

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BEIGENE USA, INC. AND BEIGENE, LTD.,
Petitioner,

v.

PHARMACYCLICS LLC,
Patent Owner.

PGR2024-00009
Patent 11,672,803 B2

Record of Oral Hearing
Held: January 30, 2025

Before: SHERIDAN K. SNEDDEN, SUSAN L. C. MITCHELL, and
TINA E. HULSE, *Administrative Patent Judges*.

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T-A-B-L-E O-F C-O-N-T-E-N-T-S

	PAGE
Presentation by Petitioner	5
Presentation by Patent Owner	53
Rebuttal by Petitioner	87
Rebuttal by Patent Owner	99

P R O C E E D I N G S

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JUDGE SNEDDEN: Please be seated. Okay. Good afternoon.
This is the final hearing of PGR2024-00009 and involving U.S. Patent No.
11,672,803 B2.

I'm Judge Snedden, and I'm joined by Judges Mitchell and Hulse.
We will begin with appearances starting with Petitioner. Please
stand, introduce yourself, and who you have with you today.

MR. BERL: Good morning, Your Honor. David Berl from
Williams & Connolly on behalf of Petitioner Beigene.

With me are Kevin Hoagland-Hanson and Christie Corn, also from
Williams & Connolly, and Jiang Lin from Beigene.

JUDGE SNEDDEN: And we understand that Mr. Hoagland-
Hanson is our LEAP practitioner today.

MR. HOAGLAND-HANSON: That's correct, Your Honor.

JUDGE SNEDDEN: Patent Owner, please stand, introduce
yourself and who you have with you today.

MR. FRAZIER: Good morning, Your Honor. David Frazier from
Latham & Watkins.

I have with me Brenda Danek also from Latham and Alyssa Dolan.

JUDGE SNEDDEN: All right. Welcome, everyone. Per our
hearing order granting this oral hearing, each party is granted 60 minutes of
total time to present its arguments.

Because Petitioner has notified us that we have a LEAP
practitioner participating in today's argument, Petitioner will have an extra

1 15 minutes of argument time.

2 Petitioner will open the argument and may reserve up to 30
3 minutes of rebuttal time. Patent Owner will then respond to Petitioner's
4 arguments and may also reserve up to 30 minutes of rebuttal time.

5 Please note that this proceeding is being streamed online to enable
6 public attendance. I would remind everyone that the recording of any PTAB
7 hearing is prohibited. The court reporter will provide a transcript of the
8 hearing that the Board will enter into the record when it becomes available.

9 We have reviewed the briefs and the evidence which we have
10 available to us on our computers along with your demonstratives.

11 So you're welcome to point us to any document in the record, and
12 we can pull that up as needed.

13 And just a reminder for both the benefit of the transcript and Judge
14 Hulse who is attending remotely, please speak clearly and identify the slide
15 numbers as you move through the presentation.

16 Does anybody have any questions?

17 Okay. With that, Petitioner, do you wish to reserve any rebuttal
18 time?

19 MR. BERL: Yes, Your Honor. We'd like to reserve 15 minutes.

20 JUDGE SNEDDEN: Fifteen minutes? Very good. You may
21 begin your arguments when ready.

22 MR. BERL: Okay. And the extra 15 minutes for the LEAP.

23 JUDGE SNEDDEN: That's for you to decide. Okay, sorry. That's
24 right. So you have a total of argument time now for 60 minutes.

25 MR. BERL: Just wanted to make sure.

1 JUDGE SNEDDEN: Thank you for that reminder.

2 MR. BERL: Good afternoon. May it please the Board. Patent
3 Owner Pharmacyclics invented and developed ibrutinib, the active
4 ingredient in Imbruvica.

5 It is the compound used in each and every one of the examples of
6 the '803 patent.

7 The overwhelming majority of the disclosure in the patent is about
8 using ibrutinib to treat various malignancies.

9 Petitioner Beigene invented and developed zanubrutinib, the active
10 ingredient in Brukinsa, a chemically distinct and clinically superior
11 molecule.

12 For years after filing the priority 2010 and 2011 applications,
13 Pharmacyclics sought and obtained numerous patents with claims limited to
14 ibrutinib.

15 It was only after FDA approved Beigene's Brukinsa in 2019 that
16 Patent Owner shifted course and obtained claims to try to cover the molecule
17 that Beigene, not Pharmacyclics, invented.

18 The written description requirement exists to prevent these very
19 attempts to claim compounds later invented by others.

20 The claims here are invalid for lack of written description, lack of
21 enablement -- as my colleague, Mr. Hoagland-Hanson will discuss -- and
22 accordingly lack priority and are anticipated by the prior art.

23 The claims lack written description, both because they fail the
24 Ariad two-part test of representative species or common structural features
25 and because the specification lacks blaze marks to the claim genus.

1 Patent Owner's response relying on modeling and techniques
2 nowhere mentioned in the specification fails because modeling cannot
3 substitute for the specification's disclosure of either representative species or
4 common structural features.

5 Patent Owner's responses are both legally foreclosed and factually
6 baseless.

7 I'll start with lack of written description. And I'll discuss both
8 prongs of the Ariad test and then I'll move to blaze marks.

9 Written description requires both a description of the outer limits
10 of the genus, so-called blaze marks, and either a representative number of
11 species or features common to the members of the genus.

12 Familiarly, the claims here have structural features, and I'm on
13 slide 12.

14 Those are shown in yellow. And they also have functional features
15 shown in other colors.

16 I'll primarily be focusing today on the one in blue, the irreversible
17 binding of BTK required by each of the claims.

18 Now we'll start with a representative species. That's the first part
19 of the Ariad test.

20 But Pharmacyclics doesn't even assert that it can meet that it can
21 meet that prong of the test.

22 Indeed, in its Patent Owner response, it never advanced a
23 representative species argument, instead asserting common structural
24 features that meet the Ariad test by irreversibly binding BTK.

25 They fail that test too. The law requires structural features in the

1 specification common to the members of the genus such that they can be
2 recognized by the person of skill.

3 And as the Federal Circuit repeatedly has held, this is especially
4 difficult to meet for a claim like this with functional limitations.

5 As the specification must disclose a correlation between structure
6 and the claimed functions, here, irreversibly inhibiting BTK and treating the
7 diseases recited in the claim.

8 Put another way, the structures disclosed in the specification must
9 be common to the members of the genus that will bind BTK irreversibly.

10 It must distinguish those structures that bind reversibly and those
11 structures that do not bind irreversibly.

12 But where, as in AbbVie v. Janssen and here, the disclosed species
13 in the specification lack structural diversity and lack structural commonality
14 to the nondisclosed species in the claim, including the accused product as
15 here, the claims fail the written description requirement. The Federal
16 Circuit --

17 JUDGE HULSE: Counsel, can I -- sorry.

18 MR. BERL: Yes, sorry, Your Honor.

19 JUDGE HULSE: The AbbVie case, my understanding though is
20 that in AbbVie, they conceded that the patents don't disclose structural
21 features common to members in the claimed genus.

22 And so if what you're saying is that Patent Owner concedes that
23 point, then do we really -- can we really apply AbbVie in our case?

24 MR. BERL: I think AbbVie is one case that applies the rubric of
25 Ariad.

1 It does talk about representative species. But it also discusses the
2 lack of commonality structurally between the species that were disclosed.

3 And we have a discussion of those in a moment ago where all of
4 the disclosed species had similar structures to each other, and yet the
5 accused product had a totally different structure.

6 That same sort of analysis goes forward. And you can see it in the
7 Idenix case, too, where the same sort of evidence is applied in regards to the
8 second prong of the Ariad test structural feature.

9 So while I agree that the representative species was the focus of
10 AbbVie, I think some of the issues and evidence that the Federal Circuit
11 found lacking there likewise apply to the lack of structural features.

12 And I think if you take the analogy that the Federal Circuit has
13 used both in regards to representative species and common structural
14 features and even blaze marks as we move forward to Fujikawa and the
15 recent Minnesota v. Gilead case, the question is you have a claim that is
16 structurally bounded.

17 It's also functionally bounded as we see here. And the question is,
18 are there structural features that are common to the members of the genus
19 that the specification discloses?

20 Or are there representative species in the claim? And they were
21 found lacking in AbbVie. They were found lacking in virtually all the cases
22 that we cite with very few exceptions that I'll address later.

23 And so I think some of the principles certainly hold. But as we
24 move past AbbVie and we move to this claim, I think it's important to note
25 that AbbVie initially tried to obtained claims that were not limited to the Z'

1 structure that they ultimately included in these claims in '803.

2 They try to get a functional claim that had no 'Z' structure where
3 anything could be in the core.

4 And that was rejected by the examiner. And now on page 25 of its
5 sur-reply in footnote 6, AbbVie agrees -- AbbVie agrees that this claim, in
6 fact, does not meet Section 112.

7 And that's why they say there is proper -- we have a proper
8 proceeding here.

9 It is eligible for PGR because that then pending claim did not meet
10 Section 112. The problem, though --

11 JUDGE MITCHELL: If I can interrupt for just a minute.

12 MR. BERL: Yes.

13 JUDGE MITCHELL: And can you make sure that you tell us
14 which slide you're on?

15 MR. BERL: Yes.

16 JUDGE MITCHELL: Because when we go back, it's --

17 (Simultaneous speaking.)

18 MR. BERL: I apologize.

19 JUDGE MITCHELL: That's all right.

20 MR. BERL: I might need another reminder. I can't promise. But
21 that was slide 22.

22 And I'll now move to slide 23 because that shows that the problem
23 here is that the present claims are not meaningfully narrower than the claims
24 that AbbVie has now agreed are invalid under Section 112.

25 And I keep saying AbbVie. AbbVie and Pharmacyclics I'm using

1 interchangeably. They have a parent/child relationship.

2 The structural limitations, there's no dispute about this, cover
3 billions of possible structures.

4 That was Dr. Showalter's opinion in his initial report. And Dr. Eck
5 at his deposition didn't dispute that calculation that the structural limitations
6 would cover billions of possible species.

7 The problem, though, is that the compounds in the claim differ
8 from each other and from the structures disclosed in the specification in
9 three very important respects.

10 First, the patent's exemplary structures are fully aromatic, and the
11 claims are not so limited, nor could they be in order to try to capture
12 Brukinsa which does not have a fully aromatic system.

13 Now there are eight examples of core structures that are provided
14 in the specification.

15 These are structures E1 through E8 that I'll be discussing
16 extensively today.

17 All of them are fully aromatic, but the claim has no such limitation.

18 The structures are shown here on slide 29, and there's no dispute
19 that seven out of the eight disclosed structures are fully aromatic.

20 Pharmacyclics challenges the eighth. That's E4, and I'll get to that
21 in a moment.

22 But before I get there, I think it's important to note that even were
23 E4 not fully aromatic, it would not help Pharmacyclics' Section 112
24 argument.

25 First, because it would be only one non-biaryl structure, it's not

1 nearly commensurate with the broad scope of the claim that would cover any
2 non-aromatic structure that has those numbers of nitrogens and atoms.

3 But also, further evidence that I'll get to a little later demonstrates
4 that that structure doesn't even bind BTK.

5 So even were it within something that's disclosed in the
6 specification, it's not within the claim because, again, the claim requires
7 irreversibly binding BTK and its limited.

8 But either way, it's not correct that that E4 is a non-biaryl structure
9 disclosure.

10 The Board so found preliminarily in the institution decision,
11 rejecting the very same arguments that Pharmacyclics is still advancing on
12 the basis of the definition of aryl in the specification.

13 And the ensuing evidence at trial, slide 31, shows that initial
14 institution decision was correct.

15 Pharmacyclics' expert agreed that the term biaryl generally means
16 two aromatic rings.

17 The specification does not deviate from that understanding as the
18 Board already found and does not show any different definition of biaryl.

19 Now if I could look for a moment at what Pharmacyclics is saying
20 today about this evidence, if we look at slide 40 of their presentation for just
21 one moment.

22 What Pharmacyclics is doing is arguing about the definition of
23 aryl, not biaryl but aryl, and points out that fluorenyl, one of the examples of
24 biaryl in the specification, is not fully aromatic.

25 It has two aromatic rings shown on the left and right of slide 40 of

1 their presentation.

2 But it's not fully biaryl. The issue here, though, is not what aryl
3 means and whether this structure is an aryl structure or not but rather what is
4 biaryl.

5 Everyone agrees. Aryl means aromatic. Biaryl means two
6 aromatic rings.

7 And that being the case, the specification discloses that the eight
8 exemplified compounds, E1 through E8, are all biaryl.

9 It says biaryl, selected from, and then it lists all eight. If we could
10 go back to our presentation now, slide 32.

11 What we see is when Pharmacyclics later in the last few years had
12 to claim some of those structures from E1 through E8, including E4 in claim
13 13, it understood the E4 structure to include two aromatic rings as they
14 added a double bond to the claim.

15 That structure as drawn is nowhere disclosed in the specification,
16 reflecting Pharmacyclics' understanding that the structure is the same and
17 supported by E4 in the specification.

