IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

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

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

Monday, October 23, 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

-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 2001
Azurity v. Exelixis
IPR2025-00210

APPEARANCES CONTINUED:

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

-and-

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BY: KURT A. MATHAS, ESQUIRE
BY: ELIZABETH GRDEN, ESQUIRE
BY: BRIAN O'GARA, ESQUIRE

For the Defendants

Also Present:

Dr. Kondal Reddy Bairy

07:49:51

*** PROCEEDINGS ***

DEPUTY CLERK: All rise. Court is now in session. The Honorable Richard G. Andrews presiding.

THE COURT: All right. Good morning and please be seated.

Is everybody ready to go?

MR. PRUSSIA: We are. Plaintiffs is, Your Honor.

MR. LOMBARDI: Yes. And defendant's as well, Your Honor.

THE COURT: All right. Well, then go ahead, Mr. Prussia.

MR. PRUSSIA: Thanks, Your Honor. And before I get started with my opening statement, just two quick things

if I can.

First, I just wanted to -- there -- there's material in their opening statement that we don't think is properly in this case. We don't think now is the right time to raise that. We think it's better to raise it in connection with a particular witness. We just wanted to make sure that was in accordance with Your Honor's expectations as well.

THE COURT: I certainly don't expect people to be objecting during opening statements.

MR. PRUSSIA: And -- and the second thing is there is some case law in their slides. We never understood that to be the appropriate thing to do.

THE COURT: Well, you know, if it turns out -- that's part of the reason why I try to limit the amount of time in these trials. So if people want to spend time telling me case law, I assume they think it's important that I understand it, so I -- you know, but, obviously, this is not the post-trial briefing. So go ahead.

MR. PRUSSIA: We have the same understanding, Your Honor. So, if it pleases the Court, may I start?

THE COURT: Yes.

MR. PRUSSIA: My name is Kevin Prussia and together with my colleagues from WilmerHale and Morris, Nichols, I represent the Plaintiff Exelixis.

08:32:36 Exelixis is an innovative biotechnology company
08:32:39 dedicated to developing targeted therapies for hard to treat
08:32:43 cancers. The Defendant MSN, they make generic drugs.
08:32:48 Now the parties were before Your Honor just last
08:32:51 year for trial and at that trial the Court learned a few
08:32:54 things. The Court learned about Exelixis' breakthrough
08:32:58 cancer drug that's called Cabometyx. The Court learned
08:33:02 about the active compound in Cabometyx and that compound is
08:33:06 called cabozantinib and the Court learned about how that
08:33:10 compound was discovered in 2003.
08:33:13 We're here now because of what happened after
08:33:17 that discovery, that work didn't end with the discovery of
08:33:21 the compound itself. What happened after that was years of
08:33:26 research and years of testing to develop a formulation of
08:33:30 cabozantinib that was safe, effective, and could be
08:33:33 delivered to patients. That work was essential to securing
08:33:39 FDA approval and it was essential to getting this
08:33:42 groundbreaking drug in the hands of patient and the
08:33:44 company's patents on that development work are what's at
08:33:45 issue in this case.
08:33:47 So I'd like to start with a quick refresher on
08:33:49 cabozantinib -- and we have our slide, so if we can give
08:33:52 them up to the Court and to the other side, that would be
08:33:54 great.
08:33:58 Cabometyx is a tyrosine kinase inhibitor.

Tyrosine kinases are enzymes involved in cellular function. When they are functioning properly, these enzymes regulate things like blood pressure in the body. But when they are not functioning properly, these enzymes actually facilitate the abnormal function of cells and they can actually help tumors grow.

Now, that abnormal activity, of course, is unwanted and so tyrosine kinases inhibitors, like Cabometyx, they work to disrupt that abnormal activity.

Now, Exelixis began investigating potential tyrosine kinase inhibitors in the early 2000s and it undertook a significantly vast discovery program. You'll learn that the company investigated nearly 5,000 different compounds, 15 of those compounds actually made it into clinical trials but just one compound made it out of those clinical trials and just one of those compounds received FDA approval and that one compound is cabozantinib.

Now, as I mentioned, that compound was discovered in 2003. It took eight years for it to be approved, first as Cometriq and then later as Cabometyx and that first approval happened in 2012.

This case is about the multiple challenges that Exelixis faced in bringing this compound to patients. First, Your Honor will learn that the company discovered that the cabozantinib compound itself, you'll here that

referred to this week as the free base. The company discovered that that free base was highly unstable. The second problem arose out of the company's novel discovery of an impurity that arose during manufacture of the cabozantinib API, the active pharmaceutical ingredient, and also during the drug product as well. The name of that impurity is 6,7-dimethoxy-quinoline-4-ol, and you'll hear it referred to this week as the 1-1 impurity.

Now, Exelixis discovered the 1-1 impurity and discovered that it was genotoxic. Now that means that this impurity itself could cause cancer, so these, of course, were significant problems. They threatened the effectiveness and safety of the drug, let me explain why.

First, when you have an unstable compound like the free base is, the problem is it can unexpectedly convert to a different compound with different properties. So when that happens, the drug that a patient is getting could actually be entirely different from the drug that the patient intended to take.

And with respect to these impurities, certain types of impurities, like in particular this 1-1 impurity, they can be significantly harmful to patients. As I mentioned, this particular impurity had the potential to cause cancer.

So, solving these problems were critical to

developing a safe and effective treatment and they were essential to obtaining FDA approval. And the Court will hear about this work from two Exelixis scientists, Dr. Khalid Shah and Dr. Jo Ann Wilson. Now, Dr. Shah who is here in the courtroom today and will testify live for Your Honor, he was a leader of the formulation development team and he's now one of the company's vice presidents.

Dr. Wilson is no longer at the company but during the development years she was vice president of chemistry, manufacturing and controls and you will hear her testimony by deposition.

Now, both Dr. Shah and Dr. Wilson will describe the work that was required to solve the problems that I just described, and first you'll hear from Dr. Shah, and he will explain what the company did to investigate how to make the cabozantinib free base more stable. And one of the things that you'll hear that the company did, it considered whether to formulate the free base as something known as a salt.

Now, at a very, very high level, a salt can be formed by the reaction of an acid and a base under certain conditions. And here, the base -- the base is the free base, the cabozantinib compound itself. To try to form a salt you need to react that free base with an acid. This is a gross oversimplification. As Your Honor will learn, salt formation is a chemical reaction and like most other

chemical reactions it's highly unpredictable. You don't know what you're going to get until you actually do the work.

And you will hear that Exelixis investigated several potential salts of cabozantinib. Each salt had a different mix of properties; some were more stable, others were more soluble, others more pure.

Now, ultimately Exelixis identified something called a malate salt -- a crystalline malate salt as the salt that provided the best suite of properties for cabozantinib. And as you'll hear, malate salts are very rarely used in pharmaceutical drug development. You'll learn that it's just -- it has been used just 0.26 percent of the time. And you'll -- there are reasons for that and Your Honor will learn those reasons, the reasons why the malate salt is so rarely used.

But Dr. Shah will tell you that Exelixis discovered that the crystalline malate salt was the right choice for cabozantinib and he'll explain to you why. It was the result of extensive testing, extensive characterization, and most importantly it was the result of having a unique -- an understanding of the unique properties of the cabozantinib free base itself.

Dr. Shah will describe those properties to you and he'll explain why identifying the crystalline malate

salt as the salt that was best suited for the properties of the free base compound, that was not predictable. In fact, it was unexpected and you'll learn that the company submitted evidence of unexpected results to the Patent Office, the Patent Office credited those results and allowed the claims.

But the work didn't end there. After identifying this stable salt, crystalline malate salt, there was another challenge and that's this 1-1 genotoxic impurity and one of the critical issues that the Court will learn was the amount of the 1-1 impurity that formed during the manufacturing process. The manufacturing process, I should say, of the active ingredient, the API, which is the crystallin cabozantinib malate salt that I just described.

The company discovered that 1-1 would form during that manufacturing process, but the amount was too high. It was too variable. It was not consistently able to be controlled.

So, the company worked to identify the root causes of 1-1 formation, and in the course of doing so they discovered that the 1-1 impurity could form as a degradation product as a result of exposure to heat and water. So, that discovery led the company to do two things.

The first thing it needed to do was change the method it was using to make the cabozantinib malate itself,

the active pharmaceutical ingredient. The API.

The second thing it needed to do was to control the impurity during manufacturing of the drug product. The formulated API with excipients. So that was extensive work. It involved investigating changes to this synthetic chemistry, Your Honor will learn that it involved investigating changes to the process conditions. It was laborious trial and error and there were multiple tradeoffs along the way.

And you will hear that these changes to the process for making the API, that they were critical. But it didn't end there because, of course, the ultimate drug product that's delivered to patients is not just the API. It's the API that's been formulated and -- with excipients and been made into tablets and capsules.

And this also presented a challenge. As Dr. Shah will testify, the company discovered that the 1-1 impurity actually increased as the drug was exposed to things like heat, water and oxygen. But you'll learn that exposure to things like heat, water and oxygen is absolutely essential and necessary in the process for making a tablet and a capsule.

So there's this dilemma. The company needed to have -- needed to ensure that the end product, these tablets and capsules, it was important to ensure that the end

product was pure and stable over time. And when I say "pure," I mean free of this 1-1 impurity. It took a lot of work. You'll hear about dozens of experiments. Multiple simulations. But only after that work was the company able to finally control the levels of 1-1 in the drug product.

And Dr. Wilson will testify that it took eight years from start to finish to arrive at the inventions claimed in the '349 patent. The result of that work were, of course, submitted to the Patent Office. And that's why we're here today.

The inventions in this case enabled cabozantinib to go from a laboratory discovery to a real world cancer therapy. And to date, the commercial embodiments have been used to treat over 54,000 patients. Now, this -- the next slide shows the label from one of those commercial embodiments, Cabometyx. Currently Cabometyx is approved to treat three types of cancers: Renal cell carcinoma which is a type of kidney cancer, hepatocellular carcinoma which is a type of liver cancer, and differentiated thyroid cancer.

Exelixis actually continues to investigate new therapeutic areas for Cabometyx to potentially help additional cancer patients in need and you'll learn that multiple clinical trials with the drug are ongoing.

The Court will hear from Dr. Daniel George, who is a medical oncologist at Duke University school of

medicine. He specializes in the treatment of kidney cancer. The Court may remember Dr. George from the first trial.

And he will explain how Cabometyx changed the landscape for patients with cancer, and this is particularly true for patients who had developed -- who were on another drug, developed a resistance to that drug, may have had no other options. Cabometyx provided a lifeline for those patients.

Today, patients on Cabometyx, they're not just postponing death by a few months. They're actually surviving and living with their cancer for years. And the fact -- and this is important because the fact that patients are actually taking Cabometyx for years, that makes this discovery of a safe formulation -- safe formulation that's free of genotoxins like the 1-1 impurity, it makes it even more critical.

So, let's talk about the patents.

There are four of them in the case. And they fall into two categories. First is the crystalline malate salt patents, and second is the low impurity patent. I'll start with the crystalline malate salt patent. They consist of the '439, the '440, and the '015 patents. And they all claim priority to January of 2009.

One claim from each asserted -- one claim from each patent asserted in this case. It's Claim 4 for the

'439 patent, and that claim covers the crystalline malate salt of cabozantinib, the API itself. Claim 3 of the '440 patent claims a pharmaceutical composition of the crystalline malate salt of cabozantinib. And Claim 2 of the '015 in the bottom right-hand corner of the screen, that claims a method of treating kidney cancer with the crystalline malate salt of cabozantinib.

Now, MSN does not dispute that its generic drug product infringes the crystalline malate salt patents. It's stipulated to, infringement. That's not an issue for this trial.

The only issue for this trial is the validity of the crystalline malate salt patents. And on that, MSN makes two arguments.

First they argue that the claims are invalid for lack of written description. The second thing they argue is that the claims are invalid for obviousness-type double patenting.

Now, MSN initially has also asserted claims for lack of enablement and statutory obviousness under Section 103.

THE COURT: Right. I saw they were dropped last week.

MR. PRUSSIA: That's exactly right, Your Honor. They also no longer challenge the priority date. We had a

discussion about that at the pretrial conference. That's not an issue that's in dispute either. So let's talk about what's in dispute.

First written description. And as we talked a little bit during the pretrial conference, we previewed this for Your Honor. MSN makes an argument that the crystalline malate salt patents, they cover -- they cover what they say is a genus of what they call crystalline forms. And they say for us to satisfy 112, there needs to be written description support for these different forms in the specification.

But as Your Honor will learn, the claims don't require that. There's no reference to forms anywhere in these claims. You won't see it, and that's because it's not there.

This entire concept of forms, this is something that MSN has created and has is inserting into the claims. All the claims require is a malate salt of cabozantinib that is crystalline. The word "crystalline" is simply used in the claims to describe the state of matter of the cabozantinib material. It tells you that the material is crystalline as opposed to amorphous. That's it.

I'm sure MSN will profess to you that they're not reading anything into the claims, but that's what they're doing. They're trying to rewrite these claims to

make them require something that they do not.

There's another thing. I took a look at their slides last night, and I suspect that MSN will suggest to Your Honor that there may be something improper about these claims, either based on their scope or the timing of them. And, in fact, Your Honor may have -- may remember during the pretrial conference Mr. Cooper referred to these as pop-up patents. He also said they broadened the scope of what Exelixis invented to cover MSN. That's wrong on both counts.

These patents didn't just pop up. Exelixis first filed claims to crystalline cabozantinib and malate all the way back in January of 2010. That was years before MSN came on the scene. And these patents, they don't broaden the scope of what Exelixis invented. They're continuations of an application that was filed in 2010, and the interesting thing about it, there hasn't been any added matter. It's the same material that's been in the disclosure since then.

So, the idea that Exelixis somehow broadened the scope of this invention just to cover MSN, it's entirely disconnected from the actual facts. But not only that, it's disconnected from any actual issue in this case. Your Honor may remember there were some equitable claims that they tried to assert. Those have been dismissed.

The Court will hear from Dr. Bernard Trout. He's been a professor of chemical engineering at MIT for over 25 years. Now, Dr. Trout will walk the Court through the claims, and he will explain that the plain and ordinary meaning of the term crystalline is a solid having long-range order in its molecular structure. That's the plain and ordinary meaning.

Nothing more is required.

And Dr. Trout will explain that the specification plainly supports the claims under that ordinary meaning. But his analysis doesn't stop there. He will explain that even if MSN is right in its interpretation of the claims, there's adequate written description there, too. In fact, the specification describes two crystalline malate salt polymorphs of cabozantinib. Now, a polymorph is what they're calling forms. And those two polymorphs are the N-1 and the N-2 forms.

Now, as Dr. Trout will explain to Your Honor, the specification discloses that they are highly stable, and a person of ordinary skill in the art would understand that they are the most -- the most relevant and they are representative polymorphic forms.

The law doesn't require anything more. The law doesn't require an inventor to describe every possible embodiment of his or her invention. Representative examples

will do.

Common structural features will do. And that's what we have here in this case.

MSN also argues obviousness-type double patenting, and they do so based on the claim of the compound patent that was at issue in the first case. So, let's put up on the slide Claim 5 of the compound patent. That's on the left. That's the 473 patent. It was the patent that was at issue in the first case.

And on the right we have the three -- the claims of the three crystalline malate salt patent. Now, Claim 5 covers the cabozantinib freebase -- that's the structure that you see on the screen -- or, optionally, a pharmaceutically acceptable salt thereof.

Now, in contrast, because we're supposed to -- under obviousness-type double patenting, we're supposed to be doing a comparison of the two claims, looking at the claims of the crystalline malate salt patents, there's much more. They cover a particular type of a cabozantinib salt. That's the malate salt that I described. They cover a crystalline cabozantinib malate salt. They cover a pharmaceutical composition of that crystalline malate salt. And they cover methods of treating kidney cancer with that pharmaceutical composition.

So, obviousness-type double patenting, again, it

asks the question of whether these later issued claims, are they patentably distinct from the base claim?

Here, the claims are distinct. But even if you look beyond the claims and you consider the specification, the disclosure in the '473 patent, in the compound patent, Your Honor will learn that the compound patent doesn't disclose many of the limitations required by the crystalline malate salt patents. It does not disclose any malate salt of cabozantinib. And I want to emphasize this. There is not a single example in the '473 patent of any cabozantinib salt. It's not there.

There's no disclosure of any crystalline cabozantinib material. There's no disclosure of any example of a pharmaceutical composition of cabozantinib. And there's no disclosure of any example of treating kidney cancer with cabozantinib.

All of that is missing from the compound patent. It's not in the claims. It's not in the specification. But all of that is required by the asserted claims of the crystalline malate salt patents.

But there's more. You will learn that the compound patent, it actually has a definition of pharmaceutically acceptable acids that relates to what a pharmaceutically acceptable salt is. And I have that definition on the screen. The interesting thing about it is

that it lists 24 acids that could be used to form a salt with the cabozantinib -- with a freebase. 24 different acids are listed. Malic acid is not one of them.

Now, there's a reference to maleic acid, M-A-L-E-I-C. When I first saw that, I thought, is that a typo? No. It's actually a different thing. Malic acid is not listed within the definition of pharmaceutically acceptable acid addition salt.

Now, MSN will ask you to ignore that and everything else that I just said, and I expect they'll suggest to you two things.

First, that a person of skill would have been motivated to form a salt with cabozantinib because it had what they will say is poor water solubility. You'll hear it referred to as aqueous solubility, but obviously that's just referring to the water solubility of cabozantinib.

The second thing they'll say is that the skilled person would have arrived at the malate salt from what MSN will characterize as a routine salt screen. Let's talk a little bit about that.

On the first point you'll hear from Dr. Trout that there were no reports of any problems with the solubility of cabozantinib in the prior art. And there's a real simple easy to understand reason for that. And that's because there was no information at all in the prior art

about the solubility of cabozantinib.

But even if a skilled person could have somehow determined on its own that cabozantinib had poor water solubility, Dr. Trout will explain to Your Honor why that's not how -- that's not -- that would not have motivated a person of skill in the art to formulate a salt. That's not how drug development works. You don't consider individual properties in a vacuum. Poor water solubility by itself is not a barrier. And Dr. Trout will explain why.

You will also learn that cabozantinib, it actually has unique properties that allows it to overcome its poor water solubility. So, solubility by itself, that would not have been a motivating factor to form a salt.

But even if we assume that's -- even if we assume that I'm wrong, they're right, that a person of skill in the art would have been motivated to form a salt, that goal would not have led a skilled artisan to the malate salt. And here's why.

And Dr. Koleng will testify on this issue. Now, Dr. Koleng, as Your Honor will remember, I said during the pretrial conference and you'll learn during trial, he's the only expert in this case who has actually done this work. He's the only one who's advised the pharmaceutical drug company on selecting the best salt from a salt screen. He's worked on multiple salt screening projects and he has over

20 years of experience in the field of drug development.

Now, what Dr. Koleng will explain to you is the numerous considerations that go into conducting a salt screen. As well as identifying the best salt. Now, you will learn that malic acid is what's referred to in the literature as a complicated choice for salt formation. And Dr. Koleng will explain the reasons why malic acid is a complicated choice.

He'll also explain to you why the properties of cabozantinib, why they actually matter, why you need to know them. And why, if you did, it would have made the choice of malic acid an even more complicated choice for cabozantinib.

Now, at the end of the day, the Court will learn that salt selection is highly unpredictable. There's no reasonable expectation that you'll even get a salt to begin with, let alone identify what the right -- identifying the right salt.

And even if you do get a salt, identifying that right salt depends on the properties of the base compound. You don't know what problems you're looking to solve with the salts if you don't know that a problem even exists.

There was no information in the -- in the prior art that would have led a person of skill to select the malate salt. The only way they get there is through hindsight.

Now, there's one more thing on this point. The Patent Office allowed the claims after receiving evidence -- experimental evidence demonstrating the unexpected results of the invention. Dr. Shah will explain those results to the Court. And there's something that's really important that I want to emphasize for Your Honor.

You will not see any experimental evidence from their side contradicting this evidence.

The crystalline malate salt patents are not invalid for obviousness-type double patenting.

Let me pivot to talk about the low impurity patent.

Now, the '349 patent discloses a pharmaceutical composition for cabozantinib malate that's essentially free of the genotoxic 1-1 impurity. Claim 3 is the only asserted claim. And there are two issues for the Court on this patent: Infringement and validity.

Now, the infringement dispute focuses on just one thing, and that's the requirement that the drug -- the drug product includes what's called a glidant. There is no dispute that all of the other limitations are met. The only issue is this glidant limitation.

The invalidity challenge focuses on MSN's assertion that the claims are obvious. I'll take the infringement issues first.

Now, as the Court will learn, a glidant is a type of excipient. As Your Honor knows, excipients are inactive ingredients and they can serve a variety of functions. Sometimes they can serve more than one function at a time.

Now, an example of an excipient is if you have a situation where the amount of active ingredient is really low, but you need to bulk it up to make a tablet, you may use an excipient called a filler to help you do so. If you have an active ingredient that's difficult to dissolve, you might need an excipient called a disintegrant to help the tablet do so.

In this case, where you have API mixture that does not flow well, you need an excipient called a glidant. A glidant improves flow and allows the powder to mix evenly so that the blend is -- the blended mixture is uniformly distributed in the tablet.

Now, there -- as the Court will learn, there is no explicit definition of a glidant in the '349 patent, but the parties all agree on the plain meaning of the term. The Court will first hear from Dr. Koleng this morning. And he will testify that a that a glidant is a substance that improves the flow characteristics of a powder mixture.

The Court will also hear testimony from MSN's witnesses, including its expert, Dr. Maureen Donovan. And

she will acknowledge that the common definition of a glidant is an excipient that improves flow characteristics of tablet granulations.

So, where's the dispute? There is an excipient in the MSN drug product called granulated corn starch. It's a modified version of corn starch. The parties dispute whether that granulated corn starch fits the definition of a glidant, and the evidence will show that it does.

That evidence will include MSN's own words. The Court will learn that MSN submitted documents to the FDA in their ANDA, and in those documents, they reported that the cabozantinib malate that's used in their drug product, it "exhibits poor flow properties," that's a quote. And this is precisely the reason that glidants are used, to improve flow in a poorly flowing API.

MSN went on to explain to the FDA that it used granulated corn starch specifically to enhance the flowability of the granules. That's highlighted on the screen and Your Honor will see that evidence later this morning.

And then later, they stated to the FDA that "granulated corn starch plays an important role in flow characteristics." Now, these are MSN's own words. They made them in a sworn document submitted to the FDA.

But MSN, I'm sure, will come in and try to wave

them off and suggest to you that they don't believe -- that they don't mean what they say. MSN will tell Your Honor that the statements it made to the FDA about its cabozantinib drug product, they were not actually statements about its cabozantinib drug product. They're going to suggest to you that they were just parroting information from the background literature. The documents don't say that. MSN never told the FDA that. MSN told the FDA that they were describing their own drug product.

Now, MSN will also suggest that it added its granulated corn starch, not -- its granulated corn starch not as a glidant but as something referred to as diluent. And they will show you a table from their ANDA where the granulated corn starch is in a row next to the term diluent.

Now, a diluent is an excipient that dilutes the API, as you might suggest -- as you might understand. And we deny that the addition of granulated corn starch dilutes the API. The reason for that is, as you'll learn, the addition of any excipient will do that. Any excipient is a diluent. But just because granulated corn starch dilutes the API, that doesn't mean that it doesn't -- it's not also a glidant.

It doesn't take away from the fact that MSN -- that it does what MSN told the FDA that it does -- that it worked. It doesn't take away from the fact that it also

09:05:15 1 does what MSN told the FDA it does, which is improve the
09:05:21 2 flow of the mixture.
09:05:22 3 And you will hear from both sides' experts that
09:05:25 4 an excipient can have multiple functions. And an excipient
09:05:30 5 that improves flow, that's a glidant.
09:05:33 6 And, again, you'll hear from Dr. Koleng on this
09:05:35 7 issue. He reviewed MSN's ANDA filings, their manufacturing
09:05:40 8 data, as well as other materials. And he will explain why
09:05:43 9 he concluded that granulated corn starch is a diluent -- is
09:05:48 10 a glidant in MSN's generic product.
09:05:51 11 Now, Dr. Koleng will telling you that the
09:05:55 12 granulated corn starch is added at a point in the
09:05:59 13 manufacturing process at which glidants are typically added.
09:06:03 14 Now, that's a telltale sign. The point in which the
09:06:06 15 manufacturing process -- the glidant is added in the
09:06:09 16 manufacturing process by MSN is consistent with the point in
09:06:14 17 which it's usually added as a glidant.
09:06:18 18 The next thing he'll tell you is that the
09:06:21 19 granulated corn starch in their drug product is added at a
09:06:24 20 concentration that's consistent with that of glidants. And
09:06:29 21 another thing he'll tell you is that the literature, it
09:06:32 22 identifies starch and its derivatives as a commonly used
09:06:38 23 glidant.
09:06:40 24 The evidence will show that the granulated corn
09:06:44 25 starch in MSN's drug product is a glidant. MSN told the FDA

that its granulated corn starch improves flow. If it improves flow, it's a glidant. And the Court should take MSN's own words for it.

So, this brings me to the last issue: MSN's challenge to the validity of Claim 3 on obviousness grounds.

The '349 patent teaches the following three key concepts: First, the need to minimize this 1-1 impurity in pharmaceutical compositions; second is the disclosure of an improved method for making the cabozantinib malate API with consistently low levels of the 1-1 impurity; and the third is formulations of pharmaceutical compositions that are essentially free of the 1-1 impurity.

Now, returning to the claim, Claim 3, as the Court will see, requires that the drug composition be "essentially free of the 1-1 impurity." And there's a definition for "essentially free" in the patent. And it's defined to mean 200 parts per million or less. And as you'll learn, that corresponds to 0.02 percent of the final drug composition. It's an exceedingly small amount.

MSN will argue that Claim 3 is obvious. And to make that argument, they depend on Exelixis' own work. That's described in a patent publication called Brown. And MSN takes the Brown reference and they combine it with generic references discussing impurities and formulations. None of those references have anything to do with

09:08:39 cabozantinib.

09:08:39 Now, Brown, as I mentioned, is a patent
09:08:44 application that -- for which Exelixis is -- is an assignee.
09:08:51 And that patent application ultimately led to the
09:08:55 crystalline malate salt patents that I discussed earlier.

09:08:58 And according to MSN, there's a process in Brown
09:09:02 that inherently produces crystalline malate, the API, that's
09:09:08 essentially free of the 1-1 impurity. And MSN will tell you
09:09:12 that once you have this API, it would then be obvious to
09:09:15 formulate a drug product that's also essentially free of the
09:09:18 1-1 impurity. There are several flaws with this argument,
09:09:22 I'm just going to highlight three of them for the Court.

09:09:25 The first problem they have is that Claim 3,
09:09:29 it's not directed to API. It's directed to a pharmaceutical
09:09:33 composition. Which, as the Court knows, is the API with the
09:09:37 formulated drug product.

09:09:39 The problem for MSN is the Brown process does
09:09:42 not produce a drug product. It's, instead, directed to a
09:09:47 process for making the API before it's formulated into a
09:09:51 drug product. The issue in this case, the issue is not
09:09:56 whether the Brown process produces API that's essentially
09:10:00 free of the 1-1 impurity. That doesn't answer the question.
09:10:04 The question in this case is whether the final drug product
09:10:08 is essentially free of 1-1. And they won't be able to show
09:10:13 you any evidence of that with the Brown process.

09:10:16 The second problem for MSN, as Your Honor will
09:10:20 learn, is that the 1-1 impurity, it wasn't in the prior art.
09:10:25 Nothing in the prior art taught the existence of 1-1.
09:10:29 Nothing in the prior art taught that 1-1 would be harmful to
09:10:33 humans. And nothing in the prior art taught that the 1-1
09:10:38 impurity should be avoided in pharmaceutical products.
09:10:42 There was simply no information. No information
09:10:45 that would have motivated a person of skill to make a
09:10:48 cabozantinib formulation that was essentially free of the
09:10:52 1-1 impurity.
09:10:53 If you don't know that something is a problem,
09:10:57 why would you be motivated to avoid it?
09:11:00 And on these points, Your Honor, we'll hear from
09:11:03 Dr. David MacMillan and Dr. Allan Myerson. Dr. MacMillan,
09:11:08 of course, is the Princeton professor and Nobel prize winner
09:11:12 in chemistry who testified at trial last year. Dr. Myerson
09:11:15 is professor of chemical engineering at MIT.
09:11:21 And they will tell you and you will learn that
09:11:23 nothing in the prior art taught a person of skill that the
09:11:25 1-1 compound would be in the API, or that it would arise in
09:11:29 synthesizing the API, or during the formulation of the drug
09:11:33 product.
09:11:34 And you will also hear that a skilled artisan
09:11:36 would have had reasonable expectation of controlling the 1-1
09:11:39 impurity, given the utter lack of teachings in the prior

art. And they will explain for you why a person of skill would have needed this missing information to arrive at the claimed inventions.

The third problem for MSN is that even if you just consider the Brown process by itself, they won't even be able to show you that the Brown process inherently produces API that's essentially free of 1-1. They won't even be able to show you that.

And it's a simple thing. If the Brown process does not inherently produce API that's essentially free of 1-1, then it follows that the Brown process is not inherently produced formulated drug product that's essentially free of the 1-1 impurity.

Now, as Your Honor knows, the standard for inherency is exceedingly high. MSN must establish that this Brown process necessarily and inevitably results in the claimed invention; not going to be able to show you that. Instead, what the evidence will show is that the Brown process results in a wide range of the 1-1 impurity and that range includes levels that far exceed those allowed by the claims.

You will learn that the Brown process discloses a method of making the cabozantinib malate API that allows for significant variation in the process. In fact, it uses the word "approximately" multiple different times to

identify the conditions that can be varied.

And there's more. When MSN makes their inherency argument, there's something you will not see. You will not see any experimental evidence from them of any testing done by any of their experts to replicate the Brown process to meet their burden to show that inherently produces material that's essentially free of 1-1.

Instead, what they'll do is they'll show you and talk about three batches of cabozantinib malate, three batches that were made 15 years ago by a contract manufacturer called Regis. This is a company that Exelixis retained to help make development batches of cabozantinib malate.

Now, those three batches, they had low levels of the impurity, but those three batches are not enough to demonstrate that the Brown process would always and necessarily and inevitably produce cabozantinib malate that's free of the 1-1. And here's why. The evidence will actually demonstrate that it didn't. Dr. Shah will testify to this.

Years before this litigation, years before MSN came onto the scene with allegations of inherency, Exelixis submitted sworn documents to the FDA reporting that the Brown process resulted in unacceptably high levels of the 1-1 impurity. And you will learn that the Brown process was

referred to internally at Exelixis as Process A-2, and you'll see -- you see on the slide they are highlighted Process A-2. You'll learn that these documents show the A-2 process resulted in 1-1 levels in the API that were sometimes as high as 411 PPM. That's more than two X required by the claims.

And that's in the API. Remember Claim 3 is about the drug product. There's no inherency there. The fact that the A-2 process did not consistently produce low levels of the API, that's going to be demonstrated by the documents. And as Dr. Shah will explain, it's the entire reason why Exelixis had to develop a new process.

The company had to develop -- had to -- had to move off of Process A-2 precisely because it didn't consistently deliver low levels of the 1-1 impurity. And you will hear deposition testimony of Dr. Wilson. She was in charge of the team that developed that new process. It's called B-2. And on the screen, you'll see and she will show you, as well as Dr. Shah, that the process B-2 resulted in controlled levels of the 1-1 all the way down to the two PPM level.

Now, Dr. Wilson will tell that you it took eight years for Exelixis to develop and arrive at process B-2 and MSN will suggest to you with its allegations of inherency that all of this work, it wasn't necessary because A-2, that

was good enough. But that's counterfactual. It belies the eight years of work that Exelixis invested in arriving at a different process.

And that process is B-2. That B-2 process is what's disclosed in the patent.

And there are two more things. The first is this: The Patent Office considered Brown -- actually, it's a U.S. counterpart to Brown. The Patent Office had it during prosecution and they didn't make any rejection for it based on inherency.

The second thing is that the Patent Office allowed the claim after receiving experimental evidence describing unexpected results of the invention and Dr. Shah will describe those events to Your Honor.

And finally, in addition to unexpected results, the Court will hear evidence of additional objective indicia of non-obviousness. You'll hear from Dr. George and Mr. Tate. Dr. George will explain the long felt unmet need by Cabometyx and its remarkable clinical success. And Mr. Tate will explain how that success in the clinic has resulted in significant commercial success of Cabometyx.

Collectively, the patents in this case are a critical part of that success. The Court heard a lot about the cabozantinib compound in the first trial and I just want to be very clear that inventing the compound was a critical

breakthrough.

But the work didn't end there. What works in the lab doesn't always result in something that works in the real world.

The patents in this case helped bridge that gap and help deliver cabozantinib into the hands of patients. Cancer patients fighting for their lives must know that the drug they're taking is not only effective in treating their cancer, but is stable and is safe. Cancer patients want their drug that they're taking to treat their cancer. They want to know that that drug is not itself causing cancer.

Exelixis spent years researching and developing a formulation that would achieve these things. And the patents in this event -- in this case are the result of that work, and that's why in the end we'll ask the Court to render judgment in favor of Exelixis on all counts and we will ask the Court to enjoin MSN from launching its generic drug product until after the patents expire.

Thank you.

THE COURT: Thank you, Mr. Prussia.

Mr. Lombardi.

MR. LOMBARDI: Yes, Your Honor. May I hand a couple of these up?

THE COURT: Sure.

MR. LOMBARDI: Good morning, Your Honor. And

09:19:20 for the record, George Lombardi on behalf of MSN.

09:19:24 Your Honor, we're going to talk about two
09:19:28 separate sets of patents, the crystalline malate salt
09:19:31 patents and the formulation patents that, as you've heard.
09:19:34 And I'm going to start with the crystalline salt patents and
09:19:37 we'll talk about our two invalidity arguments and then the
09:19:40 formulation patent where we'll talk about a non-infringement
09:19:43 argument and invalidity argument.

09:19:44 But first, I wanted to give Your Honor a little
09:19:47 bit of the background, just remind Your Honor of what you've
09:19:51 heard about before.

09:19:53 As you know, about a year-and-a-half ago, the
09:19:55 parties were before you for trial and we had a trial on the
09:19:59 '473 compound patent and a trial on the '776 polymorph
09:20:05 patent. Put those claims up just to show you, but
09:20:08 they're -- those were the claims that were at issue in
09:20:12 that -- at issue in that case.

09:20:13 In that case Your Honor issued a decision in
09:20:17 which you found that the '473 patent was valid and you found
09:20:22 that the '776 polymorph patent was not infringed. In other
09:20:27 words, the polymorph that MSN used did not infringe the '776
09:20:32 patent. So, that's the context in which we start this case.

09:20:37 And in this case we're talking about two types
09:20:42 of patents. Obviously there are multiple patents in the
09:20:45 crystalline malate salt patent group, but two types of

patents, two family of patents.

The crystalline malate salt patents involve crystalline malate salt of cabozantinib, as you've -- as you've heard, and the '349 formulation patent involves a particular formulation that they have claimed an invention on.

So that's what we're going to be talking about today is those patents claim up, were filed during the litigation that was going on concerning the '473 and '776, and now they are they are out there and we're dealing with them and they're the ones that are at issue in this case.

The malate salt patents -- crystalline malate salt patents, Your Honor. I want to talk about written description.

As Your Honor knows, the hallmark of the written description inquiry is whether the specification demonstrates to the person of skill in the art that the inventor actually possessed the full scope of the invention that's claimed. That's the gist of it. And there are other wrinkles, which we'll talk about as we go through the case.

So, the question here is essentially going to be: Did Exelixis -- did the inventors possess the full scope of what they claim, which is claims to the crystalline -- the malate salt -- the crystalline form of the malate salts.

09:22:10 And so here are the claims themselves,
09:22:12 Your Honor, that are at issue. You saw this before. And
09:22:15 what's common in each of these claims is a malate salt of
09:22:20 cabozantinib wherein the salt is crystalline. And when you
09:22:27 talk about a crystalline salt, Your Honor, what you're
09:22:30 talking about -- crystalline means it's an ordering of the
09:22:33 atoms or molecules within a compound. It's a pattern is a
09:22:39 way of thinking about it.
09:22:40 And when you have a crystalline form of a
09:22:44 substance, it has this pattern of atoms or molecules.
09:22:49 Frequently, when you have one crystalline form of a
09:22:53 compound, there are multiple crystalline forms of a
09:22:56 compound. Not always, but frequently. Most often.
09:23:00 And so what we're talking about here when there
09:23:03 is a claim to the cabozantinib -- the malate salt of
09:23:09 cabozantinib and the crystalline form of that salt, you're
09:23:13 talking about a claim that covers all crystalline forms of
09:23:16 the salt. And I don't think we'd be here today if that
09:23:21 wasn't true because we have a different crystalline form of
09:23:24 the salt than they do and they say we're covered by the
09:23:28 claim. So the full scope of the claims here is as to all
09:23:32 crystalline forms of the salt.
09:23:35 And actually the patent itself, the
09:23:37 specification of the patent makes clear that we're talking
09:23:40 about multiple forms of crystalline. This is from the

patent -- the '439 at Column 8 and it says: Another aspect of this disclosure relates to crystalline forms, plural, of Compound I, which is the cabozantinib, and that each form of the cabozantinib is a separate aspect of the disclosure.

So we're talking about crystalline forms and all -- the scope of the invention is that all crystalline forms of the salt are covered.

So the question here is: Did the specification -- does the specification show possession of the full scope of what they claim as the invention? And here's what the specification actually shows, Your Honor. It shows possession of forms N-1 and N-2. And you can see on the screen, I've just taken some charts from the patent which are representative of ways that a person of skill in the art identifies or characterizes crystalline forms of compounds.

And so, the upper left is something called XRPD which is a way of identifying the peaks of crystalline forms. The one on the right is the thermogravimetric analysis. The one on the bottom left is called differential scanning calorimetry. And the one on the right deals with moisture absorption. These are standard ways for people of skill in the art to identify crystalline forms of compounds and so they did this. They did this in the patent with respect to the N-1 and N-2 forms.

And those are the only forms they disclosed and that's because it's the only forms they invented. They're required when they go to the FDA and they make their filings with the FDA to identify all forms, all polymetric -- polymorphic forms that they're aware of that exist. And when they went to the FDA they told them that forms N-1 and N-2 were the only ones.

And here is the NDA -- the -- what was disclosed to the FDA. They say that the cabozantinib malate exists in two neat, closely related crystalline solid forms, the N-1 and N-2, and then they confirm no other forms were identified in those studies. No other forms.

So, they only disclose the N-1 and the N-2 because they only had the N-1 and the N-2, that's what they disclosed.

And the question for purposes of written description is: Is that sufficient to support claims to all crystalline malate salts? And it is not. And here's why, Your Honor. Because there are other crystalline cabozantinib malate salts out there. There are 11 reported different crystalline salts out there. You have Exelixis. You have MSN's form S. And then you have Mylan and Cipla have also made disclosures.

When you have different forms, you have different patterns, different structures of the atoms inside

09:27:12 the compound. And when you have a different structure, a
09:27:18 different pattern there, that has an effect on the
09:27:22 properties of the compound.
09:27:26 But these 11 forms, Your Honor, are not
09:27:31 necessarily the only forms that exist -- crystalline forms
09:27:35 that exist for cabozantinib. The universe is actually
09:27:40 likely larger than that. We don't know today how many forms
09:27:44 there are or how many might emerge in the future. And
09:27:49 that's because the universe of crystalline salt forms is
09:27:53 potentially limitless and that's because, Your Honor, when
09:27:56 you manufacture and you change parameters of manufacture,
09:28:01 you can make different forms -- different crystalline forms.
09:28:05 So, just on the right here, we've listed a
09:28:08 number of the elements that can go into the manufacture. If
09:28:13 you vary those, you can come up with different forms. And
09:28:16 so, we don't know today how many forms actually might exist
09:28:21 out there. You can't predict how many forms might be out
09:28:25 there based on the chemical structure of cabozantinib. You
09:28:29 can't know how many forms might be out there on that basis.
09:28:32 And so, they do not possess -- they certainly do
09:28:37 not possess the full scope of the 11 forms. And they do not
09:28:41 possess all that could be out there that haven't been
09:28:45 reported as of this time. So it is true that they don't
09:28:52 necessarily have to disclose and describe every single form.
09:28:56 But they can't satisfy the requirement that the forms, the

two forms they did disclose were representative of the entire scope of the claims.

Different forms have different properties. And you're going to hear that different forms of compounds can have -- they do have different crystal structures, different crystalline structures. They have different melting points. They can have different hygroscopicity. They can have different stability, whether it be physical or chemical stability. They can have different solubility. They can have different dissolution rates. They can have different bioavailability and different processing characteristics. And form S, MSN's form, is different in terms of its properties from forms N-1 and N-2 which Exelixis actually discovered.

These differences in properties, Your Honor, can lead to differences in the way -- the effectiveness of the drug, the way the drug is manufactured, the way the drug is taken up by patients. In short, differences in structure, differences in crystalline structure can make a difference in the way that the compound functions. So disclosing N-1 and N-2 does not give a person of skill in the art any prediction as to what other forms might exist. It doesn't give a prediction as to what those forms' success might be as a drug product. It doesn't give the person of skill in the art any prediction or knowledge about what the

properties are.

So, in summary, they invented, they discovered two forms, N-1 and N-2. That's far short, and that's what they disclosed. That's far short of the full scope of the claims. And so, there's no written description. And that's our first argument related to the crystalline malate salt patents.

The second defense that we raise on the crystalline salt malate patents is obviousness-type double patenting, Your Honor. And the gist of obviousness-type double patenting is it's a doctrine that's there to prevent the unjustified time-wise extension of a patent monopoly. And so here's the extension that we're concerned about here today, the reference patent, as it's sometimes referred to. An obviousness-type double patenting analysis is the '473 that we previously talked about. It is to cabozantinib and pharmaceutically acceptable salts of cabozantinib. It expires in August of 2026.

And then the patents at issue here are the malate salt patents. The crystalline malate salt patents are contained within the claims of the '473 patent as to all pharmaceutically acceptable salts and get continued patent protection as things stand now out until January of 2030. So, it is a four-year extension of the patent monopoly. And we believe that it's not justified because it is an obvious

09:32:36 extension of the previous claims.

09:32:39 And so, let me talk about the fact that it's an
09:32:42 obvious extension of the previous claims for a few minutes.

09:32:45 On the left is the claim to the reference -- the
09:32:49 claim of the reference patent that's at issue, the '473, and
09:32:52 on the right are the claims of the crystalline malate salt
09:32:59 patents that expire later. And you can see that's
09:33:02 cabozantinib and -- cabozantinib and the pharmaceutically
09:33:08 acceptable salts thereof are claimed in the '473. And then
09:33:13 in the malate salt patents, crystalline malate salt patents,
09:33:18 there are claims to the crystalline malate salt throughout
09:33:22 all three of those patents as you can see highlighted in
09:33:28 green and yellow.

09:33:30 And there's also some additional claims which I
09:33:33 don't think we'll take much time to show you are obvious.
09:33:37 The idea that you put it into a pharmaceutical composition
09:33:41 was obvious at the time. The idea that it was crystalline,
09:33:45 90 percent plus of all small molecule pharmaceuticals are
09:33:50 crystalline, Your Honor. So, that was obvious. And the
09:33:53 idea that it could be used to treat cancer, that was
09:33:56 specifically disclosed in a published patent application.
09:34:01 Actually it's the published patent application that led to
09:34:05 the '473 patent. So all of those points will not be a
09:34:08 significant issue in the obviousness analysis.

09:34:11 The issue in the obviousness analysis is going

to be whether it would have been obvious to select a malate salt for purposes of this case. And that's what we're going to be talking about.

Your Honor, counsel previewed for you that I did have a case cited in -- in opening. I'm not going to spend a lot of time on this, but I just did want to bring Your Honor's attention to the *Pfizer v. Apotex* case. And I wanted to bring your attention to it because of some factual similarities that I'm going to be -- we're going to be pointing out throughout.

But this case did involve a prior patent, a reference patent that was to pharmaceutically acceptable salts and then claims to a specific salt within that general category. And the Court concluded that it was obvious. And the Court specifically said that because the only parameter that varied is the anion with which to make the salt, which is what we're talking about here, this was routine work. It's the kind of routine work that a person of skill in the art does. And the Court said below, "Nothing more than routine application of well-known problem-solving strategies, developing salts and determining which salts are the ones that will work and are acceptable for use in a pharmaceutical is what formulation scientists do every day."

So, let's talk specifically about the malate salt, Your Honor. And this is just a series of lists that

09:35:57 1 show that malic acid or the malate salt are recognized in
09:36:02 2 the art as acceptable. They have been used in FDA-approved
09:36:08 3 formulations of compounds. And there's still other things,
09:36:16 4 but malate salt is within the universe of things that a
09:36:19 5 person of skill in the art would think about as being a
09:36:23 6 suitable salt for use under these circumstances.
09:36:26 7 In addition, but in addition, there are other
09:36:29 8 things that point towards the malate salt. There's
09:36:32 9 something called the Rule-of-2, and I won't get into all the
09:36:36 10 details here right now. You'll sometimes hear it called
09:36:39 11 Tong, T-O-N-G, Tong's Rule-of-2 as well, Your Honor. And
09:36:44 12 it's a comparison of the pK_a of the compound, in this case
09:36:50 13 cabozantinib, and the acid that's going to be used hopefully
09:36:55 14 to make the salt. If you satisfy the Rule-of-2, then a
09:36:59 15 person of skill in the art would believe it's likely you're
09:37:02 16 going to be able to do it. In this case all the components
09:37:05 17 satisfy the Rule-of-2.
09:37:06 18 The acid used here is generally recognized as
09:37:10 19 safe. It's not toxic. That's another important
09:37:13 20 consideration that would point a person of skill in the art
09:37:16 21 towards the malate -- malate salt. And there's a structural
09:37:20 22 compatibility between the malic acid and cabozantinib that
09:37:25 23 would also make a person of skill in the art believe that
09:37:32 24 malate salt would have a reasonable chance of succeeding.
09:37:37 25 And so, you take the malate salt, Your Honor, and you make

it and then you do the standard testing and a salt screen that any person of skill in the art would do and has done over the years for decades. And you would find out when you did this that it was -- these salts were suitable for use in a pharmaceutical product.

And so, that shows that the selection of malate salt was obvious and shows that obviousness-type double patenting applies in this case to prevent the unjustified time-wise extension of the patents.

One moment, Your Honor. Excuse me, Your Honor.

And so, with that I'll move to the next patent, the formulation patent, the '349 patent. Counsel referred to this, I believe, as the 1-1 impurity patent. We have two arguments here, two positions here, as counsel said, the first of which is that this patent is not infringed. And I do agree with counsel that the only issue for non-infringement is the claim term glidant. And glidant does appear among a list of other excipients in that second paragraph of the claim.

So, what is a glidant? It is an excipient that's used to improve the flowability of a compound, but in scientifically specific ways. The literature notes that there are five ways, five mechanisms of action in which glidants work to help improve flowability.

So, it's not just that a glidant improves

flowability. It has scientifically specific ways in which it does that.

And as you'd expect me to say, Your Honor, MSN does not use a glidant, but that is clear from the ANDA. This is the ANDA that was filed with the FDA, and you can see there are no glidants listed in Table 2.

The substance that Exelixis has pointed to as being a glidant is granulated corn starch. GRASTAR in parenthesis there is the manufacturer, and you'll probably hear that name as we go on. But MSN used granulated corn starch as a diluent. They used it as a diluent. And if you look at GRASTAR's technical manual, technical data, you can see that GRASTAR says in Number 5 that it's corn -- it's granulated corn starch can act as a filler, a binder and a disintegrant. Filler is essentially the same thing as a diluent, Your Honor, but that's the way the technical data says that it's used.

Now, I highlighted in the third paragraph there where it said that it also can have good flowability, but the fact that it can have an impact on flowability doesn't make it a glidant. It has to meet those specific scientific ways of performing in order to be a glidant. And just you'll see that in the art diluents, for instance, are referred to sometimes as affecting flowability. That doesn't make them glidants.

And so here's that, Your Honor. This is from a noted text on formulation dosage forms, drug delivery systems. It defines a diluent as something that's used as fillers to create the desired bulk. That is it's to kind of dilute what's in the tablet or the capsule so that you can create more bulk. And it says it has flow properties and compression characteristics. That doesn't make it a glidant. It's still a diluent. And so, a glidant is not anything. It simply has some impact on flow properties.

In fact, MSN actually did do work with the granulated corn starch as you'd expect, but its work was all around seeing if they could use the granulated corn starch to improve the dissolution profile, not for glidant purposes. And this is testing that you're going to see in the case, in the testimony in the case, Your Honor, where they worked with the granulated corn starch. They varied the amounts of granulated corn starch all to see how that affected the dissolution profile of the compound, not for glidant purposes, not for glidant purposes.

And you're actually going to see lab notebooks about work that they did and considered where they considered some flow properties. You'll see that there's nothing that suggest that the granulated corn starch was being used as a glidant. Now, counsel said that MSN's -- I tried to make a note here -- MSN's own documents show that

09:43:24 the granulated corn starch was being used as a glidant
09:43:30 because there were comments about an effect on flow
09:43:33 properties. Well, first, the fact that something has an
09:43:36 effect on flow properties doesn't in itself make it a
09:43:39 glidant. But, second, those documents predated the actual
09:43:47 testing that was done in house at MSN. And you'll see that
09:43:51 testing. And that testing will show that granulated corn
09:43:56 starch did not improve the flow properties of the compound,
09:44:02 and so glidant is not in the MSN formulation. And there's
09:44:08 no infringement for that reason, Your Honor.

09:44:10 And the last defense, Your Honor, that I want to
09:44:19 discuss with you this morning is the formulation patent, the
09:44:23 defense was it being obvious. Take a look at the claims.
09:44:32 One thing I just want to note, Your Honor, this is maybe
09:44:36 different than some other formulation patent cases you've
09:44:38 seen before because it is very, very broad. It is not the
09:44:47 type of formulation claim that is to very specific amounts
09:44:52 of particular ingredients.

09:44:54 So, for instance, there are claims to it being a
09:44:59 tablet or a capsule and excipients down there in that second
09:45:04 paragraph of text. It just refers to excipients as one or
09:45:09 more fillers. There are many, many things that fall within
09:45:13 that category, one or more disintegrants. Also many, many
09:45:17 things that fall into that category. One or more glidants,
09:45:20 same thing. And lubricants.

09:45:22 So this is an extremely broad claim that simply
09:45:26 says they're claiming that it's inventive to say that some
09:45:30 filler, some disintegrant, some glidant, some lubricant
09:45:35 should be used in this formulation. And our position is
09:45:39 going to be that this is a fundamentally not -- not
09:45:44 inventive, but I get a little bit ahead of myself,
09:45:48 Your Honor.
09:45:48 The other -- the other categories here, the
09:45:50 other elements are that it's a pharmaceutical composition,
09:45:53 as you can see. That's the chemical structure for the
09:45:56 cabozantinib (L)-malate salt. Then the paragraph on tablet
09:46:00 and capsule and excipients.
09:46:03 And then the last paragraph, which Your Honor, I
09:46:06 believe, is going to be the paragraph that's really at issue
09:46:10 here, is the one that deals with having a composition
09:46:14 essentially free of -- and I'll just continue to refer to
09:46:18 that as the 1-1 impurity. And essentially free, as counsel
09:46:24 pointed out, is defined in the patent as being less than 200
09:46:30 parts per million.
09:46:31 So, let me walk through what I think is really
09:46:36 not going to end up being a -- significantly at issue, and
09:46:39 then I'm going to talk in more detail about the essentially
09:46:43 free of the 1-1 impurity in a little bit more detail.
09:46:49 But if you go through here, Your Honor, first,
09:46:51 the cabozantinib (L)-malate salt was previously disclosed in

09:46:57 a piece of art called Brown. So you're going to hear a lot
09:47:00 about Brown in this case. But there's no dispute that that
09:47:04 was disclosed. There's no dispute that Brown also disclosed
09:47:10 the use of cabozantinib in a pharmaceutical composition. No
09:47:15 dispute that it disclosed -- Brown disclosed using
09:47:19 cabozantinib in tablets and capsules. So, those, I don't
09:47:25 believe, will be in dispute.

09:47:26 There is no dispute that Brown discloses
09:47:31 excipients to be used in a composition. So if you look on
09:47:35 the right, you see we've highlighted that Brown calls out
09:47:42 using fillers, just as the claim does. That's in green.
09:47:46 Using disintegrating agents, as the claim does. That's in
09:47:51 blue. Using lubricants, just as the claim does. That's in
09:47:56 purple, I guess you'd call that.

09:47:58 It doesn't specifically list the word "glidant"
09:48:02 as an excipient, but it does list talc, which is known in
09:48:07 the art to be a glidant. So, those are the excipients.

09:48:13 Now, even if glidant isn't specifically
09:48:17 mentioned in Brown, it's very well known in the art. And
09:48:22 it's not just that glidants were known. Glidants were known
09:48:26 to be used in that same group of four excipients that are in
09:48:30 the claims there.

09:48:31 So, in each of these references that we've put
09:48:34 up here, there are formulations suggested that use all four
09:48:39 of those excipients, exact same categories of excipients in

09:48:45 formulations. The one on the right is actually a tyrosine
09:48:50 kinase inhibitor, same class of drug as we're talking about
09:48:54 here.

09:48:54 So, we don't believe there's going to be any
09:48:59 doubt that it was obvious to use those different excipients
09:49:06 in the formulation.

09:49:06 So, let's talk about the impurity. We're not
09:49:10 going to have to spend a lot of time getting into the
09:49:13 chemical structure of the impurity in this case, Your Honor,
09:49:16 but just a few background facts. It's a quinoline, that's
09:49:20 the kind of chemical it is, that's the category it falls
09:49:25 into.

09:49:25 In this case, it's used as the starting material
09:49:30 for making cabozantinib. And when it's an impurity, it can
09:49:36 last throughout that process, perhaps. But if it's in the
09:49:42 cabozantinib formulation or compound at the end, that's what
09:49:47 makes it an impurity. It is a particular type of impurity,
09:49:52 which is important in this case, Your Honor. It's
09:49:56 genotoxic.

09:49:56 And a genotoxic impurity is one that tests
09:50:01 positive in tests for genotoxicity. The most probably
09:50:07 famous test for genotoxicity is called the Ames assay, which
09:50:11 helps you determine genotoxicity. If something is
09:50:16 genotoxic, it's a red flag. It doesn't mean that the
09:50:19 impurity is necessarily carcinogenic, but it -- it is

genotoxic, which means it's something you need to pay attention to. It is a toxic impurity.

And so, it's called the 1-1 impurity. And that, I believe, is the way you're going to hear that referred to throughout this case.

And so, our position, as counsel said, is that the Brown reference sets forth a method of making cabozantinib that inherently is essentially free of the 1-1 impurity. That's our position.

And so, here's what happens in Brown. I'm not going to go through all the steps, Your Honor, but on the right is the basic scheme for the creation for the synthesis of cabozantinib. And when you go through that process, you end up with -- inherently with a compound that is essentially free of the impurity.

How do we know that? We know that from Exelixis' testing. This is testing that they did back in, I think, around 2005, in some of the early testing that they did. I've highlighted the site of the manufacturer. Regis is the name of the manufacturer of three lots. These are important lots, Your Honor. They were used in the -- throughout the process of development. But the three lots from Regis were manufactured according to the Brown process.

And they reported to the FDA about the 1-1 impurity. You can see that down -- highlighted, kind of the

middle of the table. XL 184 is, you can see 1-1, that's the 1-1 impurity. And ND as the result indicates that the impurity was not detected.

And these particular tests, the impurity -- the test was done at a level of detection of 200 parts per million. And so, if it's not detected, it's less than 200 parts per million of the impurity, of the 1-1.

They did further testing at Exelixis. They honed their testing to make it more specific, to make it a finer determination. And we call that GTI testing because it's genotoxicity, you're trying to really be able to locate genotoxic elements. And so, they did that kind of testing. And when they did that kind of testing, they got more precise results. These are all the Regis lots there on the left. And the precise results show levels considerably below 200 parts per million.

So, that shows that when you follow the Brown process to make the active pharmaceutical ingredient, you inherently get something below 200 parts per million.

Now, counsel made reference, he pointed to a document where it showed that the parts per million went up to 411. And there are two notes I'd like to make about that. When we saw that document in discovery, we immediately asked them for the underlying testing, the underlying test results, and they told us that they don't

have them.

Second, we think we know where those results came from. They came from another batch that was manufactured by another organization called Girindus, G-I-R-I-N-D-U-S, Girindus. And Girindus, you'll see, Your Honor, it's very plain on the -- their method of manufacturing, that they deviated from the Brown technique in a number of different ways. They deviated from the Brown technique. They got a different level of -- of impurity.

So, when the -- when the -- the method of synthesis of Brown was followed, you got below 200 parts per million.

Now, that's for the API, the active pharmaceutical ingredient, making that. And you -- the next step is, would it have been obvious to maintain that level of impurity when you go into the actual tablet or capsule? The actual dosage form? And the answer is yes, Your Honor.

Any person of skill in the art would want to minimize impurities, but specifically genotoxic impurities. A person of skill in the art would be motivated to do that. If there's any doubt, this is a reference out there in the art that specifically talks about formulators should know that no toxic substances are being formed in the process.

This is also something that the FDA requires. There's an FDA guidance that says that you need to know what

09:55:45 the toxins are. So a person of skill in the art would be
09:55:49 motivated to keep the 1-1 impurity below 200 parts per
09:55:56 million.

09:55:56 And as to whether that requires something
09:56:02 inventive to take it from the API of less than 200 parts per
09:56:08 million to a capsule or a tablet that's less than 200 parts
09:56:12 per million, the patent provides -- the claims don't tell
09:56:16 you any specific means of accomplishing getting to the
09:56:20 essentially pure composition here. No specific means that
09:56:27 you have to employ to get there.

09:56:29 And, actually, the text of the patent itself
09:56:32 says that formulations of this kind can be done using the
09:56:37 knowledge of the art, using the routine skill and the
09:56:43 knowledge that exists in the art and known techniques.

09:56:46 So, not anything other than routine work to take
09:56:50 an API that's essentially free of impurity and move to a
09:56:55 capsule or a tablet that is as well.

09:56:57 And so, for that reason, Your Honor, we believe
09:57:00 that the formulation patent is obvious.

09:57:05 I'll just pop up here -- I'm not going to talk
09:57:07 about all this, Your Honor. I think you've met all of these
09:57:10 experts that we're going to present in the past case and
09:57:15 perhaps in other cases. But I'll let them introduce
09:57:18 themselves to you. But that's the lineup of witnesses that
09:57:21 you're going to be seeing on our part in this case.

09:57:24 So, thank you very much, Your Honor.

09:57:26 THE COURT: All right. Thank you, Mr. Lombardi.

09:57:34 MR. PRUSSIA: So, Your Honor, for our first witness, Ms. Wigmore is going to introduce the first witness.

09:57:43 THE COURT: All right.

09:57:43 MR. PRUSSIA: Thank you.

09:57:51 MS. WIGMORE: Good morning, Your Honor. We'll now be moving to the plaintiff's case-in-chief, and we have a couple of housekeeping matters we just wanted to raise with the Court.

09:58:00 First of all, for the crystalline malate salt patents, which are -- the asserted claims are the '439 patent, Claim 4, the '440 patent, Claim 3, and the '015 patent, Claim 2. The parties have stipulated to infringement, and that's at Docket Number 26, filed on June 21st, 2022. I just wanted to make sure that was clear in the record. So our case will focus on infringement of the '349 patent.

09:58:29 Another housekeeping matter is after we play a deposition designation, our first live witness will be Dr. John Koleng. As we explained to the Court at the pretrial conference, he will testify about infringement during our case-in-chief and then respond to the validity arguments raised by MSN when we rebut that case.

09:58:50 I will be presenting his testimony on
09:58:53 infringement. And my colleague, Kevin Yurkerwich, will be
09:58:57 presenting his testimony on validity. We've made that clear
09:59:00 to MSN without objection, but wanted to make sure the Court
09:59:03 was aware of that.
09:59:04 THE COURT: Okay.
09:59:05 MS. WIGMORE: So at this point, we will now play
09:59:08 the deposition testimony by video from the March 15th, 2023,
09:59:14 deposition of Mr. Ravikumar Nithiyanandam, the head of
09:59:19 formulations R&D at MSN. And in connection with
09:59:23 Mr. Nithiyanandam's testimony, Exelixis will offer three
09:59:28 exhibits which, with your permission, Your Honor, I'd like
09:59:31 to hand up to the Court.
09:59:32 THE COURT: All right.
09:59:35 MS. WIGMORE: And those exhibits will be
09:59:39 PTX-724, which is referred to in the deposition as
09:59:43 Exhibit 7; PTX-676, which is referred to in the deposition
09:59:50 as Exhibit 5; and PTX-678, which is referred to in the
09:59:57 deposition as Exhibit 4.
10:00:00 And just for the record, PTX-678 is the same
10:00:05 document as DTX-215, which will be offered through other
10:00:10 witnesses.
10:00:10 So the time allocation for these designations
10:00:15 are, for Exelixis, ten minutes and 57 seconds, and for MSN,
10:00:21 four minutes and 27 seconds.

10:00:28 May we proceed with the testimony, Your Honor?
10:00:30 THE COURT: Yeah.
10:00:32 (Beginning of videotape deposition.)
10:00:32 Q. Good afternoon. Could you please state your full
10:00:36 name for the record?
10:00:36 A. Good morning. My name is Ravikumar Nithiyanandam.
10:00:45 Q. What was your role when you joined MSN?
10:00:48 A. As head of formulations R&D.
10:01:00 Q. What is your -- and -- but has your title of head of
10:01:05 formulations R&D remained consistent from 2016 to the
10:01:09 present?
10:01:10 A. Yes.
10:01:15 Q. My question is: Why did MSN want to explore this
10:01:19 excipient that it had never used before?
10:01:21 A. Well, it was a granulated starch. So when I say
10:01:29 "granulated starch," it's a processed material. And this
10:01:35 excipient had some special characteristics. And based on
10:01:40 that, MSN reached out for a sample.
10:01:44 Q. What special characteristics was -- was MSN focused
10:01:49 on?
10:01:54 A. As I said, it's a granulated starch, so any
10:01:59 granulated particle in general have a, you know, bigger
10:02:03 particle size.
10:02:07 Q. And you are familiar with the composition of MSN's
10:02:11 ANDA product. Correct?

10:02:12 A. Yes.
10:02:18 Q. What is a glidant?
10:02:19 A. A glidant is a chemical that improves the flow
10:02:30 properties of a -- of a -- of a blend.
10:02:35 Q. So Tab 11A is a document with Bates Number MSN
10:02:41 Cabo_99752. And my question for you is whether Exhibit 4 is
10:02:50 Section 3.2.P.2 from MSN's ANDA?
10:02:55 A. Yes.
10:03:01 Q. And is this the pharmaceutical development report you
10:03:05 just mentioned a few minutes ago?
10:03:07 A. That's correct.
10:03:15 Q. And if we go to the next page, 99786, there is a
10:03:22 heading that says Process Selection.
10:03:34 A. Is this the page you are referring to?
10:03:36 Q. Yes.
10:03:38 Under the heading, there is a table entitled
10:03:42 flow properties of the drug substance. Do you see that?
10:03:45 A. Yes.
10:03:49 Q. And if you look below the table, there's a statement
10:03:54 that the API exhibits poor flow properties. Correct?
10:04:02 A. That's correct.
10:04:07 Q. So MSN's cabozantinib drug substance exhibits poor
10:04:17 flow properties. Correct?
10:04:19 A. That's correct.
10:04:25 Q. Now, the pharmaceutical development report in -- that

we're looking at was submitted to FDA. Correct?
A. Yes.
Q. So MSN told the FDA that its cabozantinib drug substance had poor flow properties. Correct?
A. Yes. That's what the document states.
Q. And MSN has not withdrawn this statement. Correct?
A. That's correct.
Q. Okay. And on Page 99787, there is a table entitled justification for the initial risk assessment of the formulation variables.
Do you see that?
A. Yes.
Q. Is the information in this table truthful and accurate, as far as you're aware?
THE WITNESS: Based on the initial risk assessment, what all is mentioned is true.
Q. Do you see the statement that: Granulated corn starch is used as a diluent in minimal concentration and it enhances its flowability of the granules.
A. Yes, I see the statement.
Q. Okay. So it's a true statement that granulated corn starch enhances the flowability of the granules. Correct?
THE WITNESS: So as I mentioned before, counsel, this table reflects the risk assessment that was performed before the formulation development trials were initiated.

10:06:32 And this statement is purely based on literature
10:06:36 information.
10:06:39 BY MS. PIROZZOLO:
10:06:40 Q. So the literature information says granulated corn
10:06:45 starch enhances the flowability of the granules. Is that
10:06:48 right?
10:06:51 A. Yeah. It's -- it's a general statement that the
10:06:56 literature contains. However, this will actually depends on
10:07:00 the specific formulation in which this excipient is used.
10:07:07 Q. And MSN has not withdrawn the information provided in
10:07:13 this table from its ANDA submission. Correct?
10:07:17 A. That's correct.
10:07:21 Q. And my question is: Here on the page with Bates
10:07:31 Number 99849 is a figure entitled final manufacturing
10:07:37 process flow chart of cabozantinib tablets. Correct?
10:07:42 A. That's correct.
10:07:48 Q. Okay. And my question for you is: Does this flow
10:07:51 chart truthfully and accurately depict the final
10:07:56 manufacturing process for MSN's ANDA product?
10:08:04 A. Yes.
10:08:08 Q. Section 2.3.1.9 of the product development report
10:08:16 describes optimization of level of granulated corn starch.
10:08:22 Correct?
10:08:23 A. That's correct.
10:08:31 Q. And the first sentence of the discussion of the

optimization of granulated corn starch level says: The level of granulated corn starch plays an important role in flow characteristics. Correct?

A. Yes. That's what the document states.

Q. Okay. And that's what MSN told the FDA. Correct?

A. That's correct.

Q. And that's a true statement. Correct?

A. Yeah. It's a true statement based on the literature information.

Q. Well, this is referring to testing done by MSN. Correct?

A. That's correct.

Q. Okay. So this is not based on literature, but is based on the studies done by MSN. Correct?

A. That's correct. Let me -- I would like to just see the conclusion of this experiment.

Q. Okay. I mean, if you want control of the document, then, to --

A. Sure.

THE WITNESS: Oh. Well, the conclusion reads as follows: Based on the above results, no significant difference was observed in the dissolution profiles of cabozantinib tablets 60-milligram with low, in parenthesis, 6.7 percent weight by weight, optimal, 9.70 percent weight by weight. And high, 12.7 weight by weight, concentration

of diluent, granulated corn starch. Hence, 9.7 percent of granulated corn starch was proposed as optimum concentration. And this conclusion was based more on the dissolution rather than the flow property of granulated corn starch.

Q. So that we have the full understanding here, MSN described for the FDA investigation it had done into three different weight by weight percentages of granulated corn starch. Correct?

A. That's correct.

Q. And the very first sentence of its description of those experiments was that the level of granulated corn starch plays an important role in flow characteristics. Correct?

A. That's correct.

Q. What was the basis of the conclusion that 9.71 weight by weight was optimal?

A. So the basis of this conclusion to be optimal was more so based on the dissolution.

Q. Could you go a little up to the section optimization of level of granulated corn starch.

A. Yeah.

Q. And so, in the Section 2.3.P of the ANDA regarding the drug product, MSN told the FDA that the level of granulated corn starch plays an important role in flow

10:12:29 characteristics. Correct?
10:12:30 A. Yes, that's what the document states.
10:12:39 Q. And that's what MSN told the FDA?
10:12:41 A. Yes.
10:12:47 Q. Exhibit 7 is Bates numbered MSN CABO_1830. That's
10:12:55 the starting page. And it's titled justification for
10:13:01 microbial method validation.
10:13:04 And my question is: Did MSN prepare this
10:13:09 document?
10:13:10 A. Yes.
10:13:16 Q. What is the purpose of this document?
10:13:17 A. Well I say -- see from the conclusion that, you know,
10:13:28 method validation protocol number MVP/100942/01 and summary
10:13:38 report number MVR/100942/01 was used for -- for testing the
10:13:51 microbial enumeration test and specified microorganisms and
10:13:56 -- so this microbial -- I mean, the conclusion is that this
10:14:00 specific report and protocol holds good for granulated
10:14:06 starch as well.
10:14:09 Q. And then 5.1.4 has an additional statement.
10:14:16 Do you see that?
10:14:16 A. Yes.
10:14:25 Q. Okay. And it -- it starts off saying "strach" but do
10:14:30 understand that -- that word to be intended to be starch?
10:14:35 A. Yes.
10:14:37 Q. Okay. And the second sentence of 5.1.4 says:

Starched are -- starch are used in pharmaceutical industry for a wide variety of reasons, such as an excipient in tablet and capsule as a diluent, as a glidant, or as a binder.

Do you see that?

A. Yes.

Q. And that's a true statement. Correct?

A. Yes. I think this statement is based on literature.

Q. Did MSN use granulated corn starch to function as a glidant in its cabozantinib ANDA product?

A. No.

Q. Has MSN conducted any tests to determine whether the granulated corn starch acts as a glidant in its ANDA product?

A. MSN used granulated starch as a diluent and all the evaluation that was performed by MSN on granulated starch was to evaluate this function as a diluent.

(Conclusion of videotape deposition.)

THE COURT: All right. So why don't we take a morning break of 15 minutes here -- or did you want to do something else?

MS. WIGMORE: Your Honor, I just wanted to offer formally those exhibits that I referenced previously.

THE COURT: Sure.

MS. WIGMORE: So the plaintiffs offer PTX-724,

PTX-676 and PTX-678.

THE COURT: All right. And I'm just curious, you said that PX-678 also had some DX number.

MS. WIGMORE: That's correct.

THE COURT: You sort of said it's the same thing. Couldn't we just -- wherever we're planning on using that DX, call it by the PX-678 number?

MS. WIGMORE: There had been an agreement by the parties to call it by DTX-215, but then it was in the deposition as 678. We would be happy to switch out 215 if MSN is willing.

THE COURT: Well, why don't you work on that because I really only want to have it in the record as one thing. Okay. I don't really care which thing, but let's have it as one thing.

MS. WIGMORE: All right.

THE COURT: All right. So, we'll take a 15-minute break.

DEPUTY CLERK: All rise.

(Recess was taken.)

DEPUTY CLERK: All rise.

THE COURT: All right. Everyone be seated. And let's proceed.

MS. WIGMORE: Your Honor, we have resolved the exhibit number issue. We will replace the PTX-678 with

DTX-215. And we will offer DTX-215.

THE COURT: Okay. Admitted without objection, I assume.

MR. COOPER: No objection.

(DTX Exhibit No. 215 was admitted into evidence.)

MS. WIGMORE: And as our next witness, plaintiffs call Dr. John Koleng.

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

THE WITNESS: John, J-O-H-N. Joseph, J-O-S-E-P-H. Koleng, K-O-L-E-N-G. Junior.

JOHN JOSEPH KOLENG, JR., the witness herein, after having been duly sworn under oath, was examined and testified as follows:

MS. WIGMORE: May I proceed, Your Honor?

THE COURT: Yes.

DIRECT EXAMINATION

BY MS. WIGMORE:

Q. Good morning, Dr. Koleng, would you please introduce yourself?

A. Yes.

Good morning. My name is Joe Koleng.

Q. Dr. Koleng, have you been retained as an expert by Exelixis, Inc. in this case?

10:32:57 A. I have.
10:32:58 Q. Are you being compensated for the time you spend
10:33:01 working on this case?
10:33:02 A. I am.
10:33:04 Q. Is your compensation dependent in any way --
10:33:09 A. No.
10:33:09 Q. -- on the outcome of the litigation or the substance
10:33:12 of your opinions?
10:33:12 A. No, ma'am.
10:33:14 Q. Now, generally speaking, what issues have you been
10:33:16 asked to address in this case?
10:33:18 A. I've been asked to address issues related to
10:33:21 invalidity against the '349 and certain sections of validity
10:33:25 related to the crystalline malate patents.
10:33:28 Q. And just to clarify in terms of infringement, your
10:33:31 addressing the '349 patent; is that right?
10:33:33 A. At this time, yes.
10:33:34 Q. Okay. And for the purposes of your testimony here
10:33:37 this morning, will you be focusing on the infringement
10:33:39 issue?
10:33:40 A. Yes, ma'am.
10:33:41 Q. And will you testify later in the case about the
10:33:44 validity of the crystalline malate salt patents?
10:33:46 A. Yes.
10:33:48 MS. WIGMORE: If we could please have PDX-2.2.

BY MS. WIGMORE:

Q. Dr. Koleng, can you please describe your educational background?

A. Yes. I have a undergraduate degree in pharmacy and a graduate degree in pharmaceutics, both from the University of Texas in Austin. I am a licensed pharmacist in Texas.

Q. Where are you currently employed?

A. I'm currently employed as a vice president at TFF Pharmaceuticals in Austin, Texas.

Q. What is your -- what are your responsibilities in that position?

A. I lead a group that is responsible for the product development activity related to incorporation of the proprietary technology for particle engineering in creating products both for development in animals and human use for the company.

Q. What type of products?

A. These particular products, this company focuses on inhalation dry powder products.

Q. Are they pharmaceutical products?

A. Yes, ma'am.

Q. Are you familiar with the term drug formulation?

A. Yes, ma'am.

Q. What is drug formulation?

A. So, it's a reasonably broad term that encompasses a

multitude of things, the first being an active pharmaceutical ingredient, the drug substance which is the active moiety in a product, for instance, and the manufacturing process then that is used to incorporate ingredients that ultimately result in a product that a patient or a subject would ultimately consume.

Q. At a high level, what types of formulation projects have you been involved in?

A. Solid oral dosage forms. These would be things people would understand to be tablets, capsules, for instance. Dry powder inhalation products like we're doing at TFF currently as well as periorbitals, like injectables, topicals, things applied to the skin, among others.

Q. For how long have you been involved in drug formulation?

A. As far back as 1991.

Q. Do have any teaching responsibilities?

A. I hold an adjunct appointment at the University of Texas where I'm invited to give lectures from time to time. Yes.

Q. What subjects do you teach?

A. Drug delivery, drug formulation, manufacturing technology, experience in the pharmaceutical industry as well as quality and regulatory considerations.

Q. Have you published any books or papers related to

drug formulation?

A. Yes, ma'am.

Q. Are you the inventor of any patents or patent applications relating to drug formulation?

A. Yes, ma'am. Currently 19 U.S. patents and applications.

Q. Do you work as a consultant for the pharmaceutical industry?

A. Yes, I do.

Q. If you could please turn to Tab 1 in your binder, and if we could have PTX-0777. What is this document?

A. This is my CV.

Q. Does this provide an accurate summary of your educational experience and your professional experience?

A. Yes, ma'am.

MS. WIGMORE: Your Honor, Exelixis offers Dr. John Koleng as an expert in pharmaceutical formulation.

MR. COOPER: No objection.

THE COURT: You may proceed.

BY MS. WIGMORE:

Q. Dr. Koleng, if you could turn, please, to Tab 2 of your binder which is JTX 0004. Do you recognize this as U.S. Patent Number 11,298,349.

A. Yes, ma'am.

Q. Can we refer to this as the '349 patent for short?

10:37:10 A. Yes.
10:37:11 Q. If you could turn, please, to Claim 3 of the '349
10:37:14 patent which appears on Page 20.
10:37:17 Do you understand Exelixis is asserting Claim 3
10:37:20 of the '349 patent against MSN in this case?
10:37:23 A. That's my understanding, yes.
10:37:26 Q. If you could turn, please, to Tab 3 in your binder,
10:37:29 this is the amended statement of uncontested facts. And if
10:37:34 we could pull up paragraph 63.
10:37:39 A. 63?
10:37:39 Q. Which is on Page 10.
10:37:41 A. 63.
10:37:42 Q. Yeah. Page 10. 63.
10:37:45 A. Okay.
10:37:45 Q. Could you please read paragraph 63 of the statement
10:37:48 of uncontested facts?
10:37:50 A. MSN submitted ANDA Number 213878 to the FDA under 21
10:38:00 U.S.C. Section 355(j), seeking FDA approval to engage in the
10:38:07 commercial manufacture, use, or sale of cabozantinib
10:38:12 tablets, 20-milligram, 40-milligram, and 60-milligram
10:38:18 ("MSN's proposed ANDA products").
10:38:21 Q. And are those the accused products for the '349
10:38:24 patent in this case?
10:38:25 A. They are.
10:38:26 Q. And they refer to here as MSN's proposed ANDA

products. Can we use the term "MSN ANDA products" here today for your testimony?

A. Yes.

Q. Do you understand that Exelixis is alleging that the MSN ANDA products would infringe Claim 3 of the '349 patent?

A. I do.

Q. Let's have PDX-2.3. What evidence did you review in connection with analyzing whether MSN infringes Claim 3 of the '349 patent?

A. As shown on my demonstrative, the '349 patent, various relevant sections of MSN's ANDA submissions and relevant publications from the prior art, other MSN documents as well as a product license and supply agreement between Zydus and MSN.

Q. And we'll come back to the details in a moment, but what conclusion did you reach?

A. It's my opinion that the MSN ANDA products would infringe Claim 3.

Q. And what conclusion did you reach as to whether MSN would induce infringement of Claim 3 of the '349 patent?

A. It's my opinion they would induce infringement.

Q. Do you understand that a patent claim is analyzed from the perspective of a person of ordinary skill in the art at the time of the claimed invention?

A. I do.

Q. Can we refer to that as a POSA for short?
A. Yes.
Q. Could we please turn back to the amended statement of uncontested facts, which is Tab 3 in your binder. And I want to call your attention to paragraph 44 on Page 7 which is PDF Page 8.
Could you please read paragraph 44 of the amended statement of uncontested facts?
A. "The priority date of Claim 3 of the '349 patent is February 10, 2011."
Q. Is that the priority date you are applying for purpose of your opinions in this case?
A. Yes.
Q. Do you have an opinion as to the level of experience of a POSA for the '349 patent as of that priority date?
A. I do.
Q. If we could please have PDX-2.4. What is your opinion?
A. "A POSA as of the date of the invention of the '349 patent 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 also have been part of a team which would have included synthetic organic chemists and

process chemists, formulation scientists, analytical scientists and clinicians."

Q. Did you apply this definition in analyzing the question of infringement?

A. Yes.

MS. WIGMORE: Could we please have PDX-2.5?

BY MS. WIGMORE:

Q. What is shown on this slide?

A. This is the definition of a POSA offered by Dr. Donovan, MSN's witness.

Q. And would your analysis of infringement change depending on which definition of a POSA is applied, your definition or Dr. Donovan's?

A. No.

Q. As of February 2011, did you meet the qualifications for a person of ordinary skill in the art under both parties' definitions?

A. Yes.

Q. Now, before we return to the details of your opinion, let's go over some technology background. If we could please have PDX-2.6. What is a pharmaceutical composition?

A. Again, generally a pharmaceutical composition is the makeup of an active pharmaceutical ingredient oftentimes abbreviated API or known also as a drug substance. This is the active moiety that exerts the therapeutic effect when a

product is administered. The active pharmaceutical ingredient, or API, is then -- is often combined with excipients. Excipients have multiple functions. They can do multiple things up to and including facilitation of dose, manufacturing, control of release, among others. And those materials through the manufacturing process result in a product, and it's the product that ultimately is consumed or administered to a patient or subject.

MS. WIGMORE: Now, if we could return to the '349 patent, which is Tab 2, JTX-4. Back to Claim 3.

If we could highlight the first two lines of the claim.

BY MS. WIGMORE:

Q. It says, "A pharmaceutical composition for oral administration comprising Compound IB."

Do you see that?

A. I do.

Q. What is Compound IB?

A. This is cabozantinib (L)-malate.

MS. WIGMORE: If you could now highlight the limitation below the chemical structure.

BY MS. WIGMORE:

Q. What is addressed in that portion of Claim 3?

A. That the pharmaceutical composition is a tablet or capsule and that it contains -- or comprises one or more

fillers, one or more disintegrants, one or more glidants and one or more lubricants.

Q. Now, focusing on the tablet or capsule portion of that limitation, what is a tablet?

A. A tablet generally is a compressed solid oral dosage form that is put into the shape using a tablet machine through compression.

Q. What is a capsule?

A. In contrast, a capsule is usually defined as having a shell that's been preformed in order to hold the contents of a composition.

Q. What is a filler?

A. Generally fillers are materials -- I believe we've also heard them referred to as diluents. They are added to pharmaceutical compositions typically to increase bulk to facilitate handling.

Q. So, are the terms "filler and diluent" synonymous?

A. Yes.

Q. Now, what is a disintegrant?

A. Generally a disintegrant is an excipient material that's added to a pharmaceutical composition that will physically break it up upon ingestion.

Q. And we'll come back to this term in more detail later, but what is a glidant?

A. A glidant is a material that's added to a composition

to enhance the flow or to improve the flow characteristic of a powder.

MS. WIGMORE: If we could please have PDX-2.7.

BY MS. WIGMORE:

Q. Focusing on the left-hand side of this slide, what is flow?

A. So generally flow in solid oral dosage manufacturing starts with a powder blend. So we have a solid material. That solid material is comprised of a mixture of materials that have been processed in some way. It is important in a manufacturing that solid material is able to move from one piece of equipment to the other in a controlled and uniform method at a rate that is consistent with the manufacturing process.

And in this particular case, it is important that material moves freely and uniformly from what we call the final blend of the blender consistently onto a tablet press whereby that powder fills volumetrically into a rotating turret, and then the tablet tools compress the tablets and then they are ejected and collected.

Q. Now, focusing on the right-hand side of the slide, how does flowability impact the properties of a pharmaceutical composition?

A. So, good flow will translate through to good content uniformity of the dosage forms, in this particular case

10:46:01 tablets so there's consistent dose, the amount of active
10:46:04 ingredient from tablet to tablet. It also results in a
10:46:08 homogenous set of tablets that are manufactured that have
10:46:12 consistent appearance, mechanical properties such as
10:46:16 strength and ultimately consistent performance like
10:46:19 dissolution.
10:46:21 MS. WIGMORE: Can we please turn back to Claim 3
10:46:22 of the '349 patent?
10:46:22 BY MS. WIGMORE:
10:46:24 Q. We were walking through the list of excipients. What
10:46:28 is a lubricant?
10:46:29 A. A lubricant is a material added to a composition,
10:46:32 typically to reduce friction during manufacturing.
10:46:37 Q. And if we could highlight the last two sentences of
10:46:41 Claim 3. What does that portion of Claim 3 address?
10:46:45 A. Wherein the pharmaceutical composition is essentially
10:46:48 free of 6,7-dimethoxy-quinoline-4-ol referred to today as
10:46:55 the 1-1.
10:46:58 Q. Now, let's turn to your infringement analysis.
10:47:01 MS. WIGMORE: Could we please have PDX-2.9?
10:47:01 BY MS. WIGMORE:
10:47:04 Q. Does this slide identify the limitations of Claim 3
10:47:07 of the '349 patent?
10:47:08 A. It does.
10:47:10 Q. And if we could refer back to the amended statement

10:47:12 of uncontested facts, which is Tab 3, at paragraphs 65 through 69 on Page 9 of the document, Page 10 of the PDF.

Based on uncontested facts 65 through 69, which limitations of Claim 3 of the '349 patent are not in dispute in this case?

A. The -- the -- being a pharmaceutical composition, for oral administration, that it contains cabozantinib (L)-malate. It contains a filler. It contains a disintegrant. And it contains a lubricant.

Q. And does it also involve a tablet?

A. Yes. Thank you.

MS. WIGMORE: And if we could have PDX-2.9, please.

BY MS. WIGMORE:

Q. Can we check off every limitation other than one or more glidants?

A. Except for number 70 addresses the last point.

Q. Oh, number 70 in the uncontested facts?

A. Yes.

Q. So taking into account undisputed facts -- uncontested facts 65 through 70, can we agree that all the limitations "except for one or more glidants" are uncontested?

A. Yes.

Q. Now, did the parties --

10:48:30 MS. WIGMORE: And we can take that down.
10:48:30 BY MS. WIGMORE:
10:48:31 Q. Did the parties ask the Court to construe the term
10:48:34 "glidant" in this case?
10:48:35 A. No.
10:48:37 Q. Is it your understanding that the plain and ordinary
10:48:39 meaning of glidant should be applied in this case?
10:48:42 A. Yes.
10:48:43 Q. What is the plain and ordinary meaning of glidant?
10:48:46 A. It's a material added to a powder blend to improve
10:48:50 the flow characteristic of the material.
10:48:52 Q. Is the term "glidant" defined in the specification of
10:48:55 the '349 patent?
10:48:56 A. No.
10:48:58 MS. WIGMORE: If we could turn back to Tab 2,
10:49:00 the '349 patent, and turn to Column 20, Line 38.
10:49:00 BY MS. WIGMORE:
10:49:08 Q. Do you see the heading "Pharmaceutical Compositions"?
10:49:12 A. Yes.
10:49:17 Q. And in that section, about midway through, do you see
10:49:21 the reference to *Remington: The Science and Practice of*
10:49:26 *Pharmacy*?
10:49:26 A. I do.
10:49:27 Q. And after that reference, do you see the reference to
10:49:31 J. Swarbrick and J.C. Boylan, the encyclopedia --

10:49:35 A. *Encyclopedia of Pharmaceutical Technology*.
10:49:38 Q. Thank you.
10:49:41 If we could now turn to Tab 4 of your binder,
10:49:44 which is PTX-572A.
10:49:47 What is this document?
10:49:48 A. This is an excerpt from the Remington document we
10:49:52 just referenced.
10:49:53 Q. Is this document referenced in the '349 patent?
10:49:56 A. Yes.
10:49:57 Q. If you could turn, please, to PDF Page 13 of this
10:50:02 document, which is Page 893 and Bates Number 6148.
10:50:08 Do you see the heading "Glidants"?
10:50:10 A. I do.
10:50:11 Q. Could you please read the first sentence under the
10:50:14 heading "Glidants"?
10:50:15 A. "A glidant is a substance that improves the flow
10:50:18 characteristics of a powder mixture."
10:50:21 Q. And how does that compare to the plain meaning that
10:50:24 you just provided?
10:50:25 A. It's consistent with my meaning.
10:50:27 Q. If you could please read the second sentence of that
10:50:30 same paragraph.
10:50:31 A. "These materials always are added in the dry state
10:50:36 just prior to compression (that is during the lubrication
10:50:42 step.)"

10:50:43 Q. And does that provide information as to when glidants are typically added in the manufacturing process?

10:50:45 A. Yes.

10:50:47 MS. WIGMORE: If we could please have Tab 5, which is PTX-0394.

10:50:49 BY MS. WIGMORE:

10:50:51 Q. What is this document?

10:50:55 A. This is an excerpt from the *Encyclopedia of Pharmaceutical Technology*, edited by Swarbrick and Boylan.

10:50:56 Q. Is this document referenced in the portion of the '349 patent you just read for us?

10:51:02 A. Yes.

10:51:05 MS. WIGMORE: If you could please turn to Page 26 of PTX-394.

10:51:08 BY MS. WIGMORE:

10:51:10 Q. I'd like to direct your attention to the first bullet toward the bottom of the page, beginning "glidant excipients," do you see that?

10:51:12 A. I do.

10:51:14 Q. Could you read that bullet for us, please?

10:51:14 A. "Glidant excipients improve the flow characteristics of tablet granulations (and capsule powder blends)."

10:51:18 Q. And how does that definition compare to the plain meaning that you provided in your testimony?

10:51:22 A. It's consistent.

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10:51:44 Q. Is there any dispute between Exelixis and MSN that a glidant improves flow?

10:51:48 A. No. No dispute.

10:51:49 Q. Now, if we could turn, please, to Tab 6 of your binder, which is DTX-215.

10:51:53 What is this document?

10:52:00 A. This is an MSN document "Pharmaceutical Development Report of Cabozantinib Tablets." I believe it was part of the ANDA submission.

10:52:01 Q. If you could go to Page 96 of the PDF, which is Bates Number ending 6804.

10:52:07 Do you see Section 2.44, titled "Final Manufacturing Formula"?

10:52:12 A. Yes. Yes.

10:52:15 Q. What information is contained in this section of the MSN ANDA?

10:52:19 A. So this particular section tells us a few different things. First, it describes the qualitative composition of the -- of the products, both in ingredients. It's quantitative in that it gives you the milligram amount per tablet per strength. And it also gives you -- gives an indication of where in the manufacturing process certain things are added.

10:52:22 Q. Did you identify any ingredients on this list that serve as a glidant in MSN's ANDA products?

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10:53:15 A. I did.
10:53:17 Q. And what did you identify?
10:53:18 A. I'll direct your attention to Line Number 7,
10:53:22 granulated corn starch.
10:53:24 Q. Do you see the term "GRASTAR" next to that?
10:53:26 A. I do.
10:53:27 Q. Is that a brand name for granulated corn starch?
10:53:30 A. I believe it to be a brand name.
10:53:32 Q. And for purposes of your testimony here today, can we
10:53:35 use the term "granulated corn starch"?
10:53:36 A. Yes.
10:53:39 Q. Where in the process the manufacturing of MSN's ANDA
10:53:43 products is the granulated corn starch added?
10:53:46 A. So, you'll notice the word above Line Number 7
10:53:51 "extragranular." This specifically means that it's added in
10:53:55 a final step prior to lubrication and compression.
10:54:00 Q. Now, you testified earlier about an excerpt from
10:54:05 Remington's. How does where the granulated corn starch is
10:54:10 added in the MSN ANDA process compare to what Remington has
10:54:14 described as where a glidant would typically be added?
10:54:18 A. Very consistent. Remington's clearly states glidants
10:54:22 are added in the terminal steps just prior to lubrication.
10:54:25 MS. WIGMORE: Could we please have PDX-2.10?
10:54:25 BY MS. WIGMORE:
10:54:29 Q. At a high level, Dr. Koleng, how did you determine

10:54:32 whether MSN's ANDA products include a glidant?
10:54:36 A. I looked at a number of things, including MSN's
10:54:39 statements that it made in its own ANDA submission. I
10:54:43 evaluated the scientific literature. As well as the
10:54:49 manufacturing process was supported in forming my opinion
10:54:50 for MSN ANDA's products.
10:54:52 MS. WIGMORE: Let's go to PDX-2.11.
10:54:52 BY MS. WIGMORE:
10:54:56 Q. And focus on the first prong of your analysis, the
10:54:58 review of MSN's statement in its ANDA submission.
10:55:02 What did you conclude from that review?
10:55:05 A. That MSN's statements support that granulated corn
10:55:10 starch is a glidant in this formulation.
10:55:13 MS. WIGMORE: Let's return to DTX-215, which is
10:55:16 Tab 6.
10:55:19 BY MS. WIGMORE:
10:55:19 Q. And, again, you testified this is a portion of MSN's
10:55:21 ANDA submission; is that right?
10:55:23 A. Specifically the pharmaceutical development report;
10:55:25 correct.
10:55:26 MS. WIGMORE: If you could please turn to
10:55:28 Page 34, which ends in Bates Number 6742.
10:55:28 BY MS. WIGMORE:
10:55:32 Q. Do you see the table --
10:55:41 A. I do.

10:55:42 Q. Do you see the table titled "Flow Properties of the Drug Substance"?
10:55:45 A. Yes.
10:55:45 Q. What information is contained in this table?
10:55:46 A. So, this particular table reports data on two different lots or batches of MSN's drug substance. This is the cabozantinib (L)-malate drug substance.
10:55:48 Q. Is this the API before any excipients are added?
10:55:52 A. Yes, this is the neat materials.
10:55:57 Q. Now, just to go over some of the terminology.
10:56:00 Do you see the reference to compressibility index in this table?
10:56:03 A. I do.
10:56:06 Q. What is that?
10:56:10 A. The compressibility index, also called the Carr's index commonly, is a calculation that provides a number that allows one to characterize the flowability of a material.
10:56:12 Q. And for the compressibility or Carr index, does a lower or a higher number indicate improvement in flow?
10:56:14 A. Lower number.
10:56:14 Q. Beneath that, do you see the term "Hausner's ratio"?
10:56:15 A. Correct.
10:56:20 Q. What is that?
10:56:24 A. Again, it's another calculation that's performed in order to arrive at a number that can then be assessed for
10:56:28
10:56:33
10:56:36
10:56:38
10:56:42
10:56:42
10:56:43
10:56:47

10:56:51 flowability of a powder.
10:56:54 Q. And for Hausner's ratio, does a lower or higher
10:56:57 number indicate an improvement in flow?
10:56:59 A. Improvements are indicated by a lower number.
10:57:03 Q. Could you please read the sentence that appears below
10:57:06 the table we've been looking at?
10:57:09 A. "From the above compressibility index, it is evident
10:57:11 that the API exhibits poor flow properties."
10:57:16 Q. And is that referring to the cabozantinib API before
10:57:19 the excipients are added?
10:57:21 A. Yes.
10:57:22 Q. How does that statement bear on your opinion in this
10:57:25 case?
10:57:26 A. That a poorly flowing API would benefit from a
10:57:31 careful selection of excipients and manufacturing process to
10:57:34 improve flow.
10:57:36 MS. WIGMORE: Please turn to Page 35 of DTX-215,
10:57:40 this is Bates number ending 6743.
10:57:40 BY MS. WIGMORE:
10:57:44 Q. Do you see the table beginning in the middle of the
10:57:46 page?
10:57:47 A. Yes.
10:57:48 Q. And that table, do you see, carries on to the next
10:57:52 page, Page 36?
10:57:54 A. I do.

10:57:55 Q. And on that next page, do you see the portion of the
10:58:00 table that in the left-hand column says "granulated corn
10:58:05 starch level"?
10:58:05 A. I do.
10:58:08 Q. Could you please read the first sentence on the
10:58:10 right-hand side of that row?
10:58:12 A. "Granulated corn starch is used as a diluent in
10:58:17 minimal concentration and it enhances the flowability of the
10:58:22 granules."
10:58:24 Q. And what did this reveal about whether granulated
10:58:29 corn starch serves as a glidant in MSN's ANDA products?
10:58:32 A. Material that improves flow characteristics is a
10:58:36 glidant. Here, it enhances the flowability of granules
10:58:40 consistent with a glidant.
10:58:42 Q. Now, you are mentioned the statement "used as a
10:58:44 diluent in minimal concentration." Do you see that?
10:58:47 A. I do.
10:58:48 Q. Does that change your opinion?
10:58:49 A. No, not at all.
10:58:50 Q. Why not?
10:58:51 A. In assessing whether or not granulated corn starch is
10:58:54 a glidant in this formulation, concentration was -- is one
10:58:58 of the -- was one of my considerations. The fact that they
10:59:02 call it a diluent does not detract from that as materials
10:59:05 like this are known to have multi -- multiple functions.

