:11
spot [1] - 776:19
squares [1] - 890:19
Squibb [2] - 914:5, 1016:6
stability [26] - 730:4, 730:7, 730:13, 730:21, 734:7, 739:15, 760:2, 760:25, 777:4, 803:7, 825:5, 851:5, 860:20, 860:22, 860:23, 860:25, 861:10, 861:13, 885:24, 893:25, 919:12, 919:19, 926:7, 926:14, 1008:10
Stability [1] - 776:25
stable [8] - 849:8, 849:14, 861:2, 861:13, 895:1, 926:16, 958:10, 1008:7
staff [1] - 990:24
stage [2] - 815:15, 817:9
Stahl [13] - 833:5, 833:18, 928:24, 929:2, 929:3, 929:16, 929:22, 931:14, 931:16, 931:18, 934:1, 934:15, 934:20
STAHL [1] - 929:16
standard [9] - 921:23, 950:16, 951:4, 951:12, 954:2, 965:5, 998:25, 999:1, 999:2
standpoint [1] - 998:5
stands [1] - 934:4
start [18] - 712:25, 748:6, 757:17, 762:8, 763:10, 788:21, 838:8, 838:10, 860:7, 862:2, 868:18, 872:8, 895:19, 921:6, 985:14, 992:7, 1014:15, 1015:24
started [4] - 743:14, 807:13, 872:22, 1016:8
starting [20] - 708:25, 709:6, 709:9, 721:14, 721:17, 801:18, 804:5, 804:16, 808:7, 819:1, 845:21, 845:22, 847:12, 847:17, 848:7, 872:7, 880:21, 889:1, 906:4
starts [6] - 814:6, 835:2, 835:3, 847:25, 849:17, 852:8
startups [1] - 842:16
state [10] - 839:18, 844:20, 845:25, 923:16, 923:17, 923:20, 938:13, 976:17, 989:6, 1011:20
statement [8] - 734:2, 759:2, 790:17, 791:3, 833:20, 891:15, 920:23, 986:1
statements [1] - 936:8
states [1] - 845:23
States [1] - 876:10
STATES [1] - 705:1
statistically [1] - 1000:6
status [12] - 832:8, 832:12, 832:16, 834:2, 835:13, 835:23, 837:9, 837:17, 882:24, 883:4, 930:25, 947:22
staying [1] - 851:21
steady [1] - 997:5
Steed [40] - 800:21, 819:7, 825:17, 834:12, 843:11, 853:15, 853:16, 854:14, 858:24, 859:1, 861:19, 863:5, 863:11, 863:13, 864:3, 864:7, 864:16, 865:3, 865:20, 867:12, 873:4, 874:4, 878:10, 880:20, 882:9, 882:19, 882:23, 883:7, 885:6, 891:15, 892:20, 894:2, 913:22, 913:25, 915:13, 916:7, 930:18, 933:12, 935:16, 935:20
Steed's [20] - 803:15, 807:15, 812:2, 816:2, 818:13, 823:20, 826:3, 829:24, 833:23, 859:20, 866:2, 867:18, 872:25, 880:12, 880:19, 882:12, 883:1, 884:20, 891:11, 914:19
Steering [1] - 940:23
stemming [1] - 809:3
stems [1] - 808:22
stenographic [1] - 1031:9
step [35] - 709:10, 709:13, 710:6, 710:9, 721:18, 721:20, 734:25, 738:2, 738:12, 751:10, 753:19, 755:5, 763:20, 768:1, 769:3, 793:4, 793:6, 793:7, 796:4, 796:17, 796:23, 799:7, 809:5, 839:13, 875:19, 938:8, 976:7, 988:23, 989:2, 1001:25, 1011:13, 1027:19, 1027:20
stepping [3] - 798:8, 976:7, 1011:13
steps [7] - 709:9, 709:11, 717:20, 721:19, 721:20, 768:19, 768:21
stepwise [1] - 813:10
still [23] - 711:2, 711:4, 711:14, 717:1, 739:19, 797:8, 815:17, 817:12, 837:20, 838:16, 877:9, 885:23, 901:10, 921:21, 922:1, 922:8, 922:16, 957:6, 957:9, 962:13, 1004:1, 1004:20, 1028:20
stomach [1] - 878:4
stop [1] - 954:24
stops [1] - 1009:2
storage [4] - 741:4, 757:10, 760:21, 768:22
straightforward [1] - 816:13
STRAWN [1] - 706:4
streams [1] - 838:25
Street [1] - 705:10
strength [1] - 1017:20
stress [1] - 759:21
stricken [1] - 706:23
strike [13] - 706:24, 711:24, 715:19, 735:6, 762:8, 864:10, 864:22, 880:11, 882:25, 917:5, 923:12, 931:19, 1004:13
strong [8] - 803:14, 814:22, 815:17, 824:14, 920:4, 1018:4, 1019:3
stronger [4] - 809:1, 813:8, 817:10, 817:12
structural [16] - 767:2, 767:4, 767:7, 767:8, 767:12, 767:19, 768:1, 768:24, 770:10, 853:17, 860:5, 866:12, 866:16, 866:25, 867:4, 867:11
structurally [4] - 735:12, 735:13, 736:17, 808:1
structure [28] - 722:19, 723:3, 723:20, 723:23, 767:16, 769:8, 769:9, 769:11, 769:18, 770:3, 770:7, 771:12, 771:18, 809:10, 809:12, 810:1, 810:3, 847:12, 847:14, 847:15, 847:17, 847:19, 847:20, 866:17, 866:23, 869:20, 912:5, 912:10
structures [17] - 723:16, 724:14,