18 The specification discloses fully aromatic structures. The claim is
19 not so limited.

20 That is not a structural feature common to the members of the
21 genus.

22 The second way that the members of the genus on slide 34 also
23 differ from both each other and from the exemplary structures is in the
24 number and position of heteroatoms.

25 The specification, we see it again, E1 through E8, discloses eight

1 particular structures --

2 JUDGE SNEDDEN: Just for the record, this is slide 35. You said
3 34.

4 MR. BERL: Sorry, I apologize. Maybe I should say it less. I'll
5 get it wrong less.

6 It discloses eight particular structures with particular heteroatom
7 substitutions.

8 The claim, of course, is not so limited, nor could it be in order to
9 capture Brukinsa later invented with a different heteroatom substitution
10 pattern.

11 And the members of the genus also differ from each other and
12 from the structures disclosed in the specification as we see on slide 36 in the
13 identity and location of substituents which varies vastly amongst the
14 structures.

15 The specification structures all have the same pattern of three
16 substituents shown here on slide 37 and the only examples of inhibitors in
17 the specification.

18 The substituents are all the same. It's a phenoxyphenyl substituent,
19 an amino substituent, and a particular warhead substituent.

20 The claims have no such limitation, allowing any substituent to be
21 used in any of these positions other than the phenoxyphenyl and the warhead
22 that are fixed.

23 That's what allows the claim, of course, to cover what came later,
24 including Brukinsa.

25 The problem here, though, is that it's even worse than that as we

1 see on slide 39 because only a small minority of structures meeting the
2 claim's structural limitations are actually within the claim by meeting the
3 functional limitations.

4 There is no disclosure in the specification of which of the
5 numerous structures that meet the structural limitations of the claim will also
6 meet the functional limitations and which ones will not.

7 That is what is required under Idenix and other such cases to meet
8 the written description requirement.

9 And even today, 15 years later, not that it matters because you
10 can't satisfy a written description later, Pharmacyclics still doesn't tell us
11 what those common structural features are that make the claim compound
12 inhibit irreversibly BTK.

13 The first argument that Pharmacyclics advanced on slide 41 is
14 basically that everything will work.

15 All the claim structures will work as irreversible inhibitors. And
16 so they don't need to explain which ones work and which ones don't.

17 But that argument did not survive trial for the cross examination of
18 their expert.

19 What we see on slide 42 is again that Dr. Eck and Dr. Showalter
20 agreed the structural limitations cover billions of compounds.

21 But then when asked on slide 43, how many would be acceptable
22 Z' structures?

23 He used the term, acceptable Z' structures that rotate the molecule
24 correctly so that it will bind BTK irreversibly.

25 Far fewer structures then are within the scope of the claim. He

1 said that it would comfortably be more than hundreds.

2 Even if it's thousands out of billions, that's one in a million. This is
3 finding needles in haystacks.

4 Not everything works. Contra Pharmacyclics' argument that it's
5 the fixed portions like the phenoxyphenyl and warhead that dictate BTK
6 binding.

7 And the reason for that is elucidated on slide 45 where
8 Pharmacyclics admitted in the POR at pages 23 and 52 that the Z' structure,
9 the core is important because it's what orients the rest of the molecule and
10 positions it in a particular way to either bind or not bind depending on the
11 positioning of the warhead as well as the hydrophobic structure.

12 And it needs to make particular hydrogen bonds in a particular
13 orientation and confirmation in order to do that.

14 It's an important piece of the molecule. And now I'm on slide 46.

15 I submit it's the single most important slide I'm going to present
16 today because here at his deposition, we asked Dr. Eck basically the key
17 question in the case.

18 Can you identify the structures that would be common to all the
19 species of Z' scaffolds that would satisfy these requirements, these
20 functional requirements in the claim?

21 But he couldn't do it. He couldn't do it. What he did instead is he
22 talked about the linker-warhead and the phenoxyphenyl. Those are fixed.

23 And he said with respect to the Z' structure, it has to appropriately
24 position the phenoxyphenyl and the warhead to bind Cys481 so it will
25 irreversibly bind.

1 And additionally, it has to form from one to three hydrogen bonds
2 with the hinge.

3 Those are not structural features. Those are more functional
4 features.

5 He can't identify what structures these successful compounds
6 within the claim have that bind.

7 He just says what they have to do. And in fact, I would submit that
8 on page 5 of its sur-reply, Pharmacyclics gives the game away unwittingly.

9 Identifying these very features that Dr. Eck is talking about,
10 orienting the molecule correctly so that the hydrophobic area and the
11 warhead are in the right place, forming one to three hydrogen bonds.

12 It identifies those as functions which is right. That's what they are.

13 They're not structures. They're functions. And Pharmacyclics on
14 page says just that.

15 There is no structure to function relationship. There are no
16 structures of Z' that correlate with irreversible binding compared to
17 structures that don't.

18 And they can't identify them even now, 15 years after filing the
19 application.

20 Instead, what Patent Owner has retreated to is the use of modeling
21 based on references like Marcotte that they say will help visualize members
22 of the genus.

23 But even with modeling which, by the way, is nowhere discussed
24 or disclosed in the specification, they and their expert still cannot identify
25 the features that are common to members of the genus, the structural

1 features, not functional features.

2 Now I want to be clear about one thing about modeling here
3 because I think it can be confusing from the papers.

4 Modeling does not generate structure. They're not saying that you
5 go and you ask a computer, find me the Z' molecules or Z' plus the rest of
6 the substituents molecules that are going to bind.

7 And then I let the computer do its thing, and I go home early for
8 lunch.

9 That's not how this works. What modeling does, it creates an
10 iterative process by which a human being or human beings, medicinal
11 chemists working with others, including the modelers, make molecules.

12 They design and make molecules. And then the computer with its
13 software provides some prediction about whether and how it will fit into an
14 enzyme such as BTK.

15 It does not spit out the structures. It simply evaluates the
16 structures.

17 That's not nearly enough under governing case law. The
18 specification must disclose common structural features of the claimed
19 compounds of the Z' structures that work compared to the Z' structures that
20 do not work.

21 Not functional features, structural features like the amino acid
22 sequences that were missing in the Juno Kite case.

23 JUDGE MITCHELL: Can I ask you a quick question?

24 MR. BERL: Yes.

25 JUDGE MITCHELL: I want to push back a little bit on that slide

1 46 where you're saying these are really functional requirements that that's
2 first talking about.

3 They really don't translate to structure. But when you're talking
4 about having the appropriate positioning, the Z' gives you the appropriate
5 positioning of the other constituents.

6 I mean, wouldn't with those two -- I mean, it seems to me that is
7 telling you something about the structure because there's only so many
8 structures that would be able to do that. There's provided examples in this
9 spec.

10 Is that so far afield from providing you some structural knowledge
11 versus just functional, hey, this particular molecule is going to bind and
12 we're not -- I mean, here they're telling you we've got to have one to three
13 hydrogen bonds and a hinge.

14 You've got to have the positioning of the two constituents just right
15 for that binding. Isn't that somewhat enough --

16 MR. BERL: Well, they don't --

17 JUDGE MITCHELL: -- structure?

18 MR. BERL: But they don't associate that with structure. They
19 could have said, for example, you need a nitrogen in this position or you
20 need an amino group in that position or you need a hydrogen bond donor or
21 you need a substituent that has a free electron pair in this substituent so that
22 it can be a hydrogen bond donor or a hydrogen bond acceptor.

23 They could've identified those sorts of structural features. That's
24 what Idenix demands.

25 That's what Juno v. Kite demands. And that's what Ariad

1 demands.

2 To say, well, it's whatever is going to situate it correctly. Some
3 things with three bonds will situate it correctly.

4 Some things with three bonds will not situate it correctly. Their
5 whole point is you give it to a model, you give it to a computer, and the
6 computer will tell you whether it worked or not.

7 But structural features require something more than it's going to
8 orient it properly because they can't say what structures will orient the
9 phenoxyphenyl properly.

10 They could've tried to come in and say, you need to have two
11 nitrogens in the left-hand ring and those have to be at these locations.

12 And they have to have a substituent in between. And they're going
13 to make those three bonds. They could've done that. They never have.
14 They never have.

15 JUDGE MITCHELL: What about some of the examples in this
16 spec?

17 Would that not fill in kind of, oh, I'm looking and I can see these
18 structures and they are going to create that irreversible binding?

19 Could I not, as a POSA, I'll look at that, look at kind of what I
20 expect to be there and have enough of the structure?

21 MR. BERL: So actually, in theory, one could have enough
22 structural information to provide that by way of example.

23 The problem is that they don't have that. The examples in the
24 specification, those eight examples don't, for example, have substituents.

25 So they don't say, okay, here's this whole structure with an amino

1 substituent here and it makes these bonds.

2 And so I know, okay, I'm going to want an amino there and it's
3 going to work.

4 In fact, they have nothing other than those eight structures in the
5 specification, E1 through E8, with potential substituents drawn simply as
6 lines.

7 But they don't have examples. I mean, consider our molecule
8 which has different arrangements of nitrogens, which has different
9 substituents in different locations, including, for example, in the amine
10 group that is in none of the examples and not a preferred substituent in the
11 '803 patent.

12 It lacks the amino substituent which is an important part of binding
13 as our slide 66 shows and their testimony shows.

14 They take that out. We add something else. But there's no
15 disclosure that any of that is going to work.

16 All you have is the core groups. And also, I think it's important to
17 note -- and we can skip ahead to this perhaps.

18 The core groups for the most part don't even show that they work
19 to bind. It's not as if they have data for the core groups and their
20 specification. And they say, okay, we've tried all these core groups and they
21 all work. And here's how they bind. And this is what's going on. And you
22 have a hydrogen bond donor here.

23 And when the nitrogen is here, it acts as a hydrogen bond acceptor.
24 When you have this substituent, it acts as a hydrogen bond donor. They
25 didn't do that at all in their specification. In fact, what they say is you would

1 use modeling.

2 I'm now -- I skipped ahead to slide 63. And we basically said what
3 about these other examples in E1 through E8 other than ibrutinib?

4 Did you look at those? Did you do the analysis to confirm that, in
5 fact, those bind?

6 Because they say, oh, this is all easy. You just go to the computer
7 and you can see whether it bonds.

8 So simple. Did he do that? The answer, no, he didn't. So we did
9 on slide 64.

10 And we went and we were the ones who modeled using what they
11 say is a predictive system, E2, E3, and E4, three of the eight core groups that
12 are disclosed in this specification.

13 And what the modeling shows according to Dr. Veal is that they do
14 not irreversibly bind BTK.

15 So even the things within the specification don't work, much less
16 the things outside the specification that are nowhere disclosed or hinted at.
17 And I think this is important to note, this evidence, for two reasons at least.

18 First, as we see on slide 65, the E4 which is their one theoretical
19 disclosure of a non-biaryl system which is a typo as I think the Board found
20 properly in the institution decision.

21 E4 doesn't work is what this shows. And so even if they had a
22 non-biaryl structure, it's not in the claim because it doesn't irreversibly bind
23 BTK.

24 And the other issue is this is their response in the sur-reply on our
25 slide 66 on 13 of the sur-reply.

1 They don't ever dispute this testimony. They do cross examine Dr.
2 Veal about it.

3 Did they come back in the sur-reply and say, he screwed up the
4 modeling, he did it wrong, he pushed the wrong button, he should've done
5 this structure rather than that structure? None of that.

6 They didn't ask us for a response of declaration to say, we want our
7 own model to refute this or ask the Board for permission to file a sur-reply.
8 None of that.

9 Instead, they complained that Dr. Veal only modeled a single
10 compound for this E2 and E3 system.

11 But what did he model? Well, he modeled exactly what the
12 specification says you should use.

13 He modeled with the phenoxyphenyl as required, the warhead, and
14 the amino.

15 He actually did it with and without the amino. But it doesn't
16 matter.

17 None of it binds, even with the preferred substituent. So the notion
18 that Dr. Veal had to go on some wild goose chase in order to figure
19 structures that bind, that's the problem with their specification.

20 They're asking for a research plan. That's, in fact, what's going on
21 with the modeling.

22 They are saying, here are some tools. Here's some literature and
23 here are some tools.

24 Go out and find other inhibitors that will work. That's a research
25 plan.

1 That's not a written description. That's not a disclosure in the
2 specification as required that actually provides common structural features.

3 And as I said, the little disclosure that they have, three out of eight
4 don't even work.

5 The only one they actually have data for is E7. That's the ibrutinib
6 molecule.

7 The other ones, we don't even know if they bind in a wet bench
8 activity assay. If I could go back --

9 JUDGE HULSE: Counsel?

10 MR. BERL: Yes. Yes, Your Honor.

11 JUDGE HULSE: Counsel, a quick question. To what extent can
12 Patent Owner rely on the knowledge of the skill in the art to satisfy the
13 written description of the requirement?

