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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner

v.

HALOZYME, INC.,
Patent Owner.

PGR2025-00017 (12,110,520 B2)
PGR2025-00033 (12,049,652 B2)
PGR2025-00039 (12,104,185 B2)
PGR2025-00046 (12,091,692 B2)
PGR2025-00024 (12,060,590 B2)
PGR2025-00030 (12,054,758 B2)
PGR2025-00052 (12,264,345 B1)
PGR2025-00042 (12,037,618 B2)
PGR2025-00050 (12,077,791 B2)
PGR2025-00053 (12,195,773 B2)

Record of Oral Hearing
Held: July 23, 2026

Before JEFFREY N. FREDMAN, SUSAN L. C. MITCHELL, CYNTHIA M. HARDMAN, and MICHAEL A. VALEK, *Administrative Patent Judges*.

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The above-entitled matter came on for hearing Thursday, July 23, 2026, commencing at 1:00 p.m. EDT, at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia

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1 P-R-O-C-E-E-D-I-N-G-S

2 1:00 p.m.

3 JUDGE FREDMAN: Good afternoon. We are convened for oral
4 arguments in PGR-2025-00017, 00024, 00030, 00033, 00039, 00042, 00046,
5 00050, 00052, and 00053, which pertain to patentability challenges and
6 related matters. I'm Judge Fredman. We're joined by Judge Mitchell, and
7 we're also joined remotely -- by Judge Hardman and Judge Valek.

8 Welcome to the USPTO's Alexandria office. We understand that in
9 every case that comes before us, the parties, both petitioner and patent
10 owner, have a lot at stake. We do have a copy of your slides, the briefs, and
11 the evidence available to us on our computers. So, if we look away or look
12 down during the hearing, we may be consulting the documents in the record
13 or actually taking notes. Please know that we are paying close attention to
14 your arguments and carefully considering the cases.

15 If we interrupt you, I do apologize in advance, but we do so to ask
16 questions that may be essential to a resolution of issues or to keep the
17 hearing on track. Recording of a PTAB hearing is prohibited. The court
18 reporter will provide a transcript of the hearing that will become part of the
19 record and proceeding at a later date. To ensure that the transcript of the
20 hearing is clear, we ask that you speak directly to the microphone, which

1 you should be doing, and identify specific slide numbers, numbering, and
2 figures or any other pertinent identifying information when referring to your
3 demonstratives.
4 For this hearing, the parties will each have 90 minutes in the main
5 argument section. Petitioner will open as they have the burden and may
6 reserve rebuttal time, which may not exceed more than half of the
7 petitioner's total argument time. Patent Owner will then respond to
8 Petitioner's arguments and may reserve surrebuttal time, also not to exceed
9 more than half of patent owner's total argument time. We remind the parties
10 that Petitioner's has the ultimate burden of establishing unpatentability by a
11 preponderance of the evidence. I'll be maintaining a clock and will notify
12 each party of five-minute warning during their argument and an appropriate
13 warning near the end of their time.
14 Let's get started with appearances for both parties for those who are
15 arguing today. You don't have to introduce everyone on your side, but feel
16 free to do so and if your client is attending. And then, of course, following
17 the hearing, if you would confer with the court reporter about more basic
18 spelling questions -- I know each party here is usually good at spelling in
19 most cases. We'll start with the appearances for the petitioner and how
20 much rebuttal time you'd like.

PGR2025-00017 (12,110,520 B2)
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1 MR. KUSHAN: Good afternoon, Your Honors. Jeff Kushan from
2 Sidley Austin for petitioner. With me are Leif Peterson, Amy Mahan, and
3 Sue Wang. There are other people I won't go through, and we would like to
4 reserve 45 minutes for rebuttal.
5 JUDGE FREDMAN: So, 45 minutes for rebuttal, all right.
6 MR. KUSHAN: Thank you.
7 MR. SUMMERS: Good afternoon, Your Honors. Zach Summers,
8 Quinn Emanuel for Patent Owner. With me is Lauren Martin and Elliot
9 Choi, also from Quinn Emanuel, patent owner. We also have from Sterne,
10 Kessler, Eldora Ellison and Ralph Powers. And then we have three
11 representatives from our client here today, Mark Snyder, Josh Mack, and
12 Aubrey Dash. And we also have some summer associates that would fill up
13 the rest of the bill.
14 JUDGE FREDMAN: And do you want to reserve rebuttal time?
15 MR. SUMMERS: Could I reserve tentatively 20 minutes of
16 surrebuttal time?
17 JUDGE FREDMAN: 20 minutes, okay.
18 MR. SUMMERS: Thank you.
19 JUDGE FREDMAN: Okay. Petitioner, you can begin your
20 argument.

1 MR. KUSHAN: Good afternoon. Today, what I'd like to do is start
2 with some claim construction issues that have been raised. Then we'll move
3 over to the two patentability issues. Before doing that, I'd like to just
4 address a couple of foundational issues before I get into the claim
5 construction points. Can we put up Slide 113?
6 First, all 10 patents that we're seeing in this set of the argument relate
7 to a set of modified PH20s that exist within a very large, what I call,
8 sequence space. It's important to recognize that the portion of that sequence
9 space that correlates to the enzymatically active forms of modified PH20s is
10 a fraction of the whole. Could you go to Slide 114 and 115?
11 There's no real dispute between the two sides that that's the picture,
12 that there is only a portion of that set of sequences that will actually fold and
13 turn into enzymatically active proteins. Slide 68. Dr. Naismith explained
14 during the proceeding what else is in that sequence space, and it's important
15 to keep that in mind. There are sequences that will not -- cannot be
16 produced. There are sequences that will never get secreted out of the cell.
17 There are sequences that are going to be misfolded. There are sequences
18 that fold, but then they're unstable, and they fall apart. And a lot of those
19 will exist in a form of aggregates. It's important to recognize this mixture of

1 structures is what constitutes what I've heard from Halozyme as the inactive
2 modified PH20s.
3 From day one, we've said in our petitions and since then we believe
4 the claims are correctly read as being limited to the enzymatically active
5 modified PH20s. We recognize there is a claim construction dispute where
6 the claims could be read more broadly, and we've explained why that doesn't
7 help them. It actually makes the 112 problems worse because they have to
8 also enable and describe this very heterogeneous set of sequences, which
9 they have not.
10 So, what I'd like to do is go to Slide 8. As you know, as you pointed
11 out, there are 10 proceedings in this set of the argument. You've already
12 issued final written decisions in four previous cases. We note that yesterday
13 the director declined to review the final written decisions of those four, and
14 we're grateful for that finding. What I'd like to try to do is walk through a
15 set of these claims in these 10 patents and show you how they all use the
16 same claim elements to define the modified PH20s that creates a common
17 deficiency across the whole set of patents. Slide 9.
18 Slide 9 compares the patent claims of the 09 proceeding, which you
19 have found to be unpatentable, to the claims of the 33 proceeding, the 652
20 patent. I've highlighted some bits of the claims just to kind -- these are the

1 common elements defining that universe of claimed modified PH20s. The
2 modified PH20 polypeptide term implicates two defined terms in the patent,
3 PH20 and modified PH20 polypeptide. Next, you have in yellow the
4 sequence parameters. One is the description of the unmodified PH20 that's
5 being changed. That's important because that's the starting point for the
6 proteins that are being changed. The second one is in blue. You have the
7 position which is being changed. That's a common element across the
8 family. And the last yellow bit is the variability of the universe around the
9 sequence identity.
10 If you can go to Slide 10, and I'm just going to do this quickly. You
11 can see these all kind of have the exact same claim format. These are the 17,
12 24, and 30 proceedings. I should mention all of our cites are to the 24
13 proceeding record. And then slide 11, you'll see again these don't have
14 identical forms, but they use the same kind of parameters to define the
15 modified PH20 polypeptides.
16 The 345 patent has a slightly different format, but again, you see the
17 same positional requirement for one substitution. One difference between
18 these and the last set is that they don't list a number of positions or number
19 of amino acids that you have to change the position to from the wild type.
20 That's one difference. We don't think it was a consequence in the final

1 written decision that have issued so far. We don't think it changes anything
2 here. Go to Slide 12.
3 These three patents are a little bit different because they start to now
4 introduce additional variables: one, the 185 patent is a method of increasing
5 delivery, and then, of course, they define the method as using that kind of
6 same way of defining the modified PH20 polypeptides in the other patents.
7 Claims.
8 The 791 patent and the 50 proceeding requires increased
9 hyaluronidase activity. This is a term -- this claim format is something has it
10 was issued in a lot of the patents in this family. Halozyme's disclaimed that
11 form of claim as a dependent claim in many of the proceedings. I think the
12 thing to take away from that: we believe it signals their concern about the
13 validity of that claim. But also, remember this is a requirement for
14 increasing the activity of the modified PH20, which presumes that the one
15 that you're modifying already is active.
16 And then finally, you have a soluble human PH20 polypeptide.
17 There, these are also modified PH20 polypeptides, so they put the definition
18 of them in the patent. But again, they're defining the set in a very similar
19 way.

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1 If you go to Slide 48, I just want to flag one thing about the 195. This
2 is the same genus of PH20 polypeptides that are being used in the method of
3 delivery that were invalidated in the 003 proceeding. There's basically no
4 difference in the scope.
5 So, if I could direct you to Slide 24. Now, in your institution
6 decisions, you found in each of the cases that the claims require
7 enzymatically active PH20s, and you've then confirmed that in your final
8 written decisions. We believe that's obviously the correct way to read this.
9 You can go to Slide 16. The disclosure defines PH20 to be a neutral,
10 active hyaluronidase. Why is that significant? It's because that's the thing
11 being modified by the claims to yield modified PH20. The other thing to
12 take note about this notice -- is that the naturally occurring form is active.
13 It's neutral active at that neutral PH. It's also sequence ID 7. So, sequence
14 ID 7, when you see that, that's the form on the sperm cell in humans, and
15 that's an active PH20.
16 There's also a reference in the definition of the PH20. It says,
17 Reference to PH20 includes, among other things, truncated forms that have
18 activity. Why is that relevant? Every seq ID that's listed in the claims, you
19 see, in this instance, there's 6 patents that have the same kind of first
20 element. Seq ID 3, 7, and 32 to 66 are all truncated forms of Seq ID 7, and

1 they all are active. And that's an instance of the claim language reinforcing
2 this definition. Could you go to 42, please?
3 This is just a citation to the US 457 publication, which is incorporated
4 by reference into the disclosure of these patents. And this is where they are
5 confirming. Halozyme's confirming, that all of those sequence IDs that I
6 just listed are active PH20s. There's some different numbers at the sequence
7 IDs in that one, but you can look at Dr. Naismith's declaration at 211 to 218,
8 Exhibit 1133, which explains what those are. So, go back to 16.
9 As I said, this element of defining what the starting sequence is, is
10 part of their claims. So, it's not just the definition of PH20. It's now
11 restricting it to particular sequences that are the basis of the modified PH20.
12 Go to Slide 17.
13 The other defined term is modified PH20 polypeptide, and this has in
14 its definition -- this is the bit on the bottom. First, it explains that a modified
15 PH20 polypeptide has at least one amino acid modification relative to the
16 unmodified PH20 polypeptide that's the starting point. Second, it defines
17 what a modified PH20 polypeptide is. That continues in the second
18 sentence, where it says, A modified PH20 polypeptide can have up to 150
19 amino acid replacements, so long as the resulting modified PH20
20 polypeptide exhibits hyaluronidase activity. This is an instance of you like

1 putting pieces together. PH20, active, right? That's what you're starting
2 with. You make changes to retain activity in that PH20. This is in the
3 definition section of the patent, and this is what, if you read the word
4 modified PH20, especially in a very compatible way with the definition of
5 PH-PH20, it is referring to a protein that has activity. So, the two terms
6 together would do enough to demonstrate that these claims are directed to
7 modified PH20s that have activity. We have extrinsic evidence that supports
8 that construction. Go to Slide 21.
9 Experts from both sides addressed the meaning of PH20 and the
10 modified PH20 and found, especially through the lens of what a PH20 is,
11 that is an enzymatically active form of the protein. The top quote is from
12 their expert, Dr. Simpson, interpreting what she takes away as the meaning
13 of PH20 as it's been defined in the patent. Slide 33, please.
14 So, we even note -- these are quotes out of the patent owner response
15 from Halozyme. One thing that strikes us about this, the way they're
16 describing what they're claiming, it actually aligns with this definition we've
17 seen in the patent. First, they say that their claims are directed to nine
18 variants of modified PH20s. Each one of those starts with the enzymatically
19 active unmodified PH20 and introduces one amino acid change at position
20 307. Every one of those is active. That syncs up with that explanation we

1 just walked through of modified PH20 polypeptide. And then the rest of
2 what's being claimed is portrayed as being a sub-variant of those nine active
3 modified PH20s. It's a very natural reading that aligns with what the patent
4 has defined to be a modified PH20. Could you go to Slide 23, please?
5 One thing that's also important to recognize in the claim language is
6 that Halozyme's patents don't claim modified polypeptides that match a
7 certain sequence identity with reference sequences. They claim modified
8 PH20 polypeptides. And that just signals that it's improper to read these
9 claims in a way which omits the role of PH20 in defining what's being
10 claimed. So, they want you to read the claims in a way which basically
11 crosses out the word PH20 from their claims, which we think is not a proper
12 reading.
13 I'd like to next talk a little bit about very briefly the issue of folding.
14 And this folding issue has come up because for the first time in their reply as
15 Halozyme criticizes the idea that there's a requirement that these sequences
16 have to fold in order to do anything in their surreply. And it's at patent
17 owner surreply at three. This is something which actually --
18 JUDGE FREDMAN: I mean, in the sense that presumably the
19 enzyme reacts, it has to have some folding to be an enzymatic reaction. I
20 mean, if it isn't, it doesn't. And for the contraceptive activity of the catalytic

1 also relies on, I suppose, folding of the last 10 residues. So, the total activity
2 would have to actually be those other things that can give it totalization in
3 that.
4 MR. KUSHAN: Yeah, I think you hit two points that are important to
5 flag, Your Honor. One is that point about if it's active, it means a protein is
6 properly folded. That's what all the experts have said, and there's a
7 correlation between those.
8 JUDGE FREDMAN: Probably it's been a little, but then it's folded in
9 some way, right?
10 MR. KUSHAN: Yes.
11 JUDGE FREDMAN: Clearly, the nature of the protein would be
12 unlikely to --
13 MR. KUSHAN: Correct. I think the way the experts have portrayed
14 it is that you have to fold enough to position the protein in a way to have that
15 catalytic site. And then particularly for the PH20s, the mammalian ones also
16 have to have the high EGF domain properly folded because if you take that
17 off, it doesn't work. With contraceptive applications, that's a little bit hard to
18 talk about because there's no illustration of what might work. We don't
19 believe any of them work based on the evidence, but the form obviously is
20 even harder to decipher on that. I think one thing you can take away is that

1 most of the experts agree that you can't have activity without a proper fold.
2 This is actually a quote from Dr. Petsko. It's at Exhibit 1131 75, 5 to 12. So
3 at least from the experts you have in front of you, we're all in agreement on
4 that front. Go to Slide 27.
5 I want to take up an issue that has been alleged by Halozyme, and that
6 is that Dr. Naismith abandoned any activity requirement in his certain of his
7 declarations and opines the claims only require proper folding. We do not
8 believe that is consistent with either the declarations he filed or the
9 testimony he provided at his deposition. First, what I'm quoting here is
10 Paragraph 109. On the left, it's from the PGR 03 proceeding. On the right,
11 it's from the 42 proceeding. And the punch line here from Dr. Naismith's
12 analysis is that he believes that when a POSA considers all of the language
13 used in certain claims, 5 and 7, and does that in conjunction with the
14 common disclosure, she would have concluded that the claims, all of the
15 claims of the patent, define a set of modified PH20s that exhibit
16 hyaluronidase activity. We've seen some comments about particular claims
17 being called out.
18 Remember, when we filed our petitions, many of the patents had
19 dependent claims that required increased activity. Some claims were to
20 soluble forms of the protein. So, when we were addressing the effect of

1 interpreting the claims, we were certainly looking at different claims and
2 what they were telling us that main independent claim was requiring. They
3 canceled those after we filed our petition. So, the record's kind of a little bit
4 skewed that we have these references to individual claims being used to
5 explain something, and then they're no longer there in the case.
6 So, again, we think in this setting that Dr. Naismith's testimony has
7 been consistent. If you go to Slide 28, these are some excerpts from his
8 deposition. This is the second deposition they took of Dr. Naismith, and
9 they put the questions directly to him about what his views were. And you
10 see him saying, "Do you agree that PH20 as expressly defined with form of
11 POSA that would have to understand that it's folded?" And he says, "It's
12 active," which means it's folded. He's clearly saying as he sees the
13 definition and understands the claims, they are directed to active forms.
14 The large chunk of text I put on the right is him explaining that the
15 panel obviously is entrusted with the task of interpreting the claims and if
16 you determine that they did include not just the active PH20s, but others, the
17 claims, in his view, would still be unpatentable because they claim at a
18 minimum the active PH20s regardless of what else they claim. And because
19 of that, there's no written description for that. There's no enablement for

1 those, and his meanings don't change. So, he's aware of his role as a
2 scientist to explain what he's interpreting the claims to cover.
3 All right, I'm going to move on to some 112 issues. If we could go to
4 Slide 35. One thing we pointed out in the original set of proceedings and all
5 of our petitions, and it's not disputed: the claim language places no
6 restrictions on location of change, the nature of the change. You can change
7 any of the amino acids to any of 19 others. You can have deletions from
8 within the protein sequence. And what that does is it tells us that the
9 sequence space is not only huge, but it's also incredibly structurally diverse.
10 Because when you start making those types of dramatic changes throughout
11 the protein, big impacts can happen. And that's actually what two of the
12 experts have pointed out in their testimony in Slide 69.
13 Dr. Petsko, in his declaration, pointed out that if the sequences are
14 truly random, meaning that there are changes made indiscriminately
15 throughout the whole protein, billions of sequences will not fold. So, this is
16 their expert confirming that in that space that we've described, there are
17 billions, and we'd probably say that's undercounting, of sequences that won't
18 fold. And that's because you're allowed to change positions that are
19 important to fold, maintain stability, et cetera. That point was made by Dr.
20 Hecht in his declaration as well, again, pointing to this concept that billions

1 of sequences are possible that will not fold or exhibit activity. And then go
2 back to 68, and just that puts home the point, you know. This is that space
3 outside of the green box that we're talking about where you make all these
4 indiscriminate changes where all these billions of sequences are found.
5 We also pointed out there's a lot of unpredictability relating to PH20
6 about making changes to that sequence. If you go to Slide 72. In our last
7 hearing, we pointed out when you look at the single substitution mutants, 57
8 percent of them are classified as inactive. It's a little bit hard to decipher
9 what that ultimately means, but it's something very bad happened to the
10 sequence. One thing I also want to flag is 11 percent on the right chart -- 11
11 percent of the single substitution mutants they made. They tested them, but
12 they don't report what happened. We don't know what happened with those.
13 JUDGE FREDMAN: I wonder if you could address the single
14 substitution mutations in light of Teva v. Lilly. I mean, we did have it in
15 our earlier final written decision, but I think it probably fell between your
16 hearing and this, so you didn't have a chance because it came out, I think, at
17 the time, if my memory is correct, to discuss it. But it's very close anyway.
18 If you could discuss that, please.
19 MR. KUSHAN: Just to clarify, you're talking about the most recent
20 Teva decision?

1 JUDGE FREDMAN: The Teva v. Lilly the written description on
2 the CGRP antibodies.
3 MR. KUSHAN: Yes. And there, so there's one of those relating to
4 the compounds and one relating to the method of using it to treat headaches.
5 JUDGE FREDMAN: Yeah.
6 MR. KUSHAN: You want the second one?
7 JUDGE FREDMAN: Probably.
8 MR. KUSHAN: Yeah. So that one implicates one of the patents,
9 which is the method of treatment. And what you will see in that decision is
10 reasoning which found that there was no dispute that the set of molecules
11 worked basically to treat the headaches. And there's a caveat that's
12 explained in that decision saying, This is not a case where we don't know if
13 the things are going to work as they need to in order to treat, carry out the
14 method. That is this case where there's no agreement about what is the
15 universe of molecules being used in the method. And we've also flagged,
16 and I can talk about that in a minute, there is, for the delivery, method of
17 delivery claim, there is a requirement beyond activity, we believe, that we
18 pointed out and they haven't responded to it, but it's an additional qualifier
19 on the properties of the PH20. We did address this in our 39 proceeding in
20 our petitioner reply. We didn't see a response to our points in the sur-reply.