10:59:08 Q. And do you see the reference to minimal concentration next to diluent?
10:59:12 A. Yes.
10:59:14 Q. Would a material that's added at a minimal concentration be expected to have a substantial impact as a diluent?
10:59:21 A. For where granulated corn starch is used in the process, for this particular formulation, it is unlikely.
10:59:30 MS. WIGMORE: Now, if we could turn back to the title of this table on Page 35.
10:59:32 BY MS. WIGMORE:
10:59:35 Q. What is the title of the table?
10:59:37 A. "Justification for the initial risk assessment of the formulation variables."
10:59:42 Q. Does the fact that this table refers to initial risk assessment impact your opinion?
10:59:47 A. No, not at all.
10:59:49 Q. Why not?
10:59:49 A. In generating these types of tables that I've done myself, these are done once a core formulation has been identified. So, you understand the materials you're working with and the formulation that you hope to evaluate. The fact that this is initial risk assessment and the acknowledgment of this would be consistent with where it's at in this table.

11:00:11 Q. And at this point, had granulated corn starch been
11:00:14 identified as an excipient for MSN's ANDA products?
11:00:17 A. Yes. The drug substance attributes and others that
11:00:20 are listed here are specifically for the formulation they
11:00:24 hope to move forward with.
11:00:25 MS. WIGMORE: If you could turn, please, to
11:00:28 Page 58 of DTX-215, ending in Bates Number 6766.
11:00:28 BY MS. WIGMORE:
11:00:36 Q. Do you see Section 2.3.1.9?
11:00:39 A. I do.
11:00:41 Q. Could you please read the first sentence under that
11:00:44 heading?
11:00:45 A. "The level of granulated corn starch plays an
11:00:49 important role in flow characteristics."
11:00:52 Q. Is that a statement MSN made to the FDA in its ANDA?
11:00:56 A. Yes.
11:00:57 Q. Is that statement consistent with the statement we
11:01:00 just looked at about granulated corn starch enhancing the
11:01:04 flow?
11:01:04 A. Yes.
11:01:09 Q. Now, how do these statements collectively bear on
11:01:12 your opinion regarding whether MSN's ANDA products contain a
11:01:17 glidant?
11:01:18 A. Their statement responsibility consistent with the
11:01:20 use of granulated corn starch as a glidant in this

formulation.

Q. Now, there's been reference in the ANDA to granulated corn starch serving as a diluent.

Can a particular substance function as both a diluent and a glidant?

A. Yes.

Q. Were you here during opening statements when Mr. Lombardi stated that the fact that something has an impact on flow properties does not make it a glidant?

A. Yes.

Q. If a material improves or enhances flow, is it a glidant?

A. Yes.

MS. WIGMORE: If you could please have PDX-2.12.

BY MS. WIGMORE:

Q. After reviewing MSN's ANDA, what was the next step of your infringement analysis?

A. I look at the scientific literature for -- to assess the -- whether or not these types of materials were known or recognized as glidants.

Q. Were you here for the deposition testimony of Mr. Nithiyanandam?

A. I was.

Q. What did he testify about the literature with respect to whether granulated corn starch is a glidant?

11:02:28 A. His opinion or his statements seem to support that, yes, that that glidant function was known in the literature.

11:02:35 MS. WIGMORE: Now, if you could turn, please, to Tab 5 of your binder, which is PTX-394.

11:02:37 BY MS. WIGMORE:

11:02:41 Q. This is the Swarbrick/Boylan chapter we looked at earlier. Correct?

11:02:46 A. Yes.

11:02:49 MS. WIGMORE: If could you turn, please, to Page 44 of the PDF, which is Page 105 and Bates Number 9326.

11:02:50 BY MS. WIGMORE:

11:02:57 Q. Do you see Table 2 on that page?

11:03:00 A. I do.

11:03:02 Q. What is Table 2 called?

11:03:04 A. Glidants.

11:03:06 Q. And on the left-hand side of this table, what information is provided?

11:03:09 A. This is a list of different materials that they're considering to be glidants.

11:03:14 Q. And do you see the reference to starch dry flow a little more than halfway down that list?

11:03:15 A. I do.

11:03:21 Q. Now, what is shown in the right-hand side of this table?

11:03:22 A. These are numerical values for suggested percentages

11:03:30 in compositions.
11:03:32 Q. And are those percentages concentrations?
11:03:35 A. Yes.
11:03:36 Q. Now, looking at the list as a whole, what is the
11:03:40 range of suggested percentage concentrations for the
11:03:43 glidants listed?
11:03:44 A. The range goes from 0.1 to 10 percent.
11:03:51 Q. And focusing specifically on the starch dry flow row,
11:03:56 what is the suggested percentage concentration for starch?
11:04:01 A. One to 10 percent.
11:04:04 Q. Now, if we could look at the language below the
11:04:09 table.
11:04:09 Do you see where it says "commonly used glidant
11:04:12 excipients are given in Table 2"?
11:04:14 A. I do.
11:04:15 Q. And what does that reveal about the items listed in
11:04:18 Table 2?
11:04:18 A. That is listing commonly used glidants.
11:04:22 Q. If you could turn to the beginning of the next
11:04:25 sentence.
11:04:25 Do you see where it says "Starch and its
11:04:28 derivatives find extensive use for such effects?
11:04:31 A. Yes.
11:04:32 Q. What is he referring to there?
11:04:35 A. That starch and things related to starch find

11:04:39 extensive use as glidants.
11:04:41 Q. And what does that reveal, if anything, about whether
11:04:44 granulated corn starch is a glidant?
11:04:46 A. Again, that these types of materials were known to be
11:04:49 commonly used glidants.
11:04:51 Q. Is granulated corn starch a starch derivative?
11:04:54 A. Yes.
11:04:56 MS. WIGMORE: Please turn to Tab 7 of your
11:04:58 binder, which is PTX-553A.
11:04:58 BY MS. WIGMORE:
11:05:02 Q. What is this document?
11:05:04 A. This is an excerpt from, "Pharmaceutical Dosage
11:05:08 Forms: Tablets", edited by Lieberman.
11:05:12 Q. And is this often also referred to as the Lachman
11:05:16 reference?
11:05:16 A. Yes.
11:05:17 MS. WIGMORE: If you could please turn to
11:05:20 Page 178, which is PDF Page 198 and Bates Number 7092. And
11:05:30 look for Table 8.
11:05:34 THE WITNESS: I'm sorry. What was the PDF page?
11:05:36 BY MS. WIGMORE:
11:05:36 Q. PDF page is 190, and it's Page 178 in the upper
11:05:41 right-hand corner -- upper left-hand corner.
11:05:50 A. I see you have it up.
11:05:52 Q. And what is the title of Table 8?

11:05:54 A. "Commonly used glidants and usual concentration
11:05:58 range."
11:06:01 Q. Now, focusing again on the left-hand side, do you see
11:06:05 the reference to starch dry flow?
11:06:08 A. I do.
11:06:08 Q. And do you see the reference to Starch 1500?
11:06:10 A. I do.
11:06:11 Q. Are those both identified as commonly used glidants
11:06:15 in this table?
11:06:15 A. They are.
11:06:17 Q. What is Starch 1500?
11:06:18 A. Starch 1500 is a brand name for pregelatinized
11:06:24 starch.
11:06:24 Q. What is pregelatinized starch?
11:06:26 A. So, it is a mechanically processed corn starch.
11:06:30 Q. How does that compare to granulated corn starch?
11:06:32 A. Granulated corn starch is also -- meets the
11:06:37 corresponding testing chapters in USP for pregelatinized
11:06:41 corn starch as well.
11:06:42 Q. Is Starch 1500 a starch derivative?
11:06:44 A. Yes.
11:06:45 Q. Is granulated corn starch a starch derivative?
11:06:48 A. Yes.
11:06:49 Q. What is shown in the right-hand column of Table 8?
11:06:52 A. Again, these are percent use usual concentration

ranges in a composition.

Q. And for starch dry flow and Starch 1500, what is the usual concentration range provided?

A. 1.0 to 10.0 percent.

Q. And looking at the complete list of glidants in this table, what is the concentration range?

A. 0.1 to 10.0 percent.

Q. So we've now looked at two tables relating to commonly used glidants. How do they bear on your opinion?

A. That the literature supports that starch and its derivatives were commonly used glidants.

MS. WIGMORE: Could we please have PTX-243, which is Tab 8 in your binder?

BY MS. WIGMORE:

Q. What is this document?

A. This is U.S. Patent 6,030,643 titled "Potassium, Sodium and Tris Oxaprozin Salt Pharmaceutical Formulations."

Q. What is the dates of this patent?

A. February 29, 2000.

Q. Who is this patent assigned?

A. G.D. Searle & Company.

Q. And what was G.D. Searle & Company as of 2000?

A. They were a known pharmaceutical company.

MS. WIGMORE: Could we turn, please, to Column 14, Line 41, which is on PDF Page 8.

11:08:19 BY MS. WIGMORE:

11:08:23 Q. Do you see at Column 40 the paragraph beginning, "Any glidant"?

11:08:28 A. I'm there.

11:08:31 Q. Now, in that paragraph, do you see the reference to pregelatinized corn starch?

11:08:38 A. I do.

11:08:38 Q. What does this patent reveal about pregelatinized corn starch?

11:08:43 A. That pregelatinized corn starch can be used as a glidant for them preferably from about zero to about 10 percent.

11:08:51 Q. And is granulated corn starch pregelatinized corn starch?

11:08:56 A. Yes.

11:08:58 MS. WIGMORE: Could we please have PTX-724, which is Tab 9 in your binder.

11:09:01 BY MS. WIGMORE:

11:09:07 Q. What is this document?

11:09:08 A. This is an MSN document titled, "Justification of microbial method validation product corn starch, granulated corn starch." I believe it's part of their ANDA submission as well.

11:09:24 Q. What is the microbial method validation?

11:09:27 A. So, these are methods to assess the -- the quality of

a pharmaceutical composition as it relates to said bacteria and fungus. This particular document relates to how the method was demonstrated to be used with, specifically, the starting raw material, granulated corn starch.

MS. WIGMORE: Could you please turn to Section 4.0 at the middle of Page 1?

BY MS. WIGMORE:

Q. What does this table show?

A. So this table shows what the particular table -- what the particular method is applicable to and it's shown here it's three types of corn starch.

Q. So, the title of Section 4.0 is "List of different grades of corn starch available."

Do you see that?

A. I do.

Q. And how many different types of corn starch are listed there?

A. There are three listed here.

Q. And is granulated corn starch one of them?

A. Yes. I'll direct your attention to the last row, corn starch, granulated corn starch, GRASTAR.

Q. If you could please turn to Page 2 at the bottom. First of all, what is the header on the top of the page?

A. The head --

Q. Product material name. Sorry.

11:10:49 A. Oh, product name. Again, corn starch, granulated,
11:10:52 corn starch, GRASTAR.
11:10:53 Q. And please turn to Section 5.1.4. Could you please
11:10:59 read the second sentence in that section?
11:11:01 A. "Starch are used in pharmaceutical industry for a
11:11:04 wide variety of reasons, such as an excipient in a tablet
11:11:09 and capsule, as a diluent, as a glidant, or as binder."
11:11:14 Q. What does that statement reveal about whether the
11:11:17 starches identified in this portion of the ANDA are
11:11:21 glidants?
11:11:21 A. That they are generally known in the industry to
11:11:24 fulfill these functions.
11:11:26 Q. Do you agree with that statement?
11:11:28 A. Yes.
11:11:30 Q. Now, you've walked through some literature and your
11:11:34 analysis of it. How did it bear on your infringement
11:11:38 analysis in this case?
11:11:39 A. These documents and these statements further support
11:11:43 my opinion that granulated corn starch is a glidant in the
11:11:47 MSN ANDA products.
11:11:50 MS. WIGMORE: Can we please have PDX-2.13?
11:11:50 BY MS. WIGMORE:
11:11:53 Q. What was the next step in your infringement analysis?
11:11:55 A. So we discussed a little bit earlier that Remington
11:11:59 describes where in the manufacturing process a glidant is

added. One of the considerations was confirming that the manufacturing process and use of the granulated corn starch, where it's added, to see if it's consistent with what's been published.

Q. And did you review MSN's manufacturing process?

A. Yes.

Q. What did you conclude?

A. That the location and placement of the granulated corn starch in the manufacturing process is consistent with the use of granulated corn starch as a glidant in this formulation.

Q. Let's return to DTX-215 which is Tab 6.

Is this the portion of the ANDA we looked at previously called the pharmaceutical development report?

A. Yes.

Q. Please turn to Page 97 which ends in Bates Numbers 6805. What information is provided here?

A. This is a manufacturing process flow chart for MSN's final manufacturing process for its cabozantinib tablets.

Q. Do you recall Mr. Nithiyanandam's testimony about this section of the ANDA?

A. I do.

Q. Were you here when he testified that this flow chart truthfully and accurately depicts the final manufacturing process for MSN's ANDA products?

11:13:30 A. I recall that. Yes.
11:13:32 Q. Have you prepared a slide summarizing aspects of the
11:13:35 MSN manufacturing process?
11:13:37 A. I have.
11:13:39 MS. WIGMORE: Could we please have PDX-2.14?
11:13:39 BY MS. WIGMORE:
11:13:43 Q. Can you please explain what is shown on this slide?
11:13:45 A. Sure. So I've tried to make all the boxes a little
11:13:49 more readable for everyone as it relates to schematics and
11:13:53 steps, the general steps, one of the main steps within the
11:13:56 manufacturing process used by MSN for the cabozantinib
11:13:59 tablets.
11:14:01 What you'll note at the top part of the slide is
11:14:03 that there's what we're going to refer to as an
11:14:06 intragranular portion and then there's an extragranular
11:14:09 portion. The intragranular portion starts with delumping
11:14:13 and sifting materials to make sure that they're
11:14:15 deagglomerated. That includes the starting material, the
11:14:19 diluents, a portion of the disintegrant, those powders are
11:14:25 then put into a machine. That's called a granulator.
11:14:29 A binder solution which has been prepared -- in
11:14:31 this case it's the hydroxypropyl cellulose that's in the
11:14:35 formulation that is dissolved in water and added while that
11:14:38 powder blend is mixed. That is the active wet granulation.
11:14:44 That wet mass is then moved to a dryer in order

to remove the water. And in doing so, you have resulting granules. Those resulting granules are then sized and brought forward then into the extragranular side of the slide. So it's input into the blend along with the granulated corn starch and an extragranular disintegrant. Those materials are mixed, and the next step, the lubricant is added resulting in a final blend which is then fed to a tablet press to produce tablets and ultimately those tablets are coated.

Q. So just to follow up on a few points there, at what step of the manufacturing process is the granulated corn starch added?

A. Again, extragranular, near terminal and the final blending steps prior to compression.

Q. And in your experience and based on the literature, at what step are glidants typically added?

A. At that step.

Q. Do you recall -- what -- if we could turn to the concentration of the granulated corn starch.

At what concentration is it added?

A. Their composition has 9.71 percent granulated corn starch.

Q. And going back to the step at which it's added, how, if at all, does the step at which granulated corn starch is added to MSN's manufacturing process bear on your opinion as

11:16:08 to whether it is a glidant?
11:16:10 A. Considering the concentration and the location within
11:16:14 the -- in the manufacturing process, it further supports my
11:16:18 opinion that granulated corn starch is acting as a glidant
11:16:22 or is a glidant in this formulation.
11:16:24 Q. Now, you mentioned the concentration. Let's turn to
11:16:27 PTX-677, which is Tab 10 in your binder.
11:16:35 Do you see the title "Description and
11:16:38 Composition of the Drug Product"?
11:16:40 A. I do.
11:16:41 Q. Is this part of MSN's ANDA?
11:16:42 A. Yes. Specifically the 3.2.P.1 section.
11:16:45 Q. Could you turn, please, to Page 3 which is ending in
11:16:49 Bates Number 9740?
11:16:52 Do you see Table 3 titled "Unit Dose
11:16:55 Composition"?
11:16:56 A. I do.
11:16:58 Q. And looking at the row titled "Granulated corn
11:17:02 starch," toward the bottom, what does the table tell us
11:17:05 about the concentration of granulated corn starch?
11:17:10 A. That it's used in each tablet at 9.71 percent in its
11:17:14 final composition.
11:17:15 Q. How does that compare to the typical concentration
11:17:18 used for a glidant?
11:17:20 A. It's within the range that we've discussed and

11:17:24 reported earlier in the two references that go up to 10
11:17:28 percent.
11:17:28 Q. And are you referring to the Lachman and the
11:17:31 Swarbrick references you testified about previously?
11:17:34 A. Yes.
11:17:35 Q. What, if anything, does the 9.71 percent
11:17:38 concentration for granulated corn starch reveal about
11:17:43 whether its primary function in MSN's ANDA products is as a
11:17:48 glidant or a diluent?
11:17:49 A. Again, taken in consideration of everything that we
11:17:54 discussed and presented, it just further supports my opinion
11:17:58 that granulated corn starch is a glidant in this
11:18:02 formulation.
11:18:03 Q. So you walked us through the concentration of the
11:18:06 granulated corn starch, the place it is added in MSN's
11:18:10 manufacturing process and MSN's statements in its ANDA about
11:18:15 enhancing flow. In view of that evidence, what is your
11:18:19 response to MSN's argument that granulated corn starch is
11:18:24 only serving as a diluent not a glidant?
11:18:27 A. It would seem inconsistent with that statement that
11:18:30 everything we just described -- discussed would indicate
11:18:34 it's a glidant.
11:18:37 Q. Now, did you consider any internal work conducted by
11:18:41 MSN in your analysis of infringement?
11:18:42 A. Yes.

11:18:45 Q. Generally speaking, what type of information did you
11:18:47 consider?
11:18:47 A. So, I reviewed some early development notebooks that
11:18:53 were early on in MSN's product development starter history
11:19:01 that lead up ultimately to identification of the formula for
11:19:06 the formulation. Was looking for information or data that
11:19:08 further may have indicated or provided support, but during
11:19:12 the course of the case, it was brought to -- it was found
11:19:16 that there was considerable data discrepancy, that the
11:19:20 numbers could not be reproduced, the numbers were
11:19:24 contradictory to each other, et cetera.
11:19:26 Q. Are you relying on any data from MSN's lab notebooks
11:19:29 in your testimony here today?
11:19:31 A. No. Not at all.
11:19:33 Q. And why not?
11:19:33 A. Again, the data was disparate. The source of that
11:19:39 disparity could not be identified within the context of the
11:19:42 documents provided. Therefore, I thought it was unreliable
11:19:47 and should not be used.
11:19:50 Q. Taking those discrepancies into account, does that
11:19:53 change your opinion about whether or not MSN's ANDA products
11:19:56 contain a glidant?
11:19:57 A. No, the totality of the information that still
11:20:00 resides supports my opinion.
11:20:02 Q. And just briefly describe what totality you're

11:20:05 speaking of?
11:20:05 A. MSN's own statements in their ANDA submission to the
11:20:10 FDA, a review for support of starch and its derivatives in
11:20:15 the scientific literature for glidants, the amount of
11:20:19 granulated corn starch that's in the product and where it's
11:20:22 actually added in the manufacturing process.
11:20:25 Q. Now, did you do any testing on MSN's ANDA products to
11:20:28 determine whether the granulated corn starch is a glidant?
11:20:32 A. No.
11:20:33 Q. And for what reason?
11:20:34 A. I believe the strength of the statements made by MSN
11:20:38 in their ANDA documents and submissions combined with the
11:20:44 literature as well as the use and the level in the product
11:20:49 support my position without actual testing.
11:20:53 Q. Did you think testing was necessary?
11:20:55 A. No.
11:20:56 Q. Now, let's change gears and focus on MSN's position.
11:21:02 You understand that MSN's infringement expert, Dr. Donovan,
11:21:05 will testify later in this case; is that right?
11:21:08 A. Yes.
11:21:10 Q. Do you understand her position -- what do you
11:21:12 understand her position to be as to whether the granulated
11:21:15 corn starch in MSN's ANDA products is a glidant?
11:21:18 A. Well, first, her position is that it's a diluent,
11:21:22 that it's in a glidant, that in order to be a glidant, it

must be known by what mechanism it's functioning, and that, lastly, that it was used to facilitate dissolution instead of a glidant function.

MS. WIGMORE: And if we could please have PDX-2.15.

BY MS. WIGMORE:

Q. You just talked us through items 1, 3 and 4 on this slide, but is there another reason that Dr. Donovan has given in support of her opinions?

A. And lastly that she believes that the wet granulation process alone was enough to provide flow for the product.

Q. Do you agree with any of these positions of Dr. Donovan?

A. No.

Q. Let's take them one by one.

MS. WIGMORE: If we could please have PDX-2.16.

BY MS. WIGMORE:

Q. What is the position that Dr. Donovan has taken?

A. That granulated corn starch is just a diluent, it's not a glidant.

Q. And have you already provided testimony relating to that point?

A. Yes, I believe everything we just discussed supports that it's used as a glidant over a diluent.

Q. Can we put an X next to Dr. Donovan's first point?

11:22:35 A. Please.

11:22:36 MS. WIGMORE: And if we could turn, please, to
11:22:38 PDX-2.17.

11:22:38 BY MS. WIGMORE:

11:22:41 Q. What is Dr. Donovan's next point?

11:22:42 A. That the granulation process alone was sufficient to
11:22:47 impart flow for the product.

11:22:49 Q. Do you agree?

11:22:49 A. No.

11:22:50 Q. Why not?

11:22:52 A. Several reasons. In reviewing the manufacturing
11:22:55 documents for MSN, it came to -- it's -- it's very apparent
11:23:00 to me that they're creating a very fine granulation. Fine
11:23:04 granulations can have flow problems themselves. Couple that
11:23:09 with it is common to also add a glidant in addition to a
11:23:14 granulation to provide the final flow character for a final
11:23:18 mixture for tablet.

11:23:20 Q. Now just stepping back a bit. What is wet
11:23:23 granulation, at a high level?

11:23:24 A. As we've just discussed, it's a manufacturing
11:23:27 process, specifically here utilizing a liquid binder to
11:23:32 agglomerate materials.

11:23:32 Q. And what impact does wet granulation typically have
11:23:36 on a poorly flowing substance?

11:23:38 A. It can improve flowability of the overall mixture as

11:23:42 well.
11:23:43 Q. If wet granulation is used, does that mean no glidant
11:23:46 is needed?
11:23:47 A. No.
11:23:48 Q. In your years of experience with drug formulation,
11:23:51 have you ever used a glidant in a mixture after wet
11:23:55 granulation?
11:23:56 A. Quite frequently, yes.
11:23:58 Q. And in view of the circumstances of MSN's
11:24:02 manufacturing process that you just walked us through, what
11:24:06 is your opinion as to whether a glidant was needed after wet
11:24:09 granulation?
11:24:10 A. Based upon the fineness of their granulation, I
11:24:14 believe a glidant would have been needed.
11:24:16 Q. Could we put an X next to Dr. Donovan's second point?
11:24:20 A. Please.
11:24:22 MS. WIGMORE: If we could have PDX-2.8 (sic).
11:24:22 BY MS. WIGMORE:
11:24:25 Q. What is Dr. Donovan's third point?
11:24:28 A. That the granulated corn starch was used to improve
11:24:32 dissolution, not flow.
11:24:33 Q. What is dissolution?
11:24:34 A. So dissolution is the rate at which the drug
11:24:38 substance dissolves out of the dosage form.
11:24:41 MS. WIGMORE: Could we please pull up Slide 27

11:24:44 from MSN's opening statement?
11:24:44 BY MS. WIGMORE:
11:24:47 Q. Were you here when Mr. Lombardi showed this slide
11:24:51 during opening?
11:24:52 A. I was.
11:24:54 Q. Do you agree with MSN that the granulated corn starch
11:24:57 in its ANDA products was added to optimize the dissolution
11:25:02 profile?
11:25:02 A. I do not agree.
11:25:04 Q. Do you see that this slide contains an excerpt from
11:25:07 DTX-215?
11:25:08 A. Yes.
11:25:09 Q. Is that the document we've been discussing here
11:25:12 today?
11:25:12 A. Product development report, yes.
11:25:14 Q. Could we turn, please, to DTX-215 which is Tab 6 in
11:25:18 your binder. And go to that same page that was on
11:25:24 Mr. Lombardi's slide, which is at Page 60, Bates Page 8768.
11:25:31 Is this the first -- let me let you get there.
11:25:34 A. What was the PDX page again?
11:25:37 Q. PDF Page 60. Bates Page 8768.
11:25:45 A. 60. Okay.
11:25:47 Q. Now, is this the same graph that appeared on the
11:25:49 opening slide we just looked at?
11:25:51 A. Yes. Yes.

11:25:52 Q. What is the title of the graph?
11:25:53 A. "Comparative Dissolution Profile of Cabozantinib
11:25:57 Tablets 60 MG."
11:26:00 Q. And what does this graph reveal?
11:26:03 A. This graph reveals that when the extragranular
11:26:09 granulated corn starch was varied, from 6.7 percent to
11:26:12 12.7 percent, there was no impact on the dissolution
11:26:17 profile.
11:26:17 Q. Does this graph say anything about flow
11:26:21 characteristics?
11:26:21 A. No, it was in the introduction to this set of
11:26:25 experiments.
11:26:25 Q. So, these experiments relate to dissolution; is that
11:26:29 right?
11:26:29 A. That's correct.
11:26:30 MS. WIGMORE: If we could go back to the opening
11:26:32 slide from MSN's presentation, Slide 27.
11:26:32 BY MS. WIGMORE:
11:26:36 Q. Do you see that there's one highlighted sentence on
11:26:39 that slide, the last sentence of the conclusion?
11:26:41 A. I do.
11:26:43 Q. Can you please read the first sentence of the
11:26:46 conclusion which is not highlighted?
11:26:48 A. "Based on the above results, no significant
11:26:52 difference was observed in the dissolution profiles of

cabozantinib tablets, 60-milligram, with low (6.70 percent weight/weight), optimum (9.70 percent weight/weight), and high (12.70 percent weight/weight) concentration of diluent granulated corn starch."

Q. What does that conclusion reveal about whether granulated corn starch was added to MSN's ANDA products to optimize dissolution?

A. It had no effect, therefore, it was not added to optimize dissolution.

Q. And how does that information relate to Dr. Donovan's opinion regarding dissolution?

A. That it was not added as an extragranular material to affect dissolution.

Q. If we could please go to the beginning of this same section of DTX-215.

Do you see Section 2.3.1.9?

A. I do.

Q. Now, under that heading, what is the first sentence which you have read for us previously?

A. "The level of granulated corn starch plays an important role in flow characteristics."

Q. In view of the information that is provided after that statement, does this statement provide any information or any reference to dissolution?

A. Repeat your question, please.

11:28:20 Q. Sure. In light of the graph that we just looked at, which appears below this statement, does the statement you just read about it playing an important role in flow characteristics relate to dissolution?

11:28:30 A. No.

11:28:31 Q. What does it relate to?

11:28:32 A. It relates to the importance of granulated corn starch in the flow of the product.

11:28:39 Q. Now, if you could turn to Section 2.3.1.4 in the same document, P -- DTX-215, which is on Page 41 of the PDF.

11:28:50 And we have it on the screen as well.

11:28:56 A. 41, okay.

11:28:59 Q. What does the study referenced here involve?

11:29:02 A. This is a study that's evaluating the level of disintegrant on the dissolution of cabozantinib tablets.

11:29:13 Q. And what was the outcome of that study?

11:29:16 A. In this particular study, we actually did see that when they varied another material, like a disintegrant, there was an impact on the dissolution of cabozantinib from their tablets.

11:29:28 Q. Does the addition of this disintegrant tell us anything about whether a granulated corn starch impacts dissolution?

11:29:37 A. It would show us that if it did impact it, that it would -- this method was sensitive enough to see it.

That if it -- had there been a reliance on granulated corn starch, we would have seen it.

Q. Now, going to Slide 2.19, can we put an X next to Dr. Donovan's third point?

A. Yes, please.

Q. And what is the final point that Dr. Donovan raised?

A. She has raised that it's only a glidant if a specific mechanism can be identified.

Q. Do you agree with that?

A. No.

Q. Why not?

A. First, glidants are not defined by any specific mechanism. The definitions we went over before never referred to or relied upon any mechanism for a glidant. It's just an improvement in the flow characteristics of the blend.

In review of the patent, I don't find where there is a -- a mechanism requirement to function as a filler, a lubricant, or anything, much less a glidant.

Q. Does Claim 3 itself make any reference to a particular mechanism for a glidant?

A. No. Not at all.

Q. Does the specification of the '349 patent make any reference to a particular mechanism for a glidant?

A. No. No.

11:30:55 MS. WIGMORE: If we could please have PDX-2.20.

BY MS. WIGMORE:

Q. What is shown here?

A. So, these are five proposed hypothetical postulated glidant mechanisms in the literature.

Q. Do you --

A. These are five that Dr. Donovan has put forth.

Q. Do you agree that these five hypothetical proposed mechanisms are set forth in the literature?

A. They are proposed, yes.

Q. And do you agree with Dr. Donovan that you have to meet one or more of these mechanisms to qualify as a glidant?

A. No.

Q. Are any of these mechanisms definitively proven?

A. No.

Q. Even if one or more of these mechanisms were required, would granulated corn starch and in MSN's ANDA products qualify as a glidant?

A. I believe it's very likely or more likely than not, yes.

Q. And would it be more likely than not?

A. Yeah.

Q. If you could briefly walk through each one of these, starting with reduce electrostatic forces.

11:31:56 What does that mean?
11:31:57 A. So electrostatic forces, you often hear them referred
11:32:01 to as static, static electricity. And in this particular
11:32:05 mechanism -- this particular mechanism, it is about friction
11:32:13 between particles, generating charges, distributing charges,
11:32:17 or neutralizing charges.
11:32:19 I believe if, in taking into consideration the
11:32:23 physical, chemical properties of granulated corn starch,
11:32:25 that it could operate through this mechanism.
11:32:29 Q. And why is that?
11:32:30 A. Because as a reduction in charge, a distribution of
11:32:35 charge, by facilitating uniform mixing, it could distribute
11:32:41 the charge. And granulated corn starch has a sufficient
11:32:44 water content that could actually be used to dissipate the
11:32:48 charges.
11:32:48 Q. Turning to the next bullet, what does absorb fine
11:32:52 particles refer to?
11:32:53 A. So, in this particular instance, fine particles are
11:32:57 very small particles in a formulation that can actually work
11:33:02 against flow. So a certain amount is beneficial, but above
11:33:05 that, it actually begins to hinder flow.
11:33:08 In this particular glidant mechanism, glidants
11:33:11 can go in and adhere those fine particles onto its surface,
11:33:15 thereby diminishing the effective amount of the fine
11:33:18 particles in the blend, and thereby facilitating or

11:33:21 improving flow.
11:33:22 Q. Could granulated corn starch absorb fine particles in
11:33:26 MSN's ANDA products?
11:33:27 A. I believe it's more likely than not, yes.
11:33:29 Q. How?
11:33:30 A. Because of the structure of granulated corn starch, I
11:33:35 believe that, one, it could adhere and attach to itself.
11:33:39 The other is that the granulated component of this provides
11:33:43 a porous surface that would actually allow the fine
11:33:47 particles to lock into.
11:33:50 MS. WIGMORE: Could we please have PTX-447,
11:33:53 which is Tab 11 in your binder.
11:33:53 BY MS. WIGMORE:
11:33:59 Q. What is this document?
11:33:59 A. This is the improvement effect of flowability by
11:34:06 GRASTAR by Japan Corn Starch.
11:34:09 Q. And what is the date on this document?
11:34:11 A. December 19th, 2022.
11:34:14 Q. What is Japan Corn Starch Co., Ltd.?
11:34:17 A. They are the manufacturer of GRASTAR.
11:34:20 Q. How did you obtain this document?
11:34:22 A. By reaching out to the company directly, or I should
11:34:26 say the U.S. Evercorn subsidiary, who then provided
11:34:30 information. My request was information on GRASTAR.
11:34:34 Q. What is the title of this document?

11:34:35 A. "Improvement Effect of Flowability By GRASTAR."
11:34:39 Q. If you could turn, please, to the section of this
11:34:42 document titled "Results and Discussion," which is PDF
11:34:47 Page 2 and Bates number ending 2956.
11:34:52 Do you see the first two sentences under that
11:34:55 heading?
11:34:55 A. I do.
11:34:56 Q. What do they say?
11:34:57 A. The first two sentences are "Figure 2 and 3 show that
11:35:01 GRASTAR has better flowability than JPCS." This is Japanese
11:35:05 Corn Starch.
11:35:07 "The flowability improvement of micronized
11:35:10 fenofibrate by blending with GRASTAR are much greater than
11:35:13 that with JPCS, which can be attributed by more effective
11:35:17 reduction of fenofibrate interparticle cohesion in GRASTAR."
11:35:23 Q. What is fenofibrate?
11:35:24 A. So fenofibrate is another drug substance.
11:35:27 Q. Now, turning to the second sentence from the end of
11:35:31 this paragraph, beginning "this may be because."
11:35:34 A. I see that.
11:35:34 Q. Could you read that, please?
11:35:36 A. "This may be because most of the small fenofibrate
11:35:39 particles can preferably adhere to the void space of GRASTAR
11:35:43 particles' surfaces, rather than adhere to themselves, and
11:35:47 do not affect BD or bulk density."

11:35:51 Q. And what, if anything, does this document tell you
11:35:55 about whether granulated corn starch can improve flow by
11:36:00 absorbing fine particles in MSN's ANDA products?
11:36:04 A. So, this particular document supports the mechanism;
11:36:08 right. That gray -- that granulated corn starch has the
11:36:11 ability to adhere to fine particles.
11:36:14 Q. Now does this document relate to cabozantinib?
11:36:17 A. No, not at all.
11:36:18 Q. Does it relate to another compound called
11:36:21 fenofibrate?
11:36:21 A. Yes.
11:36:22 Q. Did you take that into account in forming your
11:36:24 opinion?
11:36:25 A. I did. The fenofibrate here is representative of
11:36:28 fine particles which -- which would be equivalent to fine
11:36:32 particles in their granulation or final blend.
11:36:35 Q. And when you say "in their granulation," which
11:36:37 granulation are you referring to?
11:36:39 A. MSN's.
11:36:42 Q. So is it the case that the fine particles in the
11:36:44 fenofibrate are consistent with the fine particles that are
11:36:48 part of the MSN cabozantinib formulation?
11:36:51 A. Generally.
11:36:54 MS. WIGMORE: Turning to PDX-2.20.
11:36:54 BY MS. WIGMORE:

11:36:58 Q. The third bullet, what does it mean to absorb gases?
11:37:02 A. So, absorb gases -- the powder blends are not solids. They are not solid constructs. They have void spaces with them that can entrain air. That entrained air can also include water vapor. The materials themselves can pick up water vapor or can hold entrained air and resist flow.
11:37:24 Q. Could granulated corn starch in MSN's ANDA product absorb gases?
11:37:29 A. I believe more likely than not, yes.
11:37:32 Q. Why is that?
11:37:32 A. Corn starches and granulated -- and starch derivative are known to be hygroscopic so they will pick up moisture. So in formulations, they will preferentially absorb water and thereby limit its effect on the rest of the powder blend rendering the blend more flowable.
11:37:50 Q. Turning to the fourth bullet it says, "Reduction in van der Waals interactions.
11:37:55 What does that refer to?
11:37:56 A. So this is a situation where we have separation of particles that are wanting to stick together due to short range intermolecular forces.
11:38:07 Q. And in terms of the granulated corn starch in MSN's ANDA products, could it reduce van der Waals interactions?
11:38:15 A. I believe more likely than not because grace -- granulated corn starch could disrupt particle to particle

11:38:24 van der Waals interactions and physically separate those
11:38:28 from one another.
11:38:29 Q. Why is that?
11:38:30 A. Because it's large enough and heavy enough to insert
11:38:34 itself in between particles.
11:38:36 Q. Turning to the final bullet, "Coating - adherence."
11:38:41 What does that refer to?
11:38:42 A. So in this particular mechanism, glidants are
11:38:46 postulated to absorb or stick onto the surface of larger
11:38:49 materials, smooth out irregularities, reduce friction for
11:38:54 instance.
11:38:54 Q. Could the granulated corn starch in MSN's ANDA
11:38:58 products function by that mechanism?
11:38:59 A. This one very likely.
11:39:01 Q. Why is that?
11:39:02 A. The surface of -- there is a portion of granulation,
11:39:07 albeit fine, that it still larger than the granulated corn
11:39:10 starch that could be a substrate for adherence of granulated
11:39:14 corn starch onto its surface to smooth it out and render the
11:39:19 blend more flowable.
11:39:19 MS. WIGMORE: Let's turn to PDX-2.21.
11:39:19 BY MS. WIGMORE:
11:39:22 Q. Now just to reiterate, do you -- is it your opinion
11:39:25 that any specific mechanism is required for something to be
11:39:29 a glidant?

11:39:29 A. A mechanism is not required.
11:39:31 Q. Even if it is, would Dr. Donovan's identified
11:39:36 proposed mechanisms be satisfied here?
11:39:38 A. One or more, yes.
11:39:41 MS. WIGMORE: Now, could we please have
11:39:44 PDX-2.22?
11:39:44 BY MS. WIGMORE:
11:39:45 Q. You've identified that the only claim term in dispute
11:39:50 is one or more glidants. Based on the testimony you just
11:39:54 provided, do MSN's ANDA products contain one or more
11:39:58 glidants?
11:39:58 A. Yes.
11:39:59 Q. Can we put a green checkmark next to that limitation?
11:40:02 A. Please.
11:40:03 Q. Do MSN's ANDA problems meet all the limitations of
11:40:06 Claim 3 of the '349 patent?
11:40:08 A. Yes.
11:40:10 Q. Will the importation, sale, offer to sell, or use of
11:40:14 the MSN's ANDA products in the United States infringe
11:40:18 Claim 3 of the '349 patent?
11:40:19 A. Yes.
11:40:21 Q. Who is the ANDA holder for the MSN ANDA products?
11:40:24 A. MSN.
11:40:25 MS. WIGMORE: Could we turn, please, to PTX-698,
11:40:28 which is Tab 12 of your binder?

11:40:28 BY MS. WIGMORE:
11:40:34 Q. What is this document?
11:40:34 A. This is -- this is the proposed label from MSN for
11:40:40 their cabozantinib tablets. Their ANDA products.
11:40:43 Q. And who was responsible for submitting this proposed
11:40:46 label to the FDA?
11:40:47 A. MSN.
11:40:49 Q. Does MSN have a relationship with any other party
11:40:53 with respect to the MSN ANDA products?
11:40:55 A. Yes.
11:40:56 MS. WIGMORE: If you could turn back one last
11:40:57 time to the amended statement of uncontested facts; I
11:41:03 believe it's Tab 3. And refer to the Uncontested Fact
11:41:09 Number 71 on Page 9, PDF Page 10.
11:41:09 THE WITNESS: I'm there.
11:41:22 BY MS. WIGMORE:
11:41:22 Q. Could you please read Uncontested Fact 71?
11:41:24 A. "MSN has entered into an agreement with Zydus
11:41:31 Worldwide DMCC, which has agreed to exclusively market,
11:41:34 distribute, and sell MSN's proposed ANDA products in the
11:41:40 United States upon FDA approval of MSN's ANDA."
11:41:46 MS. WIGMORE: Could you please turn to Tab 13,
11:41:47 which is PTX-744.
11:41:47 BY MS. WIGMORE:
11:41:50 Q. What is this document?

11:41:56 A. This is the product license and supply agreement
11:42:00 between Zydus and MSN.
11:42:02 Q. And is this the agreement referenced in the
11:42:04 uncontested fact you just read?
11:42:06 A. Yes.
11:42:08 Q. Who will manufacture the MSN tablets?
11:42:10 A. MSN.
11:42:11 Q. Based on your work in this case, is MSN aware of the
11:42:16 '349 patent?
11:42:17 A. Yes.
11:42:18 Q. Is MSN aware of the infringement opinions you have
11:42:22 presented in this case?
11:42:22 A. Yes.
11:42:24 Q. Will MSN induce infringement of Claim 3 of the
11:42:27 '349 patent if the MSN ANDA products are commercialized in
11:42:33 the United States before the patent expires?
11:42:35 A. Yes.
11:42:38 MS. WIGMORE: I have no further questions at
11:42:40 time, Your Honor, but I would like to move certain exhibits
11:42:42 into evidence.
11:42:43 THE COURT: All right.
11:42:44 MS. WIGMORE: JTX-4, PTX-243, PTX-394, PTX-724,
11:42:58 PTX-447, PTX-553A, PTX-572A, PTX-677, PTX-698, PTX-744, and
11:43:17 PTX-777.
11:43:21 In addition, I believe DTX-215 was entered

11:43:24 through Dr. Nithiyanandam.

11:43:35 MR. COOPER: No objection, Your Honor.

11:43:36 THE COURT: All right. And just so I'm clear,
11:43:37 there's no objection to PTX-744, the agreement between Zydus
11:43:42 and MSN?

11:43:44 MR. COOPER: No, Your Honor.

11:43:45 THE COURT: Okay. All right. Well, they're
11:43:47 admitted without objection.

11:43:48 MS. WIGMORE: Thank you.

11:42:45 (JTX Exhibit No. 4 was admitted into evidence.)

11:42:47 (PTX Exhibit Nos. 243, 394, 447, 553A, 572A,
11:42:56 677, 698, 724, 744, and 777 were admitted into evidence.)

11:43:49 THE COURT: So, Dr. Koleng, I didn't quite hear
11:43:55 the point where you were talking about Dr. Donovan's opinion
11:43:58 that it's -- that the corn starch is not a glidant. You
11:44:04 said something about diluent.

11:44:07 Is your opinion that it's both a glidant and a
11:44:11 diluent?

11:44:12 THE WITNESS: My opinion in this case,
11:44:14 Your Honor, is that it's a glidant, but I'm not refuting
11:44:17 that it could have a multifunctional diluent effect.

11:44:22 THE COURT: All right. And you also said at
11:44:26 some point that you basically didn't rely on any MSN lab
11:44:32 notebooks because of discrepancies. The discrepancies
11:44:38 you're talking about, you describe them in more detail in

your expert report?

THE WITNESS: They -- the data is in more detail in the report, sir, yes. But not the -- the discrepancies were discussed during deposition.

THE COURT: Okay. All right. Thank you.

All right. Go ahead.

Mr. Cooper; right?

MR. COOPER: That's right, Your Honor.

May we approach with binders?

THE COURT: Sure. Yes.

MR. COOPER: May it please the Court?

THE COURT: Yes. Go ahead.

CROSS-EXAMINATION

BY MR. COOPER:

Q. Good morning, Dr. Koleng. Good to see you again.

A. Good morning, sir.

Q. Now, Dr. Koleng, you and Dr. Donovan disagree about the way to evaluate whether something is functioning as a glidant; is that fair to say, in a specific formulation?

A. Could you be more specific?

Q. Yeah. Let me ask you this: Your opinion is that any excipient that improves the flowability of a powder mixture would be considered a glidant by a POSA; correct?

A. By definition, yes.

Q. And glidants in your view are simply characterized by

11:46:38 their directional improvement in flow; correct?
11:46:40 A. Yes.
11:46:42 Q. And I want to talk about that definition in a bit,
11:46:45 but first let's talk about that data that you relied on.
11:46:49 So, in your -- providing your testimony today,
11:46:52 as you said, you did not talk about any of the data in MSN's
11:46:55 laboratory notebooks; correct?
11:46:57 A. Correct.
11:46:57 Q. But you did rely on that data generated by MSN and
11:47:01 reported in their laboratory notebooks when forming your
11:47:05 infringement opinions in writing your expert reports in this
11:47:08 case; correct?
11:47:08 A. In part, yes.
11:47:10 Q. All right. Now, first, you agree there are methods
11:47:13 that a POSA can use to characterize powder flow; correct?
11:47:17 A. Yes.
11:47:19 Q. And the Hausner ratio and compressibility index that
11:47:23 you talked about, those are two of those methods; right?
11:47:25 A. Yes.
11:47:26 Q. And compressibility index, that's also referred to as
11:47:29 Carr index; right?
11:47:30 A. Yes.
11:47:30 Q. And those are simple, fast, and popular methods in
11:47:34 characterizing powder flow. Do you agree?
11:47:37 A. I'll agree that they're methods used. Simple, fast,

et cetera seem to be qualifiers. I'm not familiar -- I wouldn't -- I'd need time to think about.

Q. Okay. Well, you wrote in your expert report that those are simple, fast, and popular methods of characterizing powder flow. Didn't you?

A. If it's there, the words, then yes.

MR. COOPER: All right. Let's pull up DTX-358.

BY MR. COOPER:

Q. Now the USP contains information about various tests?

A. I'm sorry. Is it also in here?

Q. It is.

A. You said 358?

Q. Correct. And it's right there on your screen.

And so the USP contains information about tests performed on pharmaceutical materials; correct?

A. It can, yes. Or does.

Q. And this one that we're looking at here, DTX-358, that's one on powder flow; right?

A. The chapter is powder flow; correct.

Q. And you relied on this reference in forming your opinions in this case; correct?

A. In my report, but not sitting here today.

Q. That right. And so let's go to Page 4 of this exhibit and call out the equations at the top of that page and also Table 2.

11:48:43 Do you see that on your screen?
11:48:44 A. You said Table 2. I do.
11:48:50 Q. All right. And the USP explains how to calculate the
11:48:54 Carr index and Hausner ratio values that you talked about
11:48:58 earlier based on data that you have on bulk density and
11:49:03 tapped density of a sample; correct?
11:49:05 A. Correct.
11:49:05 Q. And you've calculated Hausner and Carr values many
11:49:09 times in your career; right?
11:49:10 A. Yes.
11:49:11 Q. And the USP table also reports there, Table 2, how
11:49:15 the flow character of a sample can be characterized based on
11:49:19 the Carr and Hausner values; right?
11:49:22 A. Yes.
11:49:23 Q. And so you can see here that an improvement in
11:49:26 flow -- and I think you mentioned this on your direct -- an
11:49:28 improvement in the flow character means the Hausner and Carr
11:49:32 values are numerically getting lower; correct?
11:49:34 A. Correct.
11:49:35 Q. And so a worsening of flow character means that the
11:49:38 Hausner and Carr values are getting higher; right?
11:49:42 A. Yes.
11:49:42 Q. And in your view, there is no minimum magnitude of
11:49:47 change in Hausner or Carr values that a POSA needs to see to
11:49:51 reflect a meaningful difference in flowability of a powder;

11:49:55 correct?
11:49:56 A. Correct.
11:49:57 Q. So, for example, if a Carr index of sample A is
11:50:01 27.7 percent and the Carr index of sample B is 27.6 percent,
11:50:07 to you, a POSA, or your view is a POSA would understand
11:50:11 sample B shows an improvement in flow. That's your opinion;
11:50:14 correct?
11:50:14 A. Yes.
11:50:15 Q. Okay. So let's look at the actual flow character
11:50:19 data from MSN's product development. Let's pull up DTX-215.
11:50:24 And this is the MSN product development report. Let's go to
11:50:28 Page 34 of this exhibit.
11:50:29 Let's call out the section entitled "Process
11:50:33 Selection." And now, you showed us this during your direct
11:50:37 examination; correct?
11:50:38 A. Yes.
11:50:39 Q. And the PDR at the top reports, "During initial
11:50:43 development, drug substance" -- drug substance is the API;
11:50:47 right?
11:50:47 A. Correct.
11:50:47 Q. -- "drug substance was evaluated for bulk properties
11:50:51 of different lots." Do you see that?
11:50:52 A. I do.
11:50:53 Q. And those properties that were measured included bulk
11:50:57 density and tapped density; correct?

11:50:59 A. Correct.
11:50:59 Q. And the calculated compressibility index of the API
11:51:03 was about 34 percent; is that correct?
11:51:05 A. It's what's shown here.
11:51:07 Q. And under the chart you see, "From the above
11:51:09 compressibility index, it is evident that the API exhibits
11:51:15 poor flow properties."
11:51:16 Do you see that?
11:51:17 A. I do.
11:51:17 Q. And actually if you refer to that USP table, a
11:51:21 compressibility index of 34 percent would actually be
11:51:24 characterized by the USP as very poor; right?
11:51:31 That's okay you don't need to check. Withdrawn.
11:51:33 So then after that, MSN states, "Hence, the
11:51:36 process of choice was wet granulation over direct
11:51:38 compression."
11:51:40 Do you see that?"
11:51:41 A. I do.
11:51:41 Q. And granulation can improve flow properties of a
11:51:44 powder mixture; true?
11:51:46 A. I believe I discussed that on direct, yes.
11:51:48 Q. All right. And also for this ANDA product, you agree
11:51:52 that MSN's wet granulation process ultimately improved the
11:51:57 flowability of the granules over the dry mix of
11:52:02 intragranular components; correct?

11:52:04 A. Over the dry mix, yes.
11:52:10 Q. Okay. And so now let's look at how MSN's excipient
11:52:14 selection affected flow. Now, you understand that MSN
11:52:19 prepared several prototype formulations during development;
11:52:21 correct?
11:52:22 A. I'll -- I'll say yes for now.
11:52:27 Q. Okay. And early formulations you know did not use
11:52:31 granulated corn starch; correct?
11:52:32 A. I'm aware of at least one formulation that did not.
11:52:36 Correct.
11:52:36 Q. All right. And early formulations, at least one,
11:52:39 used maize starch B as an extragranular component in the
11:52:44 formulation; correct?
11:52:45 A. It's what I recall.
11:52:47 Q. And MSN replaced the maize starch B with granulated
11:52:52 corn starch in the extragranular layer of the formulation at
11:52:56 some point during development; correct?
11:52:58 A. That's my understanding, yes.
11:53:00 Q. All right. And just so it's clear, maize starch B,
11:53:02 that is an unmodified type of corn starch; correct?
11:53:07 A. That's my understanding.
11:53:08 MR. COOPER: So, let's pull up DTX-196.
11:53:08 BY MR. COOPER:
11:53:12 Q. And now, Doctor, you recognize this exhibit; right?
11:53:15 A. Yes.

11:53:17 Q. And MSN documented its formulation development work in laboratory notebook 252 which is in front of us; right?
11:53:24 A. Correct.
11:53:26 Q. And you relied on this notebook and data in forming your opinions in this case and writing your expert reports, but you didn't talk about it today; correct?
11:53:36 A. Not using that information today, that's correct.
11:53:38 Q. All right.
11:53:38 MR. COOPER: Let's pull up DDX -- Koleng 2.
11:53:38 BY MR. COOPER:
11:53:44 Q. Now, Doctor, you recognize this chart; right?
11:53:46 A. Yes.
11:53:46 Q. And that's because you prepared it; right?
11:53:48 A. Yes.
11:53:50 Q. All right. And this chart reproduces information from MSN's lab notebook that you thought was important to your infringement analysis in this case; correct?
11:53:58 A. I thought it was correct information, yes.
11:54:00 Q. Uh-huh. Okay. All right. So on the left-hand side of the chart is information about MSN's batch 252/023; correct?
11:54:03 A. It's what it says.
11:54:11 Q. And then on the right-hand side is batch number 252/044; correct?
11:54:13 A. Correct.
11:54:17
11:54:18

11:54:19 Q. And the formulations are identical except for that
11:54:24 the earlier one in batch 023 has 30 milligrams of corn
11:54:28 starch in it. And the batch 044, it's been swapped, and
11:54:32 there's 30 milligrams of granulated corn starch in it; is
11:54:35 that right?
11:54:36 A. That's my understanding.
11:54:37 Q. And then so in your chart that you prepared, you also
11:54:40 wrote down the bulk density and tapped density measurements
11:54:44 that were taken by MSN and reported in the lab notebooks for
11:54:49 those batches; correct?
11:54:50 A. As well as Carr's and Hausner ratio; correct.
11:54:53 Q. And so for batch 23 the bulk density was .515 and the
11:54:57 tapped density was .708; correct?
11:55:00 A. Well, that's what was in the notebook, yes.
11:55:02 Q. Right. And the bulk density was .541, and the tapped
11:55:06 density was .825; correct?
11:55:07 A. That's what was in the notebook; correct.
11:55:09 Q. All right. And then you also, as you said, you put
11:55:11 down the Carr index and Hausner ratio values that were
11:55:14 listed in the notebook; right?
11:55:16 A. Those were the values reported in the notebooks;
11:55:18 correct.
11:55:18 Q. All right. So for batch number 23, the Carr value
11:55:22 was 27.7 and the Hausner was 1.375; correct?
11:55:27 A. Again, that was what was written in the notebooks;

11:55:30 correct.
11:55:30 Q. And for batch 44, the Carr was 25.92 and the Hausner
11:55:34 was 1.35; correct?
11:55:36 A. That's what was written in the notebooks; correct.
11:55:39 Q. Now, based on the Carr and Hausner values, the USP
11:55:43 table would actually describe the flow character of batch 23
11:55:47 as poor; correct?
11:55:48 A. That's correct.
11:56:05 Q. And the USP would also describe the flow character of
11:56:09 batch 44 as poor based on the Hausner and Carr values;
11:56:13 correct?
11:56:13 A. They fall in that range, yes.
11:56:15 Q. All right. And so the USP would categorize both of
11:56:19 these batches as having poor flow character if you used the
11:56:23 values in the table by the USP; correct?
11:56:25 A. Correct.
11:56:26 Q. But in -- at least in forming your opinions in this
11:56:28 case, you concluded that there was still a meaningful
11:56:33 difference in the Carr and Hausner values between those two
11:56:36 batches; correct?
11:56:37 A. Yes.
11:56:39 Q. So, because for infringement, for your infringement
11:56:42 opinion, you relied on the directional reduction of the Carr
11:56:47 and Hausner values when granulated corn starch replaced
11:56:50 maize starch B in the formulation; correct?

11:56:52 A. At the time it was one of the pillars of my opinion,
11:56:55 yes.
11:56:56 Q. And you concluded that where the only modification to
11:56:59 MSN's prototype formulation was the replacement of
11:57:02 unmodified corn starch with granulated corn starch in the
11:57:06 extragranular component, the resulting formulation exhibited
11:57:10 a reduction in both the compressibility index and the
11:57:13 Hausner ratio thus indicating an increase in flowability of
11:57:17 the final blend. That was your conclusion; right?
11:57:19 A. Yes, in that report, yes.
11:57:23 Q. And so, this is the -- here on the chart is the only
11:57:26 data available where the MSN prototype formulations are
11:57:31 identical except for the presence of either maize starch B
11:57:35 or granulated corn starch in the extragranular layer;
11:57:39 correct?
11:57:39 A. These were the closest; correct.
11:57:41 Q. So, this comparison, between batch 23 and batch 44,
11:57:47 well, that was important to your infringement opinion that
11:57:51 granulated corn starch is functioning as a glidant in MSN's
11:57:54 ANDA product; correct?
11:57:55 A. Again it was one consideration, yes.
11:57:58 Q. Well, it wasn't just one consideration, Doctor. It
11:58:00 was actually important to your infringement opinions in this
11:58:03 case regarding the use of GRASTAR as a glidant; correct?
11:58:08 A. Yeah.

11:58:11 1 Q. Probably know where we're going here, but the Carr
11:58:14 2 and Hausner values for batch 44 that's in your chart are
11:58:17 3 actually wrong, aren't they, Dr. Koleng?
11:58:19 4 A. I don't know actually.
11:58:21 5 Q. Well, there's a mathematical error in calculating the
11:58:26 6 Carr index and Hausner ratio from the bulk density and
11:58:28 7 tapped density listed; correct?
11:58:30 8 A. There is a math but --
11:58:33 9 Q. Thank you. When you correctly calculate the Carr
11:58:36 10 index from the density -- bulk density and tapped density
11:58:39 11 measurements that are listed on your chart, the correct
11:58:43 12 value for batch 44 is 34.42; correct?
11:58:47 13 A. I don't know.
11:58:49 14 Q. Well, let's look at your deposition transcript.
11:58:51 15 Okay?
11:58:52 16 A. Okay.
11:58:52 17 Q. Would you -- let me ask you the question again.
11:58:54 18 A. Sure.
11:58:54 19 Q. Now, when you calculate -- when you look at the bulk
11:58:57 20 density and tapped density numbers that are listed in your
11:59:00 21 chart --
11:59:00 22 A. Right.
11:59:01 23 Q. -- if you just calculate the Carr index from the
11:59:05 24 density measurements, you actually get 34.42; correct?
11:59:09 25 A. Using those numbers, I got a different number;

11:59:12 correct.
11:59:12 Q. And it's 34.42; correct?
11:59:14 A. I believe so. Yes.
11:59:15 Q. All right. And, again, you get a different number if you calculate the Hausner ratio from the bulk and tapped density measurements that are identified in your chart, and that's 1.52; correct?
11:59:28 A. If that's what we calculated during the deposition, yes.
11:59:33 MR. COOPER: Okay. So let's pull up DDX Koleng 4.
11:59:36 BY MR. COOPER:
11:59:37 Q. And so if we look at the corrected values, the Carr and Hausner values for batch 44, at least as identified on the chart, based on the measurements that were listed in the lab notebooks for density, the values for batch 44 are actually higher than batch 23; correct?
11:59:52 A. Using an unverified bulk and tapped, that would be correct.
11:59:57 Q. Okay. Well, but that's the data that you looked at and reviewed in the course of forming your opinions and writing your report; correct?
12:00:03 A. I looked at all of the data, yes.
12:00:04 Q. All right. And so, in reality, if you looked at just the Carr index and Hausner ratio numbers between the 23
12:00:06
12:00:09

12:00:12 batch and the 44 batch, there's actually a directional
12:00:16 reduction in flow character for batch 44 with the granule
12:00:21 and corn starch, compared to batch 23 without it; correct?
12:00:24 A. Again, based upon these calculations, yes.
12:00:30 Q. And before -- I just want to make sure. You were not
12:00:32 asked in this case to provide an absolute opinion on whether
12:00:35 the maize starch B in batch 23 is or is not functioning as a
12:00:39 glidant; correct?
12:00:43 A. Correct.
12:00:47 Q. All right. Let's look at one of the things that you
12:00:49 did talk about during your direct. And pull up PDX-2.14.
12:00:56 THE REPORTER: Mr. Cooper, can you slow down,
12:00:59 please?
12:00:59 MR. COOPER: I can. I'm sorry.
12:01:00 THE WITNESS: Which PDX?
12:01:03 BY MR. COOPER:
12:01:03 Q. PDX-2.14?
12:01:07 A. Okay.
12:01:08 Q. Now, you showed us this chart, and you identified
12:01:12 that granulated corn starch in MSN's formulation is added
12:01:17 during the pre-lubrication stage of their manufacturing
12:01:21 process; correct?
12:01:21 A. Correct.
12:01:22 Q. And you said that addition of a -- an excipient at
12:01:27 the pre-lubrication stage is consistent with its use as a

12:01:31 glidant; correct?
12:01:32 A. Well, I was restating Remington saying that's where a
12:01:36 glidant would typically go.
12:01:37 Q. Right. And I'm just getting at the fact that you
12:01:39 said it was consistent --
12:01:40 A. Yes.
12:01:40 Q. -- with where a glidant would be at; correct?
12:01:42 A. Yes.
12:01:43 Q. All right. But disintegrants can also be added in
12:01:46 pharmaceutical formulations during the pre-lubrication
12:01:49 stage; correct?
12:01:49 A. Yes.
12:01:50 Q. In fact, there is one in the MSN product, a
12:01:53 disintegrant that's added at the pre-lubrication stage;
12:01:56 correct?
12:01:56 A. Yes.
12:01:57 Q. And fillers can be added during the pre-lubrication
12:02:00 stage as well; right?
12:02:01 A. It may be.
12:02:02 Q. And there are other excipients that can be added
12:02:05 during the pre-lubrication stage, too; correct?
12:02:07 A. There may be.
12:02:13 MR. COOPER: All right. Let's pull up DTX-215,
12:02:16 the MSN product development report. And let's go to Page 34
12:02:21 to 36 of this exhibit. And pull up that initial risk

12:02:26 assessment of the formulation variables table that has the
12:02:30 entry for granulated corn starch.
12:02:30 BY MR. COOPER:
12:02:40 Q. And you showed us this callout during your direct
12:02:42 exam; correct?
12:02:43 A. Correct.
12:02:43 Q. And we can agree that MSN's initial risk assessment
12:02:47 for granulated corn starch does refer to it as a diluent;
12:02:51 right?
12:02:51 A. The word is there; correct.
12:02:53 Q. And you focused on the fact that it also says "it
12:02:56 enhances the flowability of the granules."
12:02:59 Do you see that?
12:02:59 A. I do.
12:03:00 Q. Now, you didn't talk to anyone from MSN about the
12:03:03 basis for this statement in the initial risk assessment;
12:03:07 correct?
12:03:07 A. No.
12:03:07 Q. And you didn't ask anyone from MSN if there was any
12:03:11 data showing that the granulated corn starch enhanced
12:03:14 flowability of the granules; correct?
12:03:16 A. No.
12:03:17 Q. But you did review the deposition transcript of
12:03:21 Mr. Nithiyanandam, MSN's formulation scientist, during the
12:03:25 course of your work on this case; correct?

12:03:27 A. Yes.
12:03:28 Q. Now, you recall that Mr. Nithiyanandam testified that
12:03:32 MSN's initial risk assessment was performed before the
12:03:37 formulation development trials, and that the statement about
12:03:41 granulated corn starch enhancing the flowability of the
12:03:44 granules was based on information from the scientific
12:03:47 literature; you recall that generally?
12:03:49 A. I recall that generally; correct.
12:03:51 Q. And you understand that Mr. Nithiyanandam took an
12:03:53 oath to tell the truth at his deposition; correct?
12:03:55 A. Sure.
12:03:57 Q. It's the same oath you took today; right?
12:03:59 A. Yes. I understand that.
12:04:01 Q. And but you just don't credit Mr. Nithiyanandam's
12:04:05 sworn testimony and explanation as accurate; correct?
12:04:08 A. Correct.
12:04:10 Q. Okay. Well, we can at least agree that in this
12:04:12 document, the initial risk assessment comes before the
12:04:16 description of Formulation Development, Study Number 1 and
12:04:20 Number 2 that have -- that report on formulation studies
12:04:25 with granulated corn starch in it; correct?
12:04:27 A. So from the document order, yes.
12:04:36 Q. Let's look at a few other excipients in this initial
12:04:40 risk assessment table.
12:04:42 MR. COOPER: So, let's call out the next row for

magnesium stearate in the table on Page 36.

BY MR. COOPER:

Q. MSN's initial risk assessment also states, "Magnesium stearate enhances the flow properties, which does not impact the assay and content uniformity of the tablet?"

Do you see that?"

A. I do.

Q. And MSN's ANDA identifies magnesium stearate as a lubricant in its ANDA products; correct?

A. Correct.

Q. You agree that magnesium stearate is a lubricant in MSN's ANDA products; correct?

A. I agree it's at least a lubricant, yes.

Q. Well, you haven't offered an opinion --

A. That's correct.

Q. -- that magnesium stearate is serving any other function in MSN's ANDA product other than as a lubricant; correct?

A. Correct.

Q. All right.

MR. COOPER: Let's go back to Page 35 and call out the lactose monohydrate row in this table.

BY MR. COOPER:

Q. Do you see that?

A. I do.

12:05:38 Q. MSN's initial risk assessment states, "Lactose
12:05:42 monohydrate level can impact the flow properties of the
12:05:45 blend."
12:05:47 It goes on from there. Do you see that?
12:05:48 A. I see that.
12:05:49 Q. MSN's ANDA identifies the function of lactose
12:05:52 monohydrate in its ANDA products as a diluent; correct?
12:05:56 A. Correct.
12:05:57 Q. And you agree that lactose monohydrate is a diluent
12:06:01 in MSN's ANDA products; correct?
12:06:03 A. That's my opinion; correct.
12:06:04 Q. You haven't offered an opinion that lactose
12:06:07 monohydrate is serving any other function in MSN's ANDA
12:06:11 product; correct?
12:06:11 A. Correct.
12:06:13 Q. All right. Let's step back from the data in the MSN
12:06:17 statements in the document and talk about excipient
12:06:20 definitions and flow properties more generally, okay.
12:06:24 Now, every pure solid material or ingredient in
12:06:27 a formulation can be assessed for its own flow properties;
12:06:31 correct?
12:06:31 A. Generally, yes.
12:06:34 Q. So, for instance, a pure solid API, it has its own
12:06:39 flow properties that can be measured; correct?
12:06:43 A. Generally, yes.

12:06:44 Q. And the flow properties of each individual excipient
12:06:46 can generally be measured, too; correct?
12:06:49 A. Generally, yes.
12:06:49 Q. So, for example, a powder filler, before you put it
12:06:52 into a blend, it has its own flow properties that generally
12:06:56 can be measured; correct?
12:06:57 A. When you say "powder filler," you mean a diluent?
12:07:00 Q. Yeah.
12:07:01 A. Okay. Yes. Yes.
12:07:03 Q. And then if you put an API and multiple excipients,
12:07:07 and you combine them into a powder blend, then that powder
12:07:10 blend's overall flow properties could be measured as well;
12:07:15 correct?
12:07:15 A. Yes.
12:07:16 Q. Now, as we said at the beginning, it's your opinion
12:07:18 that glidant excipients are simply characterized by their
12:07:22 directional improvement in flow; correct?
12:07:24 A. I believe my definition was one that it improved flow
12:07:28 characteristics of a blend, yes.
12:07:30 Q. And they're simply characterized by their directional
12:07:33 improvement in flow; correct?
12:07:35 A. Yes.
12:07:35 Q. All right. And that improvement does not have to be
12:07:38 of any minimum magnitude; correct?
12:07:41 A. Not that I'm aware of, no.

12:07:43 Q. And that improvement does not have to result from any
12:07:46 certain mechanism; correct?
12:07:47 A. Correct.
12:07:49 Q. So, if the addition of a filler directionally
12:07:53 improves the overall flow properties of a powder blend, that
12:07:56 means that the filler must also be functioning as a glidant.
12:08:00 That's your opinion at the highest level; correct?
12:08:03 A. Again, in this particular case, the filler would have
12:08:08 to be taken into consideration.
12:08:10 Q. I'm not talking about this case.
12:08:11 A. No. No. But that's a broad -- you have to take into
12:08:14 consideration the manufacturing process, et cetera, right.
12:08:18 My opinion was not -- my opinions are not that generic.
12:08:21 Q. Okay. All right. Let's turn to what the literature
12:08:24 says --
12:08:24 A. Sure.
12:08:25 Q. -- about fillers.
12:08:26 MR. COOPER: So let's pull up DTX-363.
12:08:26 BY MR. COOPER:
12:08:31 Q. And you recognize the Ansel reference; correct?
12:08:33 A. Yes.
12:08:35 Q. All right. Let's go to Page 33. There's a table of
12:08:40 examples of pharmaceutical ingredients?
12:08:42 A. Well, you're ahead of me, sorry, sir.
12:08:44 Q. All right.

12:08:44 A. You said Page 33 or Table 33?
12:08:46 Q. Page 33. Table 3.3. And it's also right there on
12:08:51 your screen.
12:08:55 A. It's Table 3.3.
12:09:13 Q. All right. It's right there, Table 3.3, do you see
12:09:16 that?
12:09:16 A. Yes, I see it on the screen, but I usually like to
12:09:20 see it in the context of the entire document.
12:09:22 Q. Okay. Well, I'm going to pull up --
12:09:24 A. At least -- I'm sorry. It's not coming up quickly in
12:09:27 my papers. Go ahead.
12:09:29 Q. All right. So in that table, if you go to Page 35,
12:09:33 there's an entry for tablet and capsule diluents, do you see
12:09:36 that on your screen?
12:09:37 A. Hold on a second. Which DTX is this, sir, I'm sorry.
12:09:41 Q. This is DTX-363.
12:09:43 A. 363. Okay.
12:09:55 What was the last four -- three of the Bates?
12:09:58 Q. Well, it's Page 35 of the exhibit. And that's in
12:10:01 the --
12:10:01 A. The exhibit's not -- is the exhibit -- oh, there's
12:10:04 the number, okay.
12:10:05 Q. Okay.
12:10:06 A. Sorry.
12:10:09 Q. And I'm only going to be talking about --

12:10:11 MS. WIGMORE: Objection, Your Honor. I believe I may have a different version than they do. I just want to make sure we're working from the same exhibit, because I'm not seeing it.

12:10:24 (Discussion held off the record:)

12:10:25 MS. WIGMORE: It's not the same.

12:10:43 MR. COOPER: All right. We'll come back to that.

12:10:47 BY MR. COOPER:

12:10:47 Q. Doctor, you agree that fillers are added to formulations to provide an increased bulk to a formulation; correct?

12:10:55 A. They can; correct.

12:10:57 Q. And you also agree that a POSA would consider other properties that an excipient may have when selecting it for a formulation; correct?

12:11:04 A. Correct.

12:11:07 Q. And that can include an excipient's effects on disintegration properties; right?

12:11:13 A. Potentially.

12:11:14 Q. And dissolution properties; right?

12:11:15 A. Potentially, yes.

12:11:16 Q. And flow properties; correct?

12:11:17 A. Potentially, yes.

12:11:18 Q. All right. Now, Mr. Prussia said something during

his opening statement that I want to ask you about. Now, he said that because every excipient dilutes the API, any excipient is a diluent.

So, Doctor, do you agree that a POSA would consider every excipient that is used in a formulation to fall within the definition that pharmaceutical textbooks identify for fillers?

A. Not always.

MR. COOPER: All right. Let's pull up DTX-344.

BY MR. COOPER:

Q. Now, you were -- this is an article that you reviewed during your work on this case; correct?

A. 344? Mm-hmm.

Q. And the title here is, "An overview of the different excipients useful for the direct compression of tablets."

Do you see that on your screen?

A. I do.

Q. Okay. And the first author is Jivraj; correct?

A. Correct.

Q. And you reviewed this article during your course of work on this case; correct?

A. It's not coming immediately to mind, but if it's in my work cited. There was a lot of documents.

Q. Okay. You -- you reviewed documents that Dr. Donovan cited as well; correct?

12:12:52 A. Correct.
12:12:53 Q. And you respond to --
12:12:54 A. Yes.
12:12:54 Q. -- some of the articles that she raised in your reply report; correct?
12:12:57 A. Correct.
12:12:59 MR. COOPER: Now, let's call out the first paragraph.
12:13:00 BY MR. COOPER:
12:13:02 Q. And here, Jivraj -- in second sentence, Jivraj says, "This review will outline the various excipients that have been used as fillers in direct compression formulations, with particular emphasis on what is expected from such excipients in terms of their functionality."
12:13:20 Do you see that?
12:13:21 A. I do.
12:13:22 MR. COOPER: All right. Let's go to Page 3 and call out the last full paragraph in the left-hand column.
12:13:23 BY MR. COOPER:
12:13:27 Q. And that paragraph starts by referring to microcrystalline cellulose.
12:13:32 Do you see that there?
12:13:33 A. Oh, there it is. Yes.
12:13:39 Q. And microcrystalline cellulose, we can refer to that as MCC; correct?

12:13:43 A. Sure.
12:13:43 Q. And you're generally familiar with MCC as an
12:13:46 excipient; correct?
12:13:47 A. Yes.
12:13:48 Q. MCC may serve as a diluent, a binder, and absorbent
12:13:53 or a disintegrant in tablet and capsule formulations;
12:13:57 correct?
12:13:57 A. It's what it says.
12:13:58 Q. You've personally used MCC as a diluent in a tablet
12:14:02 formulation; correct?
12:14:03 A. Yes.
12:14:05 Q. And at your deposition, anyway, you are couldn't
12:14:07 recall ever personally using MCC as a glidant in any
12:14:11 formulation; correct?
12:14:12 A. Correct.
12:14:14 Q. Now, Jivraj reports microcrystalline cellulose is
12:14:18 "regarded as being chemically inert and compatible with most
12:14:21 drugs."
12:14:22 Do you see that?
12:14:22 A. I see that.
12:14:23 Q. And he continues, "The limitation of poor flow can be
12:14:26 offset by mixing with another filler with good flowability,
12:14:31 such as alpha-lactose monohydrate or dicalcium phosphate
12:14:36 dihydrate."
12:14:37 Do you see that?

12:14:37 A. I see that.
12:14:38 Q. You're also generally familiar with lactose
12:14:42 monohydrate as an excipient; correct?
12:14:44 A. Yes.
12:14:44 Q. And you agree lactose is a common diluent; right?
12:14:47 A. Yes.
12:14:50 Q. As of your deposition, anyway, you couldn't recall
12:14:53 ever personally using lactose monohydrate as a glidant in
12:14:58 any formulations; correct?
12:14:59 A. Correct.
12:15:00 Q. And you've been involved in hundreds of
12:15:02 formulation -- formulations in the course of your career;
12:15:05 right?
12:15:06 A. Yes.
12:15:07 MR. COOPER: All right. Let's look at one more
12:15:08 filler Jivraj discusses. And let's go to Page 5. And call
12:15:14 out the section on granulated lactitol.
12:15:18 Do you see that section?
12:15:19 A. Granulated lactitol, yes.
12:15:23 Q. And Jivraj writes, "Lactitol is a direct compression
12:15:26 filler derived from the catalytic hydrogenation of lactose."
12:15:32 Do you see that?
12:15:32 A. I do.
12:15:33 Q. In the last sentence of that paragraph it says, "This
12:15:35 form of lactose is freely soluble in water, has reasonably

12:15:38 1 good flow properties, and formulations containing granulated
12:15:43 2 lactitol do not require a glidant."
12:15:45 3 Do you see that?
12:15:45 4 A. I see it. I see the words.
12:15:47 5 Q. All right. Let's talk more specifically about
12:15:47 6 starches.
12:15:52 7 Now, you agree that starch is a common filler;
12:15:54 8 correct?
12:15:55 9 A. It's listed as a common filler, yes.
12:15:58 10 Q. We can agree that not all starches that are
12:16:01 11 functioning as a filler must also be functioning as a
12:16:05 12 glidant; correct?
12:16:06 13 A. Correct.
12:16:07 14 Q. There's a long list of different types and grades of
12:16:11 15 starches available to formulators; correct?
12:16:13 16 A. Yes.
12:16:15 17 Q. The different types and grades of the same excipient
12:16:17 18 could have different physical properties; correct?
12:16:20 19 A. They may. Correct.
12:16:22 20 Q. Including flow properties; right?
12:16:24 21 A. They may, yes.
12:16:27 22 Q. All right. You also talked about pregelatinized
12:16:30 23 starch. And, again, you agree that pregelatinized starch
12:16:34 24 can serve as a filler in tablets; agreed?
12:16:37 25 A. It may, yes.

12:16:39 Q. And pregelatinized starch can serve as a binder; correct?
12:16:42 A. It may, yes.
12:16:44 Q. Pregelatinized starch can serve as a lubricant; correct?
12:16:44 A. It may; correct.
12:16:47 Q. And also a disintegrant; correct?
12:16:48 A. It may.
12:16:50 Q. So we can agree that not all pregelatinized starches that are used as a filler or a disintegrant in a formulation must also be functioning as a glidant; correct?
12:16:54 A. To the extent you'd have to see how the formulation as a whole and where it's incorporated, but okay.
12:16:58 Q. But otherwise you agree; right?
12:17:00 A. Generally, yeah.
12:17:07 Q. Now, the reason people in the industry pregelatinize starch is to change the unmodified starch's physical properties; correct?
12:17:08 A. I know when you changed product -- change them, they can get a change in the properties.
12:17:09 Q. Some grades of pregelatinized starch have been rendered more flowable than their unmodified versions; correct?
12:17:14 A. That's my understanding, yes.
12:17:18 Q. Now, you showed us a couple of references -- well,
12:17:19
12:17:22
12:17:23
12:17:26
12:17:29
12:17:29
12:17:33

12:17:36 one reference that specifically referred to pregelatinized
12:17:40 starch during your direct examination, U.S. patent -- the
12:17:45 '643 patent; correct?
12:17:46 A. Correct.
12:17:47 MR. COOPER: So let's pull up PTX-243.
12:17:47 BY MR. COOPER:
12:17:52 Q. Now, you showed us in this patent that there was a
12:17:57 list and that list identifies pregelatinized corn starch and
12:18:01 a list of potential -- potential optional glidant components
12:18:05 of the pharmaceutical formulations of this invention;
12:18:08 correct?
12:18:09 A. Correct.
12:18:10 Q. And in forming your opinions in this case, this is
12:18:13 the only patent you identified that had pregelatinized
12:18:19 starch specifically by name identified as a potential
12:18:21 glidant for a formulation; correct?
12:18:22 A. Repeat the first part of your question, sir.
12:18:25 Q. Yeah. In preparing your expert reports in this case,
12:18:28 this is the only patent that you identified in those reports
12:18:31 where pregelatinized starch by that name was specifically
12:18:36 identified as a potential glidant for a formulation;
12:18:39 correct?
12:18:39 A. Patent, correct.
12:18:41 Q. In the left-hand column you see that this patent
12:18:44 refers back to a provisional application from 1996; correct?

12:18:49 A. I see the date.
12:18:50 Q. So that's -- that's over 20 years before MSN began
12:18:53 formulating its ANDA product; correct?
12:18:55 A. I'll trust your math.
12:18:59 MR. COOPER: Let's go to Page 7. And call out
12:19:02 Column 11, Line 21 through 33.
12:19:02 BY MR. COOPER:
12:19:07 Q. And now, also in this patent there are references to
12:19:11 potential binders that can be used for the formulation;
12:19:14 correct?
12:19:14 A. Correct.
12:19:16 Q. Here, the specification provides a list of potential
12:19:20 binders for the claimed formulation; correct?
12:19:22 A. It appears so.
12:19:24 Q. And pregelatinized corn starch you'll see is one of
12:19:28 those options; right?
12:19:29 A. It's what it says.
12:19:30 MR. COOPER: All right. Let's go to Page 9,
12:19:32 Column 15, Lines 5 through 16.
12:19:32 BY MR. COOPER:
12:19:36 Q. And here its specification identifies a list of
12:19:41 anti-adherents that may optionally be used with the
12:19:43 formulation.
12:19:43 Do you see that?
12:19:44 A. I do.

12:19:45 Q. And pregelatinized corn starch is one of the options listed here, too; right?
12:19:47
12:19:49 A. That's what it says.
12:19:50 MR. COOPER: All right. Let's go to Page 9. Column 15, Line 25 through 35.
12:19:52
12:19:52 BY MR. COOPER:
12:19:57 Q. Now, here the patent identifies potential fillers that can be used with the formulation.
12:20:01
12:20:03 Do you see that?
12:20:03 A. I do.
12:20:05 Q. And pregelatinized corn starch is once again identified as one of the options; right?
12:20:08
12:20:10 A. Correct.
12:20:11 MR. COOPER: Let's go to Page 5, Column 7. And look at the chart going -- at the bottom going over to the right-hand column.
12:20:15
12:20:18
12:20:18 BY MR. COOPER:
12:20:20 Q. Now, here, this is what the patent specification identifies as the most preferred formulation of the claimed invention; correct?
12:20:23
12:20:26
12:20:27 A. It's what it says.
12:20:29 Q. And if you look at the formulation, the inventors say that pregelatinized corn starch is being used as a binder; correct?
12:20:33
12:20:37
12:20:37 A. That's how they have it labeled.

12:20:40 Q. And if you look at the formulation it says colloidal
12:20:44 silicon dioxide is the excipient that's being used as a
12:20:46 glidant; correct?
12:20:47 A. That's what they have labeled.
12:20:48 Q. There are no examples anywhere in the patent
12:20:51 describing where the inventors used pregelatinized starch as
12:20:55 a glidant in any specific formulation; correct?
12:20:57 A. Not that I recall.
12:20:58 Q. And there are no claims in the patent that refer to
12:21:00 pregelatinized corn starch as a glidant; correct?
12:21:03 A. Not that I recall.
12:21:07 Q. Now, one example of a partially pregelatinized starch
12:21:11 that you talked about on direct was Starch 1500; correct?
12:21:14 A. That's one brand name, correct.
12:21:16 MR. COOPER: Let's pull up PTX-553 at Page 2.
12:21:19 BY MR. COOPER:
12:21:24 Q. And so, this is the Lieberman or Lachman reference
12:21:27 that you showed us during direct; right?
12:21:29 A. Yes.
12:21:30 Q. And this is the reference you showed us. And you can
12:21:33 see it here as at Page 105 of PTX-533 where Starch 1500 is
12:21:41 identified in a table of what it described as commonly used
12:21:45 glidants; correct?
12:21:46 A. Correct.
12:21:46 Q. Now, you have not identified, in the course of your

12:21:51 preparation of your expert reports, any other textbook
12:21:55 tables where pregelatinized starch or Starch 1500 is
12:21:58 identified in a table of commonly used glidants; correct?
12:22:01 A. Not directly.
12:22:04 Q. Let's go to page -- well, the Lachman reference, you
12:22:07 know is from 1989; correct?
12:22:09 A. Okay.
12:22:10 Q. Well, do you know that? Let's --
12:22:12 A. Sure.
12:22:13 Q. Let's go to Page 4 of the document. Do you see on
12:22:15 Page 4, the Lachman reference is from 1989?
12:22:19 A. Okay.
12:22:20 Q. All right. So, almost 30 years before MSN formulated
12:22:23 its ANDA product; correct?
12:22:24 A. I'll trust your math.
12:22:27 Q. All right. So, you've read -- also read multiple
12:22:30 technical brochures on Starch 1500 in your career; correct?
12:22:34 A. I've read brochures; correct.
12:22:39 Q. Actually, before we get to that, let's go to Page 119
12:22:42 of 553, of PTX-553, Page 119.
12:22:49 All right. And so, still in this Lieberman
12:22:54 Lachman reference, about halfway down, let's call out the
12:22:58 paragraph that says "directly compressible starch."
12:23:01 Do you see that?
12:23:01 A. Yes.

12:23:03 Q. And here, Lieberman is talking about or he refers to Starch 1500.

Do you see that?

12:23:08 A. Market is Starch 1500. I see that.

12:23:13 Q. And Lieberman refers to Starch 1500 there in the third sentence. It says, "A free-flowing directly compressible excipient, which may be used as a diluent, binder and disintegrating agent."

Do you see that?

12:23:25 A. I see the words.

12:23:26 Q. And he says, "When compressed alone, is self-lubricating and self-disintegrating, but when combined with as little as 5 to 10 percent of an ingredient that is not self-lubricating, it requires additional lubricant and usually a glidant, such as colloidal silicon dioxide at 0.25 percent."

Do you see that?

12:23:47 A. I see the words.

12:23:48 Q. All right. Now, back to the Starch 1500 technical brochures.

12:23:52 MR. COOPER: You can take that down. Thank you.

BY MR. COOPER:

12:23:53 Q. Now, you didn't refer or cite to any Starch 1500 technical brochure in support of your opinions in this case; correct?

12:24:00 A. Correct.
12:24:00 Q. And at your deposition, you didn't recall the
12:24:03 manufacturer of Starch 1500 ever referring to that product
12:24:07 as a glidant in any of the literature; correct?
12:24:10 A. That's correct.
12:24:11 Q. But you did rely on a technical brochure from the
12:24:15 GRASTAR manufacturer in preparing your reports in this case;
12:24:19 correct?
12:24:19 A. Two, I believe.
12:24:21 Q. What's that?
12:24:22 A. Two reports, I believe.
12:24:24 Q. All right.
12:24:24 MR. COOPER: Let's pull up DTX-296.
12:24:24 BY MR. COOPER:
12:24:28 Q. So, this is one of the GRASTAR technical data sheets
12:24:32 that you relied on; correct?
12:24:33 A. Hold on.
12:24:35 Q. And let's go --
12:24:36 A. Hold on.
12:24:37 Q. Let's go to Page 2.
12:24:38 A. Hold on a second. Let me get there.
12:24:44 Okay. Thank you.
12:24:45 MR. COOPER: Let's go to -- we're on Page 2.
12:24:47 Let's call out Number 3 on this page.
12:24:47 BY MR. COOPER:

12:24:50 Q. And the GRASTAR manufacturer says its granulated corn
12:24:53 starch has good flowability; correct?
12:24:56 A. It's what it says.
12:24:57 Q. And it says it has oral -- excellent oral
12:25:00 disintegrant properties; correct?
12:25:02 A. That's what it says. Correct.
12:25:04 MR. COOPER: And let call out Number 5 on this
12:25:05 page.
12:25:05 BY MR. COOPER:
12:25:08 Q. The GRASTAR manufacturer lists filler as one of the
12:25:11 functions of GRASTAR; correct?
12:25:12 A. It's what it says.
12:25:14 Q. And it lists disintegrants in orally disintegrating
12:25:19 tablets as one of the functions of GRASTAR; correct?
12:25:21 A. It's what they say here.
12:25:23 Q. And the manufacturer doesn't identify anywhere in
12:25:25 this document that GRASTAR acts as a glidant; correct?
12:25:29 A. Not directly in this direct document; correct.
12:25:31 Q. You haven't seen the word "glidant" in any literature
12:25:34 by the GRASTAR manufacturer; correct?
12:25:36 A. No.
12:25:38 Q. You understand MSN identifies the function of GRASTAR
12:25:43 granulated corn starch in its ANDA as a diluent; right?
12:25:46 A. I understand that. Yes.
12:25:48 Q. You don't disagree that GRASTAR dilutes the API in

12:25:52 MSN's ANDA products; correct?
12:25:54 A. Correct.
12:25:59 Q. All right.
12:25:59 MR. COOPER: Let's pull up PDX-2.20.
12:25:59 BY MR. COOPER:
12:26:08 Q. You've offered an opinion on whether GRASTAR likely
12:26:11 acts through each one of these five mechanisms in MSN's ANDA
12:26:17 product; correct?
12:26:18 A. That it could, yes.
12:26:21 Q. And you've offered an opinion on whether it's more
12:26:24 likely than not that GRASTAR is acting as a glidant in MSN's
12:26:29 ANDA formulation through these five mechanisms; correct?
12:26:33 A. I believe I was specifically -- coating adherence was
12:26:36 very likely, not more likely than not.
12:26:37 Q. At least more likely than not; right? And I guess
12:26:41 first you agreed, I think, on your direct that these five
12:26:44 mechanisms are identified in multiple prior art references
12:26:49 including the Swarbrick reference that you used, PTX-394;
12:26:53 right?
12:26:53 A. I agree the proposed mechanisms are in multiple
12:26:57 literature references; correct.
12:26:58 Q. You've opined -- you just said that it's very likely
12:27:02 that granulated corn starch improves flowability of the
12:27:06 powder blend of MSN's ANDA products by coating other
12:27:09 particles in MSN's powder blend; correct?

12:27:13 A. Sorry. Repeat that.
12:27:14 Q. So your opinion, you said it's very likely that
12:27:17 granulated corn starch improves flowability of the powder
12:27:20 blend in MSN's ANDA products by coating other particles;
12:27:24 correct?
12:27:24 A. Has a potential glidant mechanism, yes.
12:27:27 Q. Now, you agree that the average particle size of
12:27:31 GRASTAR is 81.58 microns; correct?
12:27:35 A. The average is; correct.
12:27:39 Q. And you agree that about 90 percent of the GRASTAR
12:27:45 particles are more than about 30 to 35 microns; correct?
12:27:51 A. Correct.
12:27:55 Q. And now, based on MSN particle size distribution data
12:28:00 that you reviewed and relied on in writing your expert
12:28:04 reports, you have estimated that about 48.38 percent of the
12:28:10 MSN dry granules are less than 150 microns; correct?
12:28:14 A. Correct -- correct.
12:28:18 Q. And so that means 52.42 percent of the MSN dry
12:28:23 granules are more than 150 microns; correct?
12:28:26 A. Correct.
12:28:28 Q. Now, in your review of documents for this case, you
12:28:30 didn't see any electron microscope results or any other
12:28:35 report demonstrating that GRASTAR adheres to the surface of
12:28:38 other particles in MSN's powder blend; correct?
12:28:41 A. Correct.

12:28:43 Q. Now, you've also opined that it is more likely than
12:28:47 not that granulated corn starch improves flowability of the
12:28:51 powder blend of MSN's ANDA products by absorbing small, fine
12:28:56 particles; correct?
12:28:57 A. Correct.
12:29:00 Q. You're not offering an opinion that all larger
12:29:03 excipients of a powder blend are going to absorb smaller
12:29:07 particles in a powder blend; correct?
12:29:09 A. My analysis was specific to granulated corn starch.
12:29:12 Q. And so you're not offering an opinion on --
12:29:16 A. Correct.
12:29:17 Q. Right. Okay.
12:29:17 So, you showed us a document from the GRASTAR
12:29:22 manufacturer talking about fenofibrate.
12:29:25 Do you recall that?
12:29:25 A. I do.
12:29:26 Q. Now, you would expect micronized jet milled
12:29:29 fenofibrate to be on the order of 5 to 30 microns; correct?
12:29:33 A. I believe in the deposition it was like 10s of
12:29:38 microns, but yes.
12:29:41 Q. Well, let's see. Just to be clear --
12:29:45 A. It's --
12:29:45 Q. -- you would expect that the micronized jet milled
12:29:49 fenofibrate, you would expect it to be on the order between
12:29:53 5 and 30 microns; correct?

12:29:56 A. Okay. Correct.
12:29:58 Q. And to be clear, it is unknown by you what the
12:30:03 particle size distribution is for what you have called fines
12:30:07 in MSN's formulation are other than that they are less than
12:30:14 150 microns; correct?
12:30:15 A. I don't have numerical data; correct.
12:30:19 THE COURT: Mr. Cooper, we probably ought to
12:30:22 take a break for lunch here. So, we'll resume at 1:30.
12:30:26 All right. We'll be in recess.
12:30:28 DEPUTY CLERK: All rise.
12:32:55 (Luncheon recess was taken.)
01:29:24 DEPUTY CLERK: All rise.
01:29:24 THE COURT: All right. Let's be seated, and
01:29:27 Dr. Koleng can retake the stand.
01:29:31 And, Mr. Cooper, you can continue.
01:29:58 MR. COOPER: May it please the Court?
01:29:59 THE COURT: Yeah.
01:30:00 BY MR. COOPER:
01:30:00 Q. Dr. Koleng, before we pick up where we left off, I'd
01:30:04 like to just introduce DTX-160 which I've handed you.
01:30:08 Do you see that document?
01:30:09 A. I do.
01:30:10 Q. Okay. And there was a question about when MSN -- or
01:30:13 I wasn't clear on when MSN's ANDA was submitted. So, can I
01:30:18 point you to the top of that page and see that this is THE

application to market a new or abbreviated new drug or biologic for human use.

Do you see that?

A. Okay.

Q. And then down under Number 9, this is an ANDA for cabozantinib tablets.

Do you see that?

A. I do.

Q. And Number 2, the name of the applicant is MSN Laboratories.

Do you see that?

A. I do.

Q. And the dates of submission up at the top right-hand corner is August 16th, 2019.

Do you see that?

A. Yes, sir. Thank you.

Q. Okay. Thank you, Doctor.

A. Okay.

MR. COOPER: Now, let's pull back up PDX-2.20.

BY MR. COOPER:

Q. And now, I think the third thing we haven't talked about yet is dispersing electrostatic charges. Now, Doctor, you've opined that it is more likely than not that granulated corn starch improves flowability of the powder blend of MSN's ANDA products by dispersing electrostatic

charges on the surface of the granulation; correct?
A. Correct.
Q. And you're not saying that electrostatic charges impact flow properties in all powder mixtures; right?
A. Correct.
Q. In your review of MSN documents, you didn't see any specific instance or report of powder sticking to a equipment or any other specific indication of electrostatic charges being an issue; correct?
A. Correct.
Q. Now, fourth thing you've opined on is that it is more likely than not that granulated corn starch improves flowability of the powder blend of MSN's ANDA products by the preferential absorption of gases; correct?
A. Correct.
Q. And you're not offering an opinion that gases within a powder blend are going to impact the flow properties of all powder mixtures; correct?
A. Correct.
Q. And in your review of MSN's development documents, you didn't see any specific report or indication of gas building up or displacing the powder blend; correct?
A. Correct.
Q. All right. Fifth one, you've also opined that it is more likely than not that granulated corn starch improves

flowability of the powder blend of MSN's ANDA products by reducing van der Waals forces between the granules; correct?

A. Correct.

Q. You're not saying that van der Waals forces cause flow problem in all powder mixtures; right?

A. Correct.

Q. You agree that a glidant is not necessary to reduce van der Waals forces in all powder mixtures; right?

A. Restate the question, please.

Q. Sure. You -- a glidant is not necessary in order to reduce van der Waals forces in all powder mixtures in order to create acceptable flowability.

You agree with that; right?

A. I don't recall proffering an opinion on all -- all powders.

Q. Yeah, that -- that's my question.

A. You have something specific or...

Q. I'm just making sure that you are not saying that van der Waals sources is going to be an issue that will require a glidant in all powder mixtures; correct?

A. I'm having a difficult time with your question, Counsel, sorry. Because I'm trying to -- because, obviously, it's not a question I think I've opined on, so --

Q. Okay. Then that's enough. I apologize. Thank you, Doctor.

01:33:49 A. Okay.
01:33:50 Q. You're not offering an opinion that all excipients
01:33:53 that act as spacers in a powder blend are necessarily
01:33:55 reducing van der Waals forces; correct?
01:33:57 A. Correct.
01:33:59 Q. Let's pull the Swarbrick reference up, PTX-394.
01:34:09 You showed us the Swarbrick reference on your
01:34:17 direct; correct?
01:34:18 A. Correct.
01:34:18 MR. COOPER: Let's go to Page 44. And call out
01:34:20 Table 2 at the top of the page.
01:34:20 BY MR. COOPER:
01:34:23 Q. Now, YOU showed us a list of commonly used glidants
01:34:25 from the Lachman reference; right?
01:34:27 A. Yes.
01:34:28 Q. And here we see a list of commonly used glidants in
01:34:31 the Swarbrick reference; correct?
01:34:32 A. Correct.
01:34:33 Q. Now, starch is on that list; correct?
01:34:35 A. Yes.
01:34:37 Q. Pregelatinized starch is not specifically identified
01:34:39 in this list; correct?
01:34:40 A. No.
01:34:42 Q. Talc is on the list; correct?
01:34:43 A. Correct.