14 MR. BERL: Yes.

15 JUDGE HULSE: It seems like that's what they're primarily relying
16 on, not the disclosure of the spec.

17 MR. BERL: I think they are. I agree with your interpretation,
18 Your Honor.

19 And I think the answer to that question, if I can skip ahead to that
20 analysis, somewhere around slide 69.

21 The issue here is that -- and this is what they're doing. They're
22 saying the POSA would've been aware of numerous elements.

23 And so we can basically fill in with the prior art what is missing in
24 our specification.

25 And I would submit that the case law almost never permits

1 patentees to do that.

2 They cite a few cases where reference to the prior art was
3 permitted to help fulfill Section 112.

4 They cite Invitrogen. They cite Falko. They cite UroPep. In each
5 of those case, in each of those cases, the prior art was replete with disclosure
6 of structures within the scope of the claim.

7 There were hundreds of known PDE5 inhibitors in UroPep. So
8 that can help satisfy the claims.

9 Invitrogen, there were known sequences of reverse transcriptase
10 genes.

11 And so that was known. And in Falko, the Federal Circuit said
12 that the essential genes for poxvirus were known.

13 So there was a disclosure in the prior art of the actual members of
14 the genus and this common structure feature to the members of the genus.

15 Let's see what we have here by stark contrast. And this is slide 69
16 which shows part of their Patent Owner response at pages 52 and 56.

17 And what they say is a POSA would've been aware of numerous
18 hinge-binding elements, including those with non-aromatic portions.

19 But then -- and so they basically try to fill in with the prior art what
20 they don't have in the claim themselves.

21 But if you look a little more closely about what's going on here, a
22 few details emerge.

23 First, one very important point, nearly all of the structures that
24 Pharmacyclics points to are not disclosed in the prior art to be BTK
25 inhibitors.

1 They're disclosed as potential inhibitors for other kinases. So
2 Pharmacocyclics argument is that you should look into the prior art for these
3 structures, these non-BTK inhibitor structures.

4 Modify them by putting on, for example, the phenoxyphenyl
5 substituent, the warhead potentially doing other things, then model them.

6 And then maybe you'll have successful BTK inhibitors within the
7 scope of the claim.

8 That is an obviousness argument. That's not a recitation of the
9 structures in the prior art.

10 That is an invitation to start with some structures in the prior art as
11 starting materials and then modify them to make new compounds nowhere
12 disclosed in the prior art.

13 There is no law, none that permits that. And in fact, the Federal
14 Circuit case law assiduously prevents it.

15 In Ariad, they said, obviousness is not enough for written
16 description.

17 In Idenix, the patent owner said, well, you could've found these
18 two substituents.

19 And the Federal Circuit says, who cares. It doesn't matter if
20 someone could've found them.

21 That is obviousness. That's looking to modify things in the prior
22 art in order to occupy the claim and fill in the claim, not enough for written
23 description.

24 So that's what they're doing here. These are not for the most part
25 BTK inhibitors.

1 But it's worse than that for them actually because most of the prior
2 art structures that they cite are not Z' structures.

3 They're not within the structural scope of the claim. That's true for
4 everything shown in yellow here on slide 72.

5 So what they're doing is they're taking prior art disclosures of
6 things not within the scope of the claim and suggesting that somehow that
7 provides written description for their claim which excludes those structures
8 even if they were disclosed as BTK inhibitors which for the most part they
9 weren't.

10 That, of course, doesn't work. You need a disclosure of things
11 within your claim, not disclosure of things without your claim.

12 Now most of the structures are also biaryl to the extent that they
13 are within the Z'.

14 So the ones that matter, the ones within the scope of Z', those are
15 for the most part biaryl such as the 2027 exhibit shown in blue where they
16 show structures that are very similar or identical in some cases to the
17 structures that are in the specification.

18 It doesn't really help them. There are two and only two examples
19 that they point to of references that they say show inhibitors that are not
20 fully aromatic within the scope of Z', within the scope of their structural
21 claim.

22 That's Exhibit 2023 and Exhibit 2055. Again, neither of them are
23 disclosed in the prior art as BTK inhibitors.

24 This is not even close to a situation like UroPep or Invitrogen or
25 Falko.

1 They're just disclosed as molecules that could inhibit a different
2 kinase.

3 And so the question arises, of course, are they BTK inhibitors?
4 Will they, in fact, inhibit BTK if you put on their preferred phenoxyphenyl
5 and warhead substituents?

6 Unbelievably, despite asserting that it's really easy to do this and
7 all you have to do is put it into the computer and the computer will tell you,
8 is it in the claim, is it out of the claim?

9 That's how you know. They didn't do it. Their expert never
10 looked at these non-biaryl compounds in the prior art, the only ones they
11 identify that are within the scope of their claims structurally.

12 So again, we did it. We modeled it, and we looked at the
13 molecules in these exhibits.

14 Here you see on slide 73 Exhibit 2023, which is not fully aromatic
15 and Exhibit 2055, also not fully aromatic.

16 And what did it show? What it showed is that these molecules per
17 the modeling if one takes that as predictive as Patent Owner suggests do not
18 bind BTK.

19 They're failures. So what does the claim actually look like where
20 they're trying to fill it in with structures from the prior art?

21 What you actually have in reality the evidence shows is some
22 structures that as Your Honor pointed out are disclosed in the specification.

23 Those are E1 through E8. Some of those aren't even in the claim.

24 We saw E2, E3, E4. Those aren't in the claim. The other ones we
25 don't know outside of E7 whether they actually bind.

1 There's no data in the claims or the specification that says, this
2 successful bound BTK.

3 We have a few prior art systems that are likewise by biaryl, very
4 similar to and in some cases, like 1073, identical to what's disclosed in the
5 specification.

6 And then you have a whole bunch of prior art scaffolds that are not
7 within the claim.

8 They're not Z' structures. They're different. And you're going to
9 hear a lot about them after I sit down.

10 But remember, none of them are in the claim, and that can't be a
11 written description by referring to something that's not even in the structure
12 of the claim.

13 And you have two disclosures, 2023 and 2055, of non-biaryl Z'
14 substitute structures that don't work.

15 They're also not in the claim. They haven't come close to
16 identifying the common structural features of this claim that work.

17 They rely on the eight structures. Those are common to the rest of
18 the claim because they're not -- those are all biaryl in the claim.

19 It's not different positions of heteroatoms, different substituents at
20 different locations, not commonality.

21 But even within that area of E1 through E8, a very narrow area,
22 some of those aren't even in the claim at all.

23 And as you go outside that narrow portion of the genus, they have
24 nothing at all in the non-biaryl substituent -- in the non-biaryl structures.

25 They either have things that aren't in the claim because of structure

1 or aren't in the claim because of function.

2 And so I think that the effort to say that the prior art can sort of fill
3 in the gaps which is a very narrow exception to the case law like Gilead and
4 Ariad that says we don't use obviousness.

5 It's an exception where things are well known and the prior art is
6 replete with examples so that when you say PDE5 inhibitor, everyone knows
7 those are the hundreds of structures that had been well exemplified and
8 known in the prior art and there in my claim.

9 And likewise, these RT genes are in the claim in Invitrogen. That's
10 how those cases work.

11 That's not this case where there's no examples of non-biaryl in the
12 prior art.

13 There are not even BTK inhibitors. You've got to modify them to
14 try to turn them into BTK inhibitors.

15 And there's no disclosure anywhere of doing this. This is a project.

16 This is an argument. I don't think it's a very good one to be honest.

17 But there are various molecules within this claim that the person of
18 ordinary skill through their knowledge of the prior art, ingenuity, and
19 modeling could find somehow.

20 And that even if it were true, and I don't think it is. I think it's very
21 hard to find these molecules.

22 That wouldn't help. That's not what written description is. That's
23 what obviousness is.

24 And the Federal Circuit time and again has reaffirmed that
25 distinction.

1 Oh, sorry. I thought you had a question, Your Honor. If I could
2 go back for a quick moment to slide -- well, why don't we keep going with
3 this because this is something that they continue to rely on as well.

4 They rely on Dr. Veal's paper, suggesting that somehow there's a
5 disclosure of non-aromatic systems too within the scope of the claim.

6 But that's not correct. We see here, and I'm on slide 78, one of Dr.
7 Veal's papers.

8 This is Exhibit 2021. And the issue here is that there are quite a
9 few structures that Dr. Veal disclosed.

10 But only one of them, molecule 9, has a Z' structure. That's it. It's
11 a biaryl core so it doesn't help them with any disclosure of non-biaryl.

12 And there's no evidence in the record, none, not in the prior art, not
13 to date that this molecule is actually a BTK inhibitor.

14 It's not disclosed in the prior art as a BTK inhibitor. They didn't
15 model it as a BTK inhibitor.

16 So it's not helpful at all with respect to occupying the claim, even
17 as another biaryl structure.

18 The molecules that they cite in their presentation are not biaryl or
19 are not within the scope of Z'.

20 Again, they're attempting to occupy their claim with prior art
21 molecules that are neither BTK inhibitors, nor are they within the scope of
22 the claim.

23 That's the opposite of written description. That's description of
24 some other claim that doesn't have the Z' limitation or doesn't have
25 dysfunctional limitations of BTK inhibition, not this one.

1 And they fare no better with Dr. Veal's other article in the prior art.

2 This is slide 79, Exhibit 2120. It likewise does not disclose that
3 the molecules are BTK inhibitors.

4 They're disclosed only in figure 16-5 of structures that can be used
5 in developing screening libraries.

6 So they're not even disclosed as kinase inhibitors, let alone BTK
7 inhibitors.

8 The only core structure within the scope of Z' in this article and it's
9 shown right here, is again another biaryl core.

10 And it's actually the same thing as E2. This doesn't expand the
11 specification.

12 This is another one that's already in the specification. And as we
13 saw a moment ago, E2 doesn't even work based on the modeling of Dr. Veal
14 that is not refuted.

15 So again, there's no disclosure either in the rest of the prior art or in
16 Dr. Veal's prior papers of what they need.

17 What they need are, as in UroPep, as in Invitrogen, as in Falko,
18 they need the prior art to be replete with structures within the scope of the
19 claim that were disclosed to meet the functional limitation.

20 They have none of that here. They have no biaryl structure in the
21 prior art in order to fulfill their claim.

22 Now with my remaining time, I'd like to move to the blaze marks
23 issue quickly.

24 And so I'll be on slide 100. And in the Fujikawa case, it was
25 discussed by the Federal Circuit that one of these blaze marks in the

1 specification to get to the subgenus or species claim.

2 And it's not enough to get close to the claim. One actually has to
3 get to the claim.

4 The blaze marks are shown in number 101, and that's the yellow
5 circle.

6 And what they said in Fujikawa is if your claim is close to where
7 the blaze marks guide you but not exactly the same, not good enough, no
8 blaze marks, no written description.

9 And the Federal Circuit explained this more last year in the
10 Minnesota Gilead case where they say if your prior disclosure differs
11 substantially from what you later claim.

12 So you have to make a bunch of choices. That is also not
13 sufficient for blaze marks.

14 And in that case, it was actually easier, much easier than this case
15 here because the Gilead case involved just a structural genus, no functional
16 limitation.

17 So it was a sort of neat genus like this. But what the Federal
18 Circuit said is if there's no specific blaze marks to the particular subgenus,
19 here it would be the Z' structure with five and six membered ring, two to
20 four nitrogens.

21 That's got to be the particular subgenus to which you have blaze
22 marks.

23 Then it doesn't work, and that's what they had in Gilead. And
24 that's the problem that we have here too.

25 They provide two arguments on blaze marks. First, they say

1 they're Formula E with this Ball shown on the upper right of 104 somehow
2 is a blaze mark.

3 That's really wrong. The Ball provides no structural information.

4 They try to limit the Ball by the prior art. But again, the prior art
5 can't provide written descriptions, especially on this record where the prior
6 art does not occupy nearly the claim that they have.

7 Effectively, the Ball genus is everything that works irrespective of
8 its core structure.

9 It's all of the yellow trees on slide 106. But that doesn't provide
10 blaze marks to the subgenus that they've claimed.

11 Particular yellow trees that have a structure that they concocted
12 during prosecution a decade later in order to capture our molecule.

13 There are no blaze marks to that subgenus anywhere in the
14 specification.

15 And nor are there blaze marks via E1 through E8. As we've seen,
16 those structures are severely limited and they do not provide blaze marks to
17 the broader scope of the claim now, not biaryl but non-biaryl, different
18 substitutions in different places, different heteroatom patterns, and different
19 numbers of heteroatoms.

20 There are blaze marks to none of those. I would submit that they
21 don't even have blaze marks to the E1 through E8 subgenus if they tried to
22 claim that because there, they don't provide blaze marks to the part of that
23 subgenus that actually will work.

24 And as we've seen, some of those structures don't work. And there
25 are no blaze marks to the broad location and number of substituents that can

1 work there.

2 So that claim would be doomed ab initio as well. But what they're
3 saying here is that they can get around Gilead v. Minnesota and they can
4 claim some broader subgenus as long as that genus encompasses the
5 described embodiments.