1 JUDGE FREDMAN: And so, they distinguished Capon, essentially,
2 which is sort of an older case than this case.
3 MR. KUSHAN: Yes. Capon doesn't really fit the facts of this case
4 because in Capon, you were looking at a patent which pointed you to known
5 things, and that was being used basically to show that what was being used
6 as the terminology in the patent was actually adequately understood from the
7 prior art. Here, the structure of human PH20 wasn't published until 2024, so
8 there's nothing there to draw from. There's no understanding of the impacts
9 of multiple changes to PH20s in the prior art, so it doesn't really fit anything
10 on the Capon case. Could you go to 126?
11 The other thing, just a point. In his opening declaration, Dr. Petsko
12 also recognized that the data I just showed you is kind of telling him as a
13 scientist that PH20 is not resilient. It doesn't withstand mutation very well,
14 and that kind of just feeds into our point about unpredictability of changes.
15 Go to 75, please.
16 Just very briefly, we had Dr. Naismith also study that data in the
17 patent. One thing that's interesting about this finding that he made in his
18 declaration is that these positions that you see being charted are all the
19 positions that Dr. Petsko said were the most tolerant, 100 percent tolerated
20 positions. But you still see a lot of impact of each amino acid on the activity

1 of the protein. Impact is also far away from the active site, so these are these
2 long-distance effects that you can actually see manifested in the data.
3 Now, if we go to Slide 74, the other thing I mentioned in the last
4 hearing was this data relating to the C-terminal truncation mutants of the
5 wild type form of PH20. And what you see is a lot of what I call erratic
6 behavior. The activity's going up and down and up and down based on these
7 individual single amino acid differences at the end of the protein. At the last
8 hearing, I think counsel for Halozyme suggested that fluctuation in activity
9 is inherent to the assays being used to measure the proteins. I think that
10 would be -- I don't think it's accurate, but also it's not very helpful for Dr.
11 Petsko's opinions. Because if you can go to Slide 150, Dr. Petsko's
12 positional tolerance table, just make sure we understand how this was
13 created. Dr. Petsko, for each position, determined how many of the mutants
14 were classified as active or classified as unactive. In unactive, inactive was
15 classified below 20 percent; active was above 40 percent. If the assay
16 variability is 100 percent, that swamps whatever this line is that they've
17 drawn between the two categories. And if you move the numbers around in
18 terms of classifications, all these colors change. That's the weakness that we
19 pointed out in this analysis but kind of signals that there's a problem of
20 attributing that variation to just assay activity.

1 JUDGE MITCHELL: So, can I ask you a question about Dr. Petsko's
2 tolerance table here from what you're saying? So would you disagree based
3 on, you know, depending on whether it's, you know, 20 percent and whether
4 it gets basically, there's no activity depending on how you look at it. So,
5 would you change any of these to say it's tolerated or not, or do you think
6 this is fairly reflective of single substitution and where there's tolerance
7 there?
8 MR. KUSHAN: I think our experts have expressed the view that this
9 is really not a legitimate way to measure tolerability of positions to change.
10 But they've also pointed out it doesn't make sense to kind of use this when
11 you're combining changes because the combinations have bigger impacts, so
12 it's not very informative about making more than one change.
13 On the actual classifications, we pointed out a number of concerns
14 with that data. The inactive mutants don't reveal what the measured activity
15 was, and all the experts recognize that 20 percent activity would be generally
16 seen as an active enzyme. It has activity. You have to get down to about
17 five percent for the experts to say, this protein doesn't have activity because
18 now you're getting into the range of experimental error and you can't know if
19 it's actually active or not. But that 20 percent line doesn't make sense

1 scientifically to indicate whether a PH20 has activity. It's really, it'll have
2 activity if it's measurable at about five percent or higher.
3 As it's used in this -- this is, we think, not a credible, you know,
4 description of how you might modify changes. Certainly, some positions are
5 more resilient. If you tested -- I think Dr. Naismith explained in his
6 declaration that if you have enough diversity of testing, if you test enough
7 different kinds of amino acids at the position, and they all are tolerated, you
8 can infer that would be something that's more tolerant to change for that one
9 position. But again, when you start putting multiple changes into the
10 protein, that position may not have the same environment it does when it as
11 a native protein.
12 JUDGE MITCHELL: So, if I'm understanding what you're saying --
13 so at least for some of the single substitutions, if you're getting at least five
14 percent activity, you would agree that that has some hyaluronidase activity?
15 MR. KUSHAN: Correct. That's --
16 JUDGE MITCHELL: Okay.
17 MR. KUSHAN: Yep.
18 JUDGE MITCHELL: Okay. Thank you.
19 JUDGE FREDMAN: Do you think there's a difference here between
20 5 and 20 percent? I'm just curious in terms of the utility here -- essentially

1 the utility here with adjunct to help, you know, compounds penetrate cells,
2 right? Or enter those basement membrane cells.
3 MR. KUSHAN: I think you've kind of touched on the issue that's
4 specific to the one patent.
5 JUDGE FREDMAN: Right.
6 MR. KUSHAN: But maybe we just go through some of those points
7 because I think the issue it does matter, and that's one of the reasons why we
8 think there's an additional deficiency for those patents -- for that one patent,
9 the method of delivery patent. If I could go to Slide 47. We think it's pretty
10 clear when you read the patent that having activity isn't enough according to
11 the patent to be useful to increase delivery. And that's because maybe that
12 five percent is not enough to do anything. Dr. Hecht, when he looked at that
13 assay -- this is and you see in the patent there's a unique assay they run to
14 tell if the protein will cause spreading or not. They only tested one of the
15 mutants for that. But when Dr. Hecht looked at this, he recognized that there
16 might be scientific reasons why there is a problem of an active protein
17 causing the spreading necessary for delivery. What he pointed out was, for
18 example, if you go to Slide 49. Slide 49. Thanks. Dr. Hecht pointed out
19 that one of the features of the PH20 is this thing called a high L1 EGF
20 domain. EGF domains are known to be involved in protein-protein

1 interactions. Maybe that has something to do with the behavior in the cell.
2 But regardless, he identified reasons from the patent, the independent testing
3 that's required for spreading, scientific reasons why that would be necessary.
4 If you go to Slide 50, and you, I think, picked this up and you invited
5 them to address that point we had made in our petition. And I think they've
6 unfortunately declined to answer -- you know, declined your invitation.
7 What they did in their response, the patent owner response, they only cited
8 one paragraph of expert testimony, and I've just reproduced it here:
9 paragraph 392. It doesn't say anything about the phenomenon that Dr. Hecht
10 identified or the issues we raised about this distinct property. But to your
11 point, Judge Fredman, we believe there's a reason they said you had to test
12 these things in order to see if they are able to cause spreading. And it has to
13 -- the fairest interpretation of that is that they're testing because activity by
14 itself is not enough. That, for example, the F204P mutant that they did test
15 in spreading has plenty of activity.
16 JUDGE VALEK: Let me ask you a question about that, Counsel.
17 MR. KUSHAN: Sure.
18 JUDGE VALEK: So, the one that they did test which is the one that
19 has a mutation at, I think, F204P, as you said, that one it was found to

1 exhibit both enzymatic activity as well as this, what you call spreading
2 activity, correct?
3 MR. KUSHAN: Correct.
4 JUDGE VALEK: And that's the only data point that's in the patent,
5 right, as far as spreading activity?
6 MR. KUSHAN: Correct. That's the only tested mutant in the patent.
7 JUDGE VALEK: Okay. Is there any evidence in the record of a
8 PH20 polypeptide that showed enzymatic activity but did not also exhibit
9 spreading activity, that is, the ability to act as a spreading agent to improve
10 diffusion of a therapeutic agent?
11 MR. KUSHAN: There's no evidence in the patent about PH20
12 causing spreading except that one mutant. All the prior art deals with native
13 sequences that aren't modified, and they're just individual products that were
14 commercially marketed.
15 JUDGE FREDMAN: Those all do have spreading activity? Just for
16 clarity, those all have spreading activity?
17 MR. KUSHAN: The ones that -- yeah, so the ones -- the ones that
18 were known, were in approved products.
19 JUDGE FREDMAN: Right.
20 MR. KUSHAN: And they had activity, so that met the FDA standard.

1 JUDGE VALEK: So let me ask you --
2 MR. KUSHAN: Sure, go ahead.
3 JUDGE VALEK: Oh, sorry.
4 MR. KUSHAN: No, please.
5 JUDGE VALEK: You can finish, Mr. Kushan, if you --
6 MR. KUSHAN: No.
7 JUDGE VALEK: Need to finish your answer.
8 MR. KUSHAN: I'm fine.
9 JUDGE VALEK: Okay. I want to ask you about a passage in the
10 specification. This is in column 174 of the specification of the 185 patent,
11 the one that's at issue in the 039 case. So, this is at column 174, beginning at
12 line 22. You can turn there if you want, but I'll quote it to you. It says that,
13 "Provided herein are methods and uses of any of the modified PH20
14 polypeptides provided herein that exhibit hyaluronidase activity." And then
15 it continues and it says that "due to such activity, they can be used as a
16 spreading factor to increase the delivery of therapeutic agents." Doesn't that
17 passage teach that any modified PH20 polypeptides can be used in the
18 methods claimed in the 185 patent so long as that peptide has hyaluronidase
19 activity?

1 MR. KUSHAN: I think the way our experts -- I don't -- the answer to
2 that is no. And the way our experts have read that as meaning it's necessary
3 but may not be sufficient for the agent to cause spreading. And that's again
4 because when you're measuring the activity in the patent, you're measuring it
5 in a supernatant or in an isolated form on an assay. The effect of spreading
6 is happening under the skin, in the tissue and it's a very different
7 environment in which you have to see this activity do something and also
8 have to act on the substrate as it exists in under the skin. So, it's a different
9 environment where it's has to exhibit the spreading activity than what's been
10 tested with activity. So, we think from our expert's perspective, it's going to
11 be a subset of the active proteins. All of them, if has spreading, it has to
12 have activity at a minimum.
13 JUDGE FREDMAN: Can you say the difference about the EGF you
14 said there earlier? Is that a different molecule that you would find in just the
15 hyaluronate that they're testing in the activity assay?
16 MR. KUSHAN: The reference to EGF was that the PH20 protein has
17 an EGF domain.
18 JUDGE FREDMAN: Right.
19 MR. KUSHAN: All right. And --

1 JUDGE FREDMAN: Presumably, that's being used as a binding
2 domain.
3 MR. KUSHAN: Right and we know that PH20 does have kind of
4 distinct parts of it. One is the catalytic site. This high L1 EGF is another
5 part. They're both required for activity. But that's the part that Dr. Hecht
6 had suggested may have a role in, you know, moving through the tissue,
7 interacting with other proteins on cells in that environment of degradation of
8 the --
9 JUDGE FREDMAN: Is it known what that binds to?
10 MR. KUSHAN: They haven't really, I don't think they've figured that
11 out yet. This is, you know, going back to the Chao paper, which is Exhibit
12 1007.
13 JUDGE FREDMAN: So, it's not when it binds the substrate, it brings
14 it into the assay?
15 MR. KUSHAN: No. No. This is something which I don't believe it
16 was known exactly what it did in 2011, but this came from the Chao paper.
17 We're also, of course, relying on the fact that they have a separate test for
18 this property, which is necessary for the method.
19 I'm going to try to hit a few points before I sit down. I'm happy to, of
20 course, address any other questions that you have and happy to focus on

1 what you're interested in. So, what the record, in our view, shows is that
2 there's a lot of unpredictability in this field. It's a very huge, very large
3 space. There's a subset that you have to find out of that space that will fold
4 properly and exhibit activity, and there's not much -- there's very little
5 guidance in the patent disclosure. So, this is an equation of enablement, we
6 believe, demonstrates unpatentability.
7 Before I touch on that, I just want to flag the only evidence, I believe,
8 in the record that actually looked at the effect of putting 4 to 19 amino acid
9 changes into as a mutation in a protein is the paper we identified, which was
10 Exhibit 1144. That's an enzyme that has an alpha beta barrel motif. And
11 what that paper did show -- and that's slide 76, if you can put it up. This is
12 the paper that we provided that showed that there's a lot of unpredictability
13 and impacts of making that number of changes, very conservative changes,
14 in the loops between the domains in order on the ability of the protein to
15 fold. So, this is another bit of evidence of unpredictability of this kind of
16 protein.
17 We explained in our petitions and in our reply that the facts of this
18 case demonstrate that the claims are not enabled. You can go to slide 146.
19 There were two ways that the patent are at issue as to how you can make
20 modified PH20s. The description of how you do it in the patent is a directed

1 evolution technique where you make a bunch of random mutations and then
2 you screen libraries. And what we had pointed out in our petition, if you go
3 to 147, you hit the limits of screening technology in 2011, 2012 that prevent
4 you from exploring the entire space of the sequence space that's being
5 claimed. So, it's literally impossible to use this technique of directed
6 evolution and screening to practice even a fraction of the space of the
7 claimed invention. So, and the thing to take away is the one to five --
8 JUDGE FREDMAN: Would that change? You said that's 2011. I
9 mean, if you're saying you could have done some in this file.
10 MR. KUSHAN: I think people trying to do this today would find the
11 same problem. I don't know if you've gotten past 10 to the 9th libraries as
12 screening, certainly not up to the scale of 10 to the 50th or even 10 to the
13 29th. It's just the point of this is the vast majority of the sequence space is
14 beyond the capacity of skilled artisans in 2011 and 2012 to explore to find
15 modified PH20s. The other issue -- the other way that had been identified in
16 the briefing about how a POSA could find modified PH20s with multiple
17 mutations, was using the data in the patent in conjunction with homology
18 models. And I think this vastly overstates what you can do with homology
19 models in 2011 and possibly even today. Go to slide 127.

1 First, to be very clear, there is no mention of homology modeling in
2 the patent disclosure. There is no mention of using homology modeling in
3 conjunction with the data to find multiple combinations to --
4 JUDGE FREDMAN: I mean, that was developed then.
5 MR. KUSHAN: It was a known technique, but you would have
6 thought they would have --
7 JUDGE FREDMAN: Yeah.
8 MR. KUSHAN: Pardon?
9 JUDGE FREDMAN: That was in the ‘80s and ‘90s.
10 MR. KUSHAN: Yeah, homology modeling, I mean, we're not
11 disputing homology modeling was available back then. It's what they do
12 with it to tell you how to navigate the uncertainty, and they don't provide
13 any guidance about how you might do that.
14 There's also no structural information in the patent, which is another
15 defect. And that is something which impairs the ability of the person to
16 practice the scope. There wasn't any prior art that Halozyme identified that
17 had a viable PH20 model, homology model to use. The only one that had
18 been published flagged problems with the back end of that model because
19 there was no structural information to base it on, and that's another problem
20 with homology modelings. If you could go to Slide 138.

1 When you make a homology model, you have to have an
2 experimentally determined structure of a protein to actually determine what
3 the structure is. That's called the template. And then the model is based on
4 the template. But one big problem here is that the PH20 protein has 60
5 amino acids more than the template does, which is Hyal1. So, there's 60
6 amino acids at the end of PH20 that cannot be modeled because there's no
7 corresponding template. Why is that important in this case? Well, in that 60
8 amino acid region is part of the Hyal-EGF domain, which has been shown to
9 be very important to the ability of the protein to fold and have activity.
10 It's also all of those amino acids at the end of the protein that cause
11 that variability in activity when you made C-terminal truncations. So,
12 there's a very unpredictable area of the patent that is not capable of being
13 modeled with a homology model. So, again, they can't practice the full
14 scope even under the methodology they're telling us. 141.
15 Another problem is that they only tested one mutant, the 447 residue
16 mutant. So that means, and remember, the claims cover unmodified PH20s
17 that go up to 465. So, there is zero data on single mutants in PH20s that go
18 from 448 to 465. Again, in the equation they're trying to present for how
19 you enable this, there are these huge gaps that prevent you from carrying out
20 even the methodology they're describing. And of course, 137, in 2011, we

1 were not in the era of AlphaFold. We were almost a decade before that, and
2 the literature shows that the technology was not capable of making accurate
3 predictions of structure from sequence. So, we believe this approach can't
4 enable these claims, even a fraction of them.
5 Last thing I'll touch on, I do want to talk briefly about the two unique
6 patents, but before I do that very quickly: 117, on written description. I
7 mean, our positions are very clear. They have exemplified one type of
8 modified PH20. They are claiming a tremendous variety and scale of
9 modified PH20s that are not exemplified, and there's really no demonstration
10 that they have possession of any of these various combinations that are in
11 this huge space. It's a research plan at best. It's not description. It fails the
12 description test.
13 I'll just point you to the Novozymes case because that is a case that's
14 interesting because it's the same kind of approach. One required change,
15 homology identification as a percent identity, and they basically said the fact
16 that you might be able to put these things together around a research plan
17 doesn't demonstrate possession. When we challenged them on written
18 description, what they came back with was something called the alpha-beta
19 barrel fold, and our briefing has, I think, exhaustively demonstrated why that
20 is not accurate. A big reason it's not a common structural feature of the

1 genus of active proteins is that it doesn't have the active site in it, which
2 would be important for activity. It also doesn't show you what you have to
3 have in the protein, much less demonstrate that it has predictable attributes.
4 And I think one of the problems was that the description they gave you from
5 their experts was inaccurate. This is an atypical alpha/beta barrel structure.
6 A lot of confusion about what it is. It's certainly not a vehicle. And finally,
7 if you look in the patent, you'll see no mention of an alpha/beta barrel fold as
8 being a common structural feature of this genus.
9 You mentioned contraception a few times. I'll just put up slide 157.
10 We're kind of lucky in this case to have a snapshot of what a POSA actually
11 believed -- before the invention -- in 2011 based on all the evidence that
12 Halozyme has been relying on to prove that contraception is a viable utility.
13 And what you have is an impartial party, who's not one of our experts, in
14 this paper from before 2011 telling you that taking together the data from
15 non-primate and primate models suggests that PH20 is not a useful antigen
16 for inclusion in immunocontraceptive vaccines. And what this is doing is
17 interpreting the data for us in the 2011 time frame that had been made
18 available before then. So, this, we think, is a very credible insight into the
19 question of utility. But regardless, you still have to enable this. There are
20 no examples. If we go to slide 155.