724:15, 725:6, 725:7, 725:12, 726:14, 766:17, 766:21, 767:1, 767:15, 769:7, 883:7, 918:5, 918:12, 918:22, 922:13
studied [6] - 822:2, 822:4, 822:18, 956:15, 961:7, 969:7
studies [13] - 713:8, 713:10, 739:18, 754:5, 762:14, 762:16, 762:25, 763:5, 763:8, 776:25, 777:4, 1000:16, 1001:5
study [43] - 769:22, 808:6, 948:23, 950:1, 950:3, 950:4, 950:23, 951:18, 951:19, 951:25, 952:12, 953:6, 953:13, 953:21, 953:24, 956:13, 960:23, 968:22, 969:8, 970:5, 971:4, 971:12, 999:24, 1000:1, 1000:10, 1000:15, 1000:22, 1001:1, 1001:2, 1001:6, 1001:8, 1001:22, 1002:12, 1003:8, 1003:11, 1003:12, 1003:21, 1003:22, 1003:23, 1004:3, 1004:6
Study [1] - 821:25
studying [1] - 824:4
stuff [3] - 1030:14, 1030:16, 1030:17
Stuttgart [1] - 841:5
subject [8] - 772:15, 882:5, 973:10, 995:21, 1014:21, 1019:16, 1020:21, 1020:23
sublimation [1] - 909:11
submission [2] - 716:21, 892:23
submitted [4] - 719:5, 783:14, 892:7, 937:24
subsequent [15] - 774:23, 945:16, 945:17, 949:13, 953:17, 954:4, 954:14, 962:14, 968:5, 972:13, 972:14, 972:18, 1003:9, 1004:17, 1009:18
subsequent-line [2] - 972:18, 1003:9
subsequently [3] - 992:13, 994:12, 994:15
substance [14] - 720:9, 757:10, 757:13, 760:20, 798:24, 800:17, 837:10, 837:20, 840:13, 898:5, 920:17, 922:15, 1007:22, 1008:11
substances [8] - 727:10, 727:16, 756:18, 798:6, 822:5, 836:24, 837:7, 975:23
substitute [1] - 736:18
substitutes [1] - 735:14
substitution [1] - 736:11
substitutional [3] - 736:19, 736:20, 736:23
success [76] - 737:7, 737:10, 738:1, 738:17, 738:23, 741:23, 742:1, 742:6, 742:8, 742:14, 742:15, 825:25, 826:2, 826:9, 868:15, 883:12, 883:16, 884:3, 885:12, 894:8, 894:15, 937:6, 939:8, 939:10, 942:9, 942:11, 946:23, 948:18, 954:11, 959:21, 960:13, 960:17, 973:7, 973:11, 973:14, 977:7, 978:2, 978:14, 978:19, 979:4, 979:6, 982:16, 982:18, 986:4, 986:13, 987:22, 988:9, 988:12, 992:5, 1005:4, 1006:25, 1007:12, 1007:15, 1007:23, 1013:13, 1013:19, 1014:10, 1014:13, 1014:16, 1014:19, 1014:23, 1016:24, 1019:4, 1019:5, 1019:14, 1020:18, 1022:5, 1022:22, 1022:24, 1023:7, 1023:21, 1024:10, 1024:15, 1024:22, 1025:3
Success [1] - 734:21
successful [9] - 742:10, 742:15, 806:15, 954:9, 1008:6, 1017:2, 1018:9, 1024:2, 1024:25
successfully [1] - 972:21
suffering [1] - 1009:10
sufficient [7] - 806:8, 849:20, 877:10, 892:12, 893:1, 903:25, 1022:13
suggest [5] - 708:14, 708:18, 725:6, 731:10, 835:18
suggests [2] - 764:7, 956:1
suit [3] - 991:18, 1020:19, 1027:5
suitable [14] - 754:10, 799:22, 805:14, 806:7, 814:4, 828:15, 849:24, 850:1, 851:4, 851:9, 860:15, 883:22, 885:15, 928:20
suite [6] - 851:9, 888:19, 889:3, 889:7, 889:20, 926:11
suits [1] - 1016:17
sulfate [1] - 952:22
sulfonic [1] - 817:7
sulfuric [1] - 815:12
summarize [4] - 712:1, 757:8, 995:19, 1024:19
summarizing [1] - 1014:1
Summary [1] - 751:3
summary [10] - 842:21, 858:11, 892:3, 939:14, 947:20, 978:9, 985:23, 986:7, 1013:10, 1027:1
sunitinib [36] - 823:19, 824:11, 824:13, 950:24, 951:1, 951:2, 951:12, 951:20, 952:2, 956:17, 956:20, 963:9, 965:8, 965:24, 968:1, 968:17, 968:24, 969:8, 969:13, 969:15, 970:8, 970:20, 971:4, 971:18, 971:21, 972:20, 994:16, 1000:1, 1000:9, 1000:12, 1000:14, 1000:17, 1000:21, 1001:4, 1001:11, 1001:21
Sunitinib [2] - 824:9, 999:22
superior [2] - 969:13, 969:14
superiority [3] - 956:18, 956:20, 1001:11
support [1] - 803:4
supports [1] - 826:1
supposed [1] - 728:17
surprise [1] - 764:10
surprisingly [1] - 888:24
survey [1] - 930:25
survival [18] - 948:22, 949:12, 950:14, 951:11, 952:2, 952:3, 953:7, 955:23, 955:24, 957:15, 968:23, 1000:7, 1000:10, 1000:11, 1000:18, 1010:13, 1010:21
survivals [2] - 955:15, 955:17
Sutent [7] - 823:16, 823:17, 823:22, 824:1, 927:11, 927:24, 951:2
SUTENT [1] - 927:11
Swarbrick [1] - 775:9
switch [1] - 998:20
sworn [4] - 797:8, 839:23, 938:18, 989:11
synergistic [1] - 1002:7
synonymously [2] - 902:25, 922:19
synthesis [14] - 707:18, 708:15, 708:25, 709:17, 721:14, 721:20, 752:9, 753:11, 754:14, 757:9, 757:19, 757:24, 758:11, 760:6
synthesized [2] - 757:18, 849:19
synthesizing [1] - 707:13
synthetic [26] - 709:25, 712:4, 713:16, 715:14, 715:17, 715:21, 720:10, 734:25, 735:22, 740:25, 744:25, 745:3, 755:6, 773:10, 785:25, 786:7, 786:16, 787:5, 787:7, 787:17, 788:1, 796:2, 796:4, 844:22
system [3] - 875:23, 998:21, 998:23
systemic [1] - 945:14