6 As long as it encompasses E1 through E8, that's good enough and
7 they can claim any subgenus that does that.

8 I would submit that's not right and Gilead and Minnesota says it's
9 not right.

10 In order to do that, the features in the specification must constitute
11 the near entirety of the structures being compared.

12 In other words, the disclosure in the claim has to be similar. They
13 have to be commensurate.

14 You can't have one very broad and one very narrow and say that I
15 have blaze marks and I've satisfied the requirement.

16 There is no blaze marks to any of the subgenus that one could
17 craft.

18 And one could craft a lot of them that encompass the portion of E1
19 through E8 that actually work, taking out E2, E3, E4.

20 They could've arbitrarily crafted this subgenus that we see in 117,
21 this one that we've seen in 118, this one in 119, this one in 120, and this one
22 in 121.

23 Those are all subgenera that encompass some of E1 through E8.
24 But the problem is there aren't blaze marks to any of them.

25 Where do they say this is the subgenus that we're later going to

1 claim?

2 Where do they have this disclosure of Z', five and six membered
3 rings fused, no aromaticity required, no amino substituent required, even
4 though they say that's important for making hydrogen bonds.

5 That's slide 66 of our presentation. Two to four hydrogen -- two to
6 four nitrogen atoms, any substitutions anywhere, any other heteroatoms
7 anywhere, that's nowhere in the specification.

8 It's an arbitrary subgenus later created in order to capture our
9 molecule.

10 The written description requirement doesn't permit it. And with
11 that, subject to questions, I'll turn it over to my colleague, Mr. Hoagland-
12 Handson, to discuss enablement.

13 JUDGE MITCHELL: I do have one quick question --

14 MR. BERL: Yes.

15 JUDGE MITCHELL: -- in Formula E because it talks about that
16 moiety is going to bind to the active site of a kinase.

17 I mean, wouldn't a POSA know that the active site of kinase is
18 somewhat conserved?

19 And doesn't that help Patent Owner, if you know, I've got a certain
20 way to bind to most kinases? Isn't that -- would that not be enough?

21 MR. BERL: The whole kinase field is about trying to make
22 selective kinases, kinases that will bind one kinase and not another.

23 And so it's true. There is some conservation among kinases along
24 the hinge region because ATP binds all kinases.

25 But the differences are what's key. Not every structure that will

1 bind one kinase will bind another.

2 And in fact, the whole field is about trying to find those differences
3 and seize on those differences in order to have kinases that are clean and not
4 dirty, that they're selective, that will hit one kinase and not another.

5 So there's no disclosure from E1 through E8 of saying, okay, these
6 are the particular structures that will bind BTK in particular.

7 And knowing that generally speaking most kinases make one to
8 three hydrogen bonds, which is the function they articulate, that doesn't tell
9 you, what are the particular structures I need to bind BTK?

10 The best evidence in a sense that they didn't tell you what
11 structures will work or the fact that three of their E structures when we
12 model them don't work at all with their preferred substituents.

13 And so -- and we don't even know because we don't have activity
14 data on E1, E5, E6, and E8.

15 For all we know, those don't work either. And so they -- E1
16 through E8 isn't enough.

17 Those are not full molecules even. They're just cores without
18 substituents.

19 And so that's the whole work of a kinase program. Virtually every
20 pharmaceutical company across the world had kinase programs.

21 They were all looking at, how can we modify these molecules in
22 order to find kinases that will bind well in order to put our substituents in the
23 right place so that they'll make these bonds, like the irreversible inhibition.

24 The answer isn't, oh, you just hire a modeler and you go home
25 early for lunch.

1 And you can find them all and you're done. That's not how it
2 works.

3 These companies work on it because it's hard, because just
4 knowing that you want one to three hydrogen bonds in the hinge region isn't
5 enough to spit out for your what structures will actually accomplish that
6 function.

7 And again, Dr. Eck, their expert, never spit it out. We said, what
8 are the structures that are common?

9 And instead, he came back to us with more functions like making
10 hydrogen bonds.

11 They don't have the structures in the specification which is not
12 required.

13 I submit they still don't have them today. Is that responsive to
14 Your Honor's question?

15 JUDGE MITCHELL: Thank you.

16 JUDGE HULSE: Could you also address Marcotte? Patent Owner
17 relies pretty heavily on it in their papers.

18 MR. BERL: Yes.

19 JUDGE HULSE: So I'd like to hear your thoughts.

20 MR. BERL: Yes, and again, Marcotte just like the modeling
21 software, that doesn't spit out structures.

22 That just provides a structure of an inhibitor that's bound. It's not
23 even an irreversible inhibitor.

24 It's one molecule. And so that shows how one BTK inhibitor binds
25 in the active site of BTK.

1 Marcotte doesn't say, therefore, these are the structural features
2 that will be required.

3 If it did, you would have all those structural features that are
4 present in the Marcotte structure.

5 But of course, their claim is not limited to those structural features.

6 You can move the nitrogens around. You can have a different
7 number of nitrogens.

8 You can have oxygens or sulfurs in the rings. You can have
9 different aromaticity in the rings.

10 You can take out the amino. You can add a different substituent
11 like an amide which is what we use in a different place.

12 So Marcotte just like the modeling software doesn't provide
13 structures for you.

14 It doesn't provide new molecules that would occupy the claim. It
15 doesn't even suggest which of these structures within the one molecule that
16 they bind are necessary to conserve.

17 If it did, you would have to conserve the entire left side of that ring
18 that binds the hinge.

19 We conserve none of that. Their claim isn't limited to the amino
20 substituent.

21 It's not limited to that particular arrangement of heteroatoms in the
22 ring or the aromaticity, all of which were present in the Marcotte structure.

23 So it's not a broad disclosure of structures. I think the key is what
24 the Federal Circuit said in the Alonzo case.

25 It's not enough to identify a way to find new structures in the

1 claim.

2 That's not a written description, and that's exactly what they do
3 with Marcotte in the modeling.

4 They give you a way. They say to find more structures. The
5 written structure requirement requires disclosure of structures and common
6 structural features, not a way to find structures.

7 That's a research plan that's not a written description as Alonzo
8 explains.

9 So subject to further questions, I will sit down and yield to my
10 colleague, Mr. Hoagland-Hanson, to discuss. Thank you, Your Honors.

11 JUDGE SNEDDEN: Thank you, Mr. Berl. And Mr. Frazier, I'm
12 going to give you five extra minutes because I know we had extra --

13 (Simultaneous speaking.)

14 MR. FRAZIER: Thank you, Your Honor.

15 JUDGE SNEDDEN: Just letting you know of your time.

16 MR. FRAZIER: Thank you.

17 MR. HOAGLAND-HANSON: Thank you, Your Honors. Kevin
18 Hoagland-Hanson on behalf of Petitioners.

19 And I'd like to address the second ground of the petition, the lack
20 of enablement.

21 And what we have on slide 124 is the familiar Wands factors. And
22 obviously, the factual record that was developed at trial is very similar
23 between the enablement issues and the written description issue that that Mr.
24 Berl talked about.

25 And I obviously don't want to belabor the factual record that Mr.

1 Berl already discussed at length that I hope he talked fast enough for
2 everyone, including the court reporter.

3 But I do want to address the unique enablement legal issues here.

4 And really the disputes between the parties boil down to two. The
5 first is what quantity of experimentation is required to practice the full scope
6 of the claims.

7 And the record showed that a very large quantity of
8 experimentation was required here in view of the millions or billions of
9 compounds that fall within the structural limitations, but the much smaller
10 number in the thousands or less that meet the functional limitations.

11 And the fact that all of the experts in the case agreed on both sides
12 that the only way to determine which of the millions and billions fall within
13 the thousands of functional compounds is to consider each compound
14 individually.

15 And the second issue, of course, is whether the specification
16 provides some guidance to allow the person of skill to cut through that
17 experimentation to somehow short circuit it, to identify some common
18 features in the genus to rule in or rule out compounds.

19 And what the record showed is that there was very little guidance
20 in the specification or the prior art to allow the POSA to cut through the
21 experimentation.

22 So first, with respect to the quantity of experimentation and the
23 breadth of the claims, the law is clear from the McRO case that we have on
24 slide 126 that undue experimentation includes the work that the POSA needs
25 to do to look at the structural limitations of the claim and figure out which

1 compounds meet the functional requirements.

2 That's exactly what the Federal Circuit said in McRO. And so here
3 the question is, which compounds with the Z' structure that's a 6:5 bi-cycle
4 with two to four nitrogens distributed among the two rings would
5 irreversibly bind BTK would be therapeutically effective to treat cancer.

6 The cancer is recited in the claims and would result in
7 lymphocytosis.

8 And that analysis of the claimed breadth for undue
9 experimentation is not limited to the compounds that meet the functional
10 limitations.

11 That's exactly what the Federal Circuit rejected and called the
12 backwards analysis in Idenix as we show on slide 127.

13 The question is analyzed starting from the structural limitations of
14 Z'.

15 What compounds meet the structural limitations first? And then
16 determining which ones meet the functions.

17 It's not an analysis of, well, once we're done figuring out which
18 compounds meet the functions, how many compounds are left to practice the
19 full scope of the claim?

20 That's exactly what the Idenix court rejected. Here the evidence
21 showed, and Mr. Berl already showed this testimony that we have on slide
22 128, that both experts agreed that billions of compounds meet the structural
23 limitations.

24 And likewise on slide 129, the testimony that Mr. Berl showed
25 earlier, there was no dispute that most compounds that meet the structural

1 limitations don't meet the functional ones.

2 Dr. Eck in his declaration and in his deposition said only
3 acceptable Z' structures will work.

4 And there are far fewer of those than there are of the billions that
5 meet the structural limitations.

6 And so the question is, how does the POSA determine the
7 compounds that meet the structural limitations meet the functional ones?

8 And the record established that the only way is to consider each
9 compound individually.

10 They accused us in and our experts of applying the wrong analysis
11 by somehow saying that our experts looked at the effort required to make
12 every embodiment of the claims.

13 But that's not right. The record established that the only way to
14 determine which compounds were functional was to make and test them
15 individually.

16 No expert on either side proposed any method that would rule out
17 or in categories of compounds at once.

18 The evidence from both sides shows the compounds have to be
19 considered individually.

20 And likewise, Pharmacyclics devotes a substantial amount of its
21 brief to contending that we haven't shown that there's a large number of
22 inoperative embodiments or that we haven't met the tests set out in Atlas
23 Powder that the inoperative embodiments propound of the operative ones.

24 But again, that's not the analysis that applies under these facts.
25 The question under Idenix where you have structural limitations that are not

1 connected to the functional limitations is, how do you get from one to the
2 other?

3 How do you practice the full scope of the claim without exercising
4 undue experimentation?

5 And first, Pharmacyclics tried to narrow the scope of the
6 experimentation by having its expert, Dr. Scott, point to these various
7 pharmacokinetic and in vitro determinations that chemists can make to look
8 at solubility, lipophilicity, ionization, permeability, and the interaction with
9 transporters to look at all of these features.

10 But when we asked him, would this let you rule out any
11 compounds or, like, categories of compounds, he said, no.

12 A chemist would look at all the properties of a compound and all
13 the data to decide which ones to pursue.

14 And when we asked him at his deposition which is shown on slide
15 131, are there any substituents of the ones that are listed out in the patent
16 that you can rule out that you wouldn't have to make and test, he said, I've
17 not seen any evidence that any of those substituents wouldn't work.

18 And so for all of Dr. Scott's proposed testing, it doesn't actually
19 help you narrow the experimentation because you still have to draw out each
20 compound and then consider its PK properties.

21 And similarly -- and so we made some assumptions with respect to
22 even assuming that Dr. Scott's assumptions were correct, how many
23 compounds would remain?

24 And Dr. Showalter calculated four and a half million compounds.

25 And they never came back and said that, oh, Dr. Showalter applied

1 the wrong assumptions or he calculated that four and a half million wrong.

2 So even assuming all of these assumptions that we don't think are
3 well supported and we don't think that Dr. Scott would defend at his
4 deposition, there's still four and a half million compounds to test to figure
5 out which ones meet the functional limitations.

6 And with respect to Dr. Eck, he likewise applied a compound-by-
7 compound analysis, modeling, he posited at his deposition and in his report
8 at his declaration at Exhibit 2010, paragraph 210, describes a compound-by-
9 compound iterative process where the POSA draws out an inhibitor.

10 They draw out the core. They attach the phenoxyphenyl. They
11 attach the linker-warhead.

12 They attach whatever other substituents are necessary having
13 considered the full list.

14 And then they modeled that compound. But this is not an analysis
15 that lets you short circuit any experimentation.

16 This analysis is just the exact same analysis that the Federal Circuit
17 considered and rejected in Idenix that the Supreme Court just considered and
18 rejected in Amgen v. Sanofi.

19 It's just somehow done virtually instead of on the wet bench. But
20 when we asked Dr. Eck how long does the modeling take, even under Dr.
21 Eck's assumptions, the modeling is, of course, not trivial.