01:34:44 Q. You agree Talc is a commonly used glidant; right?
01:34:47 A. I'd say it's a used glidant, correct.
01:34:49 Q. Now, a POSA would understand that Talc may serve as
01:34:52 both a lubricant and glidant in a tablet or capsule
01:34:56 formulation; right?
01:34:57 A. Depending on the formulation, potentially.
01:34:59 Q. Silica aerogels like Cabosil are also on the commonly
01:35:04 used glidant list in Swarbrick; correct?
01:35:06 A. Yes.
01:35:07 Q. The suggested percentage of those are 0.1 to
01:35:10 0.5 percent; correct?
01:35:12 A. It's what's listed.
01:35:13 Q. All right.
01:35:14 MR. COOPER: Let's go down on the same page but
01:35:15 to the third paragraph.
01:35:15 BY MR. COOPER:
01:35:19 Q. And Swarbrick writes, "Recently, various forms of
01:35:21 silica have" -- and first, recently, the Swarbrick reference
01:35:26 was published around 1991; right?
01:35:28 A. If you want to check, but I'll take your word for it.
01:35:32 Q. Swarbrick writes, "Recently, various forms of silica
01:35:35 have been used successfully to increase powder and granule
01:35:39 flow."
01:35:39 Do you see that?
01:35:40 A. I see that.

01:35:41 DEPUTY CLERK: Mr. Koleng, can you try to speak
01:35:45 up a little bit?
01:35:45 THE WITNESS: I'm sorry?
01:35:46 DEPUTY CLERK: Could you speak up just a little
01:35:47 bit?
01:35:47 THE WITNESS: Oh, I'm sorry. I may need to be
01:35:49 closer. My apologies
01:35:50 BY MR. COOPER:
01:35:51 Q. Swarbrick continues, "Such excipients have been
01:35:52 identified as the best glidants currently available."
01:35:55 Do you see that?
01:35:55 A. I see the words.
01:35:56 Q. Let's go to the patent, JTX-4. We'll pull up Page 6
01:36:05 of the patent, Column 5, Table 1.
01:36:10 Now, there are a series of tables in Columns 5
01:36:13 through 7 in the specification of the '349 patent that
01:36:18 identify seven examples of tablet or capsule formulations of
01:36:21 the claimed invention; correct?
01:36:22 A. That's my understanding.
01:36:24 Q. And those seven examples are the only specific
01:36:28 examples of pharmaceutical compositions provided in the
01:36:31 '349 patent; correct?
01:36:33 A. I believe so, yes.
01:36:34 Q. So here in Table 1, you see silicon dioxide colloidal
01:36:38 is identified as an ingredient; correct?

01:36:40 A. I see that, yes.
01:36:42 Q. Colloidal silicon dioxide, you know, is a micro --
01:36:45 submicroscopic with a particle size of about 15 nanometers;
01:36:50 correct?
01:36:50 A. It's -- it's generally my recognize -- understanding.
01:36:55 Q. In the Table 1 formulation here, silicon dioxide is
01:36:59 present in a concentration of .30 percent; correct?
01:37:03 A. For this formulation, yes.
01:37:05 Q. You've personally used colloidal silicon dioxide as a
01:37:09 glidant in a fair number of tablet or capsule formulations
01:37:11 in your career; correct?
01:37:13 A. It would be a fair assessment, yes.
01:37:16 Q. Now, looking at -- again, at the patent, in all seven
01:37:20 examples of the patent, there is a fumed silica or colloidal
01:37:24 silicon dioxide excipient in the formulation at a
01:37:27 concentration of less than 1 percent; correct?
01:37:30 A. It appears so, yes.
01:37:37 Q. Granulated corn starch is not identified as an
01:37:39 excipient in any of the examples provided in the patent;
01:37:42 correct?
01:37:42 A. Correct.
01:37:44 Q. Granulated corn starch is not identified or described
01:37:47 as a glidant anywhere in the patent; correct?
01:37:49 A. No.
01:37:52 Q. No as in I'm -- that's correct though; right?

01:37:54 A. Correct. It's not identified as a glidant in the
01:37:56 patent, correct. It's not identified anywhere in the
01:37:58 patent.
01:37:58 Q. All right. Now, last questions.
01:38:00 A POSA would understand that the presence of
01:38:02 impurities may affect the quality, safety, and efficacy of
01:38:06 drug products; do you agree?
01:38:08 A. Restate the question, please, I'm sorry.
01:38:10 Q. Sure. A POSA would understand that the presence of
01:38:12 impurities may affect the quality, safety, and efficacy of
01:38:17 drug products, do you agree?
01:38:18 A. They may.
01:38:21 Q. Well, they would; right?
01:38:22 A. Well, they may. They may. I don't know -- you want
01:38:25 to give me a specific example?
01:38:26 Q. Well, I -- do -- okay. Thank you, Doctor.
01:38:33 A person of skill in the art understands that
01:38:37 control of impurities is one of the most important goals in
01:38:41 the development of APIs and drug products; do you agree with
01:38:45 that?
01:38:45 A. I know it's a goal. And it may or may not be more or
01:38:51 less important. Again, if you want to give me something
01:38:53 specific.
01:38:53 Q. Well, I want to know your opinion. And I believe
01:38:56 your opinion is that control of impurities is one of the

most important goals in the development of APIs and drug products; correct?

MS. WIGMORE: Object. This is outside of the scope of the infringement examination.

THE COURT: Sorry, could you speak louder.

MS. WIGMORE: This is outside the scope of the infringement examination.

THE COURT: Well, it probably is. Isn't it?

MR. COOPER: It's my last question, but we can ask it again in -- tomorrow.

THE COURT: All right. Well, ask it during the right time.

All right. So the objection is sustained.

MR. COOPER: Thank you.

(Discussion held off the record.)

MR. COOPER: Your Honor, I'd like to move in DTX-358, DTX-196, DTX-363, DTX-344, PTX-553, DTX-296, and DTX-160.

MS. WIGMORE: No objection.

THE COURT: All right. Admitted without objection.

(DTX Exhibit Nos. 358, 196, 363, 344, 296, 160, were admitted into evidence.)

(PTX Exhibit No. 553 was admitted into evidence.)

01:40:04 MS. WIGMORE: May I proceed, Your Honor?

01:40:05 THE COURT: Yes.

01:40:06 REDIRECT EXAMINATION

01:40:06 BY MR. WIGMORE:

01:40:06 Q. Good afternoon, Dr. Koleng. Mr. Cooper showed you a
01:40:10 number of articles from the literature about excipients. Do
01:40:14 you recall that?

01:40:14 A. Yes.

01:40:16 Q. What did MSN's witness, Mr. Nithiyanandam, say in his
01:40:20 testimony about whether the literature identifies granulated
01:40:25 corn starch as a glidant?

01:40:26 A. The statements and testimony clearly state that those
01:40:30 statements came from the literature.

01:40:32 MS. WIGMORE: If we could please have DTX-296.

01:40:32 BY MS. WIGMORE:

01:40:35 Q. You were shown this on cross-examination so it would
01:40:37 be in your cross-examination binder. It is the technical
01:40:42 data document for GRASTAR.

01:40:44 Do you have that?

01:40:44 A. 290 -- yes, ma'am.

01:40:49 Q. Do you recall testifying that the word "glidant" does
01:40:53 not appear in the GRASTAR technical documents?

01:40:57 A. Correct.

01:40:58 Q. If you could please turn to Page 2 of DTX-296.

01:41:03 Do you see Item 3 on that page?

01:41:05 A. I do.
01:41:07 Q. Do you see where it says "pharmaceutical additives
01:41:10 with good flowability"?
01:41:11 A. Yes.
01:41:13 Q. If we could turn now, please, to PTX-447, which is
01:41:19 Tab 11 in your direct examination binder.
01:41:22 Is this a document provided by the manufacturer
01:41:32 of GRASTAR?
01:41:34 A. Yes.
01:41:35 MR. COOPER: Your Honor, this has not been
01:41:37 introduced.
01:41:38 MS. WIGMORE: Yeah, it has. It was introduced
01:41:40 on direct.
01:41:40 MR. COOPER: I'm sorry.
01:41:43 THE WITNESS: Yes, it is.
01:41:45 BY MS. WIGMORE:
01:41:45 Q. And can you read the title of this document, please?
01:41:47 A. "Improvement Effect of Flowability By GRASTAR."
01:41:50 Q. What does that tell you about whether GRASTAR or
01:41:55 granulated corn starch is a glidant?
01:41:56 A. It affects -- it improves flowability and would have
01:41:59 a glidant functionality.
01:42:01 MS. WIGMORE: We can take that down, please.
01:42:01 BY MS. WIGMORE:
01:42:03 Q. Dr. Koleng, can excipients have more than one

01:42:06 function in a -- in a mixture?
01:42:09 A. Yes.
01:42:10 Q. Is there any dispute between the parties about that?
01:42:13 A. Not that I'm aware of, no.
01:42:16 Q. Can a single material be serve -- serve as a glidant
01:42:20 and also have another function in a mixture?
01:42:23 A. Yes.
01:42:24 Q. What did MSN tell the FDA about whether granulated
01:42:30 corn starch enhances flow in its ANDA products?
01:42:32 A. They stated in their documents it enhanced flow.
01:42:36 Q. Now, do you recall being asked about the MSN lab
01:42:40 notebook on cross-examination?
01:42:41 A. Yes.
01:42:43 Q. Now, you were shown a table from your report. I'm
01:42:46 going to pull that up.
01:42:47 MS. WIGMORE: I believe it's from your reply
01:42:48 report at Page 18, Paragraph 25.
01:42:48 BY MS. WIGMORE:
01:42:57 Q. Do you recall being shown this table on
01:42:59 cross-examination?
01:43:00 A. Yes.
01:43:01 Q. Now, where did the data in this table come from?
01:43:05 A. The 252 notebook.
01:43:08 Q. Is that an MSN notebook?
01:43:09 A. Yes.

01:43:11 Q. And you were asked during cross-examination to recalculate the numbers at the bottom of the page.

01:43:20 Do you recall that?

01:43:21 A. I do.

01:43:21 Q. And at some point in the course of this case, did you discover a discrepancy with respect to the numbers in this table?

01:43:30 A. Yes.

01:43:31 Q. Is that a discrepancy that you caused?

01:43:34 A. Did I cause? No.

01:43:37 Q. Where did the discrepancy come from?

01:43:39 A. The MSN documentation.

01:43:41 Q. Did you rely on calculations that MSN performed in its notebooks?

01:43:46 A. Yes.

01:43:48 Q. Did you learn during the course of discovery that MSN's numbers were incorrect?

01:43:52 A. Yes.

01:43:53 Q. Now, do you see there are -- in the highlighted portion at the bottom of this table, there's four different categories: Bulk density, tapped density, Carr index, and HR which is the Hausner ratio.

01:44:08 Do you see those?

01:44:08 A. I do.

01:44:09 Q. Can you identify from MSN's lab notebooks which, if

any, of those numbers were actually wrong?
A. No, that's what -- that's why I'm saying I couldn't use this information more because there was discrepancy and I couldn't find the source of that discrepancy.
Q. And is that why you're not relying on the MSN lab notebooks in this case?
A. Yes.
Q. Is there anything about the MSN lab notebooks and the errors you identified that support the position that GRASTAR or granulated corn starch is not a glidant?
A. No.
Q. Does this data in this table from the MSN lab notebooks come from testing of MSN's final ANDA products?
A. No, these were all prototype product.
Q. Now, did you need that data to show that MSN is infringing Claim 3 of the '349 patent?
A. No. I had other elements that led to my opinion.
Q. What are those elements?
A. MSN's ANDA statements. The literature supporting starches, derivatives as glidants in the range used for this particular material in their final formulation, as well as aligning where the material is at in the manufacture -- is added during the manufacturing process.
MS. WIGMORE: Thank you, Dr. Koleng. No further questions.

01:45:33 THE COURT: All right. Dr. Koleng, thank you.
01:45:35 You may step down. I assume you're going to be testifying
01:45:38 again, so watch your step because I don't need an injured
01:45:41 person.
01:45:42 THE WITNESS: Thank you.
01:45:43 THE COURT: All right. What's next?
01:45:47 MS. WIGMORE: Your Honor, Plaintiffs rest their
01:45:52 infringement case.
01:45:53 THE COURT: Okay.
01:46:02 MR. COOPER: Apologies for the delay,
01:46:41 Your Honor.
01:46:41 THE COURT: If it's charged to you, it's okay.
01:46:43 MR. COOPER: MSN calls for the first witness,
01:46:46 Dr. Maureen Donovan.
01:47:27 DEPUTY CLERK: Please state and spell your full
01:47:32 name for the record.
01:47:32 THE WITNESS: Maureen Donovan, M-A-U-R-E-E-N
01:47:38 D-O-N-O-V-A-N.
01:47:38 MAUREEN DONOVAN, the witness herein, after
01:47:38 having been duly sworn under oath, was examined and
01:47:48 testified as follows:
01:47:48 THE WITNESS: Yes, I do.
01:47:48 DIRECT EXAMINATION
01:47:51 BY MR. COOPER:
01:47:51 Q. Good morning -- or afternoon. Could you please

01:47:55 introduce yourself to the Court?
01:47:56 A. Good afternoon. I'm Maureen Donovan.
01:47:58 Q. Dr. Donovan, have you prepared slides to assist in
01:48:01 explaining your testimony today?
01:48:02 A. Yes, I have.
01:48:04 MR. COOPER: For the record, those slides are on
01:48:05 the screen and marked in the bottom right-hand corner as
01:48:08 DDX Donovan and then the slide number.
01:48:08 BY MR. COOPER:
01:48:11 Q. Now, first -- I'd like to first ask you about your
01:48:13 education and employment and qualifications.
01:48:16 MR. COOPER: Could we please pull up DTX-505,
01:48:19 and go to Page 2 of the exhibit.
01:48:19 BY MR. COOPER:
01:48:21 Q. Dr. Donovan, can you please tell us what this
01:48:23 document is?
01:48:24 A. Yeah. This is the front page of my -- of my CV.
01:48:27 Q. Does it accurately describe your employment,
01:48:29 education, and publications?
01:48:31 A. Yes, it does.
01:48:32 MR. COOPER: Could we go to DDX Slide 2.
01:48:32 BY MR. COOPER:
01:48:35 Q. Who are you currently employed by?
01:48:37 A. The University of Iowa.
01:48:38 Q. Could you describe your research interests for us?

A. I have an interest in understanding mechanisms of drug absorption across epithelial cells and then the interplay between formulations, materials that we could use to improve or optimize those absorption problems.

Q. Are you a member of any professional organizations?

A. I am. I am a member of American Association of Pharmaceutical Scientists. I'm a fellow of that organization. I'm a member of the American Chemical Society. I'm member of the American Association of Colleges of Pharmacy, and a number of other professional or academic societies.

Q. Do you serve on any government panels?

A. I do. I've just completed a term on the FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee. And for the past 20 years, I've served as both chair and member of a number of NIH study section panels.

Q. Have you published articles over the course of your career?

A. Yes, I have.

Q. Have you researched, designed and tested pharmaceutical solid, oral dosage formulations, such as tablets and capsules?

A. Yes, I have.

Q. Have you given testimony as an expert in the field of pharmaceutics and patent litigations in this district court

and elsewhere?

A. Yes.

MR. COOPER: Your Honor, defendants proffer Dr. Maureen Donovan as an experts in the field of pharmaceutics, including solid dose drug formulation.

MS. PIROZZOLO: No objection, Your Honor.

THE COURT: You may proceed.

BY MR. COOPER:

Q. Doctor, have you been engaged by MSN to render an opinion on whether the proposed MSN cabozantinib ANDA product infringes Exelixis' '349 patent?

A. Yes, I have.

Q. Did you hear the full testimony from Dr. Koleng on his opinion about that subject?

A. Yes.

MR. COOPER: Can we go to DDX Slide 3?

BY MR. COOPER:

Q. Before we get into the details of your opinion, can you provide the Court with a brief overview of what you're going to be testifying about today?

A. Sure. So I'm going to start with a little bit of a technical background so that there's a good understanding of the vocabulary I'll be using and some of the concepts, and then I'll speak about my opinion about the infringement of the '349 patent -- or non-infringement of the '349 patent by

MSN's ANDA product, and that's going to be based in discussions regarding the fact that granulated corn starch -- the GRASTAR granulated corn starch was not added as a glidant in MSN's ANDA product, that the GRASTAR granulated corn starch material was added as a filler used to adjust disintegration and dissolution properties, that none of the testing provided by MSN shows any flow improvement regarding the -- following the addition of GRASTAR granulated corn starch and there's no evidence that GRASTAR functions like a glidant in MSN's ANDA products. And then I'll speak about some of Dr. Koleng's opinions and how textbook references and other data don't support the opinions that he has communicated.

Q. When you were forming your opinions in this case --

DEPUTY CLERK: Can you try slowing just as best as you can?

BY MR. COOPER:

Q. When you were forming your opinions in this case, did you consider the issues from the perspective of a person of skill in the art or a POSA?

A. Yes, I did.

MR. COOPER: Can we go to DDX Slide 4.

BY MR. COOPER:

Q. Dr. Donovan, could you read what you have on the left-hand side as far as your definition of a person of

ordinary skill in the art?

A. So, my definition of an ordinary -- person of ordinary skill is somebody who is a doctor, or a lesser degree, in pharmacy, chemistry, or related discipline. One with three years or greater experience, working in research and development of formulations for the preparation of drug substances. And one who would be collaborating with others so that the team would collectively have had experience in synthesizing and analyzing complex small molecular compounds and impurities or degradation of products of those compounds.

Q. Would your opinions in this case change if the definition of a POSA proposed by Exelixis is adopted?

A. No, it wouldn't.

Q. Were you, yourself, a POSA as of the priority date using either party's proposed definition?

A. Yes, I was.

MR. COOPER: Doctor, let's go to DDX Slide 5 and go over the relevant technical background first.

BY MR. COOPER:

Q. Now, first, we've heard a bit about this, but could you describe in your own words what is powder flow in the pharmaceutical context?

A. In the context of pharmaceuticals, powder flow is the movement of a powder mixture from one position to another.

01:52:51 Oftentimes we are concerned about powder flow through
01:52:55 transfer through equipment pieces and in their transfer and
01:52:58 we're certainly concerned with the flow into the final
01:53:02 equipment that's going to produce a capsule or a tablet. So
01:53:05 when they're being filled at an individual dose powder flow
01:53:10 becomes a concern.
01:53:11 Q. What are some features of ingredients in a
01:53:14 formulation that can affect flow properties of a powder
01:53:16 blend?
01:53:17 A. Typically we're concerned with things like particle
01:53:20 size and especially differences in particle size among the
01:53:23 materials in the mixture can have an impact on powder flow.
01:53:27 Powder shape or the particle shape, in addition, has
01:53:31 significant impact on the resulting powder flow properties
01:53:34 or the contributions to the powder flow.
01:53:38 Q. Have you prepared a demonstrative to help you explain
01:53:40 that concept?
01:53:40 A. Yes, I have.
01:53:42 MR. COOPER: Can we go to Slide DDX 6.
01:53:42 BY MR. COOPER:
01:53:45 Q. Doctor, which ingredients in a formulation contribute
01:53:48 to the overall flow of a powder blend?
01:53:50 A. Well, each ingredient is actually going to contribute
01:53:52 to the overall powder flow, some more than others depending
01:53:55 on their component amounts or characteristics.

01:53:58 Q. So what are you showing on DDX Slide 6?
01:54:00 A. So, what I've shown here is just a random API
01:54:04 material and two excipients that we might think about
01:54:08 combining.
01:54:10 Q. Generally speaking, what would you expect about the
01:54:11 flow properties for an API like the one you have shown in
01:54:14 your demonstrative?
01:54:15 A. Well, the API, so the photo on the left shows what we
01:54:18 classify as needle-like materials. And you can think about
01:54:22 those flowing through a system that they won't -- they won't
01:54:26 all be parallel. So they'll start crossing over and so
01:54:29 forth. That can cause flow problems. So typically you
01:54:32 would estimate needle-like crystals might have flow
01:54:35 problems.
01:54:36 Q. And generally what would you expect about the flow
01:54:38 properties for the other two ingredients you have shown in
01:54:40 this demonstrative?
01:54:41 A. The other two ingredients probably have better flow
01:54:43 properties than the API that I've shown. I'm going to start
01:54:48 with ingredient 2 in particular. Usually our best flowing
01:54:52 properties are materials that move past each other and along
01:54:54 with the powder blend quite well are things that are
01:54:56 spherical.
01:54:57 And so, the more spherical-like the particle,
01:55:00 the more likely it is to have reasonably good flow

01:55:03 properties. Ingredient 2 is our best somewhat spherical
01:55:08 material. Ingredient 1, not quite as spherical. It
01:55:11 probably can tumble past its other particles, and the other
01:55:17 particles in the mixture reasonably well, but may also have
01:55:20 some powder flow limitation.
01:55:21 Q. How do the flow properties of each individual
01:55:24 ingredient in a formulation impact the flow properties of
01:55:26 the powder blend when you put them all together?
01:55:28 A. Again, those ingredients interact with one another,
01:55:31 and they all -- they all contribute to the overall powder
01:55:35 flow.
01:55:36 Q. Let's talk about characterizing powder flow. Were
01:55:39 you able to listen to Dr. Koleng's testimony describing
01:55:42 methods for characterizing flow properties of a powder such
01:55:46 as its Hausner ratio and Carr index?
01:55:48 A. Yes, I was.
01:55:49 Q. Do you agree that the Hausner ratio and Carr index
01:55:51 are commonly used to characterize flow properties of a
01:55:54 powder?
01:55:55 A. Yes, they are.
01:55:56 Q. And do you agree with how Dr. Koleng testified that
01:55:59 you perform those calculations according to the equations
01:56:03 set out in the USP on powder flow DTX-358?
01:56:07 A. Yes, agree with the calculation shown.
01:56:09 Q. Did you also review and rely on that USP chapter in

01:56:13 forming your opinions in this case?
01:56:14 A. Yes, I did.
01:56:17 Q. Doctor --
01:56:17 MR. COOPER: You can take that down. Thank you.
01:56:17 BY MR. COOPER:
01:56:19 Q. Is there a minimum flow character that all
01:56:22 pharmaceutical powders must have in order to be suitable for
01:56:25 a tablet formulation?
01:56:26 A. No, there's no numerical value that's assigned to a
01:56:29 minimum value.
01:56:30 Q. If a formulator determines that an API has poor flow
01:56:34 properties that they want to improve, are there techniques
01:56:37 for doing so?
01:56:38 A. Yes, there are.
01:56:39 Q. Could you give an example?
01:56:41 A. Sure. So one of the things we could do is maybe
01:56:43 change the characteristics of the API. That's oftentimes
01:56:47 not the first choice. It's maybe -- maybe a bit -- that's
01:56:50 challenging, and so, there are other formulation techniques,
01:56:54 like regulation processes, wet granulation, dry granulation
01:56:56 are common processes to address poor flow.
01:56:59 Q. Thank you, sir.
01:57:00 MR. COOPER: Now, could you go to DDX Slide 7.
01:57:00 BY MR. COOPER:
01:57:03 Q. And we've heard a bit about wet granulation so far.

01:57:06 Can you describe how that technique works using your
01:57:09 demonstrative?
01:57:09 A. Sure. So, on the left-hand side of the image, what I
01:57:13 have shown is the blue oblong materials are supposed to
01:57:17 represent the API. They're not spherical. They're --
01:57:20 they've got some rough edges. They may have somewhat poor
01:57:24 flow properties, and then another excipient that's -- may
01:57:26 have reasonably good flow properties.
01:57:29 And I want to make a granulation out of that,
01:57:32 and so, what I do is dampen the powder mass. I take
01:57:36 material that we call a binder that's going to help the
01:57:38 powder aggregate stick together a little bit more. And I
01:57:42 make the whole powder mass a little bit wet, and I start
01:57:46 forming aggregates out of powder.
01:57:49 Those aggregates then I dry. I remove the water
01:57:52 from the system, and I'm left with larger sort of chunky
01:57:55 particles which then I can size reduce to make the size
01:58:00 granules that I'd like for my formulation. And then the
01:58:03 granules end up being more uniform in size, more controlled
01:58:06 in size, more controlled in shape, more spherical-like, and
01:58:09 those granules then have improved flow properties. They
01:58:12 contain the API, which may have had poor flow properties,
01:58:16 but now it's the flow properties of the granules that are
01:58:18 controlling the powder mixture.
01:58:20 Q. Can granulation resolve a formulator's concern about

an API's poor flow properties for a powder blend?

A. Yes, it can.

Q. Now, if a formulator still has concerns after granulation, about a formulation's powder flow, are there other techniques a POSA could consider to achieve acceptable flow properties?

A. Yes. And one of the things that they'll consider is adding other excipients to the glidants.

Q. Does the literature --

A. The granules. Sorry.

Q. Does the literature describe the types of excipients that typically affect flow properties of a powder blend?

A. Yes. It does.

MR. COOPER: Mr. Figera (phonetic), can we pull up DTX-363?

BY MR. COOPER:

Q. Doctor, what is this exhibit?

A. This is the cover page of an Ansel, and we've already talked about it as a text that describes pharmaceutical dosage forms and materials.

MR. COOPER: Can we go to Page 35 and call out the top of the Table 3.3? And then also call out the entry for tablet and capsule diluent on that table.

BY MR. COOPER:

Q. Can you tell us, what is the definition of tablet and

01:59:21 capsule diluent that Ansel provides?
01:59:22 A. The definition provided that tablet and capsule
01:59:26 diluents are inert substances used as fillers to create the
01:59:29 desired bulk, to create flow properties, and to create
01:59:32 compression characteristics in the preparation of tablets
01:59:35 and capsules.
01:59:36 Q. Is the definition from Ansel a commonly accepted
01:59:40 definition of a filler in the literature from your
01:59:42 perspective?
01:59:43 A. Yes, it is.
01:59:44 Q. With respect to how fillers can help create desired
01:59:48 flow properties, have you prepared a slide to help explain
01:59:51 that?
01:59:51 A. Yes, I have.
01:59:52 MR. COOPER: Could we go to DDX Donovan 8?
01:59:52 BY MR. COOPER:
01:59:56 Q. Can you please explain what you're showing on this
01:59:58 slide?
01:59:58 A. Sure. So, again, what I have on the left-hand panel
02:00:01 is the API again, perhaps not perfectly spherical, and an
02:00:07 excipient that perhaps I've decided needs to be with my
02:00:09 formulation but maybe it doesn't have the optimal flow
02:00:14 properties either. So I'm going to add a filler to improve
02:00:16 the flow properties. And I choose a filler that now has the
02:00:19 right shape to improve flow properties, and I add an amount

of it that would essentially -- what it essentially does is add material to the -- to the formulation so it bulks up the -- the powder mixture, and the API and the other excipients have less of a chance of bumping into each other as we're moving this powder blend and flowing through the system. And it improves flow as a result. The filler characteristics of good flow start to predominate.

Q. Does the literature also provide examples of how the selection of fillers affect the overall flow properties of a powder blend?

A. Yes, it does.

MR. COOPER: Can we pull up DTX-355? And call out the abstract on Page 1.

BY MR. COOPER:

Q. Dr. Donovan, what is this exhibit?

A. This is a research article describing three different grades of Avicel, or microcrystalline cellulose, and the impact of those grades on various tablet characteristics.

Q. Could you say it again? What does Avicel refer to?

A. Avicel is microcrystalline cellulose.

Q. And what type of excipient is microcrystalline cellulose --

(Reporter clarification.)

MR. COOPER: Yeah.

BY MR. COOPER:

02:01:29 Q. What is Avicel?

02:01:36 Could you say again what Avicel --

02:01:37 A. Avicel is microcrystalline cellulose.

02:01:40 Q. What type of excipient is microcrystalline cellulose?

02:01:43 A. It's frequently used as a filler.

02:01:45 Q. All right.

02:01:45 MR. COOPER: Let's go to Page 6 of the exhibit and call out the last full paragraph on the right-hand column.

02:01:50 BY MR. COOPER:

02:01:50 Q. And what does the Lahdenpaa article report on the flow properties of the different grades of Avicel?

02:01:58 A. Well, they first state that Avicel PH-101, one grade of the microcrystalline cellulose exhibited the poorest flow properties of the three. And then when they mixed PH-101 grade with PH-102 and PH-200, they saw significantly better flowability of the mixture.

02:02:15 Q. Does Lahdenpaa ever refer to any of the Avicel microcrystalline cellulose grades discussed in this article as glidants?

02:02:22 A. No.

02:02:23 MR. COOPER: Can we please pull up DTX-344?

02:02:23 BY MR. COOPER:

02:02:30 Q. And we saw this article before, the Jivraj article. Did you also review this article, Dr. Donovan?

02:02:35 A. Yes, I did.
02:02:36 Q. And did you hear Dr. Koleng describe some of the
02:02:38 passages in this article?
02:02:39 A. Yes, I did.
02:02:40 Q. Could you explain, how does this reference support
02:02:42 your opinion about the functions of potential fillers for
02:02:45 tablet formulations?
02:02:46 A. And part of the reviews in this article are
02:02:49 descriptions of fillers or diluents that are used in -- in
02:02:53 this case in direct compression, but the same fillers get
02:02:55 used in other pharmaceutical manufacturing sequences also.
02:02:59 So it gives a -- further information about fillers.
02:03:03 Q. Doctor, thank you.
02:03:04 MR. COOPER: You can take that down.
02:03:04 BY MR. COOPER:
02:03:05 Q. Do you agree that glidant excipient -- are glidant
02:03:08 excipients that can be used by a POSA to impact the overall
02:03:13 flow properties of a powder blend?
02:03:14 A. I'm sorry. Can you repeat that?
02:03:16 Q. Yeah, Doctor, are glidants one type of excipient that
02:03:20 a POSA can use to impact the overall flow properties of a
02:03:23 powder blend?
02:03:24 A. Yes, glidants can be used to do that.
02:03:28 Q. Now, if the addition of an ingredient into a
02:03:32 pharmaceutical powder has any kind of positive effect on its

overall powder flow, does that mean the ingredient must be a glidant?

A. No, not necessarily.

Q. Have you ever seen any scientific literature stating that the only excipient that can have a positive effect on powder flow is a glidant?

A. No.

Q. Doctor, does the literature explain how glidants act to improve flow characteristics in a pharmaceutical powder?

A. Yes, it does.

MR. COOPER: Can we pull up DTX-134?

BY MR. COOPER:

Q. Doctor, you've seen this exhibit. Do you recognize DTX-134?

A. I do. The encyclopedia of pharmaceutical technology.

Q. All right.

MR. COOPER: Let's go to Page 33 of this exhibit and call out the bottom paragraph going over to the bullets on Page 34.

BY MR. COOPER:

Q. Doctor, what does this reference report about glidants?

A. Well, first it states that glidants are excipients usually added to improve the flowability of powder blends and granulations through one or more of several proposed

physical mechanisms. And then it gives us five bullet points where it's summarizing what those understood mechanisms are.

Q. Now, Dr. Koleng referred to these as proposed mechanisms. Does that affect your opinion about how the glidants are known to operate?

A. It doesn't. These are well accepted mechanisms of glidant behaviors.

Q. Does other scientific literature besides the Swarbrick report on these five mechanisms in a similar manner?

A. Yes, it does.

Q. Is one of the mechanisms by which glidants are reported to operate more common than others?

A. Currently, yes. The fifth bullet point describing reduction on the surface rugosity which is surface roughness of the particles and the friction of the host surfaces by adherents of glidant particles to host particle surfaces. So, it's saying that the glidants are covering the particle surfaces and it reduces the friction of force between those original particles.

Q. Thank you for that technical background, Dr. Donovan. Let's go to slide DDX-9 and move on to your infringement analysis.

MR. COOPER: Mr. Figera, please pull up DTX-231.

BY MR. COOPER:

Q. Dr. Donovan, what is this exhibit?

A. This is a portion of the MSN ANDA supplement -- or ANDA application. It's the 2.3.P drug product portion of their ANDA submission regarding cabozantinib tablets, 20-milligram, 40-milligram, and 60-milligram.

MR. COOPER: Let's go to Page 2 of this exhibit. And call out the chart in Section 2.3.P.1, going to Page 3.

BY MR. COOPER:

Q. What is provided in this chart?

A. This chart is a description of the cabozantinib tablets that were being submitted with the application. The ingredients that are contained in those tablets, the functions of the ingredients, and the amounts of the ingredients in each dose strength.

Q. What is the function of GRASTAR granulated corn starch that is identified by MSN?

A. Well, at the very bottom of the table, where it says "granulated corn starch," the function is identified as a diluent.

Q. What is the amount of GRASTAR in the formulation?

A. It's 9.71 percent of the core tablet formulation.

Q. Is that an amount consistent with what the scientific literature reports for potential use of granulated corn starch as a filler in pharmaceutical compositions?

A. Yes, it is. Fillers are -- diluents are used in a wide variety of concentrations, as low as a couple percent up to maybe as high as 75, 80, 90 percent even. So, 10 percent is certainly in keeping with a filler concentration.

MR. COOPER: Can you go to Page 4 of the exhibit and call out the table on that page.

BY MR. COOPER:

Q. What does this table in MSN's ANDA provide?

A. This is a comparison between the ingredients and the functions of the reference product, the Cabometyx tablets, and the MSN ANDA product being submitted. And so, they did a side-by-side comparison of ingredients for those products.

Q. Can you describe what MSN's ANDA identifies in its row of -- with granulated corn starch?

A. So, in the row that says "granulated corn starch," GRASTAR, in the second-to-left column, it's identifying its function as a diluent.

Q. And is there a MSN excipient that's used as a glidant?

A. No, there is nothing identified as a glidant.

Q. Have you reviewed other MSN development documents in and ANDA documents in the course of your work on this case?

A. Yes, I have.

Q. Does MSN ever identify the function of GRASTAR to be a glidant in its ANDA product formulation?

02:08:18 A. No.
02:08:19 Q. Does the manufacturer of GRASTAR provide any
02:08:22 information about the functions of the excipient?
02:08:24 A. Yes, the manufacturer does.
02:08:26 MR. COOPER: Can we please pull up DTX-296.
02:08:26 BY MR. COOPER:
02:08:31 Q. Did you review this document?
02:08:32 A. I did.
02:08:34 Q. What is it?
02:08:34 A. This is the technical data document for GRASTAR, yes,
02:08:38 I did review that.
02:08:39 MR. COOPER: Let's go to Page 2 of the exhibit
02:08:41 and call out the top portion.
02:08:41 BY MR. COOPER:
02:08:44 Q. And this says, "Met to the specification of
02:08:47 pregelatinized starch listed in United States Pharmacopeia."
02:08:51 Can you explain what that means?
02:08:52 A. Well, starch is a very, very broad category. Lots of
02:08:56 different materials have the word "starch" in them.
02:08:59 Pregelatinized starch itself is a specific grouping of
02:09:03 starches. And the USP has monographs for various types of
02:09:08 materials for quality standards and so forth that those
02:09:11 types have to meet.
02:09:12 So, there is a USP monograph for pregelatinized
02:09:16 starch materials. And the GRASTAR granulated starch product

meets the USP criteria for pregelatinized starch material.

Q. Do pregelatinized starches have different properties than unmodified starches?

A. Yes, they do.

MR. COOPER: Let's call out the third bullet on the list of properties on this page.

BY MR. COOPER:

Q. What are the properties of GRASTAR that the manufacturer identifies?

A. The manufacturer identifies that it has good flowability, direct compressibility, and excellent orally disintegrating properties.

Q. And so by the GRASTAR saying "good flowability" there, does that suggest that GRASTAR is a glidant?

A. No.

MR. COOPER: Let's call out the fifth bullet on the list of properties on this page.

BY MR. COOPER:

Q. What does the GRASTAR manufacturer identify as potential functions for the excipient?

A. The functions identified by the manufacturer are as a filler, a binder, or a disintegrant. And they describe in orally disintegrating tablets, which is -- means -- those are usually faster disintegrating systems than traditional tablets, so it would be a disintegrant in traditional

02:10:21 tablets also.
02:10:24 Q. All right.
02:10:24 MR. COOPER: Let's go to Page 3 of the exhibit
02:10:26 and call out the third bullet.
02:10:26 BY MR. COOPER:
02:10:31 Q. What does the manufacturer report about the particle
02:10:33 size of GRASTAR?
02:10:34 A. They report an average diameter of 81.58 microns.
02:10:39 Q. How does the particle size of GRASTAR impact your
02:10:43 analysis of whether it functions as a glidant in MSN's ANDA
02:10:47 product?
02:10:47 A. Well, again, particle size is important to how
02:10:49 materials flow. Usually glidants are typically much
02:10:56 smaller-size materials, given the way that glidants interact
02:10:59 with particles. And so, this is a much larger particle than
02:11:03 I would expect for a glidant.
02:11:05 Q. Does the scientific literature also describe the
02:11:08 potential functions of pregelatinized starch?
02:11:10 A. Yes, it does.
02:11:12 Q. Can we please pull up DTX-275.
02:11:14 Dr. Donovan, what is this exhibit?
02:11:23 A. This is the cover page of a text called the Handbook
02:11:26 of Pharmaceutical Excipients. And this is -- it's a series
02:11:29 of monographs on individual excipient materials. Talks
02:11:32 about their characteristics, their behaviors, their uses.

02:11:35 And it includes many of the commonly used pharmaceutical
02:11:40 excipients.
02:11:41 Q. Does the handbook discuss pregelatinized starch?
02:11:44 A. It does.
02:11:45 MR. COOPER: Let's go to Page 754. And call out
02:11:49 the title and the sixth and seventh bullets on that page.
02:11:49 BY MR. COOPER:
02:11:52 Q. What are the functions that the handbook identifies
02:11:55 for pregelatinized starch?
02:11:57 A. For pregelatinized starch, the material acts in
02:12:01 oral -- it's used in oral capsule and tablet formulations as
02:12:06 a binder, a diluent, and disintegrant.
02:12:08 Q. Does the handbook identify glidant as a function for
02:12:10 pregelatinized starch?
02:12:11 A. It does not.
02:12:12 Q. Does the handbook also have a monograph for
02:12:15 unmodified starch?
02:12:16 A. It does have a separate monograph for starch,
02:12:18 unmodified starch.
02:12:20 MR. COOPER: Let's go to Page 748. And call out
02:12:22 the title of the sixth and seventh bullets on that page.
02:12:26 BY MR. COOPER:
02:12:26 Q. What are the functions that the handbook identifies
02:12:28 for unmodified starch?
02:12:30 A. It identifies unmodified starch as behaving as a

02:12:33 glidant, a tablet, and capsule diluent, a tablet and capsule
02:12:36 disintegrant, and a tablet binder.
02:12:38 Q. So a glidant is identified as a function for
02:12:40 unmodified starch?
02:12:41 A. Unmodified starches have been used as glidants.
02:12:44 Q. Would a POSA consider scientific references
02:12:48 discussing the properties or functions of unmodified starch
02:12:52 to apply equally to pregelatinized starch?
02:12:54 A. No. They're two different materials.
02:12:57 Q. Are the functions described in the handbook that
02:13:00 we've just seen for unmodified starch and pregelatinized
02:13:04 starch consistent with other scientific literature you have
02:13:08 reviewed describing the use of those excipients?
02:13:10 A. Yes, they are.
02:13:11 Q. Now, did you see Dr. Koleng present the Lachman
02:13:16 textbook and a patent that had statements in them that
02:13:21 pregelatinized starch could be potentially used as a glidant
02:13:25 in pharmaceutical formulations?
02:13:26 A. Yes, I did see that.
02:13:27 Q. Does that change your opinion about the use of
02:13:29 pregelatinized starch in tablet formulations?
02:13:32 A. No, it doesn't.
02:13:33 Q. Can you explain why not?
02:13:35 A. Well, regarding the textbook table -- for example,
02:13:37 when you look through the chapter that that table is

included in, there are no examples of the pregelatinized starch material being used as a glidant in any of the examples provided in the chapter.

And regarding the patent that was -- was shown, again, there's -- there was no example of pregelatinized corn starch used as a glidant.

Q. In your experience, have you seen a pregelatinized starch used in a pharmaceutical formulation as a glidant?

A. Not in -- no, I haven't.

Q. Okay. Let's talk about MSN's ANDA product formulation development. Generally, what MSN development documents have you reviewed as part of your work in this case?

A. Well, I reviewed the -- the portions of the ANDA supplement or ANDA application, some other research reports, the lab notebook, then some other project reports.

MR. COOPER: Let's pull up DTX-215, which is the MSN product development report. And let's go to Page 34 of the exhibit, call out the table "flow properties of the drug substance."

BY MR. COOPER:

Q. We've seen this a bit. So could you just describe briefly what MSN's testing showed about the cabozantinib (L)-malate API?

A. Yes. So this is their testing of their API. And

they determined that their API would exhibit poor flow properties.

Q. What flow character does the USP assign to a sample that has the compressibility index of about 34 and a Hausner ratio of about 1.52?

A. My recollection is it's actually the very poor category.

Q. What did MSN decide to do to address the poor flow properties of the API?

A. As the last -- or the sentence below the table states -- or one below that, "Hence, the process of choice was wet granulation over direct compression."

So, they -- they decided they wanted to granulate to try to address some of those poor flow properties.

Q. Did MSN's decision to use wet granulation address their concern with the poor flow properties of the API?

A. Yes. I was -- I did not see any other experiments where they tried to address direct -- where they tried to address the flowability of the product mixtures or granules.

Q. So did your review of MSN documents indicate that MSN ever considered making any formulation changes during development in order to add a glidant or further improve flow properties?

A. No.

02:16:07 Q. Did you review development documents related to when
02:16:10 MSN decided to add granulated corn starch to its
02:16:13 formulation?
02:16:13 A. Yes, I did.
02:16:15 Q. Can we pull up DTX-196.
02:16:18 And this is the MSN laboratory notebook we've
02:16:20 seen. Did you review this document as well?
02:16:22 A. Yes, this is the 252 laboratory notebook.
02:16:25 Q. Let's go to Page 46 of the exhibit, and pull up the
02:16:28 formulation on that page. Is there a batch number
02:16:31 associated with this formulation?
02:16:32 A. This is batch number 252/023.
02:16:37 Q. And, Dr. Donovan, is there anything notable about the
02:16:40 ingredients in this formulation?
02:16:41 A. Well, regarding the topics we've been discussing, if
02:16:44 you look at line numbers -- that's numerically marked number
02:16:48 7, in the extragranular mixture, corn starch is included as
02:16:54 a -- content of the extragranular mixture.
02:16:57 Q. And is that what we've seen also referred to as maize
02:17:01 starch B?
02:17:01 A. Yes, it is.
02:17:03 MR. COOPER: Let's also go to Page 84 in the
02:17:05 exhibit and pull up the formulation on that page next to it.
02:17:05 BY MR. COOPER:
02:17:07 Q. Is there a batch number associated with this

02:17:09 formulation on Page 84?
02:17:10 A. Yes. The formulation shown on the right of the
02:17:13 screen, it's 252/044.
02:17:16 Q. What is notable about the ingredients in that batch?
02:17:18 A. Again, at Line 7 again in the extragranular mixture
02:17:23 of granulated corn starch of the GRASTAR material is being
02:17:25 used in the extragranular mixture.
02:17:27 Q. Are there any other differences in the formulations
02:17:29 between batch 23 and batch 44?
02:17:32 A. No. They're not.
02:17:34 Q. Now, based on your review of the MSN development
02:17:36 documents, what properties of the formulations was MSN
02:17:39 focused on when they made this formulation change?
02:17:42 A. Throughout their documents they were focused on the
02:17:46 disintegration and dissolution properties of the tablet
02:17:49 dosage form.
02:17:50 Q. Did you review data in the MSN notebook associated
02:17:53 with these batches that is related to bulk and tapped
02:17:57 density of each formulation?
02:17:59 A. I did.
02:18:00 Q. In your opinion, did the addition of granulated corn
02:18:04 starch result in any meaningful improvement in the flow
02:18:06 properties of the formulation for batch 44?
02:18:09 A. No, in my evaluation there was no material difference
02:18:14 in the values between those.

02:18:16 Q. Did MSN make any other formulation changes during
02:18:19 development to adjust the disintegration and dissolution
02:18:23 properties of their prototype products?
02:18:25 A. Yes, they did spend some time adjusting the
02:18:28 disintegrant component of the formulation.
02:18:30 MR. COOPER: All right. Let's go to DDX Slide
02:18:32 10.
02:18:33 BY MR. COOPER:
02:18:35 Q. And this slide references that DTX-215 that we've
02:18:41 seen before, and specifically Pages 38, 41 and 44.
02:18:46 Could -- could you describe what is on the
02:18:49 left-hand part of this slide that's called out?
02:18:51 A. Sure. So this is a graph describing the outcome of
02:18:58 Formulation Development Study 1. So they prepared
02:18:59 60-milligram tablets, you -- and this is one of the very
02:19:02 early formulation attempts -- and measured the dissolution
02:19:08 of the drug.
02:19:09 So when we look at the graph, the -- as the
02:19:11 graph goes up, the amount of cabozantinib in solution is
02:19:15 going up or being released from the tablet. And what's
02:19:18 shown at that very top curve is the reference products
02:19:22 performance. So that's the cabozantinib being released from
02:19:25 the reference product.
02:19:26 The curve below that is the cabozantinib release
02:19:30 that was observed from this early Formulation Development,

02:19:33 Study Number 1 batch.
02:19:35 Q. And what does MSN conclude about the prototype
02:19:38 formulation in Formulation Development, Study Number 1?
02:19:40 A. Well, they determined that the -- the dissolution was
02:19:45 slow at the initial time points and that they want -- they
02:19:49 then moved on to try to improve the dissolution rate at
02:19:52 those earlier time points.
02:19:53 Q. What did MSN change in the next prototype to address
02:19:57 the concern from Formulation Development, Study Number 1?
02:20:00 A. So in the next Formulation Development, Study
02:20:03 Number 2, what they did was change the intergranular
02:20:08 disintegrant concentration.
02:20:09 Q. All right. And so just to be clear, this -- these
02:20:11 particular trials, is there any change in the amount or type
02:20:15 of the extragranular corn starch or granulated corn starch?
02:20:20 A. No.
02:20:21 Q. Okay. Now, what does MSN conclude about the
02:20:24 prototype formulation used in Formulation Development, Study
02:20:28 Number 2?
02:20:28 A. On the Formulation Development, Study Number 2, you
02:20:31 can see the curves are closer together. They've done -- the
02:20:34 next modified formulation does a better job of early
02:20:37 dissolution and disintegration, and that's what they -- they
02:20:40 determined that the dissolution was similar to the reference
02:20:43 product.

02:20:44 Q. Did MSN perform any other formulation development
02:20:49 studies to assess the dissolution and disintegration
02:20:52 profiles of the drug?
02:20:54 A. Yes, they did.
02:20:55 MR. COOPER: All right. Let's pull up DTX-215
02:20:57 again. And go to Page 58 of the PDR, Section 2.3.1.9. And
02:21:06 then call out the table going over to Page 59 containing the
02:21:10 MSN compositions for these trials.
02:21:10 BY MR. COOPER:
02:21:13 Q. Now, it looks like there are three different batches
02:21:16 reported in this trial; is that right?
02:21:17 A. Yes, there are.
02:21:19 Q. What is the purpose of the formulation trials that
02:21:21 MSN is reporting on in this section of the PDR?
02:21:24 A. What they're doing in these trials is comparing the
02:21:27 amount of the GRASTAR granulated corn starch in the
02:21:31 extragranular mixture. So, the -- if we look at the top
02:21:35 row, it's easiest to understand that the first column of
02:21:38 numbers represents the composition of a 6.7 percent
02:21:45 containing GRASTAR formulation. So the total components in
02:21:50 the core tablets, 6.7 percent of it was GRASTAR. Middle was
02:21:55 9.7 percent as GRASTAR. And in the right-hand column, a
02:21:59 study where 12.7 percent of the total tablet composition was
02:22:04 GRASTAR.
02:22:05 Q. Now, Dr. Koleng pointed out the first sentence in

this section says, "The level of granulated corn starch plays an important role in flow characteristics."

Do you see that?

A. Yes.

Q. Does this section of the PDR report on testing of flow characteristics of any of these batches?

A. One of the batches had density numbers associated with it, but no flow testing.

MR. COOPER: Let's go to Page 60 of the PDR and call out the figure and text underneath.

BY MR. COOPER:

Q. Now, is this the results of the trials we were just looking at?

A. Yes. These are what MSN determined from their trials that all of the physical and chemical parameters were found to be satisfactory for those batches, there was no significant difference in the level of GRASTAR included in the extragranular mixture, and as a result they chose to move forward with 9.7 percent of granulated corn starch.

Q. Now, Dr. Koleng pointed out that the dissolution profiles did not ultimately change between the 6.7 and 9.7 and 12.7 percent batches of when you use that amount of GRASTAR in the trials.

Do you recall that?

A. I do recall that, yes.

02:23:15 Q. He suggested that meant that MSN was not going -- using GRASTAR as a excipient to adjust dissolution or disintegration.

Do you recall that generally?

A. Yes.

Q. Do you agree with that?

A. No.

Q. Why is that?

A. Well, in the -- in these -- in the study they're only reporting the lowest level of GRASTAR as 6.7 percent. And so to be able to make the statements that Dr. Koleng did, we would need to more -- we would need to know more about what would happen with zero percent.

Q. And so what does, based off these trials, MSN conclude on the last -- in the last sentence of their conclusion?

A. They just -- they concluded that 9.7 percent weight/weight of granulated corn starch was proposed as the optimum concentration in their formulation.

Q. Did you see any evidence in your review of MSN development documents that MSN added granulated corn starch to function as a glidant or to improve the flow properties of the powder blends?

A. No, I didn't see any evidence.

Q. Did you review the deposition testimony of MSN's

02:24:12 formulation scientist, Ravikumar Nithiyanandam?
02:24:15 A. Yes, I did.
02:24:16 Q. Is your opinion consistent with his explanation of
02:24:19 why MSN used granulated corn starch in the ANDA product
02:24:23 formulation?
02:24:23 A. Yes, it is.
02:24:25 Q. Okay. Now, let me ask you this --
02:24:27 MR. COOPER: You can take that down. Thank you.
02:24:27 BY MR. COOPER:
02:24:29 Q. Let's assume for a moment that using GRASTAR in MSN's
02:24:34 formulation did have some meaningfully positive impact on
02:24:38 the flow character of the MSN powder blend as Dr. Koleng
02:24:42 alleges.
02:24:43 Are you with me so far?
02:24:44 A. Okay. Yes.
02:24:45 Q. Would that mean that GRASTAR must be functioning as a
02:24:49 glidant in MSN's formulation?
02:24:50 A. No, it doesn't.
02:24:51 Q. Why not?
02:24:52 A. Well, again, fillers. We went through a definition,
02:24:55 fillers can improve flow properties also. GRASTAR had good
02:24:59 flow properties so it would be expected that the addition of
02:25:03 GRASTAR could improve the flow properties if that actually
02:25:07 had been the case.
02:25:08 Q. Is there any evidence that GRASTAR is operating in

MSN's formulation through any of the glidant mechanisms that appear in the literature that you've described?

A. No, there's not.

Q. All right. Let's discuss those mechanisms.

MR. COOPER: Let's go to Slide DDX 11. And this slide is titled, "Adherence to particle surfaces."

BY MR. COOPER:

Q. Can you first remind us what that is in reference to?

A. Sure. And that's -- this is the picture of the -- of the mechanism in the bottom, the last bullet on the slide that I showed, talking about a glidant being able to fill in the surface roughness, the surface of a granule or a powder particle and then acting to either smooth out the surface and/or decrease the friction between those particles to keep them flowing past one another.

Q. And so what are you showing on left-hand side?

A. So what I'm showing is a granule on the silver balls on the surface are the glidant particles that are adhered to the surface acting as the glidant.

Q. And so is that the mechanism that would be described in the literature?

A. Yes. That's a very frequent mechanism described, actually.

Q. And did you consider whether GRASTAR is likely to adhere to other particles in MSN's formulation to

meaningfully improve the powder flow?

A. I did.

Q. And what was your conclusion?

A. So on the right-hand side what I'm trying to show is and what I already talked about, the average particle size of GRASTAR granulated corn starch is about 80 microns and the average size of the granules of the MSN ANDA powder mixture batch is a little bit less than 150 microns or so.

And so, there's -- there isn't a physical way for an 80-micron particle to decorate the surface of 150-micron particle, one that's only twice its size such that it acts in the way a glidant acts. Only, you know, maybe one or two could fit on and they wouldn't stay on.

Q. And you -- you -- I noticed that you said it's about -- MSN granules are about 150 microns.

Who performed the calculations to identify the size of the MSN granules?

A. I believe -- well, there were calculations provided in Dr. Koleng's report.

Q. And are you accepting Dr. Koleng's calculations for the size of the MSN granules?

A. Yes. I looked at those calculations and I agree with them.

MR. COOPER: Let's go to Slide DDX 12.

BY MR. COOPER:

02:27:29 Q. Now, the title of this slide is "Sorption of fine
02:27:32 particles."
02:27:33 Can you remind us what that refers to?
02:27:35 A. Okay. So this is the sort of alternative mechanism
02:27:38 where the glidant particle is actually bigger than the
02:27:41 smallest particles in the powder mix. So in this case, the
02:27:45 orange diamond shaped materials are actually part of the
02:27:49 powder mixture, but are very small particles. The glidant
02:27:52 is bigger than that and the glidant is able to let those
02:27:55 small particles adsorb onto the surface and then the flow
02:27:59 properties of the powder mixture improve.
02:28:01 Q. And for the record, that mechanism you've just
02:28:03 described is on the left-hand side of this slide; is that
02:28:05 correct?
02:28:06 A. That's correct.
02:28:06 Q. Did you consider whether GRASTAR's likely to adsorb
02:28:10 what Dr. Koleng has called fines in MSN's formulation to
02:28:15 meaningfully improve powder flow?
02:28:17 A. Yes, I did consider that.
02:28:18 Q. What did you conclude?
02:28:20 A. I -- I don't think that that's a mechanism -- or
02:28:22 that's not how GRASTAR is acting in this powder mixture.
02:28:26 Q. Why is that?
02:28:27 A. The reason is again in the pictures, GRASTAR, again,
02:28:30 about 80 microns in size. The granules average particle

size less -- a little bit less than 150 microns, and the only thing that Dr. Koleng defines as fines is all those particles less than 150 microns. And so we're talking particles that are right about the same size, some bigger. I don't know, potentially some smaller, but unlikely to be smaller than the actual starting materials that were used in the formulation. And so they're all about the same size. They're not going to be able to be materials that stick to the surface of GRASTAR and then act as having GRASTAR act as a glidant.

Q. Dr. Koleng testified about work with fenofibrate by the manufacturer of GRASTAR.

Do you recall that testimony?

A. I do.

Q. And you recall the document that Dr. Koleng showed us?

A. Yes, I do.

MR. COOPER: Let's pull that up PTX-447 and call out Section 1.

BY MR. COOPER:

Q. And do you see where it refers to micronization there?

A. Yes.

Q. And it says, "Micronization increases its solubility and absorption." Oh, I'm sorry. Strike that.

02:29:41 Do you see where it says, "Micronization reduces
02:29:44 flowability and formability"?
02:29:45 A. Yes, I see that.
02:29:47 Q. Do you have an understanding of the size of the
02:29:50 micronized fenofibrate that is being used in this document?
02:29:53 A. I do. Based on -- in the document it describes that
02:29:55 the fenofibrate was micronized using a technique called jet
02:30:00 milling.
02:30:01 Q. What do you conclude from that?
02:30:02 A. Well, jet milling usually results in particles that
02:30:04 are smaller than 10 microns.
02:30:06 Q. And how does the particle size of micronized
02:30:08 fenofibrate described in this exhibit compare to the
02:30:11 particle size of what Dr. Koleng is referring to as fines in
02:30:14 the MSN ANDA product?
02:30:15 A. So, once again, the particle size of the fines
02:30:19 Dr. Koleng describes are defined as fines as less than
02:30:24 150 microns, and these particles are less than 10 microns.
02:30:27 Q. So does anything in this exhibit about fenofibrates
02:30:30 suggest that GRASTAR is adsorbing fines in the MSN ANDA
02:30:34 product formulation or functioning as a glidant?
02:30:36 A. Not -- not as GRASTAR acts in the MSN ANDA product.
02:30:40 Q. Thank you.
02:30:41 MR. COOPER: You can take that down.
02:30:41 BY MR. COOPER:

Q. Did you also consider whether GRASTAR disperses electrostatic charges in MSN's formulation to meaningfully improve powder flow?

A. I did consider that, and I didn't see again any indication in any of the experimental reports where electrostatic or static would be -- was an issue. There was no powder sticking to the vessels as powders were transferred and so forth, and that's a classic observation. No observations like that. No experimental attempts to address electrostatics.

Q. Did you also consider whether GRASTAR adsorbs gas in MSN's formulation to meaningfully improve powder flow?

A. I also considered that, and again, there's no experimental notations or work that was done to address any potential gas surface associated gas and the need to disperse that.

Q. If that was a problem, what would you expect to see?

A. I would expect to see probably even in dissolution studies in particular, where they would report perhaps poor wetting of the powder mixture because water can't associate with the powder surface. It's -- the gas is sent in between, and I saw no descriptions of that, no changes in dissolution methodologies, no request to change formulation.

Q. Finally, did you consider whether GRASTAR reduces van der Waals forces and MSN's formulation to meaningfully

02:32:02 improve powder flow?
02:32:03 A. I did.
02:32:04 Q. What was your conclusion?
02:32:05 A. And I don't believe van der Waals forces could even
02:32:09 be considered for these particles again.
02:32:10 Q. Why is that?
02:32:11 A. Because they're large particles. Again, as we've
02:32:13 heard, van der Waals forces are atomic forces. They involve
02:32:18 interactions of the electron clouds of the atoms on the
02:32:21 surface of each particle. And when we have really large
02:32:24 particles, you have to have an awful lot of atoms
02:32:26 interacting in order to have enough strength to hold those
02:32:29 particles together and thus have a glidant allow them to be
02:32:33 pulled apart.
02:32:34 In these large particles, there's just not
02:32:37 enough point of contact surface area to have enough atoms
02:32:40 involved to hold them together.
02:32:42 Q. All right. Thank you, Doctor. Let's move now to
02:32:44 Slide DDX-13 and address your response to some of the
02:32:51 testimony that Dr. Koleng gave.
02:32:53 At a high level why do you disagree with the
02:32:56 conclusions Dr. Koleng drew from the literature and MSN
02:33:00 documents that he showed today?
02:33:01 A. Well, first, Dr. Koleng seems to define glidants
02:33:06 as -- or yeah, it seemed to define any material that

02:33:10 improves flow properties is a glidant. And that's not
02:33:14 consistent with the textbook definitions we've seen. And
02:33:18 it's not -- and GRASTAR acting as a glidant in the MSN
02:33:25 powder mixtures isn't consistent with any of the data that's
02:33:28 been presented.
02:33:29 Q. All right.
02:33:29 MR. COOPER: Let's pull up DTX-161.
02:33:29 BY MR. COOPER:
02:33:32 Q. And this is the justification for microbial method
02:33:36 validation document that we saw.
02:33:38 MR. COOPER: Let's call out Section 1 on Page 1
02:33:41 and Sections 5.1.3 and 5.1.4 on Page 2.
02:33:41 BY MR. COOPER:
02:33:47 Q. Doctor, first, what is the purpose of this document?
02:33:49 A. Okay. So this document was a document to show that
02:33:54 the microbial method that they were using to test corn
02:33:58 starch and now granulated corn starch as the GRASTAR product
02:34:02 was adequate to test for microbial growth or microbial
02:34:05 contamination as an excipient that they were going to use in
02:34:10 a pharmaceutical product. So they needed to validate
02:34:12 that -- their testing method to show what the microbial
02:34:15 population was adequate.
02:34:17 Q. Does this document have anything to do with measuring
02:34:20 or evaluating flow properties in corn starch, granulated
02:34:24 corn starch or MSN's ANDA product?

02:34:25 A. No, it doesn't.
02:34:27 Q. Let's look at the statement in Section 5.1.4. And in
02:34:31 the second sentence it says, "Starch are used in
02:34:35 pharmaceutical industry for a wide variety of reasons, such
02:34:38 as an excipient in tablet and capsule, as a diluent, as a
02:34:42 glidant or as a binder."
02:34:44 Do you see that?
02:34:44 A. Yes, I see that.
02:34:46 Q. Now, first, is that a true statement of how
02:34:48 starch-based excipients may be used in the pharmaceutical
02:34:51 industry depending on its formulation?
02:34:53 A. It's true about unmodified starches, yes.
02:34:56 Q. You saw other literature references about starch or
02:34:59 unmodified starch that Dr. Koleng showed that made similar
02:35:03 statements; correct?
02:35:04 A. Yes.
02:35:04 Q. Does this document or those references generally
02:35:07 describing uses of starch suggest to you that the granulated
02:35:11 corn starch is being used as a glidant in MSN's ANDA
02:35:14 product?
02:35:14 A. No, it doesn't.
02:35:15 MR. COOPER: Let's pull up DTX-215 MSN's PDR.
02:35:20 Let's go to Page 34. Call out the initial risk
02:35:25 assessment that we've looked at previously and the entry for
02:35:30 granulated corn starch in the table.

BY MR. COOPER:

Q. First, Doctor, what is your understanding of when an initial risk assessment is performed?

A. Well, it's performed early on in formulation development, usually before formulation development starts or when there's a critical point in decision making about formula -- further formulation development activities because what it's doing is directing and prioritizing what should be evaluated for a formulation.

Q. And so here we see that granulated corn starch is used as a diluent in minimal concentrations. Do you see that?

A. I see that.

Q. And then Dr. Koleng pointed out that it goes on and says, "And it enhances the flowability of the granules."

Do you see that?

A. I do.

Q. What is your understanding for the basis of that statement in this document in this chart?

A. Well, again, it's this -- this initial risk assessment was done before a lot of the formulation development was completed. But even in the statement, the statement that granulated corn starch is used as a diluent in minimal concentration and then potentially could enhance the flowability of granules -- they haven't done any

02:36:38 experiments yet -- is totally in keeping with it being a
02:36:42 diluent. Again, it's a diluent. It's a material that was
02:36:44 known to have good flow properties.
02:36:49 Q. And to be clear, did you then see any evidence that
02:36:51 granulated corn starch ended up meaningfully enhancing the
02:36:54 flowability of the granules in MSN's formulations?
02:36:57 A. No, I didn't.
02:36:58 MR. COOPER: Let's go to Page 39. I'm sorry.
02:37:02 Strike that.
02:37:02 Let's pull up PDX-2.14.
02:37:02 BY MR. COOPER:
02:37:16 Q. Do you recall Dr. Koleng talking about this slide?
02:37:18 A. I do.
02:37:19 Q. Do you recall Dr. Koleng's testimony that he believed
02:37:22 the pre-lubrication stage at which GRASTAR is added to the
02:37:27 powder blend supports his opinion that the excipient is
02:37:30 functioning as a glidant?
02:37:33 A. I heard him state that, yes.
02:37:35 Q. Well, first, do you agree that if one is using
02:37:38 glidant that it is usually added at the pre-lubrication
02:37:42 stage of a tablet manufacturing process?
02:37:43 A. I agree that's true. It's often added at the
02:37:47 pre-lubrication stage.
02:37:48 Q. So do you agree with the conclusion that Dr. Koleng
02:37:52 draws from that fact?

02:37:52 A. No. Just because it's added at the pre-lubrication
02:37:55 stage does not mean it's a glidant. Other things are
02:37:57 also -- other types of excipients are also added at the
02:38:01 pre-lubrication stage.
02:38:02 Q. What types of excipients are also added at the
02:38:05 pre-lubrication stage?
02:38:06 A. So as we've already discussed, disintegrants can be
02:38:09 added, coloring agents, sweeteners, other things. A number
02:38:13 of other things, other fillers can be added at the
02:38:14 pre-lubrication step.
02:38:17 MR. COOPER: Thank you, Dr. Donovan.
02:38:19 Pass the witness.
02:38:20 THE COURT: I'm sorry. Dr. Donovan, I'm --
02:38:22 perhaps you said this somewhere. One of the things that
02:38:25 Dr. Koleng said at the beginning of his testimony was what
02:38:29 he understood the plain and ordinary meaning of a glidant to
02:38:32 be. What -- have you got an opinion on that?
02:38:36 THE WITNESS: An opinion on what Dr. Koleng said
02:38:39 about the plain and ordinary meaning?
02:38:41 THE COURT: No. I mean, what does a glidant
02:38:42 mean to a person of ordinary skill in the art?
02:38:44 THE WITNESS: That a glidant does improve flow
02:38:49 properties, but it does it by -- does it in ways that we
02:38:52 understand glidants act to accomplish that improvement.
02:38:57 THE COURT: Okay.

02:38:59 Cross-examination.

02:39:01 THE WITNESS: Your Honor, would it be okay if I
02:39:04 grabbed a glass of water?

02:39:05 THE COURT: Yes.

02:39:38 MS. PIROZZOLO: Good afternoon, Your Honor.
02:39:39 Lisa Pirozzolo for Plaintiff Exelixis.

02:39:39 CROSS-EXAMINATION

02:39:39 BY MS. PIROZZOLO:

02:39:42 Q. Good afternoon, Dr. Donovan.

02:39:44 A. Good afternoon.

02:39:45 Q. Now, you agree that a glidant is an excipient that
02:39:49 improves the flow characteristics of a powder mixture;
02:39:53 correct?

02:39:53 A. A glidant can improve the flow properties of a powder
02:39:57 mixture, yes.

02:39:58 Q. Okay. You have defined glidant as "a glidant is a
02:40:02 substance which improves the flow characteristics of a
02:40:05 powder mixture"; right?

02:40:06 A. Yes.

02:40:07 Q. Okay. Now, let's pull up Claim 3 of the '349 patent
02:40:15 which is at Tab 5 in your binder, and it's Joint Exhibit 4.

02:40:22 Claim 3 of the '349 patent refers to glidants;
02:40:29 correct?

02:40:29 A. Claim 3 has glidants included in it, yes.

02:40:33 Q. Okay. Claim 3 of the '349 patent does not refer to

any glidant mechanism; correct?

A. It doesn't specify a particular mechanism, no.

Q. Okay. Now, the specification of the patent has a discussion of pharmaceutical compositions; correct?

A. Correct.

Q. We can --

A. Yes.

Q. -- go to Column 20, Line 38.

Do you see that?

A. Yes.

Q. Okay. And in the patent there's a reference to *Remington: The Science and Practice of Pharmacy*; correct?

A. Yes, there is.

MS. PIROZZOLO: Okay. And if you could turn to Tab 6 in your binder. That's Plaintiff's Exhibit 572A, which is an excerpt from the Remington chapter on solid oral dosage forms.

BY MS. PIROZZOLO:

Q. Could you turn to Page 893 of the exhibit?

A. I'm there.

Q. And do you see the heading "Glidants"?

A. Yes.

Q. And the very first line says, "A glidant is a substance that improves the flow characteristics of the powder mixture"; correct?

02:42:00 A. Yes, and that's a classic definition.
02:42:01 Q. Okay. And you have relied on that definition in
02:42:06 Remington in rendering your opinions in this case?
02:42:09 A. I have.
02:42:12 Q. Now, the patent also refers to Swarbrick's
02:42:16 Encyclopedia of Pharmaceutical Technology; correct?
02:42:20 A. Yes.
02:42:21 Q. Okay. And you referred to Swarbrick during your
02:42:25 direct examination; correct?
02:42:26 A. Yes.
02:42:27 Q. Okay. Could you please look at Tab 7 in your binder,
02:42:33 which is Plaintiff's Exhibit 394, which is Swarbrick. And
02:42:40 if you turn to Page 26, near the bottom of the page, it's
02:42:48 the PDF Page 26, which we're pulling up here.
02:42:55 There are three bullets, do you see that?
02:42:57 A. I see those, yes.
02:42:59 Q. Okay. And there's -- the first bullet says, "Glidant
02:43:03 excipients improve the flow characteristics of tablet
02:43:07 granulations (and capsule powder blends)." Correct?
02:43:11 A. That's what it says, yes.
02:43:13 Q. Okay. And you agree that the statement in Swarbrick
02:43:15 is a reasonable definition of a glidant in the art; correct?
02:43:19 A. Yes.
02:43:22 MS. PIROZZOLO: Now, could you turn to Page 44
02:43:25 of the Swarbrick reference.

02:43:25 BY MS. PIROZZOLO:

02:43:29 Q. There's a table entitled "Glidants." Do you see
02:43:33 that?

02:43:33 A. Yes.

02:43:35 Q. Okay. And the table lists percentage concentrations
02:43:39 for various glidants; correct?

02:43:40 A. Correct.

02:43:42 Q. And Table 2 identifies the suggested percentage for
02:43:46 starch (dry flow) as 1 to 10 percent; correct?

02:43:50 A. That's what the table states is -- yes, starch dry
02:43:54 flow.

02:43:54 Q. Okay. And as you testified on direct, the
02:43:57 concentration for granulated corn starch in MSN's ANDA
02:44:02 products is 9.71 percent; correct?

02:44:05 A. It is, yes. They also tested higher concentrations.

02:44:10 MS. PIROZZOLO: Now, if we could pull up Claim 3
02:44:14 of the '349 patent again.

02:44:14 BY MS. PIROZZOLO:

02:44:19 Q. Claim 3 is directed to a tablet or capsule
02:44:24 pharmaceutical formulation of cabozantinib (L)-malate;
02:44:30 correct?

02:44:30 A. Yes.

02:44:31 Q. MSN's ANDA products are tablet pharmaceutical
02:44:34 compositions of cabozantinib (L)-malate; correct?

02:44:38 A. Yes.

02:44:39 Q. Claim 3 also requires that the pharmaceutical
02:44:42 composition have certain excipients; correct?
02:44:45 A. Certain categories of excipients, yes.
02:44:48 Q. And you're not disputing that MSN's ANDA products
02:44:51 contain a filler, a disintegrant, and a lubricant; correct?
02:44:55 A. That's correct. I'm not disputing that.
02:44:58 Q. Okay. And Claim 3 also requires that the
02:45:01 pharmaceutical composition be essentially free of what I
02:45:07 think you called on your direct the 1-1 impurity; correct?
02:45:11 A. That's correct.
02:45:12 Q. And there's no dispute that MSN's ANDA products are
02:45:15 free of the 1-1 impurity; correct?
02:45:18 A. Correct.
02:45:18 Q. Okay. So the only basis for your opinion that MSN's
02:45:22 ANDA products don't infringe is that they do not contain a
02:45:25 glidant; correct?
02:45:26 A. That's correct.
02:45:27 Q. Okay. Now, in offering your opinions in this case,
02:45:36 that the granulated corn starch in MSN's ANDA product is not
02:45:42 a glidant, you didn't undertake any testing to determine the
02:45:45 flow characteristics of the granulated corn starch in MSN's
02:45:49 ANDA products; correct?
02:45:50 A. That's correct.
02:45:55 Q. You did not have any communications with any of the
02:45:58 scientists at MSN about the role of granulated corn starch

02:46:03 in MSN's ANDA products; correct?
02:46:05 A. That's correct.
02:46:08 Q. You're relying on documents to support your opinion;
02:46:12 correct?
02:46:12 A. Yes, I am.
02:46:13 Q. Now, let's pull up the pharmaceutical development
02:46:16 report that you talked about on your direct. That's
02:46:22 Defendants' Exhibit 215.
02:46:25 Now, this pharmaceutical development report
02:46:28 summarizes the development of MSN's ANDA products; correct?
02:46:33 A. Yes.
02:46:35 Q. And the information in the pharmaceutical development
02:46:38 report was submitted to the FDA; correct?
02:46:40 A. That's my understanding.
02:46:42 Q. Okay. And you agree, I think, and you testified on
02:46:46 your direct that MSN in this report described cabozantinib
02:46:52 (L)-malate as having poor flow properties; correct?
02:46:54 A. There is a statement that they describe it as having
02:46:59 poor flow properties, the API.
02:47:00 Q. Okay. So, let's turn to Page 35 of the document,
02:47:07 which has the initial -- justification for the initial risk
02:47:12 assessment of the formulation variables. Okay?
02:47:16 A. Okay.
02:47:17 Q. And you --
02:47:18 A. Can you direct me to what tab you're using?

02:47:20 Q. Oh, sure. I'm sorry. It's -- the pharmaceutical
02:47:24 development report is -- let me just -- at Tab 9 in your
02:47:32 binder. And the risk assessment is at Page 35.
02:47:47 Do you see that?
02:47:48 A. As soon as I get to Page 35, but yes.
02:47:54 I'm there.
02:47:54 Q. Okay. And then, if you go to Page 36, that's the
02:47:58 entry for granulated corn starch that you talked about in
02:48:01 your direct examination; correct?
02:48:03 A. Yes.
02:48:04 Q. And in the entry it says, "Granulated corn starch is
02:48:08 used as a diluent in minimal concentration and it enhances
02:48:12 the flowability of the granules." Correct?
02:48:15 A. That's what it says, yes.
02:48:17 Q. And that's written in the present tense; correct?
02:48:19 A. It -- yes, it's written in the present tense.
02:48:23 Q. Okay. And you agree that the rationale MSN provided
02:48:27 to the FDA for selection of granulated corn starch was that
02:48:30 it enhances the flowability of the granules; correct?
02:48:33 A. Well, it identified granulated corn starch as acting
02:48:40 as a diluent in its product.
02:48:41 Q. And it also identified granulated corn starch as
02:48:45 enhancing the flowability of the granules --
02:48:47 A. Well --
02:48:47 Q. -- correct?

02:48:48 A. Well, in the statement and initial risk assessment
02:48:52 describing the roles of various of the -- the excipients
02:48:57 under -- under consideration, and their potential risk for
02:49:02 inclusion, yes, they state that it enhances the flowability
02:49:06 of the granules.
02:49:07 But, again, it's a diluent and it's a
02:49:11 good-flowing diluent. And it would be expected, even before
02:49:16 experiments, to potentially enhance the flowability of the
02:49:19 granules.
02:49:20 Q. Okay. Well, let's go to tab -- Page 58 of the
02:49:26 pharmaceutical development report. Okay?
02:49:33 Now, in this section of the pharmaceutical
02:49:35 development report, there's a Section 2.3.1.9; correct?
02:49:42 A. Yes.
02:49:43 Q. Okay. And you talked about this on your direct.
02:49:46 This is a section of the pharmaceutical development report
02:49:51 that describes the optimization of the level of granulated
02:49:56 corn starch; correct?
02:49:56 A. That's correct.
02:49:59 Q. And the very first line of this section, in that very
02:50:05 first line MSN told the FDA that "the level of granulated
02:50:10 corn starch plays an important role in flow
02:50:12 characteristics." Correct?
02:50:14 A. That's what it states.
02:50:15 Q. And so, the word "important" was used in MSN's

02:50:22 characteristic -- characterization of the role that
02:50:26 granulated corn starch was playing on flow; correct?
02:50:29 A. Yes, the -- yeah, important, it occurs there the
02:50:33 sentence.
02:50:33 Q. And you don't have any basis to disagree with the
02:50:36 statement MSN made to the FDA, do you?
02:50:39 A. I don't. And, again, granulated corn starch is
02:50:42 acting as diluent, which could improve flow characteristics.
02:50:46 Q. And you didn't speak with anyone at MSN about the
02:50:49 statement in this pharmaceutical development report;
02:50:52 correct?
02:50:52 A. No, I didn't.
02:50:54 Q. Okay. Now, I'd like to ask you about the testing
02:50:57 that's described in this section. In this section, MSN is
02:51:06 describing tests it performed on three different prototype
02:51:10 formulations; correct?
02:51:11 A. Yes.
02:51:12 Q. Okay. In the three prototype formulations, the
02:51:18 concentration of granulated corn starch was either
02:51:22 6.7 percent, 9.7 percent, or 12.7 percent; correct?
02:51:28 A. That's correct.
02:51:32 Q. And if you go to the conclusion section of this
02:51:39 section of the pharmaceutical development report, MSN
02:51:44 concluded that "based on these experiments, that there were
02:51:50 no significant differences observed in the dissolution

02:51:54 profiles of the three prototypes"; correct?
02:51:56 A. Yes.
02:51:58 Q. Okay. So, MSN told the FDA that nearly doubling the
02:52:05 level of GRASTAR from 6.7 percent to 12.7 percent did not
02:52:11 make a significant difference in dissolution; correct?
02:52:15 A. That's what their results show, yes.
02:52:18 Q. Okay. So if you look at the entirety of this section
02:52:21 on optimization of the level of granulated corn starch, what
02:52:26 we can see is it begins with the statement that "granulated
02:52:34 corn starch plays an important role in flow
02:52:37 characteristics." Correct?
02:52:40 A. I believe that's what this statement said, yes.
02:52:42 Q. Okay. And the conclusion is that it did not -- these
02:52:48 level -- changing the level of corn starch did not impact
02:52:51 dissolution; correct?
02:52:52 A. A change between 6.7 percent and 12.7 percent did not
02:52:57 change dissolution. It doesn't say anything about any other
02:53:00 changes that could have -- could have been tested.
02:53:09 Q. Now, I'd also like to ask you about another
02:53:16 experiment you talked about in your direct examination.
02:53:21 MS. PIROZZOLO: Could we go to Page 38 of the
02:53:25 pharmaceutical development report?
02:53:25 BY MS. PIROZZOLO:
02:53:33 Q. And you relied on a section of the pharmaceutical
02:53:39 development report describing testing on two different

prototypes that MSN made; correct?

A. Study 1 and study 2, is that what you're referring to.

Q. Yes. Yes.

A. Yes. Right.

MS. PIROZZOLO: And if we go to Page 38.

BY MS. PIROZZOLO:

Q. The -- there's a description of the first prototype; correct?

A. That's correct.

Q. Okay. And in that prototype, there was regular corn starch in both intergranular layer and the extragranular layer correct?

A. That's what the PDR states.

Q. Okay. And it also had 9 milligrams of croscarmellose sodium; correct?

A. In the intergranular layer, it had 9 milligrams also in the extragranular.

Q. Okay. Now, the second prototype was described in MSN's development study 2; correct?

A. That's correct.

Q. Okay.

MS. PIROZZOLO: And if we go to study 2, which is Page 41. And blow up the objective.

BY MS. PIROZZOLO:

02:54:55 Q. The objective of study 2 was to prepare and evaluate
02:55:00 cabozantinib tablets by increasing disintegrant
02:55:04 concentration to improve the dissolution; correct?
02:55:09 A. That's what it states.
02:55:10 Q. And croscarmellose sodium is a disintegrant; correct?
02:55:13 A. Yes, it is.
02:55:14 Q. Okay. And the second prototype increase the
02:55:17 concentration of the disintegrant croscarmellose sodium in
02:55:23 the intergranular component; correct?
02:55:25 A. It did, yes.
02:55:29 Q. And the pharmaceutical development report also says
02:55:32 that MSN changed the corn starch in the extragranular layer
02:55:38 from maize corn starch B to GRASTAR; correct?
02:55:42 A. Can you point me to that, please?
02:55:44 Q. Sure. If you compare the table at Page 41 with the
02:55:55 table at page -- I'm sorry -- page 38, the first prototype
02:56:09 references maize starch B; right?
02:56:17 A. Correct.
02:56:17 Q. And the second prototype on Page 41 references
02:56:22 GRASTAR; correct?
02:56:23 A. Yes, that's what's described in the PDR.
02:56:26 Q. Okay. But you've since learned that there might be
02:56:31 an error in MSN's report on this test; correct?
02:56:34 A. That's my recollection, yes.
02:56:36 Q. Okay. As far as you understand, both of these

prototypes used granulated corn starch in the extragranular layer correct?

A. Yes, I think so.

Q. So the only difference between the two prototypes you discussed on your direct examination was the inclusion of greater amount of croscarmellose sodium in the intergranular layer; correct?

A. Correct. That's what -- and the dissolution results improved.

Q. Okay. So, based on comparing two prototypes with -- the only difference of which was the increased amount of croscarmellose sodium, MSN concluded that the dissolution profile of the second prototype was improved?

A. I guess I'd like to go to the graph and the words beneath that to be able to agree or not with that statement.

Q. Sure. You have the pharmaceutical development report in your binder; right?

A. Yes.

MS. PIROZZOLO: And if we can go to the statement about the improvement in dissolution. I think it's on the next page.

BY MS. PIROZZOLO:

Q. Well, you said on your direct examination that the dissolution profile of prototype 2 was improved; correct?

A. Can you show me what page you're on?

02:58:31 Q. Sure. It's --
02:58:32 A. I went to the wrong page.
02:58:43 Q. It's Page 4.
02:59:12 A. Okay. Can you either re-ask the question or...
02:59:24 Q. So, in prototype 2 -- for prototype 2 in the
02:59:29 pharmaceutical development report, the conclusion states,
02:59:33 "Dissolution profile of cabozantinib tablets 40-milligram
02:59:37 found similar with reference product."
02:59:40 And that was an improvement over the first
02:59:45 prototype in the first experiment; correct?
02:59:48 A. In Formulation Study 1?
02:59:51 Q. Yes.
02:59:52 A. Which was done with 60-milligram tablets, I believe.
02:59:57 Q. Yes. You referred to the improvement in dissolution;
03:00:01 correct?
03:00:01 A. I did, but I believe I was referring to a
03:00:06 60-milligram tablet example.
03:00:07 Q. Okay. It's true, is it not, that in the example
03:00:14 given that you referred to the amount of intergranular
03:00:17 croscarmellose sodium was increased; correct?
03:00:20 A. Yes, I did.
03:00:21 Q. Okay. And you don't know -- well, let me strike
03:00:26 that.
03:00:27 Increasing the amount of intergranular
03:00:31 croscarmellose sodium contributed to the increase in

dissolution; correct?

A. It appeared to, yes.

Q. Okay. Because croscarmellose sodium is a super disintegrant; right?

A. It's referred to as a super disintegrant, yes.

Q. And you don't know from this experiment whether the granulated corn starch in the extra granulator -- granulated -- in the extragranular layer impacted dissolution; correct?

A. Well, it was present in the extragranular layer, so it -- it may have been playing a role.

Q. Okay. But it may or may not have played a role given the change in the amount of croscarmellose sodium; correct?

A. I don't know. I don't have any data to evaluate to make that determination.

Q. Okay. Because there was no test that had everything the same but only varied the extragranular corn starch; correct?

A. Or tests with lesser amounts of the -- of the various components or greater amounts of various components in comparison.

MS. PIROZZOLO: Okay. Now, let's put up Tab 11 in your notebook, Plaintiff's Exhibit 770.

BY MS. PIROZZOLO:

Q. This is an India patent application with the number

20164104 -- 41042600; correct?

A. That's correct.

Q. And this patent application was filed in 2016; correct?

A. Can you point me toward --

Q. Sure. On --

A. -- the date.

Q. -- on the first page it says filing date, 12/14/2016.

A. All right.

Q. And Ravi Nithiyanandam Kumar is listed as an inventor; correct?

A. Yes, that's correct.

Q. Okay. And Mr. Nithiyanandam is an MSN formulation scientist; correct?

A. I'm familiar with somebody with that name who's an MSN formulation scientist and since the application -- applicant in the patent is MSN, I would believe it's the same person.

Q. Okay. And we heard from Mr. Nithiyanandam this morning; correct?

A. Yes.

Q. Okay. If you look at Page 16 of the patent application, there's a paragraph describing glidants.

Do you see that?

A. I do. Yes.

Q. The MSN patent includes a list of glidants; correct?
A. It does.
Q. But one of the glidants on the list is starch; correct?
A. Starch appears there, but that would be unmodified starch.
Q. It doesn't say unmodified starch, does it?
A. That's -- that's the typical understanding in these kinds of lists, unless...
Q. But we can agree that a patent application filed by MSN in 2016 included starch as a glidant?
A. Right. An unmodified starch is -- is identified as a glidant.
Q. Okay. Now, you testified about wet granulation as one way to improve flow; correct?
A. Yes.
Q. Okay. Glidants and wet granulation can be used together; correct?
A. Yes.
Q. Okay. Glidants can be used to improve the flow of wet granulation formulations; correct?
A. Yes. Usually after you finish the granulation procedure.
Q. So, even if wet granulation improves flow to some degree, you could use a glidant to improve flow further;

correct?

A. You could if there was a need.

Q. Okay. Now, you have testified that the granulated corn starch in MSN's ANDA product is a diluent; correct?

A. Yes, I have.

Q. Okay. A diluent is a type of excipient that is sometimes referred to as a filler; correct?

A. Yes.

Q. And they can be used to bulk up a drug mixture; correct?

A. That's correct.

Q. Excipients can have multiple functions; correct?

A. They can, yes.

Q. Okay. And as you said, you agree that a glidant is an excipient that improves flow?

A. Yes.

Q. And you also agree that a diluent can improve flow?

A. Yes.

Q. In fact, it's your opinion that diluents can improve flow properties just as glidants do; correct?

A. Well, again, both are known to be able to improve the flow properties of a powder blend.

Q. Now, in your testimony earlier you talked about the mechanisms by which an excipient may improve flow; correct?

A. By which a glidant.

Q. A glidant, I'm sorry. Yes.
A. Yes.
Q. And one of the mechanisms you mentioned was a reduction in van der Waals forces; correct?
A. Correct.
Q. And one way to reduce van der Waals forces is by physically separating particles; correct?
A. Yes. But, again, we're talking on an atomic level of separation.
Q. But increasing the space between host particles decreases van der Waals forces; correct?
A. Only if there were van der Waals forces present to decrease between those particles. So, they would have had to have been within atomic level of distances of each other to begin with.
Q. Well, granulated corn starch can act as a spacer between particles in a powder formulation; correct?
A. Granulated corn starch is another material in that -- in that mixture in a granulation. It's taking up space, yes.
Q. And so it can improve flow by acting as a spacer between particles in the formulation; correct?
A. It's -- it's acting as -- it's present as a diluent.

Diluents are spacers and so these are overlapping terms that -- in a situation with a glidant,

we're usually talking about specific particle/particle interactions right at their surfaces.

Q. Okay. But you have said granulated corn starch can act as a spacer between particles in a powder formulation; correct?

A. Again, as it's acting as a diluent. Yes.

Q. Okay. Now, you talked on your direct testimony about the size of the MSN granules.

Do you remember that?

A. Yes.

MS. PIROZZOLO: Okay. Let's take a look at -- back at Defendant's Exhibit 215, it's Tab 9 in your book, which is the pharmaceutical development report. Okay?

A. Okay. I'm there.

MS. PIROZZOLO: Could you turn to Page 81 of the pharmaceutical development report.

BY MS. PIROZZOLO:

Q. And do you see next to Number 6 there's a discussion -- there's a statement, "particle size by distribution"?

A. I'm sorry. Say that again.

Oh, yes. I see it.

Q. Okay.

A. Thanks.

Q. And the table provides particle size information on

03:08:21 the granules in MSN's ANDA product; correct?
03:08:23 A. It does, yes.
03:08:26 Q. And the way it provides this information is by the
03:08:30 amount of particles that passes through various sieves;
03:08:35 correct?
03:08:35 A. Yes.
03:08:37 Q. And it lists the sieves and the smallest one is the
03:08:41 Number 100 cumulative.
03:08:44 Do you see that?
03:08:44 A. Yes.
03:08:45 Q. Okay. And the Number 100-sieve corresponds to a
03:08:49 150 microns; correct?
03:08:51 A. That's correct.
03:08:52 Q. And below that it says, 55.612 percent.
03:08:58 Do you see that?
03:08:58 A. Right.
03:08:59 Q. Okay. So, that means 55.612 percent of the particles
03:09:05 passed through the 150-micron sieve; correct?
03:09:12 A. Correct.
03:09:14 Q. So, the table tells us that more than half the
03:09:17 mixture was smaller than 150 microns per particle; correct?
03:09:22 A. It does. It's essentially telling us almost the
03:09:26 median particle size.
03:09:27 Q. Well, it tells us that over half of MSN's particles
03:09:31 are less than 150 microns?

A. That's -- that's what the data are, yes.
Q. Okay. And more than half -- so, more than half of MSN's blend is considered fine particles; correct?
A. I think by Dr. Koleng's statements, yes, but I wouldn't agree that I would call those fines.
MS. PIROZZOLO: I have no further questions.
THE COURT: All right. Any redirect?
MR. COOPER: Very briefly.

REDIRECT EXAMINATION

BY MR. COOPER:
Q. Doctor, I just I want to make sure the record is clear about something since there was some references to a typo.
MR. COOPER: Can you pull up -- first, let's pull up DDX Koleng 2.
BY MR. COOPER:
Q. And you recall Dr. Koleng's testimony about this chart; right?
A. Yes.
Q. And you also reviewed the data from MSN's laboratory notebooks on this that's reported in the chart; right?
A. Yes.
Q. And so, this data is from two batches, the batch 23 and batch 44 batches that are reported on in MSN's laboratory notebooks; right?

03:10:48 MS. PIROZZOLO: Your Honor?
03:10:49 THE WITNESS: Correct.
03:10:50 MS. PIROZZOLO: I didn't ask about this in the
03:10:52 cross-examination.
03:10:53 MR. COOPER: Well, I'm going to clarify. I'm
03:10:54 going to go to the next question, but I'm going to clarify
03:10:57 what the typo is in Study Number 1.
03:10:59 THE COURT: All right. Well, I'm going to allow
03:11:01 it.
03:11:01 MR. COOPER: Okay.
03:11:02 Okay. So, now let's pull up DDX Donovan 10.
03:11:02 BY MR. COOPER:
03:11:11 Q. And so, now these are formulation development trials
03:11:14 that were discussed in MSN's PDR DTX-215; correct?
03:11:18 A. Correct.
03:11:19 Q. Now, the Formulation Development Trial Number 1 and
03:11:23 Formulation Development Trial Number 2 in the MSN PDR, those
03:11:27 are not the same batches that were reported in the MSN
03:11:31 laboratory notebook; right?
03:11:32 A. As indicated by the keys in the graph, they're
03:11:35 reporting on different batches.
03:11:37 Q. Okay. All right. I just want to make sure that
03:11:39 that's clear.
03:11:44 MR. COOPER: Can we pull up PTX-770? PTX-770.
03:11:44 BY MR. COOPER:

03:12:00 Q. And this is the patent application by
03:12:04 Mr. Nithiyanandam that you were shown on cross-examination.
03:12:07 Do you remember that?
03:12:08 A. Yes.
03:12:08 Q. And if we -- and counsel showed you a list of
03:12:15 potential glidants for the formulation described in this
03:12:17 patent. And in that list, starch was identified as a
03:12:21 potential glidant.
03:12:22 Do you recall that?
03:12:23 A. Yes.
03:12:23 Q. All right.
03:12:24 MR. COOPER: Let's go to Page 15.
03:12:26 I'm sorry. Page 16 of the exhibit.
03:12:31 And now, if you call out the paragraph that
03:12:35 begins diluents.
03:12:36 BY MR. COOPER:
03:12:36 Q. Do you see that paragraph?
03:12:37 A. Yes.
03:12:38 Q. And now this paragraph provides a list of diluents
03:12:42 that can be used in the formulation described in this patent
03:12:45 application; is that right?
03:12:46 A. That's correct.
03:12:47 Q. And do you see down about halfway through identified
03:12:50 there is pregelatinized starch?
03:12:52 A. Yes, I see that.

Q. And then a couple -- right next to it, it also identifies corn/maize starch.

Do you see that?

A. Yes.

Q. All right. And then also on that page, let's pull up the paragraph below that that starts "disintegrants."

And now, there's a list of potential ingredients, excipients that can be used as disintegrants in this formulation; correct?

A. That's based on this, yes.

Q. And do you see about halfway in there pregelatinized starch is identified as a potential disintegrant.

Do you see that?

A. I see that.

Q. So, does this patent application differentiate between starch and pregelatinized starch in the excipients that it identifies?

A. Yes, it does in these instances. Yes.

Q. Now, Doctor, I think we've -- you've agreed now, as Dr. Koleng did as well, that glidants are used in formulations to improve flow properties; is that right?

A. Yes.

Q. Now, is the converse automatically true? Would every excipient used in a formulation that has a positive impact on flow properties, no matter its amount, or its identity be

03:14:12 considered by a POSA to be a glidant?
03:14:14 A. No, it wouldn't.
03:14:16 MR. COOPER: No further questions.
03:14:17 THE COURT: All right. Dr. Donovan, thank you.
03:14:20 You may step down. Watch your step.
03:14:23 THE WITNESS: Thank you.
03:14:24 THE COURT: All right. Well, so let's take the
03:14:26 afternoon break until 3:30.
03:14:29 DEPUTY CLERK: All rise.
03:14:30 (Recess was taken.)
03:29:37 DEPUTY CLERK: All rise.
03:29:38 THE COURT: All right. Everyone be seated and
03:29:42 let's go on to the next thing.
03:29:44 MR. COOPER: Your Honor, we have exhibits to
03:29:46 move into evidence.
03:29:47 THE COURT: Okay.
03:29:47 MR. COOPER: DTX-505. DTX-355. DTX-231. And
03:29:54 DTX-275.
03:29:57 THE COURT: All right.
03:29:57 MS. PIROZZOLO: And, Your Honor, we would also
03:29:59 move in PTX-770.
03:30:02 THE COURT: Okay. All right. I guess they're
03:30:05 all admitted without objection.
03:30:07 MR. COOPER: No objection.
03:30:08 MS. PIROZZOLO: No objection.

(DTX Exhibit Nos. 231, 275, 355 and 505 were admitted into evidence.)

(PTX Exhibit No. 770 was admitted into evidence.)

THE COURT: All right. Let's go on.

MR. MATHAS: Good afternoon, Your Honor. Kurt Mathas on behalf of MSN. For its next witness MSN calls Dr. Salvatore Lepore.

Your Honor, may we hand up binders while Mr. -- Dr. Lepore is taking the stand?

THE COURT: All right.

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

THE WITNESS: My full name is Salvatore Lepore, S-A-L-V-A-T-O-R-E, L-E-P-O-R-E.

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

DIRECT EXAMINATION

BY MR. MATHAS:

Q. Good afternoon, Dr. Lepore.

A. Good afternoon.

Q. Can you hear me okay?

Would you like to put those on?