T

T-A-T-E [1] - 976:20
T-R-O-U-T [1] - 839:21
tab [4] - 714:3, 886:8, 899:22, 944:7
Tab [40] - 708:4, 714:4, 714:5, 714:24, 720:2, 723:7, 724:21, 725:14, 726:25, 731:6, 735:25, 737:17, 783:25, 795:13, 804:24, 810:16, 813:13, 819:15, 820:11, 821:18, 823:13, 842:18, 847:5, 868:21, 876:3, 886:3, 886:9, 890:10, 891:20, 893:5, 941:3, 944:4, 946:21, 949:22, 950:19, 951:15, 952:5, 978:6, 979:21, 980:19
table [22] - 717:12, 719:1, 724:2, 779:1, 780:6, 780:15, 811:1, 820:15, 820:20, 821:9, 835:9, 836:7, 851:22, 858:11, 858:16, 865:3, 928:22, 931:16, 947:18, 947:20, 948:3, 949:3

Table [36] - 715:5, 715:9, 715:24, 718:23, 724:3, 779:1, 789:7, 795:14, 795:16, 805:5, 805:7, 805:9, 805:17, 805:19, 806:1, 819:22, 820:1, 820:3, 820:9, 820:14, 820:15, 822:8, 822:10, 822:16, 822:21, 834:15, 834:24, 835:2, 835:3, 835:6, 835:7, 850:18, 850:19, 850:25, 851:7
Tables [1] - 777:7
tables [4] - 776:1, 780:13, 834:2, 834:11
tablet [6] - 733:23, 734:8, 734:12, 776:8, 776:10, 885:25
tablets [9] - 713:13, 728:15, 728:16, 728:19, 729:2, 740:18, 741:12, 978:25
Tabs [1] - 843:24
tabs [2] - 929:7, 929:8
Takagi [1] - 876:6
talc [2] - 731:15, 731:17
talks [12] - 715:4, 720:10, 725:25, 727:11, 733:10, 733:12, 738:7, 746:17, 775:11, 930:6, 931:18
targeted [3] - 842:11, 945:22, 955:13
targeting [1] - 952:18
targets [6] - 958:23, 964:14, 964:19, 964:22, 965:1
tartrate [1] - 818:7
task [1] - 886:22
tasks [1] - 777:14
TATE [1] - 976:21
Tate [17] - 742:3, 742:5, 742:14, 976:15, 976:16, 976:19, 977:2, 977:3, 978:13, 986:3, 986:22, 986:24, 987:14, 987:16, 988:23, 1016:22, 1019:18
Tate's [13] - 742:7, 742:11, 894:14, 1013:24, 1014:6, 1020:13, 1021:3, 1022:11, 1022:18, 1023:23, 1024:5, 1024:12, 1027:1
taught [7] - 832:16, 841:16, 841:18, 841:20, 841:21, 920:12, 922:10
teach [7] - 707:13, 707:17, 707:22, 713:23, 714:7, 721:4, 732:13
teaches [2] - 750:13, 851:8
teaching [8] - 740:1, 837:17, 841:10, 841:13, 841:14, 921:24, 937:10, 1013:8
teachings [3] - 936:2, 936:5, 936:10
team [5] - 753:22, 844:21, 913:25, 975:14, 975:25
technical [5] - 842:11, 986:10, 986:11, 986:20, 1026:5
technically [4] - 888:18, 923:10, 934:6, 1025:18
technique [2] - 827:12, 827:14
techniques [19] - 758:13, 758:22, 761:8, 761:15, 761:17, 772:7, 773:16, 773:19, 773:20, 774:23, 801:5, 801:7, 801:10, 801:14, 857:16, 903:3, 903:7, 903:9, 933:2
technologies [1] - 754:10
Technology [1] - 840:19
temperature [5] - 710:9, 713:12, 760:22, 788:7, 849:1
temperatures [2] - 806:24, 921:19
ten [1] - 799:10
tend [1] - 864:8
tendency [1] - 889:9
tender [1] - 842:24
tens [1] - 1026:18
term [15] - 729:18, 786:23, 787:25, 799:4, 802:2, 803:10, 807:20, 813:9, 848:11, 852:10, 852:21, 853:8, 856:6, 964:1, 992:8
termed [4] - 802:22, 973:8, 992:5, 1005:3
terminology [1] - 918:8