22 It requires significant effort. He's got to go back to his office. He's
23 got to talk to a medicinal chemist colleague.

24 And then he says it would take an hour to elaborate a scaffold into
25 a fully formed inhibitor.

1 So what's being described even if this virtual experimentation
2 would work for four and a half million compounds, we have -- Dr. Veal,
3 assumed, okay, model four million compounds at one minute per compound,
4 and he came up with seven years.

5 So of course, even on these conservative assumptions, we're far
6 beyond the length of experimentation that the Federal Circuit has said
7 constitutes undue experimentation.

8 And that, of course, assumes as Dr. Eck must that modeling is all
9 that needs to be done and that it's predictive of the functional properties.

10 But what we show on slide 137 is, of course, modeling is not as
11 precise and accurate as Patent Owner suggests.

12 What happened when we had compounds modeled that show
13 different IC-50s, of course, these are not in the prior art.

14 But what happens is that modeling is not always predictive of real
15 world measured values.

16 Everyone agrees that these docking scores of these compounds
17 should bind well.

18 But the compounds that we show, Compound 81 and Compound 9
19 from Exhibit 1108 and Exhibit 1109, don't, in fact, when measured
20 empirically display good affinities.

21 And no one disputed that those compounds don't have good
22 affinities.

23 And so modeling is not predictive, even among the handful of
24 compounds that have ever been made and tested within the scope of the
25 genus.

1 And of course, all of the experts except Dr. Eck agreed on that
2 point.

3 Dr. Showalter and Dr. Veal, of course, testified that you have to
4 test compounds after you model them because modeling in a computer
5 model is not sufficient predictive of activity to rely on.

6 And of course, as we show on slide 138, when we asked
7 Pharmacyclics' medicinal chemistry expert, he said that it's always valuable
8 to validate predictions of modeling with data.

9 And that's something that he would've done when working on a
10 medicinal chemistry program.

11 And so, of course, it's not the case that modeling is fully predicted.

12 And so you're actually exactly under the fact pattern of the Idenix
13 case, exactly the fact pattern of the Wyeth case, where what you need to do
14 is make all the nucleosides or make all the rapamycin analogs or make all
15 the potential BTK inhibitors and then test them for activity.

16 And there's no way to know from modeling alone what the results
17 of that testing will be.

18 And of course, as we noted in our briefs, that's not the end of the
19 experimentation.

20 Even Pharmacyclics conceded as we show on slide 139 that further
21 testing is required in patients and its expert testified at his deposition pre-
22 clinically.

23 So the question then remains whether the specification provides
24 some guidance to cut through this to determine which compounds need to be
25 modeled, tested, and then tested in patients.

1 And the record at trial showed that the specification is bereft of any
2 guidance other than ibrutinib itself.

3 Patent Owner contended in its briefs that we disregarded the
4 POSA's informed choices.

5 Of course, that's inconsistent because no one has ever proposed
6 how a POSA's informed choices would actually lead you to rule in or rule
7 out any particular compounds.

8 Instead, all the experts have consistently testified that the POSA
9 would consider each compound individually.

10 And furthermore, even if the POSA were to focus on the
11 compounds that are just around ibrutinib as a starting point and recognize
12 those first, thereby finding the compounds most likely to work.

13 That's entirely inconsistent with the argument that the Federal
14 Circuit rejected in Idenix.

15 Patentee and Idenix made the exact same argument, that
16 experimentation would be limited to compounds that mimicked the hydroxyl
17 group at 2'-down.

18 But the Federal Circuit rejected that argument because the claims
19 were not so limited.

20 And a target for starting experimentation is not enough. So just
21 because the specification might provide some guidance as to which
22 compounds to start with, that would be most likely to fruitfully results in
23 BTK inhibitors.

24 That's not what the law requires. The law requires, well, what
25 experimentation needs to be done to practice the full scope of the claim?

1 Next, Patent Owner, of course, pointed to Formula E. And I don't
2 want to go over Mr. Berl's extensive discussion of Formula E.

3 But of course, even as among those eight cores, Dr. Eck was not
4 able to testify as we show on slide 145 which ones would work and which
5 ones he would test.

6 He said he hadn't even done that analysis. And when Mr. -- and
7 when Dr. Veal rather modeled those compounds, three of the eight don't
8 work.

9 So once again, Patent Owner looks entirely beyond the patent at
10 what the prior art teaches for some structure function relationship that
11 allegedly existed for BTK.

12 But as Mr. Berl already explained, no such relationship existed
13 here.

14 Of course, the only prior art compound within the scope of the
15 genus is ibrutinib itself.

16 And there were no other structures within the genus known to have
17 the function of binding BTK.

18 And as we show once again on slide 148, the only thing that Dr.
19 Eck was able to point to as the structure function relationship is the functions
20 that he's trying to achieve but not the structures that go with those functions.

21 And essentially what he's saying is you're going to need to then
22 model compounds that had never been designed, considered by anyone.

23 See what happens in the modeling exercise and then take him at his
24 word that he can model everything across the entire scope of the genus to
25 determine what works and what doesn't.

1 That's simply exactly the same research plan that was discussed
2 and rejected by the Federal Circuit in Idenix.

3 And it's the exact same thing that the Federal Circuit considered
4 and rejected in Wyeth.

5 And it's the exact same thing that the Supreme Court rejected in
6 Amgen v. Sanofi just because the patent specification provides a roadmap
7 for the experimentation or tells you how the experimentation is to be done is
8 not enough.

9 The guidance here of making one to three hydrogen bonds to the
10 BTK hinge is no different than the guidance provided in Amgen which, of
11 course, was here are the amino acids on the epitope that you're trying to bind
12 to.

13 That's just a description of the goal of the research. It's not a
14 shortcut to figure out how to get from here to there.

15 And likewise, telling a POSA that they need to make one to three
16 hydrogen bonds to the hinge, that's just telling them what they're trying to
17 achieve with the inhibitors.

18 It doesn't actually let them then say, okay, I don't need to make this
19 one or that one because you just don't know which ones are going to form
20 those hydrogen bonds.

21 And so even if -- and even if you make the conservative
22 assumptions that Dr. Showalter made, you have four and a half million
23 compounds to then try to figure out which are going to achieve this one to
24 three hydrogen bond binding.

25 We submit that's exactly the type of research planned that the

1 Supreme Court has determined renders claims invalid and that the Board
2 should find these claims not enabled for the same reason.

3 JUDGE HULSE: So, Counsel, is it Petitioner's position then that
4 112, the written description and enablement rise and fall together in this
5 case?

6 MR. HOAGLAND-HANSON: I think, Your Honor, the way that
7 the record developed the facts that apply to the two are very similar.

8 I think in many respects what they have provided, though, actually
9 makes my side of the case probably weaker in the sense that we agree that
10 there is the outline of a research plan.

11 And you can identify from the prior art what to do. But I would
12 submit that doesn't suffice to provide a written description in the
13 specification of what the inventors had actually invented and claimed.

14 JUDGE HULSE: So then are you saying that the person of
15 ordinary skill in the art would have had to test all four million compounds in
16 order to satisfy the enablement requirement?

17 MR. HOAGLAND-HANSON: I don't think that's necessarily the
18 case in every case.

19 But I think there, there was no way other than by a compound-by-
20 compound analysis.

21 And so if the question is which compounds within the scope of the
22 structural features will have the requisite functions, no one was able to
23 predict on a more than single compound by single compound basis how to
24 do that.

25 JUDGE HULSE: So if we disagree with you that there were

1 common structural features, then would the enablement argument fail?

2 MR. HOAGLAND-HANSON: I think if there were common
3 structural features that were sufficient to allow you to determine which
4 compounds are in or out, then that could provide some way to cut through
5 the experimentation.

6 But I don't think there's ever been any identification of such
7 features here.

8 JUDGE HULSE: Thank you.

9 MR. HOAGLAND-HANSON: Thank you, Your Honor.

10 JUDGE SNEDDEN: Thank you. Mr. Frazier, would you like to
11 reserve any rebuttal time?

12 MR. FRAZIER: Yes, if I could reserve ten minutes, Your Honor.

13 JUDGE SNEDDEN: Ten minutes. And I'll give an additional five
14 minutes should you need that.

15 MR. FRAZIER: Thank you. Thank you, Your Honor. Advance
16 to slide 3. May it please the Board. May I begin?

17 JUDGE SNEDDEN: When you're ready.

18 MR. FRAZIER: Thank you, Your Honor. So Your Honor, we just
19 heard a discussion about Section 112 and its application here.

20 And I would submit to you that it's a very narrow approach to
21 Section 112.

22 It's a narrow approach to Section 112 that guts the incentives for
23 those of skill in the art to actually innovate and instead encourages
24 incremental movement around things that have already been disclosed in the
25 patent itself.

1 And I want to start here to just go back to what is the invention that
2 we're actually looking at.

3 And this is an invention that changed the entire paradigm for
4 treating CLL and SLL that what the inventors here actually discovered and
5 what's set forth in the '803 patent is this method of continuous dosing despite
6 an increase in lymphocytes.

7 And of course, treating lymphoma, usually more lymphocytes, is
8 bad.

9 And so what they found out is that treating through that
10 lymphocytosis was actually helpful.

11 And if I get the next slide. And the result was that it changed the
12 entire paradigm.

13 So they found you could treat despite the lymphocytosis and that
14 patients were actually getting better due to the inhibition of the BTK.

15 And so if we see here on slide 4, the comparison, the treatment
16 regimen in 2008 showed an increase of lymphocytes was something that was
17 considered -- refractory disease was considered active, ongoing disease.

18 But in 2018, after the invention, the entire field had adopted this
19 idea, recognizing that kinase inhibitors can cause lymphocytosis and that in
20 such cases, the increased lymphocytosis alone is not a sign of treatment
21 failure.

22 So this was a complete change in a way to approach the treatment
23 of this disease using these kinase inhibitors.

24 This was not an ibrutinib effect. This is a class effect. This is due
25 to BTK inhibition.

1 If we get the next slide. And so what have we done here? To be
2 clear, this is a structural claim.

3 And of course, it's a structural claim that is grounded in the
4 structure of ibrutinib which is where the patent demonstrates this effect.

5 And so when you look at this, you see up on the top left there the
6 phenoxyphenyl moiety, that's critically important for establishing the
7 position and the specificity of the molecule.

8 The linker-warhead over here on the right-hand side, that's the
9 whole point is this irreversible binding.

10 And we're going to get into this. But this is what's critically
11 important about this class of BTK inhibitors is that they're irreversible
12 binders.

13 And so that warhead, it's not like a reversible inhibitor where you
14 have to have such a tight configuration that it fits exactly right in order to do
15 its job.

16 This irreversibility of that warhead means that once you get close
17 to the right orientation, it fires.

18 The warhead fires, and you lock it in place together with the
19 phenoxyphenyl moiety.

20 And then you have the in between this scaffold part that we've
21 labeled Z'.

22 And that makes the hydrogen bonds that we're talking about. But
23 to hear Mr. Berl talk, you would think that was just -- we said essentially,
24 well, anything in Z'.

25 But of course, that's not the case. It says specifically that Z' is

1 optionally substituted heterocyclic ring comprising of two to four nitrogens
2 and that it has to be a five membered ring and a six membered ring.

3 So structurally, this is fixed, right? It's a six-member ring and a
4 five-member ring.

5 And you can substitute it with two to four nitrogens. And you
6 substitute it with other things that a person of skill understands go in
7 positions that get to the necessary hydrogen bonds.

8 And we'll talk about that makes sense here because the portion that
9 a Z' is what binds to the most conserved part of BTK.

10 And what the entire field understood was the part that essentially
11 was unchanging from kinase to kinase.

12 And so they knew precisely where to make those hydrogen bond
13 interactions.

14 They knew what the moieties were that would make the hydrogen
15 bond interactions. And therefore, this makes sense in that context.

16 JUDGE MITCHELL: Can I ask you a question about where
17 would you point me to show me that a POSA would know from the prior art
18 what substitutions to make on that Z'?

19 Like, what was acceptable to do, and how common of a knowledge
20 would that have been?

21 Would that have just been a routine understanding of how to bind
22 to a kinase?

23 MR. FRAZIER: I think when you look at some of the Ghose
24 articles, it's probably one of the best ones for showing that conservation.

25 And if I could just find our drawing here. Yeah, it appears we're at

1 slide 28.

2 And at slide 28, this is actually an article that was cited by Dr.
3 Showalter in his initial -- in the initial petition, his declaration for the initial
4 petition.

5 And Dr. Showalter essentially didn't address the modeling
6 meaningfully at all.

7 But when you look at what's actually recited in this Ghose article,
8 it talks about the high degree of structural similarity of the ATP binding site
9 and the presence of key interactions are the sites for ligand recognition lend
10 itself to an informatics driven analysis of protein-ligand interactions across
11 the kinome.