THE WITNESS: Your Honor, I am a little hard of

hearing.

THE COURT: That's okay.

THE WITNESS: Could you try?

BY MR. MATHAS:

Q. Yeah. Dr. Lepore, can you hear me okay?

A. Yes, mm-hmm.

Q. Dr. Lepore, have you prepared some slides to assist in explaining your testimony here today?

A. I have.

Q. All right. And we put on the slide here, the first one, DDX Lepore and then a number, and in this instance it is the Number 1. And that's how we'll proceed through those slides.

I'd like to start by talking about your education, employment and qualifications, Dr. Lepore.

MR. MATHAS: And to do that, can we please pull up DTX-522 at Page 2.

BY MR. MATHAS:

Q. Dr. Lepore, what is this?

A. This is my CV.

Q. And does it accurately reflect your employment, education and publications?

A. It does, mm-hmm.

Q. All right?

MR. MATHAS: Let's turn to DDX-2.

BY MR. MATHAS:

Q. And, Dr. Lepore, can you briefly describe for the Court your education and employment history?

A. Sure. I have a bachelor's degree in engineering and from there I went onto earn a Ph.D. in organic chemistry from Purdue University, followed by a postdoctoral fellowship at Eli Lilly and Company.

I'm currently a professor of chemistry at Florida Atlantic University.

Q. Doctor, are you a -- have you been published?

A. Yes. I've been published, co-authored textbooks -- rather co-authored book chapters and reviews. I'm also an inventor of a number of patents.

MR. MATHAS: And let's go to DDX-3.

BY MR. MATHAS:

Q. And, Dr. Lepore, can you tell the Court about some of the professional honors and awards that you have received?

A. Sure. I'm part of the National Academy of Inventors. I have been continuously funded through competitive grants by the NIH and NSF for my entire career, and I'm really proud to say I've been nominated at FAU as distinguished science teacher of the year several times in my career at FAU.

Q. Dr. Lepore, have you given testimony as an expert in the field of chemistry in any other litigations?

03:33:52 A. I have.
03:33:53 Q. Have you done so in this Court?
03:33:55 A. I have.
03:33:57 MR. MATHAS: Your Honor, defendants would
03:33:58 proffer Dr. Salvatore Lepore as an expert in the field of
03:34:01 chemistry.
03:34:03 MS. WIGMORE: No objection.
03:34:04 THE COURT: All right. You may proceed.
03:34:05 BY MR. MATHAS:
03:34:07 Q. Dr. Lepore, let's talk about the '349 patent, and to
03:34:11 do so, let's pull up JTX-4 at Page 1.
03:34:15 What do you recognize JTX-4 to be, Dr. Lepore?
03:34:18 A. Yeah, it is the '349 patent.
03:34:20 Q. And is this the patent to which your opinions will
03:34:23 relate for purposes --
03:34:23 A. Yes.
03:34:24 Q. -- of your testimony today?
03:34:24 A. Mm-hmm. Yes.
03:34:26 Q. All right.
03:34:26 MR. MATHAS: Let's go to Page 2 of this document
03:34:29 and pull up the related U.S. application data.
03:34:29 BY MR. MATHAS:
03:34:33 Q. Dr. Lepore, what do you understand Exelixis' claims
03:34:35 to be the priority date for the '349 patent?
03:34:38 A. Yes, it would be February 10th, 2011.

03:34:41 Q. And in forming your opinions in this case, is that
03:34:44 the priority date that you applied?
03:34:46 A. It was.
03:34:48 Q. All right.
03:34:49 MR. MATHAS: Can we please go to Page 20 of the
03:34:51 document and call out Claim 3?
03:34:51 BY MR. MATHAS:
03:34:55 Q. Dr. Lepore, have you reviewed asserted Claim 3 of the
03:34:58 '349 patent?
03:34:59 A. I have.
03:35:01 MR. MATHAS: Let's go to DDX-4.
03:35:01 BY MR. MATHAS:
03:35:05 Q. Dr. Lepore, what are you showing here?
03:35:06 A. So these are the various elements of the claim. The
03:35:10 ones in red will be those that I'll be talking about in my
03:35:13 testimony today.
03:35:18 Q. And so one of the elements you'll be talking about is
03:35:20 the compound that's claimed; is that right?
03:35:22 A. That's correct.
03:35:23 Q. And then the last limitation we see here, "wherein
03:35:27 the pharmaceutical composition is essentially free of what
03:35:31 we've all been calling the 1-1 impurity"; is that right?
03:35:34 A. That's correct.
03:35:35 Q. Let's talk about that for a second.
03:35:37 MR. MATHAS: Go to DDX-5, please.

BY MR. MATHAS:

Q. Dr. Lepore, what are you showing here?

A. So, this is the 1-1 impurity. This is a structure of the 1-1 impurity. It's a class of compound known as quinoline. It's a quinoline class. It's also the starting material for the synthesis of the API, and it's also a material that's known to be genotoxic.

Q. All right.

MR. MATHAS: Now, back to DDX-6, please.

BY MR. MATHAS:

Q. And the other limitation there in the last part of the claims refers to essentially free of the 1-1 impurity.

Does the patent define what essentially free is, Dr. Lepore?

A. Yes, this was the '349 patent, and it defined it as having the 1-1 impurity or other -- any impurity to be less than or equal to 200 parts per million.

Q. All right. So when we see essentially free throughout the course of the examination today, we understand that, per the definition in the specification, to be less than 200 parts per million?

A. That's correct.

Q. All right.

MR. MATHAS: With that foundation in place, let's go to DDX-7, please.

BY MR. MATHAS:

Q. Dr. Lepore, can you please provide an overview of the opinions that you will be offering today?

A. Sure. So I'm going to give a brief technical background about how one goes about looking at impurities in APIs, what it means to be mutagenic or -- or genotoxic. I'll then go on to talk about my views on how Brown is inherently -- not -- is inherently disclosing that the API is essentially free of the 1-1 impurity.

And, also, if the Court decides that they don't agree with that view, I'm also going to be talking about how it would have been obvious to obtain the API to be essentially free of the 1-1 impurity.

Q. Dr. Lepore, in forming your opinions in this case, did you consider the issues from a perspective of a person of ordinary skill in the art, or a POSA?

A. I did.

Q. And are you applying a POSA definition provided by Dr. Donovan?

A. Yes.

Q. Okay. Do you understand that Exelixis has proposed a slightly different definition of a POSA?

A. Yes.

Q. And would any of your opinions change if the Court were to adopt Exelixis' definition?

03:37:59 A. No.
03:38:02 Q. All right.
03:38:02 MR. MATHAS: Can we please go to Slide DDX-8?
03:38:02 BY MR. MATHAS:
03:38:07 Q. And let's start with your opinions on technical
03:38:09 background, Dr. Lepore. What is the technical background
03:38:11 opinion you're going to be providing?
03:38:14 A. So, I'll be talking about, again, how to monitor for
03:38:16 impurities in an API. And I'll be talking about how one
03:38:20 goes about identifying a genotoxic impurity.
03:38:23 Q. All right. So let's break that down. We've heard
03:38:26 API before, but for the record, what is API?
03:38:28 A. So it's an active pharmaceutical ingredient.
03:38:31 Q. Okay. And what are API impurity levels?
03:38:33 A. So, this would be an API, generally, and often comes
03:38:38 with other impurities present in -- as a mixture. And so,
03:38:42 levels are just -- to what degree are those impurities
03:38:45 present. We often measure those with part-per-million
03:38:48 values.
03:38:49 Q. And so, how would a POSA go about monitoring API
03:38:53 impurities?
03:38:54 A. So, there are a number of instrumental techniques.
03:38:57 One of the most common is high-performance liquid
03:39:00 chromatography, or HPLC. And that tells us which impurity
03:39:05 often and to what degree or how much of it is present.

03:39:08 Q. And was HPLC a common method for quantifying impurity
03:39:13 levels as of February of 2011?
03:39:16 A. Yes, very common and widely available.
03:39:19 Q. All right. What are genotoxic impurities,
03:39:22 Dr. Lepore?
03:39:22 A. So, these are impurities that cause damage to the --
03:39:27 our genetic material. Sometimes -- I would say oftentimes
03:39:30 it leads to carcinogenicity. And these are just items or
03:39:36 impurities that are present with the API that we want to
03:39:39 minimize.
03:39:40 Q. Did the prior art include teachings about identifying
03:39:43 and monitoring genotoxic impurities?
03:39:46 A. Indeed.
03:39:47 MR. MATHAS: Can we please pull up DTX-328?
03:39:47 BY MR. MATHAS:
03:39:52 Q. Dr. Lepore, what is DTX-328?
03:39:54 A. So, this is a perspective review article by Robinson
03:40:00 which covers the control of genotoxic impurities and API.
03:40:04 Q. All right.
03:40:04 MR. MATHAS: Let's look at the introduction on
03:40:06 Page 1, if we can call that up.
03:40:06 BY MR. MATHAS:
03:40:08 Q. Dr. Lepore, what are you -- what are you showing
03:40:10 here?
03:40:10 A. So, we're being reminded that drug designers, you

know, need to have safety in mind. And when they're considering a drug substance or an API, realize that they often contain impurities and that these impurities can often come from starting materials. And that we need to understand which ones they are and control them within tight limits.

Q. Are there regulatory guidance documents that talk about controlling API impurities within tight limits?

A. Yes, there are.

Q. And do those documents set qualifications thresholds for impurities?

A. That's correct.

Q. Okay.

MR. MATHAS: Let's look at the third paragraph on Page 1 of DTX-328.

BY MR. MATHAS:

Q. Dr. Lepore, what are you highlighting here?

A. So, this is, again, the Robinson article just telling us that impurities that are unusually toxic, like genotoxic impurities, are of increased concern when going about doing drug design.

Q. And were there prior art methods of identifying genotoxic impurities?

A. Yes.

MR. MATHAS: Let's go to the last page -- I'm

sorry, the last paragraph on the first page of Robinson.
BY MR. MATHAS:
Q. And what does Robinson say about assessing whether an impurity is genotoxic?
A. So, Robinson teaches us that the property of genotoxicity can be easily demonstrated using well-known in-vitro tests. The one that we'll be talking about today is the Ames mutagenicity test.
Q. Okay. And does Robin discuss what limits are placed on impurities that are potentially genotoxic?
A. He does summarize the regulatory landscape in this area, yes.
Q. All right.
MR. MATHAS: Let's look at the abstract, please.
BY MR. MATHAS:
Q. What does Robinson describe in the abstract?
A. So, he's telling us that recent guidelines from the U.S. and Europe require the control of genotoxic impurities, and we want to keep those in low PPM levels.
Q. All right. We'll look at some of those guidelines in a little bit, but let's go back to DDX-9, and turn and talk about your next opinion, Dr. Lepore.
Does the prior art teach cabozantinib (L)-malate API that is essentially free of the 1-1 impurity?
A. It does.

03:42:31 Q. All right.

03:42:32 MR. MATHAS: And let's pull up DTX-291.

03:42:32 BY MR. MATHAS:

03:42:38 Q. What is DTX-291?

03:42:39 A. So this is the Brown patent that we've been referring -- we'll be referring to this afternoon.

03:42:45 Q. Okay.

03:42:45 MR. MATHAS: Can we pull up the publication dates and title?

03:42:49 BY MR. MATHAS:

03:42:49 Q. When was the Brown reference published, Dr. Lepore?

03:42:52 A. So it was published on July 22nd, 2010.

03:42:56 Q. And does Brown describe how to synthesize cabozantinib (L)-malate?

03:42:59 A. It does provide those details, yes.

03:43:04 MR. MATHAS: And can we please turn to DTX-291, Page 25, example 1?

03:43:07 BY MR. MATHAS:

03:43:09 Q. What is shown in Brown example 1, Dr. Lepore?

03:43:15 A. So this is a scheme for the synthesis of the API shown in the red box in the lower right.

03:43:19 Q. And so what is it that is in -- being shown in the red box?

03:43:23 A. Yeah, so that, again, is the cabozantinib (L)-malate API that in this case.

03:43:27

03:43:28

03:43:31

03:43:35 Q. And --
03:43:35 A. And the structure for it.
03:43:36 Q. Okay. And the scheme sets forth how to get to that
03:43:40 API?
03:43:40 A. Yes. And in a stepwise fashion, reaction by
03:43:44 reaction, how to achieve an API synthetically.
03:43:47 Q. Okay. Does Brown also disclose a narrative
03:43:50 description of the process for synthesizing cabozantinib
03:43:55 (L)-malate according to Brown example 1?
03:43:56 A. It does, yes.
03:43:59 MR. MATHAS: Can we please pull up DDX-10?
03:43:59 BY MR. MATHAS:
03:44:03 Q. And what are you showing on DDX-10, Dr. Lepore?
03:44:06 A. So this is what we call a synthetic procedure, a
03:44:09 narrative description. It just shows step-by-step how one
03:44:12 goes from the starting material to the final product,
03:44:15 reaction by reaction, solvent by solvent. Everything that's
03:44:18 needed in order to make that happen.
03:44:20 Q. And in forming your opinions in this case, did you
03:44:23 analyze the synthetic process disclosed in Brown example 1?
03:44:27 A. I did.
03:44:29 MR. MATHAS: Can we please go to the next slide,
03:44:31 DDX-11?
03:44:31 BY MR. MATHAS:
03:44:34 Q. Dr. Lepore, does Brown disclose the cabozantinib

(L)-malate of Claim 3 of the '349 patent?

A. It did. That's what's being shown here. The one on the right is the Brown structure, and it's identical to the one on the left. They're both cabozantinib of (L)-malate.

Q. Okay. Does Brown disclose anything about the purity of its compounds?

A. He does.

MR. MATHAS: Let's go to paragraph 97 of Brown on Page 24.

BY MR. MATHAS:

Q. What does paragraph 97 tell us about the purity of the cabozantinib (L)-malate disclosed in Brown?

A. So, in this patent, the API is Compound I. And what is being said here is that the term "substantially pure," with regard to Compound I, could also mean about 100 percent purity.

Q. All right. So if a compound is something less than a hundred percent pure, what else is in the compound, Dr. Lepore?

A. So there could be, as is indicated here, reaction impurities, processing impurities, and so forth.

Q. Let's look at the bottom half of paragraph 94 for a minute. Does Brown explain how to test for impurities?

A. Yes. Among other methods, among other analytical techniques that are available, one could use chromatography.

And chromatography, I just mentioned, is the -- the general heading for the type of chromatography we'll be talking about here, which is HPLC.

Q. Okay.

MR. MATHAS: Let's go to DDX-12, please.

BY MR. MATHAS:

Q. And, Dr. Lepore, does Brown disclose cabozantinib (L)-malate that is essentially free of the 1-1 impurity?

A. It does.

MR. MATHAS: Let's go to DDX-13 to help organize those opinions.

BY MR. MATHAS:

Q. What's the first topic that you'll be discussing, Dr. Lepore, to show that Brown inherently discloses cabozantinib (L)-malate that is essentially free of the 1-1 impurity?

A. So, this first topic is -- I'm going to be talking about a manufacturer, Regis, who made the API. And when the Regis batches were tested, it showed that they were free of the 1-1 impurity. Essentially free of the 1-1 impurity.

Q. All right. And so who is Regis, again?

A. So Regis is a manufacturer that was retained by Exelixis to make the API for them.

Q. Okay. And how many batches of API did Regis manufacture for Exelixis?

A. Yes, they made three batches.
Q. Okay. And have you analyzed the information showing how those batches were made by Regis?
A. I did.
MR. MATHAS: Can we please pull up DTX-38?
BY MR. MATHAS:
Q. Dr. Lepore, what is DTX-38?
A. This is a regulatory document prepared by Exelixis.
MR. MATHAS: Let's go to Page 8 of this document, Section 7.2.2.1.
BY MR. MATHAS:
Q. What is being shown in this section, Dr. Lepore?
A. So, Exelixis is showing us that one of the manufacturers of the API was Regis Technologies.
Q. Okay. Now, I see you've also highlighted a lot number there. What's the significance of lot numbers?
A. So, each batch that's made by Regis gets its own lot number, and this is one of those numbers.
Q. Okay.
MR. MATHAS: Let's go to the next page, Page 9 of the document.
BY MR. MATHAS:
Q. What is disclosed here, Dr. Lepore?
A. So, here is a general synthetic scheme for how Regis went about synthesizing the API, step-by-step reaction by

reaction.
Q. And this is -- this is in the document that Exelixis submitted to the FDA; is that right?
A. That's correct.
Q. Okay. Now -- and so, in addition to this synthetic route shown here, does DTX-38 also include a narrative description of the process by which Regis synthesized its API batches?
A. Yes, they did.
MR. MATHAS: Can we go to Slide DDX-14, please?
BY MR. MATHAS:
Q. What are you showing on DDX-14, Dr. Lepore?
A. So this is that narrative description for all the steps taken in order to make the API.
Q. Okay. And so, in forming your opinions in this case, did you analyze the synthetic process set out in by which Regis manufactured its API lots?
A. I did.
Q. And did you compare the process that Regis followed in preparing its API lots with the process that is disclosed in Brown example 1?
A. I did.
Q. And what did you conclude after comparing the two?
Dr. Lepore, what did you conclude after comparing the Regis process versus the Brown Example 1

process?
A. That the two process are virtually identical.
Q. And how did you come to that conclusion?
A. So looking at each process, each procedure side by side, looking at all of the parameters, solvents, temperatures of the agents used, the two are virtually identical in every step.
MR. MATHAS: All right. Let's walk through that starting with DDX 15.
BY MR. MATHAS:
Q. What are you comparing on DDX 15, Dr. Lepore?
A. So, here I'm showing the two synthetic schemes; one for Brown on the left, one for Regis on the right. The two schemes are -- are the very same schemes.
Q. Did you identify any differences in the schemes?
Did you identify any differences in the schemes?
A. No differences, except for just some wording, naming of the individual compounds, but they're the same chemistry, same schemes. Virtually identical.
MR. MATHAS: Can we go to DDX 16, please?
BY MR. MATHAS:
Q. And this is a comparison of Step 1 of Brown Example 1 with Step 1 of the Regis process; is that right?
A. That's correct.
Q. And did you compare these two steps?

03:50:39 A. I did.
03:50:39 Q. And what did you conclude?
03:50:41 A. They're virtually verbatim, word for word. Nearly
03:50:46 verbatim, same reagents, temperature, solvents,
03:50:51 stoichiometry. They're virtually verbatim.
03:50:54 MR. MATHAS: Let's go to DDX 17, Step 2 of the
03:50:58 Brown process.
03:50:58 BY MR. MATHAS:
03:50:58 Q. Did you conclude that Step 2 of the Brown process was
03:51:01 the same as Step 2 of the Regis process?
03:51:04 A. Yes. Again, virtually verbatim.
03:51:07 MR. MATHAS: Let's go to Step 3, DDX 18.
03:51:07 BY MR. MATHAS:
03:51:11 Q. Did you conclude that Step 3 of the Regis process was
03:51:15 the same as Step 3 in Brown Example 1?
03:51:18 A. Yes. The same.
03:51:20 MR. MATHAS: Okay. Let's go to Step 4, DDX 19.
03:51:20 BY MR. MATHAS:
03:51:24 Q. Did you reach the same conclusion with respect to
03:51:27 Step 4?
03:51:27 A. They are the same, yes. Mm-hmm.
03:51:30 MR. MATHAS: Let's go to Step 5.
03:51:32 THE WITNESS: The same.
03:51:33 MR. MATHAS: Well, for the record DDX 20.
03:51:33 BY MR. MATHAS:

Q. Same conclusion with respect to Step 5?
A. They are the same.
Q. All right. Two more.
MR. MATHAS: Step 6, DDX 21.
BY MR. MATHAS:
Q. You can --
A. They're the same.
Q. They're the same?
A. Mm-hmm.
MR. MATHAS: All right. Finally, DDX 22, which is Step 7.
BY MR. MATHAS:
Q. Did you concludes that they were the same as well?
A. That's correct. They're the same.
Q. All right. So after completing your review of the process that Regis used to manufacture its API lots, what did you concludes, Dr. Lepore?
A. Regis used the same process as the Brown procedure in order to produce the API.
Q. All right.
A. Very same process.
Q. Great.
MR. MATHAS: Let's go to DDX 23, please.
BY MR. MATHAS:
Q. After you determined that, Dr. Lepore, what was what

did you look at next in your analysis?

A. So, the next question is how much of the 1-1, if any, impurity is present in these Regis batches? So here we're going to look at an analysis of all those batches.

Q. And were you able to determine whether or not the three Regis batches were essentially free of the 1-1 impurity?

A. Yes. The data shows that they were free of the 1-1 impurity, meaning that they were less than 200 PPM at the 1-1 impurity.

MR. MATHAS: All right. Let's go to DDX 24.

BY MR. MATHAS:

Q. Dr. Lepore, can you explain for the Court how it was that the Regis lots were tested?

A. So, three analytical methods were used and I'm showing here the first of the three. We were calling it the AMRI method.

MR. MATHAS: All right. Let's pull up DTX-80 to look at the test results from the AMRI method.

BY MR. MATHAS:

Q. What is DTX-80, Dr. Lepore?

A. So, this is a regulatory document prepared by Exelixis.

MR. MATHAS: Okay. Can we pull out the top of the cover page, please.

BY MR. MATHAS:

Q. What does it tell us about what is reported in this document?

A. So, this is a release testing of the batches. They're looking at purity, impurity, that sort of thing for all the batches in their report.

MR. MATHAS: Okay. Let's go to page -- sorry. Table 1 on Page 2, please.

BY MR. MATHAS:

Q. And, Dr. Lepore, you've highlighted a couple of the numbers towards the top of the table under lot numbers.

What is -- what are you showing there?

A. So those -- those at the very top are the three batch numbers for the Regis materials that were synthesized.

Q. All right. And how do you -- how do you know that those are the Regis batches?

A. So those were given in the regulatory document and assigned Regis as the manufacturer.

Q. And when were the Regis batches manufactured?

A. Two of them were in 2005, one was manufactured in 2007.

MR. MATHAS: Okay. Let's go down to the row showing the test method.

BY MR. MATHAS:

Q. And what is the test method that is shown here in

Table 1 Dr. Lepore?

A. So they're -- the three test methods turned out to be the very same ones, but they're just given slightly different names.

Q. Okay. And have you seen evidence of that in this document?

A. Yes.

MR. MATHAS: Let's go back to page -- the bottom paragraph on Page 1.

BY MR. MATHAS:

Q. And what are you showing here, Dr. Lepore?

A. Here, it's explaining that each test method, that -- there were two different numbers refer to the same method and that the changes were made for internal purposes.

Q. Okay. And we saw that the -- the AMRI test method was given an identifier of TM-1231.

MR. MATHAS: Let's look at that test method by pulling up DTX-125.

BY MR. MATHAS:

Q. What is DTX-125, Dr. Lepore?

A. This is a test method report, again, covering the method TM-1231.

Q. So this is the test methodology setting out what we're referring to as the AMRI method?

A. That's correct.

03:55:33 MR. MATHAS: Okay. Let's go back to page 11 of
03:55:35 this document, Section 12.2.
03:55:35 BY MR. MATHAS:
03:55:39 Q. What are you showing here, Dr. Lepore?
03:55:40 A. So what I'm showing is that the AMRI method reports a
03:55:44 limit of detection as being less than 0.02 percent. This is
03:55:51 also the same as 200 parts per million.
03:55:54 Q. All right. And so if a limit of detection is 0.02 or
03:55:59 200 parts per million, what does that mean as a practical
03:56:03 matter for what this test can identify?
03:56:06 A. This means the test can't see the impurity if it's
03:56:10 below 200 parts per million. Just can't see it and won't
03:56:14 detect it.
03:56:15 Q. Okay. And if it's over 200 parts per million?
03:56:18 A. Then it would -- it would show that it was detected.
03:56:21 MR. MATHAS: All right. Let's go back to
03:56:22 Table 1 in DTX-80. And we've highlighted the row here,
03:56:29 XL 184-1-1.
03:56:29 BY MR. MATHAS:
03:56:33 Q. What is being reported in that row of this table,
03:56:36 Dr. Lepore?
03:56:36 A. So, that's the -- the longer name for the 1-1
03:56:41 impurity. And for the 1-1 impurity for all three Regis
03:56:45 batches, none of that impurity was detected.
03:56:48 Q. And how do you know it was not detected?

03:56:51 A. So, the ND was defined just a moment ago as being --
03:56:57 having less than 200 PPM and so they listed ND here as not
03:57:03 detected, which means that it was not -- it had to have been
03:57:07 less than 200 PPM.
03:57:09 Q. Because if it was detected at a level greater than
03:57:12 200 PPM, it would be reported; is that right?
03:57:14 A. Exactly.
03:57:15 Q. Okay. Now in that row under the XL 184-1-1, we see
03:57:20 an RRT equals 0.26.
03:57:24 Do you see that?
03:57:24 A. Yes. So that's like a fingerprint in the HPLC
03:57:31 instrument for that compound; it's the relative retention
03:57:35 rate. And so whenever you see a peak that arises at .26 --
03:57:40 0.26, it means you have the 1-1 impurity. You know, you
03:57:44 have it when you see that particular value.
03:57:47 Q. Okay. And so based on this AMRI testing that was
03:57:50 submitted to the FDA, Dr. Lepore, what did you conclude
03:57:53 about the level of the 1-1 impurity under the AMRI method in
03:57:58 the three Regis batches?
03:57:59 A. If it was present, it had to have been less than 200
03:58:03 PPM.
03:58:03 MR. MATHAS: Okay. Let's go to DDX 25, please,
03:58:08 and talk about the second method of testing, what we've
03:58:10 called the Exelixis method. To do so, let's pull up PTX-98,
03:58:17 please.

03:58:17 BY MR. MATHAS:

03:58:19 Q. Dr. Lepore, what is PTX-98?

03:58:21 A. So, this is another method development report; this
03:58:25 one now pertains to the Exelixis method.

03:58:28 MR. MATHAS: Okay. Let's pull out the
03:58:29 background section on Page 2.

03:58:29 BY MR. MATHAS:

03:58:32 Q. What does the background section disclose?

03:58:35 A. It's telling us that Exelixis developed a new method
03:58:39 to detect impurities, including the 1-1 impurity.

03:58:47 MR. MATHAS: Okay. Can we go to Page 19,
03:58:48 please.

03:58:48 BY MR. MATHAS:

03:58:49 Q. What -- does this document identify the level of
03:58:51 detection?

03:58:52 A. Yes. This is a slightly more refined method, but
03:58:55 even here the limit of detection was 200-part per million.

03:58:59 Q. And what about the relative retention rate? Does
03:59:02 this document also identify the relative retention rate for
03:59:06 purposes of the Exelixis method?

03:59:07 A. Yes. Here in this document it also shows it's 0.26.

03:59:14 MR. MATHAS: All right. Let's go to Page 14,
03:59:16 Table 18.

03:59:16 BY MR. MATHAS:

03:59:19 Q. What are you showing here?

03:59:19 A. So, they're using the same method, but a number of
03:59:24 different analysts are using the method. And they're
03:59:27 showing that for the 1-1 impurity, they're seeing the
03:59:32 material appear at a relative retention time at between 0.25
03:59:38 and 0.27. So essentially an average of 0.26.
03:59:42 Q. All right. So, were the Regis batches tested
03:59:45 according to the Exelixis method?
03:59:47 A. They were.
03:59:49 MR. MATHAS: Let's look at Page 14 of this
03:59:51 document. And pull up the paragraph under Table 18.
03:59:51 BY MR. MATHAS:
03:59:55 Q. What does it describe?
03:59:56 A. Yeah, so this is a -- the document -- the three
04:00:01 batches were tested by two analysts, and those results were
04:00:05 shown in Table 19.
04:00:07 Q. Okay. Now, what is the significance of there being
04:00:09 two analysts to test the samples?
04:00:11 A. It should increase your confidence in the accuracy of
04:00:17 the method.
04:00:19 Q. All right.
04:00:19 MR. MATHAS: Let's go and look at Table 19 now
04:00:22 which is found on Page 15 of the document.
04:00:22 BY MR. MATHAS:
04:00:26 Q. Dr. Lepore, what does Table 19 show us about the
04:00:30 amount of the 1-1 impurity in the Regis lots as tested under

04:00:34 the Exelixis method?
04:00:36 A. Sure. So these are the three lots, as highlighted in
04:00:40 yellow, and each of those lots were tested by two different
04:00:43 analysts. And in all three tables, we don't even see the
04:00:47 1-1 impurity listed. So that's telling us that it was not
04:00:51 detected.
04:00:51 Q. And by "not detected," what did it mean under this
04:00:54 method?
04:00:54 A. So this method is telling us that if it doesn't
04:00:56 detect it, if it is present, it must be there in less than
04:01:00 200 parts per million.
04:01:01 Q. Okay.
04:01:01 MR. MATHAS: Let's look at the next page, PTX --
04:01:04 at Page 16, PTX-98.
04:01:04 BY MR. MATHAS:
04:01:07 Q. What is being shown here?
04:01:08 A. This is a -- what they're calling a bridging study
04:01:12 where Exelixis looked at their results relative to the AMRI
04:01:16 results. For example, one of the lots, the Regis lots as
04:01:20 shown there in yellow. And here, again, we see that the 1-1
04:01:25 impurity is not listed in the table and, therefore, must not
04:01:28 have been detected.
04:01:30 Q. And does the table show testing on the left-hand side
04:01:33 under the AMRI method versus testing on the right-hand side
04:01:38 under the Exelixis method?

04:01:38 A. That's correct.
04:01:39 Q. And which lot is this for?
04:01:40 A. This is for Lot P163-183-1.
04:01:46 Q. And is there a detectable amount of the 1-1 found in
04:01:49 that lot under either method?
04:01:50 A. There is -- correct. There was no detectable amount
04:01:54 found.
04:01:55 MR. MATHAS: Let's go to Table 20B.
04:01:55 BY MR. MATHAS:
04:01:57 Q. What lot is being tested in Table 20B?
04:01:59 A. So this is the second Regis lot, and this is
04:02:05 P172-27-1.
04:02:06 Q. And was it also tested and test results reported here
04:02:10 under both the AMRI and Exelixis methods?
04:02:12 A. That's correct.
04:02:13 Q. And did any of the 1-1 impurity -- was any of the 1-1
04:02:18 impurity detected in either of the -- under either of the
04:02:22 methods for Lot 172?
04:02:23 A. Exactly it was not detected.
04:02:26 Q. Okay. Let's go back to DDX-26 and turn and talk
04:02:33 about the third method under which the Regis lots were
04:02:37 tested, the GTI method.
04:02:40 MR. MATHAS: And to do that let's pull up
04:02:42 DTX-130 at Page 9.
04:02:42 BY MR. MATHAS:

04:02:44 Q. What is this showing, Dr. Lepore?
04:02:46 A. This is the GTI method, and it's the most refined of
04:02:51 the three methods. And we can see that in part because now
04:02:54 the limit of detection is down to one part per million.
04:03:00 Q. Okay. And so under this method, at what levels could
04:03:04 the test method detect the 1-1 impurity?
04:03:08 A. So, it can detect the 1-1 impurity at 1 PPM or
04:03:13 greater.
04:03:13 Q. Okay. Now, the title of this slide says "Method
04:03:16 Validation." What does it mean to validate an analytical
04:03:20 method, Dr. Lepore?
04:03:21 A. Just -- it makes sure that what they see -- they're
04:03:25 seeing, they're seeing. So that if they're spiking with the
04:03:29 actual impurity showing, that they're able to see the actual
04:03:31 impurity, measure its presence, its amount, just double,
04:03:35 triple-check together, make sure that this method is seeing
04:03:38 what it says it's seeing.
04:03:39 Q. All right. And were each of the three test methods,
04:03:42 the AMRI method, the Exelixis method, and the GTI method,
04:03:45 were they all validated methods?
04:03:47 A. They were.
04:03:48 Q. All right.
04:03:48 A. It's a very standard common approach. Analytical
04:03:52 chemists know how to do that quite well.
04:03:54 MR. MATHAS: Let's go to Page 5 of the document.

04:03:54 BY MR. MATHAS:

04:03:57 Q. And what are you highlighting here, Dr. Lepore?

04:04:00 A. So, as I mentioned, this is the most refined method, and again by Exelixis' description we're seeing that the -- it can resolve the peaks between the various impurities. They're easily seen one from each other.

04:04:15 Also, they're using -- it's kind of like two methods because now you also have two different forms of detection. One is the LCMS. The other one is the HPLC UV-1 set of data support, the other set of data.

04:04:29 Q. All right.

04:04:29 MR. MATHAS: Let's look at Page 8 of DTX-130.

04:04:29 BY MR. MATHAS:

04:04:35 Q. What is being shown on Page 8 of DTX-130, Dr. Lepore?

04:04:39 A. So, here we see the three Regis batches on the far left, and for each of those Regis batches, you're seeing for both detection methods, LCMS and for HPLC, that the 1-1 impurity is present always in less than 50 parts per million.

04:04:58 Q. And so, under the GTI method, we can see actual numbers reported of the 1-1 impurity in this table?

04:05:04 A. That's correct.

04:05:05 Q. Okay.

04:05:05 MR. MATHAS: Let's go forward now to DTX-128.

04:05:05 BY MR. MATHAS:

04:05:12 Q. What is DTX-128, Dr. Lepore?
04:05:15 A. This is a presentation -- my understanding, a
04:05:17 presentation made by Exelixis to their business partner,
04:05:22 Bristol-Myers Squib.
04:05:22 Q. And does this presentation report results of testing
04:05:26 of the Regis lots using the GTI method?
04:05:29 A. It did.
04:05:30 Q. Let's look at Slide 72, please.
04:05:32 What is being shown on Slide 72, Dr. Lepore?
04:05:37 A. So, this is the same data set we just looked at where
04:05:39 you look at the three Regis batches for both detection
04:05:43 modes. And here the 1-1 is seen always in -- as less
04:05:48 than -- as 50 parts per million in all those samples.
04:05:52 Q. So, let's go to Slide 27 and sum up on the three test
04:05:56 methods. Based on your review of the testing of the three
04:06:00 Regis lots, under the three test methods, Dr. Lepore, what
04:06:04 did you conclude about whether or not the lots manufactured
04:06:08 by Regis, according to the Brown process, were essentially
04:06:12 free of the 1-1 impurity?
04:06:14 A. So, I concluded that they are essentially -- it is
04:06:18 essentially free of the 1-1 impurity. You have three
04:06:21 methods, each one progressively better, and in every case
04:06:25 you're seeing less than 200 PPM. The GTI method is showing
04:06:29 actually that it's even less than 50 PPM.
04:06:31 Q. Okay. Let's go to DDX-28, please. Dr. Lepore, where

04:06:35 1 did you look at next in your inherency analysis?
04:06:38 2 A. So, I looked to see how much of the 1-1 impurity, if
04:06:42 3 any, were present in the capsules that were made from the
04:06:46 4 Regis batches.
04:06:47 5 MR. MATHAS: Let's pull up PTX-9, please.
04:06:47 6 BY MR. MATHAS:
04:06:50 7 Q. What is PTX-9, Dr. Lepore?
04:06:52 8 A. This is another regulatory document prepared by
04:06:57 9 Exelixis.
04:06:58 10 MR. MATHAS: And let's turn to Page 20,
04:07:01 11 Section 2.3.P.5.4.
04:07:06 12 What is this table highlighting, Dr. Lepore?
04:07:09 13 A. So, the Regis batches on the far right. Those were
04:07:15 14 lot numbers for those batches were used to make two sets of
04:07:19 15 capsules, one at the 25-milligram level and one at the
04:07:23 16 100-milligram level. Each one of those capsule lots had
04:07:28 17 their own unique number. So you see 25 milligrams, its lot
04:07:33 18 007-0002. So, what we're seeing here is a correspondence
04:07:38 19 between Regis batches and lot -- lots of capsules being
04:07:43 20 produced.
04:07:43 21 Q. So the Regis batches that we just looked at are in
04:07:46 22 the fourth column; is that right?
04:07:47 23 A. That's correct.
04:07:48 24 Q. And the capsule lot numbers are shown in the first
04:07:52 25 column; is that right?

04:07:53 A. That's correct.
04:07:54 Q. Okay. Let's go to Page 22 and look at the
04:07:58 25-milligram capsules. What's being reported here with
04:08:02 respect to the 1-1 impurity?
04:08:04 A. So, at the very top, those again are the capsule lot
04:08:08 numbers. And for each capsule lot number, again all those
04:08:12 capsules were made using Regis material. We see that the
04:08:17 1-1 impurity, if it's present, it's less than -- it's not
04:08:23 detected. As we'll see in a moment, that means less than
04:08:27 200 parts per million.
04:08:28 Q. First, let's go to Page 23 and look at the hundred
04:08:31 milligram capsules. What do they show with respect to the
04:08:35 three Regis capsule lots?
04:08:38 A. So here we're seeing that -- again, lot numbers for
04:08:41 the 100-milligram capsules. And for all those lot numbers,
04:08:45 we see that it -- the 1-1 impurity was not detected in all
04:08:51 of those capsule lots.
04:08:53 Q. All right. You mentioned the level of detection a
04:08:55 moment ago.
04:08:56 MR. MATHAS: Let's go to Page 19.
04:08:56 BY MR. MATHAS:
04:08:58 Q. What does it tell us about its the level of detection
04:09:01 for this testing?
04:09:02 A. Yeah. So here we see that for that particular -- all
04:09:07 those tests we just looked at, the limit of detection was

less than 200 parts per million.

Q. All right. And does this document also identify the test methodology used to generate the data?

A. Yes.

MR. MATHAS: Let's go to Page 14.

BY MR. MATHAS:

Q. What is the test methodology that's --

THE COURT: Mr. Mathas, hold on.

DEPUTY CLERK: Your microphone -- we're getting some feedback. I don't know if you could maybe push it back a little bit.

THE WITNESS: Like that?

DEPUTY CLERK: So sorry.

THE WITNESS: Better.

DEPUTY CLERK: Sorry.

THE WITNESS: No problem.

The question again?

BY MR. MATHAS:

Q. I'll ask it again.

All right. Dr. Lepore, what is the test methodology under which these samples were tested?

A. So, this is an HPLC method, and the HPLC method number is QM 3950.

MR. MATHAS: Let's look at that test methodology, DTX-69, please.

04:10:05 BY MR. MATHAS:
04:10:09 Q. What is DTX-69?
04:10:10 A. So this is a document that describes the test method.
04:10:16 Q. And if we can go to Page 5, Table 2. What is that
04:10:20 identifying?
04:10:21 A. So, it's telling us that in this method as well, the
04:10:25 relative retention time is 0.26 for the 1-1 impurity.
04:10:31 Q. And so did that confirm your understanding that the
04:10:34 three Regis capsule lots had less than 200 PPM of the 1-1
04:10:38 impurity?
04:10:39 A. That's correct.
04:10:40 Q. And have you seen any other data reporting 1-1 levels
04:10:45 for the Regis capsules?
04:10:46 A. Yes, I have.
04:10:47 MR. MATHAS: Let's pull up the PTX-68, please.
04:10:47 BY MR. MATHAS:
04:10:51 Q. What is PTX-68?
04:10:53 A. So, this is Exelixis -- it's another regulatory
04:10:56 document that Exelixis prepared for a European agency.
04:11:02 MR. MATHAS: Let's turn to Table 38 on Page 86.
04:11:02 BY MR. MATHAS:
04:11:05 Q. What are you showing here, Dr. Lepore?
04:11:06 A. So, here I'm showing the capsule lot numbers at the
04:11:11 top of the table for the 25-milligram and the 100-milligram
04:11:14 batches. The ones highlighted in yellow were capsules that

were made using the Regis material.

Q. And what does this document disclose about those batches?

A. So, what it concluded is that if you look at the relative retention time, 0.26, that's the 1-1 impurity, that impurity was not detected in all four of those capsule lots.

Q. All right.

MR. MATHAS: Let's go to DDX-28.

BY MR. MATHAS:

Q. And talk about the last piece of this part of your analysis.

Dr. Lepore, what was the final step that you looked at in determining inherency?

A. So, I looked at the material prepared by Girindus and asked myself the question: Is this one that also had the 1-1 impurity of less than 200 parts per million?

Q. Okay. Let's start with, who is Girindus?

A. So Girindus is another manufacturer retained by Exelixis to make the API.

Q. And how many lots of API did Girindus make?

A. They made one lot.

Q. Okay.

MR. MATHAS: Let's go back to DTX-80, Page 2, Table 1, which we looked at earlier.

BY MR. MATHAS:

04:12:33 Q. And you've highlighted something in red here. What
04:12:35 is being highlighted?
04:12:36 A. Here, we see that the Girindus lot, which is
04:12:40 highlighted in red, has an entry for the 1-1 impurity that
04:12:44 is 0.06 percent or 600 parts per million.
04:12:50 Q. All right. And so, was the Regis -- I'm sorry, was
04:12:53 the Girindus batch essentially free of the 1-1 impurity,
04:12:57 according to this testing?
04:12:58 A. It was not.
04:12:59 Q. All right. And what is your understanding of the
04:13:01 relevance of the Girindus batch for purposes of your
04:13:04 opinions?
04:13:05 A. So, the -- if the Girindus batch was prepared using a
04:13:10 method other than the Brown procedure, then it -- it
04:13:17 wouldn't be violating the inherency issue that we're talking
04:13:25 about in this case. It's using a different set of
04:13:27 procedures or different procedure leading to a result that
04:13:30 gave an impurity at the 600 PPM level. It wouldn't be
04:13:35 inconsistent with the inherency argument.
04:13:39 Q. Got it. Have you analyzed the process that Girindus
04:13:41 used in order to manufacture its lot of cabozantinib of
04:13:45 (L)-malate?
04:13:45 A. I did.
04:13:46 Q. All right. And did Girindus use the same process as
04:13:50 is disclosed in Brown example 1?

04:13:52 A. They did not.
04:13:54 Q. All right.
04:13:55 MR. MATHAS: Let's look at DTX-62, please.
04:13:55 BY MR. MATHAS:
04:13:58 Q. What is DTX-62, Dr. Lepore?
04:14:01 A. This is the explanation on the part of Girindus for
04:14:05 how they made their API. They gave the experimental data,
04:14:09 experimental procedures, and other details for how they did
04:14:13 it.
04:14:14 MR. MATHAS: Let's look at the summary on the
04:14:16 cover page.
04:14:16 BY MR. MATHAS:
04:14:16 Q. What's being shown here, Dr. Lepore?
04:14:18 A. So, Girindus policy, the API in this case, the
04:14:22 cabozantinib (L)-malate EL S1182. And this is just a
04:14:26 campaign for their approach to manufacturing that material.
04:14:30 All the details of how they made that material.
04:14:34 Q. And so does this document report the detailed
04:14:38 description of the process used by Girindus to manufacture
04:14:42 cabozantinib?
04:14:42 A. It does.
04:14:44 Q. All right. And did you identify any places where
04:14:47 Girindus deviated from the Brown example 1 process?
04:14:50 A. I did.
04:14:52 MR. MATHAS: Let's go to DDX-30, please.

BY MR. MATHAS:

Q. What are you showing on DDX-30, Dr. Lepore?

A. So, I identified a number of deviations, but these are the ones that Girindus themselves labeled as being deviations, as well as errors.

Q. All right. And so what is a deviation in this context?

A. Well, among other things, it's when you alter the synthetic procedure, you add other steps. You do some major changes that fundamentally change the procedure.

Q. Does the fact that they are planned deviations make any difference?

A. No, they're still deviations.

Q. Okay. Dr. Lepore, let's look at some of the Girindus deviations from the Brown process.

MR. MATHAS: And to do so, let's pull up, side-by-side, DTX-291 at 26 and DTX-62 at 7.

BY MR. MATHAS:

Q. What are you showing here, Dr. Lepore?

A. So this is the first step in the synthesis of the API. And Brown is telling us that at the end of the first step, that they're adding a solvent known as methyl tert-butyl ether, MTBE. And this leads to a -- at cooler temperatures, it leads to a crystallization of the API.

The Girindus procedure on the right doesn't cool

04:16:11 the solvent down, doesn't add that particular MTBE and
04:16:15 doesn't use crystallization. Instead, they get a
04:16:17 precipitated product.
04:16:18 Q. And when you say it "crystallized out," what does it
04:16:21 mean that it crystallized?
04:16:22 A. Well, so as we'll talk about in a moment,
04:16:26 crystallization is a very common and useful method in
04:16:28 organic chemistry to purify organic compounds. It's a
04:16:30 purification procedure.
04:16:32 If you don't crystallization in this context,
04:16:34 you're not really purifying.
04:16:36 MR. MATHAS: Let's take a look at another
04:16:37 Girindus deviation. Pull up Page 14, Section 4.4.2.
04:16:37 BY MR. MATHAS:
04:16:44 Q. Dr. Lepore, can you please explain what's going on
04:16:47 here in Step 3?
04:16:47 A. Sure. So, this is step number 3. And Girindus --
04:16:52 and in this step it was required that you had to filter the
04:16:55 reactor -- reactor contents. And when you filter, you
04:16:59 produce these filter cakes.
04:17:00 And so, what Girindus did was took this filter
04:17:04 cake, dissolved it up or suspended it in water. Acidified
04:17:09 it. And then they let it stand over the weekend.
04:17:13 Presumably for like 72 hours.
04:17:15 Now, none of these steps were present in the

Brown process.

Q. And what is a filter cake?

A. So a filter cake is just what comes as a result of trying to filter something. The material passes through the filter and what's left is some usually a solid material. And they took this solid material -- again, none of this is in the Brown process -- they suspended it in water and went on and did this new chemistry.

Q. All right. Let's take a look at the next paragraph and tell the Court what happened next with the Girindus process.

A. So this resulted in a whole new compound. And they gave it an RRT value of 1.26. It was produced and in a great amount. And they don't even know exactly what this compound is, but they think it's this thing called an aminal. They never actually fully characterized it.

MR. MATHAS: If we can go to DDX-31.

BY MR. MATHAS:

Q. Dr. Lepore, what are you showing on DDX-31?

A. So, this is a deviation, pure and simple. You're adding a whole other step leading to an -- a new intermediate -- a new compound is being produced and that's what I'm trying to show here.

Instead of going from 1.3 -- 1-3 to 1-4, they went from 1-3 to something else that they're calling the

aminal.

Q. And so what did Girindus have to do next?

A. So, according to their rationale, they felt that if they further treated the aminal with another procedure, that it would produce 1-4. And indeed it did that.

Q. Okay.

A. And we can see that on the...

Q. Sure.

MR. MATHAS: Let's go to Page 15. 4. -- 4.4.3.

BY MR. MATHAS:

Q. Dr. Lepore, explain what Girindus is doing here in this deviation.

A. So, here they took this intermediate aminal. They again suspended it in water. They acidified it with hydrochloric acid, which is, you know, a very powerful acid. And they boiled the water for two hours, added more hydrochloric acid, and again boiled the water for two hours before they completed the -- what we call the workup step.

Q. And is that process described in Brown?

A. So, this is not described in Brown.

MR. MATHAS: Let's go to DDX-32.

BY MR. MATHAS:

Q. What are you showing here, Dr. Lepore?

A. This is like a schematic representation of what Girindus did. They formed an aminal by a new step that's

not present in Brown. The aminal itself is not present in Brown. And then they converted the aminal to the 1-4 product using conditions that were not present in Brown.

Q. Dr. Lepore, based on your review of the information about the Girindus process, what did you conclude about whether Girindus followed the Brown example 1 process in making its lot of cabozantinib API?

A. I have concluded that they did not follow the process.

Q. Dr. Lepore, based on all of the evidence that you reviewed, what did you ultimately conclude about whether Brown example 1 -- the Brown example 1 process inherently results in cabozantinib (L)-malate that is essentially free of the 1-1 impurity?

A. My conclusion is that if you follow the Brown process, as Regis did, you're going to always produce the API that's less than 200 PPM, containing of the 1-1 impurity.

Q. All right.

MR. MATHAS: Let's go to DDX-33 and switch gears for a minute.

BY MR. MATHAS:

Q. We've just walked through your opinions on inherency. But, alternatively, Dr. Lepore, if Brown example 1 produced API that was not essentially free of the 1-1 impurity, would

it nonetheless still have been obvious to obtain cabozantinib (L)-malate that is essentially free of the 1-1 impurity?

A. Yes, it would have been obvious.

Q. All right.

MR. MATHAS: Let's go to DDX-36.

BY MR. MATHAS:

Q. And, Dr. Lepore, what are you showing here?

A. So, the 1-1 impurity is an impurity, but it's also the starting material for the synthesis. And a POSA would have known or would have been able to easily and quickly determine that that 1-1 starting material was genotoxic.

Q. Okay.

MR. MATHAS: Let's go back to Brown example 1, DTX-291 at 25.

BY MR. MATHAS:

Q. And you've put a red box in the upper left-hand corner. What are you showing there, Dr. Lepore?

A. I'm showing here that at the very starting point for the synthesis of the API is the 1-1 impurity or the 1-1 -- in this case, the 1-1 starting material.

Q. And what is the significance of the fact that the 1-1 compound is a starting material?

A. So, in doing synthesis, starting materials can often be carried forward in the synthesis and end up in the final

product, especially at very low values such as the PPM level.

Q. Are there any regulatory guidances that discuss starting material impurities?

A. Yes, there are.

MR. MATHAS: Let's go to DTX-91.

BY MR. MATHAS:

Q. What is DTX-91, Dr. Lepore?

A. So, this is an FDA document providing guidance on how to deal with genotoxic impurities.

Q. And is this one of the FDA guidances that was referenced in the Robinson article that we talked about earlier?

A. That's correct.

MR. MATHAS: Let's pull up the introduction on Page 4.

BY MR. MATHAS:

Q. What does the introduction tell us about this guidance?

A. So, this is to give us some direction, drug designers direction on current thinking on dealing with genotoxic impurities. This is also providing thresholds, you know, goals for how to -- how much to minimize those impurities in the final product.

Q. All right.

04:23:12 MR. MATHAS: Let's go to the next paragraph on Page 4.

BY MR. MATHAS:

Q. What does this paragraph tell us?

A. So this guidance, it tells us, not surprisingly, that one needs to, you know, look at known starting materials and consider their genotoxicity in the design of a drug.

Q. All right.

MR. MATHAS: Let's go forward to the background section of the document on Pages 5 and 6.

BY MR. MATHAS:

Q. What does the background section tell us about genotoxic impurities?

A. So, this is, again, guidance on genotoxic impurities. And what we're being told here is that exposure to even low levels may be of significant concern. And so manufacturers have tried as much as technically feasible to reduce these genotoxic materials in the API.

Q. Would a POSA have been motivated to identify potential genotoxic impurities?

A. Certainly.

Q. And how would a -- would a POSA have known how to go about identifying potential genotoxicities?

A. Yeah. Yes.

Q. And does this document provide guidance to

manufacturers about that?

A. Yes.

MR. MATHAS: Let's go to Section 3 on Page 9.

BY MR. MATHAS:

Q. Dr. Lepore, what does Section 3 tell us about the recommended approaches for assessing genotoxic impurities?

A. So, it starts off by telling the drug designer, or a lot of them being organic chemists, that you need to look at the structure of the impurity, and a lot of times that very structure will provide an alert.

And then from there, it's -- you review the literature to see what does it teach about that class of compounds. And then from there, one goes on and does very readily accessible assays, in-vitro assays, you know, such as the Ames test.

Q. If a POSA in February 2011 had evaluated the 1-1 starting material for genotoxic impurity, what would the POSA have determined?

A. A POSA would have noted that it -- number one, it was a quinoline class of compounds.

Q. All right. And did the prior art disclose anything about the genotoxicity of quinolines?

A. Yes.

MR. MATHAS: Let's go to DTX-272.

BY MR. MATHAS:

04:25:23 Q. What is DTX-272, Dr. Lepore?
04:25:25 A. This is an EPA document providing, you know,
04:25:30 toxicological information about quinoline, the molecule
04:25:33 itself.
04:25:34 MR. MATHAS: Okay. Let's go to Page 30, please.
04:25:34 BY MR. MATHAS:
04:25:36 Q. What did FDA concludes in its toxicological review?
04:25:40 A. Well, the conclusion was that it's genotoxic.
04:25:45 Q. Okay. And would a POSA have considered the toxicity
04:25:47 of quinoline when assessing the toxicity of the 1-1 starting
04:25:51 material?
04:25:51 A. Sure. The 1-1 starting material was a quinoline and
04:25:55 certainly this would have set off a red flag.
04:25:58 Q. Did the prior art disclose information about the
04:26:00 toxicity of any quinoline derivatives?
04:26:03 A. Yes.
04:26:04 MR. MATHAS: Let's go to DTX-313.
04:26:04 BY MR. MATHAS:
04:26:07 Q. What is DTX-313, Dr. Lepore?
04:26:09 A. So this is a document -- this is a paper by Nagao
04:26:13 that looked at quinoline and the analogs of quinoline or
04:26:16 derivatives of quinoline as regards genotoxicity or
04:26:21 mutagenicity, which is a fairly similar term.
04:26:24 MR. MATHAS: Can we pull up the summary.
04:26:25 BY MR. MATHAS:

04:26:25 Q. What does Nagao say in the summary?
04:26:28 A. So, he confirms the -- the results of the -- of the
04:26:32 EPA study saying the quinoline is carcinogenic and
04:26:38 mutagenic.
04:26:39 Additionally, he looks at the mutagenicities of
04:26:42 quinoline analogs or quinoline derivatives and found that of
04:26:46 the 17 compounds that he tested, 12 of them turned out to be
04:26:51 mutagenic.
04:26:51 Q. Under what test?
04:26:52 A. Using an Ames test.
04:26:56 Q. And the Ames test was referenced in the FDA guidance
04:26:59 we looked at a moment ago?
04:27:00 A. That's correct.
04:27:01 MR. MATHAS: Okay. So let's look at the table
04:27:04 on Page 4 of these 17 compounds.
04:27:04 BY MR. MATHAS:
04:27:08 Q. What are you showing here?
04:27:09 A. So, here are the structure of the 17 compounds that
04:27:13 Nagao looked at and what we're seeing here is that, again,
04:27:17 those that were mutagenic had a plus symbol under the
04:27:23 mutagenic column.
04:27:25 Just calling our attention now to the one in --
04:27:27 highlighted in yellow because that one has the OH group, the
04:27:33 hydroxyl group, in the same position that one would find it
04:27:36 in its 1-1 impurity. And that compound, entry 14 -- or

04:27:42 entry 14 is hard to see from here.
04:27:44 Q. I think it's 13 --
04:27:45 A. Entry 13?
04:27:46 Q. -- is also mutagenic.
04:27:49 All right. Dr. Lepore, in light of the
04:27:52 teachings in the prior art, what would the POSA have done
04:27:55 with respect to the 1-1 starting material?
04:27:57 A. So, a POSA would have -- again, it would have been a
04:28:02 red flag that this is a mutagenic material, a genotoxic
04:28:07 material, and one now has to control for it in the sense of
04:28:11 the API.
04:28:12 Q. Would a POSA have run an Ames test?
04:28:14 A. A POSA would certainly have done this -- you know,
04:28:17 following Nagao's example would have done an Ames test.
04:28:20 Q. And what would a POSA have found in an Ames test?
04:28:22 A. They would have found it was genotoxic.
04:28:25 Q. Now, once the POSA determined that the 1-1 starting
04:28:28 material is genotoxic, what would the POSA do with that
04:28:33 information?
04:28:33 A. So genotoxicity, it's -- it's, you know, among one of
04:28:36 the worst toxicities, so there's guidance on how to control
04:28:40 for it and to keep it as low a level as possible. So POSA
04:28:43 would have looked for this guidance -- regulatory guidance.
04:28:46 MR. MATHAS: All right. Let's go to back to
04:28:48 DTX-91, the FDA guidance on genotoxicities, Pages 13 and 14,

Table 1.

BY MR. MATHAS:

Q. What did the FDA guidance teach about the levels of potential genotoxic materials?

A. So, the FDA is telling us that if there's a genotoxic impurity in the API given to patients during the clinical trial, there are acceptable daily limits depending on the exposure time that the patient will undergo.

Q. All right. Dr. Lepore, I see on this slide that it's reporting levels at micrograms per day. We've been talking so far about parts per million. How do micrograms per day and parts per million equate, if at all?

A. So it's a straightforward calculation. You can go from micrograms per day to parts per million. And in this case it's usually under 50 PPM, depending on the size of the compound involved. But it's under 50 PPM for -- starting off with 100-milligram dose and for a 12-month trial, you're going to want to keep the genotoxic material PPM level down to below 50 PPM.

MR. MATHAS: All right. Let's go to Slide DDX 35.

BY MR. MATHAS:

Q. So, Dr. Lepore, what would the POSA have done if he or she determined that cabozantinib (L)-malate API from Brown Example 1 was not essentially free of the 1-1 impurity

04:30:22 in light of these genotoxicity concerns?
04:30:25 A. Sure. So the API had too much of the 1-1 impurity
04:30:29 above 200 PMM. The first thing organic chemists do with
04:30:32 solid material in order to purify them, the first thing they
04:30:35 think to do is to re-crystalize them.
04:30:38 Q. Okay. Was re-crystallization taught in the prior
04:30:40 art?
04:30:40 A. Yes. This is a ubiquitous technique and certainly
04:30:44 was taught in the prior art.
04:30:45 MR. MATHAS: Can we pull up DTX-251, please.
04:30:48 BY MR. MATHAS:
04:30:48 Q. What is DTX-251?
04:30:50 A. So, I selected this because this is a sophomore
04:30:55 organic textbook that we use to train students on organic
04:30:59 laboratory techniques, and in this textbook is covers
04:31:03 crystallization.
04:31:04 MR. MATHAS: Can we go to Page 4 of the
04:31:06 document, please. DTX-251.4.
04:31:06 BY MR. MATHAS:
04:31:10 Q. What is -- what is being shown in this Fieser
04:31:15 reference?
04:31:15 A. So, in this chapter, Chapter 7, you know, Fieser, you
04:31:20 know, the author of this textbook, is just telling us that
04:31:23 crystallization is a highly effective method for purifying a
04:31:26 solid substance.

04:31:28 Q. Are there any FDA guidances teaching crystallization as a purification technique?

04:31:32 A. Yes.

04:31:34 MR. MATHAS: Please pull up DTX-91 at Page 14. Again, this is the genotoxic FDA guidance.

04:31:38 BY MR. MATHAS:

04:31:43 Q. What's it showing on Page 14?

04:31:45 A. So, this -- this guidance document is telling us that if you have genotoxic impurities present in your API, one way to deal with it is to change the purification route and a purification route would be, for example, to include re-crystallization and that's a great way to maximize the removal of the relevant impurity in this case, the 1-1 impurity.

04:32:08 MR. MATHAS: Okay. Let's take a look at a different FDA guidance, DTX-304.

04:32:10 BY MR. MATHAS:

04:32:13 Q. What is this, Dr. Lepore?

04:32:15 A. This is another FDA guidance document.

04:32:20 MR. MATHAS: And let's go to Section B on Page 43.

04:32:22 BY MR. MATHAS:

04:32:25 Q. What does this FDA guidance tell the POSA about recrystallization?

04:32:30 A. It's teaching us that intermediates and final product

04:32:36 APIs that sometimes have too much of an impurity, can be
04:32:42 reprocessed using crystallization. Again, it's a ubiquitous
04:32:46 technique that is well-known in the industry.
04:32:48 Q. Dr. Lepore, would a POSA as of February 2011 have
04:32:53 been aware of any examples where crystallization was used to
04:32:58 purge a genotoxic impurity at low PPM levels?
04:33:02 A. Indeed.
04:33:03 MR. MATHAS: Let's go back to Robinson one last
04:33:05 time, DTX-328 at Page 9.
04:33:05 BY MR. MATHAS:
04:33:09 Q. Dr. Lepore, what is Robinson explaining here?
04:33:12 A. So the literature abounds with examples. This is
04:33:15 just one example from Robinson that teaches us that in one
04:33:19 case that he highlights here is you had an API, he didn't
04:33:23 disclose the structure of it, that contained 11 to 12 parts
04:33:27 per million of an impurity, which they considered to be too
04:33:30 much in their case, and so they -- they recrystallized the
04:33:35 batch and in doing so it led to an API product that had the
04:33:39 impurity present in less than one part per million.
04:33:43 So, here's an example of using recrystallization
04:33:46 or crystallization to solve an impurity problem.
04:33:50 Q. Dr. Lepore, in your opinion, would a person of
04:33:52 ordinary skill in the art have reasonably expected to be
04:33:56 able to purify cabozantinib (L)-malate to be essentially
04:34:00 free of the 1-1 impurity using recrystallization techniques?

A. Yes, this is a very common, well-known, and often very successful technique. Yes, a POSA would have a reasonable expectation that it would have worked.

MR. MATHAS: Thank you, Your Honor. I have no further questions. I'll pass the witness.

THE COURT: Okay. Thank you.

MS. WIGMORE: Your Honor, may we pass up our exhibit binders?

THE COURT: All right. Yes.

MS. WIGMORE: Thank you.

May I proceed, Your Honor?

THE COURT: Sure. Yes.

CROSS-EXAMINATION

BY MS. WIGMORE:

Q. Good afternoon, Dr. Lepore. We have not formally met, but I'm Amy Wigmore and it's nice to meet you.

A. Nice to meet you.

Q. Please let me know if I need to speak up. I'll try to speak right into the microphone.

A. That's perfect. Thank you.

Q. Now, let's begin with the scope of the opinions you're offering here today.

The opinions that you are offering relate solely to the '349 patent; correct?

A. That's correct.

04:35:26 Q. Now, you understand Exelixis is asserting three other
04:35:30 patents against MSN in this case; correct?
04:35:33 A. Correct.
04:35:34 Q. And those three patents have been referred to as the
04:35:38 crystalline malate salt patents.
04:35:41 Do you recall that?
04:35:41 A. Yes.
04:35:43 Q. Now, you provided two expert reports in this case;
04:35:47 correct?
04:35:47 A. Correct.
04:35:48 Q. You provided an opening report and a reply report;
04:35:52 correct?
04:35:52 A. That's correct.
04:35:54 Q. In both of those reports, you did provide opinions
04:35:57 relating to the crystalline malate salt patents; correct?
04:36:00 A. That's correct.
04:36:01 Q. But you are not offering those opinions here today;
04:36:03 correct?
04:36:04 A. That's correct.
04:36:06 Q. So, let's focus on what you are offering an opinion
04:36:09 about. Now, you reviewed the '349 patent; correct?
04:36:12 A. Correct.
04:36:14 Q. And you understand that Claim 3 is the asserted claim
04:36:17 of the '349 patent; correct?
04:36:21 A. Yes.

04:36:21 Q. And if we could please pull up the '349 patent, which
04:36:24 is JTX-4 and turn to Claim 3?
04:36:30 A. If you --
04:36:31 Q. -- in Column 34?
04:36:34 A. Would you come a little bit closer to the microphone.
04:36:36 Q. Sure. Do you see Claim 3 of '349 patent?
04:36:39 A. Yes.
04:36:39 Q. Now, the first line refers to a pharmaceutical
04:36:44 composition comprising Compound IB; correct?
04:36:47 A. Yes.
04:36:48 Q. And you testified that Compound IB is cabozantinib of
04:36:51 (L)-malate; correct?
04:36:52 A. Correct.
04:36:54 Q. And the final limitation requires the pharmaceutical
04:36:57 composition to be essentially free of the 1-1 impurity as
04:37:02 we've been calling it; correct?
04:37:03 A. Correct.
04:37:06 Q. Now, you testified the term "essentially free" means
04:37:11 200 parts per million or less; correct?
04:37:13 A. Correct.
04:37:15 Q. And your analysis of the '349 patent focused on
04:37:20 whether the cabozantinib (L)-malate API is essentially free
04:37:25 of the 1-1 impurity; correct?
04:37:27 A. Correct.
04:37:30 Q. API refers to the active pharmaceutical ingredient;

04:37:34 correct?
04:37:34 A. I believe I also testified that the capsules were
04:37:40 free of the 1-1 impurity. Both.
04:37:44 Q. Why don't we take them one by one. You gave an
04:37:46 opinion about API; correct?
04:37:48 A. Yes.
04:37:48 Q. And in your opinions, you focused on the API
04:37:52 impurity; correct?
04:37:53 A. That's correct.
04:37:55 Q. Now, you're not offering an ultimate opinion on the
04:37:59 validity of Claim 3 of the '349 patent; correct?
04:38:03 A. That's correct.
04:38:04 Q. You're not offering any opinion on infringement;
04:38:07 correct?
04:38:07 A. That's correct.
04:38:09 Q. And you're not offering any opinion on the various
04:38:14 excipients that are listed in Claim 3 of the '349 patent;
04:38:19 correct?
04:38:19 A. Correct.
04:38:21 Q. You're not providing an expert opinion on any
04:38:23 formulation issues; correct?
04:38:24 A. That's correct.
04:38:27 Q. And your analysis was directed to the API and not the
04:38:30 excipients; correct?
04:38:32 A. Correct.

04:38:42 Q. You understand that the Court views the patent from
04:38:44 the perspective of a person of ordinary skill in the art or
04:38:47 a POSA; correct?
04:38:49 A. Yes.
04:38:49 Q. And you testified that you're relying on the
04:38:52 definition of a POSA provided by Dr. Donovan; correct?
04:38:56 A. Correct.
04:38:57 Q. If we could please have Slide PDX 2.5. This is
04:39:04 Dr. Donovan's definition of a person of ordinary skill in
04:39:07 the art for the '349 patent; correct?
04:39:09 A. Yes.
04:39:12 Q. Now, I just want to break the definition down to just
04:39:15 so we can see where you fit in here. So, if we focus on the
04:39:19 first sentence, it says, "A POSA with respect to the '349
04:39:24 patent would have had, at the time of the claimed invention,
04:39:26 a Ph.D. in pharmacy, chemistry, or a related field with at
04:39:31 least three years of postgraduate laboratory, industrial
04:39:36 experience in, for example, the research and development of
04:39:39 formulations for the preparation of drug substances."
04:39:43 Do you see that?
04:39:43 A. I see that, yes.
04:39:45 Q. Now, in terms of this definition, you don't fit
04:39:47 within that particular sentence; correct?
04:39:49 A. Well, I have a Ph.D. in chemistry and --
04:39:52 Q. You do not have -- I'm sorry. Go ahead.

A. -- working with colleagues who have done formulations.

Q. You do not personally have three years of personal experience in research and development of the formulations for the preparation of drug substances; correct?

A. Correct.

Q. You are not a formulator; correct?

A. That's correct.

Q. And you yourself have never designed a pharmaceutical formulation; correct?

A. That's correct.

Q. Now, you would not consider yourself an expert in controlling drug impurities in formulated drug products; correct?

A. I think that's correct.

Q. So let's look at the next sentence of Dr. Donovan's definition. She states that "a POSA may have an education level lower than a doctoral degree if he or she has commensurately more relevant work experience."

Do you see that?

A. Yes.

Q. And you testified you don't have work experience in research and developing drug formulations personally; correct?

A. Correct.

Q. Now, the next sentence of Dr. Donovan's definition says, "A POSA's experience would include, among other things, formulating drug substances in appropriate dosage forms and analyzing/evaluating such drug formulations for compatibility, stability, dissolution, and drug release properties. "

Do you see that?

A. Correct.

Q. You do not have those qualifications; correct?

A. That is correct.

Q. So if we look at the last sentence of Dr. Donovan's POSA definition, you do have experience in synthesizing and analyzing complex small molecule compounds; correct?

A. That's correct.

Q. And under Dr. Donovan's definition, you would be someone a POSA may have collaborated with; correct?

A. I probably use slightly stronger language that would likely have collaborated with, but, yes, I think I agree with that as well.

Q. And her definition in the last sentence says, "A POSA may have collaborated with others of skill in the art, including those with experience in synthesizing and analyzing complex small molecule compounds."

Do you see that?

A. And impurities or degradation products also

experience that.

Q. Yes. And that's where you fit in this definition; correct?

A. Correct.

Q. Now, let's start with your opinions concerning API.

You offered the opinion that a POSA would have been motivated and found it obvious to prepare cabozantinib (L)-malate salt API that is essentially free of the 1-1 impurity using the Brown synthesis process; is that right?

A. Correct.

Q. So, let's take that in pieces starting with Brown. If we could have DTX-291 which you discussed during your direct examination. Is this the Brown reference?

A. Yes.

Q. And do you see it has an international patent publication number WO 2010/083414 A1.

A. Yes.

Q. This is its Brown reference on which you rely in support of your opinion; correct?

A. Correct.

Q. And are you familiar with -- if we pull up JTX-9, this is U.S. Patent Number 8,877,776. Do you see that?

A. Yes.

Q. And can we refer to this as the '776 patent?

A. Yes.

04:43:30 Q. And you agree that the Brown reference that you
04:43:33 relied on today, that WO 414 publication has the same
04:43:39 specification as this '776 patent; correct?
04:43:44 A. I seem to recall that, but I'd have to determine that
04:43:47 remind myself.
04:43:48 Q. And have you referred in the course of your work on
04:43:51 this case to the '776 patent as Brown?
04:43:55 A. Okay. I seem to recall that, yes.
04:44:01 Q. Now, during prosecution of the '349 patent, the
04:44:05 examiner considered the '776 patent; correct?
04:44:09 A. I need -- need to remind myself of that.
04:44:17 Q. If you -- you have a binder that has your deposition
04:44:19 in it. It's a smaller binder, and if you can refer, please,
04:44:23 to Page 54 of your deposition, Line 5 through 8 and let me
04:44:32 know when you get there and we can put that on the screen
04:44:34 for you as well.
04:44:35 Do you have that page?
04:44:39 A. Yes.
04:44:41 Q. In your deposition, did you -- were you asked the
04:44:43 following question and give the following answer:
04:44:45 "QUESTION: During prosecution of the
04:44:47 '349 patent, the examiner considered U.S. patent Number 8,
04:44:52 877, 776; correct?
04:44:55 "ANSWER: Correct."
04:44:57 THE WITNESS: Yes, I -- I agree with that.

Yeah.

Q. And that refreshes your recollection?

A. Yes.

Q. Now, the examiner issued a rejection during prosecution based on the Brown '776 reference; correct?

A. Correct.

Q. But Exelixis overcame that rejection; correct?

THE WITNESS: Remind me again. It was at my deposition where I --

Q. Sure.

A. It's been a few months.

Q. We can turn to either your report or your deposition, but let's go to your deposition at Page 60, Line 20 to 24.

"QUESTION: The examiner withdrew the rejections based on the Brown reference in view of the applicant's amendments, terminal disclaimer and arguments; correct?

"ANSWER: That is what is stated here, yes."

Do you recall that?

A. Yeah, I agree with that.

Q. And you addressed that same issue in your expert report; correct?

A. Yes.

Q. Now, we can take that down. You offered two distinct opinions as to why the Brown process would have made it obvious to prepare cabozantinib (L)-malate API that is

04:46:12 essentially free of the 1-1 impurity; correct?
04:46:15 A. Yes.
04:46:16 Q. The first opinion you offered is that Brown teaches a
04:46:20 process that produces cabozantinib (L)-malate API that is
04:46:25 essentially free of the 1-1 impurity; correct?
04:46:28 A. Yes.
04:46:29 Q. And then you offered an alternative opinion that if
04:46:33 it's not inherently disclosed it would have been obvious
04:46:36 from Brown by adding a recrystallization step; is that
04:46:39 right?
04:46:39 A. That's correct.
04:46:42 Q. Now, in your expert report, you also offered a third
04:46:45 opinion that a POSA would have been motivated and found it
04:46:49 obvious to modify the Brown synthetic process to follow the
04:46:54 process disclosed in the '349 patent; is that right?
04:46:57 A. Yes.
04:46:58 Q. But you're not offering that opinion here today;
04:47:00 correct?
04:47:00 A. That's correct.
04:47:02 Q. Now, in terms of your opinion on inherent disclosure,
04:47:08 you offered the opinion that there's explicit disclosure of
04:47:14 the claimed invention in Brown; is that right?
04:47:16 A. Repeat that one more time.
04:47:19 Q. Yeah. Let me ask it this way. Your first opinion is
04:47:24 that Brown teaches a synthetic process that produces

cabozantinib (L)-malate that is essentially free of the 1-1 impurity.

A. Correct.

Q. And you contend that the process disclosed in Brown both explicitly and inherently produces API that is essentially free of the 1-1 impurity; correct?

A. Just giving you a chemist definition, when you use the process, you produce the product with less than 200 PPM of the 1-1 impurity. If that means explicitly, then I -- I agree to that language.

Q. Do you have -- same binder that your deposition is, your opening report should be found in binder 1, Tab 2.

And I'd like to --

MR. COOPER: Your Honor, I would object to this. This is a theory that has not being presented. It was not presented during his direct, so it's outside the scope of the direct.

MS. WIGMORE: I'm trying to ascertain that, Your Honor. If he -- if he tells me he's not pursuing this opinion, I'm happy to move on.

THE COURT: Well, I don't understand. He's been clear as to what opinions he's pursuing. I don't know why everybody is so busy trying to prove that he's not -- pursuing things that he's not testified about. So, I'm going to sustain the objection.

04:48:41 MS. WIGMORE: I'm sorry, Your Honor, I just
04:48:42 wasn't clear if he was or was not pursuing this particular
04:48:45 opinion.
04:48:45 THE COURT: Okay, well, he's not.
04:48:47 MS. WIGMORE: Then we'll move on to the inherent
04:48:49 disclosure.
04:48:50 BY MS. WIGMORE:
04:48:50 Q. You did testify about language in the Brown patent
04:48:54 about substantially pure, do you recall that?
04:48:56 A. Yes.
04:48:57 Q. And you said that Brown uses the word "substantially
04:49:01 pure" to describe certain crystalline forms; is that right?
04:49:06 A. Uses -- repeat that again.
04:49:11 MS. WIGMORE: Why don't we pull up paragraph 97
04:49:14 of Brown, which is DTX-291. It's at PDF Page 24.
04:49:14 BY MS. WIGMORE:
04:49:26 Q. You highlighted this language during your direct
04:49:28 testimony, do you recall that?
04:49:29 A. Yes.
04:49:30 Q. And the first sentence says, "As used herein, the
04:49:33 term 'substantially pure,' means the crystalline form of
04:49:37 Compound I referred to that contains at least about
04:49:40 90 weight percentage based on the weight of such crystalline
04:49:43 form."
04:49:43 Do you see that?

04:49:45 A. Yes.
04:49:45 Q. So, the term "substantially pure" there is referring
04:49:48 to crystalline forms; correct?
04:49:54 A. No. I don't agree with that.
04:49:55 Q. Do you see the word "crystalline form" in that
04:49:58 sentence twice?
04:49:59 A. The purity they're referring to is the crystalline
04:50:01 form and a mixture of the crystalline form and impurities.
04:50:05 So it's not a crystalline form purity, it's purity of the
04:50:09 crystalline form in a mixture that involves the crystalline
04:50:12 form and other impurities.
04:50:13 Q. Can we agree that the sentence that you highlighted
04:50:16 referring to substantially pure uses the word "crystalline
04:50:20 form" twice?
04:50:20 A. So this is -- I'm not -- I'm not legally trained, but
04:50:26 reading the whole paragraph that's what I understand that
04:50:28 first sentence to mean, that the purity of the crystalline
04:50:33 form, the API material, which is often crystalline, and a
04:50:36 mixture along with other impurities.
04:50:39 Q. Okay?
04:50:39 A. That's -- it's that type of purity. Not purity of
04:50:42 this one crystalline form versus that other crystalline form
04:50:45 or something like that. It's a little bit confusing, the
04:50:48 language. But if I read the whole paragraph, that's my
04:50:50 interpretation.

04:50:51 Q. But we can agree the words "crystalline form" appear
04:50:54 there; correct?
04:50:54 A. It's certainly written there, it's just a question of
04:50:59 how one interprets it, you know.
04:51:00 Q. Now, the purity of the crystalline form is one thing
04:51:04 and the purity of the whole API is another thing; correct?
04:51:07 A. Repeat that again.
04:51:11 Q. The purity of the crystalline form is one thing and
04:51:14 the purity of the whole API is another thing; correct?
04:51:17 A. I think here it's the same.
04:51:21 Q. Could you please turn to your deposition binder 1,
04:51:24 Tab 1, Page 84, lines 1 to 9.
04:51:30 Were you asked the following question and did
04:51:33 you give the following answer:
04:51:35 "QUESTION: Crystalline form impurities can be
04:51:37 measured using x-ray powder diffraction; correct?
04:51:41 "ANSWER: I am just trying to be clear, the
04:51:44 purity of the crystalline form is one thing and the purity
04:51:47 of the whole API is another thing.
04:51:49 "To answer your question, yes, without being an
04:51:51 experts myself, powder x-ray diffraction, I believe that's a
04:51:56 tool, but I'm not giving an opinion on that point."
04:51:59 Did you give that testimony?
04:52:00 A. Yes.
04:52:02 Q. Now, there are two different ways of thinking about

04:52:04 1 purity: The solid state or crystalline form of a material
04:52:08 2 and the chemical purity of the material; correct?
04:52:11 3 A. I think in my -- in -- in my deposition, the
04:52:19 4 conversation was about crystalline form purity. In this
04:52:23 5 paragraph and the specification, I believe the word
04:52:28 6 "crystalline form" just simply means the API, which is a
04:52:31 7 crystalline form usually, and not talking about the
04:52:34 8 crystalline form purity, which is another matter. And I was
04:52:38 9 responding to that in my deposition.
04:52:42 10 MS. WIGMORE: Can you please turn to your
04:52:43 11 deposition at Page 84, Lines 16 to 22. Were you asked:
04:52:50 12 "QUESTION: But there are two different ways of
04:52:52 13 thinking about purity, you can consider the purity with
04:52:54 14 respect to the solid state or crystalline form of a
04:52:57 15 material, and you can also consider the chemical purity of
04:53:00 16 the material; is that fair?
04:53:02 17 "ANSWER: In the abstract, I think that's a fair
04:53:05 18 statement."
04:53:05 19 BY MS. WIGMORE:
04:53:06 20 Q. Did you give that testimony?
04:53:07 21 A. Yes. Yes. That's not inconsistent with my thoughts
04:53:11 22 on -- on the specification.
04:53:12 23 Q. Now, you're not an expert on crystalline forms;
04:53:15 24 correct?
04:53:15 25 A. That's correct.

Q. And you have not opined on crystalline form purity in this case; correct?
A. Correct.
Q. You have not evaluated whether any of the techniques applied in Brown could show chemical impurities; correct?
A. One more time.
Q. You have not opined or evaluated whether any of the techniques applied in Brown could show chemical impurities; correct?
A. Reword that.
Q. Yeah, if -- I can refresh your recollection, if that would be helpful.
MS. WIGMORE: If you could turn to your deposition at Page 97, Lines 5 to 8:
"QUESTION: But you haven't evaluated whether the techniques that are being applied could show chemical impurities in this case; right?
"ANSWER: I haven't opined on that."
BY MS. WIGMORE:
Q. Did you give that testimony?
A. What was the statement before that?
Q. Yeah. We can go back to Line 24, if that's helpful.
MS. WIGMORE: So 97, Line 24:
"QUESTION: None of the figures in Brown provide information about any chemical impurities; correct?

"ANSWER: I haven't considered that, but just to point out that NMR is being used and it's possible that they should review chemical impurities.

"QUESTION: But you haven't evaluated whether the techniques that are being applied could show chemical impurities in this case, right.

"ANSWER: I haven't opined on that."

Was that your testimony?

THE WITNESS: I stand behind that.

BY MS. WIGMORE:

Q. Now, Brown does contain XRPD data; correct?

A. Correct.

Q. And Brown provides solid-state NMR data; correct?

A. Yes.

Q. Now, you testified on direct exam about high-performance liquid chromatography or HPLC; correct?

A. Correct.

Q. And you testified that it is a common way of monitoring impurity levels; correct?

A. Correct.

Q. None of the figures in Brown provide HPLC data; correct?

A. Correct.

Q. Brown does not expressly disclose a composition that contains 200 parts per million or less of any particular

04:55:46 byproducts or contaminate; correct?
04:55:48 A. Did you say "explicitly"?
04:55:52 Q. Expressly?
04:55:54 A. It's correct.
04:55:59 Q. I'm sorry, I didn't hear your answer.
04:56:01 A. Yes.
04:56:04 MS. WIGMORE: Now, if we could turn to the
04:56:06 Scheme 1 in paragraph 99 of Brown, which is Exhibit 291.
04:56:13 BY MS. WIGMORE:
04:56:14 Q. Scheme 1 you testified about on direct examination;
04:56:16 correct?
04:56:16 A. Yes.
04:56:17 Q. And that's part of Example 1 of Brown; correct?
04:56:20 A. Correct.
04:56:20 Q. And Scheme 1 describes a process for preparing what's
04:56:24 called Compound I; correct?
04:56:26 A. Correct.
04:56:26 Q. And Compound I is cabozantinib (L)-malate API;
04:56:31 correct?
04:56:31 A. Correct.
04:56:33 Q. Brown does not explicitly states that it's 1-1
04:56:36 compound is a degradation products; correct?
04:56:38 A. Correct.
04:56:41 Q. And Brown does not explicitly identify the 1-1
04:56:45 compound as a process impurity; correct?

04:56:48 A. Correct.
04:56:54 Q. Brown does not give any specific numbers for PPM
04:56:58 levels of the impurities that may or may not arise from the
04:57:01 Brown process; correct?
04:57:02 A. Correct.
04:57:04 Q. Brown does not explicitly state that the 1-1 compound
04:57:08 is genotoxic; correct?
04:57:10 A. Correct.
04:57:13 Q. Brown does not discuss genotoxicity at all; correct?
04:57:16 A. I'm not sure. It's -- the specification could have
04:57:26 mentioned it somewhere, I'm not sure.
04:57:28 Q. Not that you can think of, sitting here today?
04:57:29 A. Correct.
04:57:31 Q. Now, you understand that inherency requires a showing
04:57:36 that a claimed element would necessarily and inevitably
04:57:41 result from a process disclosed in the prior art; correct?
04:57:44 A. Correct.
04:57:51 Q. Brown describes six different ways that cabozantinib
04:57:55 can be converted to cabozantinib of (L)-malate; correct?
04:57:58 A. Correct.
04:58:02 Q. And you rely on one of those six methods to support
04:58:05 your inherency opinion; correct?
04:58:07 A. Correct. Correct.
04:58:11 Q. The Brown synthetic process that you rely on is one
04:58:15 of six different ways that Brown discloses for making

04:58:18 cabozantinib (L)-malate; correct?
04:58:20 A. At the very end, there's a final step that can be
04:58:31 done six different ways. That's a better way to represent
04:58:35 what's going on there.
04:58:37 Q. You can agree there are six different examples in the
04:58:40 patent; right?
04:58:40 A. Six ways to finish off the synthesis, according to
04:58:45 Brown, yes.
04:58:46 Q. And the one that you rely on for your opinion is
04:58:48 Example 1, Scheme 1, in paragraph 99; correct?
04:58:52 A. Can we see that?
04:58:56 Q. The example you are relying on for your inherency
04:59:00 opinion is Example 1, Scheme 1, in paragraph 99 of Brown;
04:59:06 correct?
04:59:06 A. I'd have to see the last step in my -- this is
04:59:23 showing -- I'm not really sure if the acetone, THF, is -- is
04:59:32 the solvent system used in the narrative. I think it is,
04:59:37 but if we can look at the narrative, I would like to
04:59:41 confirm.
04:59:41 Q. So you're referring to the narrative that is
04:59:43 Example 1 that is -- follows Scheme 1; is that what you're
04:59:47 referring to?
04:59:47 A. Referring to the narrative that I -- I couldn't
04:59:53 remember if there were five different -- five alternative
04:59:55 ways to produce the salt at the end. And at this step, I

don't remember now if the acetone, THF, was the one that I -- that I analyzed, or if it was one before the others. I think it was, but if I can just confirm it, it would be helpful.

Q. You testified about Scheme 1 on direct examination; right?

A. I have seen this -- the Scheme 1, yes.

Q. Now, Scheme 1 shows the use of the 1-1 compound as a starting material; correct?

A. Correct.

Q. And Scheme 1 describes a synthetic scheme by which the 1-1 compound is converted through a series of reactions to cabozantinib (L)-malate; correct?

A. Yes, it's the roadmap. Synthetic scheme is a good way of putting it as well, yes.

Q. And there are at least five different reactions involved in converting the 1-1 starting material to cabozantinib (L)-malate; correct?

A. If you follow the Brown procedures, there are only five ways. Only five reactions going from the 1-1 starting material to cabozantinib. Five, what we call the longest linear sequence is what's referred to in synthetic organic chemistry.

Q. So at each of those steps, there is a purification process; correct?

05:01:13 A. If you count extractions and workups, yes. Mm-hmm.
05:01:24 Q. Now, multiple steps in Example 1 of Brown use the
05:01:29 word "approximately"; correct?
05:01:31 A. Correct.
05:01:33 Q. The word "approximately" is used 27 times in Brown
05:01:37 Example 1; correct?
05:01:38 A. I haven't counted it. But it is used a number of
05:01:43 times, yes.
05:01:46 Q. There is no definition of the term "approximately" in
05:01:49 Brown; correct?
05:01:50 A. It's something known in -- just known in the art.
05:01:54 It's just a common -- common sense definition. But, yes. I
05:01:58 don't think it's explicitly defined in Brown.
05:02:01 Q. Dr. Lepore, would you agree that 100 percent exact
05:02:05 reproducibility is not attainable in any scientific
05:02:08 experiment?
05:02:09 A. As long as we're talking about 100 percent versus
05:02:22 99.9 percent, yes.
05:02:24 Q. Now, you understand that MSN has the burden of
05:02:27 proving inherency in this case; correct?
05:02:30 A. Yes.
05:02:32 Q. You have never carried out a process for making
05:02:35 cabozantinib (L)-malate following the scheme in Brown;
05:02:40 correct?
05:02:40 A. I wish I had this many pile reactors to do it. But

05:02:49 no, I haven't.
05:02:50 Q. And no one has done so at your directions; correct?
05:02:52 A. Correct.
05:02:54 Q. You did not prepare cabozantinib -- strike that.
05:02:58 Did you not ask anyone to carry out any of the
05:03:02 examples in Brown; correct?
05:03:04 A. Correct.
05:03:04 Q. And you did not carry any of them out yourself;
05:03:08 correct?
05:03:08 A. Correct.
05:03:09 Q. Now, during your direct examination, you discussed a
05:03:15 Girindus batch.
05:03:15 Do you recall that?
05:03:15 A. One more time.
05:03:17 Q. You discussed a batch called Girindus?
05:03:22 A. That's correct.
05:03:23 Q. Some people say Girindus. We'll go with whatever you
05:03:28 prefer.
05:03:28 A. Okay.
05:03:29 Q. In view of -- you testified you did not believe that
05:03:33 Girindus was representative of the Brown process; correct?
05:03:36 A. That's correct.
05:03:37 Q. And you testified that it was not representative
05:03:40 because of deviations from the Brown process; correct?
05:03:44 A. Correct.

05:03:47 Q. Now, the Girindus batch was not the only batch that
05:03:52 had process variations; correct?
05:03:58 A. With regard to the Brown process? Is that what
05:04:00 you're referring to or just regarding any process to make
05:04:03 the API?
05:04:03 Q. Well, you are not relying on anything other than the
05:04:07 three batches from Regis to support your inherency opinion;
05:04:11 correct?
05:04:11 A. Using the Brown process, yeah, that's right.
05:04:16 Q. And your opinion that cabozantinib (L)-malate, as
05:04:22 manufactured by the method described in Brown, would
05:04:24 inherently result in API with the claimed 1-1 impurity is
05:04:29 based on three lots of API prepared by Regis; correct?
05:04:33 A. Using the Brown process, yes.
05:04:38 Q. And in preparing your opinions, you did not consider
05:04:40 any process deviations from Brown that occurred in any of
05:04:44 the Regis batches; correct?
05:04:46 A. One more time.
05:04:49 Q. In preparing your opinions, you did not consider any
05:04:53 process deviations from Brown that occurred in any of the
05:04:57 Regis batches; correct?
05:04:59 A. None came to my attention.
05:05:02 Q. In fact, when you formed your opinions, you were not
05:05:05 aware of any process deviations that occurred from Brown in
05:05:10 the Regis batches; correct?

A. Correct. To my -- to my knowledge, there were no deviations that I -- that I have reviewed.

Q. You believe the Regis procedure was identical or virtually identical to the procedure in the Brown patent; correct?

A. That's what was disclosed to the FDA, yes.

Q. Now, Regis Lot P172-27-1 was one that you testified about here today; correct?

A. Yes. I don't remember the numbers exactly, but that sounds familiar. Yeah.

Q. And you agree that processing and reagent changes from were implemented for that Regis batch; correct?

A. I haven't seen such changes or deviations. I'm relying on what they submitted to the -- what Exelixis submitted to the FDA. According to that document, there were no changes.

MS. WIGMORE: So, let's have PTX-10 on Page 9.

And I believe this is Tab 9 in your binder, if you wish to look at it.

BY MS. WIGMORE:

Q. This is an Exelixis document submitted to the FDA.

Do you see that?

Do you have the document, Dr. Lepore?

A. Yes.

MS. WIGMORE: And if we could turn, please, to

Page 9.

BY MS. WIGMORE:

Q. Do you see there's a heading, "Figure 7.2-8, Synthetic route for the preparation of XL 184 drug substance"?

A. Mm-hmm.

Q. Do you see that heading?

A. I see that, yes.

Q. And there's some chemical -- the chemical diagram, but below that it says the following description of the process is an example of the current route and scale used in the production of the drug substance (lot number P172-27-1) at Regis Technologies, Inc., which will be used in the proposed clinical trial."

Do you see that?

A. I see that.

Q. And then skipping ahead past the next sentence. It says, "Some processing and reagent changes were implemented for the GMP batch (lot number P172-27-1)."

Do you see that?

A. Yes.

Q. You were not aware of those process and reagent changes when you formed your opinions?

A. So, I've seen this. I've read this. The procedure that Exelixis has made available to FDA for their review is

what I reviewed. I didn't see any such changes. I'm assuming that these are extremely minor things that I wouldn't even call deviation.

Q. But you don't know?

A. Instead of using HPLC grade solvent, they used, you know, technical grade solvent or something very minor, and maybe that's what they're referring to. But I have not seen changes. This -- I have nothing to really back up this statement, whereas I have reviewed the Brown process and the Regis process and those are technical details that I can, you know, sink my teeth into.

Q. So you're assuming these process and reagent changes were minor; is that right?

A. Well, first of all, they're not -- they're not being called deviations, which I think is a bigger change. But perhaps importantly, I just don't have any data to draw a conclusion here. I have to assume that -- that Exelixis, you know, put all the information that they needed to into their FDA document.

Q. Now, in terms of Exelixis's submissions to the FDA -- you've reviewed Exelixis's FDA submissions in this case; correct?

A. Yes.

Q. And information submitted to the FDA needs to be accurate; correct?

A. I assume so, yes.
Q. Information submitted to the FDA needs to be reliable; correct?
A. I assume so. Yeah.
Q. And Exelixis submitted an IND and a NDA relating to cabozantinib (L)-malate to the FDA; correct?
A. Yes.
Q. Based on the material you have reviewed, you have no reason to doubt the accuracy of statements that Exelixis has made to the FDA; correct?
A. Well, accuracy of statements, you know, there are conclusions. There are -- there are interpretations. What I rely on very heavily is actual data and so the data they submitted, I, as an expert, reviewed it and came to a determination.

If they had a slightly different view of it, that doesn't necessarily mean that it is untruthful. They just had a different interpretation.

MS. WIGMORE: Could you turn, please, to your deposition at Page 122, Lines 2 through 6?
A. Page 122 you said?
Q. 122.
A. 122.

MS. WIGMORE: "QUESTION: You have no reason to doubt the accuracy of statements that Exelixis has made to

the FDA; correct?

"ANSWER: Not based on the material that I have reviewed."

BY MS. WIGMORE:

Q. Did you -- were you asked that question and did you give that answer?

A. Yeah. I think that that proviso that I just gave, I'm not sure exactly what the context here was, but I certainly don't doubt the data that they included -- that their interpretation of data -- I did not question the accuracy, it's a question of interpretation.

But, no. I don't have any reason to not believe in the accuracy of what was reported. That's my understanding here in this statement.

Q. Now, I want to move to your obvious opinion -- obviousness opinion.

THE COURT: Ms. Wigmore, unless -- why don't we call it a day. Okay?

MS. WIGMORE: Yes, Your Honor.

THE COURT: You're not like trying to leave tonight. Are you?

THE WITNESS: No.

THE COURT: Okay. All right. We'll be in recess then until tomorrow morning at 8:30.

DEPUTY CLERK: All rise.

MR. COOPER: Your Honor, so Mr. Prussia sort of flagged that we might have an issue for the Court's attention about a future witness and he's going to be testifying tomorrow, and so I just raise that now to potentially raise it with the Court and get some guidance before he actually takes the stand and --

THE COURT: Well, you can -- okay. Actually, Dr. Lepore, you can step down and watch your step.

If it turns out that this is more time than I want to take tonight, we'll do it at 8:30 tomorrow morning and I'll charge either one of you of time.

But go ahead, I'm listening.

MR. COOPER: I expect it might take five or 10 minutes.

THE COURT: Well, go ahead. I'll be the judge of how long it takes.

MR. COOPER: Well, Your Honor, this is an issue that Exelixis raised recently after the motions in limine deadline and after expert discovery, and it relates to the disclosure of Dr. Steed who's opining on the crystalline malate salt patents.

In his expert report, Dr. Steed provided an obviousness opinion under 103 and a further opinion on obviousness-type double patenting. Both of those opinions rely very heavily on the '473 patent, which Your Honor saw

and has heard about. That's the -- the prior compound and pharmaceutically acceptable salt patent.

THE COURT: So Dr. Steed's opinion on obviousness, they're not relevant anymore, are they?

MR. COOPER: Well, no. They're relevant in that they're the analysis tracks similarly because the 1034 opinion, Dr. Steed -- and this is -- again, this is an objection about adequate disclosure in his expert report -- I believe, though, they have not sort of articulated exactly what they think is insufficient.

THE COURT: Sorry. You need to remind me, Dr. Steed is your witness?

MR. COOPER: Yes.

THE COURT: Yes. Okay.

MR. COOPER: So Dr. Steed in his expert report, he, you know, went on for a hundred pages talking about states of the art and a POSA's knowledge as of, you know, the early 2010, 2009 time period, and then he provides his opinion about 103 obviousness relying on the '473 patent, a POSA's knowledge and various other prior art that he identifies in that section.