1 There's no guidance in the patent. This is the entirety of the teachings
2 on contraceptive utility in the patent. There's no guidance that tells you how
3 to make the right kind of modified PH20. There's no evidence modified
4 PH20s have ever been tested for contraception. All right, very briefly, we've
5 talked about the spreading patent. I think the main issue there, again, is they
6 haven't demonstrated possession or enabled the full scope of PH20s to be
7 used in delivery. I just want to touch on the 773 patent, which is a 53
8 proceeding. This has a requirement for solubility, if you put up slide 53.
9 JUDGE VALEK: Before you move on --
10 MR. KUSHAN: Sure.
11 JUDGE VALEK: Sorry to interrupt. Before you move on from the
12 185 patent, what if we were to disagree with you that there's two distinct
13 activities required, and that we just take what it says in the specification
14 when it says that any of the modified PH20 polypeptides that have
15 enzymatic activity, that they can be used for that purpose? Is there still a
16 lack of written description and enablement?
17 MR. KUSHAN: Absolutely. I should have been clearer. These are
18 additional deficiencies for the 185 patent in addition to the ones that plague
19 all 10 patents. So, the fact that this method is dependent on use of an
20 uncharacterized, unidentifiable set of PH20s within this massive sequence,

1 that is also the reason why that claim lacks written description, lacks
2 enablement. You don't know which of the 10 to the 57 choices you can
3 actually use, so you basically have to make and test, and there's no
4 description of that universe that are active in the patent disclosure. So, this
5 is an additional deficiency.
6 I'll say that again, for the soluble patent as well, all of the defects
7 apply to this soluble patent. This is the -- 53, please. So, the issue here
8 that's interesting is that Halozyme has agreed with us that the solubility
9 requirement was defined, and there's two things that were in our definition.
10 One is that the PH20 polypeptide has to omit a piece at the end to make it
11 remove the GPI anchor. And the second is it has to be homogeneous in an
12 aqueous solution at physiological conditions. You don't know whether a
13 mutated PH20 protein will be homogeneous in aqueous solution at
14 physiological conditions without testing it. In fact, that's what the patent
15 says. If you can go to slide --
16 JUDGE FREDMAN: So, you're pointing just to the second
17 requirement because you're not really arguing that including the GPI anchor
18 would release it?
19 MR. KUSHAN: No. And again, the wild type, that's what has been
20 tested. So, they know the wild type sequence when truncated is soluble. But

1 the issue is what happens when you start changing the protein with up to 20
2 changes? We don't know if you're going to still be soluble. If you go to
3 slide 56, please.
4 We put in some evidence with our petition which explains if you start
5 mutating proteins, start exposing what's inside the protein to water, that is
6 why you don't have solubility, because those hydrophobic bits interact with
7 each other, form aggregates, and fall out of solution. They become
8 insoluble. This is very well established scientifically. I don't think there's
9 much of a dispute that this is something that happens and happens when you
10 introduce changes into a protein. Slide 57.
11 What you see in the patent for determining if a modified pH20 is
12 soluble is the second quote on the left. Solubility can be assessed by any
13 suitable method that demonstrates solubility under physiologic conditions.
14 Fairly generous. Our experts have explained you might do a solution where
15 you make enough protein and put it in solution and measure, you know,
16 whether it stays in solution. But it's a simple test. But it has to be performed
17 on the modified pH20 to know if it is soluble or not. Especially for the
18 fraction of the population where the activity has dropped significantly, the
19 inactive mutants, we don't have any data on those. Even approaching that

1 boundary of 40 percent activity, you're now introducing a lot of changes.
2 That's when you have this heightened risk of lack of solubility.
3 All right, and then finally just very briefly, the 345 patent, the
4 52 proceeding. Slide 60, please. In our petition, we identified not all of the
5 written description deficiencies that are common with all of the other
6 patents. We also identified an additional written description deficiency
7 driven by the claims of this patent. And that written description deficiency
8 pointed out there's nothing in this patent that shows a connection between
9 making 20 amino acid changes and restricting them to the 3 to 339 portion
10 of PH20. Our experts found that based on their analysis of the patent. We
11 have no response on this ground from the patent owner, which is a distinct
12 deficiency for a description.
13 JUDGE FREDMAN: You're saying it's a new matter issue?
14 MR. KUSHAN: This is a new matter issue because there's no
15 connection. In fact, if you look in the patent, the patent emphasizes you can
16 make mutations throughout the entirety of the sequence. They make no
17 differentiation about where you're making mutations. They point out in their
18 patent there's a portion that is similar to the bee venom protein, but they
19 haven't focused on that as an area to make mutations in. So, we believe
20 that's a new matter type of written description deficiency.

1 You asked me to not talk about obviousness. I have to say two things
2 very briefly. Our position really rests on KSR and KSR's guidance that if
3 you have a predictable alternative of something in the prior art, that's kind of
4 the essence of one of the predictable alternatives to what has been disclosed.
5 That is this case because all of those single mutants are --
6 JUDGE FREDMAN: Yeah, but your written description enables it to
7 rely on the fact that it's not predictable.
8 MR. KUSHAN: Well, we --
9 JUDGE FREDMAN: It's kind of a little hard to say now. Well, it's
10 not predictable for anyone else --
11 MR. KUSHAN: -- we're --
12 JUDGE FREDMAN: -- but for us and the -- it's a little bit maybe.
13 MR. KUSHAN: Yeah, we're -- like I said, these are one change, and
14 we're just following what the 429 patent said. But I'll just leave in your
15 mind KSR as you look at the at the record on this point.
16 JUDGE FREDMAN: Thank you. And the board with KSR.
17 MR. KUSHAN: All right. Thank you very much. If you have any
18 other questions, happy to take them.

PGR2025-00017 (12,110,520 B2)
PGR2025-00033 (12,049,652 B2)
PGR2025-00039 (12,104,185 B2)
PGR2025-00046 (12,091,692 B2)
PGR2025-00024 (12,060,590 B2)
PGR2025-00030 (12,054,758 B2)
PGR2025-00052 (12,264,345 B1)
PGR2025-00042 (12,037,618 B2)
PGR2025-00050 (12,077,791 B2)
PGR2025-00053 (12,195,773 B2)

1 JUDGE FREDMAN: Any other questions from the panel? Good.
2 Thank you, and we'll give you five -- because we have 45 minus 7, so
3 another 38 minutes.
4 MR. KUSHAN: That's fine.
5 JUDGE FREDMAN: Anyone test this?
6 MR. SUMMERS: We did test this, Your Honor. Apologies for the
7 delay here. There we are.
8 JUDGE FREDMAN: It looks like our colleagues have been knocked
9 off the screen.
10 THE CLERK: Yeah.
11 JUDGE FREDMAN: I'm very impressed. Thank you, Charlie. Over
12 to you, Zach.
13 MR. SUMMERS: May it please the board. My name is Zach
14 Summers from Quinn Emanuel. I'll be addressing the 10 PGRs you see on
15 the screen here, but I'm going to focus my arguments on two particular
16 categories. If you can go to slide 3, Elliot, please.
17 We have here a roadmap of all the patents that are at issue in the case,
18 and petitioner has a similar roadmap, maybe in a different order. We're
19 going to focus the arguments here on two of the patents that were discussed
20 that I want to highlight some differences from the last time we were here in

1 March, and that's PGR2025-00039 involving the 185 patent and PGR2025-
2 00053 involving the 773 patent. And then time permitting, we'll see if we
3 can get to some of the other issues here. But I recognize we have a lot to
4 cover, and I want to make sure we have time in particular to address those.
5 We've divided the full set into six categories, and if it's helpful at any
6 point having had the slides, if you have questions for this, please let me
7 know. Now if you can go to slide 4, Elliot. This is the category 1 method
8 for increasing delivery, and Your Honors already had some conversations
9 with petitioners about this. The claims recite a method for increasing
10 delivery of a therapeutic agent. They recite the therapeutic agent in 1A, and
11 then in 1B, as petitioner noted, they recite a modified PH20 polypeptide
12 comprising an amino acid sequence. And then I'm going to refer to these
13 Romanettes, so I just want to go through them clearly. There's Romanette
14 1B1 with a 95 percent identical limitation and Romanette 1B2, which recites
15 that the amino acid sequence of the polypeptide has that specific 320
16 mutation. And it's to one of four amino acids, that's in Romanette 1B3.
17 Those amino acids are changed to one of H, K, R, and S, and I'm sure Your
18 Honors recall those are just substitutions that result in a significant increase
19 in hyaluronidase activity. So, up to 600 percent, in fact. And what I want to
20 focus on, as you're aware from our papers and from introduction, 1B, 2, and

1 3 -- that's really the focus of this invention. Your Honors mentioned the
2 Teva case, and we've talked quite extensively in our paper about the
3 Ajinomoto case. And we've made, in both the introduction of our patent
4 owner response here and in our sur-reply, the point that really the core of the
5 invention here is that 1B, 2, and 3: that modification at position 320 to one
6 of those four amino acids that are recited in the increase in hyaluronidase
7 activity that comes with them.
8 So, in the language of the Ajinomoto case and the Teva case, that's
9 really the core of our invention, and I want to highlight the similarity here
10 then to that Ajinomoto case and to Teva's interpretation of it, as you
11 mentioned, Your Honor. I'm sure you're all familiar with the Ajinomoto
12 case. There the method was to a method of enhancing the activity of the
13 YDD gene, and that had another beneficial effect. It would then
14 overproduce L-tryptophan. That's a beneficial commercial effect. And to do
15 that, it recited a number of methods, and what was really at issue for written
16 description there and enablement was that it recited a more potent promoter
17 in the claim. The Ajinomoto case focuses on whether or not those more
18 potent promoters rendered the patent invalid under Section 112. Now, what
19 --

1 JUDGE FREDMAN: In that case, I think there was evidence that
2 promoters are pretty well known. They've been there for a long time. And
3 so, you kind of could choose whether you wanted a strong promoter or a
4 weak promoter, you wanted a promoter that had a, you know, IRES
5 sequence or whatever.
6 MR. SUMMERS: I think the Ajinomoto case is really useful actually
7 for exactly that reason. They characterize the use of promoters as routine,
8 and Teva makes that really clear. It really distinguishes between the core of
9 the invention and then the things that are routine that might be recited in the
10 claim for practicing it. And what it says about those promoters actually is
11 there's quite a bit of evidence and in Ajinomoto they talk about it, that what
12 sort of base principle was if you have similarity to a consensus sequence,
13 you'll get a more potent promoter than the wild type. That was the base
14 level evidence. But actually, there's quite a bit of evidence in that case that
15 that was not the case in E. Coli that you could have not just small changes,
16 but large changes that actually created a more potent promoter, and you
17 could have small changes that did not. So that aspect of the invention, using
18 the promoters, was routine, but the aspect of figuring out which promoters in
19 E. Coli for creating the activity of that YDD gene, that had an aspect of
20 unpredictability to it, and I think that's important in Ajinomoto.

1 If you look at our claims here, a method for increasing delivery of a
2 therapeutic agent, so this is different than the other claims we've talked
3 about from the prior. There were no methods for increasing delivery. It's a
4 narrower claim scope because you're limited to this method for increasing
5 delivery. To do that, you're provided the use of the therapeutic agent and a
6 modified PH20 polypeptide with that modification at position 320 to H, K,
7 R, and S. That increases the activity of the protein. And that 1(b)i limitation
8 there, the 95 percent identical, the further modifications, further modifying
9 PH20, making the substitutions and expressing them, that is a routine matter.
10 And what counsel's focused on and what they focused on in their arguments
11 is there's unpredictability in that. No one argues that as to 1(b)ii and iii, the
12 use of that is unpredictable in some way. Now, I know counsel has this
13 argument about somehow enzymatic activity doesn't lead to additional
14 spreading. I'll take that on separately. I want to take that on -- but I just
15 want to focus for a minute here on the similarity to this case to Ajinomoto
16 and how Teva reasoned about this type of claim, where what you have is the
17 core of the invention that you're protecting and then the ability to make
18 routine modifications, here substitutions, beyond it.
19 I actually think here we have a better factual situation than Ajinomoto.
20 Ajinomoto just recited a couple of promoters. That's all it did. It said you

1 can use a TRP promoter, a couple of other promoters. It didn't say, Here's
2 how you modify them to make them more potent, and yeah, and I'm sure as
3 Your Honors know, and it's in the record there, a promoter's about 41 amino
4 acids. There's a lot of things that you can do there. It's actually, to use the
5 language of petitioner, a quite large sequence space. They did not spend
6 time in Ajinomoto saying, Well, for each one of the sequence space, you
7 have to experiment, because it's not about numerosity. We've made that
8 point a number of times. Amgen makes that point. Here, what is important
9 is predictably a POSA could practice this invention using the 320
10 modification and then as a matter of routine practice. And Your Honors
11 found at page 77 of the prior final written decision, I don't think petitioner
12 disputes, that making and expressing modified PH20s is routine. That's
13 what puts us in line with Ajinomoto. What's actually different here is
14 Ajinomoto didn't have further information about those promoters. Here we
15 do provide in addition to that, a complete analysis of a modified PH20 at
16 every other position as well. So, you have the 320 modification. You do
17 know what it does, but then you actually did go through and modify all the
18 rest of them. It’s as if in Ajinomoto, you have taken that promoter and
19 actually modified all those amino acids to anything else and tested them to
20 see what happened. And I think that's a significant actually point in our

1 favor here as you interpret Ajinomoto. If there's no questions about that, I'll
2 move on because I do want to address --
3 JUDGE FREDMAN: Ajinomoto is focused on enablement, right? It
4 doesn't actually focus on written description.
5 MR. SUMMERS: Your Honor, unless my recollection is failing me,
6 it focuses on both.
7 JUDGE FREDMAN: I'm looking at it right now because I wanted to
8 just check because my memory was uncertain on that. And I'm looking at it
9 now, I don't see any discussion even of the word in it other than deposit
10 issues, which is a different thing, and the letter on the deposit is simply
11 satisfaction of the description, right? It has nothing to do with written
12 description. It only really is focused on enablement. So, this is kind of what
13 pushed really to the whole ability -- or fears with Centocor and I don't call
14 those written descriptions.
15 MR. SUMMERS: I'm sorry. I lost what you said at the end of that,
16 Your Honor.
17 JUDGE FREDMAN: I'm saying I think your case is actually a little
18 closer to all of those, you know, fears with Centocor or Amgen, there are a
19 lot antibody cases on this.
20 MR. SUMMERS: Look -- look --

1 JUDGE FREDMAN: Where they talk about the fact that just having
2 an antibody doesn't give you access to all the possible antibodies.
3 MR. SUMMERS: Okay. Let me take that question separately. And I
4 just glanced at Ajinomoto as well. The discussion is on representative
5 species, and that's the part that Teva discusses as part of a written
6 description. It -- what's that?
7 JUDGE FREDMAN: It's really dealing with enablement, not really
8 with written description.
9 MR. SUMMERS: No, it is a written description case, Your Honor.
10 It's in Ajinomoto.
11 JUDGE FREDMAN: Sure.
12 MR. SUMMERS: Yeah. So let me --
13 JUDGE FREDMAN: v. Archer-Daniels-Midland.
14 MR. SUMMERS: -- let me take you to that, Your Honor. So, if you
15 have Ajinomoto in front of you, you said? The discussion starts in earnest at
16 1359. It continues through 1360 and 1361.
17 JUDGE FREDMAN: This is --
18 MR. SUMMERS: And it -- it --
19 JUDGE FREDMAN: Which case does this cite?
20 MR. SUMMERS: For Ajinomoto?

1 JUDGE FREDMAN: Yeah.

2 MR. SUMMERS: 9:32, F 3 D, 13:42.

3 JUDGE FREDMAN: Okay.

4 MR. SUMMERS: Fed. Cir. At 2019. And again, the pages are 1359
5 to 1361. And you're familiar with the Teva case as well, Your Honor. And -
6 -

7 JUDGE FREDMAN: Teva.

8 MR. SUMMERS: -- Teva has both the written description and
9 enablement issues, but they say well focused on written description because
10 they have it. And they discuss that Ajinomoto's particularly for this point in
11 the context of written description, but then they also discuss it in the context
12 of enablement as well. I think here where their arguments have essentially
13 collapsed into the same issues, the same analysis applies for both, but I'm
14 happy to address different questions. Okay. Are there any other questions?
15 I don't want to move off that too quickly, Your Honors, if there's any other
16 questions about that aspect of the argument. We think, you know, the Teva
17 interpretation of Ajinomoto focusing on what the invention is and then the
18 routine aspects of the rest of that is a key point for analyzing this claim. But
19 I do want to get on to --

1 JUDGE FREDMAN: I mean, I think even understanding Ajinomoto,
2 it mentions, for example, AbbVie, which is another case where, you know, it
3 wasn't sufficient to have something but not describe it as routine.
4 MR. SUMMERS: -- in AbbVie?
5 JUDGE FREDMAN: AbbVie writes the antibody case again, right?
6 Yeah.
7 MR. SUMMERS: Sure. I'd be happy --
8 JUDGE FREDMAN: Centocor is a similar case with, you know,
9 antibodies where there's functional refinement.
10 MR. SUMMERS: Right. In each of those --
11 JUDGE FREDMAN: Here, we believe there's a functional
12 refinement.
13 MR. SUMMERS: The understanding that we do -- we still have that
14 difference, Your Honor.
15 JUDGE FREDMAN: Exactly.
16 MR. SUMMERS: But even with that, I think there is an important
17 distinction between those cases and this, which is: those cases, they both
18 have functional language. There they were functionally bound. Here,
19 there's no question that these are not functionally bound claims. We have
20 the structure right in front of us. If you don't have 1B, 1 and 2, 1, 2, and 3,

1 you're not practicing this. So, one thing we do think is a very distinct aspect
2 of those is you have claims, and Your Honors analogize to the Juno case as
3 well. There, it's something that specifically binds to something else. That's
4 all that was recited in the claim. We don't have that here. We're not saying
5 that the genus is bounded by function, by what does this. We said the genus
6 is bounded by structure. You know exactly when you're inside this claim or
7 not. You do. Now, they dispute whether that's predictable or not, but that is
8 a very distinct difference between --
9 JUDGE FREDMAN: You mean being bounded by structure? I
10 mean, I know PTO guidelines don't have any weight, and the 1999
11 guidelines I think would support your position, but I believe the 2009
12 guidelines do not. Because in the 2009 guidelines, they came out with the
13 view that if there's function associated with structure, that could fail the
14 written description requirement.
15 MR. SUMMERS: So, I want to be very clear actually about this
16 distinction because I think it's actually very important. When I say what's a
17 functionally bound claim, and when these cases talk about functionally
18 bound claims, what happens when you have those functionally bound claims
19 and don't have sufficient written description and don't have sufficient
20 enablement, is you have things that you don't know solve your problem.

1 That's what those cases talk about. You're stating a problem to be solved,
2 this function, without a solution, right?
3 Here we do not have that. We're looking for hyaluronidase activity.
4 We have a solution, and that's because it is not a functionally bound claim; it
5 is a structurally bound claim. So, in Ariad, it was recited as this: anything
6 that will bind to the target. It was functionally bound in that you don't know
7 what the structures might look like as defined in the claim -- as defined in
8 the claims of those cases --
9 JUDGE FREDMAN: You have some structure. You have, in fact,
10 even arguably some substantial structure. But the problem is we have, as
11 your opponent has pointed out, the structure that you have is a tiny fraction
12 of the genus.
13 MR. SUMMERS: Hmm. So, we disagree with that, Your Honor, but
14 let me explain why, actually. So, the function actually, and all of petitioner's
15 demonstratives will support this, the function that we have is actually inside
16 of the structure. It's not outside the structure that's described. So, for
17 Amgen, for instance, you said there's some structure, there's an antibody or –
18 JUDGE FREDMAN: Antibodies have substantial structure, the series
19 and -- you know --

1 MR. SUMMERS: all the framework. There's lots of parts of the
2 antibody that are going to probably be -- you know, presumably constant
3 often.
4 JUDGE FREDMAN: -- constant regions, I'll say it that way.
5 MR. SUMMERS: We're in agreement in that regard, but there are
6 also elements of the structure that are not described there and would
7 potentially be covered by the claims because they recite -- because they are
8 bounded by function. That's what the case law focuses on, is bounding by
9 function.
10 Here, we are not bound by function, and you can see the opposite in
11 these claims because you could not practice them. You would be outside the
12 scope of the claims if you are outside the scope of the recited structure here.
13 And it's only those that are active inside of that.
14 JUDGE FREDMAN: Understood.
15 MR. CHOI: It is a substantial difference here. I think that is a very
16 important difference for the case law. Excuse me, sorry, Your Honor.
17 JUDGE VALEK: Let me see if I can get a word in. The claim is
18 bounded by function because while you've shown in the specification that
19 the particular recited replacements at position 320, that those have activity,
20 as you put it, more activity than the native protein, you haven't shown what

1 happens when those mutations are combined with any of the others that are
2 possible under Romanette I in your slide, the 95 percent sequence identity
3 limitation. So, we don't know if a particular mutant is made that exhibits
4 multiple mutations in addition to the one that's recited in the claim. We
5 don't know if it's going to work in that claim or not unless we make it and
6 actually test it, correct?
7 MR. CHOI: We went over this at length, Your Honor, and I
8 apologize if I was missing a question from you earlier in the prior hearing.
9 We disagree that you don't know that there isn't predictability here, but let
10 me respond to the first part of your statement that it's bound by structure. It's
11 further bound by function in this claim. We agree with that. This requires
12 enzymatic activity. I agree with that, but it's within the structure. In other
13 words, you're not defining the invention by this additional -- this additional
14 function that's out there. You have to practice the structure here. That
15 wasn't the case for these other cases. But let me, if I can --
16 JUDGE VALEK: Let me push back on that a little because, I mean,
17 all of them are bound somewhat by the structure that's recited in the claim. I
18 mean, Teva, for example, it says it needs to be an anti-CGRP antagonist
19 antibody, okay? It's still going to be an antibody. The antibody's going to
20 confer to one of skill in the art some structure on what it is. You know, a

1 banana's not going to work. It has to be an antibody. And so, I'm not sure I
2 follow the distinction you're making. There's still a functional limitation that
3 you agree is in the claim. And then the question is: Do the scope of the
4 mutants that are, you know, that your claim draws a line around, does that
5 particular peptide that falls within that scope, can it be used to practice your
6 method? And that's where I'm struggling when we get beyond the single
7 point mutation that you've described in your specification where you --
8 JUDGE FREDMAN: I think, Judge Valek froze for a second. Are
9 you back, Michael?
10 JUDGE VALEK: Yes. I have a feeling that my question didn't get
11 finished.
12 MR. SUMMERS: No.
13 JUDGE FREDMAN: But I would add just to that. I mean, the point
14 he's making, I think, and I think that we're sort of wrestling with here is how
15 much structure, right? That's kind of clearly no structure, which is kind of
16 like the really old case with the three antagonists, right? Where they just
17 sort of need an antagonist and nothing else. That's insufficient, right? I
18 think if you had a 100 percent structure, right? We would hopefully agree
19 that would be sufficient, right? So here we're in somewhere in between
20 land, and I don't even know. It's an interesting question. I mean, it might be

1 different now with the Office rules. I'm not sure what I would do now, but
2 yeah. Go ahead.
3 MR. SUMMERS: So let me respond just to the first part of your
4 question. I think I can to the second part as well, even though we lost you
5 there. So, the problem in these antibody cases is you don't have the
6 sequence that performs the function, and here we do. It's recited in the
7 claim. You have to practice this. That's agreed on. Now, might there be
8 other sequences that have hyaluronidase activity? Yes, but those are not
9 claimed here. And that's --
10 JUDGE FREDMAN: But the sequences you have are not necessarily
11 in the active site, right? The mutation is positions which may be in the
12 active site, for example.
13 MR. SUMMERS: No, but the full sequence is recited in the claim.
14 JUDGE FREDMAN: Yeah, I understand the full sequence is there.
15 But so, if I'm allowed to make mutations, I could knock out the -- encompass
16 the entire active site.
17 MR. CHOI: You could. That'd be contrary to cases like CellPro,
18 Your Honor, which specifically say, Don't do things that the specification
19 teaches you not to do.