12 So what that means is it's lending itself to this idea of modeling
13 and knowing where things go.

14 And if you actually go to the next slide, it goes further and says
15 that you can make these empirical rules, so I'm on slide 29, to predict the
16 hinge-binding orientation.

17 So this is not a mysterious -- this is -- I understand the desire to try
18 to place this in the context of the various antibody and biologic cases.

19 But this is the furthest thing from antibodies. Antibodies, you have
20 hundreds of different amino acids, countless different hydrogen bondage or
21 actions and so forth.

22 This is fixed. And this is Pharmacyclics trying not to take too big
23 a bite here.

24 So they fixed the phenoxyphenyl. They fixed the warhead. They
25 said the heterocycle has to be 5:6 rings and have certain characteristics.

1 And they do that bit of open area in the middle of it because this is
2 the part that's most well known in these kinases.

3 And there are specific empirical rules that allow you to predict
4 hinge binding.

5 So again, going back to what do we talk about when we talk about
6 visualizing things that work from a written description standpoint,
7 understanding what the scope of the invention is.

8 What is it that they're in possession of? This is where it comes
9 from is this idea that the person of skill knows what the rules are to fit.

10 If I tell you I need a 5:6 ring with these substitutions, then the
11 person of skill is able to do that.

12 And that's what -- that's really what the invention is showing here.

13 And I think if we illustrate that, I just want to go back briefly if I
14 could to slide 6.

15 And this, I think, kind of makes the point which is to say that what
16 we have here is we have this comparison between ibrutinib and zanubrutinib
17 which was brought to the -- brought into the case by Petitioner here.

18 Their opening petition mentioned the zanubrutinib or Brukinsa
19 about 70-plus times.

20 And so they wanted to make this comparison. And I submit to you
21 that the comparison actually shows our point which is that these are the most
22 similar molecules.

23 And indeed, when you look at the other options that were
24 available, there is a lot -- there are a lot of ways to innovate in this field.

25 And they chose to go straight into what was already disclosed in

1 the patent.

2 And they kept exactly the phenoxyphenyl. They kept exactly the
3 warhead.

4 They used the 5:6 ring. And they got this orientation that fits to
5 make the necessary hydrogen bonds.

6 So if we can jump to slide 7 then. Just in summary here, the
7 written description divides down the fact the claims recite -- they do recite
8 common structural features.

9 And again, my friend on the other side seemed to imply that there
10 weren't common structural features.

11 I submit to you they're expressly recited. The common structural
12 features are the features that are set forth in the claim and that a POSA can
13 visualize the members of that genus because they're structurally set forth.

14 And to the extent that there's variability, they can see those
15 because the structural features that specifically bind are fixed.

16 The scaffold has to make these predictable interactions as goes to
17 another -- another prior art showed and that this modeling allows
18 visualization of the complete molecules and their binding to BTK.

19 And if we can maybe just jump forward briefly to the Marcotte.
20 Let's look at slide 18 if we could. Let's go to 19.

21 Right. So this is the Marcotte reference. And actually, this is a
22 summary of three important points here that someone reading the patent in
23 light of the prior art would know.

24 So the patent is expressly telling you -- and this is very important.

25 The patent is telling you this is not an ibrutinib effect. It's not as

1 though we just treated patients with ibrutinib and they got better.

2 And we said, oh, fantastic, the drug works. They knew why it was
3 happening because they were looking at occupancy.

4 And so occupancy is critically important here. And this didn't
5 come out as well I think in part because of the way it was presented by
6 Petitioner.

7 But even in the institution decision, I think that the point that
8 could've come out more was this positive correlation that was found between
9 the BTK active site occupancy and the actual effect in the disease.

10 And so what the patent is telling you is that it is the irreversible
11 inhibition itself that's causing this effect.

12 And so you have this whole question of, oh you know, I don't
13 know. They're making a comparison to the Idenix Gilead case.

14 That case specifically turns on the idea that nobody knew exactly
15 how those compounds were working.

16 They didn't have a structure function relationship. They didn't
17 really know which compounds were going to be the effective ones.

18 Here the patent expressly tells you, you need to be having this
19 effect on irreversible inhibition.

20 And it tells you you're going to do that by making this interaction
21 with the 16481 with a warhead.

22 And you also know how the drug is positioned. And that's what
23 you're getting from Marcotte.

24 Marcotte is a structure that allows you to put into space -- and it's
25 not a matter of I just feed it into a computer and then, like, AI, sit back, and

1 wait for the result.

2 It's actually the scientist looks at it and they visualize it so it
3 matches up.

4 It's the word we use in talking about written description, and it's
5 the way they actually do the work in the field.

6 And so if we go to the next slide, we're here on slide 20. And this
7 is now talking with Dr. Veal about the Marcotte.

8 And he agrees on questioning that the phenoxyphenyl confirms the
9 phenoxyphenyl group attached to the adenine mimic scaffold, binds within
10 the hydrophobic back pocket of BTK, right? Yes.

11 And then the adenine mimic scaffold makes hydrogen bonds to the
12 hinge region, right?

13 Yeah, that's what it's showing you. And so you get this whole
14 picture that comes up from Marcotte.

15 And that's why it's so valuable to a person of skill in the art. If we
16 go to the next slide.

17 And here even Dr. Showalter who came into this essentially
18 admitting that really he wasn't all that familiar with the structure function
19 relationships of protein kinases.

20 Even he says, well, this would've been helpful. And it certainly
21 would've been kind of an easy transition to go from the reversible inhibitor
22 that was shown in Marcotte to the irreversible inhibitor based on what was
23 known in the literature.

24 So even their expert, Dr. Showalter, recognizes the value of
25 Marcotte in understanding and visualizing the members of the genus.

1 And likewise, if you go to the next slide at 22, Pan was also in the
2 prior art.

3 Pan is important because it actually also showed you there's been
4 some discussion that, well, maybe this warhead is very finicky and it needs
5 to be in just the right spot.

6 That's not the case. So Pan shows you. They actually put the
7 warhead in several different places on a molecule that was essentially very
8 much like ibrutinib.

9 And they show that even in different orientations that there was a
10 fair amount of flexibility that would allow the warhead to still act and get
11 that molecule properly positioned without perfectly precise binding.

12 And so that was something else. And the quote from Dr.
13 Showalter, stereo chemical orientation does not have a major impact here.

14 And if we go to slide 3 -- I'm sorry, slide 23. This, I think, is one
15 of the most helpful ways to look at the whole thing which is again we heard
16 about this idea that there's so much unpredictability.

17 We heard I don't know what I would do if I were a person of skill.

18 The standard is not whether a skilled patent attorney could make
19 an argument about what's hard to understand.

20 The question is, would a chemist presented with this information at
21 the time be able to visualize what's disclosed in the patent and what's within
22 the scope of this claim?

23 And I submit to you that this is exactly what they can look at. So
24 this is the phenoxyphenyl showing up there in the middle right next to the
25 word, ibrutinib.

1 That's the phenoxyphenyl at the top, and then that's the warhead
2 down at the bottom.

3 And you know where it says 481 is. And so you've got --
4 essentially, it's like a hand.

5 I've got my thumb and I've got my pinky. And then the question
6 is, where are the fingers going to go?

7 If I'm trying to put a glove on, where am I going to put the three
8 fingers in between once I positioned my thumb and my pinky finger because
9 I know the phenoxyphenyl and the warhead?

10 And that's what this is showing you. And you can see exactly
11 where those hydrogen bonds are going to be formed.

12 And people understood what formed the hydrogen bond. So again,
13 it's not a mystery like in antibodies where we say, I have no idea what amino
14 acid goes next or what have you.

15 It was known in the field which of these moieties were capable of
16 making these hydrogen bonds.

17 And so you could make these sorts of pictures and make your
18 analysis of what should go in that space.

19 JUDGE HULSE: Counsel, do you agree, though, that you may
20 have an idea as to which substituents might create a hydrogen bond but
21 there's no way to know until you actually test the compounds?

22 MR. FRAZIER: No, I disagree with that. I think that the -- I think
23 this is something Dr. Eck was very clear on, that, well, of course, ultimately
24 to develop a drug, you're going to run that drug through physical testing and
25 everything.

1 The real value of the modeling is its ability to eliminate any sort of
2 blind alleys that you might otherwise go down.

3 And this correlation then with activities is expected to be very
4 good on the modeling.

5 So I think that the idea that somehow I have to go in and test
6 everyone to confirm the modeling, I just don't think that's the case.

7 JUDGE HULSE: And can you point us to where in the record that
8 testimony is?

9 MR. FRAZIER: Yeah, if we actually go then to -- let's look at
10 slide 26.

11 Right. So this is from Dr. Veal's publication. And it goes to the
12 idea that there's predictability.

13 So he says in his 2004 publication at Exhibit 2121 that the ATP
14 site affords a hydrophobic cleft.

15 It's common to all kinases. The commonality of binding elements
16 provides inhibitor design features that can be applied to all kinases.

17 If you go to the next slide, 27, I mean, this is an important point
18 from Dr. Showalter where he says he's not an expert in this.

19 So it's important to see this in the context of the petition that they
20 brought in.

21 This was their petition, and they came in with Dr. Showalter who
22 gave a broad opinion that there was insufficient teaching of the structure
23 function relationship in this patent.

24 And what he actually admits on questioning is he's really not an
25 expert on the structural aspects of protein kinases, right?

1 And so that's a problem for them. And so then what happened, so
2 that becomes clear that the petition is actually not getting to where they need
3 it to go.

4 And so then on reply, they bring in Dr. Veal. And so then Dr. Veal
5 for the first time comes in and he says, oh, I tested a handful of these various
6 compounds and I found that I was able to find a way to position them that
7 they don't work.

8 And we don't see him testing whole families of these. We don't
9 see him actually working with the substituents to make the appropriate
10 hydrogen bonds.

11 And instead, he just says, oh, I tested this one and it didn't work.

12 So it must not work. And then they say, oh, that's unrebutted.

13 Well, this was all done on reply, right?

14 So I guess we could've been asked for further permission to put in
15 another 150-page declaration from yet another expert on sur-reply.

16 But the fact of the matter is that they really were simply trying to
17 fill holes in what was, in fact, a defective petition when they came in that
18 they just didn't bring the evidence that they needed to bring in their petition
19 to actually make the point that they're trying to make here.

20 And so if we could go maybe to slide 49. This is -- right. So this
21 is the important point which is to say that Dr. Eck confirming this ability to
22 visualize the full scope of claim 1.

23 So he says, it's my opinion a POSA can envision all possible
24 molecules that fall within the scope of the claim.

25 There's no structure that's not possible to envision or recognize and

1 various other times that he was asked similar questions and gave similar
2 answers here.

3 And I would say unlike Dr. Veal who we found multiple instances
4 where his own publication seemed to be intentioned with positions that he's
5 taking here, we don't see that with Dr. Eck.

6 Dr. Eck is making solid points here about what a person of
7 ordinary skill in the art would know based on this.

8 And again, I just want to emphasize how different this situation is
9 from the types of cases that they're trying to analogize to in terms of these
10 antibody cases.

11 And the cases -- most of the cases, of course, are representative
12 species cases.

13 And they really don't fit here. And I can see how Petitioner is
14 trying to make them fit.

15 But this is a common structural features case. And we've defined
16 structures in the claims.

17 And the issue is only that they seem to suggest that because there
18 are few examples of things that don't work that somehow that those
19 structural features aren't sufficient.

20 But in fact, there's a full definition of common structural features.

21 And then you can use modeling to the extent that there's a need to
22 do any sorting between things that don't work and things that do work.

23 It's something that can be sorted out through the modeling by
24 putting them in the right position.

25 JUDGE HULSE: So does Patent Owner concede then that there

1 are not a representative number of --

2 MR. FRAZIER: Yes, our position is this is a common structural
3 features case.

4 All right. And I just want to go back. We talked briefly about
5 Ghose before.

6 And so if I just go back to slide 28 and 29. Let's go to 29. This
7 again really goes to -- maybe 28.

8 Let's go back to 28, I think maybe the first one, is you had asked
9 about, again, where you can put these -- the substituents.

10 And this is getting at this idea of where you put the hydrogen
11 bonds.

12 And if we go to the next one, that's exactly what we're talking
13 about.

14 The binding modes can be categorized in terms of ligand core
15 structure and a few simple empirical rules.

16 You can formulate your binding mode hypothesis. And through an
17 analysis of the binding modes, the different types of kinase ligands, you can
18 anticipate the binding mode of a related ligand with kinase inhibitor features.

19 So this is something then that would work across multiple kinases
20 into BTK.

21 And it's actually relevant here. I'd point out if we jump to slide 32.

22 This, we actually look at Guo 2019, the Petitioner itself, So Guo
23 2019.

24 It's Exhibit 2039 on slide 32. This is the Petitioner actually using
25 the same Marcotte data to model their own compound.

1 So this is something then that they're doing in their own
2 publications.

3 Of course, it's a later publication. I don't dispute that. But it tells
4 you because the information was there earlier, it's exactly what a person of
5 skill in the art could do back at the relevant time.