terms [12] - 718:16, 744:15, 760:2, 822:18, 902:25, 906:16, 908:5, 926:7, 953:10, 982:5, 1028:18, 1029:2
test [32] - 715:11, 716:8, 724:17, 759:21, 765:6, 765:7, 767:8, 767:13, 768:2, 768:4, 768:6, 768:9, 768:12, 770:13, 770:15, 770:20, 771:1, 771:3, 771:7, 771:21, 771:23, 781:6, 784:24, 791:24, 830:12, 830:14, 830:17, 838:16, 908:1
tested [12] - 780:4, 782:25, 799:9, 802:10, 806:1, 806:15, 823:7, 972:8, 1000:20, 1003:9, 1003:18
testified [32] - 710:15, 714:20, 716:14, 720:12, 721:3, 721:12, 722:1, 722:14, 782:13, 790:23, 797:17, 825:17, 828:3, 839:24, 854:14, 855:4, 877:17, 879:14, 887:16, 890:8, 912:16, 934:23, 938:19, 941:20, 960:12, 976:22, 988:16, 989:11, 999:22, 1009:22, 1012:1, 1013:15
testify [8] - 729:6, 733:3, 734:24, 741:8, 786:17, 878:11, 995:20, 1020:25
testifying [3] - 744:8, 790:24, 913:17
testimony [55] - 718:6, 731:8, 743:23, 745:2, 745:6, 750:24, 772:25, 778:3, 786:23, 791:12, 792:13, 792:20, 803:15, 803:18, 804:20, 807:15, 812:2, 814:22, 816:2, 816:6, 818:13, 818:16, 823:20, 826:4, 828:5, 829:18, 829:25, 833:24, 851:14, 853:19, 866:2, 873:1, 873:3, 873:17, 882:12, 884:20, 889:14, 891:11, 892:21, 943:23, 944:25, 975:10, 984:18, 989:21, 991:8, 991:25, 994:20, 1000:22, 1005:5, 1012:11, 1013:24, 1014:1, 1014:6, 1015:7, 1028:12
testing [14] - 718:7, 765:2, 782:7, 782:9, 782:11, 906:5, 906:8, 907:15, 907:24, 917:23, 918:2, 923:5, 924:2, 971:4
tests [4] - 718:11, 718:12, 765:13, 770:21
tetrahydrofuran [1] - 806:5
text [5] - 836:7, 836:13, 936:24, 1030:4
textbook [3] - 835:11, 836:15, 836:24
that's.. [1] - 713:25
that.. [1] - 773:21
THE [129] - 705:1, 705:2, 705:14, 706:15, 706:20, 706:24, 714:25, 715:7, 718:15, 718:19, 718:20, 718:24, 742:22, 742:25, 749:4, 751:22, 758:4, 774:2, 779:2, 795:1, 795:4, 795:7, 796:22, 797:3, 797:8, 797:10, 826:15, 826:22, 826:23, 827:2, 833:8, 833:13, 834:16, 838:2, 838:3, 838:4, 838:7, 838:20, 838:24, 838:25, 839:4, 839:10, 839:12, 839:14, 839:17, 839:20, 839:25, 843:4, 854:11, 862:8, 862:9, 862:10, 863:16, 863:20, 864:8, 864:13, 864:21, 864:22, 889:18, 889:22, 890:1, 894:4, 895:9, 895:15, 895:25, 896:4, 913:6, 929:5, 933:22, 935:4, 938:7, 938:9, 938:12, 938:15, 938:20, 938:22, 941:15, 952:7, 961:14, 961:18, 972:19, 976:6, 976:14, 976:16, 976:19, 978:16, 980:22, 987:4, 987:8, 987:11, 988:23, 989:2, 989:3, 989:4, 989:8, 989:13, 991:15, 1006:4, 1006:7, 1006:9, 1006:11, 1006:17, 1011:9, 1011:12, 1011:17, 1011:22, 1012:3, 1013:21, 1023:9, 1023:11, 1023:15, 1025:7, 1025:10, 1025:13, 1025:17, 1025:24, 1026:6, 1026:9, 1027:16, 1027:19, 1027:21, 1027:22, 1028:1, 1028:4, 1028:8, 1028:15, 1029:1, 1029:13, 1031:4
themselves [4] - 817:21, 837:18, 992:18, 995:10
theory [1] - 883:1
therapeutic [4] - 725:19, 800:20, 875:25, 1005:24
therapies [15] - 954:1, 955:7, 955:19,