1 JUDGE FREDMAN: It doesn't say not to do it, right? What does?
2 Does it say not to do it?
3 MR. CHOI: It teaches you that it inactivates the protein, Your Honor.
4 So, I don't know how much more clearly you could teach for something that
5 you want to increase activity when you're teaching where these inactivating
6 mutants are. And as a matter of fact, the case laws are replete. We've gone
7 over with cases that applaud identifying those mutations or those things in
8 your invention that will render them inactive, that will render them
9 inoperable.
10 JUDGE FREDMAN: No, even changes in the active site don't
11 necessarily render it inactive. I mean, there's a -- if you change up one rate,
12 you may have one rate of inactive site, one with a single amino acid
13 mutation.
14 MR. SUMMERS: Here, we tested that, Your Honor. I mean, that's a
15 substantial difference between all of these cases. We actually tested that.
16 We provided it in the specification that that is a substantial difference. So,
17 with all due respect, your hypothetical may be true, but the facts actually
18 here show that we did test those. So, we do know in this case there is a
19 teaching, and it's a substantial teaching. It's much further than cases like
20 Ajinomoto. Ajinomoto didn't go through and test all of those promoters, and

1 it's acknowledged, if you look at that case, it says there are facts in this
2 record that show us that some of these won't work. But the fact of the matter
3 is because we have a substantial teaching beyond that, so I think a
4 substantial difference.
5 As to these other cases, I'll try to take them on in bulk, Your Honor.
6 You named a number of them. What's important in those is they recite
7 things like binding to a target, but you don't know what will actually do that.
8 Here again, we teach what the active site is. We teach what will inactivate
9 it. We teach other inactivating changes.
10 So, Your Honor, I want to move to this question of spreading and
11 whether tests are necessary for spreading. So, counsel referred to their
12 expert, Dr. Hecht. Dr. Hecht, he showed, I think, on slide 49, Your Honor,
13 paragraph 180 of Dr. Hecht. He sort of speculates that this EGF domain
14 somehow plays a role in spreading and enzymatic activity. Dr. Hecht has no
15 experience with hyaluronidases, Exhibit 2076, page 277, 12 to 14, and their
16 other expert, Dr. Naismith, similarly had not worked with and had not heard
17 of hyaluronidases before he took this case. That's at Exhibit 2301, 21 19,
18 and 22, 23 and 60, 22 to 24. I mention that because it is pure speculation on
19 Dr. Hecht's part that this EGF domain plays a role somehow in diffusion or
20 spreading, and it is contrary to the prior art.

1 So, Your Honor mentioned the patent's own teaching in this regard.
2 That's on slide 5, if we can pull that up. As you mentioned and I just want to
3 call specific attention in this disclosure, it says, Provided herein are methods
4 and uses for any of the modified PH20 polypeptides provided herein that
5 exhibit hyaluronidase activity based on its ability to degrade
6 glycosaminoglycans, such as hyaluronan. Due to such activity, the modified
7 PH20 polypeptides can be used as a spreading factor to increase the delivery
8 and/or bioavailability of the subcutaneous administered agents. That is what
9 is in the prior art. That prior art is generally from the Halozyme because
10 they were the pioneers in it.
11 This is from petitioner's exhibit, Exhibit 1013. It's the Frost paper
12 talking about soluble hyaluronidases. It's at page 429. I highlight again
13 petitioner's expert's inexperience here because I want it to be clear how long
14 that has been known. So, the Frost paper explains, The underlying
15 mechanism behind the spreading activity remained unknown until 1939, and
16 it was when it was reported. And it explains, This enzyme activity was
17 subsequently defined as hyaluronidase due to its ability to digest hyaluronan
18 in vitro. So, this is really a closed question in our view. The speculation
19 from their expert that somehow the EGF domain is doing something other

1 than enzymatically degrading hyaluronan to allow molecules to actually
2 move between this interstitial blood barrier, it is not well-founded.
3 I want to actually talk about some further teachings of the prior art
4 that actually incorporated that reference into the patent. So, we've talked
5 about this exhibit before, it's the 429 patent book binder, Exhibit 1005, and
6 this is from column 8, lines 1 to 10. It refers to soluble human
7 hyaluronidases as SHASEGP's because what you're doing is you're
8 removing that EGP. So, it says, They open channels in the interstitial space
9 through degradation of glycosaminoglycans that permit the diffusion of
10 molecules less than 500 nanometers in size. And it goes on and explains
11 why that is. You're opening a channel in this interstitial barrier that allows
12 things to move. No one in the art has suggested these EGF domains play a
13 role in spreading somehow.
14 Quite frankly, the fact that there's a spreading assay, Exhibit 14, all it's
15 showing you is that it's an actual reduction of practice of the F204P mutation
16 showing you that ones that have enzymatic activity lead to spreading, if you
17 want to conceptualize it that way. There's no suggestion in the patent that
18 you have to test them this way to show spreading. So, I think that's clear.
19 We took this on --

1 JUDGE FREDMAN: Let me just ask, and I think this will support
2 your case --
3 MR. SUMMERS: Yeah.
4 JUDGE FREDMAN: -- but there's no common -- there's not an
5 example of a hyaluronidase that exhibits activity and does not have
6 spreading activity.
7 MR. SUMMERS: That's correct. And petitioner's offered no
8 evidence in that regard, whether it be in the prior art or through newer
9 testing like you might see in some of these other written description and
10 enablement cases. And again, we addressed this particular point. petitioner
11 suggested maybe we did not; we addressed it at the sur-reply at two to three,
12 specifically citing the passage in the patent that teaches this.
13 There are other teachings, and I will just provide them in the record in
14 case they're useful. Also, from the 185 patent at column 73, lines 22 to 47, it
15 teaches that the hyaluronidase activity accounts for spreading activity
16 observed in animal testes extracts that have been used clinically for decades
17 to increase the dispersion and absorption of drugs. And again, at column 4,
18 lines 37 to 40 of the 185 patent, since HA is a major component of the
19 interstitial barrier, hyaluronidase degrading enzymes, e.g., hyaluronidase,
20 increase tissue permeability and therefore can be used to increase the

1 dispersion and delivery of therapeutic agents. That's all right from the patent
2 book binder, and the 185 patent book binder is incorporated by reference.
3 Last but not least, Dr. Hecht, before he speculated that the EGF
4 domain may be somehow involved, he says at paragraph 173, he says, The
5 only property -- this is their expert, I want to be clear, this is Dr. Hecht, the
6 one they're citing to for this idea. He says the only property of PH20 that the
7 common disclosure suggests is important to the ability of a PH20
8 polypeptide to increase delivery of another agent is hyaluronidase activity.
9 So, he's acknowledging the spreading assay is not somehow suggesting that
10 there's something else going on right here. He says right here, that's what
11 does it.
12 JUDGE VALEK: Before you move on, let me ask you a question.
13 How do you respond to petitioner's point about the fact the specification
14 describes assays to test hyaluronidase activity, and then it describes a
15 separate assay to test the ability of a modified PH20 polypeptide to act as a
16 spreading agent?
17 MR. SUMMERS: So, in that regard, they're just two different tests
18 showing the capability of a hyaluronidase-degrading enzyme to cause
19 spreading, Your Honor. I think that's quite clear from the definition
20 provided in the patent. Please, go ahead.

1 JUDGE VALEK: I was going to say, well, doesn't that at least
2 suggest to one of skill in the art they're going to need to test for both
3 enzymatic activity as well as spreading activity to determine whether a
4 particular modified PH20 polypeptide is going to work in the methods that
5 are claimed in the 185 patent?
6 MR. SUMMERS: With all due respect, Your Honor, I don't think so
7 in view of the remaining teachings and in particular, looking at the portion
8 of the specification that teaches that it is a result of the activity that you get
9 spreading. I think doing a dye dispersion assay showing, you know, further
10 showing the additional functionality doesn't imply that somehow the original
11 tests for activity were insufficient. There's a lot of tests about the F204P
12 mutant that go on in that test. It was one of particular interest. I don't think
13 that means that you need to do tests, for instance, for denaturation to show
14 stability.
15 JUDGE FREDMAN: Do you think that there's any -- one other point
16 they made was the levels of the enzymatic activity: 20 percent, 40 percent,
17 and so on? Do you think that that has any role in the spreading activity?
18 Obviously, presumably better enzyme activity has better spreading, and vice
19 versa is worse. That would seem to be at least a natural result you'd expect.
20 I don't know that it's true, but I would expect it. Do you think there's a point

1 at which too little activity would make it incapable of spreading? I mean, I
2 suppose it was zero percent.
3 MR. SUMMERS: There's no evidence of that in the record, Your
4 Honor, none. And I think based on how the patent defines that increase in
5 delivery as tying it to enzymatic activity, I don't think there's --
6 JUDGE FREDMAN: Do you think there's any relationship --
7 MR. SUMMERS: -- for debate. Yes. I think that's the expectation.
8 And I think one other point I want to make about the F204P mutant is we
9 don't have to have an actual reduction to practice of the 320 mutation to
10 show that it's capable of spreading. You can test something else in the
11 patent and show that it has the capability based on the fundamental
12 capability. And that's really what this is in this case to the extent you want
13 to look at that example 14 assay.
14 It's not required for us to show that this would increase spreading, that
15 we did a trypan blue assay of the 320 mutant. We did one of something
16 else. I think that's, again, that's commendable. It's additional information
17 that's there for a PHOSITA to show and to confirm their expectation from
18 the prior art that an increase in enzymatic activity increases spreading.
19 Now, I want to be really clear about one thing that your question
20 suggests though, Your Honor, which is this claim doesn't require increased

1 hyaluronidase activity. It requires hyaluronidase activity and I think you're
2 suggesting that with your question about how much there is spreading.
3 I want to actually address one other thing that petitioner said in
4 response to your arguments. So, when they filed these petitions, they said
5 that and their experts gave testimony that they were addressing whether or
6 not there was written description and enablement at 40 percent activity.
7 They gave all their opinions on that. So, whatever they were saying, This is
8 not predictable, this is not enabled, they were saying that you can't do it for
9 40 percent activity as --
10 JUDGE FREDMAN: Or more.
11 MR. SUMMERS: -- 40 percent or more. Yeah, thank you, Your
12 Honor. What they didn't do is they didn't address, and you heard petitioner
13 admit that their experts have said that things do have hyaluronidase activity
14 at lower percentages. And Your Honors, when you gave your construction -
15 -
16 JUDGE FREDMAN: Could you speak to their point that the assay's a
17 little -- I mean, it has the error bars in that assay a little bit higher?
18 MR. SUMMERS: I would love to take that on, Your Honor, because
19 they're using variability from one assay from those prior patents on
20 solubility where concentration was not controlled in the assay. We do

1 control for them. In example 2, the SEP assay, we controlled for the
2 concentration of the PH20 in the supernatant. That's important. And our
3 expert, the only one who has hyaluronidase experience, Dr. Simpson, she
4 has explained that that is a very significant control, and using the variability
5 from these solubility assays to try to cast doubt on the data that Dr. Petsko
6 and Dr. Simpson rely on from the patent is actually, I think, it's just not fair.
7 It’s not accurate, and a POSA, who actually understands these assays and
8 understands the significance --
9 JUDGE FREDMAN: You do rely on that.
10 MR. SUMMERS: -- of that assay. I understand that, Your Honor. I
11 do appreciate that, but I think it's important to understand that SEP assay
12 what it's doing. I'll actually come back to that again when we get to
13 solubility as well, because the petitioners again and again sort of tried to
14 throw out or suggest that the SEP assay's not useful and that the variability
15 overwhelms the data in the patent. That's not what we see. I think if that
16 were the case, you would see petitioner having submitted some evidence,
17 and they've submitted none, showing that the data that's in the patent is
18 inaccurate. That's what you see in these other written description and
19 enablement cases. You see things showing that the data doesn't lead you
20 reliably. You see examples in the AbbVie case, Your Honor.

1 JUDGE FREDMAN: Let me go to the example just to make sure I
2 understand what's going on here. So, when you say it's controlled, they
3 control the amount of supernatant that they take. They're not actually
4 measuring the protein in the sample, are they? Or do you --
5 MR. SUMMERS: They're using essentially a reporter, so a secreted
6 alkaline phosphatase. So, what they do is they put that under control of the -
7 -
8 JUDGE FREDMAN: -- and they use that to determine --
9 MR. SUMMERS: -- CMV promoter.
10 JUDGE FREDMAN: So, they're assuming that they're the same
11 amount.
12 MR. SUMMERS: With. Yeah. Well, they put it under control of the
13 same promoter that -- that --
14 JUDGE FREDMAN: I understand that, but --
15 MR. SUMMERS: The CP and yes.
16 JUDGE FREDMAN: -- they're still making an assumption that a
17 promoter works the same for all proteins.
18 MR. SUMMERS: They're on the same -- yes. I think that's right. I
19 think that's an established test. But --
20 JUDGE FREDMAN: Yeah. Right.

1 MR. SUMMERS: -- you're not directly measuring the concentration
2 of PH20 in the supernatant. You're instead --
3 JUDGE FREDMAN: Because you could do that.
4 MR. SUMMERS: You could. I think this is an accepted, and our
5 expert explains why this is actually an accepted way of doing it for PH20s.
6 JUDGE FREDMAN: I will say in my PhD we did measure the actual
7 amount of protein when I did my assays -- but anyway, go ahead.
8 MR. SUMMERS: I think with all due respect though, Your Honor,
9 this is the test that's in here, and we have a hyaluronidase expert here who
10 explains this is the type of assay that you use to control for concentration.
11 So, I understand that there may be other proteins that people have addressed
12 in other places, and I think a lot of the evidence from petitioner relies on
13 that.
14 Here we have evidence about what someone measuring concentration
15 for PH20 would do, and she explains why it's a quite elegant assay for doing
16 that, and nobody has called into question the reliability of that SEP assay for
17 doing that. That's an important point. They sort of ignored it. So, let me
18 continue on here.

1 Again, to come back on this claim we would encourage Your Honors
2 to look at Ajinomoto just to clarify my statements in case the record was not
3 clear. Ajinomoto is a written description case. It takes it on --
4 JUDGE FREDMAN: It is.
5 MR. SUMMERS: -- quite in detail, and we think it's a really
6 informative case here for Your Honors. Let me now talk about the 773
7 patent, Your Honors, unless there's other questions here.
8 JUDGE FREDMAN: I think you can keep going
9 MR. SUMMERS: Okay. So, if you can go to slide 7, Elliot. He's
10 read my mind. So, slide 7 is up here. This is the 773 patent -- is PGR 2025
11 and then 00053. We've reproduced claims 1 and 15. Claim 1 is an
12 independent claim, and I'll go over it, and then claim 15 is a method of
13 manufacture for that soluble human hyaluronidase. And we didn't address it
14 last hearing, those methods of manufacture, but I want to focus first on claim
15 1.
16 So, claim 1 is a soluble human PH20. It comprises a modification at
17 position 320, just like the 185 patent. And then it specifies in that bottom
18 highlighted sentence that the modification at position 320 is a replacement
19 selected from the group consisting of H, K, and R. And then in the non-
20 highlighted language, quite lengthy, it specifies that you can make 19 or less

1 amino modifications after alignment with sequence ID No. 3. Now, I want to
2 call Your Honor's attention, first of all, to that soluble human PH20
3 polypeptide in the preamble. So, the parties have argued about its
4 construction. They agree, I believe, it is limiting. And petitioner's expert
5 suggested that we somehow agreed with their construction. That's not quite
6 accurate, Your Honors.
7 I think we agree that there's a definitional phrase here, but then
8 petitioner, for some reason, does not adopt that as their claim construction
9 for a soluble human PH20, and I don't quite know why. But if you can go to
10 slide 8, Elliot, please. So, this is the patent's disclosure and the phrase that,
11 if you look carefully at slide 53 where petitioner suggested that we don't
12 dispute their construction, this is what we said is the definition. As used
13 herein, soluble human PH20, sHuPH20, includes human PH20 polypeptides
14 that lack a contiguous sequence of amino acids from the C terminus of
15 human PH20 that includes all or a portion of the GPI anchor sequence, C-
16 terminally truncated PH20 polypeptides.
17 I want to call Your Honors' attention, because this is a portion
18 of the definition that I think petitioner's trying to leave out here. Such that
19 upon expression, the polypeptides are soluble under physiological conditions
20 -- such that upon expression, the polypeptides are soluble under

1 physiological conditions. So, there's two elements of that. It's upon
2 expression, and it's soluble under physiological conditions. Because almost
3 all of the evidence that petitioner is relying on, and I think it is in fact all, is
4 not under physiological conditions as to PH20 or other polypeptides. The
5 testimony that they rely on isn't, and they don't address this question of upon
6 expression. I think petitioner's sort of fundamentally mistaken the question
7 of being soluble with being stable. The patent actually provides a separate
8 definition of stability.
9 JUDGE FREDMAN: But does it matter if it's being soluble versus
10 essentially aggregates, right? Because I guess one of the concerns you have
11 when you have a protein that is less soluble, doesn't fold properly, that it
12 aggregates that are in the cell and, you know, expressed and are secreted.
13 And so, I think what they might be at least arguing is that what you're really
14 going to see for at least some of these mutations is, you know, these large
15 aggregates that are not functional.
16 MR. SUMMERS: Right. What petitioner argues is that they can
17 become insoluble through these, that they can eventually aggregate --
18 JUDGE FREDMAN: Well, they --
19 MR. SUMMERS: -- aggregate and come out of solution.

1 JUDGE FREDMAN: They are soluble. I mean, as a practical matter,
2 right? I mean -- if you're making them, you're not making one molecule,
3 right? You're making a cell that's expressing large numbers of molecules;
4 otherwise, there's no point, right? And so, as that cell expresses large
5 numbers of unfolded, you know, inoperative embodiments essentially, right?
6 They would be insoluble.
7 MR. SUMMERS: So, petitioner's not addressed this. The question is
8 upon expression. So, I think there's a couple of different places where you
9 can talk about this.
10 JUDGE FREDMAN: But expression simply means, right, the
11 ribosome's pushed it off and then it goes into the cell, right? I guess.
12 MR. SUMMERS: I'm sorry, I didn't hear you.
13 JUDGE FREDMAN: I'm sorry. I'm saying expression is just the
14 ribosome has pushed it off and it's in the cell cytoplasm, right?
15 MR. SUMMERS: So, that's right. It's been expressed under
16 physiological conditions. Let me get to this specifically. So, there's two
17 points about this. One is nothing in the definition of soluble human PH20
18 polypeptide requires enzymatic activity. The function here that's recited is
19 solubility. And petitioner's tried to read in an additional function for
20 enzymatic activity.

1 JUDGE FREDMAN: So, should there be a utility issue here, then?
2 MR. SUMMERS: We don't and I'll get to that, Your Honor. But we
3 don't. It's soluble, which is a prerequisite for a number of other utilities.
4 That's true.
5 JUDGE FREDMAN: Which utilities?
6 MR. SUMMERS: With --
7 JUDGE FREDMAN: What other utilities?
8 MR. SUMMERS: It's soluble for the other utilities such as --
9 JUDGE FREDMAN: What are the --
10 MR. SUMMERS: -- enzymatic activity or contraceptive utility, Your
11 Honor. And I don't think anybody --
12 JUDGE FREDMAN: Contraceptive activity is problematic in my
13 mind, as I think you understand. So, I mean, the enzymatic activity is the
14 real activity. I mean, there's not -- other than the alleged contraceptive
15 activity that we have referenced because it doesn't work by an independent
16 expert, the only other activity really you can argue on -- you don't have a
17 third activity, right? It's not used as animal feed or anything? Like in re
18 Fisher?