And at a very, very high level, you know, there are main points that it's obvious to conduct a routine salt screen. It's obvious to select (L)-malic acid as a counter ion to make the salt. Obvious and motivated to prepare the

crystalline version. You heard it at Mr. Lombardi's opening statement. And so, that's what he laid out in his expert's report.

And then in the OTDP section, which was the next one, as Your Honor knows, in that analysis, you look at the claims of a reference patent, and so he uses the 473 as the reference patent. And then he goes -- his analysis is very similar to what he had just gone through in the obviousness; right. So the principles of obviousness in OTDP apply as well, and so I'm happy to show Your Honor his report.

THE COURT: Well, actually, so what you're doing is you're preempting Mr. Prussia from making some objection; right?

MR. COOPER: Well, I'm raising it because I think that we -- it would be helpful to get Your Honor's guidance before he's on the stand considering, I think --

THE COURT: Well, no, no. I'm just thinking I have very little idea of where we're heading here because I don't know exactly what Mr. Prussia's objection is going to be, but I'm just thinking maybe you ought to tell me -- because it's his objection, he ought to tell me what it's going to be very briefly, and then I'll be able to focus more on what you're telling me. But right now you're giving me a lot of information, but I don't -- you know, like I'm looking for a needle here, but I don't know exactly what

color the needle is.

MR. COOPER: Understood. And, Your Honor, they haven't articulated exactly what their concern is.

THE COURT: Well, so let me see, Mr. Prussia, what's your concern?

MR. PRUSSIA: Your Honor, thank you. Your Honor I didn't realize this was going to be coming up today because I don't even have their disclosures yet for Dr. Steed, which I believe are due tonight, but I didn't --

THE COURT: So is Dr. Steed testifying tomorrow or --

MR. PRUSSIA: He's been disclosed for tomorrow, so we're supposed to get disclosures tonight. I can -- so it's hard for me to specifically articulate what's the issue is because I don't know quite yet what they plan on doing. The issue is quite simply this, is they didn't disclose obviousness-type double patenting until their final invalidity contentions. I believe it was the last day of fact discovery. And it was like a sentence.

Then in their opening report -- and Mr. Cooper is correct. It went on for 400 or so paragraphs. I think about eight paragraphs were dedicated to obviousness-type double patenting, and what he did, he cross-referenced certain things were in the preceding 400 paragraphs.

THE COURT: Uh-huh.

MR. PRUSSIA: And not everything, just certain things. And then in a reply report, he references back to his opening report. So, there's certain things, in our view, that are not in the case. For example, he doesn't incorporate -- he doesn't -- in his obviousness-type double patenting opinions, he makes -- he has no discussion about objective indicia. There's certain arguments that he made for the first time in his reply report that he does not incorporate into his opinions.

THE COURT: Does objective indicia make any difference to --

MR. PRUSSIA: It does. It does. The Federal Circuit case law is quite -- quite clear that it's required to be considered. So he has no opinions with respect to unexpected results or any other objective indicia with respect to obviousness-type double patenting because it wasn't disclosed. He also makes opinions in his reply report that were to support his statutory obviousness opinions that he didn't incorporate into his obviousness-type double patenting.

So, there are disclosures here. We're not saying that he's not able to offer an opinion on obviousness-type double patenting in totum. It depends on what exactly they intend to say. I don't know that until tonight.

THE COURT: Okay. Well, so I think I've heard enough to know that I'd be shooting in the dark to try to give you all guidance on this right now.

So, why don't you see what the disclosures are as to whatever it is that the Defendant wants to do, and if you -- and we can deal with this tomorrow morning if there is a dispute. And maybe there won't be a dispute because I'm an optimist. But if there is, I'll do the best I can with it tomorrow.

I would say generally considering that up until a week ago there was no obviousness and obviousness-type double patenting, I wouldn't be too concerned that you haven't prepared for whatever is in either section, and if there's, you know, 90 cross-references to obviousness, but there's ten places where there's not a cross-reference, I want to know how you're actually prejudiced by the fact that that cross-reference was there because I take it we're saying this is all disclosed. It's just not necessarily disclosed in the right section, or at least that's the concern.

MR. PRUSSIA: It's a bit more than that, Your Honor. I know it's late, but this has been an ongoing issue that we've had with them, is how they've been disclosing their theories and their various combinations and the like, and we didn't get any notice of what their actual

theories were until just a few weeks ago.

And, again, it's late, and it's hard to argue this in the abstract until I know exactly what it is they're going to disclose.

THE COURT: That's right, but tell me what you want, and then we'll finish.

MR. PRUSSIA: Well, all I'm going to say is I'm happy to wait until I get their disclosures tonight and we can come to Your Honor with specific requests once I have their exhibits in hand.

THE COURT: Okay. Well, I think that's the best we can do. So we'll be in recess. See you tomorrow morning.

DEPUTY CLERK: All rise.

(Court was recessed at 5:28 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 [3] - 12:22, 13:5, 57:14
'349 [62] - 11:8, 22:13, 23:19, 27:6, 36:4, 46:12, 57:19, 69:13, 69:16, 72:25, 73:2, 73:5, 73:22, 74:5, 74:9, 74:10, 74:20, 75:9, 75:15, 75:19, 77:10, 80:8, 80:23, 81:4, 82:13, 82:16, 83:8, 84:11, 116:23, 124:16, 124:20, 126:9, 126:15, 174:16, 174:22, 182:16, 186:11, 186:25, 230:20, 230:22, 230:25, 233:17, 259:10, 259:13, 259:24, 260:9, 261:15, 269:1, 311:24, 312:21, 312:24, 313:1, 313:6, 313:21, 314:11, 314:17, 315:10, 315:14, 319:9, 319:22, 321:15
'439 [4] - 12:22, 13:1, 38:1, 57:13
'440 [3] - 12:22, 13:2, 57:14
'473 [12] - 18:5, 18:10, 35:14, 35:19, 36:9, 42:15, 42:21, 43:5, 43:9, 43:23, 341:25, 342:19
'643 [1] - 157:3
'776 [9] - 35:14, 35:20, 35:21, 36:9, 318:24, 319:3, 319:7, 319:10, 320:5
'substantially [1] - 323:21

/

/s [1] - 347:19

0

0.02 [3] - 27:18, 279:6, 279:8
0.06 [1] - 293:5
0.1 [3] - 95:7, 98:7, 173:10
0.25 [2] - 162:16, 282:4
0.26 [7] - 8:13, 280:9, 280:14, 281:21, 282:5, 291:7, 292:5
0.27 [1] - 282:5
0.5 [1] - 173:11
0004 [1] - 72:22
007-0002 [1] - 288:18
023 [1] - 136:2
044 [1] - 136:3

1

1 [71] - 72:10, 100:6, 109:7, 144:19, 174:14, 174:24, 175:6, 175:16, 191:2, 196:13, 212:14, 213:1, 213:3, 213:9, 221:19, 225:11, 233:9, 240:2, 243:11, 252:7, 252:16, 257:12, 259:11, 264:21, 265:15, 267:17, 267:19, 268:9, 268:20, 272:21, 272:25, 273:22, 273:23, 274:15, 277:8, 278:1, 278:9, 279:17, 285:7, 292:24, 293:25, 294:23, 299:6, 299:12, 299:24, 300:14, 307:1, 307:25, 322:12, 325:11, 325:12, 329:8, 329:10, 329:13, 329:15, 331:10, 331:13, 331:21, 332:5, 332:7, 332:8, 332:11, 333:2, 333:6
1-1 [134] - 6:8, 6:9, 6:21, 9:9, 9:11, 9:15, 9:20, 9:21, 10:17, 11:2, 11:5, 12:15, 22:15, 27:7, 27:10, 27:12, 27:15, 28:8, 28:11, 28:22, 28:24, 29:2, 29:3, 29:4, 29:5, 29:10, 29:20, 29:24, 30:7, 30:11, 30:13, 30:19, 31:7, 31:18, 31:25, 32:4, 32:15, 32:20, 46:13, 50:17, 50:23, 53:3, 53:8, 53:24, 54:1, 54:2, 54:7, 56:2, 80:18, 234:9, 234:12, 260:22, 261:3, 261:4, 261:12, 261:16, 262:9, 262:13, 266:24, 270:8, 270:15, 270:20, 276:2, 276:6, 276:8, 276:10, 279:22, 279:23, 280:14, 280:18, 281:10, 282:3, 282:25, 283:5, 283:20, 284:4, 284:16, 285:6, 285:7, 286:17, 286:21, 287:12, 287:19, 287:21, 288:2, 289:4, 289:8, 289:16, 291:7, 291:9, 291:12, 292:5, 292:16, 293:4, 293:7, 299:14, 299:17, 299:25, 300:2, 300:9, 300:12, 300:20, 300:21, 300:22, 303:16, 304:10, 304:12, 305:25, 306:7, 306:17, 307:25, 308:2, 309:13, 310:25, 313:15, 313:23, 314:3, 318:8, 321:1, 321:5, 322:1, 322:6, 322:9, 329:21, 329:24, 330:6, 332:8, 332:12, 332:17, 332:20, 335:12
1-3 [2] - 297:24, 297:25
1-4 [3] - 297:24, 298:5, 299:2
1.0 [1] - 98:4
1.26 [1] - 297:13
1.3 [1] - 297:24
1.35 [1] - 137:3
1.375 [1] - 136:24
1.52 [2] - 140:7, 209:5
10 [18] - 73:11, 73:13, 75:10, 81:2, 95:7, 95:10, 99:12, 105:7, 106:1, 125:14, 162:13, 202:3, 212:7, 222:11, 222:18, 233:9, 252:11, 341:14
10.0 [2] - 98:4, 98:7
100 [4] - 250:8, 269:15, 333:14, 333:17
100-milligram [4] - 288:16, 289:15, 291:24, 307:17
100-sieve [1] - 250:11
103 [3] - 13:21, 341:23, 342:19
1034 [1] - 342:6
105 [2] - 94:10, 160:21
10s [1] - 167:19
10th [1] - 259:25
11 [10] - 39:20, 40:4, 40:21, 119:12, 158:6, 179:6, 218:5, 244:22, 279:1, 310:15
11,298,349 [1] - 72:23
112 [1] - 14:9
119 [2] - 161:19, 161:20
11A [1] - 60:5
12 [4] - 124:25, 219:24, 305:7, 310:15
12-month [1] - 307:17
12.2 [1] - 279:2
12.7 [7] - 63:25, 113:7, 214:23, 215:22, 238:20, 239:4, 239:16
12.70 [1] - 114:3
12/14/2016 [1] - 245:8
122 [4] - 339:20, 339:21, 339:22, 339:23
13 [5] - 83:10, 125:22, 306:2, 306:3, 306:25
14 [10] - 98:25, 281:22, 282:9, 290:5, 296:13, 305:25, 306:1, 306:25, 309:4, 309:7
15 [11] - 5:14, 31:10, 66:20, 158:19, 159:5, 175:3, 253:12, 273:9, 273:11, 282:22, 298:9
15-minute [1] - 67:18
150 [11] - 166:16, 166:19, 168:5, 219:8, 219:15, 221:1, 221:3, 222:18, 250:12, 250:21, 250:25
150-micron [2] - 219:11, 250:18
1500 [15] - 97:6, 97:11, 97:12, 97:20, 98:2, 160:13, 160:21, 161:2, 161:17, 162:2, 162:4, 162:5, 162:19, 162:23, 163:3
15th [1] - 58:8
16 [6] - 158:19, 245:22, 253:13, 273:20, 283:14, 326:11
160 [1] - 177:22
16th [1] - 169:14
17 [4] - 274:6, 305:7, 305:15, 305:18
172 [1] - 284:18
178 [2] - 96:18, 96:22
18 [4] - 180:17, 274:12, 281:23, 282:10
184 [2] - 54:1, 337:4
184-1-1 [2] - 279:18, 280:8
19 [7] - 72:5, 274:17, 281:11, 282:15, 282:21, 282:24, 289:20
190 [1] - 96:22
196 [1] - 177:22
198 [1] - 96:18
1989 [2] - 161:6, 161:11
1991 [2] - 71:16, 173:19
1996 [1] - 157:25
19th [1] - 119:18
1:30 [1] - 168:8

2

2 [55] - 13:4, 47:6, 57:15, 72:21, 77:10, 82:15, 94:12, 94:14, 95:14, 95:17, 100:22, 120:4, 120:9, 130:25, 131:2, 131:11, 135:9, 144:20, 160:15, 163:20, 163:23, 169:9, 172:11, 178:24, 184:13, 184:21, 190:20, 191:1, 201:7, 203:12, 213:11, 213:19, 213:20, 225:12, 233:8, 240:2, 240:20, 240:23, 241:1, 242:24, 243:5, 251:15, 252:17, 257:17, 259:20, 274:6,

274:9, 274:10, 277:8, 281:6, 291:4, 292:23, 322:12, 339:20
2.19 [1] - 116:3
2.3.1.4 [1] - 115:9
2.3.1.9 [5] - 62:21, 92:9, 114:16, 214:6, 237:13
2.3.P [2] - 64:23, 201:4
2.3.P.1 [1] - 201:8
2.3.P.5.4 [1] - 288:11
2.44 [1] - 85:12
2.5 [1] - 315:8
20 [10] - 21:1, 73:3, 82:16, 158:2, 185:15, 231:8, 260:5, 274:24, 288:10, 320:13
20-milligram [2] - 73:20, 201:6
200 [32] - 27:17, 50:18, 54:5, 54:7, 54:16, 54:19, 55:11, 56:2, 56:5, 56:6, 261:17, 261:21, 276:9, 279:7, 279:9, 279:12, 279:14, 280:2, 280:4, 280:6, 280:20, 283:11, 287:23, 289:10, 290:1, 291:9, 292:16, 299:17, 308:3, 313:19, 322:8, 328:25
200-part [1] - 281:17
2000 [2] - 98:19, 98:22
2000s [1] - 5:11
2003 [2] - 4:10, 5:19
2005 [2] - 53:18, 277:20
2007 [1] - 277:21
2009 [2] - 12:23, 342:18
2010 [4] - 15:13, 15:16, 267:12, 342:18
2010/083414 [1] - 318:16
2011 [6] - 75:10, 76:15, 259:25, 264:2, 303:16, 310:4
2012 [1] - 5:21
2016 [3] - 59:10, 245:3, 246:11
20164104 [1] - 245:1
2019 [1] - 169:14
2022 [2] - 57:17, 119:18
2023 [2] - 1:12, 58:8
2026 [1] - 42:18
2030 [1] - 42:23
20B [2] - 284:8, 284:10
21 [3] - 73:17, 158:6, 275:4
213878 [1] - 73:17
215 [4] - 67:10, 68:5, 235:8, 249:12
21st [1] - 57:17
22 [3] - 275:10, 289:2, 326:11
22-228-RGA [1] - 1:5
22nd [1] - 267:12
23 [13] - 1:12, 136:12, 136:23, 137:6, 138:17, 140:17, 140:25, 141:3, 141:7, 211:9, 251:23, 275:23, 289:11
231 [1] - 256:1
24 [8] - 19:1, 19:2, 269:9, 276:11, 320:13, 323:15, 327:22, 327:23
243 [1] - 127:11
25 [7] - 16:3, 159:5, 180:17, 267:17, 280:22, 288:17, 300:15
25-milligram [3] - 288:15, 289:3, 291:24
25.92 [1] - 137:2
252 [3] - 135:2, 180:23, 210:8
252/023 [2] - 135:20, 210:12
252/044 [2] - 135:24, 211:3
26 [6] - 57:16, 84:14, 232:13, 232:14, 280:13, 295:17
27 [5] - 58:25, 111:25, 113:17, 287:14, 333:5
27.6 [1] - 132:4
27.7 [2] - 132:4, 136:24
275 [1] - 256:1
29 [1] - 98:19
290 [1] - 178:20
291 [1] - 329:8
2956 [1] - 120:4
296 [1] - 177:22

3

3 [64] - 13:2, 22:15, 27:5, 27:13, 27:20, 28:13, 32:7, 57:14, 73:2, 73:4, 73:7, 74:5, 74:8, 74:18, 74:20, 75:4, 75:9, 77:10, 77:23, 80:7, 80:15, 80:22, 81:1, 81:4, 105:13, 105:15, 109:7, 116:20, 120:9, 124:16, 124:20, 125:13, 126:14, 152:17, 163:24, 178:25, 182:16, 186:16, 201:8, 205:3, 230:20, 230:22, 230:24, 230:25, 233:16, 233:19, 234:1, 234:7, 260:6, 260:8, 269:1, 274:12, 274:14, 274:15, 296:16, 296:17, 303:3, 303:5, 312:23, 313:2, 313:6, 314:11, 314:17
3.2.P.1 [1] - 105:12
3.2.P.2 [1] - 60:7
3.3 [4] - 149:2, 149:4, 149:5, 194:22
30 [8] - 136:2, 136:4, 161:13, 166:11, 167:18, 167:25, 175:7, 304:5
33 [6] - 148:22, 149:1, 149:2, 158:6, 199:17
34 [10] - 87:22, 132:12, 133:3, 133:11, 142:24, 199:19, 208:18, 209:4, 226:23, 313:4
34.42 [3] - 139:12, 139:24, 140:2
344 [2] - 151:13, 177:22
35 [12] - 89:17, 91:10, 145:21, 149:12, 149:19, 159:5, 166:11, 194:21, 235:20, 236:3, 236:5, 307:21
355 [1] - 256:1
355(j [1] - 73:18
358 [2] - 130:12, 177:22
36 [4] - 89:24, 142:25, 145:1, 236:7
363 [2] - 149:17, 177:22
38 [7] - 82:16, 212:10, 231:8, 239:21, 240:6, 241:16, 291:20
39 [1] - 228:8
394 [2] - 127:11, 232:12
3950 [1] - 290:23
3:30 [1] - 255:8

4

4 [22] - 12:25, 57:14, 58:19, 60:6, 83:3, 109:7, 127:10, 130:23, 140:11, 161:10, 161:11, 187:22, 202:5, 230:21, 243:3, 274:17, 274:20, 298:9, 301:16, 302:2, 305:15, 308:17
4.0 [2] - 100:6, 100:12
4.4.2 [1] - 296:13
4.4.3 [1] - 298:9
40 [1] - 99:2
40-milligram [3] - 73:20, 201:6, 243:7
400 [2] - 344:21, 344:24
41 [7] - 98:25, 115:10, 115:12, 212:10, 240:24, 241:15, 241:19
41042600 [1] - 245:1
411 [2] - 32:5, 54:22
414 [1] - 319:2
43 [1] - 309:21
44 [18] - 75:5, 75:7, 94:10, 137:2, 137:10, 138:17, 139:2, 139:12, 140:14, 140:16, 141:1, 141:2, 172:10, 211:9, 211:23, 212:10, 232:24, 251:24
447 [1] - 127:11
46 [1] - 210:9
473 [2] - 17:8, 343:6
48.38 [1] - 166:15

5

5 [24] - 17:7, 17:11, 47:13, 58:18, 84:4, 94:4, 154:16, 158:19, 159:14, 162:13, 164:7, 167:18, 167:25, 174:14, 174:15, 188:18, 230:21, 274:22, 275:1, 285:25, 291:4, 302:10, 319:14, 327:14
5,000 [1] - 5:13
5.1.3 [1] - 225:12
5.1.4 [5] - 65:19, 65:25, 101:3, 225:12, 226:2
50 [6] - 286:18, 287:13, 287:24, 307:15, 307:16, 307:19
505 [1] - 256:1
515 [1] - 136:12
52.42 [1] - 166:18
54 [1] - 319:14
54,000 [1] - 11:14
541 [1] - 136:15
55.612 [2] - 250:14, 250:17
553 [2] - 161:20, 177:24
553A [1] - 127:11
57 [1] - 58:24
572A [2] - 127:11, 231:15
58 [3] - 92:7, 214:6, 237:10
59 [1] - 214:7
5:28 [1] - 347:15

6

6 [13] - 85:4, 87:15, 102:12, 112:16, 174:13, 189:19, 190:1, 197:7, 231:15, 249:18, 275:4, 302:10, 339:20
6,030,643 [1] - 98:16
6,7-dimethoxy-quinoline-4-ol [2] - 6:7, 80:17
6.7 [9] - 63:24, 113:6, 214:19, 214:21, 215:21, 216:10, 238:20, 239:4, 239:16
6.70 [1] - 114:1
60 [6] - 112:18, 112:21, 112:22, 113:3, 215:9, 320:13
60-milligram [7] - 63:23, 73:20, 114:1, 201:6, 212:15, 243:13, 243:17

600 [2] - 293:5, 293:18
6148 [1] - 83:11
63 [5] - 73:9, 73:10, 73:12, 73:13, 73:15
65 [3] - 81:1, 81:3, 81:21
6742 [1] - 87:22
6743 [1] - 89:18
6766 [1] - 92:7
677 [1] - 127:12
678 [1] - 67:10
6804 [1] - 85:11
6805 [1] - 102:17
69 [2] - 81:2, 81:3
698 [1] - 127:12

7

7 [16] - 58:17, 65:5, 75:5, 86:3, 86:14, 96:8, 158:5, 159:14, 174:16, 192:23, 210:17, 211:5, 232:11, 275:11, 295:17, 308:22
7.2-8 [1] - 337:3
7.2.2.1 [1] - 271:10
70 [3] - 81:17, 81:18, 81:21
708 [1] - 136:13
7092 [1] - 96:18
71 [2] - 125:14, 125:17
72 [3] - 287:8, 287:9, 296:24
724 [1] - 127:12
744 [1] - 127:12
748 [1] - 206:20
75 [1] - 202:3
754 [1] - 206:5
770 [2] - 244:23, 256:3
776 [1] - 319:23
777 [1] - 127:12

8

8 [14] - 38:1, 75:6, 96:19, 96:25, 97:24, 98:13, 98:25, 195:15, 271:9, 286:12, 286:14, 319:14, 319:22, 327:14
8,877,776 [1] - 318:22
80 [3] - 202:3, 219:6, 220:25
80-micron [1] - 219:10
81 [1] - 249:15
81.58 [2] - 166:8, 205:8
825 [1] - 136:16
84 [4] - 210:22, 211:1, 325:12, 326:11
844 [1] - 1:10
86 [1] - 291:20
8768 [2] - 112:18, 112:21
877 [1] - 319:23
893 [2] - 83:11, 231:19
8:30 [3] - 1:12, 340:24, 341:10

9

9 [18] - 81:2, 99:17, 125:14, 158:18, 159:4, 169:5, 236:2, 240:15, 240:17, 249:12, 271:20, 284:24, 303:3, 310:9, 325:12, 336:17, 336:18, 337:1
9.7 [6] - 64:1, 214:22, 215:19, 215:21, 216:17, 238:20
9.70 [2] - 63:24, 114:2
9.71 [6] - 64:16, 104:21, 105:21, 106:6, 201:22, 233:14
90 [5] - 43:18, 166:10, 202:3, 323:23, 346:14
9326 [1] - 94:10
94 [1] - 269:22
96 [1] - 85:10
97 [6] - 102:16, 269:8, 269:11, 323:14, 327:14, 327:23
9740 [1] - 105:14
99 [3] - 329:8, 331:10, 331:13
99.9 [1] - 333:18
99786 [1] - 60:12
99787 [1] - 61:8
99849 [1] - 62:14

A

A-2 [6] - 32:1, 32:3, 32:9, 32:14, 32:25
a.m [1] - 1:12
A1 [1] - 318:16
abbreviated [2] - 76:24, 169:1
ability [1] - 121:6
able [22] - 9:17, 11:4, 28:24, 30:6, 30:8, 30:17, 45:16, 54:11, 79:11, 191:13, 216:11, 218:11, 220:9, 221:8, 242:15, 247:21, 276:5, 285:14, 300:11, 310:24, 343:22, 345:22
abnormal [3] - 5:5, 5:7, 5:9
abounds [1] - 310:12
absolute [1] - 141:6
absolutely [1] - 10:20
absorb [8] - 118:16, 119:2, 122:1, 122:2, 122:8, 122:13, 123:9, 167:7
absorbent [1] - 153:5
absorbing [2] - 121:3, 167:3
absorption [5] - 38:22, 170:14, 185:2, 185:4, 221:25
abstract [5] - 196:13, 266:14, 266:16, 326:17, 347:3
academic [1] - 185:10
Academy [1] - 258:18
acceptable [14] - 17:14, 18:23, 18:24, 19:8, 42:17, 42:22, 43:9, 44:12, 44:22, 45:2, 171:12, 194:5, 307:7, 342:2
accepted [2] - 195:7, 200:7
accepting [1] - 219:20
accessible [1] - 303:14
accomplish [1] - 229:24
accomplishing [1] - 56:8
accordance [1] - 3:7
according [10] - 28:6, 53:23, 191:22, 268:9, 282:7, 287:18, 293:8, 298:3, 331:7, 336:15
account [3] - 81:20, 107:20, 121:12
accuracy [6] - 282:18, 339:9, 339:11, 339:25, 340:11, 340:13
accurate [5] - 61:14, 72:13, 144:15, 338:25, 347:17
accurately [4] - 62:18, 102:24, 184:18, 257:21
accused [1] - 73:22
acetone [2] - 331:16, 332:1
achieve [3] - 34:13, 194:5, 268:6
acid [17] - 7:20, 7:23, 19:3, 19:4, 19:6, 19:8, 21:5, 21:7, 21:12, 45:1, 45:13, 45:18, 45:22, 298:15, 298:17, 342:24
acidified [2] - 296:22, 298:14
acids [3] - 18:23, 19:1, 19:3
acknowledge [1] - 24:1
acknowledgment [1] - 91:24
act [8] - 47:14, 172:3, 199:8, 221:9, 229:24, 248:16, 249:4
acting [11] - 105:4, 165:11, 218:13, 218:19, 220:22, 225:3, 236:20, 238:8, 248:21, 248:23, 249:6
action [1] - 46:23
active [17] - 4:8, 6:5, 9:13, 10:1, 23:7, 23:10, 54:18, 55:13, 71:1, 71:3, 76:23, 76:25, 77:1, 80:1, 103:24, 263:13, 313:25
activities [1] - 227:7
activity [3] - 5:7, 5:9, 70:13
acts [7] - 66:13, 164:17, 165:7, 206:10, 219:12, 222:22
actual [13] - 15:22, 15:23, 49:5, 55:16, 55:17, 108:14, 132:9, 221:6, 285:14, 286:20, 339:13, 346:25
add [8] - 110:15, 195:23, 195:25, 196:2, 209:23, 210:2, 295:9, 296:1
added [58] - 15:17, 25:10, 26:12, 26:13, 26:15, 26:17, 26:19, 78:14, 78:21, 78:25, 80:12, 82:10, 83:23, 84:2, 85:23, 86:13, 86:15, 86:19, 86:20, 86:22, 88:8, 89:10, 91:4, 102:1, 102:3, 103:23, 104:7, 104:12, 104:16, 104:20, 104:23, 104:25, 106:15, 108:6, 112:7, 114:6, 114:8, 114:12, 141:20, 142:9, 142:14, 142:17, 142:20, 150:10, 182:23, 187:3, 187:5, 199:24, 216:21, 228:15, 228:20, 228:22, 229:1, 229:3, 229:5, 229:8, 229:9, 298:16
adding [4] - 194:8, 295:22, 297:21, 321:9
addition [17] - 19:8, 25:17, 25:19, 33:15, 45:7, 110:15, 115:21, 126:25, 141:24, 148:4, 187:8, 189:13, 198:24, 211:21, 217:22, 272:5
additional [5] - 11:22, 33:16, 43:14, 65:19, 162:14
additionally [1] - 305:5
additives [1] - 179:2
address [13] - 69:11, 69:12, 80:15, 192:21, 209:8, 209:14, 209:16, 209:19, 209:20, 213:8, 223:10, 223:14, 224:19
addressed [2] - 77:23, 320:20
addresses [1] - 81:17
addressing [1] - 69:16
adequate [4] - 16:13, 225:18, 225:22, 342:8
adhere [6] - 118:23, 119:7, 120:23, 120:24, 121:6, 218:25
adhered [1] - 218:18
adherence [3] - 123:6, 123:18, 165:13
Adherence [1] - 218:6
adherents [2] - 158:22, 200:18
adheres [1] - 166:23

adjunct [1] - 71:18
adjust [3] - 187:6, 212:2, 216:2
adjusting [1] - 212:4
administered [2] - 77:1, 77:8
administration [2] - 77:15, 81:7
admitted [11] - 68:2, 68:5, 127:8, 127:10, 127:12, 177:20, 177:23, 177:24, 255:23, 256:2, 256:3
adopt [1] - 262:25
adopted [1] - 188:13
adsorb [2] - 220:10, 220:16
adsorbing [1] - 222:20
adsorbs [1] - 223:11
advised [1] - 20:23
Advisory [1] - 185:14
aerogels [1] - 173:7
affect [8] - 114:13, 120:25, 176:6, 176:10, 189:8, 194:12, 196:9, 200:5
affected [2] - 48:18, 134:3
affecting [1] - 47:24
affects [1] - 179:21
afternoon [13] - 59:4, 178:5, 183:25, 184:2, 230:5, 230:9, 230:10, 255:8, 256:6, 256:21, 256:22, 267:6, 311:15
agency [1] - 291:19
agent [1] - 162:8
agents [3] - 51:12, 229:8, 273:6
agglomerate [1] - 110:22
aggregate [1] - 193:12
aggregates [2] - 193:14, 193:15
ago [8] - 31:10, 35:12, 60:10, 280:1, 289:19, 305:12, 346:11, 347:1
agree [68] - 23:20, 46:16, 81:21, 101:13, 109:12, 110:8, 112:6, 112:9, 116:9, 117:8, 117:11, 129:14, 129:24, 129:25, 133:22, 143:7, 144:17, 145:11, 145:13, 146:9, 150:10, 150:14, 151:4, 154:5, 155:7, 155:10, 155:23, 156:9, 156:14, 165:20, 166:7, 166:10, 171:7, 171:13, 173:1, 176:7, 176:11, 176:19, 191:17, 191:21, 191:24, 198:16, 216:6, 219:22, 228:19, 228:22, 228:24, 230:11, 232:21, 235:15, 236:17, 242:15, 246:10, 247:14, 247:17, 251:5, 262:11, 317:18, 319:1, 319:25, 320:19, 322:10, 324:4, 324:12, 325:1, 331:5, 333:14, 336:11
agreed [4] - 125:19, 155:24, 165:16, 254:19
agreement [6] - 67:8, 74:13, 125:18, 126:1, 126:3, 127:4
ahead [11] - 2:22, 3:19, 50:6, 128:6, 128:12, 148:24, 149:11, 315:25, 337:17, 341:12, 341:15
air [3] - 122:4, 122:6
al [1] - 1:7
albeit [1] - 123:17
alert [1] - 303:10
aligning [1] - 182:22
Allan [1] - 29:14
allegations [2] - 31:22, 32:24
alleges [1] - 217:13
alleging [1] - 74:4
allocation [1] - 58:23
allow [3] - 119:9, 224:13, 252:8
allowed [4] - 9:5, 22:2, 30:20, 33:12
allows [4] - 20:11, 23:15, 30:23, 88:17
almost [2] - 161:13, 250:22
alone [4] - 21:16, 109:11, 110:6, 162:11
alpha [1] - 153:23
alpha-lactose [1] - 153:23
alter [1] - 295:8
alternative [3] - 220:4, 321:7, 331:24
alternatively [1] - 299:24
amended [5] - 73:8, 75:3, 75:8, 80:25, 125:12
amendments [1] - 320:16
American [3] - 185:6, 185:8, 185:9
Ames [8] - 52:22, 266:8, 303:15, 305:10, 305:11, 306:12, 306:14, 306:15
aminal [7] - 297:16, 298:1, 298:4, 298:13, 298:25, 299:1, 299:2
amorphous [1] - 14:22
amount [29] - 3:15, 9:11, 9:16, 23:7, 27:19, 80:1, 85:20, 108:4, 118:20, 118:24, 195:25, 201:21, 201:23, 212:19, 213:14, 214:16, 215:22, 242:6, 242:11, 243:19, 243:24, 244:13, 250:4, 254:25, 282:25, 284:4, 284:6, 285:15, 297:14
amounts [6] - 48:17, 49:17, 189:25, 201:14, 244:19, 244:20
AMRI [11] - 276:17, 276:19, 278:15, 278:24, 279:5, 280:16, 280:18, 283:18, 283:24, 284:14, 285:19
AMY [1] - 1:21
Amy [1] - 311:16
analogs [2] - 304:21, 305:6
analysis [26] - 16:11, 38:20, 42:15, 43:24, 43:25, 76:11, 80:19, 87:9, 93:17, 101:16, 101:17, 101:23, 106:24, 135:17, 167:9, 200:24, 205:10, 276:1, 276:4, 288:1, 292:11, 313:21, 314:23, 342:6, 343:5, 343:7
analysts [4] - 282:2, 282:14, 282:17, 283:4
analytical [5] - 76:1, 269:24, 276:15, 285:10, 285:23
analyze [2] - 268:20, 272:16
analyzed [4] - 74:22, 271:2, 293:20, 332:2
analyzing [5] - 74:8, 76:3, 188:9, 317:13, 317:23
analyzing/evaluating [1] - 317:4
ANDA [127] - 24:11, 25:13, 26:7, 47:4, 47:5, 59:25, 60:7, 62:11, 62:19, 64:23, 66:10, 66:13, 73:17, 73:21, 73:25, 74:1, 74:5, 74:11, 74:17, 85:9, 85:16, 85:25, 86:12, 86:19, 87:1, 87:3, 87:10, 87:18, 90:11, 92:2, 92:15, 92:22, 93:2, 93:16, 99:22, 101:9, 101:20, 102:13, 102:21, 102:25, 105:11, 106:8, 106:16, 107:21, 108:2, 108:7, 108:12, 108:23, 112:7, 114:6, 117:18, 119:3, 121:3, 122:7, 122:23, 123:12, 124:10, 124:15, 124:19, 124:22, 125:4, 125:9, 125:20, 125:21, 126:15, 133:22, 138:20, 145:8, 145:9, 145:12, 145:17, 146:6, 146:7, 146:10, 146:13, 158:3, 161:14, 164:23, 165:1, 165:7, 165:12, 165:24, 166:4, 167:3, 168:24, 169:5, 169:25, 170:13, 171:1, 180:9, 182:13, 182:19, 186:10, 187:1, 187:4, 187:10, 201:3, 201:4, 201:5, 202:8, 202:11, 202:13, 202:22, 202:25, 205:10, 208:10, 208:14, 208:15, 217:4, 219:7, 222:15, 222:20, 222:22, 225:25, 226:19, 233:13, 233:23, 234:4, 234:11, 234:15, 234:19, 234:22, 235:1, 235:10, 247:4, 250:1
ANDA's [1] - 87:6
ANDREWS [1] - 1:14
Andrews [1] - 2:14
animals [1] - 70:15
anion [1] - 44:16
Ann [1] - 7:4
Ansel [4] - 148:20, 194:18, 195:1, 195:7
ANSWER [8] - 319:24, 320:17, 325:17, 326:17, 327:18, 328:1, 328:7, 340:2
answer [7] - 28:22, 55:17, 319:20, 325:14, 325:20, 329:5, 340:6
ANTHONY [1] - 1:17
anti [1] - 158:22
anti-adherents [1] - 158:22
anyway [2] - 153:12, 154:7
apart [1] - 224:14
API [128] - 6:5, 9:13, 10:1, 10:4, 10:11, 10:13, 10:14, 13:2, 23:13, 24:15, 25:16, 25:18, 25:21, 27:9, 28:7, 28:9, 28:14, 28:15, 28:19, 28:21, 29:20, 29:21, 30:7, 30:10, 30:23, 32:4, 32:7, 32:10, 55:13, 56:5, 56:16, 60:20, 76:24, 77:2, 88:8, 89:8, 89:9, 89:14, 132:18, 133:2, 133:6, 146:23, 147:10, 151:2, 164:25, 190:2, 190:6, 190:8, 190:19, 192:11, 192:17, 193:5, 193:22, 195:20,

196:3, 208:24, 208:25, 209:1, 209:9, 209:17, 235:19, 261:6, 262:8, 262:12, 263:9, 263:12, 263:14, 263:15, 263:20, 264:9, 264:18, 265:2, 265:8, 266:24, 267:20, 267:25, 268:4, 268:6, 269:13, 270:18, 270:23, 270:24, 271:14, 271:25, 272:8, 272:14, 272:17, 272:20, 275:16, 275:19, 292:19, 292:20, 294:7, 294:14, 295:21, 295:24, 299:7, 299:17, 299:25, 300:20, 302:18, 306:11, 307:6, 307:24, 308:2, 309:9, 310:14, 310:18, 313:22, 313:25, 314:5, 314:7, 314:23, 318:5, 318:8, 320:25, 321:4, 322:5, 324:18, 325:6, 325:9, 325:19, 326:6, 329:18, 335:5, 335:12, 335:13
API's [1] - 194:1
APIs [4] - 176:19, 177:1, 262:6, 310:1
apologies [2] - 174:7, 183:10
apologize [1] - 171:24
Apotex [1] - 44:7
apparent [1] - 110:12
appear [5] - 46:18, 178:22, 218:2, 282:4, 325:1
appearance [1] - 80:4
APPEARANCES [2] - 1:16, 2:1
appeared [2] - 112:23, 244:2
applicable [1] - 100:10
applicant [2] - 169:9, 245:17
applicant's [1] - 320:15
application [20] - 15:16, 28:3, 28:4, 43:21, 43:22, 44:20, 157:25, 169:1, 201:4, 201:12, 208:15, 244:25, 245:3, 245:16, 245:23, 246:10, 253:1, 253:21, 254:15, 259:21
applications [2] - 72:4, 72:6
applied [8] - 71:13, 76:12, 82:7, 260:2, 327:5, 327:8, 327:16, 328:5
applies [1] - 46:8
apply [3] - 76:3, 207:8, 343:9
applying [2] - 75:11, 262:18
appointment [1] - 71:18
approach [3] - 128:9, 285:23, 294:16
approaches [1] - 303:6
appropriate [2] - 3:13, 317:3
approval [6] - 4:17, 5:17, 5:21, 7:2, 73:18, 125:21
approved [3] - 5:20, 11:16, 45:2
aqueous [1] - 19:15
area [2] - 224:16, 266:12
areas [1] - 11:21
argue [4] - 13:15, 13:16, 27:20, 347:2
argues [1] - 17:4
argument [9] - 14:6, 27:21, 28:11, 31:3, 35:8, 42:6, 106:18, 293:19
arguments [6] - 13:14, 35:6, 46:14, 57:25, 320:16, 345:7
arise [2] - 29:20, 330:3
arises [1] - 280:13
arose [2] - 6:3, 6:4
arrive [4] - 11:7, 30:2, 32:23, 88:25
arrived [1] - 19:18
arriving [1] - 33:2
ARSHT [1] - 1:17
art [60] - 16:20, 19:23, 19:25, 20:6, 20:16, 21:23, 29:2, 29:3, 29:4, 29:5, 29:19, 30:1, 36:17, 38:15, 38:23, 41:21, 41:25, 44:19, 45:2, 45:5, 45:15, 45:20, 45:23, 46:2, 47:23, 51:1, 51:17, 51:19, 55:18, 55:20, 55:22, 56:1, 56:13, 56:14, 74:12, 74:24, 76:16, 165:17, 176:17, 187:20, 188:1, 229:21, 232:22, 262:16, 264:11, 265:22, 266:23, 303:21, 304:14, 306:6, 308:7, 308:9, 310:23, 315:2, 315:10, 317:21, 330:16, 333:11, 342:17, 342:20
article [13] - 151:11, 151:20, 196:16, 197:11, 197:19, 197:24, 197:25, 198:3, 198:8, 264:17, 265:18, 301:12
articles [3] - 152:4, 178:6, 185:17
articulate [1] - 344:14
articulated [2] - 342:9, 344:3
artisan [2] - 20:17, 29:23
ascertain [1] - 322:18
aspect [2] - 38:1, 38:4
aspects [1] - 103:2
assay [2] - 52:22, 145:5
assays [2] - 303:14
assert [1] - 15:25
asserted [8] - 12:24, 12:25, 13:19, 18:19, 22:15, 57:13, 260:8, 312:23
asserting [2] - 73:4, 312:1
assertion [1] - 22:24
assess [3] - 93:18, 99:25, 214:2
assessed [2] - 88:25, 146:20
assessing [4] - 90:21, 266:3, 303:6, 304:10
assessment [21] - 61:9, 61:16, 61:24, 91:13, 91:16, 91:23, 143:1, 143:7, 143:16, 144:3, 144:18, 144:24, 145:3, 146:1, 175:12, 226:24, 227:3, 227:21, 235:22, 236:3, 237:1
assign [1] - 209:3
assigned [3] - 98:20, 192:9, 277:18
assignee [1] - 28:3
assist [2] - 184:3, 257:7
associate [1] - 223:20
associated [5] - 210:11, 210:25, 211:17, 215:7, 223:15
Association [2] - 185:6, 185:9
assume [9] - 3:17, 20:14, 20:15, 68:3, 183:2, 217:10, 338:17, 339:1, 339:4
assuming [2] - 338:2, 338:12
Atlantic [1] - 258:9
atomic [3] - 224:8, 248:8, 248:14
atoms [6] - 37:7, 37:10, 39:25, 224:9, 224:11, 224:16
attach [1] - 119:7
attainable [1] - 333:15
attempts [2] - 212:16, 223:9
attention [10] - 44:7, 44:8, 53:2, 75:5, 84:16, 86:3, 100:20, 305:22, 335:22, 341:3
attributed [1] - 120:14
attributes [1] - 92:3
August [2] - 42:18, 169:14
Austin [2] - 70:6, 70:9
author [2] - 151:18, 308:23
authored [2] - 258:11, 258:12
automatically [1] - 254:23
available [7] - 100:13, 138:12, 155:15, 174:10, 264:3, 269:25, 337:25
average [7] - 166:7, 166:9, 205:8, 219:5, 219:7, 220:25, 282:5
Avicel [9] - 196:17, 196:19, 196:20, 197:1, 197:2, 197:3, 197:12, 197:13, 197:18
avoid [1] - 29:12
avoided [1] - 29:6
awards [1] - 258:17
aware [11] - 39:5, 58:5, 61:14, 126:8, 126:11, 134:9, 147:25, 180:4, 310:5, 335:24, 337:22
awful [1] - 224:11

B

B-2 [5] - 32:18, 32:19, 32:23, 33:4
bachelor's [2] - 75:20, 258:4
background [15] - 25:7, 35:10, 52:10, 70:3, 76:20, 186:22, 188:19, 200:22, 262:5, 263:6, 281:6, 281:8, 302:9, 302:12
bacteria [1] - 100:1
Bairy [1] - 2:10
balls [1] - 218:17
barrier [1] - 20:9
base [14] - 6:1, 6:2, 6:15, 7:16, 7:18, 7:20, 7:21, 7:22, 7:23, 8:23, 9:2, 18:2, 21:19
based [45] - 15:5, 17:5, 33:10, 40:18, 59:17, 62:1, 63:8, 63:13, 63:14, 63:21, 64:3, 64:19, 66:8, 81:3, 104:15, 111:13, 113:24, 124:9, 126:8, 131:5, 131:12, 137:5, 137:10, 140:15, 141:4, 144:6, 166:13, 187:1, 211:11, 216:14, 222:6, 226:10, 238:24, 242:10, 254:10, 280:16, 287:15, 299:4, 299:10, 320:5, 320:15, 323:23, 335:13, 339:8, 340:2
Based [1] - 61:15
basic [1] - 53:12
basis [7] - 40:19, 64:16, 64:18, 143:16, 227:18, 234:14, 238:5
batch [45] - 55:3, 135:20, 135:23,

136:2, 136:3, 136:12, 136:23, 137:2, 137:6, 137:10, 138:17, 139:2, 139:12, 140:14, 140:16, 140:17, 141:1, 141:2, 141:3, 141:7, 210:10, 210:12, 210:25, 211:4, 211:9, 211:23, 213:1, 219:8, 251:23, 251:24, 271:17, 277:13, 293:7, 293:11, 293:13, 310:18, 334:12, 334:15, 335:1, 336:12, 337:19
batches [49] - 31:9, 31:10, 31:12, 31:14, 31:15, 88:6, 136:10, 137:14, 137:20, 211:18, 214:10, 215:6, 215:7, 215:16, 215:22, 251:23, 251:24, 252:18, 252:21, 270:19, 270:24, 271:1, 271:3, 272:8, 276:3, 276:4, 276:6, 277:4, 277:6, 277:16, 277:19, 279:24, 280:19, 282:6, 282:14, 286:15, 286:16, 287:11, 288:4, 288:13, 288:14, 288:19, 288:21, 291:25, 292:3, 335:7, 335:17, 335:21, 335:25
Bates [16] - 60:5, 62:13, 65:5, 83:11, 85:10, 87:22, 89:18, 92:7, 94:10, 96:18, 102:16, 105:14, 112:18, 112:21, 120:4, 149:18
BD [1] - 120:25
bear [5] - 89:12, 92:21, 98:9, 101:16, 104:25
becomes [1] - 189:6
BEFORE [1] - 1:14
began [2] - 5:10, 158:2
begin [3] - 21:15, 248:15, 311:21
Beginning [1] - 59:3
beginning [8] - 84:17, 89:20, 95:19, 99:2, 114:14, 120:19, 147:15, 229:15
begins [3] - 118:21, 239:9, 253:15
behalf [2] - 35:1, 256:7
behaving [1] - 206:25
behaviors [2] - 200:8, 205:25
behind [1] - 328:9
belies [1] - 33:1
believes [1] - 109:10
below [18] - 44:19, 54:16, 54:19, 55:11, 56:2, 60:19, 77:21, 89:5, 95:11, 115:2, 209:10, 209:11, 212:24, 250:14, 254:6, 279:12, 307:19, 337:10
Bench [1] - 1:13
beneath [2] - 88:21, 242:15
beneficial [1] - 118:20
benefit [1] - 89:14
Bernard [1] - 16:1
best [10] - 8:10, 9:1, 20:24, 21:4, 174:10, 187:15, 190:20, 191:1, 346:8, 347:11
better [8] - 3:5, 120:10, 190:18, 197:16, 213:22, 287:22, 290:14, 331:3
between [32] - 45:22, 74:14, 85:1, 118:5, 123:5, 126:2, 127:4, 137:19, 138:17, 140:25, 167:24, 171:2, 180:3, 185:3, 200:20, 202:9, 211:9, 211:25, 215:21, 218:14, 223:22, 239:16, 242:4, 248:10, 248:13, 248:17, 248:22, 249:4, 254:16, 282:4, 286:5, 288:19
beyond [1] - 18:4
bigger [5] - 59:22, 220:5, 220:9, 221:4, 338:15
binder [41] - 47:14, 66:4, 72:10, 72:22, 73:7, 75:4, 83:3, 85:5, 94:4, 96:9, 98:13, 99:17, 101:7, 103:21, 105:7, 110:21, 112:17, 119:12, 124:25, 153:5, 156:1, 159:23, 162:8, 178:17, 179:6, 193:11, 204:22, 206:12, 207:2, 226:6, 230:21, 231:15, 232:11, 236:3, 242:17, 319:12, 319:13, 322:11, 322:12, 325:11, 336:18
binders [5] - 128:9, 158:9, 158:13, 256:9, 311:8
bioavailability [1] - 41:11
biologic [1] - 169:2
biotechnology [1] - 4:1
bit [24] - 14:5, 19:20, 35:10, 50:6, 50:23, 101:24, 110:18, 129:3, 174:2, 174:5, 186:21, 188:21, 192:18, 192:25, 193:12, 193:13, 208:22, 219:8, 221:1, 266:21, 290:11, 313:5, 324:23, 346:21
blend [47] - 23:16, 60:4, 79:8, 79:17, 82:10, 103:24, 104:4, 104:7, 116:16, 118:25, 121:16, 122:14, 122:15, 123:20, 138:9, 146:3, 147:5, 147:11, 147:19, 148:5, 165:24, 165:25, 166:4, 166:24, 167:3, 167:7, 167:8, 169:25, 170:13, 170:17, 170:22, 171:1, 172:3, 189:9, 189:22, 190:22, 191:8, 194:1, 194:12, 196:5, 196:10, 198:18, 198:22, 217:12, 228:16, 247:22, 251:3
blend's [1] - 147:12
blended [1] - 23:16
blender [1] - 79:17
blending [2] - 104:14, 120:13
blends [3] - 122:2, 199:24, 216:23
blends) [2] - 84:22, 232:19
blood [1] - 5:3
blow [1] - 240:24
blue [2] - 51:13, 193:4
body [1] - 5:3
Boggs [1] - 1:10
boiled [2] - 298:16, 298:17
book [2] - 249:12, 258:12
books [1] - 71:25
bottom [15] - 13:5, 38:20, 84:17, 100:22, 105:19, 159:15, 181:2, 181:20, 184:7, 199:18, 201:18, 218:10, 232:13, 269:22, 278:8
box [3] - 267:21, 267:23, 300:17
boxes [1] - 103:8
Boylan [2] - 82:25, 84:9
brand [4] - 86:7, 86:8, 97:12, 160:14
break [7] - 66:20, 67:18, 78:22, 168:8, 255:8, 263:11, 315:12
breakthrough [2] - 4:6, 34:1
BRIAN [1] - 2:7
bridge [1] - 34:5
bridging [1] - 283:17
brief [2] - 186:19, 262:4
briefing [1] - 3:19
briefly [6] - 107:25, 117:24, 208:23, 251:8, 258:2, 343:22
bring [2] - 44:6, 44:8
bringing [1] - 5:23
brings [1] - 27:4
Bristol [1] - 287:4
Bristol-Myers [1] - 287:4
broad [5] - 49:16, 50:1, 70:25, 148:11, 203:18
broaden [1] - 15:15
broadened [2] - 15:8, 15:20
brochure [2] - 162:24, 163:6
brochures [3] - 161:17, 161:18, 162:20
brought [2] - 104:3, 107:8
Brown [134] - 27:22, 27:23, 28:2, 28:6, 28:17, 28:21, 28:25, 30:5, 30:6, 30:9, 30:11, 30:16, 30:18, 30:22, 31:5, 31:16, 31:24, 31:25, 33:7, 33:8, 51:1, 51:2, 51:3, 51:5, 51:8, 51:10, 51:19, 53:7, 53:10, 53:23, 54:17, 55:7, 55:8, 55:11, 262:7, 267:5, 267:11, 267:13, 267:19, 268:7, 268:9, 268:20, 268:25, 269:3, 269:5, 269:8, 269:12, 269:23, 270:7, 270:14, 272:21, 272:25, 273:13, 273:22, 274:7, 274:9, 274:15, 275:18, 287:18, 293:14, 293:25, 294:23, 295:15, 295:21, 297:1, 297:7, 298:19, 298:20, 299:1, 299:2, 299:3, 299:6, 299:12, 299:15, 299:24, 300:14, 307:25, 318:9, 318:11, 318:13, 318:18, 319:1, 319:7, 320:5, 320:15, 320:24, 321:3, 321:9, 321:14, 321:22, 321:25, 322:4, 323:8, 323:11, 323:15, 327:5, 327:8, 327:24, 328:11, 328:13, 328:21, 328:24, 329:8, 329:13, 329:21, 329:24, 330:2, 330:4, 330:6, 330:9, 330:18, 330:24, 330:25, 331:8, 331:13, 332:19, 333:2, 333:5, 333:10, 333:13, 333:23, 334:6, 334:21, 334:24, 335:3,

335:9, 335:11, 335:14, 335:16, 335:20, 335:24, 336:4, 338:9
BRYCE [1] - 2:5
building [1] - 170:22
bulk [21] - 23:8, 48:4, 48:6, 78:15, 120:25, 131:5, 132:21, 132:24, 136:8, 136:12, 136:15, 139:6, 139:10, 139:19, 140:5, 140:18, 150:11, 181:21, 195:4, 211:18, 247:9
bulks [1] - 196:2
bullet [13] - 84:16, 84:20, 118:16, 122:1, 122:16, 123:6, 200:1, 200:15, 204:5, 204:16, 205:4, 218:10, 232:17
bullets [4] - 199:18, 206:6, 206:21, 232:15
bumping [1] - 196:4
burden [2] - 31:6, 333:19
business [1] - 287:3
busy [1] - 322:23
butyl [1] - 295:23
BY [263] - 1:17, 1:20, 1:20, 1:21, 1:21, 1:22, 2:2, 2:5, 2:5, 2:6, 2:6, 2:7, 62:3, 68:19, 70:1, 72:20, 76:7, 77:13, 77:22, 79:4, 80:9, 80:21, 81:14, 82:2, 82:17, 84:6, 84:15, 86:24, 87:8, 87:16, 87:23, 89:19, 91:11, 92:8, 93:15, 94:5, 94:11, 96:10, 96:21, 98:14, 99:1, 99:18, 100:7, 101:22, 103:6, 109:6, 109:17, 110:4, 111:18, 112:2, 113:18, 117:2, 119:13, 121:25, 123:22, 124:7, 125:1, 125:16, 125:24, 128:14, 130:8, 134:23, 135:10, 140:12, 141:16, 143:3, 145:2, 145:23, 148:19, 150:9, 151:10, 152:9, 152:19, 157:6, 158:7, 158:20, 159:6, 159:17, 160:16, 162:22, 163:14, 163:25, 164:9, 165:5, 168:18, 169:20, 172:12, 173:16, 174:8, 178:4, 178:15, 179:16, 179:24, 180:18, 183:24, 184:9, 184:14, 184:22, 186:8, 186:17, 187:17, 187:23, 188:20, 189:20, 192:5, 192:24, 194:16, 194:24, 195:16, 196:14, 196:25, 197:10, 197:23, 198:15, 199:12, 199:20, 201:1, 201:9, 202:7, 203:6, 203:14, 204:7, 204:18, 205:5, 206:7, 206:22, 208:21, 210:24, 212:8, 214:9, 215:11, 217:9, 218:7, 219:25, 221:20, 222:25, 225:8, 225:13, 227:1, 228:11, 230:8, 231:18, 233:1, 233:18, 239:23, 240:7, 240:25, 242:22, 244:24, 249:17, 251:10, 251:16, 252:12, 252:25, 253:16, 256:20, 257:4, 257:18, 258:1, 258:15, 259:9, 259:22, 260:7, 260:12, 261:1, 261:10, 262:1, 263:4, 264:15, 264:22, 265:16, 266:2, 266:15, 267:3, 267:10, 267:18, 268:12, 268:24, 269:10, 270:6, 270:12, 271:6, 271:11, 271:22, 272:11, 273:10, 273:21, 274:8, 274:13, 274:18, 274:25, 275:5, 275:12, 275:24, 276:12, 276:20, 277:1, 277:9, 277:24, 278:10, 278:19, 279:3, 279:19, 281:1, 281:7, 281:13, 281:24, 282:11, 282:23, 283:15, 284:9, 284:25, 286:1, 286:13, 286:25, 288:6, 289:21, 290:6, 290:18, 291:1, 291:16, 291:21, 292:9, 292:25, 294:4, 294:12, 295:1, 295:18, 296:14, 297:18, 298:10, 298:22, 299:22, 300:7, 300:16, 301:7, 301:17, 302:3, 302:11, 303:4, 303:25, 304:6, 304:18, 304:25, 305:16, 307:2, 307:22, 308:11, 308:19, 309:6, 309:17, 309:22, 310:10, 311:14, 323:7, 323:16, 326:19, 327:19, 328:10, 329:9, 336:20, 337:2, 340:4
byproducts [1] - 329:1

C

C.A [1] - 1:5
CABO_1830 [1] - 65:5
Cabo_99752 [1] - 60:6
Cabometyx [15] - 4:7, 4:8, 4:25, 5:8, 5:20, 11:16, 11:21, 12:3, 12:7, 12:9, 12:13, 33:19, 33:21, 202:10
Cabosil [1] - 173:7
Cabozantinib [2] - 85:8, 113:2
cabozantinib [141] - 4:9, 4:15, 4:22, 5:17, 5:25, 6:5, 7:16, 7:22, 8:5, 8:11, 8:19, 8:23, 9:14, 9:25, 11:11, 13:2, 13:4, 13:7, 14:18, 14:21, 15:12, 16:15, 17:12, 17:19, 17:21, 18:9, 18:10, 18:13, 18:14, 18:16, 19:2, 19:13, 19:16, 19:23, 20:1, 20:3, 20:10, 21:10, 21:12, 22:14, 24:12, 25:4, 25:5, 27:9, 28:1, 29:9, 30:23, 31:9, 31:12, 31:17, 33:24, 34:6, 36:3, 37:4, 37:15, 37:16, 38:3, 38:4, 39:9, 39:20, 40:6, 40:18, 42:16, 42:17, 43:8, 45:13, 45:22, 50:11, 50:25, 51:4, 51:6, 52:14, 52:16, 53:8, 53:13, 60:22, 61:3, 62:15, 63:23, 66:10, 73:19, 77:19, 81:7, 88:7, 89:9, 102:19, 103:11, 114:1, 115:15, 115:19, 121:7, 121:22, 125:4, 169:6, 186:10, 201:5, 201:11, 208:23, 212:19, 212:22, 212:24, 233:20, 233:24, 235:16, 241:2, 243:7, 266:23, 267:14, 267:24, 268:8, 268:25, 269:4, 269:12, 270:7, 270:15, 293:21, 294:15, 294:20, 299:7, 299:13, 300:2, 307:24, 310:24, 313:11, 313:22, 318:7, 320:25, 321:4, 322:1, 329:18, 330:18, 330:19, 331:1, 332:13, 332:18, 332:21, 333:23, 334:4, 335:10, 339:6
cake [3] - 296:22, 297:2, 297:3
cakes [1] - 296:20
calculate [5] - 131:3, 139:9, 139:19, 139:23, 140:5
calculated [3] - 131:8, 133:2, 140:8
calculating [1] - 139:5
calculation [4] - 88:16, 88:24, 191:24, 307:13
calculations [7] - 141:4, 181:13, 191:22, 219:16, 219:18, 219:20, 219:22
Caleb [1] - 1:10
callout [1] - 143:4
calorimetry [1] - 38:21
campaign [1] - 294:16
cancer [20] - 4:7, 6:11, 6:24, 11:12, 11:18, 11:19, 11:22, 12:1, 12:4, 12:11, 13:6, 17:23, 18:16, 34:7, 34:9, 34:10, 34:11, 43:20
cancers [2] - 4:3, 11:17
capsule [38] - 10:22, 48:5, 49:20, 50:12, 55:16, 56:6, 56:17, 66:3, 77:25, 78:3, 78:8, 78:9, 84:22, 101:7, 149:13, 153:6, 173:4, 174:17, 175:10, 189:4, 194:23, 195:1, 195:2, 206:11, 207:1, 226:5, 232:19, 233:19, 288:16, 288:24, 289:5, 289:6, 289:13, 289:17, 291:9, 291:23, 292:6
capsules [16] - 10:15, 10:25, 51:6, 71:10, 185:22, 195:6, 288:3, 288:15, 288:19, 289:3, 289:7, 289:12, 289:15, 291:13, 291:25, 314:2
carcinogenic [2] - 52:25, 305:3
carcinogenicity [1] - 264:8
carcinoma [2] - 11:17, 11:18
care [1] - 67:14
career [7] - 131:9, 154:12, 161:17, 175:11, 185:18, 258:20, 258:22
careful [1] - 89:15
Carr [26] - 88:18, 129:21, 131:4, 131:8, 131:13, 131:17, 131:21, 131:24, 132:3, 132:4, 136:19, 136:23, 137:2, 137:5, 137:10,

137:19, 137:23, 139:1, 139:6, 139:9, 139:23, 140:13, 140:25, 181:21, 191:15, 191:17
Carr's [2] - 88:15, 136:11
carried [2] - 300:25, 333:22
carries [1] - 89:23
carry [2] - 334:5, 334:8
case [120] - 3:4, 3:12, 3:17, 4:20, 5:22, 11:11, 12:18, 12:25, 15:23, 17:3, 17:6, 17:9, 20:22, 23:13, 28:20, 28:23, 33:22, 34:5, 34:14, 35:17, 35:18, 35:22, 35:23, 36:11, 36:20, 44:2, 44:5, 44:7, 44:11, 45:12, 45:16, 46:8, 48:15, 51:2, 52:9, 52:13, 52:18, 53:5, 56:22, 56:25, 57:9, 57:18, 57:24, 57:25, 68:25, 69:3, 69:11, 69:22, 73:5, 73:23, 75:12, 79:15, 79:25, 81:5, 82:4, 82:7, 89:13, 101:17, 103:22, 107:8, 108:19, 121:20, 126:8, 126:12, 127:19, 129:12, 130:21, 135:5, 135:17, 137:18, 138:24, 141:6, 143:25, 148:8, 148:10, 151:12, 151:21, 157:13, 157:18, 162:24, 163:7, 166:21, 181:5, 182:6, 183:8, 187:14, 187:18, 188:12, 192:1, 198:10, 202:22, 208:13, 217:24, 220:6, 232:3, 234:18, 260:1, 262:14, 267:25, 268:19, 272:15, 287:22, 293:16, 294:14, 300:21, 307:15, 309:13, 310:14, 310:17, 312:2, 312:8, 319:7, 327:2, 327:17, 328:6, 333:20, 338:21, 345:4, 345:13
case-in-chief [2] - 57:9, 57:24
cases [2] - 49:15, 56:23
catalytic [1] - 154:21
categories [5] - 12:19, 50:8, 51:25, 181:21, 234:3
categorize [1] - 137:13
category [6] - 44:14, 49:23, 49:24, 52:11, 203:18, 209:7
caused [1] - 181:9
causes [1] - 9:20
causing [1] - 34:11
cell [1] - 11:17
cells [2] - 5:5, 185:2
cellular [1] - 5:1
cellulose [11] - 103:22, 152:21, 152:24, 153:16, 196:17, 196:20, 196:22, 197:3, 197:4, 197:14, 197:19
certain [14] - 6:20, 7:20, 69:13, 85:22, 118:20, 126:19, 148:2, 234:2, 234:3, 323:12, 344:24, 345:1, 345:3, 345:7
certainly [10] - 3:9, 40:20, 189:3, 202:4, 302:21, 304:13, 306:13, 308:8, 325:3, 340:9
Certified [1] - 347:19
certify [1] - 347:16
cetera [3] - 107:11, 130:1, 148:12
chair [1] - 185:16
challenge [5] - 9:9, 10:16, 13:25, 22:23, 27:5
challenges [1] - 5:22
challenging [1] - 192:19
chance [2] - 45:24, 196:4
change [26] - 9:24, 40:11, 76:11, 90:18, 107:21, 108:17, 131:24, 156:17, 156:19, 156:20, 188:12, 192:17, 207:20, 211:13, 213:8, 213:11, 213:14, 215:21, 223:23, 239:16, 239:17, 244:13, 262:24, 295:10, 309:10, 338:15
changed [3] - 12:3, 156:19, 241:12
changes [17] - 10:5, 10:7, 10:10, 209:22, 212:1, 223:22, 239:18, 278:14, 295:10, 336:11, 336:13, 336:16, 337:18, 337:23, 338:1, 338:8, 338:12
changing [1] - 239:14
chapter [7] - 94:6, 130:19, 191:25, 207:25, 208:3, 231:16, 308:22
Chapter [1] - 308:22
chapters [2] - 97:18, 258:12
character [12] - 110:16, 131:12, 131:17, 131:20, 132:9, 137:6, 137:9, 137:14, 141:2, 192:6, 209:3, 217:12
characteristic [3] - 79:1, 82:11, 238:1
characteristics [36] - 23:23, 24:2, 24:23, 41:11, 48:7, 59:17, 59:19, 63:3, 64:13, 65:1, 83:17, 84:21, 90:12, 92:14, 113:10, 114:21, 115:4, 116:15, 147:19, 189:25, 192:17, 195:5, 196:7, 196:18, 199:9, 205:25, 215:2, 215:6, 230:12, 230:17, 231:24, 232:18, 234:21, 237:23, 238:8, 239:11
characterization [2] - 8:21, 238:1
characterize [4] - 19:19, 88:17, 129:15, 191:18
characterized [6] - 128:25, 131:12, 133:12, 147:16, 147:20, 297:16
characterizes [1] - 38:15
characterizing [4] - 129:24, 130:5, 191:12, 191:14
charge [5] - 32:17, 118:11, 118:12, 118:13, 341:11
charged [1] - 183:12
charges [9] - 118:5, 118:6, 118:15, 169:22, 170:1, 170:3, 170:9, 223:2
chart [23] - 62:15, 62:18, 102:18, 102:23, 133:5, 135:11, 135:15, 135:20, 136:7, 138:11, 139:2, 139:11, 139:21, 140:6, 140:15, 141:19, 159:15, 201:8, 201:10, 201:11, 227:19, 251:18, 251:21
charts [1] - 38:13
check [4] - 81:15, 133:13, 173:20, 285:16
checkmark [1] - 124:13
chemical [24] - 7:25, 8:1, 16:2, 29:17, 40:18, 41:8, 50:10, 52:9, 52:11, 60:3, 75:21, 77:21, 118:8, 215:15, 326:2, 326:15, 327:5, 327:8, 327:16, 327:25, 328:3, 328:5, 337:9
Chemical [1] - 185:8
chemically [1] - 153:17
chemist [1] - 322:7
chemistry [16] - 7:10, 10:6, 29:16, 75:21, 75:24, 188:4, 258:5, 258:8, 258:25, 259:6, 273:18, 296:8, 297:8, 315:16, 315:24, 332:23
chemists [5] - 75:25, 76:1, 285:24, 303:8, 308:3
chief [2] - 57:9, 57:24
choice [8] - 8:19, 21:6, 21:8, 21:11, 21:12, 133:15, 192:18, 209:11
choose [1] - 195:24
chose [1] - 215:18
chromatography [5] - 263:24, 269:25, 270:1, 270:2, 328:16
chunky [1] - 193:16
Cipla [1] - 39:22
Circuit [1] - 345:13
circumstances [2] - 45:6, 111:9
cite [1] - 162:23
cited [3] - 44:5, 151:23, 151:25
Claim [49] - 12:25, 13:2, 13:4, 17:7, 17:11, 22:15, 27:5, 27:13, 27:20, 28:13, 32:7, 57:14, 57:15, 73:2, 73:4, 74:5, 74:8, 74:18, 74:20, 75:9, 77:10, 77:23, 80:7, 80:15, 80:22, 81:4, 116:20, 124:16, 124:20, 126:14, 182:16, 230:20, 230:22, 230:24, 230:25, 233:16, 233:19, 234:1, 234:7, 260:6, 260:8, 269:1, 312:23, 313:2, 313:6, 314:11, 314:17
claim [29] - 12:23, 12:24, 13:1, 17:5, 18:2, 22:16, 27:13, 33:12, 36:8, 36:23, 37:15, 37:17, 37:21, 38:10, 43:4, 43:5, 46:17, 46:19, 49:17, 50:1, 51:11, 51:12, 51:13, 74:22, 77:12, 124:8, 260:14, 312:23
claimed [15] - 11:8, 30:3, 30:17, 36:5, 36:19, 43:9, 74:24, 158:13, 159:19, 174:18, 260:18, 315:15, 321:22, 330:15, 335:12
claiming [1] - 50:2
claims [56] - 9:6, 13:3, 13:6, 13:15, 13:17, 13:19, 14:12, 14:14, 14:17, 14:18, 14:20, 14:24, 14:25, 15:5, 15:12, 15:24, 16:4, 16:10, 16:13, 17:10, 17:17, 17:18, 18:1, 18:3, 18:4, 18:18, 18:19, 22:2, 22:24,

30:21, 32:6, 35:15, 35:16, 36:23, 37:1, 37:3, 37:21, 39:17, 41:2, 42:5, 42:21, 43:1, 43:3, 43:6, 43:11, 43:14, 44:13, 49:13, 49:19, 51:22, 56:7, 57:13, 160:9, 259:23, 261:12, 343:6
clarification [1] - 196:23
clarify [3] - 69:15, 252:5, 252:6
class [5] - 52:2, 261:4, 261:5, 303:12, 303:20
classic [2] - 223:8, 232:1
classify [1] - 190:9
clear [18] - 33:25, 37:24, 47:4, 57:17, 58:3, 127:3, 134:19, 167:21, 168:2, 168:24, 213:13, 228:4, 251:12, 252:23, 322:22, 323:2, 325:17, 345:13
clearly [2] - 86:21, 178:12
CLERK [18] - 2:13, 67:19, 67:21, 68:9, 168:10, 168:12, 174:1, 174:4, 183:15, 187:15, 255:9, 255:11, 256:12, 290:9, 290:13, 290:15, 340:25, 347:14
clinic [1] - 33:20
clinical [6] - 5:15, 5:16, 11:23, 33:19, 307:6, 337:14
Clinical [1] - 185:14
clinicians [1] - 76:2
closely [1] - 39:10
closer [3] - 174:7, 213:21, 313:5
closest [1] - 138:16
clouds [1] - 224:9
co [2] - 258:11, 258:12
Co [1] - 119:19
co-authored [2] - 258:11, 258:12
coated [1] - 104:9
Coating [1] - 123:6
coating [3] - 165:13, 165:24, 166:4
cohesion [1] - 120:15
collaborated [3] - 317:16, 317:18, 317:21
collaborating [1] - 188:7
colleague [1] - 58:2
colleagues [2] - 3:24, 316:1
collected [1] - 79:20
collectively [3] - 33:22, 92:21, 188:8
Colleges [1] - 185:9
colloidal [6] - 160:1, 162:15, 174:24, 175:2, 175:9, 175:14
color [1] - 344:1
coloring [1] - 229:8
Column [11] - 38:1, 82:16, 98:25, 99:2, 158:6, 158:19, 159:5, 159:14, 174:14, 231:8, 313:4
column [12] - 90:2, 97:24, 152:18, 157:24, 159:16, 197:9, 202:16, 214:18, 214:22, 288:22, 288:25, 305:21
Columns [1] - 174:15
combinations [1] - 346:24
combine [2] - 27:23, 147:11
combined [3] - 77:2, 108:12, 162:12
combining [1] - 190:4
Cometriq [1] - 5:20
coming [3] - 149:10, 151:22, 344:7
commensurately [1] - 316:19
comments [1] - 49:2
commercial [4] - 11:13, 11:15, 33:21, 73:19
commercialized [1] - 126:15
Committee [1] - 185:15
common [18] - 17:2, 24:1, 37:3, 110:15, 154:5, 155:7, 155:9, 192:21, 200:14, 263:23, 264:1, 264:3, 285:23, 296:7, 311:1, 328:18, 333:12
commonly [18] - 26:22, 88:16, 95:13, 95:18, 96:5, 97:1, 97:8, 98:9, 98:11, 160:22, 161:3, 172:13, 172:16, 173:1, 173:7, 191:18, 195:7, 206:1
communicated [1] - 187:13
communications [1] - 234:24
Company [3] - 98:21, 98:22, 258:7
company [21] - 4:1, 5:13, 5:24, 6:1, 7:8, 7:15, 7:17, 9:3, 9:15, 9:19, 9:23, 10:17, 10:23, 11:4, 20:24, 31:11, 32:13, 70:16, 70:18, 98:23, 119:22
company's [3] - 4:19, 6:3, 7:7
Comparative [1] - 113:2
compare [9] - 83:18, 84:23, 86:19, 97:16, 105:23, 222:13, 241:15, 272:19, 273:25
compared [1] - 141:3
comparing [5] - 214:15, 242:10, 272:23, 272:25, 273:11
comparison [7] - 17:17, 45:12, 138:17, 202:9, 202:12, 244:21, 273:22
compatibility [2] - 45:22, 317:5
compatible [1] - 153:17
compensated [1] - 69:2
compensation [1] - 69:5
competitive [1] - 258:19
complete [1] - 98:5
completed [3] - 185:13, 227:22, 298:18
completing [1] - 275:15
complex [3] - 188:9, 317:13, 317:23
complicated [3] - 21:6, 21:8, 21:12
component [6] - 119:8, 134:12, 138:6, 189:25, 212:5, 241:9
components [6] - 45:16, 133:25, 157:9, 214:20, 244:20
Composition [2] - 105:9, 105:16
composition [39] - 13:3, 17:22, 17:24, 18:14, 22:14, 27:14, 27:19, 28:15, 43:16, 50:9, 50:15, 51:4, 51:9, 56:9, 59:24, 76:21, 76:22, 77:14, 77:24, 78:11, 78:21, 78:25, 79:23, 80:12, 80:16, 81:6, 85:18, 98:1, 100:1, 104:21, 105:22, 214:19, 214:23, 234:2, 234:8, 260:21, 313:9, 313:15, 328:24
Compositions [1] - 82:18
compositions [9] - 27:8, 27:11, 78:15, 95:1, 174:21, 201:25, 214:8, 231:4, 233:24
compound [54] - 4:8, 4:10, 4:13, 5:15, 5:17, 5:18, 5:23, 5:25, 6:14, 6:16, 7:22, 9:2, 17:5, 17:7, 18:5, 18:6, 18:17, 18:22, 21:19, 29:20, 33:24, 33:25, 35:14, 37:7, 37:12, 37:13, 40:1, 40:3, 41:20, 45:12, 46:21, 48:18, 49:8, 52:16, 53:14, 121:9, 260:18, 261:4, 269:17, 269:18, 280:12, 297:12, 297:15, 297:22, 300:23, 305:25, 307:16, 329:22, 329:25, 330:6, 332:8, 332:12, 342:1
Compound [10] - 38:3, 77:15, 77:18, 269:13, 269:15, 313:9, 313:11, 323:22, 329:16, 329:18
compounds [19] - 5:14, 5:16, 38:16, 38:23, 41:4, 45:3, 188:9, 188:11, 269:6, 273:18, 296:8, 303:13, 303:20, 305:7, 305:15, 305:18, 317:13, 317:23
compress [1] - 79:19
compressed [2] - 78:5, 162:11
compressibility [12] - 88:11, 88:15, 88:18, 89:7, 129:17, 129:20, 133:2, 133:6, 133:11, 138:7, 204:11, 209:4
compressible [2] - 161:23, 162:7
compression [12] - 48:7, 78:7, 83:24, 86:16, 104:14, 133:16, 151:15, 152:12, 154:20, 195:5, 198:10, 209:12
comprised [1] - 79:9
comprises [1] - 77:25
comprising [2] - 77:15, 313:9
concentration [34] - 26:20, 61:18, 63:25, 64:3, 90:8, 90:16, 90:22, 91:1, 91:5, 95:9, 97:1, 97:25, 98:3, 98:6, 104:19, 104:20, 105:2, 105:6, 105:20, 105:23, 106:7, 106:14, 114:3, 175:7, 175:16, 202:4, 213:12, 216:19, 227:24, 233:13, 236:12, 238:19, 241:3, 241:8
concentrations [6] - 95:2, 95:5, 202:2, 227:11, 233:5, 233:15
concept [2] - 14:16, 189:17
concepts [2] - 27:7, 186:23
concern [9] - 189:6, 193:25, 209:17, 213:9, 265:20, 302:16, 344:3, 344:5, 346:20
concerned [5] - 42:13, 189:1, 189:3, 189:10, 346:12

concerning [2] - 36:9, 318:5
concerns [2] - 194:3, 308:1
conclude [16] - 87:11, 102:7, 213:2, 213:17, 216:15, 220:20, 222:9, 272:23, 272:24, 274:2, 274:9, 274:14, 280:17, 287:17, 299:5, 299:11
concluded [10] - 26:9, 44:14, 137:18, 138:3, 216:17, 238:24, 242:12, 287:20, 292:4, 299:8
concludes [3] - 275:13, 275:17, 304:7
conclusion [26] - 63:16, 63:20, 64:3, 64:16, 64:18, 65:12, 65:16, 74:16, 74:19, 113:20, 113:23, 114:5, 138:9, 216:16, 219:3, 224:3, 228:24, 238:22, 239:13, 243:6, 273:3, 274:19, 275:1, 299:15, 304:8, 338:17
Conclusion [1] - 66:18
conclusions [2] - 224:22, 339:12
conditions [4] - 7:21, 10:7, 31:1, 299:3
conduct [1] - 342:23
conducted [2] - 66:12, 106:23
conducting [1] - 21:3
conference [5] - 14:1, 14:5, 15:7, 20:21, 57:23
confidence [1] - 282:18
confirm [4] - 39:11, 291:8, 331:19, 332:3
confirming [1] - 102:1
confirms [1] - 305:2
confusing [1] - 324:23
connection [3] - 3:6, 58:10, 74:8
consider [25] - 18:4, 20:7, 30:5, 106:23, 107:2, 150:14, 151:5, 187:19, 194:5, 194:7, 207:6, 218:24, 220:16, 220:19, 223:1, 223:4, 223:11, 223:24, 262:15, 302:7, 316:12, 326:13, 326:15, 335:15, 335:19
considerable [1] - 107:9
considerably [1] - 54:15
consideration [8] - 45:20, 106:10, 118:7, 138:21, 138:22, 148:9, 148:12, 237:3
considerations [4] - 21:3, 71:24, 90:23, 102:1
considered [16] - 7:17, 33:7, 48:21, 48:22, 128:23, 209:22, 223:13, 224:5, 251:3, 255:1, 304:9, 310:16, 319:10, 319:22, 328:1, 345:14
considering [5] - 94:19, 105:2, 265:2, 343:16, 346:10
consist [1] - 12:21
consistent [24] - 26:16, 26:20, 59:10, 79:13, 80:1, 80:4, 80:5, 83:20, 84:25, 86:21, 90:14, 91:24, 92:17, 92:24, 102:3, 102:9, 121:21, 141:25, 142:5, 201:23, 207:12, 217:3, 225:2, 225:4
consistently [5] - 9:17, 27:10, 32:9, 32:15, 79:17
constructs [1] - 122:3
construe [1] - 82:3
consultant [1] - 72:7
consume [1] - 71:6
consumed [1] - 77:7
contact [1] - 224:16
contain [8] - 92:22, 107:22, 124:10, 193:22, 234:5, 234:15, 265:3, 328:11
contained [5] - 42:21, 85:15, 88:4, 201:13, 310:15
containing [4] - 155:1, 214:7, 214:20, 299:17
contains [11] - 62:8, 77:25, 81:7, 81:8, 81:9, 112:10, 130:9, 130:14, 323:22, 328:25
contaminate [1] - 329:1
contamination [1] - 225:19
contend [1] - 322:4
content [4] - 79:24, 118:14, 145:5, 210:18
contentions [1] - 344:18
contents [2] - 78:10, 296:19
context [8] - 35:22, 107:17, 149:8, 188:23, 188:24, 295:7, 296:10, 340:8
continuations [1] - 15:16
continue [2] - 50:16, 168:15
continued [1] - 42:22
CONTINUED [1] - 2:1
continues [3] - 11:20, 153:21, 174:9
continuously [1] - 258:19
contract [1] - 31:10
contradicting [1] - 22:8
contradictory [1] - 107:11
contrast [2] - 17:15, 78:9
contribute [3] - 189:21, 189:23, 191:10
contributed [1] - 243:25
contributions [1] - 189:15
control [11] - 10:2, 11:5, 63:17, 77:5, 176:18, 176:25, 264:18, 265:5, 266:18, 306:10, 306:21
controlled [5] - 9:18, 32:20, 79:12, 193:19, 193:20
controlling [4] - 29:24, 193:24, 265:8, 316:13
controls [1] - 7:10
conversation [1] - 326:4
converse [1] - 254:23
convert [1] - 6:15
converted [3] - 299:2, 330:19, 332:12
converting [1] - 332:17
cool [1] - 295:25
cooler [1] - 295:23
Cooper [7] - 15:7, 128:7, 141:12, 168:7, 168:15, 178:5, 344:20
COOPER [188] - 2:5, 68:4, 72:18, 127:2, 127:6, 128:8, 128:11, 128:14, 130:7, 130:8, 134:22, 134:23, 135:9, 135:10, 140:10, 140:12, 141:14, 141:16, 142:23, 143:3, 144:25, 145:2, 145:21, 145:23, 148:18, 148:19, 150:7, 150:9, 151:9, 151:10, 152:7, 152:9, 152:17, 152:19, 154:15, 157:5, 157:6, 158:5, 158:7, 158:18, 158:20, 159:4, 159:6, 159:14, 159:17, 160:15, 160:16, 162:21, 162:22, 163:13, 163:14, 163:23, 163:25, 164:7, 164:9, 165:4, 165:5, 168:16, 168:18, 169:19, 169:20, 172:10, 172:12, 173:14, 173:16, 174:8, 177:9, 177:14, 177:16, 179:10, 179:14, 183:10, 183:13, 183:24, 184:6, 184:9, 184:12, 184:14, 184:21, 184:22, 186:3, 186:8, 186:16, 186:17, 187:17, 187:22, 187:23, 188:18, 188:20, 189:19, 189:20, 192:4, 192:5, 192:23, 192:24, 194:14, 194:16, 194:21, 194:24, 195:15, 195:16, 196:12, 196:14, 196:24, 196:25, 197:7, 197:10, 197:22, 197:23, 198:14, 198:15, 199:11, 199:12, 199:17, 199:20, 200:25, 201:1, 201:7, 201:9, 202:5, 202:7, 203:5, 203:6, 203:12, 203:14, 204:5, 204:7, 204:16, 204:18, 205:3, 205:5, 206:5, 206:7, 206:20, 206:22, 208:17, 208:21, 210:22, 210:24, 212:6, 212:8, 214:5, 214:9, 215:9, 215:11, 217:8, 217:9, 218:5, 218:7, 219:24, 219:25, 221:18, 221:20, 222:24, 222:25, 225:7, 225:8, 225:11, 225:13, 226:22, 227:1, 228:8, 228:11, 229:11, 251:8, 251:10, 251:14, 251:16, 252:5, 252:10, 252:12, 252:24, 252:25, 253:12, 253:16, 255:3, 255:14, 255:17, 255:24, 322:14, 341:1, 341:13, 341:17, 342:5, 342:13, 342:15, 343:14, 344:2
core [3] - 91:20, 201:22, 214:21
corn [222] - 24:5, 24:6, 24:7, 24:17, 24:22, 25:11, 25:14, 25:17, 25:20, 26:9, 26:12, 26:19, 26:24, 27:1, 47:8, 47:10, 47:13, 47:14, 48:11, 48:12, 48:16, 48:17, 48:23, 49:1, 49:7, 61:17, 61:21, 62:4, 62:22, 63:1, 63:2, 64:1, 64:2, 64:4, 64:8, 64:12, 64:21, 64:25, 66:9, 66:13, 86:4, 86:7, 86:10, 86:13,

86:18, 87:12, 90:2, 90:7, 90:11, 90:21, 91:7, 92:1, 92:13, 92:18, 92:25, 93:3, 93:25, 96:3, 96:6, 97:15, 97:16, 97:17, 97:19, 97:22, 99:6, 99:9, 99:10, 99:13, 99:21, 99:22, 100:4, 100:11, 100:13, 100:16, 100:19, 100:21, 101:1, 101:2, 101:19, 102:2, 102:9, 102:10, 104:5, 104:11, 104:19, 104:21, 104:24, 105:4, 105:18, 105:20, 106:7, 106:12, 106:15, 106:18, 108:5, 108:8, 108:23, 109:19, 111:20, 112:6, 113:6, 114:4, 114:6, 114:20, 115:7, 115:22, 116:1, 117:18, 118:8, 118:13, 119:2, 119:6, 121:2, 121:5, 122:7, 122:11, 122:22, 122:25, 123:12, 123:17, 123:19, 127:15, 134:8, 134:16, 134:20, 136:2, 136:4, 137:24, 138:5, 138:14, 138:19, 141:3, 141:20, 143:2, 143:8, 143:20, 144:5, 144:21, 157:8, 158:15, 159:1, 159:11, 159:23, 160:10, 164:1, 164:23, 165:23, 166:3, 167:2, 167:9, 169:24, 170:12, 170:25, 175:18, 175:22, 178:11, 179:20, 180:9, 182:10, 187:2, 187:3, 187:5, 187:9, 201:16, 201:19, 201:24, 202:14, 202:15, 208:6, 210:2, 210:17, 211:6, 211:21, 213:15, 214:16, 215:1, 215:19, 216:18, 216:21, 217:4, 219:6, 225:16, 225:17, 225:24, 225:25, 226:19, 226:25, 227:10, 227:23, 228:5, 233:13, 234:19, 234:21, 234:25, 236:8, 236:11, 236:18, 236:20, 236:22, 237:18, 237:22, 238:2, 238:7, 238:19, 239:8, 239:10, 239:14, 240:11, 241:12, 241:13, 242:1, 244:7, 244:17, 247:4, 248:16, 248:18, 249:3

Corn [3] - 119:16, 119:19, 120:11

corn/maize [1] - 254:2

corner [6] - 13:5, 96:23, 169:14, 184:7, 300:18

Correct [1] - 170:23

correct [601] - 59:25, 60:11, 60:20, 60:21, 60:23, 60:24, 61:1, 61:4, 61:6, 61:7, 61:22, 62:11, 62:12, 62:15, 62:16, 62:23, 62:24, 63:3, 63:5, 63:6, 63:7, 63:11, 63:12, 63:14, 63:15, 64:9, 64:10, 64:14, 64:15, 65:1, 66:7, 67:4, 87:20, 88:22, 94:7, 113:15, 128:23, 129:1, 129:7, 129:8, 129:12, 129:15, 130:13, 130:15, 130:19, 130:21, 131:6, 131:7, 131:18, 131:19, 132:1, 132:2, 132:7, 132:15, 132:20, 132:25, 133:1, 133:3, 133:25, 134:5, 134:8, 134:10, 134:13, 134:17, 134:20, 135:3, 135:6, 135:7, 135:17, 135:18, 135:21, 135:24, 135:25, 136:10, 136:11, 136:13, 136:16, 136:17, 136:22, 136:24, 137:1, 137:3, 137:4, 137:7, 137:8, 137:11, 137:15, 137:16, 137:20, 137:25, 138:15, 138:16, 138:20, 138:24, 139:7, 139:11, 139:12, 139:24, 140:1, 140:2, 140:7, 140:17, 140:19, 140:22, 141:3, 141:8, 141:9, 141:22, 141:23, 142:1, 142:7, 142:11, 142:15, 142:21, 143:5, 143:6, 143:10, 143:17, 143:21, 143:25, 144:8, 144:10, 144:15, 144:16, 144:21, 145:9, 145:10, 145:12, 145:15, 145:18, 145:19, 146:7, 146:8, 146:10, 146:11, 146:14, 146:15, 146:21, 146:24, 147:2, 147:6, 147:13, 147:17, 147:21, 147:24, 148:2, 148:3, 148:7, 148:20, 150:12, 150:13, 150:16, 150:17, 150:23, 151:12, 151:18, 151:19, 151:21, 151:25, 152:1, 152:5, 152:6, 152:25, 153:3, 153:7, 153:10, 153:14, 153:15, 154:3, 154:9, 154:10, 155:8, 155:12, 155:13, 155:15, 155:18, 155:19, 156:2, 156:5, 156:6, 156:7, 156:11, 156:18, 156:23, 157:3, 157:4, 157:11, 157:12, 157:16, 157:22, 157:23, 157:25, 158:3, 158:10, 158:11, 158:13, 159:13, 159:20, 159:24, 160:3, 160:7, 160:10, 160:13, 160:14, 160:23, 160:24, 161:3, 161:6, 161:14, 161:17, 161:18, 162:25, 163:1, 163:4, 163:5, 163:8, 163:16, 164:2, 164:5, 164:6, 164:11, 164:14, 164:17, 164:18, 164:20, 165:1, 165:2, 165:8, 165:12, 165:21, 165:25, 166:5, 166:8, 166:9, 166:11, 166:12, 166:16, 166:17, 166:19, 166:20, 166:24, 166:25, 167:4, 167:5, 167:8, 167:11, 167:18, 167:25, 168:1, 168:5, 168:6, 170:1, 170:2, 170:5, 170:9, 170:10, 170:14, 170:15, 170:18, 170:19, 170:22, 171:2, 171:3, 171:6, 171:20, 172:4, 172:5, 172:8, 172:9, 172:17, 172:18, 172:19, 172:22, 172:24, 172:25, 173:2, 173:8, 173:11, 174:18, 174:22, 174:25, 175:4, 175:7, 175:11, 175:16, 175:20, 175:21, 175:23, 175:25, 176:1, 176:2, 177:2, 178:23, 220:14, 220:15, 226:15, 230:13, 230:23, 231:1, 231:4, 231:5, 231:12, 231:25, 232:6, 232:9, 232:19, 232:22, 233:6, 233:7, 233:9, 233:14, 233:21, 233:24, 234:2, 234:5, 234:6, 234:9, 234:10, 234:12, 234:13, 234:16, 234:17, 234:22, 234:23, 235:1, 235:2, 235:4, 235:10, 235:13, 235:17, 236:9, 236:13, 236:15, 236:19, 236:25, 237:13, 237:18, 237:19, 237:23, 238:2, 238:11, 238:16, 238:20, 238:21, 239:1, 239:5, 239:11, 239:15, 240:1, 240:9, 240:10, 240:13, 240:16, 240:20, 240:21, 241:3, 241:5, 241:9, 241:13, 241:18, 241:20, 241:23, 242:2, 242:7, 242:8, 242:24, 243:10, 243:15, 243:20, 244:1, 244:9, 244:13, 244:18, 245:1, 245:2, 245:4, 245:11, 245:12, 245:14, 245:20, 246:1, 246:4, 246:15, 246:18, 246:21, 247:1, 247:4, 247:7, 247:10, 247:11, 247:12, 247:20, 247:24, 248:4, 248:5, 248:7, 248:11, 248:17, 248:22, 249:5, 250:1, 250:5, 250:12, 250:13, 250:18, 250:19, 250:21, 251:3, 252:2, 252:14, 252:15, 253:22, 254:9, 260:19, 260:23, 261:22, 265:12, 272:4, 273:24, 275:14, 278:25, 284:1, 284:6, 284:15, 286:22, 288:23, 289:1, 291:11, 301:14, 305:13, 311:24, 311:25, 312:2, 312:3, 312:9, 312:10, 312:12, 312:13, 312:15, 312:16, 312:18, 312:19, 312:21, 312:22, 312:24, 313:9, 313:12, 313:13, 313:16, 313:17, 313:19, 313:20, 313:23, 313:24, 314:1, 314:5, 314:8, 314:9, 314:11, 314:12, 314:14, 314:15, 314:18, 314:19,

314:21, 314:22, 314:24, 314:25, 315:3, 315:6, 315:7, 315:10, 315:23, 316:5, 316:6, 316:7, 316:8, 316:10, 316:11, 316:14, 316:15, 316:24, 316:25, 317:8, 317:9, 317:10, 317:13, 317:14, 317:16, 318:3, 318:4, 318:10, 318:19, 318:20, 319:3, 319:10, 319:23, 319:24, 320:5, 320:6, 320:7, 320:16, 320:21, 321:1, 321:5, 321:11, 321:18, 321:19, 322:3, 322:6, 324:3, 325:2, 325:6, 325:9, 325:16, 326:2, 326:24, 326:25, 327:2, 327:3, 327:5, 327:9, 327:25, 328:11, 328:12, 328:13, 328:16, 328:17, 328:19, 328:20, 328:22, 328:23, 329:1, 329:4, 329:11, 329:13, 329:14, 329:16, 329:17, 329:19, 329:20, 329:22, 329:23, 329:25, 330:1, 330:4, 330:5, 330:7, 330:8, 330:9, 330:13, 330:16, 330:17, 330:19, 330:20, 330:22, 330:23, 331:1, 331:10, 331:14, 332:9, 332:10, 332:13, 332:18, 332:25, 333:3, 333:4, 333:6, 333:10, 333:20, 333:24, 334:2, 334:3, 334:6, 334:7, 334:9, 334:10, 334:16, 334:21, 334:22, 334:24, 334:25, 335:2, 335:8, 335:13, 335:17, 335:21, 335:25, 336:1, 336:5, 336:8, 336:12, 338:22, 338:25, 339:3, 339:6, 339:10, 340:1, 344:21

corrected [1] - 140:13
correctly [1] - 139:9
correspondence [1] - 288:18
corresponding [1] - 97:18
corresponds [2] - 27:18, 250:11
counsel [10] - 44:4, 46:12, 46:14, 46:16, 48:24, 50:17, 53:6, 54:20, 61:23, 253:5
Counsel [1] - 171:22
count [1] - 333:1
counted [1] - 333:7
counter [1] - 342:24
counterfactual [1] - 33:1
counterpart [1] - 33:8
counts [2] - 15:10, 34:16
couple [7] - 34:23, 57:10, 110:14, 156:25, 202:2, 254:1, 277:10
course [18] - 5:7, 6:11, 9:20, 10:12, 11:9, 29:15, 107:8, 140:21, 143:25, 151:20, 154:12, 160:25, 181:5, 181:16, 185:17, 202:22, 261:19, 319:6
COURT [84] - 1:1, 2:15, 2:22, 3:9, 3:14, 3:22, 13:22, 34:20, 34:24, 57:2, 57:6, 58:6, 58:14, 59:2, 66:19, 66:24, 67:2, 67:5, 67:12, 67:17, 67:22, 68:2, 68:17, 72:19, 126:21, 127:3, 127:7, 127:13, 127:22, 128:5, 128:10, 128:12, 168:7, 168:13, 168:17, 177:5, 177:8, 177:11, 177:20, 178:2, 183:1, 183:6, 183:9, 183:12, 186:7, 229:13, 229:20, 229:25, 230:4, 251:7, 252:8, 255:4, 255:7, 255:12, 255:16, 255:19, 255:22, 256:5, 256:11, 257:2, 259:8, 290:8, 311:6, 311:9, 311:12, 322:21, 323:4, 340:17, 340:20, 340:23, 341:7, 341:15, 342:3, 342:11, 342:14, 343:11, 343:17, 344:4, 344:10, 344:25, 345:10, 346:1, 347:5, 347:11
Court [52] - 2:13, 3:21, 4:5, 4:6, 4:7, 4:9, 4:23, 7:2, 9:10, 11:24, 12:2, 16:1, 16:3, 21:13, 22:5, 22:16, 23:1, 23:18, 23:21, 23:24, 24:10, 27:2, 27:14, 28:12, 28:15, 33:16, 33:23, 34:15, 34:17, 44:14, 44:15, 44:19, 57:11, 57:22, 58:4, 58:13, 82:3, 128:11, 168:16, 184:1, 186:19, 258:3, 258:16, 259:2, 262:10, 262:24, 276:13, 297:10, 315:1, 341:5, 347:15, 347:20
court [1] - 185:25
Court's [1] - 341:2
Courthouse [1] - 1:10
courtroom [1] - 7:5
cover [12] - 14:7, 15:9, 15:21, 17:19, 17:20, 17:21, 17:23, 194:18, 205:22, 276:25, 294:11
covered [2] - 37:20, 38:7
covering [2] - 200:19, 278:21
covers [5] - 13:1, 17:12, 37:17, 264:18, 308:15
COX [1] - 1:21
create [7] - 48:4, 48:6, 171:12, 195:3, 195:4, 195:11
created [1] - 14:17
creating [2] - 70:14, 110:13
creation [1] - 53:12
credit [1] - 144:14
credited [1] - 9:5
criteria [1] - 204:1
critical [7] - 6:25, 9:10, 10:11, 12:16, 33:23, 33:25, 227:6
croscarmellose [9] - 240:15, 241:5, 241:8, 242:6, 242:12, 243:20, 243:25, 244:3, 244:13
cross [12] - 178:16, 178:17, 180:12, 180:20, 181:1, 230:1, 252:4, 253:2, 344:23, 346:14, 346:15, 346:17
CROSS [3] - 128:13, 230:7, 311:13
cross-examination [8] - 178:16, 178:17, 180:12, 180:20, 181:1, 230:1, 252:4, 253:2
CROSS-EXAMINATION [3] - 128:13, 230:7, 311:13
cross-reference [2] - 346:15, 346:17
cross-referenced [1] - 344:23
cross-references [1] - 346:14
crossing [1] - 190:11
crystal [1] - 41:5
crystalize [1] - 308:5
crystallin [1] - 9:14
crystalline [106] - 8:9, 8:18, 8:25, 9:8, 12:19, 12:21, 13:1, 13:4, 13:7, 13:9, 13:13, 14:6, 14:8, 14:19, 14:22, 15:12, 16:5, 16:14, 17:11, 17:18, 17:21, 17:22, 18:7, 18:12, 18:20, 22:9, 28:5, 28:7, 35:3, 35:5, 35:25, 36:2, 36:3, 36:12, 36:24, 37:4, 37:5, 37:6, 37:9, 37:11, 37:12, 37:16, 37:17, 37:19, 37:22, 37:25, 38:2, 38:5, 38:6, 38:15, 38:18, 38:23, 39:10, 39:18, 39:19, 39:21, 40:5, 40:9, 40:12, 41:6, 41:19, 42:6, 42:9, 42:20, 43:6, 43:10, 43:11, 43:17, 43:19, 57:12, 69:14, 69:23, 312:5, 312:15, 323:12, 323:21, 323:23, 324:3, 324:5, 324:7, 324:8, 324:9, 324:10, 324:13, 324:17, 324:18, 324:22, 325:1, 325:5, 325:8, 325:15, 325:18, 326:1, 326:4, 326:6, 326:7, 326:8, 326:14, 326:23, 327:1, 341:20, 343:1
crystallization [12] - 295:24, 296:2, 296:7, 296:10, 308:6, 308:16, 308:24, 309:1, 309:12, 310:2, 310:5, 310:21
crystallized [2] - 296:4, 296:5
crystals [1] - 190:13
cumulative [1] - 250:8
curious [1] - 67:2
current [2] - 301:21, 337:11
curve [2] - 212:21, 212:24
curves [1] - 213:21
CV [3] - 72:12, 184:17, 257:20