956:3, 956:25, 961:25, 962:11, 974:24, 994:8, 999:7, 1003:7, 1004:19, 1009:9, 1009:18, 1009:20
therapy [54] - 945:14, 946:5, 946:12, 949:13, 949:14, 950:24, 951:12, 953:17, 954:4, 954:15, 955:20, 955:22, 957:18, 965:6, 965:11, 965:17, 966:18, 966:21, 966:22, 967:1, 968:5, 968:7, 969:24, 970:15, 970:22, 971:1, 971:6, 971:13, 973:3, 974:13, 974:19, 984:17, 985:4, 994:7, 996:11, 999:21, 1000:2, 1001:20, 1002:1, 1003:2, 1003:5, 1003:9, 1003:14, 1003:15, 1004:1, 1004:4, 1004:5, 1004:12, 1005:11, 1007:9, 1007:23, 1008:1, 1008:6, 1009:3
therefore [5] - 714:18, 918:5, 918:24, 931:9, 931:10
thereof [1] - 869:21
thermal [7] - 849:7, 861:13, 898:15, 898:20, 903:11, 903:18
thermally [1] - 861:13
thermodynamic [1] - 893:24
thermodynamics [1] - 841:19
they've [3] - 757:18, 805:13, 931:22
THF [1] - 806:5
thinking [1] - 873:8
third [17] - 762:1, 762:5, 808:9, 811:7, 824:19, 841:11, 866:10, 879:7, 885:11, 930:23, 982:11, 984:5, 1009:9, 1014:12, 1018:16, 1022:14, 1024:3
third-line [1] - 1009:9
third-party [1] - 1018:16
thousand [4] - 755:19, 755:20, 756:1, 756:2
thousands [1] - 1026:18
thread [1] - 718:16
threatening [2] - 974:20, 974:23
three [39] - 716:6, 718:16, 783:14, 789:11, 789:13, 789:18, 798:9, 806:12, 807:25, 808:6, 808:24, 812:8, 841:8, 843:17, 844:2, 845:23, 846:10, 846:25, 848:7, 848:14, 853:12, 853:18, 853:25, 912:15, 913:21, 942:8, 943:10, 965:9, 968:9, 968:10, 993:24, 1014:9, 1018:14, 1020:10, 1022:21, 1024:6, 1024:19, 1025:1
throughout [5] - 798:22, 801:12, 846:6, 861:1, 985:5
thumb [4] - 931:24, 932:9, 933:15, 934:20
thyroid [3] - 943:17, 946:3, 946:20
tightens [1] - 959:1
TIME [1] - 993:14
timeline [3] - 1016:2, 1016:12, 1016:23
timely [2] - 814:5, 931:10
title [3] - 822:10, 876:7, 876:8
titled [4] - 751:3, 893:16, 944:17, 950:8
titration [1] - 830:12
TKI [20] - 956:23, 964:12, 964:13, 964:18, 964:22, 965:1, 968:24, 970:6, 971:12, 971:13, 972:18, 993:5, 993:10, 993:12, 995:8, 1001:4, 1001:10, 1004:4, 1004:5
TKIs [26] - 955:13, 956:7, 962:18, 963:17, 963:22, 964:5, 964:19, 964:23, 965:9, 968:2, 968:9, 971:4, 972:15, 972:20, 974:3, 974:9, 981:6, 982:8, 993:1, 994:11, 994:14, 997:3, 1003:19, 1004:24, 1007:4, 1007:7
today [38] - 790:24, 797:20, 799:18, 824:20, 843:9, 873:5, 877:15, 877:19, 896:14, 901:5, 901:21, 921:8, 921:14, 921:21, 922:1, 922:8, 922:16, 932:21, 943:3, 943:23, 944:25, 945:24, 956:25, 957:7, 962:13, 973:19, 978:21, 986:19, 989:21, 999:1, 999:2, 999:18, 999:20, 1004:15, 1007:5, 1012:11, 1014:2, 1024:7
together [9] - 749:16, 818:25, 843:19, 862:15, 949:1, 984:7, 988:20, 995:11, 1024:12
tolerate [5] - 960:6, 967:17, 974:5, 1009:23, 1010:4
tolerated [1] - 971:7
tolerating [1] - 954:22
tomorrow [4] - 1028:16, 1028:25, 1030:22, 1031:5
Tong [3] - 884:21, 885:6, 932:4
Tong's [5] - 829:21, 829:23, 931:21, 932:8, 934:14
took [2] - 718:23, 928:22
tool [1] - 827:20
toolbox [1] - 827:21
Top [1] - 876:9
top [15] - 757:3, 772:22, 802:24, 877:3, 914:24, 953:6, 967:5, 980:6, 983:6, 983:9, 984:19, 1002:8, 1015:24, 1016:4
topics [3] - 867:20, 1013:12, 1029:21
total [9] - 717:11, 785:12, 785:15, 795:19, 795:20, 980:4, 982:5, 983:8, 985:20
toward [3] - 801:17, 950:9, 983:23
towards [1] - 914:24
toxic [1] - 1004:8
toxicity [6] - 819:1, 974:8, 998:4, 1004:23, 1005:1, 1005:16
toxicological [3] - 725:1, 725:2, 725:5
tracking [1] - 779:12
transcript [2] - 706:23, 1031:9
transduction [1] - 992:11
transformation [1] - 919:20
translates [1] - 785:8
travel [1] - 958:9
treat [16] - 949:5, 959:23, 964:6, 971:6, 972:21, 991:1, 991:2, 993:5, 993:10, 994:9, 994:12, 997:2, 1002:14, 1002:19, 1006:21, 1009:20
treated [8] - 950:6, 950:18, 953:25, 979:13, 980:2, 980:4, 980:7, 996:23
treating [10] - 741:13, 870:12, 871:15, 927:21, 940:10, 940:12, 960:25, 993:20, 1004:11, 1004:16
treatment [58] - 750:13, 941:12, 943:16, 945:6, 945:12, 945:13, 945:16, 945:17, 945:19, 949:11, 950:13, 950:17, 951:5, 953:22, 962:14, 962:19, 965:5, 965:10, 965:18, 966:14, 967:15, 967:23, 968:2, 968:18, 969:4, 969:11, 969:15, 970:16, 972:12, 972:18, 982:10, 995:23, 995:24, 995:25, 996:9, 996:16, 996:19, 997:3, 997:8, 998:1, 998:12, 999:1, 999:18, 1002:13, 1003:19, 1004:10, 1004:15, 1004:20, 1004:21, 1005:20, 1005:21, 1005:23, 1006:15, 1007:16, 1009:13, 1026:20
treatment's [1] - 1010:13
treatments [4] - 947:8, 962:5, 962:15, 982:23
treats [2] - 974:19, 996:14
tree [8] - 814:3, 814:7, 814:11, 814:13, 815:16, 816:18, 817:9, 829:3
trees [1] - 829:7
Trial [2] - 705:6, 705:13
trial [35] - 763:11, 797:17, 803:9, 819:12, 828:19, 863:11, 863:14, 913:1, 930:16, 950:1, 955:16, 956:10, 958:5, 960:11, 968:16, 968:17, 968:20, 970:1, 970:18, 971:11, 971:12, 972:2, 972:5, 972:6, 972:25, 973:2, 999:22, 999:25, 1000:13, 1000:19, 1003:13, 1020:25, 1021:1, 1021:3, 1028:22
trials [5] - 940:3, 953:14, 972:17, 1000:13, 1023:22
tried [3] - 916:13, 956:20, 1029:17
Triozzi [1] - 1031:11
trouble [1] - 756:9
Trout [14] - 839:16, 839:20, 840:6, 840:7, 842:25, 889:19, 894:6, 895:3, 896:7, 896:13, 935:8,