1 MR. SUMMERS: Well, so let me be very clear. The function that's
2 recited in the claim, the soluble PH20, that is the function, and that actually
3 is a use for it. Being soluble is a use for it. But --
4 JUDGE FREDMAN: What is the use for it being soluble?
5 MR. SUMMERS: For specifically having something that is not
6 insoluble, Your Honor. But to the extent what you're asking, I think, is –
7 and we disagree about contraception, but to the extent what you're asking is,
8 is there a separate utility challenge from petitioner here? There isn't.
9 There's not a separate 101 utility challenge here. I want to be very clear
10 about that. They did not bring that as a ground. So that's not at issue here.
11 That's not addressed here separately. I want to be very clear about this. A
12 soluble human --
13 JUDGE FREDMAN: But in examination, I think probably even at
14 our level, utility is tied into enablement. So, that is an element of
15 enablement, really.
16 MR. SUMMERS: It isn't tied for the recited function in the claim,
17 Your Honor. The law is very clear. You do not have to describe enable
18 unclaimed function. So, whether there's a separate utility challenge the
19 petitioner could or couldn't have brought, maybe they could have, but what
20 you have to describe enable is the claimed function.

1 JUDGE FREDMAN: I'm not sure I agree with that, but go ahead.
2 MR. SUMMERS: And here is the claimed function, the claimed
3 soluble human PH20 polypeptide. And I think this is quite plain. We've
4 argued, and you heard petitioner just argue about what that function is and
5 how it's accomplished and whether it can be accomplished here. That is the
6 function that's recited in the claims. Whether, they try to read an additional
7 limitation here of enzymatic activity into the claims, but what is claimed is a
8 soluble human PH20 polypeptide with this modification and the teaching
9 here that I think they've ignored, it's extensive in the Halozyme prior art that
10 is actually incorporated by reference into these patents -- is how you
11 solubilize these and that's removal of that GPI anchor sequence. I'm happy
12 to talk more about that, but the further testing for solubility isn't required
13 without that GPI anchor sequence when it's gone.
14 I do want to be clear again, and this is where I think counsel has just --
15 they've argued that these assays in the patent don't add value. The SEP
16 assay has value. Dr. Simpson took it on at paragraphs 201 to 203 and
17 described what it provides. And what it provides, what it lets you know is
18 the concentration of the protein under physiological conditions after
19 expression. So, it is, in fact, providing that. We address that in our sur-reply
20 at 20 and 26, your Honors.

1 I want to be very clear that they've claimed there's no testing here. A
2 couple of things about that: one that a person of ordinary skill in the art
3 understand that this is how you solubilize it. This is what the routine matter
4 of making it soluble is: removing that GPI anchor. Counsel has speculated
5 that additional mutations might cause aggregation. That is a question of
6 stability, and the patent provides a definition of stability.
7 I want to show you why these are different functions, stability and
8 solubility. The patent provides a definition of stability. This is the 773
9 patent, column 50, lines 36 to 65. It says, As used herein, stability of a
10 modified PH20 hyaluronidase means that it exhibits resistance to
11 denaturation caused by a denaturation condition or to a denaturing agent.
12 And then it goes on, for example, at the bottom here around line 60. For
13 example, a modified PH20 hyaluronidase is stable if it exhibits an activity
14 upon or during exposure to one or more denaturing conditions or agents,
15 presence of a denaturing excipient or preservative, for at least one month at
16 temperatures from about 2 to 8 C inclusive, for at least three days at a
17 temperature from about 30 to 42 C. So, I think you made reference to that,
18 it's pretty routine to test for stability, Your Honor. People have formulations
19 all the time. And you see claims to stability all the time. You see claims
20 that recite a percentage of native conformation after storage. That's not

1 these claims. These are soluble claims. The patent provides a definition of
2 solubility and --
3 JUDGE FREDMAN: So, I'm going to go back to the utility because
4 it's still bothering me.
5 MR. SUMMERS: Mm-hmm.
6 JUDGE FREDMAN: Just reading Rasmussen, which you're probably
7 familiar with, it's an older case from 2005. And it just says that as this court
8 has explained, the how to use prong at 112 incorporates as a matter of law
9 the requirement of 101 that the specification disclosed as a matter of fact a
10 practical utility for the invention. And I think that my concern here is that
11 simply being soluble is not a practical utility. I don't see any practical utility
12 of just having a protein that is soluble.
13 Now, if it's has hyaluronidase activity and it can be used in medicines
14 to treat cancer patients. Sure, that clearly has utility. You know, if you
15 actually could show that it was a contraceptive, which, you know, I would
16 be unpersuaded by, you could -- yes, that would be a utility, I suppose --
17 practical utility. If there was some other utility that you raised, that would
18 be fine. But I don't see being soluble alone as a practical utility.
19 MR. SUMMERS: So, let me address that in two ways. One not
20 accepting the premise --

1 JUDGE FREDMAN: -- other than further experimentation on the
2 protein itself, which I don't think is a practical utility.
3 MR. SUMMERS: I think when you have functional language, it
4 would be strange to not refer to that as a utility, Your Honor. It is a function
5 that it's providing. It is a use. That is utility.
6 JUDGE FREDMAN: There are lots of uses that don't have -- that
7 aren't -- don't have a practical utility. In re Fisher, right? That's a case
8 where the board was affirmed a long time ago on utility where there were
9 seven utilities, I believe, that that applicant or appellant raised that were all,
10 you know, not deemed practical, right, essentially.
11 MR. SUMMERS: So, let me address this in two ways. One is just we
12 disagree. We do think that it does have utility for solubility.
13 JUDGE FREDMAN: And we disagree --
14 MR. SUMMERS: And it has -- because it is a prerequisite for using it
15 for these other purposes that it is a use and utility. But let me address your
16 other question, which is if you assume that you disagree with that, why does
17 it still have utility? And I think you hit on why it does, Your Honor, which
18 is enzymatic activity here is a utility for these. And when you're doing that
19 aspect of it from Rasmussen, it says it -- it does have an aspect of 101 utility
20 to the make and use. When you're talking about making and using the full

1 scope of the invention, you're talking about the function recited in the
2 claims. And that question of whether it then has utility is a much lower bar.
3 So, whether or not it has utility at that point, for instance, uses of, as
4 you said, as with a cancer drug to allow further spreading, it does. There is a
5 recited utility here. It meets the utility standard. I think that's why they did
6 not bring an independent 101 utility challenge on these claims. So, with
7 that, I want to, Your Honor, I think we've gone over this, but if I can go to
8 slide 9, Elliot. You'll probably recall from the institution decisions, there
9 was quite a lot of back and forth over the Boehringer cases. So, there's a
10 Boehringer 1 case that recites an ORF with a particular immunogenic
11 function, and then there's the later Boehringer case that explained very
12 clearly what our view of the law is here, which is when you have an
13 unclaimed function, and here that's enzymatic activity, you don't have to
14 describe and enable full scope. The 112 arguments here, almost all of them
15 from counsel, they sort of improperly focus on this functional requirement
16 that's not recited in the claims.
17 I do want to take on this question of aggregation and misfolding,
18 though. There is some evidence in the record. They really rely on testimony
19 from Dr. Petsko, and just for the purposes of making the record here, I want
20 to be very clear. So, if you can go to slide 11, Elliot. This is Dr. Petsko's

1 testimony. He was asked quite a bit from and it's really from pages -- I
2 would encourage Your Honors to read the entire exchange. It's from pages
3 40 to about 51 of his deposition, and I'm going to walk through some of it.
4 But he explained aggregation in this instance is generally, to the extent it's
5 relevant, to the extent you say, Well, there might be a stability aspect, we
6 think that's incorrect.
7 This question of aggregation and misfolding, he explained that's not
8 going to be the case from page 20 from mutations. He was asked
9 specifically about this in deposition. He explained it's usually not the case
10 for most root mutations and that it's rare and that it's not a common
11 consequence. So, I actually want to direct you to petitioner's slide 89,
12 though. So, petitioner's slide 89 argues aggregation is a common
13 phenomenon in mutated proteins. Now, even again, we dispute whether this
14 is relevant to the question of solubility, the question of aggregation. After
15 the fact, whether or not it remains stable is what's happening there is the
16 hydrophobic regions are going to get exposed over time and aggregate.
17 That’s a question of stability. But they reproduced some sections from Dr.
18 Petsko's deposition down below, citing to pages 42 and then page 47.
19 Now, if you look at that testimony, I just want to start from page 40 of
20 Dr. Petsko's testimony so that we make sure that we have these in context

1 because they say that this shows and their own expert said that what Dr.
2 Petsko said was, This is a common phenomenon. He said this excerpt here
3 at 326 is from Dr. Naismith's declaration that was submitted on reply. And
4 he says, at his deposition, Dr. Petsko agreed, and I agree that aggregation is
5 a common phenomenon that can occur when substitutions are made to a
6 protein.
7 So, here is what he actually said, at page 40, starting at lines 18 to 24,
8 he was asked by petitioner's counsel, so when you introduce mutations into a
9 naturally occurring protein -- mutations into a naturally occurring protein,
10 can those mutations cause the protein to misfold relative to the naturally
11 occurring protein? Occasionally, okay, for some mutations. It is usually not
12 the case for most mutations. And he was going to ask how you know, when
13 do you know? And he said, it's probably protein dependent. And then he
14 gave some additional testimony here, and this is what they rely on. So, what
15 they cite is they say, can aggregation occur during the process of protein
16 folding if there's been a mutation of the protein? And they said, it can occur
17 even if there hasn't been a mutation in the protein, depending on the external
18 conditions, okay? But usually that's concentration dependent, and typically
19 it requires non-physiological concentrations. When we are talking about
20 solubility in this patent, we are talking about under physiological conditions.

1 He's talking about this being a concentration dependent effect. He
2 says, Can aggregation occur within a cell during transcription or translation?
3 He says, Yes, it can, and often that's a result of overexpression that results,
4 for instance, say, because of a promoter mutation because you're increasing
5 that concentration beyond physiological conditions. So, that's what they
6 cite. Now, all of that is in the context of he was asked, Can mutations cause
7 proteins to aggregate? At page 42, he said, Yes, sickle cell hemoglobin is
8 one example. Again, he's talking about protein dependent questions here,
9 and I want to point that out.
10 JUDGE FREDMAN: I guess you're trying to make the distinction, I
11 think, between sort of the purified protein that the pharmaceutical company
12 would make, right, and the protein as it would exist. And it could even be, I
13 suppose, in a large, you know, plant for the pharmaceutical company that is
14 overexpressing it and has to be careful to ensure that it remains non-
15 aggregated that they're producing.
16 MR. SUMMERS: That's correct. There's no evidence in this case,
17 Your Honor, of PH20 being insoluble due to mutation. And in fact, what
18 happened was when they expressed when they made these mutations with
19 the CEPA assay, they tested to make sure they were expressing into the
20 supernatant. So that evidence, they relied on that for inactivity, but that

1 evidence shows you that for these mutations, they didn't render them
2 insoluble.
3 I want to go on because he was asked, you know, just at a high level
4 what causes proteins to aggregate, and this is again from the same portion of
5 testimony they're relying on. He said, So there are a number of factors. One
6 is concentration, all right? And he goes on and explains why at higher
7 concentrations they're more likely to aggregate and lower, but that
8 physiological conditions matter. And again, he says there are other instances
9 like sickle cell hemoglobin, as an example, and he was asked specifically --
10 this is at page 47, lines 7 to 19.
11 He said, So those interactions, this is what they cite: those
12 hydrophobic patches that become exposed on the surface of the protein.
13 And I want to be clear, they're talking about sickle cell hemoglobin. This is
14 left off the slide. So, he was not giving general testimony about this, but this
15 is what they cite for the idea that aggregation and insolubility is common.
16 So, right before this, he's talking about sickle cell hemoglobin as an example
17 of a mutation causing aggregation. He was asked about that, about sickle
18 cells. So those interactions, those hydrophobic patches that become exposed
19 on the surface of the protein. And Dr. Petsko said, Or created on the surface

1 of the protein, yes. They're the most common ways that you would see
2 aggregation would be hydrophobic.
3 He's talking about, in sickle cell, that's what you see most commonly.
4 That's the word common that they're pulling up here, and he's just saying
5 that's -- when you do see aggregation, that's the most common route. He is
6 not saying aggregation is common. That is not his testimony, and that's an
7 important fact because they have not addressed it. They've characterized his
8 testimony this way. Their expert characterized his testimony this way
9 despite having this transcript in front of him and apparently reading it, but it
10 is not an accurate characterization of his testimony.
11 He goes on to explain at length why this happens and why you don't
12 expect mutations to do this. He says it at page 48. He says: He was asked,
13 you know, All right, is this going to happen? He said, Not with any
14 reasonable affinity, page 48, because you're thinking in terms of the enthalpy
15 of interaction due to a hydrophobic patch. But remember, there's also shape
16 complementarity. That's important because you have to exclude water. So,
17 only patches that are suitably complementary are likely to form the kind of
18 interaction that would lead to the aggregation you're thinking of. So again,
19 he's just explaining why these assumptions behind the general principle that

1 sometimes mutations in, for instance, sickle cell anemia can cause
2 aggregation, why you don't actually expect them to.
3 Then last he was asked, and this is at 48 lines 23 over to 49 to 13. He
4 said, Do you agree that some amino acid mutations made to a protein can
5 cause that protein to be prone to aggregation? He said, Yes, that can happen.
6 It is not a common consequence. So again, we have their expert, and they
7 included this on their slide, Your Honor, saying, Dr. Petsko agreed that this
8 is a common phenomenon. That is not what he said. I want the record to be
9 very clear on that, and that is what his testimony is. He said, When you say
10 common, give me some context for that. He said, If you make typically 100
11 mutations in a protein, okay, one or two might do that. None of them might
12 do that. But it's -- I've never seen a case where 20 or 30 do that. The
13 characterization of his testimony that somehow he agreed that aggregation is
14 a common phenomenon from mutations is just inaccurate.
15 In this section of the testimony, Your Honors, the last thing I want to
16 point out is he pointed out that aggregation, when you do see it, typically
17 happens with a more flexible protein from mutations that would happen. He
18 said specifically, and again, he said these are protein-dependent phenomena.
19 He says specifically that would not be the case for PH20. That's the
20 testimony in the record. So, you've seen evidence flashed on the slide quite

1 quickly generally that aggregation's a common phenomenon sometimes in
2 biological formulations because you're trying to over-concentrate, you're
3 trying to increase the concentration beyond physiological conditions in order
4 to make an effective dose. You want to make that as small as possible.
5 That's not what we're talking about here. The patent's definition is very clear
6 that that's what's meant by solubility. Are there any questions about that,
7 Your Honors?
8 JUDGE FREDMAN: Don't think I see any.
9 MR. SUMMERS: I want to make sure that our remote judges aren't
10 frozen. So, I want to address a couple of other points that and this relates in
11 part to this soluble PH20 polypeptide definition. So, I anticipate counsel's
12 going to stand up and say, Well, the claim still says PH20, soluble PH20,
13 and so therefore doesn't it have to have enzymatic activity? The patent has
14 this other statement about PH20 that we've discussed previously. And they
15 specifically have said, Well, you're reading PH20 out of the claim. They
16 have that slide 23 where they cross out all the PH20s. If you did that, we are
17 not reading PH20 out of the claim. If you did that, you would not be using
18 the definition in the patent that is provided for that term. It would be a
19 soluble polypeptide, and therefore, that definition wouldn't apply.

1 Why that definition applies, and it does not recite enzymatic activity,
2 why that definition applies is because that word was included in there. That
3 is an important distinction. When you define a term in the specification,
4 when you engage in that sort of definitional work, that is the definition that
5 applies. So, when you say soluble PH20 polypeptide, that's what you're
6 talking about. I think that is a substantial difference. Let me get to a couple
7 of other points with my limited time remaining, but I want to ask if there's
8 any topics Your Honors would like me to address first.
9 JUDGE FREDMAN: I don't think so, if they do, they'll speak up.
10 MR. SUMMERS: Okay. Elliot, can –
11 JUDGE FREDMAN: If they're not frozen.
12 MR. SUMMERS: Counsel suggested that we're somehow
13 misunderstanding them and their experts about claim construction in some
14 of these proceedings. I want to address that head-on. We're not trying to
15 misrepresent what they're saying. Elliot, if you can pull up slide 12, please.
16 This is from both the 692 and the 618 PGRs. They're -- I'm sorry. Let
17 me be much more clear. The patents, this relates to the 692 patent and the
18 618 patent, and they are in PGRs 46 and 42. What they said here,
19 reproduced from their petition, is each claim either encompasses or is
20 limited to active mutant modified PH20 polypeptides meeting the sequence

1 identity parameters of the claims. So, we understood this from their
2 argument to mean that they were arguing that the inactives were
3 encompassed in this because each claim is either encompassing it or limiting
4 it -- and I think that's accurate. That's what they were, in fact, saying. If you
5 can go, Elliot, we're going to have to go all the way to slide 32. Thank you,
6 Elliot.
7 This is the testimony that he suggested that we're misrepresenting.
8 What we have here is a comparison of Dr. Naismith's testimony from the 46
9 proceeding with the 04 proceeding. The 04 proceeding is one where they
10 were arguing it was enzymatically active. The 46 is one of the ones we're
11 talking about. And you can see in the 04, he said he has all these
12 Romanettes, I read the claims as a whole as directed to these, and when you
13 get down to that fourth Romanette, he says specifically it's enzymatically
14 active. If you look over on the left in the 46 PGR, in the same PGR where
15 they made that statement that they believe that it encompasses inactives, that
16 in that 46 PGR, they didn't have that Romanette in there.
17 JUDGE FREDMAN: But the first PGR uses the phrase modified
18 PH20 polypeptide, right?
19 MR. SUMMERS: That’s. right. I think there’s a significant --

1 JUDGE FREDMAN: And so, we interpret that, and I think clearly it
2 was your specification that stating it has to have hyaluronic activity --
3 MR. SUMMERS: Yeah.
4 JUDGE FREDMAN: And you may not agree with that, but I think
5 that's the interpretation we'll probably hold, I'm going to hold.
6 MR. SUMMERS: Your Honor, I want to be clear about a couple of
7 things. One is just the inconsistency in claim construction positions with
8 their experts. So, this is again another time where it seems that he's actually
9 saying modified PH20 polypeptides in this case are not required to be
10 enzymatically active. These are claims that do involve --
11 JUDGE FREDMAN: I think that's an overstatement of what he's
12 saying. He made a statement that he didn't notice the difference. It's not
13 clear that he deleted it on purpose.
14 MR. SUMMERS: Your Honor, that goes to credibility. I don't think
15 that's a credible explanation that suddenly the fourth Romanette for
16 enzymatic activity disappeared, especially when you look at what they said
17 in their own petition. And I want to talk about one other aspect of these
18 claims -- I'll get to it. These claims don't recite the positional limitations as
19 petitioner noted, and they don't recite individual amino acids. It just recites
20 like the position without individual amino acids. I take them -- I think when

1 they filed this petition, they looked and they said, well, these encompass
2 potentially inactivating mutations. And so, to read it modified PH20
3 polypeptide as requiring activity, well, that would be reading out something
4 that's specifically recited in the claim as an inactivating mutation. And so
5 that's why they took this position. And if you can go to the next slide, Elliot,
6 slide 33.
7 JUDGE MITCHELL: So, it seems, let me make sure I understand
8 because there's no particular amino acids listed as being the ones that
9 substitute --
10 MR. SUMMERS: That's --
11 JUDGE MITCHELL: -- a particular position. It could be any amino
12 acid, and we know that some of those amino acids you're going to wind up
13 with inactive. Is that what you're saying?
14 MR. SUMMERS: That's correct. And I think that's why they put this
15 position in their petition. I think it shows you again, and with all due
16 respect, Your Honor, we disagree with this modified PH20 polypeptide
17 definition, but it because this is what their petition was founded on --
18 JUDGE FREDMAN: I understand you disagree with it
19 MR. SUMMERS: -- and that's what you have in front of you.