D

D-O-N-O-V-A-N [1] - 183:18
daily [1] - 307:7
damage [1] - 264:6
dampen [1] - 193:10
Daniel [1] - 11:24
dark [1] - 346:2
data [51] - 26:8, 47:12, 47:16, 88:5, 107:6, 107:9, 107:12, 107:16, 128:2, 129:4, 129:6, 129:9, 131:5, 132:10, 135:4, 138:12, 140:20, 140:23, 143:20, 146:16, 163:15, 166:13, 168:6, 178:18, 180:22, 182:12, 182:15, 187:12, 203:10, 211:17, 225:4, 244:14, 251:1, 251:20,

251:23, 259:21, 276:8, 286:10, 287:10, 290:3, 291:12, 294:7, 328:11, 328:13, 328:21, 338:16, 339:13, 340:9, 340:10
date [13] - 11:13, 13:25, 75:9, 75:11, 75:15, 75:19, 119:17, 158:1, 188:15, 245:7, 245:8, 259:24, 260:2
dates [3] - 98:18, 169:13, 267:9
David [1] - 29:14
DDX [30] - 135:9, 140:10, 184:8, 184:21, 186:16, 187:22, 188:18, 189:19, 190:1, 192:23, 195:15, 212:6, 218:5, 219:24, 251:15, 252:11, 257:11, 273:9, 273:11, 273:20, 274:6, 274:12, 274:17, 274:24, 275:4, 275:10, 275:23, 276:11, 280:22, 307:21
DDX-10 [2] - 268:11, 268:13
DDX-11 [1] - 268:23
DDX-12 [1] - 270:5
DDX-13 [2] - 224:19, 270:10
DDX-14 [2] - 272:10, 272:12
DDX-2 [1] - 257:25
DDX-26 [1] - 284:20
DDX-28 [2] - 287:25, 292:8
DDX-3 [1] - 258:14
DDX-30 [2] - 294:25, 295:2
DDX-31 [2] - 297:17, 297:19
DDX-32 [1] - 298:21
DDX-33 [1] - 299:20
DDX-36 [1] - 300:6
DDX-4 [1] - 260:11
DDX-5 [1] - 260:25
DDX-6 [1] - 261:9
DDX-7 [1] - 261:25
DDX-8 [1] - 263:3
DDX-9 [2] - 200:23, 266:21
deadline [1] - 341:19
deagglomerated [1] - 103:18
deal [3] - 301:10, 309:10, 346:6
dealing [2] - 36:10, 301:21
deals [2] - 38:21, 50:15
death [1] - 12:10
decades [1] - 46:3
December [1] - 119:18
decide [1] - 209:8
decided [3] - 195:21, 209:13, 210:2
decides [1] - 262:10
decision [3] - 35:18, 209:16, 227:6
decorate [1] - 219:10
decrease [2] - 218:14, 248:13
decreases [1] - 248:11
dedicated [2] - 4:2, 344:22
Defendant [2] - 4:3, 346:5
defendant's [1] - 2:20
Defendant's [1] - 249:12
Defendants [2] - 1:8, 2:8
defendants [2] - 186:3, 259:4
Defendants' [1] - 235:8
defense [3] - 42:8, 49:11, 49:13
define [3] - 224:24, 224:25, 261:13
defined [10] - 27:17, 50:18, 78:9, 82:12, 116:12, 222:17, 230:16, 261:15, 280:1, 333:13
defines [2] - 48:3, 221:2
definition [45] - 18:22, 18:25, 19:7, 23:19, 24:1, 24:7, 27:16, 76:3, 76:9, 76:12, 76:13, 84:23, 128:24, 129:3, 147:18, 151:6, 187:25, 188:2, 188:13, 188:16, 194:25, 195:2, 195:7, 195:8, 217:20, 232:1, 232:2, 232:22, 261:20, 262:18, 262:22, 262:25, 315:6, 315:9, 315:12, 315:22, 316:17, 317:1, 317:12, 317:15, 317:20, 318:2, 322:7, 333:9, 333:12
definitions [4] - 76:17, 116:13, 146:18, 225:2
definitively [1] - 117:15
degradation [4] - 9:21, 188:10, 317:25, 329:22
degree [9] - 70:4, 70:5, 75:20, 188:4, 246:25, 258:4, 263:17, 263:25, 316:18
DELAWARE [1] - 1:2
Delaware [1] - 1:11
delay [1] - 183:10
deliver [2] - 32:15, 34:6
delivered [2] - 4:16, 10:13
delivery [2] - 48:2, 71:22
delumping [1] - 103:16
demonstrate [2] - 31:16, 31:19
demonstrated [3] - 32:10, 100:3, 266:6
demonstrates [1] - 36:17
demonstrating [2] - 22:3, 166:23
demonstrative [5] - 74:10, 189:16, 190:7, 190:17, 193:2
density [25] - 120:25, 131:5, 131:6, 132:25, 136:8, 136:12, 136:13, 136:15, 136:16, 139:6, 139:7, 139:10, 139:20, 139:24, 140:6, 140:16, 181:21, 211:19, 215:7
deny [1] - 25:17
dependent [1] - 69:5
depict [1] - 62:18
depicts [1] - 102:24
deposition [35] - 7:11, 32:16, 57:21, 58:8, 58:9, 58:16, 58:17, 58:19, 59:3, 66:18, 67:10, 93:21, 128:4, 139:14, 140:8, 143:23, 144:10, 153:12, 154:7, 163:2, 167:19, 216:25, 319:12, 319:14, 319:19, 320:9, 320:12, 320:13, 322:11, 325:11, 326:3, 326:9, 326:11, 327:14, 339:20
DEPUTY [18] - 2:13, 67:19, 67:21, 68:9, 168:10, 168:12, 174:1, 174:4, 183:15, 187:15, 255:9, 255:11, 256:12, 290:9, 290:13, 290:15, 340:25, 347:14
der [16] - 122:17, 122:23, 123:1, 171:2, 171:4, 171:8, 171:11, 171:19, 172:4, 223:25, 224:4, 224:8, 248:4, 248:6, 248:11, 248:12
derivative [4] - 96:6, 97:20, 97:22, 122:11
derivatives [8] - 26:22, 95:22, 98:11, 108:3, 182:20, 304:15, 304:22, 305:6
derived [1] - 154:21
describe [28] - 7:12, 8:24, 14:20, 16:24, 33:14, 40:24, 70:2, 107:25, 127:25, 137:6, 137:9, 184:18, 184:25, 188:22, 193:1, 194:11, 198:2, 202:13, 204:22, 205:17, 208:22, 212:11, 235:18, 258:2, 266:16, 267:13, 282:12, 323:12
described [24] - 7:14, 9:14, 17:20, 27:22, 64:7, 86:20, 106:21, 160:22, 175:22, 207:10, 218:2, 218:20, 218:22, 220:13, 222:13, 235:16, 238:14, 240:19, 241:21, 253:6, 253:20, 298:19, 298:20, 335:11
describes [12] - 16:14, 62:22, 85:18, 101:25, 194:19, 222:6, 222:17, 237:17, 291:3, 329:15, 330:18, 332:11
describing [13] - 25:9, 33:13, 160:6, 191:13, 196:16, 200:15, 207:13, 212:13, 226:18, 237:2, 238:15, 239:25, 245:23
description [19] - 13:16, 14:4, 14:10, 16:13, 36:14, 36:16, 39:17, 42:5, 64:11, 144:19, 201:11, 240:8, 268:8, 268:15, 272:7, 272:13, 286:4, 294:19, 337:10
Description [1] - 105:8
descriptions [2] - 198:9, 223:22
design [2] - 265:21, 302:7
designation [1] - 57:21
designations [1] - 58:23
designed [2] - 185:20, 316:9
designer [1] - 303:7
designers [2] - 264:25, 301:20
desired [3] - 48:4, 195:4, 195:11
detail [5] - 50:22, 50:23, 78:23, 127:25, 128:2
detailed [1] - 294:18
details [8] - 45:10, 74:15, 76:19, 186:18, 267:15, 294:8, 294:17, 338:10
detect [5] - 279:13, 281:10, 283:10, 285:6, 285:7
detectable [2] - 284:4, 284:6
detected [15] - 54:3, 54:6, 279:15, 279:24, 279:25,

280:3, 280:5, 283:6, 283:7, 283:22, 284:17, 284:19, 289:9, 289:16, 292:6
detection [12] - 54:5, 279:6, 279:8, 281:15, 281:17, 285:4, 286:9, 286:17, 287:11, 289:18, 289:22, 289:25
determination [3] - 54:10, 244:15, 339:15
determine [8] - 52:23, 66:12, 86:25, 108:8, 234:20, 276:5, 300:12, 319:4
determined [9] - 20:3, 209:1, 213:4, 213:24, 215:14, 275:25, 303:18, 306:17, 307:24
determines [1] - 192:11
determining [2] - 44:21, 292:13
detract [1] - 90:24
develop [4] - 4:14, 32:12, 32:13, 32:23
developed [4] - 12:5, 12:6, 32:17, 281:9
developing [5] - 4:2, 7:1, 34:12, 44:21, 316:23
Development [11] - 85:7, 144:19, 212:14, 212:25, 213:3, 213:9, 213:10, 213:18, 213:20, 252:16, 252:17
development [68] - 4:19, 7:6, 7:9, 8:12, 20:7, 21:1, 31:12, 53:22, 60:9, 60:25, 61:25, 62:21, 70:13, 70:15, 75:23, 87:19, 102:14, 107:3, 107:4, 112:15, 132:10, 132:11, 132:18, 134:4, 134:17, 135:1, 142:24, 144:4, 170:20, 176:19, 177:1, 188:6, 202:21, 208:11, 208:18, 209:23, 210:1, 211:11, 212:2, 214:1, 216:21, 227:5, 227:7, 227:22, 235:6, 235:9, 235:10, 235:12, 236:2, 237:11, 237:13, 237:16, 238:10, 238:23, 239:22, 239:25, 240:20, 241:11, 242:16, 243:6, 249:13, 249:16, 252:13, 281:3, 315:18, 316:4
deviated [3] - 55:7, 55:8, 294:23
deviation [5] - 295:6, 296:13, 297:20, 298:12, 338:3
deviations [12] - 295:3, 295:5, 295:11, 295:13, 295:15, 334:24, 335:16, 335:20, 335:24, 336:2, 336:13, 338:15
diagram [1] - 337:9
diameter [1] - 205:8
diamond [1] - 220:7
dicalcium [1] - 153:23
difference [12] - 41:19, 63:22, 113:25, 131:25, 137:19, 211:24, 215:17, 239:5, 242:4, 242:11, 295:12, 345:11
differences [10] - 41:15, 41:16, 41:18, 41:19, 189:11, 211:8, 238:25, 273:15, 273:16, 273:17
different [80] - 5:13, 6:16, 6:18, 8:6, 14:10, 19:2, 19:6, 30:25, 33:3, 37:19, 39:21, 39:24, 39:25, 40:1, 40:2, 40:12, 40:15, 41:3, 41:4, 41:5, 41:6, 41:7, 41:8, 41:9, 41:10, 41:11, 41:12, 49:15, 52:5, 55:8, 55:9, 64:8, 85:17, 88:6, 94:18, 100:12, 100:16, 132:22, 139:25, 140:4, 150:2, 151:14, 155:14, 155:17, 155:18, 181:20, 196:16, 197:12, 203:19, 204:2, 207:9, 214:10, 238:15, 239:25, 252:21, 262:22, 278:4, 278:13, 282:2, 283:3, 286:8, 293:16, 293:17, 309:16, 325:25, 326:12, 330:18, 330:25, 331:3, 331:5, 331:24, 332:16, 339:16, 339:18
differential [1] - 38:20
differentiate [1] - 254:15
differentiated [1] - 11:19
difficult [2] - 23:10, 171:21
diffraction [2] - 325:16, 325:21
dihydrate [1] - 153:24
dilemma [1] - 10:23
diluent [64] - 25:12, 25:14, 25:15, 25:20, 26:9, 47:11, 47:16, 48:3, 48:8, 61:18, 64:1, 66:3, 66:15, 66:17, 78:17, 90:7, 90:16, 90:24, 91:2, 91:6, 93:3, 93:5, 101:7, 106:9, 106:19, 108:24, 109:19, 109:24, 114:3, 127:16, 127:18, 127:21, 143:8, 146:7, 146:9, 147:7, 151:3, 153:5, 153:9, 154:5, 162:7, 164:23, 194:23, 195:1, 201:20, 202:17, 206:12, 207:1, 226:5, 227:11, 227:23, 228:2, 236:12, 236:21, 237:6, 237:7, 238:8, 247:4, 247:6, 247:17, 248:23, 249:6
diluents [11] - 47:23, 78:14, 103:19, 149:13, 195:3, 198:9, 202:1, 247:19, 248:24, 253:15, 253:19
dilute [1] - 48:5
dilutes [5] - 25:15, 25:17, 25:20, 151:2, 164:25
diminishing [1] - 118:24
dioxide [7] - 160:2, 162:15, 174:24, 175:2, 175:6, 175:9, 175:15
DIRECT [3] - 68:18, 183:23, 256:19
direct [44] - 84:16, 86:3, 100:20, 131:16, 132:14, 133:15, 133:21, 141:11, 143:4, 151:15, 152:12, 154:20, 157:2, 160:13, 160:18, 164:18, 165:16, 172:8, 179:6, 179:13, 198:10, 204:11, 209:12, 209:19, 232:9, 233:12, 234:9, 235:7, 235:16, 235:25, 236:9, 237:15, 239:20, 242:5, 242:23, 249:7, 318:13, 322:16, 322:17, 323:17, 328:15, 329:10, 332:5, 334:11
directed [5] - 28:14, 28:18, 233:19, 314:23
directing [1] - 227:8
direction [2] - 301:20, 301:21
directional [5] - 129:1, 137:23, 141:1, 147:17, 147:20
directionally [1] - 148:4
directions [1] - 334:2
directly [5] - 119:22, 161:4, 161:23, 162:6, 164:18
disagree [4] - 128:17, 164:25, 224:21, 238:5
discipline [2] - 75:22, 188:4
disclaimer [1] - 320:16
disclose [17] - 18:7, 18:8, 39:13, 40:24, 41:1, 268:7, 268:25, 269:5, 270:7, 281:8, 292:2, 303:21, 304:14, 310:15, 328:24, 344:16, 347:4
disclosed [25] - 33:5, 39:1, 39:8, 39:15, 42:4, 43:21, 50:25, 51:3, 51:5, 268:20, 269:12, 271:23, 272:20, 293:25, 321:8, 321:15, 322:4, 330:16, 336:6, 344:12, 345:17, 346:18, 346:19
discloses [6] - 16:19, 22:13, 30:22, 51:8, 270:14, 330:25
disclosing [3] - 41:20, 262:8, 346:24
disclosure [13] - 15:19, 18:5, 18:12, 18:13, 18:15, 27:8, 38:2, 38:4, 321:20, 321:21, 323:6, 341:20, 342:8
disclosures [6] - 39:23, 344:8, 344:13, 345:21, 346:4, 347:8
disconnected [2] - 15:22, 15:23
discover [1] - 181:6
discovered [12] - 4:10, 5:19, 5:24, 6:2, 6:9, 6:10, 8:18, 9:15, 9:21, 10:17, 41:14, 42:2
discovery [11] - 4:12, 5:12, 6:3, 9:23, 11:12, 12:14, 54:23, 181:16, 341:19, 344:19
discrepancies [4] - 107:20, 127:24, 128:3
discrepancy [6] - 107:9, 181:6, 181:9, 181:11, 182:3, 182:4
discuss [6] - 49:12, 206:3, 218:4, 266:9, 301:3, 330:9
discussed [16] - 28:5, 101:24, 105:25, 106:11, 106:21, 109:23, 110:20, 128:4, 133:21, 197:19, 229:7, 242:5, 252:14, 318:12, 334:11, 334:15
discusses [1] - 154:16

discussing [5] - 27:24, 112:13, 207:7, 210:15, 270:13
Discussion [3] - 120:3, 150:5, 177:15
discussion [5] - 14:1, 62:25, 231:4, 249:19, 345:6
discussions [1] - 187:2
disintegrant [29] - 23:11, 47:15, 50:3, 78:19, 78:20, 81:9, 103:19, 104:5, 115:15, 115:18, 115:21, 142:14, 153:6, 156:7, 156:10, 164:5, 204:22, 204:25, 206:12, 207:2, 212:5, 213:12, 234:5, 241:2, 241:5, 241:8, 244:4, 244:5, 254:12
disintegrants [7] - 49:23, 78:1, 142:9, 164:13, 229:7, 254:6, 254:8
disintegrating [7] - 51:12, 162:8, 162:12, 164:13, 204:12, 204:23, 204:24
disintegration [7] - 150:19, 187:6, 211:15, 212:2, 213:23, 214:2, 216:3
dismissed [1] - 15:25
disparate [1] - 107:16
disparity [1] - 107:17
disperse [1] - 223:16
disperses [1] - 223:1
dispersing [2] - 169:22, 169:25
displacing [1] - 170:22
dispute [20] - 13:8, 14:2, 14:3, 22:18, 22:21, 24:4, 24:6, 51:2, 51:3, 51:5, 51:7, 51:8, 81:4, 85:1, 85:3, 124:8, 180:3, 234:11, 346:7
disputing [2] - 234:4, 234:6
disrupt [2] - 5:9, 122:25
dissipate [1] - 118:14
dissolution [51] - 41:10, 48:13, 48:18, 63:22, 64:4, 64:19, 80:6, 109:2, 111:21, 111:22, 111:23, 112:7, 113:7, 113:13, 113:25, 114:7, 114:9, 114:11, 114:13, 114:24, 115:4, 115:15, 115:19, 115:23, 150:21, 187:6, 211:15, 212:2, 212:16, 213:4, 213:6, 213:23, 213:24, 214:2, 215:20, 216:2, 223:18, 223:23, 238:25, 239:5, 239:15, 239:17, 241:3, 242:8, 242:12, 242:20, 242:24, 243:14, 244:1, 244:9, 317:5
Dissolution [2] - 113:2, 243:7
dissolve [1] - 23:10
dissolved [2] - 103:23, 296:22
dissolves [1] - 111:24
distances [1] - 248:14
distinct [3] - 18:2, 18:3, 320:23
distinguished [1] - 258:21
distribute [2] - 118:12, 125:20
distributed [1] - 23:17
distributing [1] - 118:5
distribution [4] - 118:11, 166:13, 168:3, 249:20
District [1] - 347:20
district [1] - 185:25
DISTRICT [2] - 1:1, 1:2
DMCC [1] - 125:19
Docket [1] - 57:16
doctor [14] - 150:10, 186:9, 188:3, 188:18, 189:21, 192:3, 194:17, 198:13, 199:8, 199:13, 199:21, 225:14, 251:11, 258:10
Doctor [12] - 134:24, 135:11, 138:22, 151:4, 169:17, 169:22, 171:25, 176:16, 198:20, 224:18, 227:2, 254:19
doctoral [1] - 316:18
doctrine [1] - 42:11
document [101] - 24:24, 54:21, 54:23, 58:21, 60:5, 61:5, 63:4, 63:17, 65:2, 65:9, 65:11, 72:11, 81:2, 83:5, 83:6, 83:8, 83:11, 84:7, 84:10, 85:6, 85:7, 96:11, 98:15, 99:19, 99:20, 100:2, 112:13, 115:10, 119:14, 119:17, 119:21, 119:25, 120:3, 121:1, 121:4, 121:7, 125:2, 125:25, 144:18, 144:22, 146:17, 149:8, 161:10, 164:17, 164:18, 167:13, 168:21, 178:18, 179:7, 179:17, 184:16, 203:7, 203:10, 210:7, 221:15, 222:5, 222:6, 225:10, 225:14, 225:15, 225:23, 226:17, 227:19, 235:20, 259:20, 260:6, 271:8, 271:10, 271:21, 272:2, 276:22, 277:3, 277:17, 278:6, 279:2, 281:14, 281:19, 281:21, 282:10, 282:13, 282:22, 285:25, 288:8, 290:2, 291:3, 291:19, 292:2, 294:18, 301:9, 302:10, 302:25, 304:2, 304:20, 308:18, 309:8, 309:19, 336:15, 336:21, 336:23, 338:19
documentation [1] - 181:12
documented [1] - 135:1
documents [32] - 24:10, 24:11, 25:7, 31:23, 32:3, 32:11, 48:25, 49:5, 74:13, 101:18, 107:18, 108:12, 110:12, 151:23, 151:24, 166:21, 170:6, 170:20, 178:22, 180:10, 202:21, 202:22, 208:12, 209:21, 210:1, 211:12, 211:14, 216:21, 224:23, 235:3, 265:7, 265:10
DOMINICK [1] - 2:2
done [24] - 20:22, 31:5, 46:2, 49:6, 54:5, 56:12, 63:10, 63:14, 64:7, 91:19, 91:20, 213:21, 223:14, 227:21, 227:25, 243:13, 259:2, 306:6, 306:13, 306:14, 307:23, 316:1, 331:3, 334:2
Donovan [33] - 23:25, 76:10, 108:18, 109:8, 109:13, 109:18, 116:6, 117:7, 117:11, 128:17, 151:24, 183:14, 183:17, 184:2, 184:3, 184:8, 184:15, 186:4, 187:24, 195:15, 196:15, 197:25, 200:22, 201:2, 205:21, 210:13, 229:11, 229:13, 230:9, 252:11, 255:4, 262:19, 315:6
DONOVAN [1] - 183:19
Donovan's [14] - 76:13, 109:25, 110:5, 111:15, 111:19, 114:10, 116:4, 124:2, 127:14, 315:9, 316:16, 317:1, 317:11, 317:15
dosage [12] - 48:2, 55:17, 71:9, 78:5, 79:7, 79:25, 111:24, 185:21, 194:20, 211:16, 231:17, 317:3
Dosage [1] - 96:12
Dose [1] - 105:15
dose [6] - 77:4, 80:1, 186:5, 189:5, 201:15, 307:17
double [18] - 13:17, 17:4, 17:16, 17:25, 22:10, 42:9, 42:11, 42:15, 46:7, 285:15, 341:24, 344:17, 344:23, 345:5, 345:16, 345:20, 345:23, 346:12
doubling [1] - 239:3
doubt [5] - 52:5, 55:21, 339:9, 339:25, 340:9
down [28] - 32:20, 49:20, 53:25, 82:1, 94:21, 136:8, 136:19, 141:12, 161:22, 162:21, 169:5, 173:14, 179:23, 183:2, 192:4, 198:14, 217:8, 222:24, 253:23, 255:5, 263:11, 277:22, 285:4, 296:1, 307:18, 315:12, 320:23, 341:8
dozens [1] - 11:3
Dr [236] - 2:10, 7:4, 7:8, 7:12, 7:14, 8:17, 8:24, 10:17, 11:6, 11:24, 12:2, 16:1, 16:3, 16:9, 16:18, 19:21, 20:4, 20:9, 20:19, 20:20, 21:2, 21:7, 22:4, 23:21, 23:25, 26:6, 26:11, 29:14, 29:16, 31:19, 32:11, 32:16, 32:19, 32:22, 33:13, 33:17, 33:18, 57:22, 68:8, 68:20, 68:24, 70:2, 72:17, 72:21, 76:10, 76:13, 86:25, 108:18, 109:8, 109:13, 109:18, 109:25, 110:5, 111:15, 111:19, 114:10, 116:4, 116:6, 117:7, 117:11, 124:2, 127:1, 127:13, 127:14, 128:15, 128:17, 139:3, 151:24, 168:14, 168:19, 178:5, 179:25, 182:24, 183:1, 183:14, 184:3, 184:15, 186:4, 186:13, 187:11, 187:24,

191:13, 191:21, 196:15, 197:25, 198:2, 200:4, 200:22, 201:2, 205:21, 207:15, 210:13, 214:25, 215:20, 216:11, 217:12, 219:19, 219:20, 220:17, 221:2, 221:11, 221:15, 222:14, 222:17, 224:20, 224:22, 224:24, 226:14, 227:14, 228:12, 228:14, 228:24, 229:11, 229:13, 229:15, 229:18, 230:9, 251:4, 251:17, 254:20, 255:4, 256:8, 256:10, 256:21, 257:5, 257:7, 257:15, 257:19, 258:2, 258:16, 258:24, 259:5, 259:10, 259:12, 259:23, 260:8, 260:13, 261:2, 261:14, 262:2, 262:14, 262:19, 263:6, 264:5, 264:16, 264:23, 265:17, 266:22, 267:11, 267:19, 268:13, 268:25, 269:19, 270:7, 270:14, 271:7, 271:12, 271:23, 272:12, 272:24, 273:11, 275:17, 275:25, 276:13, 276:21, 277:10, 278:1, 278:11, 278:20, 279:4, 279:21, 280:17, 281:2, 282:24, 285:1, 285:11, 286:2, 286:14, 287:1, 287:9, 287:16, 287:25, 288:7, 288:12, 290:20, 291:22, 292:12, 294:5, 294:13, 295:2, 295:14, 295:19, 296:15, 297:19, 298:11, 298:23, 299:4, 299:10, 299:24, 300:8, 300:18, 301:8, 303:5, 304:1, 304:19, 306:5, 307:9, 307:23, 309:18, 310:4, 310:11, 310:22, 311:15, 315:6, 315:9, 316:16, 317:1, 317:11, 317:15, 333:14, 336:23, 341:8, 341:20, 341:22, 342:3, 342:7, 342:12, 342:15, 344:9, 344:10

draw [1] - 338:16

draws [1] - 228:25

drew [1] - 224:22

dropped [1] - 13:22

drug [98] - 4:7, 4:18, 6:6, 6:13, 6:17, 6:18, 8:12, 10:3, 10:12, 10:18, 11:5, 11:23, 12:6, 13:8, 20:7, 20:23, 21:1, 22:19, 22:20, 24:5, 24:12, 25:4, 25:5, 25:9, 26:19, 26:25, 27:14, 27:19, 28:10, 28:16, 28:18, 28:20, 28:23, 29:21, 30:12, 32:8, 34:8, 34:10, 34:11, 34:18, 41:17, 41:24, 48:2, 52:2, 60:17, 60:22, 61:3, 64:24, 70:22, 70:24, 71:2, 71:14, 71:22, 72:1, 72:4, 76:24, 88:6, 88:7, 92:3, 111:5, 111:23, 120:17, 132:18, 132:21, 169:1, 176:7, 176:11, 176:19, 177:1, 185:2, 186:5, 188:6, 201:4, 208:19, 212:17, 214:3, 247:9, 264:25, 265:2, 265:21, 301:20, 302:7, 303:7, 315:19, 316:5, 316:13, 316:23, 317:3, 317:4, 317:5, 337:4, 337:12

Drug [2] - 88:2, 105:9

drugs [2] - 4:3, 153:18

dry [15] - 70:19, 71:11, 83:23, 94:20, 95:8, 97:4, 98:2, 133:24, 134:1, 166:16, 166:18, 192:20, 193:15, 233:9, 233:10

dryer [1] - 103:25

DTX [4] - 68:5, 149:15, 177:22, 256:1

DTX-125 [2] - 278:18, 278:20

DTX-128 [2] - 286:24, 287:1

DTX-130 [3] - 284:24, 286:12, 286:14

DTX-134 [2] - 199:11, 199:14

DTX-160 [2] - 168:20, 177:18

DTX-161 [1] - 225:7

DTX-196 [3] - 134:22, 177:17, 210:5

DTX-215 [21] - 58:21, 67:9, 68:1, 85:5, 87:14, 89:17, 92:7, 102:12, 112:11, 112:16, 114:15, 115:10, 126:25, 132:10, 142:23, 208:17, 212:9, 214:5, 226:22, 252:14

DTX-231 [2] - 200:25, 255:17

DTX-251 [2] - 308:10, 308:12

DTX-251.4 [1] - 308:18

DTX-272 [2] - 303:24, 304:1

DTX-275 [2] - 205:20, 255:18

DTX-291 [7] - 267:2, 267:4, 267:16, 295:17, 300:15, 318:12, 323:15

DTX-296 [5] - 163:13, 177:17, 178:14, 178:24, 203:5

DTX-304 [1] - 309:16

DTX-313 [2] - 304:17, 304:19

DTX-328 [4] - 264:14, 264:16, 265:15, 310:9

DTX-344 [3] - 151:9, 177:17, 197:22

DTX-355 [2] - 196:12, 255:17

DTX-358 [4] - 130:7, 130:17, 177:17, 191:23

DTX-363 [4] - 148:18, 149:16, 177:17, 194:15

DTX-38 [3] - 271:5, 271:7, 272:6

DTX-505 [2] - 184:12, 255:17

DTX-522 [1] - 257:17

DTX-62 [3] - 294:3, 294:5, 295:17

DTX-69 [2] - 290:25, 291:2

DTX-80 [4] - 276:18, 276:21, 279:17, 292:23

DTX-91 [4] - 301:6, 301:8, 306:25, 309:4

due [2] - 122:20, 344:9

Duke [1] - 11:25

duly [3] - 68:14, 183:20, 256:17

during [52] - 3:10, 6:4, 6:6, 7:9, 9:11, 9:16, 10:3, 14:5, 15:6, 20:20, 20:21, 29:21, 33:9, 36:8, 57:24, 80:13, 83:24, 93:7, 107:7, 112:4, 128:4, 132:14, 134:4, 134:17, 140:8, 141:11, 141:21, 142:10, 142:17, 142:21, 143:4, 143:24, 150:25, 151:12, 151:20, 157:2, 160:18, 177:11, 181:1, 181:16, 182:23, 209:22, 212:1, 232:8, 307:6, 318:12, 319:9, 319:21, 320:4, 322:16, 323:17, 334:11

During [1] - 132:17

DX [2] - 67:3, 67:7

E

early [11] - 5:11, 53:18, 107:3, 107:4, 134:7, 134:11, 212:16, 212:25, 213:22, 227:4, 342:18

earn [1] - 258:5

easiest [1] - 214:18

easily [3] - 266:6, 286:6, 300:11

easy [1] - 19:24

edges [1] - 193:6

edited [2] - 84:9, 96:13

education [6] - 184:11, 184:19, 257:15, 257:22, 258:3, 316:17

educational [2] - 70:2, 72:14

Effect [2] - 120:1, 179:18

effect [10] - 40:2, 49:2, 49:4, 76:25, 114:8, 119:15, 122:14, 127:21, 198:25, 199:5

effective [6] - 4:15, 7:1, 34:8, 118:24, 120:14, 308:24

effectiveness [2] - 6:13, 41:16

effects [2] - 95:22, 150:18

efficacy [2] - 176:6, 176:10

eight [5] - 5:19, 11:6, 32:22, 33:2, 344:22

either [14] - 14:2, 15:5, 138:13, 188:16, 195:23, 218:13, 238:19, 243:4, 284:5, 284:17, 320:12, 341:11, 346:13

ejected [1] - 79:20

EL [1] - 294:15

electricity [1] - 118:3

electron [2] - 166:22, 224:9

electrostatic [8] - 117:25, 118:2, 169:22, 169:25, 170:3, 170:8, 223:2, 223:6

electrostatics [1] - 223:10

element [1] - 330:15

elements [7] - 40:14, 50:9, 54:12, 182:17, 182:18, 260:14, 260:17

Eli [1] - 258:7

ELIZABETH [1] - 2:6

elsewhere [1] - 186:1

embodiment [1] - 16:25

embodiments [2] - 11:13, 11:16

emerge [1] - 40:8

emphasis [1] - 152:13

emphasize [2] - 18:9, 22:6

employ [1] - 56:10

employed [3] - 70:7,

70:8, 184:23
employment [5] - 184:11, 184:18, 257:15, 257:21, 258:3
enabled [1] - 11:11
enablement [1] - 13:20
encompasses [1] - 70:25
encyclopedia [2] - 82:25, 199:15
Encyclopedia [3] - 83:1, 84:8, 232:6
end [17] - 4:12, 9:7, 10:12, 10:24, 10:25, 21:13, 34:2, 34:15, 50:21, 52:16, 53:14, 120:18, 193:19, 295:21, 300:25, 331:2, 331:25
ended [1] - 228:5
ending [5] - 85:11, 89:18, 92:7, 105:13, 120:4
ends [2] - 87:22, 102:16
ENERIO [1] - 2:2
engage [1] - 73:18
engaged [1] - 186:9
engineering [5] - 16:2, 29:17, 70:14, 75:21, 258:4
enhance [4] - 24:17, 79:1, 227:24, 237:8
enhanced [2] - 143:20, 180:10
enhances [13] - 61:19, 61:22, 62:5, 90:8, 90:13, 93:11, 143:12, 145:4, 180:9, 227:15, 236:12, 236:19, 237:4
enhancing [5] - 92:18, 106:17, 144:5, 228:5, 236:23
enjoin [1] - 34:17
ensure [2] - 10:24, 10:25
entered [2] - 125:18, 126:25
entire [5] - 14:16, 32:11, 41:2, 149:8, 258:20
entirely [2] - 6:18, 15:21
entirety [1] - 239:7
entitled [5] - 60:16, 61:8, 62:14, 132:13, 233:2
entrain [1] - 122:4
entrained [2] - 122:4, 122:6
entry [9] - 143:2, 149:13, 194:22, 226:24, 236:8, 236:11, 293:4, 305:25, 306:1
Entry [1] - 306:3
enumeration [1] - 65:15
enzymes [3] - 5:1, 5:2, 5:4
EPA [2] - 304:2, 305:3
epithelial [1] - 185:2
equal [1] - 261:17
equally [1] - 207:8
equals [1] - 280:9
equate [1] - 307:12
equations [2] - 130:24, 191:22
equipment [4] - 79:12, 170:8, 189:2, 189:4
equitable [1] - 15:24
equivalent [1] - 121:15
error [3] - 10:8, 139:5, 241:23
errors [2] - 182:9, 295:5
especially [2] - 189:11, 301:1
ESQUIRE [11] - 1:17, 1:20, 1:20, 1:21, 1:21, 2:2, 2:5, 2:5, 2:6, 2:6, 2:7
essential [4] - 4:16, 4:17, 7:2, 10:21
essentially [56] - 22:14, 27:12, 27:15, 27:16, 28:8, 28:10, 28:21, 28:24, 29:9, 30:7, 30:10, 30:13, 31:7, 36:21, 47:15, 50:16, 50:17, 50:22, 53:8, 53:15, 56:9, 56:16, 80:16, 196:1, 234:8, 250:22, 260:21, 261:12, 261:13, 261:18, 262:9, 262:13, 266:24, 270:8, 270:15, 270:20, 276:6, 282:5, 287:18, 287:20, 287:21, 293:7, 299:13, 299:25, 300:2, 307:25, 310:24, 313:15, 313:18, 313:22, 318:8, 321:1, 321:5, 322:1, 322:6
establish [1] - 30:15
estimate [1] - 190:13
estimated [1] - 166:15
et [4] - 1:7, 107:11, 130:1, 148:12
ether [1] - 295:23
Europe [1] - 266:18
European [1] - 291:19
evaluate [5] - 66:17, 91:22, 128:18, 241:1, 244:14
evaluated [8] - 87:4, 132:21, 227:9, 303:16, 327:4, 327:7, 327:15, 328:4
evaluating [2] - 115:14, 225:24
evaluation [2] - 66:16, 211:24
evenly [1] - 23:15
event [1] - 34:14
events [1] - 33:14
Evercorn [1] - 119:23
evidence [33] - 9:4, 22:2, 22:3, 22:7, 22:8, 24:8, 24:9, 24:19, 26:24, 28:25, 30:18, 31:4, 31:18, 33:12, 33:16, 68:6, 74:7, 106:17, 126:20, 127:10, 127:12, 177:23, 177:25, 187:9, 216:20, 216:24, 217:25, 228:4, 255:15, 256:2, 256:4, 278:5, 299:10
evident [2] - 89:7, 133:6
exact [2] - 51:25, 333:14
exactly [12] - 13:24, 280:7, 284:19, 297:14, 336:9, 340:8, 342:9, 343:19, 343:25, 344:3, 345:24, 347:3
exam [2] - 143:5, 328:15
EXAMINATION [8] - 68:18, 128:13, 178:3, 183:23, 230:7, 251:9, 256:19, 311:13
examination [23] - 132:15, 157:2, 177:4, 177:7, 178:16, 178:17, 179:6, 180:12, 180:20, 181:1, 230:1, 232:9, 236:9, 239:20, 242:5, 242:23, 252:4, 253:2, 261:19, 318:13, 329:10, 332:5, 334:11
examined [3] - 68:14, 183:20, 256:17
examiner [4] - 319:10, 319:22, 320:4, 320:14
example [34] - 18:10, 18:13, 18:15, 23:6, 132:3, 147:4, 160:12, 176:15, 192:15, 207:24, 208:5, 243:17, 243:18, 267:17, 267:19, 268:9, 268:20, 272:21, 283:19, 293:25, 294:23, 299:6, 299:12, 299:24, 300:14, 306:14, 309:11, 310:13, 310:20, 315:18, 331:12, 337:11, 345:4
Example [10] - 272:25, 273:22, 274:15, 307:25, 329:13, 331:10, 331:13, 331:21, 333:2, 333:6
examples [15] - 16:25, 148:23, 160:5, 174:17, 174:20, 174:21, 175:14, 175:19, 196:8, 208:1, 208:3, 310:5, 310:12, 331:5, 334:6
exceed [1] - 30:20
exceedingly [2] - 27:19, 30:15
excellent [2] - 164:4, 204:11
except [5] - 81:17, 81:22, 136:1, 138:13, 273:17
excerpt [6] - 83:6, 84:8, 86:17, 96:12, 112:10, 231:16
excipient [57] - 23:2, 23:6, 23:9, 23:11, 23:14, 24:2, 24:4, 25:15, 25:19, 26:4, 46:20, 51:16, 59:14, 59:17, 62:9, 66:2, 78:20, 92:2, 101:6, 128:22, 134:2, 141:24, 146:17, 147:1, 150:15, 151:2, 151:3, 151:5, 153:3, 154:3, 155:17, 160:2, 162:7, 175:15, 175:19, 193:7, 195:21, 196:21, 197:4, 198:16, 198:20, 199:5, 202:18, 203:3, 204:20, 205:24, 216:2, 225:19, 226:5, 228:16, 230:11, 247:6, 247:15, 247:24, 254:24
excipient's [1] - 150:18
Excipients [1] - 205:23
excipients [54] - 10:4, 10:14, 23:2, 46:18, 49:20, 49:21, 50:12, 51:9, 51:17, 51:21, 51:25, 52:5, 77:3, 80:10, 84:18, 84:21, 88:8, 89:10, 89:15, 95:14, 142:20, 144:23, 147:10, 147:16, 151:15, 152:11, 152:14, 167:7, 172:2, 174:9, 178:6, 179:25, 190:3, 194:8, 194:11, 196:4, 198:17, 199:23, 206:2, 207:13, 226:10, 229:3, 229:5, 232:18, 234:2, 234:3, 237:2, 247:12, 254:8, 254:16, 314:17, 314:24
exclusively [1] - 125:19
excuse [1] - 46:10
EXELIXIS [1] - 1:4
Exelixis [69] - 3:25, 4:1, 5:10, 5:23, 6:9, 7:3, 8:4, 8:8, 8:17, 11:20, 15:9, 15:11, 15:15, 15:20, 28:3, 31:11, 31:22, 32:1, 32:12, 32:23, 33:2, 34:12, 34:16, 36:22, 39:21, 41:13, 47:7, 54:8, 58:11, 58:24,

68:25, 72:16, 73:4, 74:4, 85:1, 188:13, 230:6, 262:21, 270:23, 270:25, 271:8, 271:13, 272:2, 276:23, 280:24, 281:4, 281:9, 281:20, 282:7, 283:1, 283:18, 283:25, 284:14, 285:19, 287:3, 288:9, 291:18, 291:19, 292:19, 312:1, 320:7, 336:14, 336:21, 337:25, 338:17, 339:5, 339:9, 339:25, 341:18
Exelixis' [7] - 4:6, 27:21, 53:17, 186:11, 259:23, 262:25, 286:4
Exelixis's [2] - 338:20, 338:21
exerts [1] - 76:25
Exhibit [19] - 58:17, 58:18, 58:19, 60:6, 65:5, 68:5, 127:10, 127:11, 177:22, 177:24, 230:21, 231:15, 232:12, 235:8, 244:23, 249:12, 256:1, 256:3, 329:8
exhibit [29] - 67:25, 130:24, 132:12, 134:24, 142:25, 149:19, 149:21, 150:3, 184:13, 194:17, 196:15, 197:7, 199:13, 199:17, 201:2, 201:7, 202:5, 203:12, 205:3, 205:21, 208:19, 209:1, 210:9, 210:23, 222:13, 222:19, 231:19, 253:13, 311:8
exhibit's [1] - 149:21
exhibited [2] - 138:6, 197:14
exhibits [11] - 24:13, 58:12, 58:15, 60:20, 60:22, 66:23, 89:8, 126:19, 133:6, 255:14, 347:10
exist [5] - 39:5, 40:5, 40:6, 40:16, 41:22
existence [1] - 29:3
exists [3] - 21:21, 39:9, 56:14
expect [13] - 3:9, 19:10, 47:3, 48:11, 167:17, 167:23, 167:24, 190:5, 190:15, 205:16, 223:17, 223:18, 341:13
expectation [3] - 21:15, 29:24, 311:3
expectations [1] - 3:8
expected [5] - 91:5, 152:13, 217:22, 237:7, 310:23
experience [19] - 21:1, 71:23, 72:14, 75:14, 75:22, 104:15, 111:5, 188:5, 188:8, 208:7, 315:18, 316:4, 316:19, 316:22, 317:2, 317:12, 317:22, 318:1
experiment [5] - 63:16, 239:20, 243:10, 244:6, 333:16
experimental [9] - 22:3, 22:7, 31:4, 33:12, 223:5, 223:9, 223:14, 294:7, 294:8
experiments [8] - 11:3, 64:12, 113:12, 113:13, 209:18, 228:1, 237:8, 238:24
expert [26] - 20:22, 23:25, 68:24, 72:17, 108:18, 128:1, 129:11, 130:3, 135:5, 157:18, 161:1, 166:14, 185:24, 258:24, 259:5, 312:8, 314:20, 316:12, 320:20, 321:12, 326:23, 339:14, 341:19, 341:22, 342:8, 342:15
expert's [1] - 343:2
experts [5] - 26:3, 31:5, 56:22, 186:4, 325:21
expire [2] - 34:18, 43:7
expires [2] - 42:18, 126:16
explain [33] - 6:13, 7:15, 8:19, 8:25, 12:3, 16:4, 16:9, 16:12, 16:18, 20:4, 20:9, 21:2, 21:7, 21:9, 22:4, 24:16, 26:8, 30:1, 32:11, 33:18, 33:20, 103:7, 189:16, 195:12, 195:17, 198:5, 199:8, 203:17, 207:23, 269:23, 276:13, 296:15, 298:11
explained [1] - 57:22
explaining [4] - 184:4, 257:8, 278:12, 310:11
explains [1] - 131:3
explanation [3] - 144:15, 217:3, 294:6
explicit [2] - 23:19, 321:21
explicitly [7] - 322:5, 322:9, 329:2, 329:21, 329:24, 330:6, 333:13
explore [1] - 59:13
exposed [1] - 10:18
exposure [4] - 9:22, 10:20, 302:15, 307:8
expressly [2] - 328:24, 329:3
extension [6] - 42:12, 42:13, 42:24, 43:1, 43:3, 46:9
extensive [5] - 8:20, 10:4, 95:22, 96:1
extent [1] - 156:12
extra [1] - 244:7
extractions [1] - 333:1
extragranular [25] - 86:15, 103:15, 104:3, 104:5, 104:13, 113:5, 114:12, 134:12, 134:16, 138:6, 138:14, 210:17, 210:18, 211:5, 211:7, 213:15, 214:17, 215:18, 240:12, 240:18, 241:12, 242:1, 244:8, 244:10, 244:17
extremely [2] - 50:1, 338:2

F

faced [1] - 5:23
facilitate [3] - 5:4, 78:16, 109:2
facilitating [2] - 118:12, 118:25
facilitation [1] - 77:4
Fact [2] - 125:13, 125:17
fact [29] - 9:2, 12:12, 15:6, 16:14, 25:23, 25:25, 30:24, 32:9, 43:2, 47:20, 48:10, 49:3, 90:23, 91:15, 91:23, 93:8, 126:4, 142:4, 142:13, 143:11, 187:2, 228:25, 247:19, 295:11, 300:22, 335:23, 344:19, 346:16
factor [1] - 20:13
facts [12] - 15:22, 52:10, 73:8, 73:16, 75:4, 75:8, 81:1, 81:3, 81:18, 81:20, 81:21, 125:12
factual [1] - 44:8
fair [5] - 128:19, 175:10, 175:12, 326:16, 326:17
fairly [1] - 304:23
fall [5] - 12:19, 49:22, 49:24, 137:12, 151:6
falls [1] - 52:11
familiar [8] - 59:24, 70:22, 130:1, 153:2, 154:2, 245:15, 318:21, 336:10
family [1] - 36:1
famous [1] - 52:22
far [12] - 30:20, 42:3, 42:4, 61:14, 71:16, 187:25, 192:25, 217:14, 241:25, 286:15, 288:13, 307:11
fashion [1] - 268:5
fast [3] - 129:23, 129:25, 130:4
faster [1] - 204:24
FAU [2] - 258:21, 258:23
favor [1] - 34:16
FDA [68] - 4:17, 5:16, 7:2, 24:10, 24:16, 24:21, 24:24, 25:3, 25:8, 25:24, 26:1, 26:25, 31:23, 39:3, 39:4, 39:6, 39:9, 45:2, 47:5, 53:24, 55:24, 55:25, 61:1, 61:3, 63:5, 64:7, 64:24, 65:3, 73:17, 73:18, 92:15, 108:3, 125:6, 125:21, 180:8, 185:13, 235:13, 236:18, 237:21, 238:6, 239:3, 272:3, 280:17, 301:9, 301:11, 304:7, 305:11, 306:25, 307:3, 307:5, 309:1, 309:5, 309:16, 309:19, 309:23, 336:6, 336:15, 336:21, 337:25, 338:19, 338:20, 338:21, 338:24, 339:2, 339:6, 339:10, 340:1
FDA-approved [1] - 45:2
feasible [1] - 302:17
features [2] - 17:2, 189:7
February [7] - 75:10, 76:15, 98:19, 259:25, 264:2, 303:16, 310:4
fed [1] - 104:7
Federal [1] - 345:12
feedback [1] - 290:10
fellow [1] - 185:7
fellowship [1] - 258:7
felt [2] - 33:18, 298:3
fenofibrate [15] - 120:13, 120:15, 120:16, 120:17, 120:22, 121:10, 121:14, 121:21, 167:14, 167:18, 167:24, 221:11, 222:5, 222:7, 222:13
fenofibrates [1] - 222:19
few [10] - 4:5, 12:10, 43:3, 52:10, 60:10, 85:17, 104:10, 144:23, 320:11, 347:1
field [6] - 21:1, 185:24, 186:4, 258:25, 259:5, 315:16
Fieser [2] - 308:20, 308:22
fifth [3] - 170:24, 200:15, 204:16
Figera [2] - 194:14, 200:25
fighting [1] - 34:7
figure [2] - 62:14,

215:10
Figure [2] - 120:9, 337:3
figures [2] - 327:24, 328:21
filed [7] - 15:12, 15:16, 36:8, 47:5, 57:16, 245:3, 246:10
filing [1] - 245:8
filings [2] - 26:7, 39:3
fill [1] - 218:11
filled [1] - 189:5
filler [33] - 23:9, 47:14, 47:15, 50:3, 78:12, 78:17, 81:8, 116:19, 147:4, 147:7, 148:4, 148:6, 148:8, 153:22, 154:16, 154:21, 155:7, 155:9, 155:11, 155:24, 156:10, 164:10, 187:5, 195:8, 195:23, 195:24, 196:6, 197:5, 201:25, 202:4, 204:22, 234:5, 247:7
fillers [22] - 48:4, 49:22, 51:11, 78:1, 78:13, 142:17, 148:17, 150:10, 151:7, 152:12, 159:7, 195:3, 195:11, 196:9, 198:6, 198:9, 198:10, 198:12, 202:1, 217:20, 217:21, 229:9
fills [1] - 79:18
filter [8] - 296:18, 296:19, 296:20, 296:21, 297:2, 297:3, 297:4, 297:5
final [28] - 27:18, 28:23, 62:14, 62:18, 79:17, 86:16, 102:19, 102:24, 104:7, 104:13, 105:22, 110:16, 116:6, 121:16, 123:6, 138:9, 182:13, 182:21, 189:3, 268:16, 292:12, 300:25, 301:24, 309:25, 313:14, 331:2, 344:17
Final [1] - 85:12
finally [4] - 11:5, 33:15, 223:24, 275:10
fine [18] - 110:13, 118:16, 118:18, 118:23, 118:24, 119:2, 119:9, 121:3, 121:6, 121:15, 121:20, 121:21, 123:17, 167:3, 220:1, 251:3
fineness [1] - 111:13
finer [1] - 54:10
fines [8] - 168:3, 220:17, 221:2, 222:14, 222:16, 222:17, 222:20, 251:5
fingerprint [1] - 280:11
finish [4] - 11:7, 246:22, 331:7, 347:6
first [103] - 3:2, 5:20, 5:21, 5:24, 6:14, 7:14, 9:24, 12:2, 12:19, 13:15, 14:4, 15:12, 17:6, 17:9, 19:5, 19:12, 19:21, 22:25, 23:21, 27:7, 28:13, 33:6, 33:24, 35:9, 42:6, 46:15, 49:3, 50:24, 57:3, 57:4, 57:12, 57:21, 62:25, 64:11, 71:1, 77:11, 83:14, 84:16, 85:18, 87:9, 90:5, 92:11, 100:23, 108:24, 109:25, 112:19, 113:22, 114:18, 116:12, 120:5, 120:9, 129:4, 129:14, 151:18, 152:7, 157:17, 165:16, 173:18, 183:13, 184:10, 188:19, 188:21, 192:18, 197:13, 199:23, 214:18, 214:25, 218:8, 224:24, 225:14, 226:9, 227:2, 228:19, 231:23, 232:17, 237:20, 237:21, 240:8, 241:16, 243:9, 243:10, 245:8, 251:14, 257:10, 266:1, 270:13, 270:17, 276:16, 288:24, 289:11, 295:20, 295:21, 308:3, 308:4, 313:8, 315:14, 321:3, 321:24, 323:20, 324:17, 338:14, 345:8
fit [4] - 219:13, 315:13, 315:22, 318:2
fits [1] - 24:7
five [17] - 46:23, 117:4, 117:7, 117:8, 165:7, 165:12, 165:16, 200:1, 200:10, 331:24, 332:16, 332:20, 332:21, 341:13
flag [3] - 52:24, 304:13, 306:9
flagged [1] - 341:2
flaws [1] - 28:11
Florida [1] - 258:9
Flow [1] - 88:1
flow [215] - 23:14, 23:15, 23:23, 24:2, 24:13, 24:15, 24:22, 26:2, 26:5, 27:1, 27:2, 48:6, 48:9, 48:22, 49:2, 49:4, 49:8, 60:3, 60:17, 60:20, 60:23, 61:4, 62:15, 62:17, 63:3, 64:4, 64:13, 64:25, 79:1, 79:6, 79:7, 79:24, 82:11, 83:16, 84:21, 85:2, 88:19, 89:3, 89:8, 89:16, 90:12, 92:14, 92:19, 93:9, 93:11, 94:20, 95:8, 97:4, 98:2, 102:18, 102:23, 106:17, 109:11, 110:7, 110:14, 110:16, 111:21, 113:9, 114:21, 115:3, 115:8, 116:15, 118:20, 118:21, 119:1, 121:2, 122:6, 129:1, 129:15, 129:24, 130:5, 130:18, 130:19, 131:12, 131:16, 131:17, 131:20, 132:6, 132:9, 133:7, 133:19, 134:3, 137:6, 137:9, 137:14, 141:2, 145:4, 146:2, 146:18, 146:20, 146:24, 147:1, 147:5, 147:12, 147:17, 147:18, 147:21, 148:5, 150:23, 153:21, 155:1, 155:20, 170:4, 170:17, 171:5, 173:23, 180:9, 180:10, 187:7, 188:22, 188:24, 189:1, 189:3, 189:5, 189:8, 189:12, 189:14, 189:15, 189:22, 189:24, 190:6, 190:12, 190:13, 190:15, 190:18, 190:25, 191:5, 191:6, 191:7, 191:11, 191:12, 191:14, 191:18, 191:23, 192:6, 192:11, 192:21, 193:7, 193:8, 193:21, 193:22, 193:23, 194:1, 194:4, 194:6, 194:12, 195:4, 195:12, 195:22, 195:24, 195:25, 196:6, 196:7, 196:9, 197:12, 197:14, 198:18, 198:21, 199:1, 199:6, 199:9, 205:13, 208:19, 209:1, 209:3, 209:8, 209:14, 209:17, 209:24, 211:22, 215:2, 215:6, 215:8, 216:22, 217:12, 217:21, 217:22, 217:23, 219:1, 220:10, 220:18, 223:3, 223:12, 224:1, 225:1, 225:24, 228:3, 229:22, 230:12, 230:14, 230:17, 231:24, 232:18, 233:9, 233:11, 234:21, 235:17, 235:19, 237:22, 238:2, 238:8, 239:10, 246:15, 246:20, 246:24, 246:25, 247:15, 247:17, 247:20, 247:22, 247:24, 248:21, 254:21, 254:25
Flowability [2] - 120:1, 179:18
flowability [51] - 24:18, 46:21, 46:24, 47:1, 47:19, 47:20, 47:24, 61:19, 61:22, 62:5, 79:22, 88:17, 89:1, 90:8, 90:13, 110:25, 119:15, 120:10, 120:12, 128:22, 131:25, 133:24, 138:8, 143:12, 143:21, 144:5, 153:22, 164:2, 165:23, 166:3, 167:2, 169:24, 170:13, 171:1, 171:12, 179:3, 179:21, 197:17, 199:24, 204:11, 204:13, 209:20, 222:2, 227:15, 227:25, 228:6, 236:13, 236:19, 236:23, 237:4, 237:8
flowable [3] - 122:15, 123:20, 156:22
flowing [9] - 24:15, 89:14, 110:24, 162:6, 190:10, 190:20, 196:5, 218:15, 237:7
focus [6] - 57:18, 87:9, 108:17, 312:20, 315:13, 343:22
focused [6] - 59:19, 143:11, 211:13, 211:14, 313:21, 314:7
focuses [3] - 22:18, 22:23, 70:18
focusing [6] - 69:19, 78:3, 79:5, 79:21, 95:8, 97:3
follow [6] - 54:17, 104:10, 299:8, 299:15, 321:14, 332:19
followed [4] - 55:11, 258:6, 272:19, 299:6
following [9] - 27:6, 187:8, 306:14, 319:20, 325:13, 325:14, 333:23, 337:10
follows [6] - 30:11, 63:21, 68:15, 183:21, 256:18, 331:21
FOR [1] - 1:2
force [1] - 200:20
forces [16] - 117:25,

118:2, 122:21, 171:2, 171:4, 171:8, 171:11, 172:4, 223:25, 224:4, 224:8, 248:4, 248:6, 248:11, 248:12
foregoing [1] - 347:16
form [46] - 7:22, 9:15, 9:21, 19:1, 19:13, 20:13, 20:16, 36:24, 37:9, 37:11, 37:16, 37:19, 38:3, 39:22, 40:24, 41:12, 55:17, 78:6, 111:24, 154:25, 211:16, 323:21, 323:24, 324:5, 324:8, 324:9, 324:10, 324:11, 324:14, 324:18, 324:22, 325:1, 325:5, 325:8, 325:15, 325:18, 326:1, 326:4, 326:6, 326:7, 326:8, 326:14, 327:1
formability [1] - 222:2
formally [2] - 66:23, 311:15
formation [3] - 7:25, 9:20, 21:6
formed [6] - 7:20, 9:11, 55:23, 298:25, 335:23, 337:23
forming [16] - 87:5, 121:12, 129:10, 130:20, 135:4, 137:17, 140:21, 157:13, 187:14, 187:18, 192:1, 193:14, 260:1, 262:14, 268:19, 272:15
Forms [1] - 96:13
forms [59] - 14:8, 14:10, 14:13, 14:16, 16:16, 16:17, 16:22, 37:12, 37:17, 37:22, 37:25, 38:2, 38:5, 38:7, 38:12, 38:15, 38:19, 38:23, 38:25, 39:1, 39:2, 39:4, 39:5, 39:6, 39:10, 39:11, 39:12, 39:24, 40:4, 40:5, 40:7, 40:9, 40:12, 40:15, 40:16, 40:17, 40:19, 40:21, 40:25, 41:1, 41:3, 41:4, 41:13, 41:22, 42:3, 48:2, 71:9, 79:25, 173:17, 173:21, 194:20, 231:17, 286:8, 317:4, 323:12, 324:3, 326:23
forms' [1] - 41:23
formula [2] - 107:5, 227:7
Formula [1] - 85:13
formulate [3] - 7:18, 20:6, 28:10
formulated [7] - 10:4, 10:14, 28:16, 28:19, 30:12, 161:13, 316:13
formulating [2] - 158:3, 317:3
Formulation [11] - 144:19, 212:14, 212:25, 213:3, 213:9, 213:10, 213:18, 213:20, 243:11, 252:16, 252:17
formulation [158] - 4:14, 7:6, 12:14, 29:9, 29:21, 34:13, 35:4, 35:7, 36:4, 36:5, 44:23, 46:12, 48:2, 49:9, 49:12, 49:15, 49:17, 50:4, 52:6, 52:16, 56:19, 61:10, 61:25, 62:9, 70:22, 70:24, 71:7, 71:15, 71:22, 72:1, 72:4, 72:17, 76:1, 87:13, 90:22, 91:8, 91:14, 91:20, 91:22, 92:4, 93:1, 102:11, 103:23, 105:5, 106:13, 107:6, 111:5, 118:19, 121:22, 128:19, 134:9, 134:13, 134:16, 135:1, 137:25, 138:4, 138:6, 141:20, 143:1, 143:24, 144:4, 144:20, 146:20, 150:11, 150:16, 151:5, 153:10, 153:14, 154:12, 156:10, 156:12, 157:16, 157:21, 158:9, 158:13, 158:23, 159:8, 159:19, 159:22, 160:1, 160:7, 165:12, 168:4, 173:5, 173:6, 175:6, 175:8, 175:15, 182:21, 186:5, 189:8, 189:21, 191:7, 192:8, 192:19, 193:18, 195:22, 196:2, 201:21, 201:22, 202:25, 208:8, 208:11, 209:22, 210:3, 210:10, 210:11, 210:14, 210:23, 211:1, 211:2, 211:13, 211:19, 211:23, 212:1, 212:5, 212:16, 213:3, 213:18, 213:22, 214:1, 214:13, 214:20, 216:19, 217:1, 217:5, 217:11, 217:17, 218:1, 218:25, 220:17, 221:7, 222:21, 223:2, 223:12, 223:23, 223:25, 226:11, 227:4, 227:5, 227:7, 227:9, 227:21, 233:20, 235:22, 245:13, 245:16, 248:17, 248:22, 249:4, 252:13, 253:6, 253:20, 254:9, 254:24, 314:21, 316:10
formulation's [1] - 194:4
formulations [44] - 27:11, 27:24, 45:3, 51:24, 52:1, 56:12, 58:10, 59:8, 59:10, 122:13, 134:4, 134:7, 134:11, 136:1, 138:12, 142:10, 150:11, 152:12, 153:6, 154:9, 154:12, 155:1, 157:10, 174:17, 175:10, 185:3, 185:21, 188:6, 198:7, 206:11, 207:18, 207:21, 211:8, 211:12, 228:6, 238:16, 238:18, 246:21, 254:21, 315:19, 316:2, 316:4, 316:23, 317:4
Formulations [1] - 98:17
formulator [3] - 192:11, 194:3, 316:7
formulator's [1] - 193:25
formulators [2] - 55:22, 155:15
forth [8] - 53:7, 117:7, 117:9, 190:12, 203:22, 223:8, 268:3, 269:21
forward [6] - 92:5, 104:3, 215:19, 286:24, 300:25, 302:9
foundation [1] - 261:24
four [8] - 12:18, 42:24, 51:21, 51:24, 58:25, 149:18, 181:20, 292:6
four-year [1] - 42:24
fourth [3] - 122:16, 170:11, 288:22
free [65] - 6:1, 6:2, 6:15, 7:16, 7:18, 7:21, 7:23, 8:23, 9:2, 11:2, 12:15, 22:14, 27:12, 27:15, 27:16, 28:8, 28:10, 28:22, 28:24, 29:9, 30:7, 30:10, 30:13, 31:7, 31:18, 50:16, 50:17, 50:23, 53:8, 53:15, 56:16, 80:17, 162:6, 234:8, 234:12, 260:21, 261:12, 261:13, 261:18, 262:9, 262:13, 266:24, 270:8, 270:15, 270:19, 270:20, 276:6, 276:8, 287:19, 287:21, 293:7, 299:13, 299:25, 300:2, 307:25, 310:25, 313:15, 313:18, 313:22, 314:3, 318:8, 321:1, 321:5, 322:1, 322:6
free-flowing [1] - 162:6
freebase [2] - 17:12, 19:2
freely [2] - 79:16, 154:25
frequent [1] - 218:22
frequently [4] - 37:11, 37:13, 111:8, 197:5
friction [6] - 80:13, 118:4, 123:10, 200:17, 200:20, 218:14
front [2] - 135:2, 184:17
fulfill [1] - 101:12
full [15] - 36:18, 36:22, 37:21, 38:10, 40:21, 42:4, 59:4, 64:6, 68:9, 152:18, 183:15, 186:13, 197:8, 256:12, 256:14
fully [1] - 297:16
fumed [1] - 175:14
function [24] - 5:1, 5:5, 23:4, 66:9, 66:17, 93:4, 94:2, 106:8, 109:3, 116:18, 123:13, 145:17, 146:6, 146:13, 164:22, 180:1, 180:6, 201:16, 201:19, 202:17, 202:24, 206:13, 207:3, 216:22
functionality [2] - 152:14, 179:22
functioning [13] - 5:2, 5:4, 109:1, 128:18, 138:19, 141:7, 148:6, 155:11, 156:11, 217:16, 222:21, 228:17
functions [22] - 23:4, 26:4, 41:20, 77:3, 90:25, 101:12, 164:11, 164:14, 187:10, 198:6, 201:14, 202:10, 203:3, 204:20, 204:21, 205:10, 205:18, 206:8, 206:23, 207:7, 207:10, 247:12
fundamentally [2] - 50:5, 295:10
funded [1] - 258:19
fungus [1] - 100:2
future [2] - 40:8, 341:3

G

G.D [2] - 98:21, 98:22
gap [1] - 34:5
gas [5] - 170:21, 223:11, 223:15, 223:21
gases [5] - 122:1, 122:2, 122:8, 170:14, 170:16

GATTUSO [2] - 2:2, 2:2
gears [2] - 108:17, 299:20
general [6] - 44:13, 59:22, 62:7, 103:10, 270:1, 271:24
generally [28] - 45:18, 69:10, 76:22, 78:5, 78:13, 78:20, 79:7, 101:11, 107:1, 121:23, 144:7, 144:8, 146:18, 146:22, 146:25, 147:2, 147:3, 147:5, 153:2, 154:2, 156:15, 175:5, 190:15, 208:11, 216:4, 226:17, 263:15, 346:10
Generally [1] - 190:5
generate [1] - 290:3
generated [1] - 129:9
generating [2] - 91:19, 118:5
generic [6] - 4:3, 13:8, 26:10, 27:24, 34:17, 148:13
genetic [1] - 264:7
genotoxic [40] - 6:10, 9:9, 22:15, 52:19, 52:20, 52:24, 53:1, 54:12, 55:19, 261:7, 262:6, 263:10, 264:4, 264:12, 264:18, 265:19, 265:23, 266:4, 266:10, 266:18, 300:12, 301:10, 301:21, 302:13, 302:14, 302:18, 302:20, 303:6, 303:17, 304:8, 306:9, 306:16, 306:18, 307:4, 307:5, 307:18, 309:5, 309:9, 310:6, 330:7
genotoxicities [2] - 302:23, 306:25
genotoxicity [11] - 52:21, 52:22, 52:23, 54:11, 266:6, 302:7, 303:22, 304:22, 306:20, 308:1, 330:9
genotoxins [1] - 12:15
genus [1] - 14:8
GEORGE [1] - 2:5
George [5] - 11:24, 12:2, 33:17, 33:18, 35:1
Girindus [34] - 55:4, 55:5, 292:14, 292:17, 292:18, 292:20, 293:3, 293:7, 293:11, 293:13, 293:20, 293:24, 294:6, 294:14, 294:19, 294:23, 295:4, 295:14, 295:25, 296:13, 296:17, 296:21, 297:10, 298:2, 298:11, 298:25, 299:5, 299:6, 334:12, 334:15, 334:17, 334:21, 335:1
GIRINDUS [1] - 55:5
gist [2] - 36:19, 42:10
given [12] - 29:25, 95:14, 109:9, 185:24, 205:14, 243:19, 244:12, 258:24, 277:17, 278:3, 278:16, 307:6
glass [1] - 230:3
Glidant [1] - 232:17
glidant [217] - 22:20, 22:22, 23:1, 23:14, 23:15, 23:19, 23:22, 24:1, 24:8, 25:12, 25:22, 26:5, 26:10, 26:15, 26:17, 26:23, 26:25, 27:2, 46:17, 46:20, 46:25, 47:4, 47:8, 47:21, 47:22, 48:8, 48:13, 48:19, 48:24, 49:1, 49:5, 49:9, 50:3, 51:15, 51:17, 51:18, 60:2, 60:3, 66:3, 66:10, 66:13, 78:24, 78:25, 82:4, 82:7, 82:9, 82:12, 83:16, 84:17, 84:21, 85:2, 85:25, 86:20, 87:1, 87:13, 90:11, 90:13, 90:14, 90:22, 92:23, 92:25, 93:5, 93:9, 93:12, 93:25, 94:2, 95:13, 96:3, 99:3, 99:11, 101:7, 101:19, 101:25, 102:10, 105:1, 105:4, 105:5, 105:24, 106:9, 106:12, 106:19, 106:22, 107:22, 108:8, 108:23, 108:25, 109:3, 109:20, 109:24, 110:15, 111:2, 111:6, 111:11, 111:14, 116:7, 116:14, 116:19, 116:21, 116:24, 117:5, 117:13, 117:19, 118:22, 123:25, 127:15, 127:17, 127:20, 128:19, 128:23, 138:19, 138:24, 141:8, 142:1, 142:3, 142:7, 147:16, 148:6, 153:13, 154:8, 155:2, 155:12, 156:11, 157:9, 157:16, 157:21, 160:3, 160:7, 160:10, 162:15, 163:4, 164:17, 164:19, 165:11, 166:6, 171:7, 171:10, 171:20, 173:1, 173:2, 173:4, 173:8, 175:10, 175:23, 176:1, 178:11, 178:21, 179:20, 179:22, 180:5, 182:10, 187:4, 187:10, 198:16, 199:2, 199:6, 200:8, 200:18, 202:19, 202:20, 202:25, 204:14, 205:10, 205:16, 206:13, 207:1, 207:3, 207:17, 208:2, 208:6, 208:8, 209:23, 216:22, 217:17, 218:1, 218:11, 218:18, 218:19, 219:12, 220:5, 220:8, 220:9, 221:10, 222:21, 224:13, 225:1, 225:3, 226:6, 226:19, 228:17, 228:20, 229:2, 229:16, 229:20, 229:22, 230:11, 230:14, 230:16, 231:1, 231:23, 232:22, 234:16, 234:20, 246:11, 246:13, 246:25, 247:14, 247:25, 248:1, 248:25, 253:8, 255:1
glidants [67] - 24:14, 26:13, 26:20, 46:24, 47:6, 47:25, 49:24, 51:20, 78:1, 81:16, 81:22, 84:1, 86:21, 93:20, 94:15, 94:19, 95:6, 95:18, 96:1, 96:5, 97:1, 97:8, 98:5, 98:9, 98:11, 101:10, 104:16, 108:4, 116:12, 118:22, 123:8, 124:9, 124:11, 128:25, 160:23, 161:3, 172:13, 172:16, 174:10, 182:20, 194:8, 197:20, 198:20, 198:23, 199:8, 199:22, 199:23, 200:6, 200:13, 200:19, 205:13, 205:14, 207:5, 224:24, 229:24, 230:22, 230:24, 233:6, 245:23, 246:1, 246:3, 246:17, 246:20, 247:20, 253:6, 254:20
Glidants [4] - 83:12, 83:15, 231:21, 233:2
GMP [1] - 337:19
goal [2] - 20:17, 176:21
goals [3] - 176:18, 177:1, 301:23
good-flowing [1] - 237:7
government [1] - 185:12
grabbed [1] - 230:3
grace [1] - 122:24
grade [4] - 197:13, 197:16, 338:5, 338:6
grades [8] - 100:13, 155:14, 155:17, 156:21, 196:17, 196:18, 197:12, 197:19
graduate [1] - 70:5
grants [1] - 258:19
granulate [1] - 209:14
Granulated [2] - 105:18, 236:11
granulated [198] - 24:5, 24:7, 24:17, 24:22, 25:11, 25:14, 25:17, 25:20, 26:9, 26:12, 26:19, 26:24, 27:1, 47:8, 47:10, 47:14, 48:11, 48:12, 48:16, 48:17, 48:23, 49:1, 49:7, 59:15, 59:16, 59:21, 59:22, 61:17, 61:21, 62:4, 62:22, 63:1, 63:2, 64:1, 64:2, 64:4, 64:8, 64:12, 64:21, 64:25, 65:17, 66:9, 66:13, 66:15, 66:16, 86:4, 86:7, 86:10, 86:13, 86:18, 87:12, 90:2, 90:7, 90:10, 90:21, 91:7, 92:1, 92:13, 92:18, 92:25, 93:2, 93:25, 96:3, 96:6, 97:16, 97:17, 97:22, 99:13, 99:21, 100:4, 100:19, 100:21, 101:1, 101:19, 102:2, 102:8, 102:10, 104:5, 104:11, 104:19, 104:21, 104:24, 105:4, 105:20, 106:7, 106:12, 106:15, 106:18, 108:5, 108:8, 108:22, 109:19, 111:20, 112:6, 113:6, 114:4, 114:6, 114:20, 115:7, 115:22, 116:1, 117:18, 118:8, 118:13, 119:2, 119:6, 119:8, 121:2, 121:5, 122:7, 122:11, 122:22, 122:25, 123:12, 123:17, 123:18, 134:8, 134:15, 136:4, 137:24, 138:5, 138:14, 138:19, 141:20, 143:2, 143:8, 143:20, 144:5, 144:21, 154:17, 154:19, 155:1, 164:1, 164:23, 165:23, 166:3, 167:2, 167:9, 169:24, 170:12, 170:25, 175:18, 175:22, 178:10, 179:20, 180:8, 182:10, 187:2, 187:3, 187:5, 187:9, 201:16, 201:19, 201:24, 202:14, 202:15, 203:25, 210:2, 211:6,

211:21, 213:15, 214:16, 215:1, 215:19, 216:18, 216:21, 217:4, 219:6, 225:17, 225:24, 226:18, 226:25, 227:10, 227:23, 228:5, 233:13, 234:19, 234:21, 234:25, 236:8, 236:18, 236:20, 236:22, 237:17, 237:21, 238:2, 238:7, 238:19, 239:8, 239:9, 242:1, 244:7, 244:8, 247:3, 248:16, 248:18, 249:3
granulation [33] - 103:24, 109:10, 110:6, 110:13, 110:16, 110:19, 110:23, 111:2, 111:7, 111:12, 111:13, 121:16, 121:17, 121:18, 123:16, 133:15, 133:19, 133:23, 170:1, 192:20, 192:25, 193:9, 193:25, 194:4, 209:12, 209:16, 246:14, 246:17, 246:21, 246:22, 246:24, 248:19
granulations [5] - 24:3, 84:22, 110:14, 199:25, 232:19
granulator [2] - 103:20, 244:7
granule [4] - 141:2, 173:22, 218:12, 218:17
granules [36] - 24:18, 61:19, 61:22, 62:5, 90:9, 90:13, 104:2, 133:24, 143:12, 143:21, 144:6, 166:16, 166:19, 171:2, 193:18, 193:19, 193:21, 193:23, 194:10, 209:20, 219:7, 219:15, 219:17, 219:21, 220:25, 227:15, 227:25, 228:6, 236:13, 236:19, 236:23, 237:5, 237:9, 249:8, 250:1
graph [11] - 112:23, 113:1, 113:4, 113:5, 113:9, 115:1, 212:13, 212:18, 212:19, 242:14, 252:20
GRASTAR [86] - 47:8, 47:13, 86:5, 100:21, 101:2, 119:16, 119:20, 119:24, 120:1, 120:10, 120:13, 120:15, 120:23, 138:24, 163:7, 163:15, 164:1, 164:10, 164:11, 164:14, 164:17, 164:20, 164:22, 164:25, 165:6, 165:11, 166:8, 166:10, 166:23, 167:13, 178:18, 178:22, 179:8, 179:18, 179:19, 182:9, 187:3, 187:4, 187:9, 187:10, 201:16, 201:21, 202:16, 202:24, 203:2, 203:10, 203:25, 204:8, 204:13, 204:14, 204:19, 205:7, 205:9, 211:6, 214:16, 214:20, 214:21, 214:22, 214:24, 215:17, 215:23, 216:2, 216:10, 217:10, 217:16, 217:21, 217:23, 217:25, 218:24, 219:6, 220:22, 220:24, 221:9, 221:12, 222:20, 222:22, 223:1, 223:11, 223:24, 225:3, 225:17, 228:15, 239:4, 241:13, 241:20
GRASTAR's [2] - 47:12, 220:16
gray [1] - 121:5
GRDEN [1] - 2:6
great [4] - 4:24, 275:22, 297:14, 309:12
greater [6] - 120:13, 188:5, 242:6, 244:20, 280:5, 285:8
green [3] - 43:13, 51:11, 124:13
gross [1] - 7:24
groundbreaking [1] - 4:18
grounds [1] - 27:5
group [5] - 35:25, 51:21, 70:12, 305:23, 305:24
grouping [1] - 203:20
grow [1] - 5:6
growth [1] - 225:18
GTI [7] - 54:10, 284:22, 285:2, 285:19, 286:20, 287:6, 287:23
guess [4] - 51:14, 165:15, 242:14, 255:22
guidance [21] - 55:25, 265:7, 301:9, 301:19, 302:5, 302:14, 302:25, 305:11, 306:21, 306:23, 306:25, 307:3, 309:5, 309:8, 309:16, 309:19, 309:23, 341:5, 343:16, 346:3
guidances [3] - 301:3, 301:11, 309:1
guidelines [2] - 266:17, 266:20

H

half [6] - 35:12, 250:20, 250:24, 251:2, 269:22
halfway [4] - 94:21, 161:22, 253:23, 254:11
hallmark [1] - 36:15
hand [34] - 13:5, 34:22, 58:13, 79:5, 79:21, 90:2, 90:6, 94:16, 94:23, 96:23, 97:3, 97:24, 135:19, 135:23, 152:18, 157:24, 159:16, 169:13, 184:7, 187:25, 193:3, 195:19, 197:8, 212:12, 214:22, 218:16, 219:4, 220:13, 256:9, 283:23, 283:24, 300:17, 347:10
handbook [6] - 206:3, 206:8, 206:13, 206:16, 206:23, 207:10
Handbook [1] - 205:22
handed [1] - 168:20
handling [1] - 78:16
hands [2] - 4:18, 34:6
happy [4] - 67:10, 322:20, 343:10, 347:8
hard [5] - 4:2, 256:25, 306:1, 344:14, 347:2
harmful [2] - 6:22, 29:4
Hausner [25] - 129:17, 131:4, 131:8, 131:13, 131:17, 131:21, 131:24, 136:11, 136:19, 136:24, 137:2, 137:5, 137:10, 137:19, 137:24, 138:8, 139:2, 139:6, 140:5, 140:14, 140:25, 181:22, 191:15, 191:17, 209:4
Hausner's [2] - 88:21, 89:2
head [4] - 58:9, 59:8, 59:9, 100:24
header [1] - 100:23
heading [13] - 60:13, 60:16, 82:18, 83:12, 83:15, 92:12, 114:18, 120:6, 231:21, 270:2, 337:3, 337:7, 343:18
hear [34] - 6:7, 7:3, 7:10, 7:14, 7:17, 8:4, 8:11, 10:10, 11:3, 11:24, 16:1, 19:14, 19:21, 23:21, 23:24, 26:3, 26:6, 29:13, 29:23, 32:16, 33:16, 33:17, 41:4, 45:10, 47:10, 51:1, 53:4, 118:2, 127:13, 186:13, 198:2, 256:23, 257:5, 329:5
heard [14] - 33:23, 35:4, 35:11, 36:4, 78:14, 188:21, 192:25, 224:8, 228:18, 245:19, 263:11, 342:1, 343:1, 346:1
hearing [1] - 257:1
heat [3] - 9:22, 10:19, 10:20
Heather [1] - 347:19
heavily [2] - 339:13, 341:25
heavy [1] - 123:4
held [2] - 150:5, 177:15
help [12] - 5:5, 11:21, 23:9, 23:11, 31:12, 34:6, 46:24, 189:16, 193:11, 195:11, 195:12, 270:10
helped [1] - 34:5
helpful [4] - 327:12, 327:22, 332:4, 343:15
helps [1] - 52:23
hence [1] - 64:1
Hence [2] - 133:14, 209:11
hepatocellular [1] - 11:18
hereby [1] - 347:16
herein [4] - 68:13, 183:19, 256:16, 323:20
HEYMAN [1] - 2:2
high [15] - 7:19, 9:17, 30:15, 31:24, 32:5, 63:25, 71:7, 86:25, 110:19, 114:3, 202:3, 224:21, 263:23, 328:16, 342:22
high-performance [2] - 263:23, 328:16
higher [5] - 88:19, 89:2, 131:21, 140:17, 233:15
highest [1] - 148:7
highlight [4] - 28:12, 77:11, 77:20, 80:14
highlighted [21] - 24:18, 32:2, 43:12, 47:18, 51:10, 53:19, 53:25, 113:19, 113:23, 181:19, 271:15, 277:10, 279:17, 283:2, 291:25, 293:1, 293:2, 293:4, 305:23, 323:17, 324:12
highlighting [3] - 265:17, 286:2, 288:12
highlights [1] - 310:14
highly [5] - 6:2, 8:1, 16:19, 21:14, 308:24
hinder [1] - 118:21
hindsight [1] - 21:25
HIRZEL [1] - 2:2

history [2] - 107:4, 258:3
hmm [8] - 151:13, 257:6, 257:23, 259:18, 274:21, 275:9, 333:1, 337:6
hold [10] - 71:18, 78:10, 122:6, 149:15, 163:17, 163:19, 163:21, 224:12, 224:17, 290:8
holder [1] - 124:22
holds [1] - 65:17
homogenous [1] - 80:3
honed [1] - 54:9
Honor [117] - 2:19, 2:21, 2:24, 3:21, 4:4, 5:24, 7:6, 7:24, 8:15, 10:6, 13:24, 14:6, 14:12, 15:4, 15:6, 15:23, 16:18, 18:6, 20:4, 20:20, 22:6, 23:2, 24:19, 25:2, 29:1, 29:13, 30:14, 33:14, 34:22, 34:25, 35:2, 35:9, 35:10, 35:18, 36:13, 36:15, 37:2, 37:5, 38:11, 39:19, 40:4, 40:10, 41:15, 42:10, 43:19, 44:4, 44:25, 45:11, 45:25, 46:10, 47:3, 47:16, 48:1, 48:15, 49:10, 49:11, 49:14, 50:7, 50:13, 50:24, 52:9, 52:18, 53:11, 53:21, 55:6, 55:17, 56:18, 56:21, 57:1, 57:3, 57:8, 58:12, 59:1, 66:22, 67:24, 68:16, 72:16, 126:19, 127:2, 127:6, 127:20, 128:8, 150:1, 177:16, 178:1, 179:10, 183:7, 183:11, 186:3, 186:6, 230:2, 230:5, 252:1, 255:14, 255:20, 256:6, 256:9, 256:25, 259:4, 311:4, 311:7, 311:11, 322:14, 322:19, 323:1, 340:19, 341:1, 341:17, 341:25, 343:5, 343:10, 344:2, 344:6, 346:22, 347:9
Honor's [3] - 3:7, 44:7, 343:15
HONORABLE [1] - 1:14
Honorable [1] - 2:14
honors [1] - 258:17
hope [2] - 91:22, 92:5
hopefully [1] - 45:13
host [3] - 200:17, 200:18, 248:10
hours [3] - 296:24, 298:16, 298:17
house [1] - 49:6
housekeeping [2] - 57:10, 57:20
HPLC [11] - 263:24, 264:1, 270:3, 280:11, 286:9, 286:17, 290:22, 328:16, 328:21, 338:5
HR [1] - 181:22
human [2] - 70:15, 169:2
humans [1] - 29:5
hundred [3] - 269:18, 289:11, 342:16
hundreds [1] - 154:11
hydrochloric [2] - 298:15, 298:17
hydrogenation [1] - 154:21
hydroxyl [1] - 305:24
hydroxypropyl [1] - 103:22
hygroscopic [1] - 122:12
hygroscopicity [1] - 41:7
hypothetical [2] - 117:4, 117:8

I

IB [4] - 77:15, 77:18, 313:9, 313:11
idea [5] - 15:20, 43:16, 43:17, 43:20, 343:18
identical [8] - 136:1, 138:13, 269:3, 273:2, 273:7, 273:19, 336:3, 336:4
identification [1] - 107:5
identified [42] - 8:8, 39:12, 91:21, 92:2, 97:8, 101:9, 107:17, 116:8, 124:2, 124:8, 140:6, 140:14, 141:19, 157:14, 157:15, 157:19, 157:21, 159:12, 160:22, 160:25, 161:3, 165:17, 172:21, 174:10, 174:25, 175:18, 175:22, 176:1, 176:2, 182:9, 201:17, 201:19, 202:20, 204:21, 207:3, 236:20, 236:22, 246:12, 253:7, 253:23, 254:12, 295:3
identifier [1] - 278:16
identifies [20] - 26:22, 38:15, 145:8, 146:6, 157:8, 158:21, 159:7, 159:19, 164:22, 178:10, 202:13, 204:9, 204:10, 206:8, 206:23, 206:25, 233:8, 254:2, 254:17, 342:21
identify [25] - 9:19, 21:16, 31:1, 38:23, 39:4, 80:22, 85:24, 86:2, 151:7, 164:16, 174:17, 181:25, 202:24, 204:19, 206:13, 219:16, 273:15, 273:16, 279:10, 281:14, 281:19, 290:2, 294:22, 302:19, 329:24
identifying [12] - 8:25, 9:8, 21:4, 21:16, 21:18, 38:18, 202:16, 263:10, 264:11, 265:22, 291:5, 302:23
identity [1] - 254:25
ignore [1] - 19:9
image [1] - 193:3
immediately [2] - 54:24, 151:22
impact [24] - 47:20, 48:9, 79:22, 91:5, 91:16, 93:9, 110:23, 113:7, 115:19, 115:24, 145:4, 146:2, 170:4, 170:17, 189:12, 189:14, 191:7, 196:18, 198:17, 198:21, 205:9, 217:11, 239:14, 254:24
impacted [1] - 244:8
impacts [1] - 115:22
impart [1] - 110:7
implemented [2] - 336:12, 337:18
importance [1] - 115:7
important [28] - 3:17, 10:25, 12:12, 22:5, 24:22, 45:19, 52:18, 53:21, 63:2, 64:13, 64:25, 79:10, 79:15, 92:14, 114:21, 115:3, 135:16, 138:18, 138:23, 176:18, 176:22, 177:1, 205:12, 215:2, 237:22, 237:25, 238:3, 239:10
importantly [2] - 8:21, 338:16
importation [1] - 124:18
improper [1] - 15:4
improve [45] - 24:14, 26:1, 46:21, 46:24, 48:13, 49:8, 79:1, 82:10, 84:21, 89:16, 110:25, 111:20, 121:2, 133:19, 185:4, 192:12, 195:23, 195:25, 199:9, 199:24, 209:23, 213:6, 216:22, 217:21, 217:23, 219:1, 220:11, 220:18, 223:3, 223:12, 224:1, 229:22, 230:14, 232:18, 238:8, 241:3, 246:15, 246:20, 246:25, 247:17, 247:19, 247:21, 247:24, 248:21, 254:21
improved [7] - 27:9, 133:23, 147:18, 193:21, 242:9, 242:13, 242:24
improvement [19] - 88:19, 89:3, 116:15, 119:15, 120:12, 129:1, 131:15, 131:17, 132:6, 147:17, 147:21, 147:23, 148:1, 187:8, 211:22, 229:24, 242:20, 243:9, 243:14
Improvement [2] - 120:1, 179:18
improvements [1] - 89:4
improves [28] - 23:15, 23:23, 24:2, 26:5, 27:1, 27:2, 46:25, 60:3, 83:16, 85:2, 90:12, 93:11, 128:22, 148:5, 165:23, 166:3, 167:2, 169:24, 170:12, 170:25, 179:21, 196:6, 225:1, 230:12, 230:17, 231:24, 246:24, 247:15
improving [1] - 119:1
impurities [56] - 6:20, 6:21, 27:24, 55:19, 176:6, 176:10, 176:18, 176:25, 188:10, 262:5, 263:9, 263:16, 263:17, 263:21, 264:4, 264:6, 264:9, 264:12, 264:18, 265:3, 265:8, 265:11, 265:19, 265:20, 265:23, 266:10, 266:18, 269:21, 269:23, 281:10, 286:5, 301:4, 301:10, 301:22, 301:23, 302:13, 302:14, 302:20, 303:6, 309:9, 316:13, 317:25, 324:8, 324:11, 324:19, 325:15, 327:5, 327:8, 327:17, 327:25, 328:3, 328:6, 330:3
impurity [148] - 6:4, 6:7, 6:8, 6:9, 6:11, 6:21, 6:23, 9:9, 9:11, 9:21, 10:3, 10:18, 11:2, 12:15, 12:20, 22:11, 22:15, 27:7, 27:10, 27:12, 27:15, 28:8, 28:11, 28:22, 29:2, 29:6, 29:10, 29:25, 30:13, 30:19, 31:15, 31:25, 32:15, 46:13, 50:17, 50:23, 52:7, 52:9, 52:14, 52:17, 52:20, 52:25, 53:2, 53:3, 53:9,

53:15, 53:25, 54:2, 54:3, 54:4, 54:7, 55:9, 55:16, 56:2, 56:16, 234:9, 234:12, 260:22, 261:3, 261:4, 261:12, 261:16, 262:9, 262:13, 263:10, 263:14, 263:24, 264:1, 266:4, 266:24, 270:8, 270:16, 270:20, 276:3, 276:7, 276:9, 276:10, 277:5, 279:11, 279:23, 279:24, 280:14, 280:18, 281:10, 282:3, 282:25, 283:5, 283:21, 284:16, 284:17, 285:6, 285:7, 285:14, 285:15, 286:18, 286:21, 287:19, 287:21, 288:2, 289:4, 289:8, 289:16, 291:7, 291:10, 292:5, 292:6, 292:16, 293:4, 293:7, 293:18, 299:14, 299:18, 299:25, 300:3, 300:9, 300:20, 303:9, 303:17, 305:25, 307:6, 307:25, 308:2, 309:13, 309:14, 310:1, 310:6, 310:16, 310:19, 310:21, 310:25, 313:15, 313:23, 314:3, 314:8, 318:9, 321:1, 321:5, 322:2, 322:6, 322:9, 328:19, 329:25, 335:12

IN [1] - 1:1

in-vitro [2] - 266:7, 303:14

inactive [1] - 23:3

Inc [2] - 68:25, 337:13

INC [1] - 1:4

include [8] - 24:9, 87:1, 122:5, 150:18, 264:11, 272:6, 309:11, 317:2

included [8] - 75:25, 132:24, 208:1, 210:17, 215:17, 230:24, 246:11, 340:9

includes [5] - 22:20, 30:20, 103:18, 206:1, 246:1

including [8] - 23:25, 77:4, 87:2, 155:20, 165:18, 186:5, 281:10, 317:22

inclusion [2] - 237:4, 242:5

inconsistent [3] - 106:20, 293:19, 326:21

incorporate [4] - 71:4, 345:5, 345:9, 345:19

incorporated [1] - 156:13

incorporation [1] - 70:13

incorrect [1] - 181:17

increase [6] - 78:15, 138:8, 173:22, 241:7, 243:25, 282:18

increased [5] - 10:18, 150:11, 242:11, 243:20, 265:20

increases [1] - 221:24

increasing [3] - 241:2, 243:24, 248:10

IND [1] - 339:5

indeed [3] - 264:13, 298:5, 310:7

index [24] - 88:12, 88:15, 88:16, 88:18, 89:7, 129:17, 129:20, 129:21, 131:4, 132:3, 132:4, 133:2, 133:6, 133:11, 136:19, 138:7, 139:6, 139:10, 139:23, 140:25, 181:21, 191:15, 191:17, 209:4