938:7, 941:20, 942:21
trout [1] - 894:4
TROUT [1] - 839:22
true [42] - 748:3, 752:22, 786:14, 794:6, 827:8, 827:12, 827:21, 830:10, 831:17, 832:16, 862:25, 864:18, 865:7, 896:21, 896:22, 896:25, 919:24, 922:1, 923:1, 955:9, 962:7, 962:12, 964:16, 964:17, 964:20, 964:25, 965:17, 966:4, 969:1, 971:9, 971:10, 971:15, 972:7, 972:19, 974:6, 974:7, 974:16, 974:17, 1010:17, 1019:5, 1025:21, 1031:8
truly [1] - 1000:15
truth [2] - 955:14, 957:6
TRX [1] - 981:1
TRx [1] - 982:5
TRxs [1] - 982:5
try [10] - 738:8, 752:1, 784:15, 838:19, 879:17, 904:12, 1004:19, 1025:16
trying [11] - 735:10, 735:19, 737:3, 801:16, 916:5, 925:4, 927:8, 932:24, 933:19, 1020:17, 1029:17
tubercular [1] - 726:6
tumor [2] - 963:18, 995:8
tumors [1] - 945:11
tune [1] - 838:19
TUNNELL [1] - 705:17
turn [89] - 710:3, 710:12, 712:11, 713:15, 714:23, 715:5, 718:13, 718:21, 723:7, 724:18, 725:13, 726:20, 732:24, 733:15, 736:6, 737:16, 756:4, 778:24, 799:15, 800:2, 801:21, 802:16, 804:11, 805:4, 806:17, 810:7, 810:9, 810:15, 810:23, 813:13, 814:9, 815:21, 816:18, 817:14, 819:18, 819:25, 820:11, 821:18, 823:13, 844:13, 846:2, 846:20, 847:5, 847:6, 847:11, 847:16, 848:15, 848:24, 849:16, 855:8, 857:20, 858:7, 859:18, 861:14, 868:18, 869:15, 871:18, 872:2, 874:1, 874:10, 876:13, 877:7, 879:5, 880:1, 883:11, 887:2, 888:8, 890:11, 893:4, 893:15, 941:3, 944:4, 946:21, 947:11, 949:22, 950:8, 950:19, 951:7, 951:15, 951:22, 952:5, 952:23, 954:25, 979:20, 990:9, 992:20, 995:17, 998:20, 1017:24
turndown [1] - 992:14
turned [5] - 730:11, 815:2, 882:7, 992:12, 992:21
turning [14] - 711:23, 718:5, 798:12, 808:17, 809:21, 811:5, 813:4, 813:18, 818:4, 819:6, 819:20, 822:7, 824:19, 1023:17
turns [4] - 730:16, 877:17, 889:6, 889:14
twenty [1] - 872:15
twenty-four [1] - 872:15
twice [1] - 948:10
two [55] - 706:25, 708:13, 782:23, 785:22, 806:5, 806:11, 808:6, 808:10, 812:8, 812:23, 813:1, 813:23, 814:1, 815:9, 817:1, 817:4, 819:4, 820:18, 822:7, 842:8, 846:5, 847:23, 849:1, 850:19, 855:11, 859:2, 859:6, 862:14, 882:2, 882:5, 885:7, 889:10, 913:21, 914:23, 916:22, 932:8, 932:16, 945:1, 947:6, 950:11, 953:11, 955:17, 965:12, 969:9, 971:24, 975:3, 982:2, 983:12, 983:13, 984:6, 984:18, 996:12, 1018:12, 1024:6, 1026:10
type [18] - 738:12, 763:9, 799:6, 817:8, 818:8, 842:7, 842:12, 843:12, 867:20, 879:23, 885:24, 888:11, 898:20, 903:18, 926:18, 926:20, 1000:24, 1027:8
types [6] - 846:4, 846:5, 909:21, 963:18, 997:3, 997:19
typically [9] - 755:18, 802:10, 804:14, 806:23, 815:8, 816:11, 817:22, 958:22, 999:17
tyrosine [35] - 732:10, 939:22, 940:3, 940:6, 948:12, 950:6, 951:3, 956:19, 981:7, 982:9, 982:21, 992:9, 992:10, 992:16, 992:18, 992:20, 993:1, 993:2, 993:3, 994:1, 994:24, 995:2, 996:20, 997:6, 999:4, 1001:8, 1002:5, 1003:6, 1003:14, 1003:16, 1004:2, 1005:10, 1008:22, 1009:25