1 JUDGE FREDMAN: But so, you're also then saying, and I'm looking
2 at your claim one from this patent, right? What's the utility of the ones that
3 are inactive?
4 MR. SUMMERS: What's the utility for the one? I mean, this is
5 where we will have the discussion about contraceptive utility, Your Honor,
6 but it's --
7 JUDGE FREDMAN: Is there any evidence that they have
8 contraceptive utility? That these particular proteins, and not that there was a
9 PH20 in guinea pigs that one time was shown to have contraceptive activity
10 maybe for guinea pigs. Is there any evidence that these have it?
11 MR. SUMMERS: That's not the standard for utility that you have to
12 show that the specific --
13 JUDGE FREDMAN: Yeah, I know. But for enablement, there's kind
14 of an element that we would expect there to have to be some evidence this
15 actually works.
16 MR. SUMMERS: Well, it's --
17 JUDGE FREDMAN: And we have a reference that says it doesn't
18 work in rabbits, it doesn't work in primates. I don't see why I believe it
19 works in humans. So, I don't really see the utility unless you want to show
20 the contraceptive in guinea pigs ability.

1 MR. SUMMERS: It doesn't have to be a big use, Your Honor, and
2 actually the 318 litigation makes really clear that you don't have to have
3 things like --
4 JUDGE FREDMAN: Yeah.
5 MR. SUMMERS: -- human testing to
6 JUDGE FREDMAN: Yeah, you don't have to.
7 MR. SUMMERS: I know, but Your Honor, when you say it's not a
8 big utility, it's still a utility.
9 JUDGE FREDMAN: I don't think there's a big utility there, but yeah.
10 MR. SUMMERS: I -- I --
11 JUDGE FREDMAN: I do think it's an enabled claim.
12 MR. SUMMERS: Your Honor, none of those papers address that
13 paper, and I think it's grossly overreading the Martin-DeLeon reference,
14 which says, These papers, these limited set of papers, suggest that there's not
15 a contraceptive utility. They suggest, not conclusively determine --
16 JUDGE FREDMAN: It's a third party who was not paid by either of
17 your two parties who said this, so he's the most credible of all.
18 MR. SUMMERS: And then all he said is they don't suggest it, Your
19 Honor, and I think what you've heard --
20 JUDGE FREDMAN: They don't work.

1 MR. SUMMERS: Let and -- let me actually --
2 JUDGE FREDMAN: Well, he expressly said that they don't work.
3 MR. SUMMERS: He does not expressly say they don't work, Your
4 Honor.
5 JUDGE FREDMAN: He does.
6 MR. SUMMERS: He --
7 JUDGE FREDMAN: Martin-DeLeon at --
8 MR. SUMMERS: The passage in Martin-DeLeon that we are talking
9 about, it says, Taken together, these studies suggest that it does not have
10 contraceptive -- the immune contraceptive.
11 JUDGE FREDMAN: Okay. That means he's saying it doesn't work.
12 MR. SUMMERS: Your Honor, that is not what --
13 JUDGE FREDMAN: You can try and read that a different way, but
14 that's when a scientist writes something. That's what he's saying.
15 MR. SUMMERS: That -- that is not --
16 JUDGE FREDMAN: You can -- you can try to read it otherwise, but
17 that's not what he means.
18 MR. SUMMERS: I'm just telling you what the words were.
19 JUDGE FREDMAN: I don't think he's the first to be the scientist to
20 ever have limited in any other way.

1 MR. SUMMERS: I think you actually have a POSA here with Dr.
2 Share, who respectfully has said that is not. And he was studying in this
3 field at that time, said that is not how that was understood. And he said that
4 this is suggesting it via these routes of administration that this didn't work.
5 There's evidence as to those -- even as to those that there were higher
6 antibody titers from the administration, and if you look at the Pomerin paper,
7 it specifically suggests, as we, as Dr. Share has suggested and as we have
8 suggested -- it specifically suggests that one further route is mucosal
9 administration. The idea that scientific credibility of this was completely
10 quashed is not correct in our view. And quite frankly, petitioner put in later
11 on, petitioner put in post-filing evidence of further studies of whether this
12 was actually having a contraceptive effect. I don't know why you would do
13 that if you were to take Martin-DeLeon as you do, Your Honor, which
14 conclusively established that it has no utility.
15 JUDGE FREDMAN: That's not really asking. Has there been since
16 the publication of all these papers, has there been any showing that there is
17 contraceptive utility?
18 MR. SUMMERS: That's not the question in front of us, Your Honor.
19 JUDGE FREDMAN: I'm asking you.
20 MR. SUMMERS: That’s not on the record, Your Honor --

1 JUDGE FREDMAN: I'm just asking.
2 MR. SUMMERS: -- because that wouldn't be relevant here.
3 JUDGE FREDMAN: Okay. Let's -- so is it your --
4 MR. SUMMERS: Post-filing, I don't know the answer to that, Your
5 Honor, and it's not in the record from either party. Neither party has
6 suggested that.
7 JUDGE FREDMAN: Okay. That's fine.
8 MR. SUMMERS: It would be useless for us to put in --
9 JUDGE FREDMAN: Sure.
10 MR. SUMMERS: Evidence of contraceptive utility that was
11 established in 2024, Your Honor. That's clearly not relevant.
12 JUDGE FREDMAN: I hear you.
13 MR. SUMMERS: So, let me move on to a couple more points.
14 Counsel, I want to get to one thing. Counsel suggested that we had
15 disclaimed some claims that due to some concern about the proceedings.
16 Your Honor, we disclaimed those claims because they, in our view, as you
17 know, those are structural only claims, and we have a lot of claims in front
18 of us. We're simplifying the proceedings as to those. We asked at the
19 institution stage that you properly construe those claims as structural only,
20 and the inclusion of those would have substantially complicated these

1 proceedings. So, it's incorrect to suggest that they signal some kind of
2 concern about those claims. It is a vastly complicated or a vast
3 oversimplification as to those claims.
4 I want to address the Ochoa-Leyva reference that counsel made
5 reference to. This was slide 76. He said this is the only evidence of the
6 effect of mutations in an alpha beta barrel fold. Now, I want to be clear –
7 JUDGE FREDMAN: This is your slide 76?
8 MR. SUMMERS: This is, this was their slide, petitioner slide 76,
9 citing the Ochoa-Leyva paper, and he said this is the only evidence that the
10 alpha -- regarding mutations in the alpha beta barrel fold. The Ochoa-Leyva
11 paper made very clear in its conclusion, and that's at page 955, that they
12 were making drastic changes. That's a quote. They were making drastic
13 changes to the alpha beta barrel fold, and still, in their words, a high
14 percentage worked. So that's not an accurate characterization of the Ochoa-
15 Leyva paper that the alpha beta barrel fold is somehow unstable.
16 I want to make another point clear. Counselor suggested we only rely
17 on the alpha beta barrel fold and just generally the alpha beta barrel fold.
18 We use throughout our papers, and Dr. Petsko was clear to state that in fact,
19 what we're talking about is the PH20 alpha beta barrel fold, which is a
20 different alpha beta barrel fold. I want to also address now petitioner

1 suggested that the homology models are not reliable, and I think that's a
2 convenient position after they've essentially sort of backed out of their
3 obviousness arguments and been told that's not true.
4 But if I can just remind you that Naismith in his report specifically
5 provided an appendix on the reliability of PH20 homology models for
6 showing the structure, it is not accurate to say that we didn't have an
7 accurate homology model for PH20 here. And with that, unless there's other
8 questions, I'm going to reserve the remainder of my time.
9 JUDGE FREDMAN: Thank you, Counsel. Do either of the counsel
10 or my colleagues need a break? Okay. Do you? Are you taking a break?
11 MR. KUSHAN: Mike, I'm going to have my colleague address a
12 couple of the contraception points.
13 JUDGE FREDMAN: Okay.
14 MR. KUSHAN: Sue, Ms. Wang.
15 JUDGE FREDMAN: Okay.
16 MS. WANG: I believe your question was do we need a break, and I
17 think the answer is no.
18 JUDGE FREDMAN: Oh, fine. Okay.
19 MS. WANG: Sorry.
20 JUDGE FREDMAN: It's fine.

1 MS. WANG: Unless you want a break.
2 MR. KUSHAN: Why don't we take a break? I'd be happy to have a
3 break.
4 JUDGE FREDMAN: Yeah. We'll do, like, I'll do two minutes --
5 well, we'll do a four-minute break.
6 MR. KUSHAN: All right.
7 MS. WANG: Thank you.
8 THE CLERK: Oh, thank you. This is good. Let me take that out.
9 (Whereupon, the above-entitled matter went off the record and
10 resumed.)
11 MS. WANG: Oh, let me get the --
12 JUDGE FREDMAN: Switch that.
13 THE CLERK: Yes, Your Honor.
14 JUDGE FREDMAN: All right. Go for it.
15 MS. WANG: Thank you. My name is Sue Wang from Sidley Austin
16 on behalf of Petitioner Merck. So, I wanted to briefly address the utility
17 issue, contraceptive utility in particular, which is a through line for many of
18 these patents, and then Mr. Kushan will address the rest. So, to start off with
19 where counsel for Halozyme left off briefly, the issue of post-priority date
20 publications regarding the testing of PH20 in humans -- it's interesting that

1 Halozyme wants to avoid all of that because those were publications by
2 Halozyme scientists. Those were publications in which Halozyme presented
3 evidence that PH20 in humans, unmodified, does not cause contraception in
4 humans. In those same papers --
5 JUDGE FREDMAN: What are the dates of those papers, Ms. Wang?
6 MS. WANG: I believe the ones we cited: one was 2024, and the
7 other one was 2022.
8 JUDGE FREDMAN: Right, so these are post-filing date.
9 MS. WANG: Those are post-filing --
10 JUDGE FREDMAN: Which is -- he's going to point out I think.
11 MS. WANG: Yes.
12 JUDGE FREDMAN: I hope.
13 MS. WANG: I don't think we dispute the date of publication of the
14 papers, but what they tell us is that they confirm what the person of ordinary
15 skill knew before the priority date based on animal studies. And in fact,
16 these Halozyme publications refer back to those same animal studies to
17 confirm that PH20 does not cause contraception.
18 JUDGE FREDMAN: And you submitted these, right?
19 MS. WANG: That is correct. I was actually digging for my citations,
20 but we are happy to provide them, but this is Exhibit 1134, which is Dr.

1 Kelso's declaration at paragraph 70; Exhibit 1190, which is the Nolan paper.
2 And, I apologize, there's a second paper, which is also cited in Dr. Kelso's
3 declaration.
4 JUDGE FREDMAN: Let me just ask something that I know is in the
5 examination round that actually you don't know that in that case when it
6 comes to this. In the MPEP, it's like 2164, around there at least, the
7 examiner can rely on post-filing date evidence to show non-enablement,
8 right? In other words, the examiner can rely on post-filing reference to show
9 that it would not have been expected to work effectively at the time. That's
10 certainly allowed in the examinations. Is that allowed in our proceedings?
11 Is it in federal circuit cases, do they talk about that at ever?
12 MS. WANG: Well, Your Honor, truthfully, I'm not sure about utility
13 but because utility and the how to use --
14 JUDGE FREDMAN: No, this is enablement --
15 MS. WANG: Right. Exactly. And it is that post-priority date
16 evidence can be confirmatory of what was known before the priority date,
17 certainly.
18 JUDGE FREDMAN: In the examination context, for sure.
19 MS. WANG: And also, in a challenge as well, Your Honor.
20 JUDGE FREDMAN: You're not aware of a case?

1 MS. WANG: Not off the top of my head.
2 JUDGE FREDMAN: That's okay.
3 MS. WANG: I'd be happy to supplement.
4 JUDGE FREDMAN: That's okay.
5 MS. WANG: Yeah. But it is logical that certainly as of today, there
6 is no evidence still of any modified PH20 that has been used as a
7 contraceptive. And that is slide 156, please. Halozyme's doc expert, Dr.
8 Chaire, admitted this. Whether before 2012 or the priority date or after
9 2012, there is simply no evidence that a modified PH20 has ever been tested,
10 let alone shown to have contraceptive effect.
11 Halozyme's counsel asserted specifically with respect to solubility that
12 is a purported utility that you can ignore all other asserted utilities. Saying
13 solubility is a utility is like saying useful biological activity is a utility, and
14 that was expressly rejected in re Kirk. Utility, and also as it feeds into the
15 how to use requirement of enablement, requires a specific and present utility.
16 The ones that are asserted in the specification and in the patent are
17 enzymatic activity, which Mr. Kushan will address, and the contraceptive
18 activity. Slide 155, please.
19 This is the extent, again, of the disclosure of contraceptive activity in
20 the specification. There is no exemplification, as Your Honors already

1 found, of any modified PH20 within the scope of the claim that has
2 contraceptive effect. Halozyme's counsel mentioned that utility is a low
3 burden, or it's a low threshold. Well, however low that threshold is,
4 Halozyme hasn't met it for contraceptive utility. One specific thing we
5 know is that In re Brana permits an asserted utility in the specification to be
6 challenged by the examiner in the examination context, and here by Merck,
7 by putting forward evidence that would suggest a reason to doubt the
8 asserted utility. We have done exactly that. Slide 157, please, and that is the
9 Martin-DeLeon
10 paper. Again, we agree this is perhaps the most credible evidence there is of
11 a person of skill in the art before the priority date reviewing all of the
12 available evidence at that time and concluding that PH20 is not a useful
13 antigen. Useful is right there in the publication for inclusion in
14 immunocontraceptive vaccines. We also have shown, as we showed earlier,
15 there's no exemplification, no disclosure in the specification, and as I also
16 showed earlier, Dr. Share admitted there's no actual evidence outside of the
17 specification either that any modified PH20 was useful or has exhibited
18 contraceptive effects. Halozyme's counsel criticizes the Martin-DeLeon
19 paper. Jump to slide 169, please.

1 I think it's important to note I believe Halozyme is conflating two
2 things here. The ability to produce antibodies against PH20 does not mean
3 the same thing as having contraceptive activity. This is shown throughout
4 the animal studies that we cited, and this is acknowledged in Martin-DeLeon
5 and explained. To the extent that modified PH20 within the scope of the
6 claim can raise antibodies, and we don't even know that because they've
7 never been tested, that does not actually get you to contraceptive activity.
8 There's further testing that would need to be performed and that actually
9 shows that antibody generation without contraceptive effect is possible. And
10 therefore, which ones would generate the antibodies that actually cause
11 contraception, that needs to be taught, and it's not in the specification.
12 JUDGE FREDMAN: Understood. Generally, I obviously agree with
13 you that generating antibodies doesn't mean contraception, but I think to
14 argue that the proteins wouldn't generate antibodies -- there are very few
15 proteins that when they're injected into animals don't generate any form of
16 an antibody.
17 MS. WANG: I appreciate that. I think you inject anything foreign
18 into an animal; it generates antibodies. But that is our point, one, there's
19 been no testing. Even if modified PH20 is within the scope of the claims

1 could generate antibodies, we don't know which of those could generate
2 antibodies that have contraceptive effect.
3 JUDGE FREDMAN: That's what I was thinking.
4 MS. WANG: I think that's everything I had intended to address
5 unless Your Honors have any questions.
6 JUDGE MITCHELL: Can I just ask you, the two papers that are after
7 the filing date, did those deal with -- were those animal models or that was
8 saying there's no contraceptive activity in -- in what? Was it human or
9 animal?
10 MS. WANG: In humans. So, it recited prior experiments with animal
11 models. One of the papers, it was the Prince paper, I believe, also had its
12 own animal models, but then it also reviewed data in humans.
13 JUDGE MITCHELL: Okay. That's what I thought. Thank you.
14 MS. WANG: You're welcome.
15 MR. KUSHAN: I'm going to try to cover – there were a lot of things
16 said. I'll try to be efficient in addressing a number of points. Let's first talk
17 about the 39 proceeding, and this is the method of increasing delivery. One
18 thing you heard was a lot of criticism from counsel about Dr. Hecht and his
19 ability to express opinions on the behavior of these proteins, particularly his
20 comments on EGF domains within proteins. I can tell you one thing, Dr.

1 Hecht has a lot more experience with that than Mr. Summers does, and that's
2 relevant because there is no expert testimony that they presented in that
3 proceeding disputing Dr. Hecht's opinions. They didn't address this question
4 of the difference between activity and the ability to cause spreading until
5 their sur-reply. It's 100 percent attorney argument.
6 The issue that Dr. Hecht addressed was based on his 30-40 years of
7 expertise working with proteins and saying an EGF domain is known across
8 different proteins to have a behavior and role in protein-protein signaling.
9 That's in the Chao paper that's cited, it's Exhibit 1006. And it was his study
10 that led him to say that could have a role in the ability of a PH20 in a
11 properly formed PH20 to behave as it needs to, to degrade that environment
12 in order to cause delivery.
13 JUDGE FREDMAN: But does he have any evidence, it doesn't affect
14 the active site, and it sounds like it doesn't affect the substrate binding site.
15 So, an enzyme presumably can act on the substrate if the substrate is
16 properly presented to it.
17 MR. KUSHAN: Correct.
18 JUDGE FREDMAN: The argument you'd be making, I guess, is that
19 somewhere in the interstitial tissue, there are other proteins that would then
20 bind to and then prevent the hyaluronidase, PH20 hyaluronidase enzyme,

1 from acting. And is there any evidence of that? Because he's otherwise, just
2 speculating, right?
3 MR. KUSHAN: Well, it's not speculation. It's an analysis and an
4 opinion of our expert, and --
5 JUDGE FREDMAN: Yes, I understand that.
6 MR. KUSHAN: Yeah.
7 JUDGE FREDMAN: But if when you say that a protein's activity is
8 affected by a domain that may or may not be present in other -- or the
9 complementary domain isn't present around there, it's questionable whether
10 it matters, right? In other words, if you have a polymerase --
11 MR. KUSHAN: Right.
12 JUDGE FREDMAN: -- which is what I'm more familiar with, right?
13 If you have a polymerase that is acting on nucleic acids to extend the, you
14 know, DNA substrate, right? There are enzymes that are in there obviously
15 they interact with lots of different, you know, accessory factors, right?
16 Those would matter. But if they're not the issue, then it doesn't matter.
17 MR. KUSHAN: I think the point I'm trying to make is they had an
18 opportunity to put in testimony, evidence on the question as you asked them
19 to in their patent owner responses. If they had done that, we would have
20 then assessed whether we needed to bring additional evidence in to address

1 what they said. Raising it in a sur-reply or raising it for the first time in this
2 oral hearing, it's improper, and you shouldn't credit speculation of an
3 attorney over opinions of an expert when you're trying to assess whether --
4 and it's we're not trying to make this kind of the definitive treatise on what is
5 required for spreading. Our expert read the patent.
6 JUDGE FREDMAN: So, you're basically making a procedural point
7 that this is --
8 MR. KUSHAN: It's a procedural point, and it also has -- the patent
9 itself has a special test for measuring this property, which is necessary for
10 the practice of the method. So, like in the recent Wyeth case, the issue there
11 was whether there was adequate guidance about dosing to enable the use of
12 the thing in the method. Same thing here. Do you have evidence in the
13 patent that shows you how to use modified PH20s to increase delivery,
14 which requires assessing their capacity to spread? And it's a research plan to
15 find that out, but it's certainly not a description or an enablement of it.
16 JUDGE FREDMAN: I think Judge Valek has a question.
17 JUDGE VALEK: Yeah, I do have a question. I think the bigger
18 problem for you is not the expert testimony, but the fact that your expert's
19 testimony seems to be contrary to what the specification, the disclosure of
20 the patent, actually says. And that is in column 174, and we discussed this

1 before. It says that any of the modified PH20 polypeptides provided herein
2 can be used to increase delivery, provided that they have the ability to
3 degrade glycosaminoglycans, such as hyaluronan. So, as long as they have
4 enzymatic activity, the patent says they will work for this purpose. And isn't
5 that exactly what the Federal Circuit hung its hat on in the Teva case, where
6 it said that one reading the specification would look at that and know that
7 any anti CGRP --
8 JUDGE FREDMAN: CGRP.
9 JUDGE VALEK: Yeah, sorry, got the -- got the acronym wrong.
10 Thank you, Judge Fredman. But that any of those antibodies would work for
11 that method. I mean, it seems like the spec here is teaching you that one
12 thing. And so, I know your expert has a different opinion, but doesn't what
13 it says in the actual written description control?
14 MR. KUSHAN: I would encourage you to keep staring at that section
15 of the patent specification because it's they're not saying if a PH20 exhibits
16 hyaluronidase activity in any setting. It's speaking of the ability to degrade it
17 in that environment, and that's the central question here. They identified a
18 different test which directly measures the ability of an enzymatically active
19 PH20 to do that, to degrade the environment to the degree needed to cause
20 spreading. And so, it's very clear, we're not in our position -- I want to be a