India [1] - 244:25

indicate [4] - 88:19, 89:3, 106:21, 209:21

indicated [4] - 89:4, 107:7, 252:20, 269:20

indicates [1] - 54:2

indicating [1] - 138:8

indication [4] - 85:22, 170:8, 170:21, 223:5

indicia [4] - 33:16, 345:7, 345:10, 345:15

individual [6] - 20:7, 147:1, 189:5, 191:6, 205:24, 273:18

induce [3] - 74:20, 74:21, 126:14

industrial [1] - 315:17

industry [9] - 66:1, 71:23, 72:8, 101:5, 101:11, 156:16, 226:4, 226:11, 310:3

inert [2] - 153:17, 195:3

inevitably [3] - 30:16, 31:17, 330:15

information [47] - 19:25, 21:22, 25:6, 29:7, 30:2, 61:13, 62:2, 62:4, 62:10, 63:9, 84:1, 85:15, 88:4, 94:17, 102:17, 107:1, 107:6, 107:23, 114:10, 114:22, 114:23, 119:24, 130:9, 130:14, 135:7, 135:15, 135:18, 135:20, 144:6, 182:3, 198:12, 203:3, 235:12, 249:25, 250:3, 271:2, 299:4, 304:3, 304:14, 306:19, 327:25, 338:18, 338:24, 339:2, 343:24

infringe [5] - 35:21, 74:5, 74:18, 124:19, 234:15

infringed [2] - 35:20, 46:15

infringement [38] - 13:10, 22:17, 22:18, 22:25, 35:7, 46:17, 49:10, 57:16, 57:18, 57:23, 58:2, 69:15, 69:19, 74:20, 74:21, 76:4, 76:11, 80:19, 93:17, 101:16, 101:23, 106:24, 108:18, 126:11, 126:14, 129:11, 135:17, 137:22, 138:18, 138:23, 177:4, 177:7, 183:8, 186:24, 186:25, 200:23, 314:13

infringes [3] - 13:9, 74:8, 186:11

infringing [1] - 182:16

ingestion [1] - 78:22

ingredient [23] - 6:5, 9:13, 10:1, 23:7, 23:10, 54:18, 55:14, 71:2, 76:23, 77:2, 80:2, 146:19, 162:13, 174:25, 189:23, 190:20, 191:1, 191:2, 191:7, 198:24, 199:1, 263:13, 313:25

ingredients [19] - 23:3, 49:18, 71:5, 85:19, 85:24, 148:23, 189:7, 189:21, 190:16, 190:18, 191:9, 201:13, 201:14, 201:15, 202:9, 202:12, 210:14, 211:4, 254:8

inhalation [2] - 70:19, 71:11

inherency [16] - 30:15, 31:3, 31:22, 32:8, 32:24, 33:10, 288:1, 292:13, 293:15, 293:19, 299:23, 330:14, 330:22, 331:12, 333:20, 335:7

inherent [2] - 321:20, 323:5

inherently [15] - 28:7, 30:6, 30:10, 30:12, 31:6, 53:8, 53:14, 54:19, 262:8, 270:14, 299:12, 321:8, 322:5, 335:12

inhibitor [2] - 4:25, 52:2

inhibitors [2] - 5:8, 5:11

initial [21] - 61:9, 61:15, 91:13, 91:15, 91:23, 132:17, 142:25, 143:7, 143:16, 144:3, 144:18, 144:23, 145:3, 146:1, 213:5, 226:23, 227:3, 227:20, 235:21, 237:1

initiated [1] - 61:25

injectables [1] - 71:12

injured [1] - 183:3

innovative [1] - 4:1

input [1] - 104:4

inquiry [1] - 36:16

insert [1] - 123:4

inserting [1] - 14:17

inside [1] - 39:25

instance [9] - 47:23, 49:19, 71:3, 71:11, 118:18, 123:11, 146:23, 170:7, 257:11

instances [1] - 254:18

instead [7] - 28:18, 30:18, 31:8, 109:2, 296:2, 297:24, 338:5

instrument [1] - 280:12

instrumental [1] - 263:22

insufficient [1] - 342:10

intend [1] - 345:24

intended [2] - 6:19, 65:23

interact [2] - 191:9, 205:14

interacting [1] - 224:12

interactions [5] - 122:17, 122:23, 123:1, 224:9, 249:2

interest [1] - 185:1

interesting [2] - 15:17, 18:25

interests [1] - 184:25

intergranular [7] - 213:11, 240:12, 240:17, 241:9, 242:6, 243:19, 243:24

intermediate [2] - 297:22, 298:13

intermediates [1] - 309:25

intermolecular [1] - 122:21

internal [2] - 106:23, 278:14

internally [1] - 32:1

international [1] - 318:15

interparticle [1] - 120:15

interplay [1] - 185:3

interpretation [5] - 16:12, 324:25, 339:18, 340:10, 340:11

interpretations [1] - 339:12

interprets [1] - 325:4

intragranular [3] - 103:15, 103:16, 133:25

introduce [5] - 56:23, 57:4, 68:20, 168:20, 184:1

introduced [2] - 179:11, 179:12
introduction [4] - 113:11, 264:20, 301:15, 301:18
invalid [3] - 13:15, 13:17, 22:10
invalidity [5] - 22:23, 35:6, 35:8, 69:13, 344:18
invented [4] - 15:9, 15:15, 39:2, 42:2
inventing [1] - 33:25
invention [16] - 15:21, 16:25, 22:4, 30:17, 33:13, 36:5, 36:18, 38:6, 38:10, 74:24, 75:19, 157:10, 159:20, 174:18, 315:15, 321:22
inventions [3] - 11:7, 11:11, 30:3
inventive [3] - 50:2, 50:6, 56:5
inventor [5] - 16:24, 36:18, 72:3, 245:11, 258:13
Inventors [1] - 258:18
inventors [3] - 36:22, 159:22, 160:6
invested [1] - 33:2
investigate [2] - 7:15, 11:20
investigated [2] - 5:13, 8:4
investigating [3] - 5:10, 10:5, 10:7
investigation [1] - 64:7
invited [1] - 71:19
involve [5] - 36:2, 44:11, 81:10, 115:13, 224:8
involved [9] - 5:1, 10:5, 10:6, 71:8, 71:14, 154:11, 224:17, 307:16, 332:17
involves [2] - 36:4, 324:10
ion [1] - 342:25
Iowa [1] - 184:24
irregularities [1] - 123:10
issue [36] - 4:20, 13:10, 13:12, 14:2, 15:23, 17:6, 17:9, 20:19, 22:22, 26:7, 27:4, 28:20, 35:16, 35:17, 36:11, 37:2, 42:19, 43:5, 43:24, 43:25, 46:16, 50:14, 50:21, 67:25, 69:20, 170:9, 171:19, 223:6, 293:15, 320:20, 341:2, 341:17, 344:14, 344:16, 346:23
issued [3] - 18:1, 35:18, 320:4
issues [8] - 9:10, 22:16, 22:25, 69:10, 69:12, 187:19, 262:15, 314:21
Item [1] - 178:25
items [3] - 95:16, 109:7, 264:8
itself [20] - 4:13, 5:25, 6:11, 7:22, 8:23, 9:25, 13:2, 20:8, 20:12, 30:5, 34:11, 37:23, 49:4, 56:11, 116:20, 119:7, 123:5, 203:20, 299:1, 304:4

J

J-O-H-N [1] - 68:11
J-O-S-E-P-H [1] - 68:12
J.C [1] - 82:25
January [3] - 12:23, 15:13, 42:23
Japan [2] - 119:16, 119:19
Japanese [1] - 120:10
jet [4] - 167:17, 167:23, 222:7, 222:10
Jivraj [7] - 151:18, 152:10, 153:16, 154:16, 154:20, 197:24
Jo [1] - 7:4
job [1] - 213:22
Joe [1] - 68:23
John [4] - 57:22, 68:8, 68:11, 72:17
JOHN [1] - 68:13
joined [1] - 59:7
Joint [1] - 230:21
JONATHAN [1] - 1:21
Joseph [1] - 68:11
JOSEPH [1] - 68:13
JPCS [2] - 120:10, 120:14
JR [1] - 68:13
JTX [2] - 72:22, 127:10
JTX-4 [6] - 77:10, 126:22, 174:13, 259:11, 259:12, 313:2
JTX-9 [1] - 318:21
judge [1] - 341:15
judgment [1] - 34:16
July [1] - 267:12
June [1] - 57:17
junior [1] - 68:12
Justification [1] - 99:20
justification [5] - 61:9, 65:6, 91:13, 225:9, 235:21
justified [1] - 42:25

K

K-O-L-E-N-G [1] - 68:12
keep [5] - 56:2, 218:14, 266:19, 306:22, 307:18
keeping [2] - 202:4, 228:1
KEVIN [2] - 1:20, 1:22
Kevin [2] - 3:23, 58:2
key [1] - 27:6
keys [1] - 252:20
Khalid [1] - 7:4
kidney [5] - 11:18, 12:1, 13:6, 17:23, 18:15
kinase [3] - 4:25, 5:11, 52:2
kinases [2] - 5:1, 5:8
kind [9] - 44:18, 48:4, 52:11, 53:25, 54:12, 54:13, 56:12, 198:25, 286:7
kinds [1] - 246:9
King [1] - 1:10
knowledge [6] - 41:25, 56:13, 56:14, 336:1, 342:17, 342:20
known [30] - 7:18, 44:20, 51:16, 51:19, 51:20, 56:14, 76:24, 90:25, 93:19, 94:2, 96:4, 98:23, 101:11, 109:1, 122:12, 200:6, 228:3, 247:21, 261:4, 261:7, 266:6, 295:22, 300:11, 302:6, 302:22, 310:3, 311:1, 333:11
knows [5] - 23:2, 28:15, 30:14, 36:15, 343:5
KOLENG [1] - 68:13
Koleng [56] - 20:19, 20:20, 21:2, 21:7, 23:21, 26:6, 26:11, 57:22, 68:8, 68:12, 68:20, 68:23, 68:24, 70:2, 72:17, 72:21, 86:25, 127:13, 128:15, 128:17, 135:9, 139:3, 140:11, 168:14, 168:19, 174:1, 178:5, 179:25, 182:24, 183:1, 186:13, 191:21, 198:2, 200:4, 207:15, 214:25, 215:20, 216:11, 217:12, 220:17, 221:2, 221:11, 221:15, 222:14, 222:17, 224:20, 224:22, 224:24, 226:14, 227:14, 228:12, 228:24, 229:15, 229:18, 251:15, 254:20
Koleng's [7] - 187:11, 191:13, 219:19, 219:20, 228:14, 251:4, 251:17
Kondal [1] - 2:10
KREIGER [1] - 1:21
Kumar [1] - 245:10
Kurt [1] - 256:6
KURT [1] - 2:6

L

L)-malate [38] - 50:11, 50:25, 77:19, 81:8, 88:7, 208:24, 233:20, 233:24, 235:17, 266:23, 267:14, 267:24, 268:9, 269:1, 269:4, 269:12, 270:8, 270:15, 293:22, 294:15, 299:13, 300:2, 307:24, 310:24, 313:12, 313:22, 318:8, 320:25, 321:4, 322:1, 329:18, 330:19, 331:1, 332:13, 332:18, 333:23, 335:10, 339:6
L)-malic [1] - 342:24
L-E-P-O-R-E [1] - 256:15
lab [13] - 34:3, 48:20, 107:12, 127:23, 135:16, 136:9, 140:16, 180:11, 181:25, 182:5, 182:8, 182:12, 208:16
label [3] - 11:15, 125:3, 125:6
labeled [3] - 159:25, 160:4, 295:4
Laboratories [1] - 169:10
LABORATORIES [1] - 1:7
laboratory [11] - 11:12, 129:7, 129:10, 135:2, 210:6, 210:8, 251:20, 251:25, 252:19, 308:15, 315:17
laborious [1] - 10:8
Lachman [8] - 96:14, 106:3, 160:17, 161:5, 161:11, 161:22, 172:14, 207:15
lack [3] - 13:16, 13:20, 29:25
lactitol [3] - 154:17, 154:19, 155:2
Lactitol [1] - 154:20
lactose [10] - 145:22, 146:6, 146:9, 146:12, 153:23, 154:2, 154:5, 154:8, 154:21, 154:25
Lactose [1] - 146:1
Lahdenpaa [2] - 197:11, 197:18
laid [1] - 343:2
landscape [2] - 12:4, 266:11
language [6] - 95:11, 317:17, 322:10, 323:8, 323:17, 324:24
large [4] - 123:4, 224:7, 224:10, 224:15
larger [6] - 40:7, 123:9, 123:17, 167:6, 193:16, 205:15
last [33] - 4:4, 13:22, 15:3, 27:4, 29:16, 49:11, 50:13, 52:15,

80:14, 81:17, 100:20, 113:20, 125:11, 149:18, 152:18, 154:24, 176:4, 177:9, 197:8, 209:10, 216:15, 218:10, 260:20, 261:11, 265:25, 266:1, 292:10, 310:8, 317:11, 317:20, 331:15, 344:18
lastly [2] - 109:2, 109:10
late [2] - 346:22, 347:2
launching [1] - 34:17
law [5] - 3:12, 3:17, 16:23, 345:13
layer [10] - 134:16, 138:14, 240:12, 240:13, 240:17, 241:12, 242:2, 242:7, 244:8, 244:10
LCMS [2] - 286:9, 286:17
lead [3] - 41:16, 70:12, 107:5
leader [1] - 7:6
leading [2] - 293:17, 297:21
leads [3] - 264:8, 295:23, 295:24
learn [28] - 5:13, 5:24, 7:24, 8:13, 8:15, 9:3, 9:10, 10:6, 10:19, 11:22, 14:12, 18:6, 18:21, 20:10, 20:21, 21:5, 21:13, 23:1, 23:18, 24:10, 25:18, 27:18, 29:2, 29:18, 30:22, 31:25, 32:3, 181:16
learned [5] - 4:5, 4:6, 4:7, 4:9, 241:22
least [13] - 75:20, 134:9, 134:11, 137:17, 140:14, 144:17, 145:13, 149:10, 165:15, 315:17, 323:22, 332:16, 346:19
leave [1] - 340:20
lectures [1] - 71:19
led [7] - 9:23, 20:17, 21:23, 28:4, 43:22, 182:17, 310:18
left [29] - 17:8, 38:17, 38:20, 43:4, 54:15, 79:5, 90:2, 94:16, 96:23, 97:3, 135:19, 152:18, 157:24, 168:19, 187:25, 190:8, 193:3, 193:16, 195:19, 202:16, 212:12, 218:16, 220:13, 269:4, 273:13, 283:23, 286:16, 297:5, 300:17
left-hand [16] - 79:5, 90:2, 94:16, 96:23, 97:3, 135:19, 152:18, 157:24, 187:25, 193:3, 195:19, 212:12, 218:16, 220:13, 283:23, 300:17
legally [1] - 324:15
Lepore [96] - 256:8, 256:10, 256:14, 256:21, 257:5, 257:7, 257:11, 257:15, 257:19, 258:2, 258:16, 258:24, 259:5, 259:10, 259:12, 259:23, 260:8, 260:13, 261:2, 261:14, 262:2, 262:14, 263:6, 264:5, 264:16, 264:23, 265:17, 266:22, 267:11, 267:19, 268:13, 268:25, 269:19, 270:7, 270:14, 271:7, 271:12, 271:23, 272:12, 272:24, 273:11, 275:17, 275:25, 276:13, 276:21, 277:10, 278:1, 278:11, 278:20, 279:4, 279:21, 280:17, 281:2, 282:24, 285:1, 285:11, 286:2, 286:14, 287:1, 287:9, 287:16, 287:25, 288:7, 288:12, 290:20, 291:22, 292:12, 294:5, 294:13, 295:2, 295:14, 295:19, 296:15, 297:19, 298:11, 298:23, 299:4, 299:10, 299:24, 300:8, 300:18, 301:8, 303:5, 304:1, 304:19, 306:5, 307:9, 307:23, 309:18, 310:4, 310:11, 310:22, 311:15, 333:14, 336:23, 341:8
LEPORE [1] - 256:16
less [41] - 27:17, 50:18, 54:6, 56:5, 56:6, 116:19, 166:16, 168:4, 175:16, 176:22, 196:4, 219:8, 221:1, 221:3, 222:17, 222:18, 250:25, 261:16, 261:21, 269:17, 276:9, 279:6, 280:2, 280:4, 280:20, 283:10, 286:18, 287:12, 287:23, 287:24, 289:8, 289:9, 290:1, 291:9, 292:16, 299:17, 310:19, 313:19, 322:8, 328:25
lesser [2] - 188:3, 244:19
level [47] - 7:19, 32:21, 54:5, 55:9, 55:15, 62:22, 63:1, 63:2, 64:12, 64:21, 64:24, 71:7, 75:14, 86:25, 90:3, 92:13, 108:13, 110:19, 114:20, 115:14, 146:2, 148:7, 215:1, 215:17, 216:10, 224:21, 237:17, 237:21, 239:4, 239:8, 239:14, 248:8, 248:14, 280:5, 280:18, 281:14, 288:15, 288:16, 289:18, 289:22, 293:18, 301:2, 306:22, 307:18, 316:18, 342:22
levels [22] - 11:5, 27:10, 30:20, 31:14, 31:24, 32:4, 32:10, 32:15, 32:20, 54:15, 263:14, 263:17, 264:2, 266:19, 285:5, 291:12, 302:16, 307:3, 307:10, 310:6, 328:19, 330:3
license [2] - 74:13, 126:1
licensed [1] - 70:6
Lieberman [5] - 96:13, 160:17, 161:21, 162:1, 162:5
lifeline [1] - 12:7
light [3] - 115:1, 306:5, 308:1
likely [24] - 40:7, 45:15, 117:20, 117:22, 119:4, 122:9, 122:24, 123:14, 165:6, 165:11, 165:14, 165:15, 165:22, 166:2, 167:1, 169:23, 170:12, 170:25, 190:25, 218:24, 220:16, 317:18
Lilly [1] - 258:7
limine [1] - 341:18
limit [7] - 3:15, 122:14, 279:6, 279:8, 281:17, 285:4, 289:25
limitation [10] - 22:22, 77:21, 78:4, 81:15, 124:13, 153:21, 191:5, 260:20, 261:11, 313:14
limitations [6] - 18:7, 22:21, 80:22, 81:4, 81:22, 124:15
LIMITED [1] - 1:7
limitless [1] - 40:10
limits [4] - 265:6, 265:8, 266:9, 307:7
Line [12] - 82:16, 86:3, 86:14, 98:25, 158:6, 159:5, 211:5, 231:8, 319:14, 320:13, 327:22, 327:23
line [5] - 210:16, 231:23, 237:20, 237:21, 313:8
linear [1] - 332:22
Lines [4] - 158:19, 326:11, 327:14, 339:20
lines [2] - 77:11, 325:12
lineup [1] - 56:24
liquid [3] - 110:21, 263:23, 328:16
Lisa [1] - 230:6
LISA [1] - 1:20
list [29] - 46:18, 51:15, 51:16, 80:10, 85:24, 94:18, 94:21, 95:4, 98:5, 155:14, 157:8, 157:9, 158:12, 158:21, 172:13, 172:16, 172:19, 172:22, 172:24, 173:8, 204:6, 204:17, 246:1, 246:3, 253:5, 253:7, 253:19, 254:7
List [1] - 100:12
listed [23] - 19:3, 19:7, 40:13, 47:6, 92:4, 95:6, 95:16, 100:17, 100:18, 136:20, 139:7, 139:11, 139:20, 140:15, 155:9, 159:2, 173:12, 203:16, 245:10, 280:2, 283:5, 283:21, 314:17
listen [1] - 191:13
listening [1] - 341:12
listing [1] - 95:18
lists [7] - 19:1, 44:25, 164:10, 164:13, 233:5, 246:9, 250:7
literature [46] - 21:6, 25:7, 26:21, 46:22, 62:1, 62:4, 62:8, 63:8, 63:13, 66:8, 87:4, 93:18, 93:24, 94:2, 98:10, 101:15, 104:15, 108:4, 108:13, 117:5, 117:9, 144:7, 148:14, 163:4, 164:19, 165:21, 178:6, 178:10, 178:13, 182:19, 194:9, 194:11, 195:8, 196:8, 199:4, 199:8, 200:9, 201:24, 205:17, 207:12, 218:2, 218:21, 224:22, 226:13, 303:12, 310:12
litigation [3] - 31:21, 36:9, 69:7
litigations [2] - 185:25, 258:25
live [2] - 7:5, 57:21
liver [1] - 11:19
lives [1] - 34:7
living [1] - 12:11
LLP [3] - 1:17, 2:2, 2:4
locate [1] - 54:11
location [2] - 102:8, 105:2
lock [1] - 119:10

LOMBARDI [4] - 2:5, 2:20, 34:22, 34:25
Lombardi [5] - 34:21, 35:1, 57:2, 93:8, 112:3
Lombardi's [2] - 112:18, 343:1
long-range [1] - 16:5
longest [1] - 332:21
look [63] - 15:2, 18:4, 47:12, 49:13, 51:9, 60:19, 93:18, 95:11, 96:19, 132:9, 134:2, 139:14, 139:19, 140:13, 141:10, 144:23, 154:15, 159:15, 159:22, 160:1, 207:25, 210:16, 212:18, 214:17, 226:2, 232:11, 239:7, 245:22, 249:11, 264:20, 265:14, 266:14, 266:20, 269:22, 276:1, 276:4, 276:19, 278:17, 282:9, 282:21, 283:13, 286:12, 287:8, 287:11, 288:1, 289:2, 289:11, 290:24, 292:4, 294:3, 294:10, 295:14, 296:12, 297:9, 302:6, 303:8, 305:14, 309:15, 316:16, 317:11, 331:18, 336:19, 343:5
looked [24] - 87:2, 92:18, 94:6, 98:8, 102:13, 112:24, 115:1, 140:20, 140:23, 140:24, 219:22, 226:24, 283:18, 287:10, 288:2, 288:21, 289:25, 292:13, 292:14, 292:24, 304:21, 305:12, 305:19, 306:23
looking [16] - 17:17, 21:20, 61:1, 89:6, 95:4, 98:5, 105:18, 107:6, 130:17, 175:13, 215:13, 262:5, 273:4, 273:5, 277:5, 343:25
looks [2] - 214:10, 305:5
louder [1] - 177:5
low [15] - 12:20, 22:11, 23:8, 27:10, 31:14, 32:9, 32:15, 63:23, 114:1, 202:2, 266:19, 301:1, 302:15, 306:22, 310:6
lower [7] - 88:19, 88:20, 89:2, 89:4, 131:18, 267:21, 316:18
lowest [1] - 216:10
Ltd [1] - 119:19
lubricant [14] - 50:3, 80:11, 80:12, 81:9, 104:6, 116:19, 145:9, 145:11, 145:13, 145:17, 156:4, 162:14, 173:4, 234:5
lubricants [3] - 49:25, 51:13, 78:2
lubricating [2] - 162:12, 162:14
lubrication [16] - 83:24, 86:16, 86:22, 141:21, 141:25, 142:10, 142:14, 142:17, 142:21, 228:15, 228:20, 228:23, 229:1, 229:4, 229:6, 229:10
lunch [1] - 168:8
Luncheon [1] - 168:11

M

M-A-L-E-I-C [1] - 19:5
ma'am [9] - 69:9, 69:21, 70:21, 70:23, 72:2, 72:5, 72:15, 72:24, 178:20
machine [2] - 78:6, 103:20
MacMillan [2] - 29:14
magnesium [4] - 145:1, 145:8, 145:11, 145:16
Magnesium [1] - 145:3
magnitude [2] - 131:23, 147:24
main [2] - 103:10, 342:23
maintain [1] - 55:15
maize [9] - 134:12, 134:15, 134:19, 137:25, 138:13, 141:7, 210:19, 241:13, 241:17
major [1] - 295:9
makeup [1] - 76:23
malate [78] - 8:9, 8:11, 8:16, 8:18, 8:25, 9:8, 9:14, 9:25, 12:19, 12:21, 13:1, 13:4, 13:7, 13:9, 13:13, 14:7, 14:18, 15:12, 16:15, 17:11, 17:18, 17:20, 17:21, 17:22, 18:8, 18:20, 19:18, 20:17, 21:24, 22:9, 22:14, 24:12, 27:9, 28:5, 28:7, 30:23, 31:9, 31:13, 31:17, 35:3, 35:25, 36:2, 36:3, 36:12, 36:24, 36:25, 37:3, 37:15, 39:9, 39:18, 39:20, 42:6, 42:9, 42:20, 43:6, 43:10, 43:11, 44:1, 44:24, 45:1, 45:4, 45:8, 45:21, 45:24, 45:25, 46:6, 57:12, 69:14, 69:23, 312:5, 312:15, 341:21
maleic [1] - 19:4
malic [7] - 19:3, 19:6, 21:5, 21:7, 21:12, 45:1, 45:22
manner [1] - 200:11
manual [1] - 47:12
manufacture [11] - 6:4, 40:11, 40:14, 73:19, 126:6, 182:22, 270:25, 275:16, 293:21, 294:19
manufactured [9] - 41:17, 53:23, 55:4, 80:3, 272:17, 277:19, 277:20, 287:17, 335:11
manufacturer [25] - 31:11, 47:9, 53:19, 53:20, 119:20, 163:3, 163:7, 164:1, 164:10, 164:16, 164:20, 167:14, 179:7, 203:2, 203:4, 204:9, 204:10, 204:19, 204:21, 205:6, 221:12, 270:18, 270:22, 277:18, 292:18
manufacturers [3] - 271:14, 302:16, 303:1
Manufacturing [1] - 85:13
manufacturing [48] - 7:10, 9:12, 9:16, 10:3, 26:7, 26:13, 26:15, 26:16, 55:7, 62:14, 62:19, 71:4, 71:22, 77:5, 77:6, 79:7, 79:11, 79:13, 80:13, 84:2, 85:22, 86:12, 87:5, 89:15, 101:25, 102:2, 102:5, 102:9, 102:18, 102:19, 102:24, 103:3, 103:11, 104:11, 104:25, 105:3, 106:16, 108:6, 110:11, 110:20, 111:10, 141:21, 148:12, 182:23, 198:11, 228:21, 294:16
March [1] - 58:8
marked [2] - 184:7, 210:16
market [3] - 125:19, 162:4, 169:1
mass [3] - 103:25, 193:10, 193:13
material [80] - 3:3, 14:21, 15:18, 18:13, 31:7, 52:13, 59:16, 78:20, 78:25, 79:8, 79:9, 79:11, 79:16, 80:12, 82:10, 82:11, 88:17, 90:12, 91:4, 93:11, 100:4, 100:25, 103:18, 114:12, 115:18, 146:19, 180:5, 182:21, 182:22, 187:5, 190:3, 191:2, 193:11, 196:2, 204:1, 206:10, 208:2, 211:6, 211:24, 224:25, 228:2, 248:18, 261:6, 261:7, 264:7, 268:16, 282:4, 289:7, 292:1, 292:14, 294:16, 294:17, 297:4, 297:5, 297:6, 300:10, 300:12, 300:21, 300:23, 301:4, 303:17, 304:11, 304:12, 306:7, 306:9, 306:10, 306:18, 307:18, 308:4, 324:18, 326:1, 326:2, 326:15, 326:16, 332:9, 332:17, 332:21, 339:8, 340:2
materials [39] - 26:8, 77:6, 78:13, 79:9, 83:23, 88:9, 90:24, 91:21, 93:19, 94:18, 96:4, 103:17, 104:6, 110:22, 122:5, 123:10, 130:15, 185:3, 189:12, 190:9, 190:21, 193:4, 194:20, 203:19, 203:22, 203:25, 205:13, 205:14, 205:24, 207:9, 220:7, 221:6, 221:8, 265:4, 277:14, 300:24, 302:6, 302:18, 307:4
math [3] - 139:8, 158:4, 161:15
MATHAS [198] - 2:6, 256:6, 256:20, 257:4, 257:16, 257:18, 257:25, 258:1, 258:14, 258:15, 259:4, 259:9, 259:20, 259:22, 260:5, 260:7, 260:11, 260:12, 260:25, 261:1, 261:9, 261:10, 261:24, 262:1, 263:3, 263:4, 264:14, 264:15, 264:20, 264:22, 265:14, 265:16, 265:25, 266:2, 266:14, 266:15, 267:2, 267:3, 267:8, 267:10, 267:16, 267:18, 268:11, 268:12, 268:22, 268:24, 269:8, 269:10, 270:5, 270:6, 270:10, 270:12, 271:5, 271:6, 271:9, 271:11, 271:20, 271:22, 272:10, 272:11, 273:8, 273:10, 273:20, 273:21, 274:6, 274:8, 274:12, 274:13, 274:17, 274:18, 274:22, 274:24, 274:25,

275:4, 275:5, 275:10, 275:12, 275:23, 275:24, 276:11, 276:12, 276:18, 276:20, 276:24, 277:1, 277:7, 277:9, 277:22, 277:24, 278:8, 278:10, 278:17, 278:19, 279:1, 279:3, 279:16, 279:19, 280:22, 281:1, 281:5, 281:7, 281:11, 281:13, 281:22, 281:24, 282:9, 282:11, 282:21, 282:23, 283:13, 283:15, 284:8, 284:9, 284:23, 284:25, 285:25, 286:1, 286:12, 286:13, 286:24, 286:25, 288:5, 288:6, 288:10, 289:20, 289:21, 290:5, 290:6, 290:18, 290:24, 291:1, 291:15, 291:16, 291:20, 291:21, 292:8, 292:9, 292:23, 292:25, 294:3, 294:4, 294:10, 294:12, 294:25, 295:1, 295:16, 295:18, 296:12, 296:14, 297:17, 297:18, 298:9, 298:10, 298:21, 298:22, 299:20, 299:22, 300:6, 300:7, 300:14, 300:16, 301:6, 301:7, 301:15, 301:17, 302:1, 302:3, 302:9, 302:11, 303:3, 303:4, 303:24, 303:25, 304:5, 304:6, 304:17, 304:18, 304:24, 304:25, 305:14, 305:16, 306:24, 307:2, 307:20, 307:22, 308:10, 308:11, 308:17, 308:19, 309:4, 309:6, 309:15, 309:17, 309:20, 309:22, 310:8, 310:10, 311:4

Mathas [2] - 256:7, 290:8

mathematical [1] - 139:5

matter [7] - 14:20, 15:18, 21:10, 57:20, 254:25, 279:10, 326:8

matters [1] - 57:10

Maureen [5] - 23:25, 183:14, 183:17, 184:2, 186:4

MAUREEN [2] - 183:17, 183:19

maximize [1] - 309:12

MCC [5] - 152:25, 153:2, 153:5, 153:9, 153:13

mean [23] - 11:2, 25:2, 25:21, 27:17, 52:24, 63:17, 65:16, 111:2, 118:1, 122:1, 147:7, 199:1, 217:16, 229:2, 229:20, 229:21, 269:15, 279:9, 283:7, 285:10, 296:5, 324:17, 339:17

meaning [12] - 16:5, 16:7, 16:11, 23:20, 82:7, 82:9, 83:18, 83:20, 84:24, 229:16, 229:19, 276:9

meaningful [3] - 131:25, 137:18, 211:22

meaningfully [7] - 217:11, 219:1, 220:18, 223:2, 223:12, 223:25, 228:5

means [22] - 6:10, 37:6, 53:1, 56:8, 56:9, 86:15, 131:17, 131:20, 148:6, 166:18, 203:17, 204:23, 250:17, 262:6, 279:11, 280:3, 280:14, 289:9, 313:18, 322:9, 323:21, 326:6

meant [1] - 216:1

measure [2] - 263:18, 285:15

measured [7] - 132:24, 146:24, 147:2, 147:6, 147:12, 212:16, 325:16

measurements [5] - 136:8, 139:11, 139:24, 140:6, 140:15

measuring [1] - 225:23

mechanical [1] - 80:4

mechanically [1] - 97:15

mechanism [26] - 109:1, 116:8, 116:13, 116:14, 116:18, 116:21, 116:24, 118:4, 118:9, 118:22, 121:4, 123:8, 123:13, 123:24, 124:1, 148:2, 166:6, 218:10, 218:20, 218:22, 220:4, 220:12, 220:21, 231:1, 231:2

mechanisms [22] - 46:23, 117:5, 117:9, 117:12, 117:15, 117:17, 124:3, 165:7, 165:12, 165:17, 165:20, 185:1, 200:1, 200:3, 200:5, 200:7, 200:10, 200:13, 218:1, 218:4, 247:24, 248:3

median [1] - 250:23

medical [1] - 11:25

medicine [1] - 12:1

meet [8] - 31:6, 47:21, 76:15, 117:12, 124:15, 203:23, 311:16, 311:17

meets [2] - 97:17, 204:1

melting [1] - 41:6

member [5] - 185:5, 185:6, 185:8, 185:9, 185:16

mentioned [15] - 5:18, 6:23, 28:2, 51:19, 60:10, 61:16, 61:23, 90:15, 105:6, 131:16, 248:3, 270:1, 286:3, 289:18, 330:11

Merit [1] - 347:19

Met [1] - 203:15

met [3] - 22:21, 56:21, 311:16

method [71] - 9:25, 13:6, 27:9, 30:23, 53:7, 55:6, 55:10, 65:7, 65:13, 79:13, 99:21, 99:24, 100:3, 100:10, 115:25, 225:9, 225:16, 225:21, 264:1, 276:17, 276:19, 277:23, 277:25, 278:12, 278:13, 278:15, 278:17, 278:21, 278:22, 278:24, 279:5, 280:18, 280:23, 280:24, 281:3, 281:4, 281:9, 281:16, 281:20, 282:1, 282:2, 282:7, 282:19, 283:1, 283:8, 283:9, 283:24, 283:25, 284:5, 284:21, 284:22, 285:2, 285:5, 285:6, 285:11, 285:16, 285:19, 286:3, 286:20, 287:6, 287:23, 290:22, 291:3, 291:6, 293:14, 296:7, 308:24, 335:11

Method [1] - 285:9

methodologies [1] - 223:23

methodology [5] - 278:23, 290:3, 290:7, 290:21, 290:25

methods [23] - 17:23, 99:25, 129:14, 129:18, 129:23, 129:25, 130:4, 191:14, 265:22, 269:24, 276:15, 278:2, 284:14, 284:18, 285:3, 285:18, 285:20, 286:8, 286:17, 287:15, 287:16, 287:22, 330:21

methyl [1] - 295:22

MG [1] - 113:3

micro [1] - 175:2

microbial [10] - 65:7, 65:15, 65:16, 99:21, 99:24, 225:9, 225:16, 225:18, 225:21

microcrystalline [10] - 152:21, 152:24, 153:16, 196:17, 196:20, 196:21, 197:3, 197:4, 197:14, 197:19

micrograms [3] - 307:10, 307:11, 307:14

micronization [1] - 221:21

Micronization [2] - 221:24, 222:1

micronized [6] - 120:12, 167:17, 167:23, 222:5, 222:7, 222:12

microns [21] - 166:8, 166:11, 166:16, 166:19, 167:18, 167:20, 167:25, 168:5, 205:8, 219:6, 219:8, 219:15, 220:25, 221:1, 221:3, 222:11, 222:18, 250:12, 250:21, 250:25

microorganisms [1] - 65:15

microphone [3] - 290:9, 311:19, 313:5

microscope [1] - 166:22

middle [4] - 54:1, 89:20, 100:6, 214:21

midway [1] - 82:20

might [14] - 23:11, 25:16, 40:8, 40:16, 40:17, 40:19, 41:22, 41:23, 190:3, 190:13, 241:22, 341:2, 341:13

milled [2] - 167:17, 167:23

milligram [2] - 85:20, 289:12

milligrams [5] - 136:2, 136:4, 240:15, 240:17, 288:17

milling [2] - 222:8, 222:10

million [34] - 27:17, 50:19, 54:6, 54:7, 54:16, 54:19, 54:21, 55:12, 56:3, 56:6, 56:7, 261:17, 261:21, 263:18, 279:7, 279:9, 279:12, 279:14, 281:17, 283:11, 285:4, 286:19, 287:13, 289:10, 290:1, 292:16,

293:5, 307:11, 307:12, 307:14, 310:16, 310:19, 313:19, 328:25
mind [2] - 151:22, 265:1
minimal [8] - 61:18, 90:8, 90:16, 91:1, 91:4, 227:11, 227:24, 236:12
minimize [4] - 27:7, 55:19, 264:10, 301:23
minimum [4] - 131:23, 147:24, 192:6, 192:10
minor [3] - 338:2, 338:6, 338:13
minute [2] - 269:23, 299:21
minutes [6] - 43:3, 58:24, 58:25, 60:10, 66:20, 341:14
missing [2] - 18:17, 30:2
MIT [2] - 16:2, 29:17
mix [5] - 8:6, 23:15, 133:24, 134:1, 220:6
mixed [3] - 103:24, 104:6, 197:15
mixing [2] - 118:12, 153:22
mixture [41] - 23:13, 23:16, 23:23, 26:2, 79:9, 83:17, 110:17, 110:25, 111:6, 128:22, 133:20, 180:1, 180:6, 188:25, 189:12, 191:4, 193:24, 196:3, 197:17, 210:17, 210:18, 211:5, 211:7, 214:17, 215:18, 219:8, 220:8, 220:11, 220:22, 223:20, 230:12, 230:15, 230:18, 231:25, 247:9, 248:19, 250:21, 263:16, 324:8, 324:10, 324:19
mixtures [8] - 170:4, 170:18, 171:5, 171:8, 171:11, 171:20, 209:20, 225:4
modes [1] - 287:12
modification [1] - 138:3
modified [2] - 24:6, 213:22
modify [1] - 321:14
moiety [2] - 71:3, 76:25
moisture [2] - 38:22, 122:12
molecular [2] - 16:6, 188:9
molecule [4] - 43:18, 304:3, 317:13, 317:23
molecules [2] - 37:7, 37:10
moment [8] - 46:10, 74:15, 217:10, 280:1, 289:9, 289:19, 296:6, 305:12
Monday [1] - 1:12
monitor [1] - 263:8
monitoring [3] - 263:20, 264:12, 328:19
monograph [3] - 203:24, 206:16, 206:18
monographs [2] - 203:21, 205:24
monohydrate [8] - 145:22, 146:2, 146:7, 146:9, 146:13, 153:23, 154:3, 154:8
monopoly [2] - 42:12, 42:24
months [2] - 12:10, 320:11
morning [19] - 2:15, 23:21, 24:20, 34:25, 49:12, 57:8, 59:6, 66:20, 68:20, 68:23, 69:19, 128:15, 128:16, 183:25, 245:20, 340:24, 341:10, 346:6, 347:13
MORRIS [1] - 1:17
Morris [1] - 3:24
most [14] - 7:25, 8:21, 16:21, 37:13, 52:21, 120:22, 153:17, 159:19, 176:18, 177:1, 263:23, 285:2, 286:3
motions [1] - 341:18
motivated [11] - 19:13, 20:5, 20:16, 29:8, 29:12, 55:20, 56:2, 302:19, 318:7, 321:13, 342:25
motivating [1] - 20:13
move [16] - 32:14, 46:11, 56:16, 79:11, 92:5, 126:19, 177:16, 190:21, 200:23, 215:19, 224:18, 255:15, 255:21, 322:20, 323:5, 340:15
moved [2] - 103:25, 213:6
movement [1] - 188:25
moves [1] - 79:16
moving [2] - 57:9, 196:5
MR [402] - 2:18, 2:20, 2:24, 3:11, 3:20, 3:23, 13:24, 34:22, 34:25, 57:3, 57:7, 68:4, 72:18, 127:2, 127:6, 128:8, 128:11, 128:14, 130:7, 130:8, 134:22, 134:23, 135:9, 135:10, 140:10, 140:12, 141:14, 141:16, 142:23, 143:3, 144:25, 145:2, 145:21, 145:23, 148:18, 148:19, 150:7, 150:9, 151:9, 151:10, 152:7, 152:9, 152:17, 152:19, 154:15, 157:5, 157:6, 158:5, 158:7, 158:18, 158:20, 159:4, 159:6, 159:14, 159:17, 160:15, 160:16, 162:21, 162:22, 163:13, 163:14, 163:23, 163:25, 164:7, 164:9, 165:4, 165:5, 168:16, 168:18, 169:19, 169:20, 172:10, 172:12, 173:14, 173:16, 174:8, 177:9, 177:14, 177:16, 178:4, 179:10, 179:14, 183:10, 183:13, 183:24, 184:6, 184:9, 184:12, 184:14, 184:21, 184:22, 186:3, 186:8, 186:16, 186:17, 187:17, 187:22, 187:23, 188:18, 188:20, 189:19, 189:20, 192:4, 192:5, 192:23, 192:24, 194:14, 194:16, 194:21, 194:24, 195:15, 195:16, 196:12, 196:14, 196:24, 196:25, 197:7, 197:10, 197:22, 197:23, 198:14, 198:15, 199:11, 199:12, 199:17, 199:20, 200:25, 201:1, 201:7, 201:9, 202:5, 202:7, 203:5, 203:6, 203:12, 203:14, 204:5, 204:7, 204:16, 204:18, 205:3, 205:5, 206:5, 206:7, 206:20, 206:22, 208:17, 208:21, 210:22, 210:24, 212:6, 212:8, 214:5, 214:9, 215:9, 215:11, 217:8, 217:9, 218:5, 218:7, 219:24, 219:25, 221:18, 221:20, 222:24, 222:25, 225:7, 225:8, 225:11, 225:13, 226:22, 227:1, 228:8, 228:11, 229:11, 251:8, 251:10, 251:14, 251:16, 252:5, 252:10, 252:12, 252:24, 252:25, 253:12, 253:16, 255:3, 255:14, 255:17, 255:24, 256:6, 256:20, 257:4, 257:16, 257:18, 257:25, 258:1, 258:14, 258:15, 259:4, 259:9, 259:20, 259:22, 260:5, 260:7, 260:11, 260:12, 260:25, 261:1, 261:9, 261:10, 261:24, 262:1, 263:3, 263:4, 264:14, 264:15, 264:20, 264:22, 265:14, 265:16, 265:25, 266:2, 266:14, 266:15, 267:2, 267:3, 267:8, 267:10, 267:16, 267:18, 268:11, 268:12, 268:22, 268:24, 269:8, 269:10, 270:5, 270:6, 270:10, 270:12, 271:5, 271:6, 271:9, 271:11, 271:20, 271:22, 272:10, 272:11, 273:8, 273:10, 273:20, 273:21, 274:6, 274:8, 274:12, 274:13, 274:17, 274:18, 274:22, 274:24, 274:25, 275:4, 275:5, 275:10, 275:12, 275:23, 275:24, 276:11, 276:12, 276:18, 276:20, 276:24, 277:1, 277:7, 277:9, 277:22, 277:24, 278:8, 278:10, 278:17, 278:19, 279:1, 279:3, 279:16, 279:19, 280:22, 281:1, 281:5, 281:7, 281:11, 281:13, 281:22, 281:24, 282:9, 282:11, 282:21, 282:23, 283:13, 283:15, 284:8, 284:9, 284:23, 284:25, 285:25, 286:1, 286:12, 286:13, 286:24, 286:25, 288:5, 288:6, 288:10, 289:20, 289:21, 290:5, 290:6, 290:18, 290:24, 291:1, 291:15, 291:16, 291:20, 291:21, 292:8, 292:9, 292:23, 292:25, 294:3, 294:4, 294:10, 294:12, 294:25, 295:1, 295:16, 295:18, 296:12, 296:14, 297:17, 297:18, 298:9, 298:10, 298:21, 298:22,

299:20, 299:22, 300:6, 300:7, 300:14, 300:16, 301:6, 301:7, 301:15, 301:17, 302:1, 302:3, 302:9, 302:11, 303:3, 303:4, 303:24, 303:25, 304:5, 304:6, 304:17, 304:18, 304:24, 304:25, 305:14, 305:16, 306:24, 307:2, 307:20, 307:22, 308:10, 308:11, 308:17, 308:19, 309:4, 309:6, 309:15, 309:17, 309:20, 309:22, 310:8, 310:10, 311:4, 322:14, 341:1, 341:13, 341:17, 342:5, 342:13, 342:15, 343:14, 344:2, 344:6, 344:12, 345:1, 345:12, 346:21, 347:7
MS [175] - 57:8, 58:7, 58:15, 62:3, 66:22, 66:25, 67:4, 67:8, 67:16, 67:24, 68:7, 68:16, 68:19, 69:25, 70:1, 72:16, 72:20, 76:6, 76:7, 77:9, 77:13, 77:20, 77:22, 79:3, 79:4, 80:7, 80:9, 80:20, 80:21, 81:12, 81:14, 82:1, 82:2, 82:15, 82:17, 84:4, 84:6, 84:13, 84:15, 86:23, 86:24, 87:7, 87:8, 87:14, 87:16, 87:21, 87:23, 89:17, 89:19, 91:9, 91:11, 92:6, 92:8, 93:14, 93:15, 94:3, 94:5, 94:9, 94:11, 96:8, 96:10, 96:17, 96:21, 98:12, 98:14, 98:24, 99:1, 99:16, 99:18, 100:5, 100:7, 101:21, 101:22, 103:5, 103:6, 109:4, 109:6, 109:16, 109:17, 110:2, 110:4, 111:17, 111:18, 111:25, 112:2, 113:16, 113:18, 117:1, 117:2, 119:11, 119:13, 121:24, 121:25, 123:21, 123:22, 124:5, 124:7, 124:24, 125:1, 125:11, 125:16, 125:22, 125:24, 126:18, 126:22, 127:9, 150:1, 150:6, 177:3, 177:6, 177:19, 178:1, 178:14, 178:15, 179:12, 179:16, 179:23, 179:24, 180:16, 180:18, 182:24, 183:7, 186:6, 230:5, 230:8, 231:14, 231:18, 232:24, 233:1, 233:16, 233:18, 239:21, 239:23, 240:6, 240:7, 240:23, 240:25, 242:19, 242:22, 244:22, 244:24, 249:11, 249:15, 249:17, 251:6, 252:1, 252:3, 255:20, 255:25, 259:7, 311:7, 311:10, 311:14, 322:18, 323:1, 323:5, 323:7, 323:14, 323:16, 326:10, 326:19, 327:13, 327:19, 327:23, 328:10, 329:7, 329:9, 336:17, 336:20, 336:25, 337:2, 339:19, 339:24, 340:4, 340:19
MSN [211] - 1:7, 4:3, 13:8, 13:13, 13:19, 14:6, 14:17, 14:23, 15:3, 15:9, 15:14, 15:21, 16:12, 17:4, 19:9, 19:18, 24:5, 24:10, 24:16, 24:25, 25:2, 25:8, 25:10, 25:23, 25:24, 26:1, 26:16, 26:25, 27:20, 27:23, 28:6, 28:8, 28:17, 29:1, 30:4, 30:15, 31:2, 31:21, 32:24, 34:17, 35:1, 35:21, 47:3, 47:10, 48:10, 49:6, 49:9, 57:25, 58:4, 58:10, 58:24, 59:7, 59:13, 59:18, 59:19, 60:5, 61:3, 61:6, 62:10, 63:5, 63:10, 63:14, 64:6, 64:24, 65:3, 65:5, 65:8, 66:9, 66:12, 66:15, 66:16, 67:11, 73:5, 73:17, 74:1, 74:5, 74:8, 74:12, 74:14, 74:17, 74:19, 85:1, 85:7, 85:16, 86:19, 87:6, 92:15, 99:20, 101:20, 103:3, 103:11, 106:24, 108:11, 110:12, 112:6, 121:22, 124:22, 124:23, 125:3, 125:7, 125:8, 125:9, 125:18, 126:2, 126:6, 126:7, 126:8, 126:11, 126:14, 126:15, 127:5, 127:23, 129:9, 132:11, 133:14, 134:3, 134:15, 135:1, 136:9, 138:12, 142:13, 142:24, 143:15, 143:19, 146:16, 158:2, 161:13, 164:22, 166:13, 166:16, 166:18, 168:23, 169:9, 170:6, 180:8, 180:11, 180:24, 181:12, 181:13, 182:5, 182:8, 182:12, 182:15, 183:13, 186:9, 186:10, 187:7, 201:3, 201:17, 202:11, 202:18, 202:21, 202:24, 208:11, 208:18, 209:8, 209:21, 210:2, 210:6, 211:11, 211:12, 211:17, 212:1, 213:2, 213:8, 213:17, 214:1, 214:8, 214:14, 215:14, 216:1, 216:14, 216:20, 216:21, 217:4, 217:12, 219:7, 219:15, 219:17, 219:21, 222:15, 222:20, 222:22, 224:22, 225:3, 234:25, 235:16, 236:17, 237:21, 238:6, 238:9, 238:14, 238:23, 239:3, 240:1, 241:12, 242:12, 245:13, 245:16, 245:17, 246:1, 246:11, 249:8, 252:17, 252:18, 256:7, 312:2, 333:19
MSN's [146] - 22:23, 23:24, 24:9, 24:23, 26:7, 26:10, 26:25, 27:3, 27:4, 39:22, 41:12, 48:24, 48:25, 59:24, 60:7, 60:22, 62:19, 73:21, 73:25, 74:11, 76:10, 85:25, 86:12, 87:1, 87:2, 87:10, 87:12, 87:17, 88:6, 90:11, 92:2, 92:22, 93:16, 102:5, 102:18, 102:25, 104:25, 105:11, 106:8, 106:15, 106:16, 106:18, 107:4, 107:12, 107:21, 108:2, 108:7, 108:17, 108:18, 108:23, 111:9, 112:1, 113:17, 114:6, 117:18, 119:3, 121:3, 121:19, 122:7, 122:22, 123:12, 124:10, 124:15, 124:19, 125:20, 125:21, 129:6, 132:10, 133:23, 134:2, 135:16, 135:20, 138:4, 138:19, 141:20, 143:7, 143:24, 144:3, 145:3, 145:8, 145:12, 145:17, 146:1, 146:6, 146:10, 146:13, 165:1, 165:7, 165:11, 165:24, 165:25, 166:4, 166:24, 167:3, 168:4, 168:24, 169:25, 170:13, 170:20, 171:1, 178:9, 181:17, 181:25, 182:13, 182:19, 187:1, 187:4, 187:10, 202:8, 202:13, 205:10, 208:10, 208:23, 209:16, 216:25, 217:10, 217:17, 218:1, 218:25, 220:17, 223:2, 223:12, 223:25, 225:25, 226:19, 226:22, 228:6, 233:13, 233:23, 234:4, 234:11, 234:14, 234:19, 234:21, 235:1, 235:10, 237:25, 240:20, 241:23, 247:4, 250:1, 250:24, 251:3, 251:20, 251:24, 252:14
MTBE [2] - 295:23, 296:1
multi [1] - 90:25
multifunctional [1] - 127:21
multiple [19] - 5:22, 10:8, 11:3, 11:23, 20:25, 26:4, 30:25, 35:24, 37:12, 37:25, 77:3, 77:4, 90:25, 147:10, 161:16, 165:17, 165:20, 247:12, 333:2
multitude [1] - 71:1
must [11] - 30:15, 34:7, 109:1, 148:6, 155:11, 156:11, 192:7, 199:1, 217:16, 283:10, 283:21
mutagenic [7] - 262:6, 305:4, 305:8, 305:20, 305:21, 306:4, 306:9
mutagenicities [1] - 305:5
mutagenicity [2] - 266:8, 304:23
MVP/100942/01 [1] - 65:13
MVR/100942/01 [1] - 65:14
Myers [1] - 287:4
Myerson [2] - 29:14, 29:16
Mylan [1] - 39:22

N

N-1 [10] - 16:17, 38:12, 38:25, 39:6, 39:10, 39:13, 39:14, 41:13, 41:20, 42:3
N-2 [10] - 16:17, 38:12, 38:25, 39:7, 39:11,

39:13, 39:14, 41:13, 41:21, 42:3
Nagao [3] - 304:20, 305:1, 305:19
Nagao's [1] - 306:14
name [22] - 3:23, 6:6, 47:10, 53:20, 59:5, 59:6, 68:10, 68:23, 86:7, 86:8, 97:12, 100:25, 101:1, 157:15, 157:20, 160:14, 169:9, 183:16, 245:15, 256:13, 256:14, 279:22
names [1] - 278:4
naming [1] - 273:17
nanometers [1] - 175:3
narrative [8] - 268:7, 268:15, 272:6, 272:13, 331:17, 331:18, 331:20, 331:23
National [1] - 258:18
ND [3] - 54:2, 280:1, 280:2
NDA [2] - 39:8, 339:5
near [2] - 104:13, 232:13
nearly [3] - 5:13, 239:3, 274:3
neat [2] - 39:10, 88:9
necessarily [10] - 30:16, 31:17, 40:5, 40:24, 52:25, 172:3, 199:3, 330:15, 339:17, 346:18
necessary [5] - 10:21, 32:25, 108:15, 171:7, 171:10
need [26] - 7:23, 11:22, 21:10, 23:8, 23:11, 23:14, 27:7, 33:18, 53:1, 55:25, 130:2, 133:13, 174:6, 182:15, 183:3, 216:12, 223:15, 247:2, 265:1, 265:4, 303:8, 311:18, 319:11, 342:11
needed [11] - 9:24, 10:2, 10:23, 10:24, 30:2, 111:3, 111:11, 111:14, 225:20, 268:18, 338:18
needle [4] - 190:9, 190:13, 343:25, 344:1
needle-like [2] - 190:9, 190:13
needs [6] - 14:9, 131:24, 195:21, 302:6, 338:24, 339:2
neutralizing [1] - 118:6
never [7] - 3:12, 25:8, 59:14, 116:13, 297:16, 316:9, 333:22
new [11] - 11:20, 32:12, 32:17, 169:1, 281:9, 297:8, 297:12, 297:21, 297:22, 298:25
next [48] - 11:14, 25:14, 26:18, 46:11, 55:14, 60:12, 68:7, 86:5, 89:23, 90:1, 91:2, 93:16, 95:19, 101:23, 104:6, 109:25, 110:5, 111:15, 116:3, 118:16, 124:13, 144:25, 183:6, 210:23, 213:8, 213:10, 213:22, 242:21, 249:18, 252:6, 254:1, 255:13, 256:7, 266:22, 268:22, 271:20, 276:1, 276:2, 283:13, 288:1, 297:9, 297:10, 298:2, 302:1, 316:16, 317:1, 337:17, 343:4
nice [2] - 311:16, 311:17
NICHOLS [1] - 1:17
Nichols [1] - 3:25
night [1] - 15:3
NIH [2] - 185:16, 258:20
Nithiyanandam [13] - 58:9, 59:6, 93:22, 127:1, 143:24, 144:2, 144:9, 178:9, 217:1, 245:10, 245:13, 245:19, 253:2
Nithiyanandam's [3] - 58:11, 102:20, 144:14
NMR [2] - 328:2, 328:13
Nobel [1] - 29:15
nominated [1] - 258:21
non [4] - 33:17, 35:7, 46:17, 186:25
non-infringement [3] - 35:7, 46:17, 186:25
non-obviousness [1] - 33:17
none [8] - 27:25, 187:7, 279:24, 296:25, 297:6, 327:24, 328:21, 335:22
nonetheless [1] - 300:1
North [1] - 1:10
Nos [3] - 127:11, 177:22, 256:1
notable [2] - 210:13, 211:4
notations [1] - 223:14
note [3] - 48:25, 49:14, 103:13
notebook [15] - 135:2, 135:4, 135:16, 136:14, 136:17, 136:20, 180:12, 180:23, 180:24, 208:16, 210:6, 210:8, 211:17, 244:23, 252:19
notebooks [18] - 48:20, 107:3, 107:12, 127:24, 129:7, 129:10, 136:9, 136:21, 136:25, 137:4, 140:16, 181:14, 181:25, 182:6, 182:8, 182:13, 251:21, 251:25
noted [2] - 48:2, 303:19
notes [3] - 46:22, 54:22, 347:17
nothing [8] - 16:8, 29:3, 29:4, 29:5, 29:19, 48:23, 202:20, 338:8
Nothing [1] - 44:19
notice [2] - 86:14, 346:25
noticed [1] - 219:14
novel [1] - 6:3
NSF [1] - 258:20
number [50] - 40:14, 55:8, 65:13, 65:14, 67:3, 67:7, 67:25, 81:17, 81:18, 87:2, 88:16, 88:19, 88:20, 88:25, 89:3, 89:4, 89:18, 120:4, 135:23, 136:23, 139:25, 140:4, 149:22, 175:10, 178:6, 184:8, 185:10, 185:16, 210:10, 210:12, 210:16, 210:25, 229:8, 244:25, 257:11, 258:13, 263:22, 271:16, 271:18, 282:1, 288:17, 289:6, 290:23, 295:3, 296:17, 303:19, 318:16, 333:7, 337:12, 337:19
Number [37] - 47:13, 57:16, 60:5, 62:14, 72:23, 73:17, 83:11, 85:11, 86:3, 86:14, 87:22, 92:7, 94:10, 96:18, 105:14, 125:14, 144:19, 144:20, 163:24, 164:7, 169:5, 169:9, 213:1, 213:3, 213:9, 213:11, 213:19, 213:20, 249:18, 250:8, 250:11, 252:7, 252:16, 252:17, 257:12, 318:22, 319:22
numbered [1] - 65:5
Numbers [1] - 102:16
numbers [27] - 107:10, 139:20, 139:25, 140:25, 181:2, 181:6, 181:17, 182:1, 210:16, 214:19, 215:7, 271:16, 271:18, 277:11, 277:14, 278:13, 286:21, 288:14, 288:24, 289:6, 289:14, 289:15, 291:23, 330:2, 336:9
numerical [3] - 94:25, 168:6, 192:9
numerically [2] - 131:18, 210:16
numerous [1] - 21:3

O

O'GARA [1] - 2:7
oath [5] - 68:14, 144:10, 144:12, 183:20, 256:17
object [2] - 177:3, 322:14
objecting [1] - 3:10
objection [21] - 58:4, 68:2, 68:4, 72:18, 127:2, 127:4, 127:8, 150:1, 177:13, 177:19, 177:21, 186:6, 255:23, 255:24, 255:25, 259:7, 322:25, 342:8, 343:12, 343:19, 343:21
objective [6] - 33:16, 240:24, 241:1, 345:7, 345:10, 345:15
oblong [1] - 193:4
observation [1] - 223:8
observations [1] - 223:9
observed [4] - 63:22, 113:25, 212:25, 238:25
obtain [3] - 119:21, 262:12, 300:1
obtaining [1] - 7:2
obvious [26] - 22:24, 27:20, 28:9, 42:25, 43:3, 43:15, 43:17, 43:19, 44:1, 44:14, 46:7, 49:13, 52:5, 55:15, 56:19, 262:12, 300:1, 300:4, 318:7, 320:25, 321:8, 321:14, 340:15, 342:23, 342:24, 342:25
obviously [4] - 3:18, 19:15, 35:24, 171:23
obviousness [31] - 13:17, 13:20, 17:4, 17:16, 17:25, 22:10, 27:5, 33:17, 42:9, 42:10, 42:15, 43:24, 43:25, 46:7, 340:16, 341:23, 341:24, 342:4, 342:19, 343:8, 343:9, 344:17, 344:22, 345:5, 345:16, 345:18, 345:20, 345:23, 346:11, 346:14
obviousness-type [17] - 13:17, 17:4, 17:16, 17:25, 22:10, 42:9, 42:10, 42:15, 46:7, 341:24,

344:17, 344:22, 345:5, 345:16, 345:20, 345:23, 346:11
occurred [3] - 335:16, 335:20, 335:24
occurs [1] - 238:3
October [1] - 1:12
OF [1] - 1:2
offer [6] - 58:11, 66:22, 66:25, 68:1, 124:18, 345:22
offered [12] - 58:21, 76:9, 145:14, 146:12, 165:6, 165:10, 318:6, 320:23, 321:3, 321:7, 321:12, 321:21
offering [14] - 167:6, 167:10, 170:16, 172:2, 234:18, 262:3, 311:22, 311:23, 312:17, 312:20, 314:10, 314:13, 314:16, 321:17
offers [1] - 72:16
Office [7] - 9:5, 11:9, 22:2, 33:7, 33:8, 33:11
offset [1] - 153:22
often [13] - 37:13, 77:2, 96:14, 118:2, 228:22, 263:15, 263:18, 263:25, 265:3, 300:24, 311:1, 324:18
oftentimes [4] - 76:23, 189:1, 192:17, 264:7
OH [1] - 305:23
once [6] - 28:9, 91:20, 159:11, 222:16, 306:17, 347:9
oncologist [1] - 11:25
one [166] - 5:15, 5:16, 5:17, 7:7, 7:16, 9:10, 11:15, 12:24, 19:3, 20:23, 22:1, 22:19, 23:4, 37:11, 38:19, 38:20, 38:21, 46:10, 49:14, 49:21, 49:23, 49:24, 50:15, 52:1, 52:20, 67:13, 67:15, 77:25, 78:1, 78:2, 79:11, 81:15, 81:22, 88:17, 90:22, 90:23, 95:10, 100:19, 102:1, 103:10, 109:15, 113:19, 117:12, 117:17, 117:24, 119:7, 123:2, 123:14, 124:4, 124:9, 124:10, 125:11, 130:17, 130:18, 134:9, 134:11, 136:2, 138:1, 138:21, 138:22, 141:10, 142:13, 147:18, 154:15, 157:1, 158:15, 159:1, 159:12, 160:12, 160:14, 163:15, 164:10, 164:14, 165:7, 170:24, 176:18, 176:25, 179:25, 188:4, 188:7, 188:25, 190:6, 191:9, 192:16, 194:7, 197:13, 198:20, 199:25, 200:13, 209:11, 212:15, 215:7, 218:15, 219:11, 219:13, 228:19, 229:14, 246:3, 246:15, 248:3, 248:6, 250:7, 257:11, 260:17, 262:5, 263:9, 263:23, 266:7, 268:15, 269:2, 269:4, 269:25, 271:13, 271:18, 273:12, 273:13, 277:20, 281:4, 283:19, 285:4, 286:6, 286:9, 287:22, 288:15, 288:16, 292:15, 292:21, 301:11, 302:6, 303:13, 303:19, 305:22, 305:23, 305:24, 306:10, 306:20, 309:9, 310:8, 310:13, 310:19, 314:4, 321:23, 324:22, 325:4, 325:5, 325:8, 325:18, 327:6, 330:21, 330:24, 331:9, 332:1, 332:2, 334:2, 334:14, 335:18, 336:7, 341:11, 343:5
ones [8] - 36:11, 39:7, 44:22, 260:15, 265:5, 278:3, 291:25, 295:4
ongoing [2] - 11:23, 346:22
opening [15] - 2:25, 3:3, 3:10, 44:5, 93:7, 112:1, 112:4, 112:24, 113:16, 151:1, 312:11, 322:12, 343:1, 344:20, 345:3
operate [3] - 118:9, 200:6, 200:14
operating [1] - 217:25
opined [10] - 165:22, 167:1, 169:23, 170:11, 170:24, 171:23, 327:1, 327:7, 327:18, 328:7
opining [1] - 341:20
opinion [97] - 74:17, 74:21, 75:14, 75:18, 76:19, 87:5, 89:12, 90:18, 91:16, 92:22, 94:1, 98:9, 101:19, 104:25, 105:4, 106:11, 107:21, 107:24, 111:11, 114:11, 121:13, 123:23, 127:14, 127:17, 127:19, 128:21, 132:6, 137:23, 138:1, 138:18, 141:6, 145:14, 146:11, 146:12, 147:15, 148:7, 148:13, 165:6, 165:10, 166:2, 167:6, 167:10, 170:16, 171:14, 172:2, 176:24, 176:25, 182:17, 186:10, 186:14, 186:18, 186:24, 198:6, 200:5, 207:20, 211:21, 217:3, 228:16, 229:17, 229:18, 234:14, 235:3, 247:19, 263:7, 266:22, 310:22, 312:20, 314:5, 314:10, 314:13, 314:16, 314:20, 318:6, 318:19, 321:3, 321:7, 321:13, 321:17, 321:20, 321:21, 321:24, 322:20, 323:3, 325:22, 330:22, 331:9, 331:13, 335:7, 335:10, 340:15, 340:16, 341:23, 342:3, 342:7, 342:19, 345:22
opinions [50] - 69:8, 75:12, 109:9, 126:11, 129:11, 130:21, 135:5, 137:17, 138:23, 140:21, 148:13, 157:13, 162:24, 187:11, 187:13, 187:14, 187:18, 188:12, 192:1, 232:3, 234:18, 259:14, 260:1, 262:3, 262:14, 262:24, 263:5, 268:19, 270:11, 272:15, 293:12, 299:23, 311:21, 311:23, 312:14, 312:17, 314:7, 318:5, 320:24, 322:22, 335:15, 335:19, 335:23, 337:23, 341:24, 345:6, 345:9, 345:14, 345:17, 345:19
opposed [1] - 14:22
optimal [4] - 63:24, 64:17, 64:18, 195:22
optimist [1] - 346:8
optimization [5] - 62:22, 63:1, 64:20, 237:17, 239:8
optimize [4] - 112:7, 114:7, 114:9, 185:4
optimum [3] - 64:2, 114:2, 216:19
optional [1] - 157:9
optionally [2] - 17:13, 158:22
options [4] - 12:7, 158:16, 159:1, 159:12
or.. [2] - 171:17, 243:4
oral [11] - 71:9, 77:14, 78:5, 79:7, 81:7, 164:4, 185:21, 206:11, 231:16
orally [3] - 164:13, 204:11, 204:23
orange [1] - 220:7
order [19] - 16:6, 47:22, 78:10, 88:25, 103:25, 108:25, 144:22, 167:18, 167:24, 171:10, 171:11, 192:7, 209:23, 224:12, 268:18, 272:14, 275:19, 293:21, 308:4
ordering [1] - 37:6
ordinary [18] - 16:4, 16:7, 16:11, 16:20, 74:23, 76:16, 82:6, 82:9, 188:1, 188:2, 188:3, 229:16, 229:19, 229:21, 262:16, 310:23, 315:2, 315:9
organic [9] - 75:25, 258:5, 296:8, 303:8, 308:3, 308:14, 332:22
organization [2] - 55:4, 185:8
organizations [1] - 185:5
organize [1] - 270:10
original [1] - 200:21
OTDP [2] - 343:4, 343:9
otherwise [1] - 156:14
ought [3] - 168:7, 343:20, 343:21
outcome [3] - 69:7, 115:16, 212:13
outline [1] - 152:11
outside [3] - 177:3, 177:6, 322:16
overall [10] - 110:25, 147:12, 148:5, 189:22, 189:24, 191:10, 196:9, 198:17, 198:21, 199:1
overcame [1] - 320:7
overcome [1] - 20:11
overlapping [1] - 248:25
oversimplification [1] - 7:24
overview [3] - 151:14, 186:19, 262:2
own [15] - 20:3, 24:9, 24:23, 25:9, 27:3, 27:21, 48:25, 87:3, 108:2, 146:20, 146:23, 147:5, 188:22, 271:17, 288:17
Oxaprozin [1] - 98:17
oxygen [2] - 10:19, 10:20

P

p.m [1] - 347:15
P163-183-1 [1] - 284:3
P172-27-1 [3] - 284:12, 336:7, 337:12
P172-27-1) [1] - 337:19
page [51] - 60:12, 60:14, 62:13, 65:6, 84:17, 89:21, 89:24, 90:1, 94:12, 96:20, 96:22, 100:23, 112:17, 112:20, 130:24, 161:5, 163:24, 164:8, 168:25, 172:11, 173:14, 178:25, 181:2, 184:17, 194:18, 202:6, 204:6, 204:17, 205:22, 206:6, 206:21, 210:10, 210:23, 232:13, 241:16, 242:21, 242:25, 243:2, 245:8, 254:5, 265:25, 266:1, 271:20, 276:25, 277:7, 278:8, 279:1, 283:13, 294:11, 319:17
Page [158] - 61:8, 73:3, 73:11, 73:13, 75:5, 75:6, 81:2, 83:10, 83:11, 84:14, 85:10, 87:22, 89:17, 89:24, 91:10, 92:7, 94:10, 96:18, 96:22, 98:25, 100:6, 100:22, 102:16, 105:13, 112:18, 112:21, 115:10, 120:4, 125:14, 130:23, 132:12, 142:24, 145:1, 145:21, 148:22, 149:1, 149:2, 149:12, 149:19, 152:17, 154:16, 158:5, 158:18, 159:4, 159:14, 160:15, 160:21, 161:10, 161:11, 161:19, 161:20, 163:20, 163:23, 172:10, 174:13, 178:24, 180:17, 184:13, 194:21, 196:13, 197:7, 199:17, 199:19, 201:7, 201:8, 202:5, 203:12, 205:3, 206:5, 206:20, 208:18, 210:9, 210:22, 211:1, 214:6, 214:7, 215:9, 225:11, 225:12, 226:23, 228:8, 231:19, 232:13, 232:14, 232:24, 235:20, 236:3, 236:5, 236:7, 237:10, 239:21, 240:6, 240:24, 241:15, 241:19, 243:3, 245:22, 249:15, 253:12, 253:13, 257:17, 259:11, 259:20, 260:5, 264:21, 265:15, 267:17, 269:9, 271:9, 271:20, 277:8, 278:9, 281:6, 281:11, 281:22, 282:9, 282:22, 283:14, 284:24, 285:25, 286:12, 286:14, 288:10, 289:2, 289:11, 289:20, 290:5, 291:4, 291:20, 292:23, 296:13, 298:9, 301:16, 302:2, 303:3, 304:5, 305:15, 308:17, 309:4, 309:7, 309:21, 310:9, 319:14, 320:13, 323:15, 325:12, 326:11, 327:14, 336:17, 337:1, 339:20, 339:21
Pages [3] - 212:10, 302:10, 306:25
pages [1] - 342:16
panel [1] - 195:19
panels [2] - 185:12, 185:16
paper [1] - 304:20
papers [2] - 71:25, 149:11
paragraph [44] - 46:19, 47:18, 49:21, 50:11, 50:13, 50:14, 73:9, 73:15, 75:5, 75:7, 83:22, 99:2, 99:5, 120:19, 152:8, 152:18, 152:20, 154:24, 161:23, 173:15, 197:8, 199:18, 245:23, 253:14, 253:17, 253:19, 254:6, 265:14, 266:1, 269:8, 269:11, 269:22, 278:9, 282:10, 297:9, 302:1, 302:4, 323:14, 324:16, 324:24, 326:5, 329:8, 331:10, 331:13
Paragraph [1] - 180:17
paragraphs [4] - 81:1, 344:21, 344:22, 344:24
parallel [1] - 190:11
parameter [1] - 44:15
parameters [3] - 40:11, 215:15, 273:5
parenthesis [2] - 47:9, 63:23
parroting [1] - 25:6
part [24] - 3:15, 33:23, 56:25, 75:24, 85:8, 99:22, 103:13, 105:11, 121:22, 129:13, 157:17, 198:8, 208:12, 212:12, 220:7, 258:18, 261:11, 263:18, 285:3, 285:4, 292:10, 294:6, 310:19, 329:13
part-per-million [1] - 263:18
partially [1] - 160:12
particle [34] - 59:22, 59:23, 70:14, 122:25, 166:7, 166:13, 168:3, 175:3, 189:10, 189:11, 189:13, 190:24, 200:18, 200:19, 205:6, 205:9, 205:12, 205:15, 218:6, 218:13, 219:5, 219:10, 219:11, 220:5, 220:25, 222:12, 222:14, 222:16, 224:10, 249:19, 249:25, 250:21, 250:23
particle/particle [1] - 249:1
particles [56] - 118:5, 118:17, 118:18, 118:19, 118:23, 118:25, 119:2, 119:10, 120:23, 121:3, 121:6, 121:15, 121:16, 121:20, 121:21, 122:20, 123:5, 165:25, 166:4, 166:11, 166:24, 167:4, 167:8, 191:3, 191:4, 193:17, 200:17, 200:18, 200:21, 205:15, 218:14, 218:18, 218:25, 220:2, 220:6, 220:8, 220:10, 221:3, 221:4, 222:10, 222:18, 224:5, 224:7, 224:11, 224:13, 224:15, 248:7, 248:10, 248:13, 248:17, 248:22, 249:4, 250:4, 250:17, 250:24, 251:3
particles' [1] - 120:24
particular [40] - 3:6, 6:21, 6:23, 17:19, 36:5, 49:18, 52:17, 54:4, 70:18, 79:15, 79:25, 85:17, 88:5, 91:8, 93:4, 100:2, 100:9, 100:10, 115:17, 116:21, 116:24, 118:3, 118:4, 118:18, 118:22, 121:4, 123:8, 148:8, 152:13, 182:21, 190:20, 213:14, 223:19, 231:2, 280:15, 289:24, 296:1, 315:23, 323:2, 328:25
particularly [1] - 12:4
parties [9] - 4:4, 23:20, 24:6, 35:13, 57:15, 67:9, 81:25, 82:3, 180:3
parties' [1] - 76:17
partner [1] - 287:3
parts [30] - 27:17, 50:19, 54:5, 54:7, 54:16, 54:19, 54:21, 55:11, 56:2, 56:5, 56:6, 261:17, 261:21, 279:7, 279:9, 279:12, 279:14, 283:11, 286:18, 287:13, 289:10, 290:1, 292:16, 293:5, 307:11, 307:12, 307:14, 310:15, 313:19, 328:25
party [1] - 125:8
party's [1] - 188:16
pass [3] - 229:12, 311:5, 311:7
passages [1] - 198:3
passed [1] - 250:18
passes [2] - 250:4, 297:4
past [6] - 56:22, 185:15, 190:21, 191:3, 218:15, 337:17
Patent [10] - 9:4, 9:5, 11:9, 22:2, 33:7, 33:8, 33:11, 72:23, 98:16, 318:22
patent [182] - 11:8, 12:20, 12:21, 12:25, 13:1, 13:3, 17:6, 17:7, 17:8, 17:11, 18:5, 18:6, 18:10, 18:17, 18:22, 22:12, 22:13, 22:17, 23:19, 27:6, 27:16, 27:22, 28:2, 28:4, 33:5, 35:7, 35:14, 35:15, 35:19, 35:20, 35:22, 35:25, 36:4, 37:23, 37:24, 38:1, 38:13, 38:24, 42:12, 42:14, 42:21, 42:22, 42:24, 43:5, 43:21, 43:22, 43:23, 44:11, 44:12, 46:11, 46:12, 46:13, 46:15, 49:12, 49:15, 50:18, 56:7, 56:11, 56:19, 57:14, 57:15, 57:19, 69:16, 72:3, 72:25, 73:3, 73:5, 73:23, 74:5, 74:9, 74:10, 74:20, 74:22, 75:9, 75:15, 75:20, 77:10, 80:8, 80:23, 81:4, 82:13, 82:16, 83:8, 84:11, 98:18, 98:20, 99:8, 116:17, 116:23, 124:16, 124:20, 126:9, 126:15, 126:16, 157:2, 157:3, 157:7, 157:14, 157:19,

157:23, 157:24, 158:8, 159:7, 159:18, 160:5, 160:9, 174:13, 174:14, 174:16, 174:22, 175:13, 175:14, 175:19, 175:23, 176:2, 176:3, 182:16, 185:25, 186:11, 186:25, 207:16, 208:4, 230:20, 230:22, 230:25, 231:3, 231:11, 232:5, 233:17, 244:25, 245:3, 245:17, 245:22, 246:1, 246:10, 253:1, 253:7, 253:20, 254:15, 259:10, 259:13, 259:14, 259:24, 260:9, 261:13, 261:15, 267:5, 269:1, 269:13, 311:24, 312:21, 312:24, 313:1, 313:6, 313:21, 314:11, 314:17, 315:1, 315:10, 315:15, 318:15, 318:24, 319:3, 319:7, 319:9, 319:10, 319:22, 321:15, 323:8, 331:6, 336:4, 341:25, 342:2, 342:19, 343:6, 343:7
patentably [1] - 18:2
patenting [17] - 13:18, 17:5, 17:16, 17:25, 22:10, 42:10, 42:11, 42:15, 46:8, 341:24, 344:17, 344:23, 345:6, 345:16, 345:20, 345:23, 346:12
patents [52] - 4:19, 12:17, 12:20, 12:22, 13:9, 13:13, 14:7, 15:8, 15:11, 15:14, 17:18, 18:8, 18:20, 22:9, 28:5, 33:22, 34:5, 34:14, 34:18, 35:3, 35:4, 35:5, 35:24, 36:1, 36:2, 36:8, 36:12, 36:13, 42:7, 42:9, 42:19, 42:20, 43:7, 43:10, 43:12, 46:9, 57:13, 69:14, 69:23, 72:3, 72:5, 258:13, 312:2, 312:4, 312:5, 312:15, 341:21
patient [6] - 4:18, 6:17, 6:19, 71:6, 77:8, 307:8
patients [16] - 4:16, 5:23, 6:22, 10:13, 11:14, 11:22, 12:4, 12:5, 12:8, 12:9, 12:12, 34:6, 34:7, 34:9, 41:18, 307:6
pattern [3] - 37:7, 37:10, 40:2
patterns [1] - 39:25
pay [1] - 53:1
PDF [15] - 75:6, 81:2, 83:10, 85:10, 94:10, 96:18, 96:20, 96:22, 98:25, 112:21, 115:10, 120:3, 125:14, 232:14, 323:15
PDR [10] - 132:17, 214:6, 214:14, 215:5, 215:9, 226:22, 240:14, 241:21, 252:14, 252:17
PDX [3] - 112:20, 141:15, 315:8
PDX-2.10 [1] - 86:23
PDX-2.11 [1] - 87:7
PDX-2.12 [1] - 93:14
PDX-2.13 [1] - 101:21
PDX-2.14 [4] - 103:5, 141:11, 141:17, 228:10
PDX-2.15 [1] - 109:5
PDX-2.16 [1] - 109:16
PDX-2.17 [1] - 110:3
PDX-2.2 [1] - 69:25
PDX-2.20 [4] - 117:1, 121:24, 165:4, 169:19
PDX-2.21 [1] - 123:21
PDX-2.22 [1] - 124:6
PDX-2.3 [1] - 74:7
PDX-2.4 [1] - 75:17
PDX-2.5 [1] - 76:6
PDX-2.6 [1] - 76:21
PDX-2.7 [1] - 79:3
PDX-2.8 [1] - 111:17
PDX-2.9 [2] - 80:20, 81:12
peak [1] - 280:13
peaks [2] - 38:18, 286:5
people [6] - 3:9, 3:16, 38:22, 71:10, 156:16, 334:17
per [41] - 27:17, 50:19, 54:5, 54:7, 54:16, 54:19, 54:21, 55:11, 56:2, 56:5, 56:7, 85:20, 85:21, 250:21, 261:17, 261:20, 261:21, 263:18, 279:7, 279:9, 279:12, 279:14, 281:17, 283:11, 285:4, 286:18, 287:13, 289:10, 290:1, 292:16, 293:5, 307:10, 307:11, 307:12, 307:14, 310:16, 310:19, 313:19, 328:25
percent [64] - 8:13, 27:18, 43:18, 63:24, 64:1, 95:7, 95:10, 97:25, 98:4, 98:7, 99:12, 104:21, 105:21, 106:2, 106:6, 113:6, 113:7, 114:1, 114:2, 114:3, 132:4, 133:3, 133:11, 162:13, 162:16, 166:10, 166:15, 166:18, 173:11, 175:7, 175:16, 201:22, 202:2, 202:3, 202:4, 214:19, 214:21, 214:22, 214:23, 215:19, 215:22, 216:10, 216:13, 216:17, 233:9, 233:14, 238:20, 239:4, 239:16, 250:14, 250:17, 269:15, 269:18, 279:6, 293:5, 333:14, 333:17, 333:18
percentage [6] - 95:5, 95:9, 173:10, 233:5, 233:8, 323:23
percentages [3] - 64:8, 94:25, 95:2
perfect [1] - 311:20
perfectly [1] - 195:20
perform [2] - 191:22, 214:1
performance [4] - 80:5, 212:22, 263:23, 328:16
performed [10] - 61:24, 66:16, 88:24, 130:15, 144:3, 181:13, 219:16, 227:3, 227:4, 238:15
performing [1] - 47:22
perhaps [7] - 52:15, 56:23, 195:20, 195:21, 223:19, 229:14, 338:16
period [1] - 342:18
periorbitals [1] - 71:12
permission [1] - 58:12
person [36] - 16:20, 19:12, 19:18, 20:2, 20:6, 20:15, 21:23, 29:8, 29:19, 30:1, 36:17, 38:14, 41:21, 41:24, 44:18, 45:5, 45:15, 45:20, 45:23, 46:2, 55:18, 55:20, 56:1, 74:23, 76:16, 176:17, 183:4, 187:19, 187:25, 188:2, 229:21, 245:18, 262:15, 310:22, 315:2, 315:9
personal [1] - 316:3
personally [6] - 153:9, 153:13, 154:8, 175:9, 316:3, 316:23
perspective [6] - 74:23, 187:19, 195:9, 262:15, 264:17, 315:2
pertains [1] - 281:4
Pfizer [1] - 44:7
PH-101 [2] - 197:13, 197:15
PH-102 [1] - 197:16
PH-200 [1] - 197:16
Ph.D [4] - 1:22, 258:5, 315:16, 315:24
pharmaceutical [95] - 6:5, 8:12, 10:1, 13:3, 17:22, 17:24, 18:14, 20:23, 22:13, 27:8, 27:11, 28:14, 29:6, 43:16, 44:23, 46:5, 50:9, 51:4, 54:18, 55:14, 60:9, 60:25, 66:1, 70:20, 71:2, 71:23, 72:7, 72:17, 75:21, 75:23, 76:21, 76:22, 76:23, 77:1, 77:14, 77:24, 78:15, 78:21, 79:23, 80:16, 81:6, 87:19, 98:23, 100:1, 101:5, 102:14, 130:15, 142:10, 148:23, 151:6, 157:10, 174:21, 179:2, 185:21, 188:23, 192:7, 194:19, 198:11, 198:25, 199:9, 199:15, 201:25, 206:1, 207:18, 208:8, 225:20, 226:4, 226:10, 231:4, 233:20, 233:23, 234:1, 234:8, 235:6, 235:9, 235:12, 236:1, 237:11, 237:12, 237:16, 238:10, 238:23, 239:22, 239:24, 241:11, 242:16, 243:6, 249:13, 249:16, 260:21, 263:13, 313:8, 313:14, 313:25, 316:9
Pharmaceutical [10] - 82:18, 83:1, 84:9, 85:7, 96:12, 98:17, 185:7, 185:14, 205:23, 232:6
pharmaceutically [9] - 17:14, 18:23, 18:24, 19:7, 42:17, 42:22, 43:8, 44:12, 342:2
Pharmaceuticals [1] - 70:9
pharmaceuticals [2] - 43:18, 188:24
pharmaceutics [3] - 70:5, 185:25, 186:5
pharmacist [1] - 70:6
Pharmacology [1] - 185:14
Pharmacopeia [1] - 203:16
Pharmacy [3] - 82:22, 185:10, 231:12
pharmacy [3] - 70:4, 188:4, 315:16
phonetic [1] - 194:14
phosphate [1] - 153:23
photo [1] - 190:8
physical [7] - 41:8, 118:8, 155:18, 156:17, 200:1, 215:15, 219:9
physically [3] - 78:22, 123:1, 248:7
pick [3] - 122:5, 122:12, 168:19
picture [1] - 218:9

pictures [1] - 220:24
piece [3] - 51:1, 79:12, 292:10
pieces [2] - 189:2, 318:11
pile [1] - 333:25
pillars [1] - 138:1
Pirozzolo [1] - 230:6
PIROZZOLO [29] - 1:20, 62:3, 186:6, 230:5, 230:8, 231:14, 231:18, 232:24, 233:1, 233:16, 233:18, 239:21, 239:23, 240:6, 240:7, 240:23, 240:25, 242:19, 242:22, 244:22, 244:24, 249:11, 249:15, 249:17, 251:6, 252:1, 252:3, 255:20, 255:25
pivot [1] - 22:11
pKa [1] - 45:12
place [2] - 106:15, 261:24
placed [1] - 266:9
placement [1] - 102:8
places [2] - 294:22, 346:15
plain [10] - 16:4, 16:6, 23:20, 55:6, 82:6, 82:9, 83:18, 84:23, 229:16, 229:19
plainly [1] - 16:10
Plaintiff [4] - 1:5, 1:23, 3:25, 230:6
plaintiff's [1] - 57:9
Plaintiff's [3] - 231:15, 232:12, 244:23
Plaintiffs [1] - 183:7
plaintiffs [3] - 2:18, 66:25, 68:8
plan [1] - 344:15
planned [1] - 295:11
planning [1] - 67:6
play [2] - 57:20, 58:7
played [1] - 244:12
playing [3] - 115:3, 238:2, 244:11
plays [9] - 24:22, 63:2, 64:13, 64:25, 92:13, 114:20, 215:2, 237:22, 239:10
pleases [1] - 3:21
plural [1] - 38:2
plus [2] - 43:18, 305:20
PMM [1] - 308:3
point [30] - 19:21, 22:1, 26:12, 26:14, 26:16, 45:8, 45:20, 58:7, 81:17, 92:1, 109:22, 109:25, 110:5, 111:15, 111:19, 116:4, 116:6, 127:14, 127:23, 134:17, 168:25, 181:5, 200:15, 224:16, 227:6, 241:14, 245:5, 300:19, 325:22, 328:2
pointed [6] - 47:7, 50:18, 54:20, 214:25, 215:20, 227:14
pointing [1] - 44:10
points [8] - 29:13, 41:6, 43:23, 104:10, 200:2, 213:5, 213:7, 342:23
policy [1] - 294:14
polymetric [1] - 39:4
polymorph [4] - 16:15, 35:14, 35:20, 35:21
polymorphic [2] - 16:22, 39:5
polymorphs [2] - 16:15, 16:16
poor [28] - 19:14, 20:3, 20:8, 20:12, 24:13, 60:20, 60:22, 61:4, 89:8, 133:7, 133:12, 137:7, 137:10, 137:14, 153:21, 192:11, 192:21, 193:6, 193:22, 194:1, 209:1, 209:6, 209:8, 209:14, 209:17, 223:19, 235:17, 235:19
poorest [1] - 197:14
poorly [3] - 24:15, 89:14, 110:24
pop [3] - 15:7, 15:11, 56:20
pop-up [1] - 15:7
popular [2] - 129:23, 130:4
population [1] - 225:22
porous [1] - 119:9
portion [17] - 77:23, 78:3, 80:15, 84:10, 87:17, 90:1, 101:9, 102:13, 103:15, 103:16, 103:19, 123:16, 181:20, 201:3, 201:4, 203:13
portions [1] - 208:14
POSA [56] - 75:1, 75:15, 75:19, 75:24, 76:9, 76:12, 128:23, 129:15, 131:24, 132:5, 150:14, 151:4, 173:3, 176:5, 176:9, 187:20, 188:13, 188:15, 194:5, 198:17, 198:21, 207:6, 255:1, 262:16, 262:18, 262:22, 263:20, 300:10, 302:19, 302:22, 303:16, 303:18, 303:19, 304:9, 306:6, 306:8, 306:12, 306:13, 306:15, 306:17, 306:18, 306:22, 307:23, 309:23, 310:4, 311:2, 315:3, 315:6, 315:14, 316:17, 317:12, 317:16, 317:20, 318:6, 321:13
POSA's [3] - 317:2, 342:17, 342:20
position [13] - 50:4, 53:6, 53:9, 70:11, 108:14, 108:17, 108:21, 108:22, 108:24, 109:18, 182:9, 188:25, 305:24
positions [2] - 46:14, 109:12
positive [5] - 52:21, 198:25, 199:5, 217:11, 254:24
possess [4] - 36:22, 40:20, 40:21, 40:22
possessed [1] - 36:18
possession [2] - 38:9, 38:12
possible [3] - 16:24, 306:22, 328:2
post [1] - 3:19
post-trial [1] - 3:19
postdoctoral [1] - 258:6
postgraduate [1] - 315:17
postponing [1] - 12:10
postulated [2] - 117:4, 123:9
Potassium [1] - 98:16
potential [24] - 5:10, 6:23, 8:5, 157:9, 157:15, 157:21, 158:9, 158:12, 159:7, 166:6, 198:6, 201:24, 204:20, 205:18, 223:15, 237:3, 253:6, 253:8, 254:7, 254:12, 302:20, 302:23, 307:4
potentially [12] - 11:21, 40:10, 150:20, 150:22, 150:24, 173:6, 207:17, 221:5, 227:24, 237:8, 266:10, 341:5
powder [114] - 23:15, 23:23, 70:19, 71:11, 79:2, 79:8, 79:18, 82:10, 83:17, 84:22, 89:1, 103:24, 122:2, 122:14, 128:22, 129:15, 129:24, 130:5, 130:18, 130:19, 131:25, 133:20, 147:4, 147:7, 147:11, 148:5, 165:24, 165:25, 166:3, 166:24, 167:3, 167:7, 167:8, 169:24, 170:4, 170:7, 170:13, 170:17, 170:18, 170:22, 171:1, 171:5, 171:8, 171:11, 171:20, 172:3, 173:22, 188:22, 188:24, 188:25, 189:1, 189:5, 189:8, 189:12, 189:13, 189:14, 189:15, 189:22, 189:24, 190:22, 191:5, 191:8, 191:10, 191:12, 191:14, 191:19, 191:23, 193:10, 193:12, 193:13, 193:14, 193:24, 194:1, 194:4, 194:12, 196:3, 196:5, 196:10, 198:18, 198:22, 198:25, 199:1, 199:6, 199:9, 199:24, 216:23, 217:12, 218:12, 219:1, 219:7, 220:6, 220:8, 220:11, 220:18, 220:22, 223:3, 223:7, 223:12, 223:20, 223:21, 224:1, 225:4, 228:16, 230:12, 230:14, 230:18, 231:25, 232:19, 247:22, 248:17, 249:4, 325:16, 325:21
powders [4] - 103:19, 171:15, 192:7, 223:7
powerful [1] - 298:15
PPM [22] - 32:5, 32:20, 266:19, 276:9, 280:2, 280:4, 280:6, 280:21, 285:7, 287:23, 287:24, 291:9, 293:18, 299:17, 301:1, 307:15, 307:16, 307:18, 307:19, 310:6, 322:8, 330:2
practical [1] - 279:9
Practice [2] - 82:21, 231:12
pre [13] - 141:21, 141:25, 142:10, 142:14, 142:17, 142:21, 228:15, 228:20, 228:23, 229:1, 229:4, 229:6, 229:10
pre-lubrication [13] - 141:21, 141:25, 142:10, 142:14, 142:17, 142:21, 228:15, 228:20, 228:23, 229:1, 229:4, 229:6, 229:10
preceding [1] - 344:24
precipitated [1] - 296:3
precise [2] - 54:14, 54:15
precisely [2] - 24:14, 32:14
predated [1] - 49:5
predict [1] - 40:17
predictable [1] - 9:2
prediction [3] - 41:22, 41:23, 41:25
predominate [1] - 196:7
preempting [1] - 343:12
prefer [1] - 334:18
preferably [2] - 99:11,

120:23
preferential [1] - 170:14
preferentially [1] - 122:13
preferred [1] - 159:19
preformed [1] - 78:10
pregelatinize [1] - 156:16
pregelatinized [46] - 97:12, 97:14, 97:18, 99:6, 99:8, 99:10, 99:13, 155:22, 155:23, 156:1, 156:4, 156:9, 156:21, 157:1, 157:8, 157:14, 157:20, 158:15, 159:1, 159:11, 159:23, 160:6, 160:10, 160:12, 161:2, 172:21, 203:16, 203:20, 203:24, 204:1, 204:2, 205:18, 206:3, 206:9, 206:10, 206:14, 207:8, 207:11, 207:17, 207:21, 208:1, 208:5, 208:7, 253:24, 254:11, 254:16
prejudiced [1] - 346:16
preparation [6] - 161:1, 188:6, 195:5, 315:19, 316:5, 337:4
prepare [6] - 65:8, 241:1, 318:7, 320:25, 334:4, 342:25
prepared [18] - 103:2, 103:21, 134:4, 135:13, 136:7, 184:3, 189:16, 195:12, 212:14, 257:7, 271:8, 276:22, 288:8, 291:19, 292:14, 293:13, 335:13, 346:13
preparing [6] - 157:18, 163:7, 272:20, 329:15, 335:15, 335:19
presence [4] - 138:13, 176:5, 176:9, 285:15
present [25] - 56:22, 59:11, 175:7, 207:15, 236:15, 236:16, 244:10, 248:12, 248:23, 263:16, 263:18, 263:25, 264:9, 276:3, 280:20, 283:10, 286:18, 288:3, 289:8, 296:25, 299:1, 299:3, 309:9, 310:19
Present [1] - 2:9
presentation [4] - 113:17, 287:2, 287:3, 287:5
presented [6] - 10:16, 106:11, 126:12, 225:5, 322:15, 322:16
presenting [2] - 58:1, 58:3
president [2] - 7:9, 70:8
presidents [1] - 7:7
presiding [1] - 2:14
press [2] - 79:18, 104:8
pressure [1] - 5:3
presumably [1] - 296:24
pretrial [5] - 14:1, 14:5, 15:7, 20:21, 57:23
prevent [2] - 42:11, 46:8
previewed [2] - 14:5, 44:4
previous [2] - 43:1, 43:3
previously [7] - 42:16, 50:25, 66:23, 102:14, 106:4, 114:19, 226:24
primary [1] - 106:8
Princeton [1] - 29:15
principles [1] - 343:9
prioritizing [1] - 227:8
priority [8] - 12:23, 13:25, 75:9, 75:11, 75:15, 188:15, 259:24, 260:2
PRIVATE [1] - 1:7
prize [1] - 29:15
problem [13] - 6:3, 6:15, 21:21, 28:13, 28:17, 29:1, 29:11, 30:4, 44:20, 171:5, 223:17, 290:16, 310:21
problem-solving [1] - 44:20
problems [10] - 6:12, 6:25, 7:13, 19:22, 21:20, 110:14, 124:15, 185:4, 190:12, 190:14
procedure [14] - 246:23, 268:14, 273:4, 275:18, 293:14, 293:17, 295:9, 295:10, 295:25, 296:9, 298:4, 336:3, 336:4, 337:24
procedures [3] - 293:17, 294:8, 332:19
proceed [9] - 59:1, 67:23, 68:16, 72:19, 178:1, 186:7, 257:12, 259:8, 311:11
proceeding [1] - 347:18
PROCEEDINGS [1] - 2:11
Process [5] - 32:1, 32:3, 32:14, 60:13, 132:13
process [142] - 9:12, 9:16, 10:7, 10:11, 10:21, 26:13, 26:15, 26:16, 28:6, 28:17, 28:19, 28:21, 28:25, 30:5, 30:6, 30:9, 30:11, 30:16, 30:19, 30:22, 30:24, 31:6, 31:16, 31:24, 31:25, 32:4, 32:9, 32:12, 32:17, 32:19, 32:23, 33:3, 33:4, 52:15, 53:13, 53:22, 53:23, 54:18, 55:23, 62:15, 62:19, 71:4, 76:1, 77:6, 79:14, 84:2, 85:22, 86:12, 86:19, 87:5, 89:15, 91:8, 101:25, 102:2, 102:5, 102:9, 102:18, 102:19, 102:25, 103:3, 103:11, 104:11, 104:25, 105:3, 106:16, 108:6, 109:11, 110:6, 110:21, 111:10, 133:15, 133:23, 141:22, 148:12, 182:23, 209:11, 228:21, 268:8, 268:20, 272:7, 272:16, 272:19, 272:20, 272:25, 273:1, 273:2, 273:4, 273:23, 274:7, 274:9, 274:10, 274:14, 275:16, 275:18, 275:21, 287:18, 293:20, 293:24, 294:19, 294:23, 295:15, 297:1, 297:7, 297:11, 298:19, 299:5, 299:6, 299:9, 299:12, 299:16, 318:9, 320:24, 321:4, 321:14, 321:15, 321:25, 322:4, 322:8, 329:15, 329:25, 330:4, 330:16, 330:24, 332:25, 333:22, 334:21, 334:24, 335:2, 335:3, 335:4, 335:9, 335:14, 335:16, 335:20, 335:24, 337:11, 337:22, 338:9, 338:10, 338:12
processed [3] - 59:16, 79:10, 97:15
processes [2] - 192:20, 192:21
processing [4] - 41:11, 269:21, 336:11, 337:18
produce [12] - 28:18, 30:10, 31:17, 32:9, 104:8, 189:4, 275:19, 296:20, 298:5, 299:16, 322:8, 331:25
produced [5] - 30:12, 288:20, 297:13, 297:22, 299:24
produces [7] - 28:7, 28:21, 30:7, 31:7, 321:4, 321:25, 322:5
product [102] - 6:6, 9:22, 10:3, 10:13, 10:24, 11:1, 11:5, 13:9, 22:20, 24:5, 24:12, 25:4, 25:5, 25:9, 26:10, 26:19, 26:25, 28:10, 28:16, 28:18, 28:20, 28:23, 29:22, 30:12, 32:8, 34:18, 41:24, 46:5, 59:25, 62:19, 62:21, 64:24, 66:10, 66:14, 70:12, 71:3, 71:5, 74:13, 77:1, 77:7, 99:21, 100:25, 101:1, 107:4, 108:5, 108:13, 109:11, 110:7, 112:15, 115:8, 122:7, 126:1, 132:10, 132:11, 133:22, 138:20, 142:13, 142:24, 145:17, 146:14, 156:19, 158:3, 161:14, 163:3, 165:8, 182:14, 186:11, 187:1, 187:4, 201:4, 202:10, 202:11, 202:25, 203:25, 205:11, 208:10, 208:18, 209:20, 212:23, 213:25, 217:4, 222:15, 222:21, 222:22, 225:17, 225:20, 225:25, 226:20, 234:19, 236:21, 243:8, 247:4, 250:1, 268:16, 296:3, 299:3, 301:1, 301:24, 309:25, 310:18, 322:8
Product [1] - 105:9
production [1] - 337:12
products [73] - 29:6, 70:15, 70:17, 70:18, 70:19, 70:20, 71:11, 73:22, 74:1, 74:5, 74:17, 85:19, 85:25, 86:13, 87:1, 87:6, 90:11, 92:2, 92:22, 101:20, 102:25, 106:8, 107:21, 108:7, 108:23, 112:7, 114:6, 117:19, 119:3, 121:3, 122:23, 123:13, 124:10, 124:19, 124:22, 125:4, 125:9, 125:20, 126:15, 145:9, 145:12, 146:7, 146:10, 165:1, 165:24, 166:4, 167:3, 169:25, 170:13, 171:1, 176:7, 176:11, 176:19, 177:2, 180:9, 182:13, 187:10, 188:10, 202:12, 212:3, 212:21,