U

U-F-F [1] - 1011:24
U.S [6] - 979:18, 981:13, 985:14, 985:16, 985:21, 1031:12
U.S.D.C.J [1] - 705:14
ultimate [4] - 742:12, 799:24, 942:2, 942:4
ultimately [12] - 763:17, 804:22, 812:19, 824:24, 831:8, 837:20, 838:12, 959:10, 960:25, 961:1, 1021:19, 1023:7
UNC [1] - 1013:9
unchanged [1] - 859:24
unclear [1] - 865:13
under [32] - 739:16, 755:20, 756:2, 774:18, 776:25, 780:11, 800:10, 815:23, 816:23, 838:15, 839:23, 845:11, 849:1, 859:7, 859:13, 859:24, 867:18, 872:9, 879:2, 886:16, 892:8, 893:15, 901:3, 933:14, 936:5, 936:20, 938:18, 946:15, 946:19, 976:1, 976:22, 989:11
undergo [1] - 894:1
undergoing [1] - 946:8
undergraduate [3] - 841:1, 841:19, 841:21
underlying [4] - 780:7, 780:9, 781:3, 783:16
underperformed [1] - 1000:15
understood [5] - 714:13, 714:18, 743:23, 827:8, 827:10
undertake [1] - 933:3
undesirable [3] - 881:24, 882:1, 888:21
unevaluated [1] - 1022:4
unexpected [7] - 807:24, 888:18, 889:2, 891:3, 891:9, 891:16, 1001:19
unexpectedly [2] - 888:19, 889:15
unfavorable [1] - 1010:4
unfelt [1] - 995:18
unfortunately [4] - 787:18, 887:3, 915:15, 1005:15
Unfortunately [1] - 887:7
uniformly [2] - 993:24, 1008:21
unique [6] - 733:12, 733:13, 734:6, 886:22, 898:8, 964:13
unit [3] - 774:24, 812:23, 813:1
United [1] - 876:10
UNITED [1] - 705:1
units [3] - 853:17, 932:8, 932:16
universe [1] - 863:21
University [6] - 841:2, 939:17, 977:14, 977:17, 990:19, 1013:2
unknown [4] - 754:25, 755:2, 755:21, 756:3
unless [3] - 755:21, 766:9
unmet [14] - 942:10, 955:4, 956:22, 957:3, 962:1, 962:13, 967:19, 992:4, 995:23, 1004:10, 1004:15, 1004:21, 1005:23, 1006:5
unobjectable [2] - 837:8, 837:18
unobjectionable [2] - 836:25, 837:16
unpatentable [1] - 892:13
unpredictable [9] - 799:20, 807:23, 828:4, 828:6, 828:7, 906:23, 907:10, 910:21, 935:22
untreated [2] - 952:4, 1000:3
unusual [1] - 971:23
up [97] - 706:18, 707:9, 708:6, 709:9, 712:25, 713:20, 719:20, 720:15, 721:18, 722:16, 722:21, 723:7, 726:25, 729:3, 731:3, 731:25, 735:21, 735:24, 742:23, 743:24, 744:11, 745:19, 745:20, 750:16,

750:19, 755:17, 756:6, 758:3, 772:19, 773:8, 777:13, 778:8, 778:9, 780:21, 781:6, 782:12, 783:5, 783:21, 789:7, 790:9, 795:12, 797:22, 802:13, 802:14, 809:7, 812:10, 819:12, 826:20, 827:25, 828:18, 829:2, 829:8, 831:20, 832:21, 833:2, 833:11, 849:8, 853:10, 854:5, 858:24, 866:19, 868:20, 885:7, 890:16, 898:25, 899:4, 900:9, 913:3, 918:20, 929:3, 930:21, 931:10, 934:21, 940:5, 941:4, 944:11, 947:8, 966:7, 966:8, 970:18, 973:17, 979:7, 982:25, 984:10, 985:9, 987:9, 990:1, 997:13, 1011:19, 1012:15, 1015:3, 1015:12, 1015:22, 1020:2, 1028:22, 1030:4

updated [1] - 931:15

upper [1] - 745:22

usage [1] - 980:16

Usage [1] - 944:18

usages [1] - 984:7

useable [2] - 798:7, 861:4

useful [7] - 726:11, 769:23, 783:18, 931:11, 997:23, 1008:1, 1008:5

usefulness [1] - 741:12

utilize [1] - 799:6

utilized [1] - 999:20

V

validity [2] - 799:24, 942:2

valsartan [1] - 959:15

value [4] - 835:8, 835:10, 838:17, 953:15

values [1] - 812:7

vandetanib [2] - 964:9, 994:17

vapor [1] - 919:14

variability [3] - 785:25, 786:1, 787:7

variable [5] - 739:4, 786:7, 830:3, 920:1

variables [5] - 802:19, 802:21, 827:24, 828:14

variation [1] - 778:7

variations [2] - 714:13, 796:2

varied [4] - 983:19, 984:2, 984:21, 985:2

varies [1] - 980:14

variety [1] - 997:24

various [14] - 715:11, 734:12, 739:16, 743:10, 775:25, 858:12, 862:11, 878:3, 897:6, 897:8, 964:3, 964:6, 979:16, 1022:9

Various [2] - 774:17, 774:21

vary [6] - 786:16, 795:20, 795:22, 805:22, 805:23, 956:7

VEGF [11] - 940:3, 948:12, 950:6, 951:3, 955:13, 956:7, 956:9, 956:19, 956:23, 958:23, 1003:14

VEGFR [4] - 965:2, 965:5, 965:9, 965:13

verbally [1] - 858:14

version [4] - 706:19, 858:22, 859:20, 937:25

versus [13] - 950:5, 950:24, 951:20, 952:13, 953:5, 956:20, 968:24, 970:8, 970:20, 972:10, 1000:1, 1001:4, 1004:5

vessels [1] - 959:1

via [5] - 738:8, 767:13, 856:19, 990:19, 1014:20

vice [1] - 977:20

view [7] - 710:4, 812:11, 859:25, 892:14, 1022:18, 1024:14, 1025:3

virtually [2] - 920:13, 922:13

vitae [1] - 990:5

vivo [2] - 878:8, 878:21

vocabular [1] - 928:9

Volume [3] - 705:6, 899:20, 929:7

volume [2] - 893:8, 913:10

W

walked [1] - 861:5

warranted [1] - 766:6

watch [8] - 790:15, 796:23, 839:13, 938:8, 976:7, 989:2, 1011:13, 1027:20

water [17] - 752:11, 759:10, 759:19, 759:22, 760:22, 761:3, 761:13, 761:22, 798:13, 877:4, 877:9, 877:11, 878:1, 878:12, 878:19, 891:12, 959:2