6 Now if we could go to slide 34, there are a couple of points here
7 that it'd like to get to.

8 First of all is this aromatic versus non-aromatic divide that we
9 talked about.

10 We heard a lot in the context of both the specification and
11 zanubrutinib about an alleged difference between the 5:6 heterocycles that
12 are fully aromatic versus partially aromatic.

13 But a POSA would not make these strong distinctions. If we go to
14 the next slide, zanubrutinib itself actually ends up confirming the common
15 structural features of the claim.

16 And that's because of the way we look at it. I mean, part of it is
17 even sort of common sense.

18 Like, why would they use the phenoxyphenyl and the warhead
19 exactly the same if those weren't important structural features for holding the
20 thing in place?

21 They're changing the Z' core. But wouldn't they have used other
22 things if they had thought to be able to use them?

23 If there were other ways to get there, why are they using the
24 common features -- the exact features that were in ibrutinib?

25 It doesn't -- logically, it must be that those are providing significant

1 structural features that correspond to the function of the molecule by virtue
2 of the fact that they're using the phenoxyphenyl and the linker-warhead and
3 then have the scaffolding in between.

4 And in fact, if we go to the next slide, that's what bears out. So
5 this is then a picture, again, doing the modeling if you put those two things
6 together.

7 And what does Dr. Eck say when he analyzes this? He says,
8 ibrutinib and zanubrutinib have largely overlapping placement in three-
9 dimensional space, further confirming the two inhibitors bind to BTK in the
10 same way from a structural perspective.

11 And they maintain the hydrogen bond interactions. Again, you can
12 see those over on the side as to where they know where those interactions
13 are supposed to occur.

14 They know which moieties can be acceptors and which can be
15 donors of hydrogen bonds.

16 And if you go to the next slide, I think this is actually even more
17 illuminating.

18 It's a little abstract when you first look at it. But what it's showing
19 is that all of the interactions of BTK are the same for ibrutinib and for
20 zanubrutinib.

21 And so what we're looking at here is we're looking at -- and I'm on
22 slide 37.

23 We're looking at the circles are amino acids that make contacts --
24 meaningful contacts with the molecule.

25 And what you see is exactly the same interactions, the same amino

1 acids that are being contacted with both of these molecules.

2 So they have this whole thing that we just heard all about of, oh,
3 look, it's different.

4 The nitrogens are in different places. The rings are aromatic
5 versus non-aromatic.

6 And we asked Dr. Veal when he looks at this. My question was,
7 you didn't identify any different interactions between the zanubrutinib six-
8 membered ring and BTK and that aren't present in ibrutinib, correct?

9 And he says, that's right. There are no specific interactions
10 identified.

11 What does that mean? It means there's no difference in the
12 interactions, whether you have an aromatic six-membered ring or non-
13 aromatic six-membered ring.

14 So their own molecule is proving the point here that these are
15 relatively minor distinctions that a person of skill in the art would
16 understand at the time aren't going to necessarily make a big difference and
17 that you could model to see how these things worked.

18 JUDGE HULSE: So if these are the critical interactions, then why
19 shouldn't that be required to be in the specification to satisfy a written
20 description?

21 MR. FRAZIER: I mean, I think that it goes to the point that you
22 don't necessarily have to include things that are known in the art, right?

23 So if we go to the formula -- well, in that portion of the
24 specification, if we go to slide 15.

25 And we talked about -- so Formula E which is what's set forth

1 here, these things, the binding to and a moiety that binds to the active site of
2 the kinase is known that what was important here was the irreversibility.

3 And so that's what they're saying is to essentially put the
4 irreversible inhibitor onto the moiety that's binding to the kinase.

5 And that's what's going to get you where you need to go. And
6 that's borne out -- if we go back one slide to slide 14, that's what's borne out
7 in Pan.

8 And that's what's borne out in the occupancy concept that's in the
9 '803 patent.

10 And so the -- if a person of ordinary skill in the art knows and
11 holds constant that phenoxyphenyl from ibrutinib and if they then also have
12 a warhead that we know can be oriented in a few different ways, then the
13 middle is basically follow the rules that were set forth in the prior art for
14 making those well-known hydrogen bonds in the hinge region.

15 And so they don't necessarily need to be recited that you could put
16 this here and that there because a person of ordinary skill knows where to
17 put those.

18 And we have, in fact, structurally stated that it's a five, six-
19 membered ring.

20 And so that is a very precise structure in terms of then, yes, you
21 may want to make some different substitutions to help out.

22 And I would submit that some of the testing that they did or the
23 modeling that they did that purported to show lack of binding that they didn't
24 test just making substitutions with the goal of trying to establish those
25 hydrogen bonds the way a person of skill in the art would do.

1 That indeed substitutions as are suggested in the claim would be
2 helpful in that regard.

3 JUDGE HULSE: Can you respond, please, to the question that I
4 asked or the answer, I guess, that Petitioner provided to my question about
5 when it's proper to rely on the knowledge of the person of ordinary skill in
6 the art or the knowledge of the art at the time?

7 Because Petitioner said that all the cases that Patent Owner relied
8 on, the UroPep case, the Invitrogen case, the Falko case were all examples
9 where they were pretty definitive species within that genus.

10 And apologies, Petitioner, if I'm mischaracterizing your argument.

11 MR. FRAZIER: Yes, Your Honor.

12 JUDGE HULSE: Could you please provide -- provide us with
13 your best case on why we should be allowed to -- or why Patent Owner
14 should be allowed to rely on the functional aspects to satisfy the common
15 structural features.

16 MR. FRAZIER: Yeah, I think Ajinomoto is a good example there
17 that a person of ordinary skill was able to rely on things that were disclosed
18 in the art in order to inform the choices that they were making.

19 I think that's something that you definitely would be allowed to do
20 in that context.

21 That was -- I was particularly interested because it involved
22 bacterial promoters and there was effectively a consensus sequence.

23 And the dispute was over things that weren't the consensus
24 sequence but were getting close to it.

25 And it's essentially that they had shown a general tendency and the

1 fact that by using the generalized guidance of a consensus sequence that you
2 could essentially say, okay, these are going to be better compounds.

3 These are going to be worse compounds or better promoters or
4 worse promoters.

5 And I think the same thing applies here to the structures because
6 there is such a strong structural understanding of the hydrogen bonds and the
7 confirmation that then when you have the model and you're able to put it in
8 that context, you're able to then make the appropriate sorting to the extent
9 necessary of working compounds versus a compound that for whatever
10 reason doesn't seem to fit as well into that position.

11 But it's appropriate under Ajinomoto among others. Now I want to
12 get back to a little bit more on the written description.

13 And I think that if we looked at the aromatic rings, I think the other
14 key point that I want to get at is we go to slide 38.

15 This again was something -- and we've heard them continue to
16 make this point that somehow that there's a difference based on aromaticity
17 that one is an adenine mimetic and one is not an adenine mimetic.

18 All of these mimics the role of adenine. That's what's going on
19 here is that these are inhibitors.

20 The natural kinase binds to ATP and therefore it basically binds an
21 adenine in that active site and catalyzes it.

22 And that's why it's a kinase, that it takes phosphate off of the ATP.

23 And so all of them are, in fact, adenine mimics. And if we look at
24 this, Dr. Veal's publications talk about that the hydrogen bonds, the features
25 of a purine mimetic, purine being adenine, are hydrogen bonding

1 functionality.

2 And then he says in 2009 that the adenine mimetics for protein
3 kinase is all for potential to satisfactorily replace the two hydrogen bonds
4 formed by ATP.

5 So again, this is in the art knowing where to put the appropriate
6 things.

7 And then if we look at Dr. Eck's declaration then, this actually is
8 comparing the residues in BTK in adenine, in ibrutinib, and in zanubrutinib.

9 And you can see that they're making the same context.
10 Zanubrutinib makes one additional hydrogen bond.

11 But in terms of the basic hydrogen bonds, they're still making the
12 same context.

13 And if we go to the next slide, this is even more illuminating
14 because it involves both documents that they relied on in their own
15 reference.

16 So let's start. This is slide 39. Let's start at Guo 2023 which is
17 Exhibit 2020.

18 And it's picturing there the approved irreversible BTK inhibitors.

19 And of the five approved BTK inhibitors all have similar hinge
20 binding to ATP, right?

21 So what does that mean? That's saying that even though you look
22 at these and they look different on just to somebody here standing looking at
23 them, they have -- people of still in the art understand that they have similar
24 hinge binding to ATP.

25 They're all mimicking adenine. Same thing, Dr. Showalter recited

1 this Zhang 2021 article which, again, it talks about the approved inhibitors,
2 including ibrutinib and zanubrutinib.

3 And it says to mimic the intermolecular interactions between ATP,
4 adenine, and the hinge region, all BTK inhibitors possess a heterocycle core
5 to maintain similar interactions with hinge residues.

6 And similar down here in 2021, another references Dr. Showalter
7 cited, ibrutinib and zanubrutinib share similar bioactive confirmations within
8 the wild type BTK binding site.

9 So the entire theory here that because there's this supposedly
10 completely different structural class of molecules that would be the non-
11 aromatic or semi-aromatic 5:6 heterocycles that there's a completely
12 different binding mode that's not described within the patent.

13 It just doesn't hold up under scrutiny under the paradigm that they
14 set forth.

15 This was the whole point of their petition was just look at
16 zanubrutinib and ibrutinib and you'll see that they're so different that we
17 should conclude the claims must be overbroad because if these claims cover
18 zanubrutinib that there clearly is no description of it.

19 But what you see in fact is that zanubrutinib follows the precise
20 rules that you would expect based on the disclosure of ibrutinib.

21 That, in fact, they're binding in the same way and the mere
22 difference in the choice of that Z' core to have a non-aromatic six-membered
23 ring is not driving differences in the way they bind.

24 And I submit that again this is something that a person of skill
25 could figure out based on the actual binding -- I'm sorry, based on the

1 modeling that they would be able to do.

2 Now I do want to talk about enablement here as well. And I think
3 if we turn then to -- let's start then at slide 8 even just to get an overview.

4 So the point that we've been making -- the point that I've been
5 making about written description, again, the first two sort of the factual
6 underpinnings of written description obviously are relevant here.

7 But I do want to get to point 3 which is they have a major failure of
8 proof and are focusing on the wrong thing when it comes to enablement.

9 And we just heard the argument from my friend on the other side
10 who essentially said, oh, you would have to go through and you would still
11 have to test every molecule.

12 And they put in evidence -- essentially again going back to the
13 petition, they put in evidence from Dr. Showalter of 1,700 cores in his
14 Appendix A that would purportedly work or that would purportedly fit
15 within these claims.

16 But then when it came down to figuring out which ones of those
17 would be effective inhibitors and which ones wouldn't, he didn't do the
18 work.

19 And so if we go to slide 52. This is talking about the Appendix A
20 from Dr. Showalter that was in their petition.

21 And we asked him in his deposition, you've not done an analysis to
22 determine which of the bicyclic 5:6 systems you cite would be more or less
23 likely to be functional inhibitors of BTK if they were appended as the claims
24 describe with a phenoxyphenyl back pocket binder and the linker-warhead
25 structure that's in claim 1, right?

1 And he says, no, I haven't done such an analysis. Now they try to
2 take us to task and turn this on this and say, well, Dr. Eck didn't do a
3 complete enough analysis either.

4 This was their petition. They needed to come in with sufficient
5 evidence to make their point on non-enablement.

6 And all they established through Dr. Showalter is something about
7 the breadth of the claims.

8 They showed that there are a lot of these that they had, 1,700 of
9 these structures that they could put in there.

10 But he didn't go through and try to tell which ones -- what
11 percentage of those would be effective and which ones wouldn't.

12 Moreover -- and actually, I asked him that question. Well, you
13 didn't do any modeling.

14 You didn't do any modeling of those to determine which would be
15 more or less likely to form compounds that would meet the functional
16 limitations.

17 And he says, that's correct. No modeling was done. And he didn't
18 attempt to account for even Dr. Veal's analysis about E2, E3, or E4.

19 And he said, no, he didn't account for that either. And then if we
20 go to the next slide, he also said that he didn't assess whether those cores had
21 been used in the context of previous tyrosine kinase inhibitors.

22 So again, the guidance from the patent is use known cores that
23 have been used previously in the field ideally to make these known
24 interactions.

25 Obviously, it's still within the 5:6 heterocycle requirement of the

1 patent claim.

2 And so use those cores and put them together with the
3 phenoxyphenyl and the warhead.

4 But he didn't even look to see if any of these cores had been used
5 previously.

6 So again, all he did is he drew a lot of structures and said, these
7 must be broad claims and they aren't enabled because I can draw 1,700
8 structures that fall within them.

9 But he didn't do any of the work to figure out whether they were
10 actually active or not.

11 And I heard counsel today make a suggestion that somehow
12 they've established that only a small portion of them would work.