233:14, 233:23, 234:4, 234:11, 234:15, 234:22, 235:1, 235:10, 316:13, 317:25, 329:22
products") [1] - 73:21
profess [1] - 14:23
professional [4] - 72:14, 185:5, 185:10, 258:17
professor [4] - 16:2, 29:15, 29:17, 258:8
proffer [2] - 186:3, 259:5
proffering [1] - 171:14
Profile [1] - 113:2
profile [7] - 48:13, 48:18, 112:8, 113:8, 242:13, 242:24, 243:7
profiles [5] - 63:22, 113:25, 214:3, 215:21, 239:1
program [1] - 5:12
progressively [1] - 287:22
project [1] - 208:16
projects [2] - 20:25, 71:7
prong [1] - 87:9
properly [3] - 3:4, 5:2, 5:4
properties [121] - 6:16, 8:6, 8:10, 8:22, 8:24, 9:1, 20:8, 20:11, 21:9, 21:19, 24:13, 40:3, 41:3, 41:13, 41:15, 42:1, 48:6, 48:9, 48:22, 49:3, 49:4, 49:8, 60:4, 60:17, 60:20, 60:23, 61:4, 79:22, 80:4, 89:8, 93:9, 118:8, 132:21, 132:24, 133:7, 133:19, 145:4, 146:2, 146:18, 146:20, 146:24, 147:1, 147:5, 147:12, 148:5, 150:15, 150:19, 150:21, 150:23, 155:1, 155:18, 155:20, 156:18, 156:20, 164:5, 170:4, 170:17, 187:6, 189:8, 189:14, 190:6, 190:16, 190:19, 190:21, 191:1, 191:6, 191:7, 191:14, 191:18, 192:12, 193:7, 193:8, 193:21, 193:22, 193:23, 194:1, 194:6, 194:12, 195:4, 195:12, 195:23, 195:24, 195:25, 196:9, 197:12, 197:15, 198:18, 198:21, 204:2, 204:6, 204:8, 204:12, 204:17, 207:7, 208:19, 209:2, 209:9, 209:15, 209:17, 209:24, 211:12, 211:15, 211:23, 212:3, 216:22, 217:21, 217:22, 217:23, 220:11, 225:1, 225:24, 228:3, 229:23, 230:14, 235:17, 235:19, 247:20, 247:22, 254:21, 254:25, 317:6
Properties [1] - 88:1
property [2] - 64:4, 266:5
proposed [19] - 64:2, 73:21, 73:25, 117:4, 117:8, 117:10, 124:3, 125:3, 125:5, 125:20, 165:20, 186:10, 188:13, 188:16, 199:25, 200:4, 216:18, 262:21, 337:14
proprietary [1] - 70:14
prosecution [4] - 33:9, 319:9, 319:21, 320:5
protection [1] - 42:23
protocol [2] - 65:13, 65:17
prototype [21] - 134:4, 138:4, 138:12, 182:14, 212:3, 213:2, 213:8, 213:18, 238:15, 238:18, 240:8, 240:11, 240:19, 241:7, 241:16, 241:19, 242:13, 242:24, 243:5, 243:10
prototypes [5] - 239:1, 240:1, 242:1, 242:4, 242:10
proud [1] - 258:21
prove [1] - 322:23
proven [1] - 117:15
provide [18] - 72:13, 84:1, 109:11, 110:16, 114:23, 141:6, 150:11, 186:19, 196:8, 202:8, 203:2, 262:2, 267:15, 302:25, 303:10, 312:14, 327:24, 328:21
provided [28] - 8:10, 12:7, 62:10, 83:19, 84:24, 94:17, 98:3, 102:17, 107:7, 107:18, 109:21, 114:22, 119:23, 124:10, 174:21, 175:19, 179:7, 187:7, 195:2, 201:10, 208:3, 219:18, 236:17, 262:18, 312:8, 312:11, 315:6, 341:22
provides [10] - 56:7, 88:16, 119:8, 158:12, 195:1, 249:25, 250:3, 253:19, 328:13, 342:18
providing [6] - 129:5, 263:7, 301:9, 301:22, 304:2, 314:20
proving [1] - 333:20
provisional [1] - 157:25
proviso [1] - 340:7
PRUSSIA [15] - 1:20, 2:18, 2:24, 3:11, 3:20, 3:23, 13:24, 57:3, 57:7, 344:6, 344:12, 345:1, 345:12, 346:21, 347:7
Prussia [7] - 2:23, 3:23, 34:20, 150:25, 341:1, 343:12, 344:4
Prussia's [1] - 343:19
PTX [4] - 127:11, 177:24, 256:3, 283:13
PTX-0394 [1] - 84:5
PTX-0777 [1] - 72:11
PTX-10 [1] - 336:17
PTX-243 [3] - 98:12, 126:22, 157:5
PTX-394 [5] - 84:14, 94:4, 126:22, 165:18, 172:6
PTX-447 [4] - 119:11, 126:23, 179:5, 221:18
PTX-533 [1] - 160:21
PTX-553 [3] - 160:15, 161:20, 177:17
PTX-553A [2] - 96:9, 126:23
PTX-572A [2] - 83:4, 126:23
PTX-676 [2] - 58:17, 67:1
PTX-677 [2] - 105:7, 126:23
PTX-678 [4] - 58:18, 58:20, 67:1, 67:25
PTX-68 [2] - 291:15, 291:17
PTX-698 [2] - 124:24, 126:23
PTX-724 [4] - 58:16, 66:25, 99:16, 126:22
PTX-744 [3] - 125:23, 126:23, 127:4
PTX-770 [3] - 252:24, 255:21
PTX-777 [1] - 126:24
PTX-9 [2] - 288:5, 288:7
PTX-98 [3] - 280:24, 281:2, 283:14
publication [4] - 27:22, 267:8, 318:16, 319:2
publications [3] - 74:12, 184:19, 257:22
published [10] - 43:21, 43:22, 71:25, 102:4, 173:19, 185:17, 258:10, 258:11, 267:11, 267:12
pull [71] - 73:9, 111:25, 130:7, 132:10, 134:22, 135:9, 140:10, 141:11, 142:23, 142:25, 148:18, 149:9, 151:9, 157:5, 160:15, 163:13, 165:4, 169:19, 172:6, 174:13, 180:15, 184:12, 194:14, 196:12, 197:22, 199:11, 200:25, 203:5, 205:20, 208:17, 210:5, 210:9, 210:23, 214:5, 221:18, 225:7, 226:22, 228:10, 230:20, 233:16, 235:6, 251:14, 251:15, 252:11, 252:24, 254:5, 257:16, 259:11, 259:21, 264:14, 267:2, 267:8, 268:11, 271:5, 276:18, 276:24, 280:24, 281:5, 282:10, 284:23, 288:5, 291:15, 295:16, 296:13, 301:15, 304:24, 308:10, 309:4, 313:1, 318:21, 323:14
pulled [1] - 224:14
pulling [2] - 232:14, 278:18
Purdue [1] - 258:6
pure [14] - 8:7, 11:1, 11:2, 56:9, 146:19, 146:23, 269:14, 269:18, 297:20, 323:9, 323:12, 323:21, 324:2, 324:13
purely [1] - 62:1
purge [1] - 310:6
purification [5] - 296:9, 309:2, 309:10, 309:11, 332:24
purify [3] - 296:8, 308:4, 310:24
purifying [2] - 296:11, 308:24
purity [24] - 269:5, 269:11, 269:16, 277:5, 324:7, 324:9, 324:17, 324:21, 325:5, 325:6, 325:8, 325:9, 325:18, 326:1, 326:2, 326:4, 326:8, 326:13, 326:15, 327:1
purple [1] - 51:14
purpose [4] - 65:11, 75:12, 214:13, 225:14
purposes [11] - 39:16, 44:2, 48:14, 48:19, 69:18, 86:9, 259:15,

278:14, 281:20, 293:11
pursuing [4] - 322:19, 322:22, 322:24, 323:2
push [1] - 290:10
put [21] - 17:6, 35:15, 43:16, 51:23, 78:6, 103:20, 109:25, 111:15, 116:3, 117:7, 124:13, 136:18, 147:4, 147:10, 191:8, 244:22, 256:24, 257:10, 300:17, 319:15, 338:18
putting [1] - 332:15
PX-678 [2] - 67:3, 67:7

Q

QM [1] - 290:23
qualifications [5] - 76:15, 184:11, 257:15, 265:10, 317:9
qualifiers [1] - 130:1
qualify [2] - 117:12, 117:19
qualitative [1] - 85:18
quality [5] - 71:24, 99:25, 176:6, 176:10, 203:22
quantifying [1] - 264:1
quantitative [1] - 85:20
QUESTION [8] - 319:21, 320:14, 325:15, 326:12, 327:15, 327:24, 328:4, 339:24
questions [6] - 126:18, 176:4, 182:25, 251:6, 255:3, 311:5
quick [2] - 2:25, 4:21
quickly [2] - 149:10, 300:11
quinoline [14] - 52:10, 261:5, 303:20, 304:3, 304:10, 304:12, 304:15, 304:21, 304:22, 305:3, 305:6
quinolines [1] - 303:22
quite [9] - 111:8, 127:13, 190:22, 191:2, 285:24, 344:15, 344:16, 345:13
quote [1] - 24:13

R

R&D [3] - 58:10, 59:8, 59:10
raise [6] - 3:5, 42:8, 57:10, 341:4, 341:5
raised [5] - 57:25, 116:6, 116:7, 152:4, 341:18
raising [1] - 343:14
random [1] - 190:2
range [12] - 16:5, 30:19, 30:20, 95:5, 95:7, 97:2, 98:3, 98:6, 105:25, 122:21, 137:12, 182:20
ranges [1] - 98:1
rarely [2] - 8:12, 8:16
rate [6] - 79:13, 111:23, 213:6, 280:13, 281:18, 281:19
rates [1] - 41:10
rather [3] - 64:4, 120:24, 258:12
ratio [14] - 88:21, 89:2, 129:17, 131:4, 136:11, 136:19, 138:8, 139:6, 140:5, 140:25, 181:22, 191:15, 191:17, 209:5
rationale [2] - 236:17, 298:3
RAUCCI [1] - 1:17
Ravi [1] - 245:10
Ravikumar [3] - 58:9, 59:6, 217:1
raw [1] - 100:4
ray [2] - 325:16, 325:21
re [4] - 243:4, 308:5, 308:6, 309:12
re-ask [1] - 243:4
re-crystalize [1] - 308:5
re-crystallization [2] - 308:6, 309:12
reach [3] - 74:16, 74:19, 274:19
reached [1] - 59:18
reaching [1] - 119:22
react [1] - 7:23
reaction [9] - 7:20, 7:25, 268:5, 268:6, 268:17, 269:20, 271:25, 272:1
reactions [4] - 8:1, 332:12, 332:16, 332:20
reactor [2] - 296:19
reactors [1] - 333:25
read [23] - 73:15, 75:7, 83:14, 83:21, 84:11, 84:20, 89:5, 90:5, 92:11, 101:4, 113:22, 114:19, 115:3, 120:21, 125:17, 126:4, 161:16, 161:18, 179:17, 187:24, 324:24, 337:24
readable [1] - 103:9
readily [1] - 303:14
reading [2] - 14:24, 324:16
reads [1] - 63:20
ready [1] - 2:17
reagent [4] - 336:11, 337:18, 337:22, 338:12
reagents [1] - 274:4
Real [1] - 347:19
real [3] - 11:12, 19:24, 34:4
Real-Time [1] - 347:19
reality [1] - 140:24
realize [2] - 265:2, 344:7
really [12] - 22:5, 23:7, 50:14, 50:20, 54:11, 67:13, 67:14, 224:10, 258:20, 296:11, 331:16, 338:8
reason [14] - 3:15, 19:24, 24:14, 25:18, 32:12, 49:10, 56:18, 108:10, 109:8, 156:16, 220:24, 339:9, 339:24, 340:12
reasonable [5] - 21:15, 29:24, 45:24, 232:22, 311:3
reasonably [6] - 70:25, 154:25, 190:25, 191:4, 193:8, 310:23
reasons [8] - 8:14, 8:15, 21:7, 66:2, 101:6, 110:11, 226:4
rebut [1] - 57:25
recalculate [1] - 181:2
received [2] - 5:16, 258:17
receiving [2] - 22:2, 33:12
recent [1] - 266:17
Recently [2] - 173:17, 173:21
recently [2] - 173:18, 341:18
Recess [2] - 67:20, 255:10
recess [4] - 168:9, 168:11, 340:24, 347:12
recessed [1] - 347:15
recognize [7] - 72:22, 134:24, 135:11, 148:20, 175:5, 199:13, 259:12
recognized [3] - 45:1, 45:18, 93:20
recollection [4] - 209:6, 241:24, 320:2, 327:11
recommended [1] - 303:6
record [15] - 35:1, 57:18, 58:20, 59:5, 67:13, 68:10, 150:5, 177:15, 183:16, 184:6, 220:12, 251:11, 256:13, 263:12, 274:24
recrystallization [4] - 309:24, 310:20, 310:25, 321:9
recrystallized [1] - 310:17
red [9] - 52:24, 260:15, 267:21, 267:23, 293:1, 293:4, 300:17, 304:13, 306:9
Reddy [1] - 2:10
REDIRECT [2] - 178:3, 251:9
redirect [1] - 251:7
reduce [9] - 80:13, 117:25, 122:23, 123:10, 171:7, 171:11, 193:17, 248:6, 302:17
reduces [3] - 200:20, 222:1, 223:24
reducing [2] - 171:2, 172:4
Reduction [1] - 122:16
reduction [7] - 118:11, 120:15, 137:23, 138:7, 141:2, 200:16, 248:4
refer [21] - 50:16, 72:25, 73:25, 75:1, 80:25, 103:14, 118:17, 122:18, 123:7, 125:13, 133:10, 143:8, 152:24, 160:9, 162:23, 196:19, 197:18, 230:25, 278:13, 318:24, 319:13
reference [59] - 14:13, 19:4, 27:23, 42:14, 43:4, 43:5, 44:12, 53:7, 54:20, 55:21, 82:21, 82:24, 88:11, 91:1, 93:2, 94:20, 96:15, 97:4, 97:6, 99:5, 114:24, 116:20, 116:24, 130:20, 148:20, 157:1, 160:17, 160:20, 161:5, 161:11, 161:22, 165:18, 172:6, 172:7, 172:14, 172:17, 173:18, 198:5, 199:21, 202:10, 212:21, 212:23, 213:24, 218:8, 231:11, 232:25, 243:8, 267:11, 308:21, 318:13, 318:18, 319:1, 320:5, 320:15, 343:6, 343:7, 346:15, 346:17
referenced [9] - 66:23, 83:7, 83:8, 84:10, 115:13, 126:3, 301:12, 305:11, 344:23
references [19] - 27:24, 27:25, 51:23, 106:1, 106:4, 156:25, 158:8, 165:17, 165:21, 187:12, 207:6, 212:9, 226:13, 226:17, 241:17, 241:19, 251:12, 345:2, 346:14
referred [32] - 6:1, 6:8, 15:7, 19:15, 21:5, 25:12, 32:1, 42:14, 46:12, 47:24, 53:4, 58:16, 58:17, 58:18, 78:14, 80:17, 96:14, 116:14, 118:2,

129:20, 157:1, 200:4, 210:19, 232:8, 243:14, 243:19, 244:5, 247:7, 312:4, 319:6, 323:22, 332:22
referring [23] - 19:16, 60:14, 63:10, 89:9, 95:24, 106:3, 121:18, 152:20, 163:3, 222:14, 240:2, 243:16, 267:6, 278:24, 324:2, 324:7, 324:13, 331:20, 331:22, 331:23, 335:4, 338:7
refers [12] - 49:21, 91:15, 157:25, 162:1, 162:5, 220:3, 221:21, 230:22, 232:5, 261:12, 313:8, 313:25
refined [3] - 281:16, 285:2, 286:3
reflect [2] - 131:25, 257:21
reflects [1] - 61:24
refresh [1] - 327:11
refresher [1] - 4:21
refreshes [1] - 320:2
refuting [1] - 127:20
regard [2] - 269:15, 335:3
regarded [1] - 153:17
regarding [11] - 64:23, 92:22, 114:11, 138:24, 187:2, 187:8, 201:5, 207:24, 208:4, 210:15, 335:4
regards [1] - 304:22
Regis [64] - 31:11, 53:19, 53:23, 54:14, 270:18, 270:19, 270:21, 270:22, 270:24, 271:3, 271:14, 271:17, 271:24, 272:7, 272:17, 272:19, 272:25, 273:13, 273:23, 274:10, 274:14, 275:16, 275:18, 276:3, 276:6, 276:14, 277:14, 277:16, 277:18, 277:19, 279:23, 280:19, 282:6, 282:25, 283:19, 284:11, 284:21, 286:15, 286:16, 287:6, 287:11, 287:16, 287:18, 288:4, 288:13, 288:19, 288:21, 289:7, 289:13, 291:9, 291:13, 292:1, 293:6, 299:16, 335:7, 335:13, 335:17, 335:21, 335:25, 336:3, 336:7, 336:12, 337:13, 338:10
regular [1] - 240:11
regulate [1] - 5:2
regulation [1] - 192:20
regulatory [10] - 71:24, 265:7, 266:11, 271:8, 276:22, 277:17, 288:8, 291:18, 301:3, 306:23
reiterate [1] - 123:23
rejection [3] - 33:9, 320:4, 320:7
rejections [1] - 320:14
relate [8] - 113:13, 114:10, 115:4, 115:6, 121:7, 121:9, 259:15, 311:23
related [13] - 39:10, 42:6, 69:12, 69:14, 70:13, 71:25, 75:22, 95:25, 188:4, 210:1, 211:18, 259:21, 315:16
relates [7] - 18:23, 38:2, 100:1, 100:2, 103:9, 115:7, 341:19
relating [5] - 72:4, 98:8, 109:21, 312:15, 339:5
relationship [1] - 125:8
relative [7] - 280:12, 281:18, 281:19, 282:4, 283:18, 291:7, 292:5
release [4] - 77:5, 212:24, 277:4, 317:5
released [2] - 212:20, 212:22
relevance [1] - 293:11
relevant [8] - 16:21, 74:11, 74:12, 188:19, 309:13, 316:19, 342:4, 342:5
reliable [1] - 339:3
reliance [1] - 116:1
relied [10] - 116:14, 129:4, 130:20, 135:4, 137:23, 163:16, 166:14, 232:2, 239:24, 319:2
rely [11] - 127:23, 129:9, 163:6, 181:13, 191:25, 318:18, 330:21, 330:24, 331:9, 339:13, 341:25
relying [8] - 107:12, 182:5, 235:3, 315:5, 331:12, 335:6, 336:14, 342:19
remained [1] - 59:10
remarkable [1] - 33:19
remember [10] - 12:2, 15:6, 15:24, 20:20, 32:7, 249:9, 253:3, 331:24, 332:1, 336:9
remind [7] - 35:10, 218:8, 220:3, 319:5, 319:11, 320:8, 342:11
reminded [1] - 264:25
Remington [8] - 82:21, 83:6, 86:19, 101:24, 142:2, 231:12, 231:16, 232:3
Remington's [2] - 86:18, 86:21
removal [1] - 309:13
remove [2] - 104:1, 193:15
renal [1] - 11:17
render [3] - 34:16, 123:19, 186:9
rendered [1] - 156:22
rendering [2] - 122:15, 232:3
repeat [7] - 114:25, 157:17, 166:1, 198:19, 321:23, 323:13, 325:7
replace [1] - 67:25
replaced [2] - 134:15, 137:24
replacement [1] - 138:4
replicate [1] - 31:5
reply [6] - 152:4, 180:16, 312:11, 345:2, 345:8, 345:17
report [71] - 60:9, 60:25, 62:21, 65:14, 65:17, 87:19, 102:14, 112:15, 128:1, 128:3, 130:3, 130:22, 132:11, 138:10, 140:22, 142:24, 144:20, 152:5, 166:23, 170:7, 170:21, 180:14, 180:17, 197:11, 199:21, 200:10, 205:6, 205:8, 208:18, 215:5, 219:19, 223:19, 235:7, 235:9, 235:13, 235:16, 236:2, 237:11, 237:13, 237:16, 238:10, 238:23, 239:22, 239:25, 241:11, 241:23, 242:16, 243:6, 249:13, 249:16, 277:6, 278:21, 281:3, 287:5, 294:18, 312:11, 320:12, 320:21, 321:12, 322:12, 341:22, 342:8, 342:15, 343:3, 343:10, 344:20, 345:2, 345:3, 345:8, 345:18
Report [1] - 85:8
reported [20] - 24:11, 39:20, 40:23, 53:24, 106:1, 129:10, 136:9, 136:21, 200:14, 214:11, 251:21, 251:24, 252:18, 277:2, 279:20, 280:6, 284:13, 286:21, 289:3, 340:13
REPORTER [1] - 141:12
Reporter [2] - 196:23, 347:19
reporting [6] - 31:23, 214:14, 216:10, 252:21, 291:12, 307:10
reports [20] - 19:22, 88:5, 129:11, 131:11, 132:17, 135:5, 153:16, 157:18, 157:19, 161:1, 163:7, 163:11, 166:15, 201:24, 208:15, 208:16, 223:5, 279:5, 312:8, 312:14
represent [3] - 3:25, 193:5, 331:3
representation [1] - 298:24
representative [7] - 16:22, 16:25, 38:14, 41:1, 121:14, 334:21, 334:23
represents [1] - 214:19
reprocessed [1] - 310:2
reproduced [1] - 107:10
reproduces [1] - 135:15
reproducibility [1] - 333:15
request [2] - 119:24, 223:23
requests [1] - 347:9
require [8] - 14:13, 14:18, 15:1, 16:23, 16:24, 155:2, 171:19, 266:18
required [11] - 7:13, 16:8, 18:7, 18:19, 32:6, 39:3, 117:18, 123:24, 124:1, 296:18, 345:13
requirement [3] - 22:19, 40:25, 116:18
requires [8] - 27:14, 55:24, 56:4, 162:14, 234:1, 234:7, 313:14, 330:14
research [8] - 4:14, 184:25, 188:5, 196:16, 208:15, 315:18, 316:4, 316:23
researched [1] - 185:20
researching [1] - 34:12
resides [1] - 107:24
resist [1] - 122:6
resistance [1] - 12:6
resolve [2] - 193:25, 286:5
resolved [1] - 67:24
respect [15] - 6:20, 38:25, 93:24, 125:9, 181:6, 195:11, 274:19, 275:1, 289:4, 289:12, 306:7, 315:14, 326:14, 345:14, 345:16
respond [2] - 57:24, 152:2
responding [1] -

326:9
response [2] - 106:18, 224:19
responsibilities [2] - 70:10, 71:17
responsibility [1] - 92:24
responsible [2] - 70:12, 125:5
rest [2] - 122:14, 183:7
restate [2] - 171:9, 176:8
restating [1] - 142:2
result [17] - 8:20, 8:21, 9:22, 11:8, 34:3, 34:14, 54:2, 71:5, 77:6, 148:1, 196:6, 211:22, 215:18, 293:17, 297:3, 330:16, 335:12
resulted [5] - 31:24, 32:4, 32:19, 33:21, 297:12
resulting [5] - 104:1, 104:2, 104:7, 138:6, 189:14
results [29] - 9:4, 9:5, 22:3, 22:4, 30:16, 30:19, 33:13, 33:15, 54:14, 54:15, 54:25, 55:2, 63:21, 80:2, 113:24, 166:22, 215:12, 222:10, 239:6, 242:8, 276:19, 282:14, 283:18, 283:19, 284:13, 287:5, 299:13, 305:2, 345:15
Results [1] - 120:3
resume [1] - 168:8
retained [4] - 31:12, 68:24, 270:22, 292:18
retake [1] - 168:14
retention [6] - 280:12, 281:18, 281:19, 282:4, 291:7, 292:5
return [4] - 76:19, 77:9, 87:14, 102:12
returning [1] - 27:13
reveal [8] - 90:10, 95:16, 96:2, 99:8, 101:8, 106:7, 113:4, 114:5
reveals [1] - 113:5
review [30] - 74:7, 87:10, 87:11, 102:5, 108:3, 116:17, 143:23, 152:11, 166:21, 170:6, 170:20, 191:25, 197:25, 203:7, 203:11, 209:21, 210:1, 210:7, 211:11, 211:17, 216:20, 216:25, 264:17, 275:15, 287:15, 299:4, 303:11, 304:7, 328:3, 337:25
reviewed [22] - 26:7, 107:3, 140:21, 151:11, 151:20, 151:24, 166:14, 202:21, 207:13, 208:12, 208:14, 251:20, 260:8, 299:11, 312:21, 336:2, 338:1, 338:9, 338:21, 339:8, 339:14, 340:3
reviewing [2] - 93:16, 110:11
reviews [2] - 198:8, 258:12
reword [1] - 327:10
rewrite [1] - 14:25
RICHARD [1] - 1:14
Richard [1] - 2:14
right-hand [14] - 13:5, 79:21, 90:6, 94:23, 96:23, 97:24, 135:23, 159:16, 169:13, 184:7, 197:8, 214:22, 219:4, 283:24
rise [9] - 2:13, 67:19, 67:21, 168:10, 168:12, 255:9, 255:11, 340:25, 347:14
risk [21] - 61:9, 61:15, 61:24, 91:13, 91:15, 91:23, 142:25, 143:7, 143:16, 144:3, 144:18, 144:24, 145:3, 146:1, 226:23, 227:3, 227:20, 235:21, 236:3, 237:1, 237:3
roadmap [1] - 332:14
Robin [1] - 266:9
Robinson [10] - 264:17, 265:18, 266:1, 266:3, 266:5, 266:16, 301:12, 310:8, 310:11, 310:13
role [15] - 24:22, 59:7, 63:2, 64:13, 64:25, 92:14, 114:21, 115:3, 215:2, 234:25, 237:22, 238:1, 239:10, 244:11, 244:12
roles [1] - 237:2
root [1] - 9:19
rotating [1] - 79:19
rough [1] - 193:6
roughness [2] - 200:16, 218:12
route [5] - 272:6, 309:10, 309:11, 337:4, 337:11
routine [7] - 19:19, 44:17, 44:18, 44:20, 56:13, 56:15, 342:23
row [14] - 25:14, 90:6, 95:8, 100:20, 105:18, 144:25, 145:22, 202:14, 202:15, 214:18, 277:22, 279:17, 279:20, 280:8
RRT [2] - 280:9, 297:13
rugosity [1] - 200:16
Rule-of-2 [4] - 45:9, 45:11, 45:14, 45:17
run [1] - 306:12

S

S1182 [1] - 294:15
safe [6] - 4:15, 7:1, 12:14, 34:9, 45:19
safety [4] - 6:13, 176:6, 176:10, 265:1
sale [2] - 73:19, 124:18
Salt [1] - 98:17
salt [112] - 7:18, 7:19, 7:23, 7:24, 8:5, 8:9, 8:10, 8:16, 8:18, 9:1, 9:8, 9:14, 12:20, 12:21, 13:2, 13:4, 13:7, 13:9, 13:13, 14:7, 14:18, 16:15, 17:11, 17:14, 17:18, 17:19, 17:20, 17:21, 17:22, 18:8, 18:11, 18:20, 18:24, 19:1, 19:8, 19:13, 19:18, 19:19, 20:6, 20:13, 20:16, 20:18, 20:24, 20:25, 21:3, 21:4, 21:6, 21:14, 21:15, 21:17, 21:18, 21:19, 21:24, 22:9, 28:5, 35:3, 35:5, 35:25, 36:2, 36:3, 36:12, 36:13, 36:24, 37:3, 37:4, 37:5, 37:15, 37:16, 37:18, 37:20, 37:22, 38:7, 40:9, 42:6, 42:9, 42:20, 43:6, 43:10, 43:11, 44:2, 44:13, 44:16, 44:25, 45:1, 45:4, 45:6, 45:8, 45:14, 45:21, 45:24, 45:25, 46:1, 46:7, 50:11, 50:25, 57:12, 69:23, 312:5, 312:15, 318:8, 331:25, 341:21, 342:2, 342:23, 342:25
salts [14] - 8:5, 8:11, 21:21, 36:25, 39:18, 39:20, 39:21, 42:17, 42:22, 43:9, 44:13, 44:21, 46:4
Salvatore [3] - 256:8, 256:14, 259:5
SALVATORE [2] - 256:15, 256:16
sample [7] - 59:18, 131:6, 131:12, 132:3, 132:4, 132:6, 209:3
samples [3] - 282:17, 287:13, 290:21
satisfactory [1] - 215:16
satisfied [1] - 124:3
satisfy [4] - 14:9, 40:25, 45:14, 45:17
saw [11] - 13:22, 19:5, 37:2, 54:23, 197:16, 197:24, 223:22, 225:10, 226:13, 278:15, 341:25
scale [1] - 337:11
scanning [1] - 38:21
scene [2] - 15:14, 31:22
schematic [1] - 298:24
schematics [1] - 103:9
scheme [7] - 53:12, 267:20, 268:3, 271:24, 332:11, 332:14, 333:23
Scheme [10] - 329:8, 329:10, 329:15, 331:10, 331:13, 331:21, 332:5, 332:7, 332:8, 332:11
schemes [6] - 273:12, 273:14, 273:15, 273:16, 273:19
school [1] - 11:25
science [1] - 258:22
Science [3] - 82:21, 185:14, 231:12
sciences [1] - 75:21
scientific [12] - 47:21, 87:4, 93:18, 108:4, 144:6, 199:4, 200:9, 201:23, 205:17, 207:6, 207:12, 333:15
scientifically [2] - 46:22, 47:1
scientist [4] - 143:24, 217:1, 245:14, 245:16
scientists [5] - 7:3, 44:23, 76:1, 76:2, 234:25
Scientists [1] - 185:7
scope [16] - 15:5, 15:8, 15:15, 15:21, 36:18, 36:23, 37:21, 38:6, 38:10, 40:21, 41:2, 42:4, 177:4, 177:6, 311:21, 322:16
screen [21] - 13:5, 17:13, 18:25, 19:19, 20:24, 21:4, 24:19, 32:18, 38:13, 46:1, 115:11, 130:13, 131:1, 149:3, 149:7, 149:14, 151:16, 184:7, 211:3, 319:15, 342:24
screening [1] - 20:25
Searle [2] - 98:21, 98:22
seated [4] - 2:16, 67:22, 168:13, 255:12
second [31] - 3:11, 6:3, 10:2, 12:20, 13:16, 19:17, 27:8, 29:1, 33:11, 42:8, 46:18, 49:5, 49:20, 55:2, 65:25, 83:21, 101:4, 111:15, 120:18, 149:15, 152:10, 163:21, 202:16, 226:3, 240:19, 241:7, 241:19, 242:13, 260:24, 280:23, 284:11
second-to-left [1] - 202:16

seconds [2] - 58:24, 58:25
section [34] - 64:20, 82:20, 85:15, 85:17, 101:4, 102:21, 105:12, 114:15, 120:2, 132:13, 154:17, 154:18, 185:16, 214:14, 215:1, 215:5, 237:12, 237:16, 237:20, 238:14, 238:22, 238:23, 239:7, 239:24, 271:12, 281:6, 281:8, 302:10, 302:12, 342:21, 343:4, 346:13, 346:19
Section [25] - 13:21, 60:7, 62:21, 64:23, 73:18, 85:12, 92:9, 100:6, 100:12, 101:3, 114:16, 115:9, 201:8, 214:6, 221:19, 225:11, 226:2, 237:13, 271:10, 279:2, 288:11, 296:13, 303:3, 303:5, 309:20
Sections [1] - 225:12
sections [2] - 69:13, 74:11
securing [1] - 4:16
see [227] - 14:14, 17:13, 22:7, 24:19, 27:14, 31:3, 31:4, 32:2, 32:18, 38:12, 43:7, 43:12, 47:6, 47:13, 47:23, 48:14, 48:17, 48:20, 48:22, 49:6, 50:10, 51:10, 53:25, 54:1, 55:5, 60:17, 61:11, 61:17, 61:20, 63:15, 65:12, 65:20, 66:5, 77:16, 82:18, 82:20, 82:24, 83:12, 84:18, 85:12, 86:5, 87:24, 88:1, 88:11, 88:21, 89:20, 89:23, 90:1, 90:16, 91:1, 92:9, 94:12, 94:20, 95:13, 95:21, 96:24, 97:3, 97:6, 99:2, 99:5, 100:14, 102:3, 105:8, 105:15, 112:10, 113:19, 114:16, 115:17, 115:25, 120:5, 120:20, 128:15, 131:1, 131:15, 131:24, 132:22, 133:5, 133:8, 133:17, 143:13, 145:6, 145:24, 146:4, 146:5, 149:5, 149:7, 149:8, 149:13, 151:16, 152:15, 152:22, 153:19, 153:20, 153:25, 154:1, 154:18, 154:22, 155:3, 155:4, 156:12, 157:24, 158:1, 158:15, 158:24, 159:9, 160:21, 161:10, 161:24, 162:3, 162:4, 162:9, 162:10, 162:17, 162:18, 166:22, 167:21, 168:21, 168:25, 169:3, 169:7, 169:11, 169:15, 170:6, 170:21, 172:16, 173:24, 173:25, 174:11, 174:12, 174:24, 175:1, 178:25, 179:2, 181:19, 181:23, 207:15, 207:19, 209:18, 213:21, 215:3, 216:20, 216:24, 221:21, 222:1, 222:3, 223:4, 223:17, 223:18, 226:7, 226:8, 227:10, 227:11, 227:13, 227:16, 228:4, 231:9, 231:21, 232:15, 232:16, 233:2, 236:4, 239:9, 245:24, 249:18, 249:22, 250:9, 250:15, 253:17, 253:23, 253:25, 254:3, 254:11, 254:13, 254:14, 260:20, 261:18, 271:15, 279:11, 279:12, 280:8, 280:10, 280:13, 280:15, 283:4, 283:20, 285:3, 285:12, 285:14, 286:15, 286:20, 288:2, 288:17, 289:7, 289:9, 289:16, 289:24, 293:3, 298:7, 303:12, 306:1, 307:9, 313:6, 315:13, 315:20, 315:21, 316:20, 317:7, 317:24, 318:15, 318:22, 323:25, 324:5, 331:11, 331:15, 336:22, 337:3, 337:7, 337:8, 337:15, 337:16, 337:20, 338:1, 344:4, 346:4, 347:12
seeing [14] - 48:12, 56:25, 150:4, 282:3, 285:13, 285:16, 285:17, 286:4, 286:16, 287:23, 288:18, 289:14, 305:19
seeking [1] - 73:18
seem [5] - 94:1, 106:20, 130:1, 319:4, 319:8
select [3] - 21:23, 44:1, 342:24
selected [1] - 308:13
selecting [2] - 20:24, 150:15
Selection [2] - 60:13, 132:14
selection [6] - 21:14, 46:6, 89:15, 134:3, 196:9, 236:18
self [3] - 162:12, 162:14
self-disintegrating [1] - 162:12
self-lubricating [2] - 162:12, 162:14
sell [2] - 124:18, 125:20
sense [2] - 306:10, 333:12
sensitive [1] - 115:25
sent [1] - 223:21
sentence [35] - 62:25, 64:11, 65:25, 83:14, 83:21, 89:5, 90:5, 92:11, 95:20, 101:4, 113:19, 113:20, 113:22, 114:18, 120:18, 152:10, 154:24, 162:6, 209:10, 214:25, 216:15, 226:3, 238:4, 315:14, 315:23, 316:16, 317:1, 317:11, 317:20, 323:20, 324:6, 324:12, 324:17, 337:17, 344:19
sentences [3] - 80:14, 120:5, 120:9
separate [4] - 35:3, 38:4, 123:1, 206:18
separating [1] - 248:7
separation [2] - 122:19, 248:9
sequence [1] - 332:22
sequences [1] - 198:11
series [4] - 44:25, 174:15, 205:23, 332:12
serve [11] - 23:3, 23:4, 85:25, 153:5, 155:24, 156:1, 156:4, 173:3, 180:5, 185:12
served [1] - 185:15
serves [1] - 90:11
serving [4] - 93:3, 106:19, 145:16, 146:13
session [1] - 2:14
set [11] - 80:3, 113:11, 117:9, 191:23, 265:10, 272:16, 286:10, 287:10, 293:16, 304:13
sets [4] - 35:3, 53:7, 268:3, 288:14
setting [1] - 278:23
seven [3] - 174:17, 174:20, 175:13
seventh [2] - 206:6, 206:21
Several [1] - 110:11
several [6] - 8:5, 28:11, 75:22, 134:4, 199:25, 258:22
Shah [12] - 7:4, 7:12, 7:14, 8:17, 8:24, 10:17, 22:4, 31:19, 32:11, 32:19, 33:13
shape [5] - 78:6, 189:13, 193:20, 195:25
shaped [1] - 220:7
sheets [1] - 163:15
shell [1] - 78:10
shooting [1] - 346:2
short [6] - 41:18, 42:3, 42:4, 72:25, 75:1, 122:20
show [39] - 24:8, 25:13, 26:24, 28:24, 30:6, 30:8, 30:17, 30:18, 31:6, 31:8, 32:3, 32:18, 35:15, 38:9, 43:15, 45:1, 48:25, 49:7, 54:15, 100:8, 115:24, 120:9, 182:15, 219:4, 225:15, 225:21, 239:6, 242:25, 270:14, 279:15, 282:24, 283:23, 289:12, 297:23, 327:5, 327:8, 327:16, 328:5, 343:10
showed [20] - 54:21, 112:3, 132:14, 141:19, 143:4, 156:25, 157:7, 160:18, 160:20, 167:13, 172:7, 172:13, 178:5, 208:23, 218:11, 221:15, 224:23, 226:14, 253:5, 270:19
showing [37] - 143:20, 190:1, 195:17, 218:16, 218:17, 260:13, 261:2, 264:23, 268:13, 271:2, 271:13, 272:12, 273:12, 276:16, 277:12, 277:23, 278:11, 279:4, 279:5, 281:25, 282:3, 285:1, 285:14, 287:23, 291:22, 291:23, 295:2, 295:19, 297:19, 298:23, 300:8, 300:18, 300:19, 305:17, 309:7, 330:14, 331:16
shown [36] - 74:10, 76:8, 94:23, 97:24, 100:10, 103:7, 117:3, 133:4, 178:16, 180:14, 180:19, 190:2, 190:6, 190:16, 190:19, 191:24, 193:4, 208:4, 211:2, 212:21, 253:2, 267:19, 267:21, 267:22, 269:2, 271:12, 272:6, 277:25, 282:15, 283:16, 283:20, 286:14, 287:9,

288:24, 294:13, 308:20
shows [14] - 11:15, 38:11, 38:12, 46:6, 46:7, 54:17, 100:9, 132:6, 187:7, 190:8, 268:15, 276:8, 281:21, 332:8
sic) [1] - 111:17
side [24] - 4:23, 22:8, 79:5, 79:21, 90:6, 94:16, 94:23, 97:3, 104:3, 135:19, 135:23, 187:25, 193:3, 202:12, 218:16, 219:4, 220:13, 273:4, 273:5, 283:23, 283:24, 295:17
side-by-side [2] - 202:12, 295:17
sides' [1] - 26:3
sieve [1] - 250:18
sieves [2] - 250:4, 250:7
sifting [1] - 103:17
sign [1] - 26:14
significance [3] - 271:16, 282:16, 300:22
significant [11] - 6:12, 30:24, 33:21, 43:24, 63:21, 113:24, 189:14, 215:17, 238:25, 239:5, 302:16
significantly [4] - 5:12, 6:22, 50:21, 197:16
silica [4] - 173:7, 173:18, 173:21, 175:14
silicon [7] - 160:2, 162:15, 174:24, 175:2, 175:6, 175:9, 175:15
silver [1] - 218:17
similar [6] - 200:10, 213:24, 226:14, 243:8, 304:23, 343:8
similarities [1] - 44:9
similarly [1] - 342:6
simple [6] - 19:24, 30:9, 129:23, 129:25, 130:4, 297:20
simply [9] - 14:19, 29:7, 48:9, 50:1, 128:25, 147:16, 147:20, 326:6, 344:16
simulations [1] - 11:4
single [3] - 18:10, 40:24, 180:5
sink [1] - 338:11
site [1] - 53:19
sitting [2] - 130:22, 330:12
situation [3] - 23:7, 122:19, 248:25
six [6] - 330:18, 330:21, 330:25, 331:3, 331:5, 331:7
sixth [2] - 206:6, 206:21
size [33] - 59:23, 166:7, 166:13, 168:3, 175:3, 189:11, 193:17, 193:19, 193:20, 205:7, 205:9, 205:12, 205:14, 219:6, 219:7, 219:11, 219:17, 219:21, 220:25, 221:1, 221:4, 221:7, 222:4, 222:12, 222:14, 222:16, 249:8, 249:19, 249:25, 250:23, 307:15
sized [1] - 104:2
skill [35] - 16:20, 19:12, 20:6, 20:15, 21:23, 29:8, 29:19, 30:1, 36:17, 38:14, 38:23, 41:21, 41:24, 44:18, 45:5, 45:15, 45:20, 45:23, 46:2, 55:18, 55:20, 56:1, 56:13, 74:23, 76:16, 176:17, 187:20, 188:1, 188:3, 229:21, 262:16, 310:23, 315:2, 315:9, 317:21
skilled [4] - 19:17, 20:2, 20:17, 29:23
skin [1] - 71:13
skipping [1] - 337:17
slide [34] - 4:22, 11:15, 17:7, 32:2, 76:8, 79:5, 79:21, 80:22, 103:2, 103:7, 103:13, 104:4, 109:8, 112:3, 112:10, 112:18, 112:24, 113:17, 113:20, 184:8, 195:12, 195:18, 200:23, 212:9, 212:12, 218:6, 218:10, 220:1, 220:13, 228:12, 257:10, 268:22, 285:9, 307:9
Slide [21] - 111:25, 113:17, 116:3, 184:21, 186:16, 187:22, 188:18, 189:19, 190:1, 192:23, 212:6, 218:5, 219:24, 224:19, 263:3, 272:10, 287:8, 287:9, 287:14, 307:20, 315:8
slides [6] - 3:12, 15:3, 184:3, 184:6, 257:7, 257:13
slightly [5] - 262:22, 278:3, 281:16, 317:17, 339:16
slow [2] - 141:12, 213:5
slowing [1] - 187:15
small [10] - 27:19, 43:18, 118:19, 120:22, 167:3, 188:9, 220:8, 220:10, 317:13, 317:23
smaller [7] - 167:7, 205:14, 221:5, 221:6, 222:11, 250:21, 319:13
smaller-size [1] - 205:14
smallest [2] - 220:6, 250:7
smooth [3] - 123:10, 123:19, 218:13
societies [1] - 185:11
Society [1] - 185:9
sodium [9] - 240:16, 241:5, 241:8, 242:6, 242:12, 243:20, 243:25, 244:3, 244:13
Sodium [1] - 98:17
solely [1] - 311:23
solid [22] - 16:5, 39:10, 71:9, 75:23, 78:5, 79:7, 79:8, 79:9, 79:11, 122:3, 146:19, 146:23, 185:21, 186:5, 231:16, 297:5, 297:6, 308:4, 308:25, 326:1, 326:14, 328:13
solid-state [2] - 75:23, 328:13
solids [1] - 122:2
solubility [11] - 19:14, 19:15, 19:16, 19:23, 20:1, 20:4, 20:8, 20:12, 41:9, 221:24
soluble [2] - 8:7, 154:25
solution [2] - 103:21, 212:19
solve [3] - 7:13, 21:20, 310:21
solvent [7] - 268:17, 295:22, 296:1, 331:17, 338:5, 338:6
solvents [2] - 273:5, 274:4
solving [2] - 6:25, 44:20
someone [1] - 317:16
sometimes [8] - 23:4, 32:5, 42:14, 45:10, 47:24, 247:7, 264:7, 310:1
somewhat [2] - 191:1, 193:6
somewhere [2] - 229:14, 330:11
soon [1] - 236:5
sophomore [1] - 308:13
Sorption [1] - 220:1
sorry [34] - 96:20, 100:25, 130:10, 141:14, 148:24, 149:10, 149:15, 149:24, 166:1, 171:22, 174:3, 174:6, 176:8, 177:5, 179:14, 194:10, 198:19, 221:25, 228:8, 229:13, 236:1, 241:16, 248:1, 249:21, 253:13, 266:1, 277:7, 290:13, 290:15, 293:6, 315:25, 323:1, 329:5, 342:11
sort [6] - 67:5, 193:16, 220:4, 277:5, 341:1, 342:9
sounds [1] - 336:10
source [2] - 107:16, 182:4
sources [1] - 171:19
space [3] - 120:23, 248:10, 248:19
spacer [3] - 248:16, 248:21, 249:4
spacers [2] - 172:3, 248:24
spaces [1] - 122:3
speaking [4] - 69:10, 107:1, 108:1, 190:5
special [2] - 59:17, 59:19
specializes [1] - 12:1
specific [28] - 44:13, 46:22, 47:1, 47:21, 49:17, 54:9, 56:8, 56:9, 62:9, 65:17, 116:7, 116:12, 123:24, 128:19, 128:20, 160:7, 167:9, 170:7, 170:8, 170:21, 171:17, 174:20, 176:15, 176:23, 203:20, 249:1, 330:2, 347:9
specifically [23] - 24:17, 43:21, 44:15, 44:24, 51:15, 51:18, 55:19, 55:22, 86:15, 87:19, 92:4, 95:8, 100:3, 105:12, 110:21, 155:5, 157:1, 157:15, 157:20, 165:13, 172:21, 212:10, 344:14
specification [24] - 14:11, 16:10, 16:14, 16:19, 18:4, 18:18, 36:16, 37:24, 38:9, 38:11, 82:12, 116:23, 158:12, 158:21, 159:18, 174:16, 203:15, 231:3, 261:20, 319:3, 326:5, 326:22, 330:10
specified [1] - 65:15
specify [1] - 231:2
spell [3] - 68:9, 183:15, 256:12
spend [5] - 3:16, 44:5, 52:8, 69:2, 212:4
spent [1] - 34:12
spherical [7] - 190:23, 190:24, 191:1, 191:2, 193:5, 193:20, 195:20
spherical-like [2] - 190:24, 193:20
spiking [1] - 285:13
Squib [1] - 287:4
stability [3] - 41:8,

41:9, 317:5
stable [6] - 7:16, 8:6, 9:8, 11:1, 16:19, 34:9
stage [12] - 141:21, 141:25, 142:11, 142:14, 142:18, 142:21, 228:15, 228:21, 228:23, 229:2, 229:4, 229:6
stand [7] - 42:23, 168:14, 256:10, 296:23, 328:9, 341:6, 343:16
standard [4] - 30:14, 38:22, 46:1, 285:23
standards [1] - 203:22
Starch [20] - 95:21, 97:6, 97:11, 97:12, 97:20, 98:2, 119:16, 119:19, 120:11, 160:13, 160:21, 161:2, 161:17, 162:2, 162:4, 162:5, 162:19, 162:23, 163:3, 226:3
starch [313] - 24:5, 24:6, 24:7, 24:17, 24:22, 25:11, 25:14, 25:17, 25:20, 26:9, 26:12, 26:19, 26:22, 26:25, 27:1, 47:8, 47:11, 47:14, 48:11, 48:12, 48:16, 48:17, 48:23, 49:1, 49:8, 59:15, 59:16, 59:21, 61:18, 61:22, 62:5, 62:22, 63:1, 63:2, 64:1, 64:2, 64:5, 64:9, 64:13, 64:21, 64:25, 65:18, 65:23, 66:1, 66:9, 66:13, 66:15, 66:16, 86:4, 86:7, 86:10, 86:13, 86:18, 87:13, 90:3, 90:7, 90:11, 90:21, 91:7, 92:1, 92:13, 92:18, 92:25, 93:3, 93:25, 94:20, 95:8, 95:9, 95:25, 96:3, 96:6, 97:4, 97:13, 97:14, 97:15, 97:16, 97:17, 97:19, 97:20, 97:22, 98:2, 98:10, 99:6, 99:9, 99:10, 99:13, 99:14, 99:21, 99:22, 100:4, 100:11, 100:13, 100:16, 100:19, 100:21, 101:1, 101:2, 101:5, 101:19, 102:2, 102:9, 102:10, 104:5, 104:12, 104:19, 104:22, 104:24, 105:4, 105:19, 105:20, 106:7, 106:12, 106:15, 106:18, 108:3, 108:5, 108:8, 108:23, 109:19, 111:20, 112:6, 113:6, 114:4, 114:6, 114:20, 115:8, 115:22, 116:2, 117:18, 118:8, 118:13, 119:2, 119:6, 121:2, 121:5, 122:7, 122:11, 122:22, 122:25, 123:12, 123:18, 123:19, 127:15, 134:8, 134:12, 134:15, 134:16, 134:19, 134:20, 136:3, 136:4, 137:24, 137:25, 138:5, 138:13, 138:14, 138:19, 141:3, 141:7, 141:20, 143:2, 143:8, 143:20, 144:5, 144:21, 155:7, 155:23, 156:1, 156:4, 156:17, 156:21, 157:2, 157:8, 157:15, 157:20, 158:15, 159:1, 159:11, 159:23, 160:6, 160:10, 160:12, 161:2, 161:23, 164:2, 164:23, 165:23, 166:3, 167:2, 167:9, 169:24, 170:12, 170:25, 172:19, 172:21, 175:18, 175:22, 178:11, 179:20, 180:9, 182:10, 187:3, 187:5, 187:9, 201:17, 201:19, 201:25, 202:14, 202:15, 203:16, 203:18, 203:19, 203:20, 203:25, 204:1, 205:18, 206:3, 206:9, 206:10, 206:14, 206:17, 206:18, 206:19, 206:24, 206:25, 207:4, 207:7, 207:8, 207:11, 207:12, 207:17, 207:21, 208:2, 208:6, 208:8, 210:2, 210:17, 210:20, 211:6, 211:22, 213:15, 214:16, 215:1, 215:19, 216:18, 216:21, 217:4, 219:6, 225:17, 225:24, 225:25, 226:10, 226:13, 226:14, 226:18, 226:19, 226:25, 227:10, 227:23, 228:5, 233:9, 233:10, 233:13, 234:19, 234:21, 234:25, 236:8, 236:11, 236:18, 236:20, 236:22, 237:18, 237:22, 238:2, 238:7, 238:19, 239:8, 239:10, 239:14, 240:12, 241:12, 241:13, 241:17, 242:1, 244:7, 244:17, 246:3, 246:5, 246:6, 246:7, 246:11, 246:12, 247:4, 248:16, 248:18, 249:3, 253:7, 253:24, 254:2, 254:12, 254:16
starch's [1] - 156:17
starch-based [1] - 226:10
starched [1] - 66:1
starches [12] - 101:9, 122:11, 155:6, 155:10, 155:15, 156:9, 182:20, 203:21, 204:2, 204:3, 207:5, 226:12
start [15] - 3:21, 4:21, 11:7, 12:21, 35:5, 35:22, 186:21, 190:11, 190:19, 193:13, 196:7, 257:14, 263:5, 292:17, 318:5
started [1] - 2:25
starter [1] - 107:4
starting [28] - 52:13, 65:6, 100:4, 103:18, 117:25, 221:6, 261:5, 265:4, 268:16, 273:9, 300:10, 300:12, 300:19, 300:21, 300:23, 300:24, 301:4, 302:6, 303:17, 304:10, 304:12, 306:7, 306:17, 307:16, 318:11, 332:9, 332:17, 332:20
starts [7] - 65:22, 79:8, 103:16, 152:20, 227:5, 254:6, 303:7
state [15] - 14:20, 59:4, 68:9, 75:23, 83:23, 178:12, 183:15, 197:13, 228:18, 237:4, 256:12, 326:1, 326:14, 328:13, 330:6
statement [58] - 2:25, 3:3, 60:19, 61:6, 61:17, 61:20, 61:21, 62:1, 62:7, 63:7, 63:8, 65:19, 66:7, 66:8, 73:8, 73:15, 75:3, 75:8, 80:25, 87:10, 89:12, 90:15, 92:15, 92:17, 92:24, 101:8, 101:13, 106:20, 112:1, 114:23, 115:2, 125:12, 143:16, 144:4, 151:1, 226:2, 226:9, 227:19, 227:22, 227:23, 232:21, 235:18, 237:1, 238:6, 238:10, 239:9, 239:12, 242:15, 242:20, 249:19, 326:18, 327:21, 338:9, 340:14, 343:2
statements [23] - 3:10, 25:3, 25:4, 87:3, 87:12, 92:21, 93:7, 94:1, 101:18, 106:16, 108:2, 108:11, 146:17, 178:12, 178:13, 182:19, 207:16, 216:11, 226:15, 251:4, 339:9, 339:11, 339:25
States [4] - 124:19, 125:21, 126:16, 203:16
STATES [1] - 1:1
states [17] - 61:5, 63:4, 65:2, 86:21, 133:14, 145:3, 146:1, 199:23, 209:10, 233:10, 237:24, 240:14, 241:4, 243:6, 316:17, 329:21, 342:17
static [3] - 118:3, 223:6
stating [1] - 199:4
statutory [2] - 13:20, 345:18
stay [1] - 219:13
stearate [5] - 145:1, 145:4, 145:8, 145:11, 145:16
Steed [7] - 341:20, 341:22, 342:7, 342:12, 342:15, 344:9, 344:10
Steed's [1] - 342:3
stenographic [1] - 347:17
step [36] - 55:15, 83:25, 86:16, 93:16, 101:23, 104:6, 104:11, 104:16, 104:17, 104:23, 104:24, 146:16, 183:2, 183:3, 229:10, 255:5, 268:15, 271:25, 273:7, 292:12, 295:20, 295:22, 296:17, 296:18, 297:21, 298:18, 298:25, 321:9, 331:2, 331:15, 331:25, 341:8
Step [15] - 273:22, 273:23, 274:6, 274:9, 274:10, 274:12, 274:14, 274:15, 274:17, 274:20, 274:22, 275:1, 275:4, 275:11, 296:16
step-by-step [2] - 268:15, 271:25
stepping [1] - 110:18
steps [12] - 53:11, 86:22, 103:10, 104:14, 272:14, 273:25, 295:9, 296:25, 332:24, 333:2

stepwise [1] - 268:5
stick [4] - 122:20, 123:9, 193:12, 221:8
sticking [2] - 170:7, 223:7
still [9] - 45:3, 48:8, 107:23, 123:17, 137:18, 161:21, 194:3, 295:13, 300:1
stipulated [2] - 13:10, 57:15
stoichiometry [1] - 274:5
stop [1] - 16:11
strach [1] - 65:22
straightforward [1] - 307:13
strategies [1] - 44:21
STRAWN [1] - 2:4
Street [1] - 1:10
strength [5] - 80:5, 85:21, 108:11, 201:15, 224:12
strike [4] - 221:25, 228:9, 243:22, 334:4
stronger [1] - 317:17
structural [2] - 17:2, 45:21
structure [17] - 16:6, 17:12, 40:1, 40:18, 41:18, 41:19, 50:10, 52:9, 77:21, 119:6, 261:3, 268:2, 269:3, 303:9, 303:10, 305:18, 310:15
structures [3] - 39:25, 41:5, 41:6
students [1] - 308:14
studies [5] - 39:12, 63:14, 144:20, 214:2, 223:19
Study [10] - 144:19, 212:14, 213:1, 213:3, 213:9, 213:10, 213:18, 213:20, 243:11, 252:7
study [14] - 115:13, 115:14, 115:16, 115:17, 185:16, 214:23, 216:9, 240:2, 240:20, 240:23, 241:1, 283:17, 305:3
subject [3] - 71:6, 77:8, 186:14
subjects [1] - 71:21
submicroscopic [1] - 175:3
submission [9] - 62:11, 85:9, 87:3, 87:10, 87:18, 99:22, 108:2, 169:13, 201:5
submissions [4] - 74:11, 108:12, 338:20, 338:21
submitted [20] - 9:4, 11:9, 24:10, 24:24, 31:23, 61:1, 73:17, 168:24, 201:12, 202:11, 235:13, 272:3, 280:17, 336:14, 336:15, 336:21, 338:24, 339:2, 339:5, 339:14
submitting [1] - 125:5
subsidiary [1] - 119:23
substance [27] - 23:22, 37:10, 47:7, 60:17, 60:22, 61:4, 69:7, 71:2, 76:24, 83:16, 88:6, 88:7, 92:3, 93:4, 110:24, 111:24, 120:17, 132:18, 132:21, 208:20, 230:17, 231:24, 265:2, 308:25, 337:5, 337:12
Substance [1] - 88:2
substances [6] - 55:23, 188:7, 195:3, 315:19, 316:5, 317:3
substantial [1] - 91:5
substantially [5] - 269:14, 323:9, 323:11, 324:2, 324:13
substrate [1] - 123:18
succeeding [1] - 45:24
success [5] - 33:19, 33:20, 33:21, 33:23, 41:23
successful [1] - 311:2
successfully [1] - 173:22
sufficient [3] - 39:17, 110:6, 118:13
suggest [11] - 15:3, 19:11, 25:1, 25:6, 25:10, 25:16, 32:24, 48:23, 204:14, 222:20, 226:18
suggested [7] - 51:24, 94:25, 95:5, 95:9, 173:10, 216:1, 233:8
suitable [3] - 45:6, 46:4, 192:7
suite [1] - 8:10
suited [1] - 9:1
sum [1] - 287:14
summarize [1] - 266:11
summarizes [1] - 235:10
summarizing [2] - 103:2, 200:2
summary [6] - 42:2, 65:13, 72:13, 294:10, 304:24, 305:1
super [2] - 244:3, 244:5
supplement [2] - 201:3, 208:15
supply [2] - 74:13, 126:1
support [19] - 14:10, 39:17, 87:12, 94:1, 101:18, 107:7, 108:3, 108:14, 109:9, 162:24, 182:9, 187:12, 198:5, 235:3, 286:10, 318:19, 330:21, 335:7, 345:18
supported [1] - 87:5
supporting [1] - 182:19
supports [8] - 16:10, 98:10, 105:3, 106:11, 107:24, 109:23, 121:4, 228:16
supposed [4] - 17:15, 17:16, 193:4, 344:13
surface [21] - 118:23, 119:9, 123:9, 123:16, 123:19, 166:23, 170:1, 200:16, 218:12, 218:13, 218:18, 218:19, 219:10, 220:10, 221:9, 223:15, 223:21, 224:10, 224:16
surfaces [6] - 120:24, 200:17, 200:18, 200:20, 218:6, 249:2
surprisingly [1] - 302:5
surviving [1] - 12:11
suspect [1] - 15:3
suspended [3] - 296:22, 297:7, 298:14
sustain [1] - 322:25
sustained [1] - 177:13
swapped [1] - 136:3
Swarbrick [17] - 82:25, 84:9, 106:4, 165:18, 172:6, 172:7, 172:17, 173:8, 173:17, 173:18, 173:21, 174:9, 200:10, 232:8, 232:12, 232:21, 232:25
Swarbrick's [1] - 232:5
Swarbrick/Boylan [1] - 94:6
sweeteners [1] - 229:8
switch [2] - 67:10, 299:20
sworn [6] - 24:24, 31:23, 68:14, 144:15, 183:20, 256:17
symbol [1] - 305:20
synonymous [1] - 78:17
synthesis [11] - 53:12, 55:11, 261:6, 267:20, 295:20, 300:10, 300:20, 300:24, 300:25, 318:9, 331:7
synthesize [1] - 267:13
synthesized [2] - 272:7, 277:14
synthesizing [6] - 29:21, 188:9, 268:8, 271:25, 317:12, 317:22
synthetic [15] - 10:5, 75:25, 268:14, 268:20, 271:24, 272:5, 272:16, 273:12, 295:9, 321:14, 321:25, 330:24, 332:11, 332:14, 332:22
Synthetic [1] - 337:4
synthetically [1] - 268:6
system [4] - 190:10, 193:16, 196:6, 331:17
systems [2] - 48:3, 204:24

T

Tab [33] - 60:5, 72:10, 72:21, 73:7, 75:4, 77:10, 81:1, 82:15, 83:3, 84:4, 85:4, 87:15, 94:4, 96:8, 98:13, 99:17, 102:12, 105:7, 112:16, 119:12, 124:25, 125:13, 125:22, 179:6, 230:21, 231:15, 232:11, 236:2, 244:22, 249:12, 322:12, 325:12, 336:18
tab [2] - 235:25, 237:10
table [73] - 25:13, 54:1, 60:16, 60:19, 61:8, 61:13, 61:24, 62:11, 87:24, 88:1, 88:4, 88:5, 88:12, 89:6, 89:20, 89:23, 90:2, 91:10, 91:12, 91:15, 91:25, 94:16, 94:24, 95:12, 97:9, 98:6, 100:8, 100:9, 105:19, 131:11, 133:10, 137:6, 137:15, 143:1, 144:24, 145:1, 145:22, 148:22, 149:12, 160:22, 161:3, 180:14, 180:19, 180:22, 181:7, 181:20, 182:12, 194:23, 201:18, 202:6, 202:8, 207:24, 207:25, 208:19, 209:10, 214:7, 226:25, 233:2, 233:5, 233:10, 241:15, 241:16, 249:25, 250:20, 277:11, 279:20, 283:21, 283:23, 286:21, 288:12, 291:24, 305:14
Table [36] - 47:6, 94:12, 94:14, 95:14, 95:17, 96:19, 96:25, 97:24, 105:15, 130:25, 131:2, 131:11, 149:1, 149:2, 149:4, 149:5, 172:11, 174:14, 174:24, 175:6, 194:22, 233:8, 277:8, 278:1, 279:17, 281:23, 282:10, 282:15, 282:21, 282:24,

284:8, 284:10, 291:4, 291:20, 292:24, 307:1
tables [5] - 91:19, 98:8, 161:2, 174:15, 283:4
tablet [57] - 10:21, 23:8, 23:12, 23:17, 24:2, 48:5, 49:20, 50:11, 55:16, 56:6, 56:17, 66:3, 77:24, 78:3, 78:4, 78:5, 78:6, 79:17, 79:19, 80:2, 81:10, 84:22, 85:21, 101:6, 104:8, 105:21, 110:17, 145:5, 149:13, 153:6, 153:9, 173:4, 174:17, 175:10, 189:4, 192:8, 194:23, 194:25, 195:2, 196:18, 198:7, 201:22, 206:11, 207:1, 207:2, 207:21, 211:15, 212:20, 214:23, 226:5, 228:21, 232:18, 233:19, 233:23, 243:17
Tablets [2] - 85:8, 113:3
tablets [38] - 10:15, 10:24, 51:6, 62:15, 63:23, 71:10, 73:20, 79:20, 80:1, 80:3, 96:13, 102:19, 103:12, 104:8, 114:1, 115:15, 115:20, 125:4, 126:6, 151:15, 155:24, 164:14, 169:6, 185:22, 195:5, 201:5, 201:12, 201:13, 202:10, 204:23, 204:25, 205:1, 212:15, 214:21, 241:2, 243:7, 243:13
talc [1] - 51:16
Talc [3] - 172:24, 173:1, 173:3
talks [2] - 55:22, 205:24
tapped [12] - 131:6, 132:25, 136:8, 136:13, 136:15, 139:7, 139:10, 139:20, 140:5, 140:18, 181:21, 211:18
targeted [1] - 4:2
Tate [2] - 33:18, 33:20
taught [6] - 29:3, 29:4, 29:5, 29:19, 308:6, 308:9
teach [4] - 71:21, 266:23, 303:12, 307:3
teacher [1] - 258:22
teaches [5] - 27:6, 266:5, 310:13, 321:3, 321:25
teaching [3] - 71:17, 309:1, 309:25
teachings [3] - 29:25, 264:11, 306:6
team [4] - 7:7, 32:17, 75:24, 188:8
technical [19] - 47:12, 47:16, 161:17, 162:19, 162:24, 163:6, 163:15, 178:17, 178:22, 186:22, 188:19, 200:22, 203:10, 262:4, 263:5, 263:6, 338:6, 338:10
technically [1] - 302:17
technique [8] - 55:7, 55:9, 193:1, 222:7, 308:8, 309:2, 310:3, 311:2
techniques [12] - 56:14, 192:12, 192:19, 194:5, 263:22, 269:25, 308:15, 310:25, 327:4, 327:8, 327:16, 328:5
Technologies [2] - 271:14, 337:13
Technology [3] - 83:1, 84:9, 232:6
technology [4] - 70:14, 71:23, 76:20, 199:15
teeth [1] - 338:11
telltale [1] - 26:14
temperature [1] - 274:4
temperatures [2] - 273:6, 295:24
ten [2] - 58:24, 346:15
tense [2] - 236:15, 236:16
term [21] - 16:5, 23:20, 25:14, 46:17, 70:22, 70:25, 74:1, 78:23, 82:3, 82:12, 86:5, 86:10, 88:21, 124:8, 185:13, 269:14, 304:23, 313:18, 323:21, 324:2, 333:9
terminal [3] - 86:22, 104:13, 320:16
terminology [1] - 88:10
terms [9] - 41:12, 69:15, 78:17, 122:22, 152:14, 248:25, 315:22, 321:20, 338:20
tert [1] - 295:23
tert-butyl [1] - 295:23
test [39] - 52:22, 54:5, 54:25, 65:15, 225:16, 225:18, 241:23, 244:16, 266:8, 269:23, 276:19, 277:23, 277:25, 278:2, 278:12, 278:15, 278:17, 278:21, 278:23, 279:10, 279:11, 282:17, 284:13, 285:6, 285:18, 287:14, 287:16, 290:3, 290:7, 290:20, 290:24, 291:3, 303:15, 305:9, 305:10, 305:11, 306:12, 306:14, 306:15
tested [14] - 185:20, 233:15, 239:18, 270:19, 276:14, 282:6, 282:14, 282:25, 283:3, 284:10, 284:13, 284:22, 290:21, 305:7
testified [28] - 29:16, 68:15, 86:17, 87:17, 102:23, 106:4, 144:2, 183:21, 191:21, 221:11, 233:12, 235:15, 246:14, 247:3, 256:18, 313:11, 313:18, 314:2, 315:5, 316:22, 322:24, 328:15, 328:18, 329:10, 332:5, 334:20, 334:23, 336:7
testify [11] - 7:5, 10:17, 11:6, 20:19, 23:22, 31:19, 57:23, 69:22, 93:24, 108:19, 323:8
testifying [5] - 178:21, 183:2, 186:20, 341:4, 344:10
testimony [43] - 7:11, 23:24, 32:16, 48:15, 58:1, 58:3, 58:8, 58:11, 59:1, 69:18, 74:2, 84:24, 86:9, 93:21, 102:20, 107:13, 109:21, 124:9, 129:5, 144:15, 178:10, 178:12, 184:4, 185:24, 186:13, 191:13, 216:25, 221:13, 224:20, 228:14, 229:15, 247:23, 249:7, 251:17, 257:8, 258:24, 259:17, 260:16, 323:18, 325:23, 326:20, 327:20, 328:8
testing [42] - 4:14, 8:20, 31:5, 46:1, 48:14, 49:6, 49:7, 53:17, 53:18, 54:8, 54:9, 54:10, 54:12, 54:13, 54:24, 63:10, 65:14, 97:18, 108:7, 108:14, 108:15, 182:13, 187:7, 208:23, 208:25, 215:5, 215:8, 225:21, 234:20, 238:13, 239:25, 277:4, 280:16, 280:23, 283:23, 283:24, 287:5, 287:15, 289:23, 293:8
tests [10] - 52:20, 52:21, 54:4, 66:12, 130:9, 130:14, 238:15, 244:19, 266:7, 289:25
Texas [4] - 70:6, 70:9, 71:19
text [6] - 48:2, 49:21, 56:11, 194:19, 205:22, 215:10
textbook [8] - 161:1, 187:12, 207:16, 207:24, 225:2, 308:14, 308:15, 308:23
textbooks [2] - 151:6, 258:11
TFF [2] - 70:8, 71:12
THE [119] - 1:1, 1:2, 1:14, 2:15, 2:22, 3:9, 3:14, 3:22, 13:22, 34:20, 34:24, 57:2, 57:6, 58:6, 58:14, 59:2, 61:15, 61:23, 63:20, 66:19, 66:24, 67:2, 67:5, 67:12, 67:17, 67:22, 68:2, 68:11, 68:17, 72:19, 96:20, 125:15, 126:21, 127:3, 127:7, 127:13, 127:19, 127:22, 128:2, 128:5, 128:10, 128:12, 141:12, 141:15, 168:7, 168:13, 168:17, 168:25, 174:3, 174:6, 177:5, 177:8, 177:11, 177:20, 178:2, 179:15, 183:1, 183:5, 183:6, 183:9, 183:12, 183:17, 183:22, 186:7, 229:13, 229:18, 229:20, 229:22, 229:25, 230:2, 230:4, 251:7, 252:2, 252:8, 255:4, 255:6, 255:7, 255:12, 255:16, 255:19, 255:22, 256:5, 256:11, 256:14, 256:25, 257:2, 257:3, 259:8, 274:23, 290:8, 290:12, 290:14, 290:16, 311:6, 311:9, 311:12, 319:25, 320:8, 322:21, 323:4, 328:9, 340:17, 340:20, 340:22, 340:23, 341:7, 341:15, 342:3, 342:11, 342:14, 343:11, 343:17, 344:4, 344:10, 344:25, 345:10, 346:1, 347:5, 347:11
the.. [1] - 298:7
themselves [6] - 37:1, 56:24, 110:14, 120:24, 122:5, 295:4
theories [2] - 346:24, 347:1

theory [1] - 322:15
therapeutic [2] - 11:21, 76:25
therapies [1] - 4:2
therapy [1] - 11:13
thereby [3] - 118:24, 118:25, 122:14
therefore [3] - 107:18, 114:8, 283:21
thereof [2] - 17:14, 43:9
thermogravimetric [1] - 38:19
they've [3] - 193:6, 213:21, 346:23
THF [2] - 331:16, 332:1
thinking [6] - 37:8, 301:21, 325:25, 326:13, 343:17, 343:20
third [14] - 27:10, 30:4, 47:18, 111:19, 116:4, 122:1, 162:6, 169:21, 173:15, 204:5, 205:4, 265:14, 284:21, 321:12
thoughts [1] - 326:21
threatened [1] - 6:12
three [52] - 11:17, 17:10, 17:11, 27:6, 28:12, 31:9, 31:14, 31:15, 43:12, 53:20, 53:22, 58:11, 64:7, 100:11, 100:18, 149:18, 188:5, 196:16, 197:15, 214:10, 232:15, 238:15, 238:18, 239:1, 271:1, 276:6, 276:15, 276:16, 277:13, 278:2, 279:23, 280:19, 282:13, 283:2, 283:4, 285:3, 285:18, 286:15, 287:11, 287:14, 287:15, 287:16, 287:21, 289:13, 291:9, 312:1, 312:4, 315:17, 316:3, 335:7, 335:13
thresholds [2] - 265:10, 301:22
throughout [7] - 43:11, 44:10, 52:15, 53:5, 53:22, 211:14, 261:19
thyroid [1] - 11:19
tight [2] - 265:5, 265:8
time-wise [2] - 42:12, 46:9
timing [1] - 15:5
title [15] - 59:9, 91:10, 91:12, 96:25, 100:12, 105:8, 113:1, 119:25, 151:14, 179:17, 206:6, 206:21, 220:1, 267:9, 285:9
titled [9] - 65:6, 85:12, 88:1, 98:16, 99:20, 105:15, 105:18, 120:3, 218:6
TM-1231 [2] - 278:16, 278:22
today [34] - 7:5, 11:10, 12:9, 36:8, 37:18, 40:7, 40:16, 42:14, 74:2, 80:17, 86:9, 107:13, 112:14, 129:5, 130:22, 135:6, 135:7, 144:12, 184:4, 186:20, 224:23, 257:8, 259:17, 260:16, 261:19, 262:3, 266:7, 311:22, 312:17, 319:2, 321:17, 330:12, 336:8, 344:7
together [9] - 3:24, 122:20, 191:8, 193:12, 213:21, 224:13, 224:17, 246:18, 285:16
tomorrow [9] - 177:10, 340:24, 341:4, 341:10, 344:10, 344:12, 346:6, 346:9, 347:12
Tong [1] - 45:11
TONG [1] - 45:11
Tong's [1] - 45:11
tonight [6] - 340:21, 341:10, 344:9, 344:13, 345:25, 347:8
took [10] - 5:19, 11:2, 11:6, 15:2, 32:22, 144:9, 144:12, 296:21, 297:6, 298:13
tool [1] - 325:22
tools [1] - 79:19
top [16] - 100:23, 103:13, 130:24, 132:17, 168:25, 169:13, 172:11, 194:22, 203:13, 212:21, 214:17, 276:24, 277:11, 277:13, 289:5, 291:24
topic [2] - 270:13, 270:17
topicals [1] - 71:13
topics [1] - 210:15
total [2] - 214:20, 214:23
totality [2] - 107:23, 107:25
totally [1] - 228:1
totum [1] - 345:23
toward [3] - 84:17, 105:19, 245:5
towards [3] - 45:8, 45:21, 277:11
toxic [4] - 45:19, 53:2, 55:23, 265:19
toxicities [1] - 306:21
toxicity [3] - 304:9, 304:10, 304:15
toxicological [2] - 304:3, 304:7
toxins [1] - 56:1
tracks [1] - 342:6
tradeoffs [1] - 10:8
traditional [2] - 204:24, 204:25
train [1] - 308:14
trained [1] - 324:15
transcript [3] - 139:14, 143:23, 347:17
transfer [2] - 189:2
transferred [1] - 223:8
translate [1] - 79:24
treat [5] - 4:2, 11:14, 11:17, 34:10, 43:20
treated [1] - 298:4
treating [4] - 13:6, 17:23, 18:15, 34:8
treatment [2] - 7:1, 12:1
Trial [4] - 1:6, 1:13, 252:16, 252:17
trial [17] - 3:19, 4:5, 10:8, 12:2, 13:11, 13:12, 20:21, 29:16, 33:24, 35:13, 35:14, 214:11, 307:7, 307:17, 337:14
trials [15] - 3:16, 5:15, 5:16, 11:23, 61:25, 144:4, 213:14, 214:8, 214:13, 214:15, 215:12, 215:14, 215:23, 216:14, 252:13
tried [6] - 15:25, 48:25, 103:8, 209:19, 302:17
Triozzi [1] - 347:19
triple [1] - 285:16
triple-check [1] - 285:16
Tris [1] - 98:17
Trout [7] - 16:1, 16:3, 16:9, 16:18, 19:21, 20:4, 20:9
true [15] - 12:5, 37:19, 40:23, 61:16, 61:21, 63:7, 63:8, 66:7, 133:20, 226:9, 226:12, 228:22, 243:18, 254:23, 347:16
trust [2] - 158:4, 161:15
truth [1] - 144:10
truthful [1] - 61:13
truthfully [2] - 62:18, 102:24
try [10] - 3:15, 7:22, 24:25, 174:1, 187:15, 209:14, 213:6, 257:3, 311:18, 346:2
trying [10] - 14:25, 54:11, 171:22, 219:4, 297:4, 297:23, 322:18, 322:23, 325:17, 340:20
tumble [1] - 191:3
tumors [1] - 5:6
TUNNELL [1] - 1:17
turn [61] - 72:10, 72:21, 73:2, 73:7, 75:3, 80:7, 80:19, 82:15, 82:16, 83:3, 83:10, 84:13, 85:4, 87:21, 89:17, 91:9, 92:6, 94:3, 94:9, 95:19, 96:8, 96:17, 98:24, 100:5, 100:22, 101:3, 102:16, 104:18, 105:6, 105:13, 110:2, 112:16, 115:9, 120:2, 123:21, 124:24, 125:11, 125:22, 148:14, 178:24, 179:5, 231:14, 231:19, 232:13, 232:24, 235:20, 249:15, 257:25, 266:21, 267:16, 284:20, 288:10, 291:20, 313:2, 320:12, 325:11, 326:10, 327:13, 329:7, 336:25, 339:19
turned [2] - 278:2, 305:7
turning [5] - 118:16, 120:18, 121:24, 122:16, 123:6
turns [2] - 3:14, 341:9
turret [1] - 79:19
twice [3] - 219:11, 324:6, 324:14
two [65] - 2:25, 7:3, 9:23, 12:19, 13:14, 16:14, 16:16, 17:17, 19:11, 22:16, 32:5, 32:20, 33:6, 35:2, 35:6, 35:23, 35:25, 36:1, 39:10, 41:1, 42:3, 46:13, 46:14, 54:22, 77:11, 80:14, 88:5, 98:8, 106:1, 120:5, 120:9, 129:18, 137:19, 163:9, 163:11, 190:3, 190:16, 190:18, 207:9, 219:13, 239:25, 242:4, 242:10, 251:23, 272:23, 273:2, 273:6, 273:12, 273:13, 273:25, 275:3, 277:20, 278:13, 282:14, 282:17, 283:3, 286:7, 286:8, 288:14, 298:16, 298:17, 312:8, 320:23, 325:25, 326:12
type [33] - 11:18, 11:19, 13:17, 17:4, 17:16, 17:19, 17:25, 22:10, 23:2, 42:9, 42:10, 42:15, 46:7, 49:17, 52:17, 70:17, 107:1, 134:20, 196:21, 197:4, 198:20, 213:14, 247:6, 270:2, 324:21, 341:24, 344:17, 344:22, 345:5, 345:16, 345:20, 345:23, 346:11
types [17] - 6:21, 11:17, 35:23, 35:25,

71:7, 91:19, 93:19, 96:4, 100:11, 100:16, 155:14, 155:17, 194:11, 203:21, 203:23, 229:3, 229:5
typical [2] - 105:23, 246:8
typically [12] - 26:13, 78:15, 80:13, 84:2, 86:20, 104:16, 110:23, 142:3, 189:10, 190:12, 194:12, 205:13
typo [3] - 19:6, 251:13, 252:7
tyrosine [4] - 4:25, 5:8, 5:11, 52:1
Tyrosine [1] - 5:1

U

U.S [11] - 33:8, 72:5, 72:23, 98:16, 119:23, 157:2, 259:21, 266:18, 318:22, 319:22, 347:20
U.S.C [1] - 73:18
U.S.D.C.J [1] - 1:14
ubiquitous [2] - 308:8, 310:2
ultimate [2] - 10:12, 314:10
ultimately [11] - 8:8, 28:4, 71:5, 71:6, 77:7, 80:5, 104:8, 107:5, 133:23, 215:21, 299:11
unacceptably [1] - 31:24
Uncontested [2] - 125:13, 125:17
uncontested [11] - 73:8, 73:16, 75:4, 75:8, 81:1, 81:3, 81:18, 81:21, 81:23, 125:12, 126:4
under [41] - 7:20, 13:20, 16:10, 17:16, 45:6, 60:16, 68:14, 73:17, 76:16, 83:14, 92:11, 114:18, 120:5, 133:5, 169:5, 183:20, 237:3, 256:17, 277:11, 280:8, 280:18, 282:10, 282:25, 283:7, 283:24, 283:25, 284:5, 284:14, 284:17, 284:21, 285:5, 286:20, 287:16, 290:21, 305:9, 305:20, 307:15, 307:16, 317:15, 341:23
undergo [1] - 307:8
undergraduate [1] - 70:4
underlying [2] - 54:24, 54:25
underneath [1] - 215:10
understood [4] - 3:12, 200:2, 229:16, 344:2
undertake [1] - 234:20
undertook [1] - 5:12
undisputed [1] - 81:20
unexpected [6] - 9:3, 9:4, 22:3, 33:13, 33:15, 345:15
unexpectedly [1] - 6:15
uniform [3] - 79:12, 118:12, 193:19
uniformity [2] - 79:25, 145:5
uniformly [2] - 23:16, 79:16
unique [4] - 8:22, 20:11, 288:17
Unit [1] - 105:15
United [4] - 124:19, 125:21, 126:16, 203:16
UNITED [1] - 1:1
universe [3] - 40:6, 40:9, 45:4
University [6] - 11:25, 70:5, 71:18, 184:24, 258:6, 258:9
unjustified [2] - 42:12, 46:8
unknown [1] - 168:2
unless [1] - 340:17
unless.. [1] - 246:9
unlikely [2] - 91:8, 221:5
unmet [1] - 33:18
unmodified [18] - 134:20, 138:5, 156:17, 156:22, 204:3, 206:17, 206:19, 206:24, 206:25, 207:4, 207:5, 207:7, 207:11, 226:12, 226:14, 246:5, 246:7, 246:12
unpredictable [2] - 8:1, 21:14
unreliable [1] - 107:18
unstable [2] - 6:2, 6:14
untruthful [1] - 339:17
unusually [1] - 265:19
unverified [1] - 140:18
unwanted [1] - 5:8
up [122] - 4:23, 15:7, 15:11, 17:7, 23:8, 34:23, 35:15, 36:8, 40:15, 41:18, 50:21, 51:24, 53:14, 54:21, 56:20, 58:13, 64:20, 73:9, 77:4, 78:22, 96:24, 104:10, 106:1, 107:5, 111:25, 122:5, 122:12, 130:7, 132:10, 134:22, 135:9, 140:10, 141:11, 142:23, 142:25, 148:18, 149:9, 149:10, 151:9, 157:5, 160:15, 163:13, 165:4, 168:19, 169:13, 169:19, 170:22, 172:6, 174:2, 174:4, 174:13, 180:15, 184:12, 193:19, 194:15, 196:2, 196:12, 197:22, 199:11, 200:25, 202:3, 203:5, 205:20, 208:17, 210:5, 210:9, 210:23, 212:19, 212:20, 214:5, 221:18, 225:7, 226:22, 228:5, 228:10, 230:20, 232:14, 233:16, 235:6, 240:24, 244:22, 247:9, 248:19, 251:14, 251:15, 252:11, 252:24, 254:5, 256:9, 257:17, 259:11, 259:21, 264:14, 264:21, 267:2, 267:8, 268:11, 271:5, 276:18, 278:18, 280:24, 282:10, 284:23, 287:14, 288:5, 291:15, 295:16, 296:13, 296:22, 300:25, 301:15, 304:24, 308:10, 309:4, 311:7, 311:18, 313:1, 318:21, 323:14, 338:8, 344:7, 346:10
upper [4] - 38:17, 96:22, 96:23, 300:17
useful [2] - 151:15, 296:7
uses [7] - 30:24, 205:25, 226:18, 323:11, 323:13, 324:13, 343:6
USP [17] - 97:18, 130:9, 130:14, 131:3, 131:11, 133:10, 133:12, 137:5, 137:9, 137:13, 137:15, 191:23, 191:25, 203:21, 203:24, 204:1, 209:3
usual [3] - 97:1, 97:25, 98:3
utilizing [1] - 110:21
utter [1] - 29:25
UV-1 [1] - 286:9

V

vacuum [1] - 20:8
valid [1] - 35:19
validate [2] - 225:20, 285:10
validated [1] - 285:20
validation [5] - 65:7, 65:13, 99:21, 99:24, 225:10
Validation [1] - 285:10
validity [8] - 13:12, 22:17, 27:5, 57:24, 58:3, 69:13, 69:23, 314:11
value [6] - 136:23, 139:12, 192:9, 192:10, 280:15, 297:13
values [21] - 94:25, 131:4, 131:8, 131:13, 131:18, 131:21, 131:24, 136:19, 136:21, 137:5, 137:10, 137:15, 137:19, 137:24, 139:2, 140:13, 140:14, 140:16, 211:25, 263:19, 301:1
van [16] - 122:17, 122:23, 123:1, 171:2, 171:4, 171:8, 171:11, 171:18, 172:4, 223:24, 224:4, 224:8, 248:4, 248:6, 248:11, 248:12
vapor [2] - 122:5, 122:6
variable [1] - 9:17
variables [4] - 61:10, 91:14, 143:1, 235:22
variation [1] - 30:24
variations [1] - 335:2
varied [6] - 31:1, 44:16, 48:16, 113:6, 115:18, 244:17
variety [5] - 23:3, 66:2, 101:6, 202:2, 226:4
various [17] - 74:11, 130:9, 152:11, 173:17, 173:21, 196:18, 203:21, 233:6, 237:2, 244:19, 244:20, 250:4, 260:14, 286:5, 314:16, 342:20, 346:24
vary [1] - 40:15
vast [1] - 5:12
verbatim [4] - 274:3, 274:4, 274:5, 274:11
version [3] - 24:6, 150:2, 343:1
versions [1] - 156:22
versus [4] - 272:25, 283:24, 324:22, 333:17
vessels [1] - 223:7
vice [3] - 7:7, 7:9, 70:8
video [1] - 58:8
videotape [2] - 59:3, 66:18
view [11] - 106:17, 111:9, 114:22, 128:25, 131:23, 132:5, 262:11, 320:15, 334:20, 339:16, 345:4
views [2] - 262:7, 315:1
violating [1] - 293:15
virtually [7] - 273:2, 273:6, 273:19, 274:3, 274:5, 274:11, 336:4
vitro [2] - 266:7, 303:14
vocabulary [1] -

186:23
void [2] - 120:23, 122:3
Volume [1] - 1:6
volumetrically [1] - 79:18

W

Waals [16] - 122:17, 122:23, 123:1, 171:2, 171:4, 171:8, 171:11, 171:19, 172:4, 223:25, 224:4, 224:8, 248:4, 248:6, 248:11, 248:12
wait [1] - 347:8
walk [4] - 16:3, 50:20, 117:24, 273:8
walked [4] - 101:15, 106:14, 111:10, 299:23
walking [1] - 80:10
wants [1] - 346:5
watch [3] - 183:3, 255:5, 341:8
water [23] - 9:22, 10:19, 10:20, 19:14, 19:16, 20:3, 20:8, 20:12, 103:23, 104:1, 118:14, 122:5, 122:6, 122:13, 154:25, 193:15, 223:20, 230:3, 296:22, 297:7, 298:14, 298:16, 298:17
wave [1] - 24:25
ways [16] - 38:14, 38:22, 46:22, 46:23, 47:1, 47:22, 55:8, 229:23, 325:25, 326:12, 330:18, 330:25, 331:3, 331:7, 331:25, 332:20
week [4] - 6:1, 6:8, 13:23, 346:11
weekend [1] - 296:23
weeks [1] - 347:1
weight [12] - 63:24, 63:25, 64:8, 64:16, 64:17, 323:23
weight/weight [4] - 114:2, 114:3, 216:18
well-known [4] - 44:20, 266:6, 310:3, 311:1
wet [19] - 103:24, 103:25, 109:10, 110:18, 110:23, 111:2, 111:6, 111:11, 133:15, 133:23, 192:20, 192:25, 193:13, 209:11, 209:16, 246:14, 246:17, 246:21, 246:24
wetting [1] - 223:20
whereas [1] - 338:9
whereby [1] - 79:18
wherein [3] - 37:4, 80:16, 260:20
whole [10] - 95:4, 156:13, 193:13, 297:12, 297:21, 324:16, 324:24, 325:6, 325:9, 325:19
wide [5] - 30:19, 66:2, 101:6, 202:2, 226:4
widely [1] - 264:3
WIGMORE [149] - 1:21, 57:8, 58:7, 58:15, 66:22, 66:25, 67:4, 67:8, 67:16, 67:24, 68:7, 68:16, 68:19, 69:25, 70:1, 72:16, 72:20, 76:6, 76:7, 77:9, 77:13, 77:20, 77:22, 79:3, 79:4, 80:7, 80:9, 80:20, 80:21, 81:12, 81:14, 82:1, 82:2, 82:15, 82:17, 84:4, 84:6, 84:13, 84:15, 86:23, 86:24, 87:7, 87:8, 87:14, 87:16, 87:21, 87:23, 89:17, 89:19, 91:9, 91:11, 92:6, 92:8, 93:14, 93:15, 94:3, 94:5, 94:9, 94:11, 96:8, 96:10, 96:17, 96:21, 98:12, 98:14, 98:24, 99:1, 99:16, 99:18, 100:5, 100:7, 101:21, 101:22, 103:5, 103:6, 109:4, 109:6, 109:16, 109:17, 110:2, 110:4, 111:17, 111:18, 111:25, 112:2, 113:16, 113:18, 117:1, 117:2, 119:11, 119:13, 121:24, 121:25, 123:21, 123:22, 124:5, 124:7, 124:24, 125:1, 125:11, 125:16, 125:22, 125:24, 126:18, 126:22, 127:9, 150:1, 150:6, 177:3, 177:6, 177:19, 178:1, 178:4, 178:14, 178:15, 179:12, 179:16, 179:23, 179:24, 180:16, 180:18, 182:24, 183:7, 259:7, 311:7, 311:10, 311:14, 322:18, 323:1, 323:5, 323:7, 323:14, 323:16, 326:10, 326:19, 327:13, 327:19, 327:23, 328:10, 329:7, 329:9, 336:17, 336:20, 336:25, 337:2, 339:19, 339:24, 340:4, 340:19
Wigmore [3] - 57:4, 311:16, 340:17
willing [1] - 67:11
WILMERHALE [1] - 1:19
WilmerHale [1] - 3:24
Wilmington [1] - 1:11
Wilson [6] - 7:4, 7:8, 7:12, 11:6, 32:16, 32:22
winner [1] - 29:15
WINSTON [1] - 2:4
wise [2] - 42:12, 46:9
wish [2] - 333:25, 336:19
withdrawn [3] - 61:6, 62:10, 133:13
withdrew [1] - 320:14
witness [16] - 3:6, 57:4, 57:5, 57:21, 68:7, 68:13, 76:10, 178:9, 183:13, 183:19, 229:12, 256:7, 256:16, 311:5, 341:3, 342:12
WITNESS [31] - 61:15, 61:23, 63:20, 68:11, 96:20, 125:15, 127:19, 128:2, 141:15, 174:3, 174:6, 179:15, 183:5, 183:17, 183:22, 229:18, 229:22, 230:2, 252:2, 255:6, 256:14, 256:25, 257:3, 274:23, 290:12, 290:14, 290:16, 319:25, 320:8, 328:9, 340:22
witnesses [3] - 23:25, 56:24, 58:22
WO [2] - 318:16, 319:2
word [19] - 14:19, 30:25, 51:15, 65:23, 86:14, 143:10, 164:19, 173:20, 178:21, 203:19, 237:25, 274:3, 323:11, 324:5, 324:13, 326:5, 333:3, 333:5
wording [1] - 273:17
words [12] - 24:9, 24:23, 27:3, 35:21, 130:6, 155:4, 162:10, 162:18, 174:12, 188:22, 242:14, 325:1
works [4] - 20:7, 34:2, 34:3, 193:1
workup [1] - 298:18
workups [1] - 333:1
world [2] - 11:12, 34:4
Worldwide [1] - 125:19
worsening [1] - 131:20
worst [1] - 306:21
wrinkles [1] - 36:20
writes [3] - 154:20, 173:17, 173:21
writing [4] - 129:11, 135:5, 140:22, 166:14
written [13] - 13:16, 14:4, 14:9, 16:13, 36:13, 36:15, 39:16, 42:5, 136:25, 137:4, 236:15, 236:16, 325:3
wrote [2] - 130:3, 136:8

X

x-ray [2] - 325:16, 325:21
XL [4] - 54:1, 279:18, 280:8, 337:4
XRPD [2] - 38:17, 328:11

Y

year [5] - 4:5, 29:16, 35:12, 42:24, 258:22
year-and-a-half [1] - 35:12
years [25] - 4:13, 4:14, 5:19, 7:9, 11:7, 12:11, 12:13, 15:13, 16:3, 21:1, 31:10, 31:21, 32:23, 33:2, 34:12, 46:3, 75:22, 111:5, 158:2, 161:13, 185:15, 188:5, 315:17, 316:3
yellow [5] - 43:13, 283:3, 283:20, 291:25, 305:23
YOU [1] - 172:13
yourself [6] - 68:21, 184:1, 188:15, 316:9, 316:12, 334:8
Yurkerwich [1] - 58:2
YURKERWICH [1] - 1:22

Z

zero [2] - 99:11, 216:13
Zydus [4] - 74:14, 125:18, 126:2, 127:4