ways [11] - 761:1, 761:11, 763:24, 841:12, 897:6, 897:8, 898:11, 898:12, 925:7, 947:6, 993:19

weak [7] - 803:14, 808:25, 810:14, 811:15, 812:1, 829:11, 881:24

weaker [1] - 817:20

Wednesday [1] - 705:12

week [7] - 846:7, 857:19, 861:1, 862:4, 930:9, 1015:8, 1015:17

weeks [3] - 838:22, 838:24, 839:5

weigh [1] - 1019:23

weighing [2] - 1022:8, 1023:21

weight [2] - 881:25, 889:9

weights [1] - 817:25

welcome [1] - 902:20

well-defined [1] - 822:5

well-flowing [1] - 728:25

well-known [3] - 775:6, 931:24, 932:1

whatnot [1] - 967:18

whereby [1] - 814:4

Wherein [2] - 900:18, 901:9

whichever [2] - 778:14, 930:11

white [1] - 736:17

whole [10] - 749:10, 821:14, 841:22, 870:5, 936:21, 958:25, 960:22, 961:1, 1006:14, 1008:22

wide [2] - 799:23, 1024:3

widely [2] - 770:23, 805:23

WIGMORE [36] - 705:21, 938:10, 938:21, 938:24, 939:11, 939:12, 940:15, 940:16, 941:4, 941:5, 941:11, 941:16, 942:5, 942:6, 942:14, 942:16, 943:5, 943:6, 946:21, 946:24, 947:11, 947:13, 952:5, 952:8, 952:23, 952:24, 954:25, 955:1, 957:20, 957:21, 961:9, 976:5, 991:14, 1006:19, 1011:8, 1027:25

willing [1] - 1029:13

WILMERHALE [1] - 705:20

Wilmington [1] - 705:11

wing [1] - 724:8

WINSTON [1] - 706:4

wish [1] - 764:24

WITNESS [45] - 714:25, 715:7, 718:19, 718:24, 758:4, 774:2, 779:2, 797:10, 826:23, 827:2, 834:16, 838:3, 838:7, 838:24, 839:4, 839:14, 839:20, 839:25, 854:11, 862:8, 862:10, 864:13, 864:21, 889:22, 894:4, 913:6, 929:5, 938:9, 938:15, 938:20, 952:7, 972:19, 976:19, 980:22, 989:3, 989:8, 989:13, 1006:7, 1006:11, 1011:22, 1012:3, 1023:11, 1025:17, 1026:6, 1027:21

witness [13] - 764:13, 833:10, 839:22, 840:8, 895:7, 938:11, 938:17, 976:21, 989:10, 1006:3, 1011:16, 1011:25, 1025:5

wondered [1] - 1003:25

word [16] - 748:5, 786:6, 786:8, 786:9, 786:17, 786:24, 788:14, 788:20, 788:24, 853:7, 854:22, 855:6, 855:17, 897:20, 900:11, 901:1

words [13] - 837:4, 837:6, 850:17, 853:16, 862:22, 863:2, 873:1, 890:20, 893:2, 902:2, 926:5, 1026:1

works [1] - 1029:10

world [3] - 910:24, 920:8, 920:10

worry [2] - 959:24, 960:8

worst [1] - 766:2

worth [1] - 1030:17

worthwhile [1] - 1010:19

write [4] - 787:13, 821:2, 872:16, 1030:17

written [9] - 843:11, 854:3, 857:6, 857:21, 859:19, 914:21, 936:15, 936:20, 982:6

wrote [3] - 853:17, 915:19, 920:20

X

X-axis [1] - 862:12

x-axis [1] - 862:15

X-ray [2] - 857:17, 862:5

XL184 [3] - 720:11, 720:13, 720:21

XRPD [10] - 862:1, 865:2, 865:9, 897:11, 897:17,

897:18, 897:22, 898:6, 898:8, 903:9
XRPDs [1] - 862:3
Xs [1] - 805:13

Y

year [10] - 952:10, 955:15, 955:19, 957:16, 985:14, 985:15, 985:19, 993:25, 1020:25
years [14] - 735:18, 838:22, 840:24, 844:19, 930:25, 940:8, 940:14, 949:20, 954:6, 955:17, 960:10, 990:15, 1006:16, 1023:21
yellow [2] - 824:9, 870:8
yesterday [22] - 743:9, 750:1, 779:5, 851:13, 853:15, 854:14, 856:25, 859:1, 860:4, 861:19, 869:9, 874:3, 877:17, 877:21, 880:24, 881:6, 885:6, 888:23, 889:14, 890:9, 890:15, 891:11
yield [3] - 717:9, 849:20, 885:24
you-all [1] - 1029:8
you.. [1] - 899:16
yourself [7] - 827:17, 830:14, 840:4, 939:1, 977:1, 989:17, 1012:7
Yurkerwich [1] - 797:12
YURKERWICH [41] - 705:22, 797:11, 797:14, 797:22, 797:23, 799:15, 799:16, 800:2, 800:3, 801:21, 801:22, 802:16, 802:17, 804:23, 804:25, 805:4, 805:6, 806:17, 806:19, 808:17, 808:18, 809:7, 809:8, 809:21, 809:23, 810:9, 810:11, 810:15, 810:17, 810:23, 810:25, 811:5, 811:6, 811:16, 811:19, 821:2, 821:4, 826:10, 833:7, 833:9, 839:11

Z

zero [3] - 890:16, 890:17, 890:20