1 100 percent clear. You absolutely need a modified PH20 that has
2 hyaluronidase activity because it has to break down the HA in the
3 environment. But the patent itself is identifying a function, a characteristic
4 of those that have activity in order to do that. Also, step back a bit. We are
5 very different from Teva. In Teva, it was agreed and the court found there
6 was no dispute that every molecule that was being used in that method, in
7 the claimed method, would work.
8 We are 100 percent opposite of that case. We have 10 to the 57
9 possibilities. We have no idea which of them have activity or which have
10 additionally the ability to cause this effect. But there's no agreement
11 between us and them about whether they have enabled or described the
12 agents to be used in that methodology.
13 JUDGE VALEK: I don't think it was agreed in Teva. I think that it
14 was the procedural posture that it came up on appeal, right? There was a
15 jury verdict there that was in the patent owner's favor. And so, when it went
16 up on appeal, the Federal Circuit said, you know, so long as a reasonable
17 juror could find this. So, I suspect that at trial, the parties vehemently
18 disagreed on this point.
19 MR. KUSHAN: I think the way that the Federal Circuit kind of
20 framed the issue was to recognize that it was not a disputed issue that the

1 claimed molecules would carry out the function required by the method.
2 And it differentiated that case, those facts, from ones where there was a
3 question about whether the claimed molecules could achieve that role. So, I
4 think that's the thing that is really particularly relevant here, because we've
5 presented a tremendous amount of evidence that a lot of these sequences
6 don't turn into things that are enzymatically active PH20s. I also, you know,
7 again, take a look at Wyeth, because Wyeth is very helpfully telling you,
8 you have to provide guidance in carrying out the method, and the guidance
9 here is which PH20s cause spreading. And all they've identified is a test for
10 doing that. And that's another point which supports finding no enablement.
11 Ultimately, foundationally, they have not enabled and described the
12 genus of molecules they're using in this method, and that's an independent
13 reason why you should find these claims unpatentable. I'd like to quickly
14 address -- can you put up slide 29? So, we heard again them trying to say
15 what our position on claim instruction is. These are two pages of quotes
16 from our petition, where we're very clearly framing the legal question of
17 enablement and description through the lens of whether PH20s have
18 hyaluronidase activity. Go to slide 30. That's good. All right. The point of
19 29, 30 of the slides lay out our statements from the petition from day 1 of
20 these proceedings that we're talking about PH20s that have hyaluronidase

1 activity. On the SEAP issue, on the assay, I want to just make a simple point
2 about that. You can look in the assay itself. We've explained, and I'll give
3 you a citation, but in the 46 proceeding, paragraph 248 of Exhibit 1133, Dr.
4 Naismith explained that -- and I'll talk about aggregation in a second. Dr.
5 Naismith explained that the assay that was performed in example 3, they
6 produced the antibodies in wells. They took the supernatants out of the
7 wells. They --
8 JUDGE FREDMAN: The hyaluronidase.
9 MR. KUSHAN: -- the hyaluronidase, when they did that screening
10 assay, and then they tested for activity using the supernatant. There is no
11 experiment done to prove there's any protein, any PH20 protein, in the
12 supernatant. None.
13 JUDGE FREDMAN: Yeah. Your opposing counsel did say they
14 used the same promoter, and that they tracked for the presence --
15 MR. KUSHAN: Right.
16 JUDGE FREDMAN: So, there's some evidence that that promoter
17 was at least expressing stuff.
18 MR. KUSHAN: The problem with relying on expression of a stable
19 naturally occurring protein as your control is you're making proteins that are
20 mutated. And so, you may not have success in transcription of the mutated

1 sequence in the cell, in which case you get plenty of normal SEAP and no
2 protein produced. You can also have a misformed PH20 from the mutated
3 form, which doesn't get out of the cell because it gets broken down as an
4 unstable thing inside the cell. And you can also have it get secreted, and it
5 could aggregate and --
6 JUDGE FREDMAN: So, these are all speculations. Do we have
7 evidence that any of this actually happens in this case?
8 MR. KUSHAN: These are phenomena that our experts are familiar
9 with.
10 JUDGE FREDMAN: There's -- yes, I understand this can happen.
11 MR. KUSHAN: Yeah.
12 JUDGE FREDMAN: Some of the experience we mentioned in the
13 paper.
14 MR. KUSHAN: Right.
15 JUDGE FREDMAN: There's no evidence in this case that any of
16 these things happened.
17 MR. KUSHAN: We would love to have evidence, but their patent
18 doesn't reveal the evidence. Remember, there are all of these inactive
19 mutants --

1 JUDGE FREDMAN: I mean, one of the things that I often think is
2 you are allowed to do more experiments and things like that. You know,
3 there's limited time to keep those --
4 MR. KUSHAN: Right.
5 JUDGE FREDMAN: But you could do the experiments too.
6 MR. KUSHAN: I think --
7 JUDGE FREDMAN: You chose not to.
8 MR. KUSHAN: I think in this setting, it's a matter of crediting Dr.
9 Petsko's comments that if you make indiscriminate changes throughout the
10 sequence, billions won't fold, right? If it doesn't fold, it's not coming out of
11 the cell. Right? That's foundational. You can find that in Petsko. So, I
12 think there's a lot of science supporting those opinions that all these
13 scenarios that Dr. Naismith and Dr. Hecht each identified as happening, as
14 being possible reasons. And again, they made 11 percent of the population,
15 and they didn't report results on it. You could probably infer that's the set of
16 sequences that didn't get out of the cell, or maybe it could. Who knows?
17 But the point of it is there's a lot of scientific foundation supporting that
18 testimony from our experts. Keep in mind, a protein that did get out and had
19 18 percent activity is also inactive. So, it just can't differentiate. It doesn't
20 give you the capacity information to answer those questions.

1 On the issues of aggregation, could I please have slide 71? Dr. Petsko
2 in his textbook has this illustration of a single mutation causing the protein
3 to become unstable, be secreted from the cell, and then with one mutation,
4 that instability causes it to aggregate. Right? This is his textbook, kind of
5 with a simple illustration that even a single change in a protein can induce
6 the disforming of that protein that would lead to aggregation. And slide --
7 JUDGE FREDMAN: Is this peer-reviewed online? That's sort of
8 one aggregation present that --
9 MR. KUSHAN: Well, I mean, I find that textbooks, you have to get
10 to a level of comfort with the phenomenon before you put it in a textbook,
11 right? There's --
12 JUDGE FREDMAN: Certainly.
13 MR. KUSHAN: But let's also look at slide 91. This is a paper that --
14 sorry, this is a textbook; Branden and Tooze explaining why any protein has
15 a phenomenon of aggregation as a risk. It's because when they're inside the
16 cell, they get carried around in chaperones, which prevent their disformed
17 state from causing aggregation. Once they get into the extracellular space,
18 there's no chaperone. If the, you know, hydrophobic bits are still exposed,
19 you have aggregation. Aggregation leads to insolubility. Go to --

1 JUDGE VALEK: What about the testimony that Mr. Summers
2 referred to, I believe it was from Dr. Petsko, where he said that this
3 aggregation problem where you have a single mutation causing a protein to
4 aggregate, and that's a relatively rare phenomenon?
5 MR. KUSHAN: I'd encourage you to read his paper, which is Exhibit
6 1152, Ring and Petsko. It's addressing the same thing I just mentioned from
7 the textbook about chaperones being important to prevent aggregation. He's
8 saying, if you have marginally stable proteins in the environment, such
9 molecules can aggregate with another -- or with properly functioning
10 proteins with deleterious consequences to the cell. Protein chaperones
11 prevent these unwanted associations by sequestering unfolded and misfolded
12 proteins.
13 If it happens only when you modify a protein with 100 changes, and
14 only once or twice in that protein, why is he putting it in his paper? This is a
15 phenomenon that you find in textbooks. It's well-documented, and it occurs
16 when proteins are modified. It's the mutations that give rise to non-normal
17 folding, which then has the risk of exposing parts of the protein that
18 normally aren't exposed to the aqueous environment. But again, they could
19 have put all this in responsive expert testimony, and they chose to not do
20 that. So, we're having a fight about foundational science issues for the first

1 time in front of this panel, which I think is the wrong way to have a fight. I
2 think we need --
3 JUDGE VALEK: Well, but --
4 MR. KUSHAN: -- we need to look at the record and trust some of
5 these testimony, some of the statements from these experts, which are
6 founded on and based on these well-established scientific principles. Sorry,
7 you were going to ask a question.
8 JUDGE FREDMAN: Judge Valek.
9 JUDGE VALEK: Yeah, I was just going to say, well, I think that
10 your point about them not putting in responsive testimony from their own
11 expert. I think their response to that might be that, Well, we got an
12 admission on cross from your expert, and isn't that even more probative on
13 the point?
14 MR. KUSHAN: They didn't get an admission from our expert on
15 aggregation. This is their expert's testimony in cross-examination, which
16 you can weigh that a little bit differently because it's not responsive. So, I'll
17 just -- if they had induced one of our experts to admit that aggregation never
18 occurs, we'd be having a very different conversation. But --

1 JUDGE VALEK: I don't think the point was that it never occurs, but
2 that kind of it's the exception rather than the rule. It's relatively rare, I
3 believe, was the quote in the testimony they cited.
4 MR. KUSHAN: Well, we --
5 JUDGE VALEK: You don't dispute that.
6 MR. KUSHAN: I think it's -- I don't -- I wouldn't -- I wouldn't, -- I
7 can't agree with that as it's a little bit too broad of a statement and the point
8 is there's two points to that. One is it very much depends on what you've
9 done to the protein, right? What the what the textbooks tell us is if you have
10 distorted the protein significantly, then you're going to expect to see a lot
11 worse aggregation. Second point is: out of 10 to the 57 possibilities, small
12 turns into only, like, what? 10 to the 30. I mean, it's the scale is also
13 dwarfing some of these points they're making. And finally, rare wasn't our
14 testimony. It was their expert's testimony, which I don't believe is credible.
15 You can also look in the data. In my opening, I pointed out if there's
16 not a problem with mutating PH20, then why did Dr. Petsko say it's not a
17 stable protein? It's something that even little changes to has an impact on;
18 70 percent or more of the single mutations are deleterious. That's a signal
19 that this protein isn't doing well coping with modifications to the sequence.

1 We heard a comment about the paper from the Ochoa group, which I
2 believe is 1144. Again, another topic where we had our experts address this
3 paper and its findings from the literature, explain why this is a good analogy
4 to this case because it's putting 4 to 19 changes at the same time into the
5 protein of the scale that we're dealing with here. And contrary to Mr.
6 Summers' comments, the paper is actually explaining they put them in the
7 loop regions in between the segments that are more rigid, and that was done
8 in order to increase the likelihood of folding. So, it was surprising that when
9 you put those changes into that part of the protein, the flexible portion in
10 between the rigid bits, so many fail to fold, which is basically signaling the
11 unpredictability of making this many changes at the same time in a protein,
12 in an enzyme, in the same kind of conceptual class as PH20.
13 Homology models. I would very much ask that you look at the
14 testimony that Dr. Park and Dr. Hecht and Dr. Naismith have put in on this
15 case on homology models. One of the things that you will see in there is Dr.
16 Park's very careful explanation that homology models give you a rating of
17 quality of the model across the modeled region. Do we have that slide with
18 all those blue and purple colors? Anyway, so you get a rating of – yeah --
19 this is basically what you see in a PH20 data file, the model that was created,
20 and it's a rating of the quality of the model.

1 JUDGE FREDMAN: I think it's slide 140.

2 MR. KUSHAN: That's slide 140, Exhibit 1133 in Appendix B. The
3 point of this is that the scientists using homology models know that you can
4 assess how well the homology model is modeling the protein with factors to
5 judge the quality at that position. All of the testimony that we put in based
6 on homology models in this case are at positions with sufficient quality, and
7 Dr. Park very clearly explains that was a condition of him reaching
8 conclusions based on the model, on the homology model. Here, what we
9 said are two things. One, we didn't condemn homology models as a tool.
10 What we did was we condemned them as a tool for modeling the end of the
11 protein where there is no model. Like, you cannot use a homology model to
12 tell you what 20 changes you can introduce in the last 60 residues of PH20
13 because there's no model. It's not just not there.

14 JUDGE FREDMAN: Would you agree that you could reliably do it
15 in the rest of the protein or not?

16 MR. KUSHAN: No. And that's where it's -- there is you can do one,
17 two, three. I think the experts all have kind of focused on at some point
18 around five, you've exceeded the capacity of the model to be reliable
19 because you're now introducing too many changes relative to the known
20 structure to be reliable. So, all of our testimony has been clear from day

1 one. Homology models are a useful tool. They have limits in terms of what
2 you can do with them. There's quality limits. You need to have the right
3 template, and so you have to limit your analysis to where you have a
4 credible, reliable structure. And you could do it for one, you could do it for
5 two, possibly three, depending on which changes are being made. But at
6 some point, you lose the ability to have any confidence in the model.
7 I also will point out that Dr. Naismith -- you heard a number of
8 comments about predictability -- Dr. Naismith has explained there's this
9 phenomenon called epistasis, which is where you put more than one change
10 in at the same time, and they start to interact the protein in a very
11 unpredictable way. You cannot detect epistasis or epistatic effects in a
12 homology model because it's a dynamic process depending on all the
13 different changes happening at the same time. When you're doing a
14 homology model like Dr. Park did, everything is the same as a naturally
15 occurring protein, same sequence, same structure, one change, and that is
16 something which was feasible. Could you go to slide 148?
17 The other thing you heard from Mr. Summers was that discussing the
18 ease with which somebody like Dr. Petsko could navigate predictions around
19 changes made into a PH20 sequence. I want to make sure you understand
20 what Dr. Naismith was addressing in paragraph 131. He basically took the

1 best-case scenario where the positions being investigated for change were all
2 the ones that were highly tolerated or 60 percent or higher tolerated changes.
3 You're limiting it to the ones that actually did work as single changes, and
4 you also limited to five changes at once. All we're saying here is if you just
5 understand how much labor assessing that best case scenario from Dr.
6 Petsko, 60 billion days of working 24 hours a day, right? That's the scale of
7 assessment where you're putting the different amino acids in the homology
8 model and doing some kind of a quick assessment of viability. Computer
9 technology was not at the level that let you do it automated. So, this is them
10 saying, look at it in a homology model and give us a readout.
11 The point of this is, when we say they haven't even explored a sliver
12 of the sequence space, that's true. These examples are the ones that they're
13 so small that you probably wouldn't even get a percentage above like point
14 many zero before you get a number. I think it's important to appreciate the
15 scale of what's been put on the shoulders of the public to figure out which of
16 the modified PH20 polypeptides are enzymatically active and useful. It's
17 unfair. This is the essence of why we have the requirements of 112, both
18 written description and enablement. You get what you give, right? You
19 have entitlement to a claim that's commensurate in scope with your
20 contributions. If they claim their single mutants, we wouldn't be having a

1 dispute with them. When they claim mutants with 20 changes that span this
2 scope, we have a problem under 112. Any other questions?
3 JUDGE FREDMAN: Any further questions? Thank you. You
4 ready?
5 MR. SUMMERS: My apologies. While he works through that, no
6 need to wait.
7 JUDGE FREDMAN: Go ahead.
8 MR. SUMMERS: So, I wanted to start from counsel's discussion of
9 Dr. Hecht's speculation about this EGF domain's role in spreading. I want to
10 make a really basic point, which is --
11 JUDGE FREDMAN: Did you bring it up earlier?
12 MR. SUMMERS: -- the --
13 JUDGE FREDMAN: That it was in there. It was in Dr. Hecht's
14 testimony, correct?
15 MR. SUMMERS: -- the EGF domain?
16 JUDGE FREDMAN: Yes.
17 MR. SUMMERS: The speculation. We -- we --
18 JUDGE FREDMAN: The speculation -- just say it was originally in
19 his testimony, right?

1 MR. SUMMERS: We did, actually. Let me get exactly to what I
2 think is this. Dr. Simpson talks about in her report the, and I don't think it's
3 disputed, it was known in the art that bee venom hyaluronidase lacks an
4 EGF domain. We talked about that in Dr. Simpson's report. Of course, the
5 reason hyaluronidase is present in bee venom is to help venom spread. That
6 also was known in the art. The idea, again, it comes back to this sort of lack
7 of familiarity with hyaluronidases and hyaluronidase. Like, there is no EGF
8 domain in bee venom. It still functions as spreading. I just want to make
9 that one point. Dr. Simpson talks about what was known about bee venom
10 as well as the how.
11 JUDGE FREDMAN: You just --
12 MR. SUMMERS: If you're --
13 JUDGE FREDMAN: Can you point us to that -- for us?
14 MR. SUMMERS: I can. I'm just going to --
15 JUDGE FREDMAN: You can get him to do that.
16 MR. SUMMERS: -- ask my counsel to hand me those paragraphs. I
17 could make a copy of them for you while I do this as well. So, I also want to
18 say, I think Your Honor pointed out something very important about the
19 Teva case, which is, like the Teva case here, the patent says that spreading is
20 a function of enzymatic activity. I know counsel tried to take some issue

1 with what that disclosure in the spec says, but it says, Due to such activity,
2 and then it's referring to hyaluronidase activity. It's not saying you need to
3 do some other test. And then --
4 JUDGE FREDMAN: But before you get to that, let me just finish the
5 procedural point. I think that's still important to me, at least. So, in response
6 to this argument that they made, you didn't bring out evidence other than
7 what problems as Dr. Simpson stated earlier, and you brought it up in your
8 sur-reply but not previous.
9 MR. SUMMERS: Because they are the same -- because enzymatic
10 activity is a function of spreading, that's what was addressing it, Your
11 Honor. I don't know.
12 JUDGE FREDMAN: So --
13 MR. SUMMERS: In our view, there's no --
14 JUDGE FREDMAN: In your view, there's no difference --
15 MR. SUMMERS: Right.
16 JUDGE FREDMAN: And you already did it, but they would argue
17 that you didn't.
18 MR. SUMMERS: And then when counsel tried to sort of bring in this
19 additional and as you noted, we have discussed this in our sur-reply. When
20 they, and within their reply, they said, Well, there's this additional test that

1 you really need to do additionally. And we addressed that. We, we
2 addressed what the spec actually says, and it comes back to that point, Your
3 Honor.
4 JUDGE FREDMAN: Okay.
5 MR. SUMMERS: So, sorry if I was not answering the complete
6 question. Thank you for the opportunity there. I also just want to focus on
7 something that maybe will get us to some common ground here, which is
8 there is an actual reduction in practice on which counsel is relying, example
9 14, showing that an enzymatically active modified PH20 causes spreading.
10 That's that mice assay which they say, when counsel said –
11 JUDGE FREDMAN: It's PF 204F.
12 MR. SUMMERS: That's right. He said the test is necessary for
13 practice of the method, and that is not what the claim says. It's not what the
14 spec says. The spec says that what's necessary for practice of the method is
15 enzymatic activity. But to the extent we're looking for common ground
16 here, everyone agrees there's an actual reduction of practice showing that
17 that enzymatic activity -- it doesn't have to be increased enzymatic activity --
18 but enzymatic activity leads to further spreading. You don't have to test just
19 the specific 320 mutation that's at issue in the 185 patent. It was sufficient
20 that they tested the F 204 key. And let me just give you one last cite on this

1 bee venom point. That's the Jung reference, Exhibit 1010. It has a high L
2 homology model over bee venom, showing that bee venom lacks what they
3 refer to as the EGF domain, and I think that's relatively insignificant to this
4 idea that Dr. Hecht was raising, the point that you weren't given any rebuttal
5 other than showing the symptomatic activity. We did, in fact, put that in.
6 That paper is in the record, and I'm going to get you the cites for Dr.
7 Simpson.
8 Counsel also suggested this is somehow very different from Teva, and
9 I think Your Honors got it correct what the actual posture was there when he
10 suggested that it was about all molecules. And this is where I really think
11 the Ajinomoto case is telling. And Teva says it's operating on the same
12 principles that helped decide Ajinomoto. So, I just want to come back to
13 this section of the Ajinomoto case because I think it's very important for us.
14 This is 932 F 3 D 1360. And they say, CG -- that's the Defendant here --
15 disputes the similarity to the consensus sequence that finds a common
16 structural feature, citing several articles indicating that a promoter closer to
17 the consensus sequence will not always be stronger than one farther from the
18 sequence. Then it goes on to list that evidence out.
19 Counsel suggested inaccurately that Teva -- that they agreed that they
20 were all useful, that the anti-C G R P molecules were all useful. But what's

1 very clear is that in Ajinomoto, they don't agree. They actually go through
2 the evidence saying that it does not -- that these principles with them, which
3 they are relying to make more current promoters. It says specifically, and
4 again, this is 1360, Did not hold true for E. Coli where you're using these
5 promoters. It says, Here, the promoters which either had an error in the
6 consensus sequence or a shorter spacer were relatively strong. So actually,
7 the things that got further away. So, there's quite a bit of unpredictability
8 related to that there was not agreement that all of the promoters worked or
9 all promoters worked -- that's not a necessary prerequisite to apply this line
10 of cases from Teva and Ajinomoto.
11 Counsel also suggested that, as to solubility, that we were having a
12 fight for the first time in front of the panel about some fundamental science.
13 I want to make two points about that. The first is it's their burden, and if this
14 was an issue that they thought was raising to the level of needing to address
15 it previously, they should have addressed it. The second is I'm actually quite
16 glad we all seem to agree that Dr. Petsko, between the two of us, that Dr.
17 Petsko is quite an expert on this phenomena of aggregation, and you saw
18 them relying on his testimony about aggregation and about the effect of
19 mutations on aggregation.

1 Now again, I think they're mistaking principles of aggregation when
2 things aggregate over time with solubility. But if you look at Dr. Petsko's
3 testimony in that regard, he provided it on cross-examination. It's of record.
4 They have relied on it, and we are relying on it because we think if you look
5 at that entire section, you will see he said it is not a common phenomenon.
6 And that is relevant here to the question of, like they're trying to throw into
7 the air, that you don't know whether they're going to be soluble. But what
8 we do know, there's no data suggesting that. Not a single assay provided by
9 petitioner, and petitioner's had an opportunity to stand up and rebut and say,
10 Well, no, you do know that sometimes mutations cause aggregations in
11 PH20. Didn't say that. Dr. Petsko testified he would not expect that for
12 PH20. He testified that from 40 to 50 of his deposition, he testified it is a
13 protein-dependent question, and he showed you something from his
14 textbook talking about amyloid fibers that do aggregate and cause,
15 tragically, ALS. That is again protein-dependent. For PH20, he testified
16 you don't expect it. And we do have a test in the record, the SEP assay that
17 does test for expression in the supernatant. Now, the petitioner pointed to --
18 JUDGE FREDMAN: How many of the mutations were actually
19 tested in that assay?

1 MR. SUMMERS: -- all of the mutations that are provided across the -
2 -
3 JUDGE FREDMAN: Yes, but do they show that the protein was
4 expressed in --
5 MR. SUMMERS: The protein was expressed into the supernatant.
6 That's correct.
7 JUDGE FREDMAN: But all of them were tested?
8 MR. SUMMERS: That -- that's correct. So, all --
9 JUDGE FREDMAN: Even the inactive ones?
10 MR. SUMMERS: -- all the reported mutations in the patent were
11 tested via the SEP assay.
12 JUDGE FREDMAN: So, does that mean the 11 percent that were not
13 reported may not have been tested or were found that --
14 MR. SUMMERS: The 11 percent, they would've been excluded out
15 from the SEP assay otherwise. Yeah. So, and let me -- the testimony that
16 petitioner pointed to, 11:33, page 187, the only thing they said about this
17 assay, and this he said, We addressed this. This is in a reply declaration,
18 again, and all they say is it's row net, far down, there's D, E, F, G, H, and I.
19 And it just says, No protein-level evidence that PH20 was expressed or

1 secreted from mutants classified as inactive and no validation that SEP
2 normalization controlled for consorts.
3 JUDGE FREDMAN: So how do you know it was there if there was
4 no activity? What were they measuring then? Were they doing antibody
5 testing? I'm just curious.
6 MR. SUMMERS: Okay, I'm sorry. I didn't hear.
7 JUDGE FREDMAN: In other words, if you have the PH20 that was
8 supposedly expressed in an inactive mutation, you're not going to see
9 hyaluronidase activity, right? So, what was the assay? How was it actually
10 operating?
11 MR. SUMMERS: The -- the --
12 JUDGE FREDMAN: Was it an antibody test?
13 MR. SUMMERS: Sure. So, Dr. Simpson takes this on, Your Honor,
14 and provides a three-paragraph-long explanation about the SEP assay. I
15 wouldn't --
16 JUDGE FREDMAN: What is the SEP assay?
17 MR. SUMMERS: Presume --
18 JUDGE FREDMAN: Where is it?
19 MR. SUMMERS: I wouldn't presume to take her place in that regard,
20 Your Honor, but let me make sure I've got the paragraphs ready for you to

1 evaluate here. In the case in question, in particular, I'll give you the
2 paragraphs. So --
3 JUDGE FREDMAN: Which exhibit is it?
4 MR. SUMMERS: It is Exhibit 2068. That's common across all --
5 JUDGE FREDMAN: All right.
6 MR. SUMMERS: -- exhibit numbers, and it is paragraphs 201 to 203.
7 And she starts in 201 by explaining, in addition to measuring hyaluronidase
8 activity, SEP activity in the supernatant was also measured. And then she
9 goes on to cite where that is provided in the where that's described in the
10 patent, and she goes on to also explain how they were testing in order to --
11 JUDGE FREDMAN: Okay, so the SEP assay, somebody using an
12 alpha phosphatase, it doesn't actually measure the presence of P H 20 at all.
13 The issue is there's an assumption that they're co-expressed, but there's no
14 evidence that the PH20, which potentially could have been malformed and
15 therefore was inactive because of that, was expressed.
16 MR. SUMMERS: Two things about that, Your Honor. There's no
17 evidence, and petitioner's not arguing --
18 JUDGE FREDMAN: Well, I understand, but there's no evidence
19 either way. So, it's silent.
20 MR. SUMMERS: -- they --

1 JUDGE FREDMAN: So, basically, all we have is we know that
2 they're inactive. Maybe there was protein. Maybe there wasn't. We just
3 don't know.
4 MR. SUMMERS: For inactives that had an SEP reading, maybe they
5 expressed --
6 JUDGE FREDMAN: Well, but --
7 MR. SUMMERS: And maybe they weren't expressed.
8 JUDGE FREDMAN: Right.
9 MR. SUMMERS: If you don't take the SEP activity assay at its face
10 for showing co-expression, then that would be the case. But Dr. Simpson --
11 JUDGE FREDMAN: Well, it doesn't --
12 MR. SUMMERS: -- Dr. Simpson.
13 JUDGE FREDMAN: -- it shows, I mean, one doesn't map because
14 the answer is ultimately no. In other words, it could be expressed but
15 immediately disintegrated by internal stuff. I mean, I'm just -- the SEP assay
16 is simply telling you without alpha --
17 MR. SUMMERS: I see. I see your question. No, it's not. It's not
18 measuring if there were immediate degradation. I understand your question
19 now.

1 JUDGE FREDMAN: -- or anything like that, or any of the other
2 problems.
3 MR. SUMMERS: Yeah. I think I misheard you. One thing I do want
4 to make clear, though, too is still we haven't focused on this, but you did in
5 the prior hearing.
6 JUDGE FREDMAN: Mm-hmm.
7 MR. SUMMERS: The patent does teach you that it is essential to
8 know from the art what residues, what, and what mutations will actually
9 have an effect on folding, right? So, you do know from this process by just
10 changing each individual amino acid which ones will have an effect on
11 folding.
12 JUDGE FREDMAN: I mean, clearly having multiple changes could
13 have other effects that a single change would not have because it would
14 interact with cross-barrels across them. I mean, I hear your point.
15 MR. SUMMERS: Again, there's no evidence --
16 JUDGE FREDMAN: No, there's evidence that multiple mutations
17 affect folding and maybe that. So, there is evidence there, but I hear your
18 point.
19 MR. SUMMERS: Yeah, okay. And we respectfully disagree about
20 the evidence as to PH20 in the --

1 JUDGE FREDMAN: I'm not going to get into that.
2 MR. SUMMERS: -- record, and I think that is –
3 JUDGE FREDMAN: Their burden to put forward. Let me give you
4 that cite just finally.
5 JUDGE FREDMAN: Oh, sure.
6 MR. SUMMERS: Apologies. So, this is Exhibit 2068, paragraphs
7 117, 118, and 120 to 125. Let me just make -- and, yeah, that's the -- that is,
8 that's from her declaration in the 733.
9 JUDGE FREDMAN: Is that the spreading? That's the spreading.
10 MR. SUMMERS: Yes.
11 JUDGE FREDMAN: That's the spreading.
12 MR. SUMMERS: Yeah. That's what we started out talking about,
13 Your Honor. I want to address with my remaining time a couple of other
14 comments that counsel made. Now, counsel came and said they've been
15 very careful and consistent about homology modeling and its reliability and
16 saying that it can't be used. I'm going to again point you to Naismith, their
17 reply declarant, summarized their positions on homology models and
18 whether they are reliable. That's appendix B 12. And it specifically says
19 that there was a reliable model, homology model of PH20. Now, one thing,
20 Counsel, I think was --

1 JUDGE FREDMAN: I think the discussion with that is talking about
2 common mutation. For a single mutation, perhaps, number 5, I think it's
3 pretty clear most of the experts are saying 5 doesn't work, and clearly you're
4 right.
5 MR. SUMMERS: They say five do work --
6 JUDGE FREDMAN: Actually, up to five work. That is their
7 testimony. Your claim goes well beyond five, so it doesn't really matter.
8 MR. SUMMERS: Whatever you think of that testimony, that is, that -
9 -
10 JUDGE FREDMAN: Your claim includes, like, 6, 7, 8, 9, 10, 11, 12,
11 13, 14, 15, 17, 18, 19.
12 MR. SUMMERS: The -- the --
13 JUDGE FREDMAN: Quite a bit more.
14 MR. SUMMERS: This is where I want to get at something counsel
15 suggested, which is no one is suggesting that you're going to introduce those
16 mutations into the homology model and see what you get. That is not how
17 protein engineering proceeds. That's not how their expert proceeded in their
18 obviousness analysis. They agreed that what you do is a visualization.
19 You’re going to use that homology model as a visualization tool, but you're
20 also going to use all of the data in the patent because you know what the

1 effect of activity is, and you're going to use your knowledge of the effect of
2 individual amino acids on structure in making that evaluation. I just want to
3 be clear about that one point. This is not a case where we're saying you just
4 plug in 20 modifications into a homology model, and that was sufficient.
5 JUDGE FREDMAN: But your claim encompasses all that.
6 MR. SUMMERS: You --
7 JUDGE FREDMAN: In fact, your claim is a product claim.
8 MR. SUMMERS: I'm just talking about --
9 JUDGE FREDMAN: So, it expressly encompasses that, and you're
10 claiming all of that.
11 MR. SUMMERS: No, no, I'm talking about the routine methods that
12 POSAs use to make these mutations.
13 JUDGE FREDMAN: But you're claiming all that. Whether or
14 POSAs do it or not, you're claiming it.
15 MR. SUMMERS: We're somewhere at odds and we're missing each
16 other, Your Honor. So let me just try to say it the same. I agree that the
17 claims encompass modified PH20s in the instance. For instance, your
18 claims in the last tranche is generally 19 amino acids. Sometimes it varies
19 depending on the sequence like --
20 JUDGE FREDMAN: Okay.

1 MR. SUMMERS: I agree with you there. I'm not trying to say
2 anything to the contrary. Counsel suggested that what we're talking about
3 when we talk about how POSAs would reliably practice this invention, what
4 they would do and why it's predictable, that what they would do is plug
5 these into a homology model. Now, that's not what anybody has said. I just
6 want the record to be clear about that.
7 Dr. Petsko goes pretty painstakingly through what that method is. Dr.
8 Hecht talks about that method. We've quoted before you the fact that this is
9 a common method that POSAs use in protein engineering to make this
10 visualization-based assessment. But what I'm saying, Your Honor, is just
11 we're not trying to say that what you do when you're trying to make practice
12 that routine method is just plug it into a homology model and let it run and
13 then make your decision. You're looking at the homology model of hyal1,
14 which counsel and annexed their own expert, Dr. Naismith, in his D12, he
15 says that's reliable.
16 JUDGE FREDMAN: I mean, I think the argument here is: for any
17 particular single mutation or multiple mutations, you might do that. Their
18 point is you can't do that at scale.

PGR2025-00017 (12,110,520 B2)
PGR2025-00033 (12,049,652 B2)
PGR2025-00039 (12,104,185 B2)
PGR2025-00046 (12,091,692 B2)
PGR2025-00024 (12,060,590 B2)
PGR2025-00030 (12,054,758 B2)
PGR2025-00052 (12,264,345 B1)
PGR2025-00042 (12,037,618 B2)
PGR2025-00050 (12,077,791 B2)
PGR2025-00053 (12,195,773 B2)

1 MR. SUMMERS: They've argued that you can't do that at scale. I
2 want to be very clear about that. Our experts who are performing this
3 visualization based --
4 JUDGE FREDMAN: I'm just curious. One of my colleagues is
5 raising this. Do you have any narrower claims that are not challenged, that
6 are just limited to single mutations?
7 MR. SUMMERS: Narrower claims that are not challenged? Your
8 Honor, I don't want to represent across the --
9 JUDGE FREDMAN: But it --
10 MR. SUMMERS: Full portfolio. I'm not comfortable doing that.
11 JUDGE FREDMAN: Okay. That's fine.
12 MR. SUMMERS: I'm sorry.
13 JUDGE FREDMAN: No -- no.
14 MR. SUMMERS: I wish I could give you that answer, but it's --
15 JUDGE FREDMAN: That's okay.
16 MR. SUMMERS: There's a relatively large portfolio, and I wouldn't
17 want to --
18 JUDGE FREDMAN: You don't want to be sure you're --
19 MR. SUMMERS: -- face up to misrepresentation later on.
20 JUDGE FREDMAN: In this case, yeah -- yeah.

1 MR. SUMMERS: -- especially with one like that.
2 JUDGE FREDMAN: Sure. Absolutely. Fair.
3 MR. SUMMERS: Okay. I -- I appreciate your forbearance there. Let
4 me just address one last point about contraception here, and I think I'm close
5 to my end. Counsel made reference to, you know, cases where the utility is
6 useful biological utility, useful biological activity outlining cases that you
7 can't just cite useful biological activity and specifically said you can't just
8 recite a generic utility. Solubility is not a generic utility. The natural PH20,
9 the PH20 that we've talked about, is not soluble. It is a function of some of
10 them when they have had the GPI anchor --
11 JUDGE FREDMAN: I mean, I think that's --
12 MR. SUMMERS: -- to be soluble.
13 JUDGE FREDMAN: When they're talking about that, that's really
14 just saying you can't claim something that's just a non-practical utility, and I
15 think arguably that's a non-practical utility for basically a mutation, right?
16 You're trying to claim any mutation that happens to be soluble. There's no
17 practical utility for solubility other than being used if you want to put it in a
18 vial and give it for a targeted treatment of a patient with cancer, really, or
19 some other disease where you're trying to get the drug in. So that's the

1 utility. The utility is treatment of a patient. The utility is not, Oh, but it's
2 soluble, so now we can have it in a tube, and it won't aggregate too fast.
3 MR. SUMMERS: Again, I respectfully disagree, but let me just also
4 get to the second point, which is, to the extent you think there needs to be an
5 additional utility, that enzymatic activity for the method of increasing
6 activity claim, that is a utility.
7 JUDGE FREDMAN: Yeah.
8 MR. SUMMERS: I -- I --
9 JUDGE FREDMAN: That I don't remember.
10 MR. SUMMERS: I agree with you on that.
11 JUDGE FREDMAN: I don't think they've argued on that one.
12 MR. SUMMERS: And I don't think anybody's challenged the
13 scientific credibility of that.
14 JUDGE FREDMAN: They argue that but --
15 MR. SUMMERS: I appreciate again your forbearance with me, Your
16 Honor, and making that clear, but I do want to make that very clear. Let me
17 take on just this last question --
18 JUDGE HARDMAN: Counsel, it's Judge Hardman. Can I jump in
19 real quick and just shift gears? On the 0052 case -- that's the 345 patent --
20 those claims introduce the term hyaluronidase domain that I don't think

1 appears in any of the other patents. Mr. Kushan identified in his opening
2 arguments what he called the new matter issue that the specification doesn't
3 focus on mutations in the hyaluronidase domain, and that's one reason why
4 they argue 112 issues. Do you have a response to that?
5 MR. SUMMERS: Yeah, so I think the specification does the example
6 11 and I've gone and gotten my note on this, Your Honor, to respond to this.
7 But example 11 deals with two variants. One's the F204P; one's the P58R.
8 And both of those variants have ROLME change within the hyaluronidase
9 domain. So, I think what you see is that there is in fact something that's not
10 new matter in that regard, Your Honor. Let me -- I'm sorry. If there's any
11 other questions on that, I'd like to address them.
12 JUDGE HARDMAN: Ok, thank you.
13 MR. SUMMERS: Does that answer your question, Your Honor?
14 JUDGE HARDMAN: Yes, thank you.
15 MR. SUMMERS: Great. Thank you. I want to address this last
16 question of post-priority evidence. In some cases, post-priority evidence can
17 be relied on for evidence of non-enablement. That is true. It cannot be
18 relied on for enablement. I think counsel suggested that as a possibility.
19 Post-priority evidence cannot be relied on as evidence of enablement. That's
20 generally --

1 JUDGE FREDMAN: For non-enablement?

2 MR. SUMMERS: -- for non-enablement, there are some cases where
3 it's been allowed.

4 JUDGE FREDMAN: Right, right. But we're talking about
5 contraceptives and papers that show that a PH20 does not function as a
6 human contraceptive, so that would be relying on the evidence to show that
7 you're not enabled.

8 MR. SUMMERS: So, this is --

9 JUDGE FREDMAN: So, you're agreeing that that would be allowed?

10 MR. SUMMERS: -- so this is the point that I want to make about
11 this. Credible utility is still judged at the time of filing, and that's what Dr.
12 Share addressed. They've relied on some post-priority evidence here.

13 JUDGE FREDMAN: Sure.

14 MR. SUMMERS: We can't -- we can't certainly rely on post-priority
15 evidence of enablement. So, to your question earlier --

16 JUDGE FREDMAN: I see. Here's the way that if you happened to
17 have that --

18 MR. SUMMERS: That -- that's --

19 JUDGE FREDMAN: -- it wouldn't be available to you.

20 MR. SUMMERS: -- it would be strictly incorrect.

1 JUDGE FREDMAN: Or it shouldn't be.

2 MR. SUMMERS: That is correct.

3 JUDGE FREDMAN: Right.

4 MR. SUMMERS: But what we addressed is that credible utility at the
5 time of filing. And to that end, I think it's important that at that point in time
6 Dr. Share takes on, and he's the only person who has experience in this field.
7 He wasn't working in this field during this time. He takes on why it's still
8 maintained scientific credibility. The last point I want to make about this
9 too, post-priority, is they were not trying to use PH20 as a contraceptive
10 there. That isn't their hypothesis in that way. So, that's just one last point I'd
11 like to make. And with that, unless there's any further questions, I will sit
12 down.

13 JUDGE FREDMAN: Well, thank you very much.

14 MR. SUMMERS: Thank you very much, Your Honors.

15 MR. KUSHAN: Your Honor, I normally would never ask for this. I
16 just would like 10 seconds to give you two citations.

17 JUDGE FREDMAN: I think you're going to hear I'm sorry. I think
18 there's just no time.

19 MR. KUSHAN: It’s just a matter of --

PGR2025-00017 (12,110,520 B2)
PGR2025-00033 (12,049,652 B2)
PGR2025-00039 (12,104,185 B2)
PGR2025-00046 (12,091,692 B2)
PGR2025-00024 (12,060,590 B2)
PGR2025-00030 (12,054,758 B2)
PGR2025-00052 (12,264,345 B1)
PGR2025-00042 (12,037,618 B2)
PGR2025-00050 (12,077,791 B2)
PGR2025-00053 (12,195,773 B2)

1 JUDGE FREDMAN: I hear you, but I think, you know, we can't.
2 There's not time. I think we are off the record. Thank you for coming today
3 and answering our questions. We'll take the case under advisement. We'll
4 ensure that the decision will be due first. If you would stay and help the
5 court reporters, because I think we said a lot of things and to be sure it's
6 clear. I appreciate you coming in today. You asked about all clarity; we can
7 fix that. Have a wonderful day.
8 (Whereupon, the above-entitled matter went off the record at
9 3:21 p.m.)

PGR2025-00017 (12,110,520 B2)
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