13 And I haven't seen that evidence at all. The closest I've seen is I
14 saw them put a quote from Dr. Eck on the Board where he said he hadn't
15 specifically done that analysis either of counting up or determining a
16 percentage of those that would work from those that wouldn't work.

17 And he said, I haven't done it, I haven't done it. And then they
18 said, well, but guess anyway.

19 And he said, well, it'd be more than hundreds. And so they said,
20 oh, well, I guess he meant hundreds, right?

21 But that's not evidence that the number is hundreds. That's
22 evidence that Dr. Eck didn't solve the problem that was created by Dr.
23 Showalter's failure to do what he needed to do to show enablement. And so
24 then when it comes to --

25 JUDGE HULSE: Counsel, isn't it --

1 MR. FRAZIER: Yeah?

2 JUDGE HULSE: Sorry to interrupt. Isn't it telling, though, that
3 they -- or I guess convince me that it's not, that they tested the structure that
4 you -- I don't recall what numbers they were, but that they tested those.

5 And with the required structural moiety and the linker-warhead
6 and it didn't work.

7 MR. FRAZIER: I guess there are a couple of things that I would
8 say about that.

9 One -- I believe we even have a slide on this point here. Let me
10 turn to that one.

11 Yes, slide 60, just to summarize the point on this. First of all is of
12 course the fact that you model it and you get something that tells you don't
13 go forward with that compound is actually part of our point here.

14 So there's no undue experimentation filling out this genus because
15 you get from the modeling thumbs up, thumbs down.

16 And this is sort of they have the two competing ideas going on and
17 their response to this where first they're trying to tell you modeling is not
18 any good and you wouldn't rely on it.

19 And then Dr. Veal says, well, actually, I tested E4 and it doesn't
20 work.

21 And so the first point here is assuming that you're actually going to
22 take the modeling at face value, that's actually helpful to show that it doesn't
23 work.

24 Second, he only modeled the one compound with the E4 scaffold.

25 And he didn't attempt to identify the substitutions that would work.

1 And so I would submit that what Dr. Veal is doing here is not what
2 a person of ordinary skill would do which is to be basically trained to find
3 things that do work.

4 I think what we were looking at with Dr. Veal is him trying to do
5 experiments to show what doesn't work.

6 And that's not what a person of skill in the art would be obviously
7 trying to accomplish here.

8 I would point as well, I think it's very telling that they don't raise
9 any of this modeling until the reply and that indeed there's no evidence in the
10 record about other compounds with the E4 scaffold would bind to BTK.

11 So is it relevant? Of course it's relevant. But I think it goes to the
12 point of how you can use modeling to save time.

13 You don't go through and try to synthesize four million different
14 compounds.

15 You look at the ones that you're interested in and you make a
16 distinction.

17 And I just want to go back again to this idea under the patent law.

18 So the critical point is that for enablement purposes, it is
19 abundantly clear under the Supreme Court Amgen standard that you have
20 to -- if I go to slide 51, you don't just add up the amount of work.

21 It's not measured against the cumulative time and effort it takes to
22 make every embodiment within the claim.

23 So that's the wrong analysis. Essentially, the analysis needs to be,
24 are there parts of this claim that I can't access?

25 Are there things in the claim that is this a needle in a haystack

1 problem?

2 I would submit to you that the record as it is, is they found a few straws of
3 hay in a stack full of needles.

4 There's no evidence in the record that the vast majority of these
5 don't work.

6 And so it's not about how long would it take me to test every
7 compound that's within the claim.

8 It's the question of, if I say I want to -- I'm interested in making
9 Compound X, do I know without undue experimentation that that is a viable
10 path to take or not a viable path to take?

11 And they're trying to analogize the modeling with wet bench
12 experimentation.

13 And it's obviously a very different thing. Again, if we go back to
14 Ghose, if you read that publication, it even talks about how chemists could
15 drop things down on paper and essentially say, oh, I can orient it this way.

16 And now instead of just having a piece of paper, they can put it
17 onto the screen and show and see how it orients in three dimensions and get
18 a really good sense of whether this is a productive compound or a
19 nonproductive compound.

20 And that is not undue experimentation. We have this -- they
21 pointed to Dr. Eck who said for any given compound, I could probably work
22 this out in about an hour as to whether it's an effective compound within the
23 genus or not.

24 And they're actually taking the position that that's undue
25 experimentation.

1 And I would go back to where I started by saying that if that's the
2 standard for undue experimentation, that basically looking at it in your office
3 for an hour is undue experimentation, then we have no protection at all in the
4 patent.

5 That can't possibly be the definition of undue experimentation. If I
6 put something in a computer model, look at it for an hour or less and decide,
7 this is either great, I should go forward, or this is not great and I should put it
8 aside, that somehow that reflects undue experimentation.

9 I think it most clearly does not. I do want to go briefly into the
10 idea of also if we could have slide 63.

11 Again, there's some discussion of what's required from a
12 therapeutic standpoint.

13 And the idea that there's no undue experimentation would be
14 needed in order to figure out how to use these therapeutically.

15 So again, undue experimentation is about actual innovation that's
16 required, if it requires more than ordinary skill to carry things forward.

17 So the fact that these are human compounds that ultimately --
18 where it's a human treatment method that ultimately you would need to
19 make a physical compound and put it into people is not meaningful for the
20 purpose of undue experimentation because you're screening.

21 You do upstream in terms of this modeling. You don't screen by giving the
22 drug to people and say, oh, does that one work or does that one not work?

23 You screen upstream by showing that it actually has the ability and
24 the modeling to fit and would be expected to be an effective inhibitor.

25 You obviously then could do a quick bench top test to show that it

1 is an inhibitor.

2 And then you would carry it forward as needed to use in people.

3 And what we see here again is this idea that when it comes time to figure out
4 the dose and to actually use it in people, all you do is you're looking at the
5 occupancy.

6 And it's a unique characteristic of this irreversible binding that
7 essentially once this drug comes in contact with the BTK itself that it's
8 irreversible.

9 That's what it means here. And so you can isolate that out in a
10 blood test and look and make sure that it's doing what it's supposed to be
11 doing.

12 And so that allows you to give a dose and then look at the dose in
13 the context of a patient that's been treated.

14 And that, I would submit, is in view of what's taught in the patent
15 is not undue experimentation.

16 Likewise, if we go to the next slide, we see Dr. Rosen submitted
17 the declaration in the original petition.

18 And it really did not move the ball at all because he focused on a lot of
19 things that just don't matter.

20 So enablement doesn't require regulatory approval. So Dr. Rosen
21 made a number of statements about the differences in the labeling and so
22 forth between zanubrutinib and ibrutinib which really wasn't on point.

23 Also, and this was dealt within the institution decision. I think
24 there's no dispute now that the claims as currently interpreted don't have a
25 requirement for safety.

1 That's the way the Board has interpreted them here and that, again,
2 preclinical testing before clinical trials is a standard sort of industry practice.

3 If we go to the next slide, slide 65, this is very important. And Dr.
4 Rosen was asked at his deposition whether he had identified BTK inhibitors
5 that binds to another protein or induces some problem.

6 In other words, does he have negative results? Once you have an
7 effective BTK inhibitor, is he aware of effective BTK inhibitors that would
8 not be effective in the method?

9 And he says he doesn't know of any such negative results. So I
10 wonder if I could save my remaining seven minutes here and add them to the
11 ten minutes that I've reserved, unless the panel has any more questions.

12 JUDGE SNEDDEN: All right.

13 MR. FRAZIER: Thank you.

14 JUDGE SNEDDEN: So we'll give you 17 minutes for rebuttal.

15 MR. FRAZIER: Thank you, Your Honor.

16 JUDGE SNEDDEN: Whenever you're ready.

17 MR. BERL: Thank you, Your Honor. Sorry. If we could just get
18 the -- thank you, Your Honor.

19 We heard just now that our case had holes and that's why we all of
20 a sudden introduced modeling later.

21 I would submit it's not our case that holes. It's their patent that has
22 holes.

23 Almost nothing you've just heard came from their patent. This is a
24 remarkable defense of a written description challenge where they avoid the
25 patent like the plague.

1 We didn't do modeling originally because modeling is irrelevant.

2 Modeling is not disclosed in the patent. And as much as he wants
3 to talk about modeling, he never said that modeling actually creates the
4 structures in the claims.

5 That's not what it does. Modeling evaluates structures that people
6 create by their ingenuity and medicinal chemistry.

7 They do exactly what the Federal Circuit said is not enough in the
8 Alonzo case.

9 They created or identified a method by which one can identify
10 molecules that will work compared to ones that won't.

11 Not a very good method. We don't think it works very well. But
12 the Federal Circuit was clear as day in Alonzo.

13 That's not enough of a written description. You actually have to
14 identify the structures, the common structural features.

15 And we basically challenge them. I stood up here and said several
16 times an hour ago they can't identify a single molecule in the prior art that is
17 a non-biaryl structure within the scope of the claim.

18 And no response. They have none. They have nothing that's in
19 their claim, even if one includes the prior art other than biaryl structures.

20 So what do they do? They look at our molecule, zanubrutinib, and
21 they say, look how similar it is.

22 And in retrospect now that someone has invented zanubrutinib,
23 modeled and invented, we didn't, they say, look, it all looks similar.

24 Actually, it doesn't. If you go to their slide 37, I would submit
25 they're mischaracterizing our expert's testimony on their slide 37 as

1 suggesting that he said there are no differences between zanubrutinib and
2 ibrutinib.

3 That's not correct. If you actually look at his testimony on 197 and
4 the areas surrounding it, it's clear he's talking about in this flat two-
5 dimensional picture, there are no differences in interactions identified.

6 He was very clear in his testimony and in his declaration that there
7 are, in fact, differences in how they bind.

8 And there are major differences in structure. There's been this
9 whole dispute about whether it's a mimetic and what's a mimetic.

10 Mimetic is not in the claims. It's not even in the specification.
11 Here are the facts, and I think they're not disputed.

12

13 There is a different interaction that zanubrutinib makes. It makes
14 an additional hydrogen bond.

15 But more fundamentally, the hydrogen bonds it makes are different
16 than the hydrogen bonds ibrutinib makes and ATP makes.

17 That's because it uses different structures to make them. It has a
18 hydrogen bond acceptor where they don't.

19 It has an amine substituent that makes two different hydrogen
20 bonds.

21 ATP doesn't do that. They don't do that. So you can call mimetic.

22 You can call it a duck. It doesn't matter what you call it. The
23 reality is it's a different structure.

24 They didn't invent it. They admit they didn't invent it. A model
25 didn't invent it.

1 We invented it later. Now their answer to all of this basically is --
2 and you can look at slide 26 for this -- their slide 26.

3 All of the kinases have the same binding site. And so it's all the
4 same.

5 We don't need to identify any BTK structures because everyone
6 knew what the kinase binding site looks like.

7 Well, the reality actually is if you look at the publication, even the
8 part that they don't highlight on the screen, they talk about the binding site
9 being highly varied in shape.

10 And then they say it's the exploitation of unique structural features
11 provides the basis for achieving selectivity.

12 In other words, what matters about the binding site is not what it
13 shared between various kinases but how they differ.

14 That's what you're looking for. What will bind BTK as opposed to
15 other kinases?

16 And so it's not the case that everything that binds other kinases will
17 bind BTK, especially with these substituents.

18 This is not mixing and matching. This is actually inventing new
19 molecules and they don't do it.

20 What they do on slide 29 is similar. They say, well, slide 29 shows
21 this is Ghose and it makes it very clear that you can just substitute in.

22 Everyone knows what this is going to look like. The problem is
23 where it's -- what it talks about in Ghose even in this section that they have
24 on the screen is that these rules are helpful to formulate a binding mode
25 hypothesis, hypothesis for a potential ligand.

1 And then later on page 21 of this same exhibit, Exhibit 1052 which
2 is Ghose, he explains that this method is, quote, suitable only for idea
3 generation rather than the routine prediction of high affinity ligands.

4 And when one looks at the actual structure that Ghose discloses, all
5 16 scaffolds in Ghose that are Z' structures, they're all biaryl.

6 Do you think that's some coincidence that everywhere you look in
7 the prior art and you see these six structures, they're all biaryl, of course it's
8 not a coincidence.

9 That's because that was the structure that's known. Those are the
10 structures they put in their specifications.

11 Those are the structures that everyone was working with. And in
12 fact, as I explained before, no response to this either.

13 The only non-biaryl structures in the prior art, again, never
14 discloses BTK and they don't work for BTK.

15 They don't work. They have nothing within the scope of their
16 claim.

17 That's a biaryl -- non-biaryl structure that works as of the prior art.

18 So they basically say you figured it out. That's their essential
19 argument, and you can see it on slide 23.

20 They look at Marcotte. They look at these pictures, and they say,
21 this is the answer.

22 These are the common structural features. And as I heard this, I
23 was reminded of that whole line from the Supreme Court that Federal
24 Circuit often repeats.

25 That is something along the lines of a patent is not awarded for a

1 search.

2 It's awarded for the successful completion of the search. We give
3 patents not for questions, what will fit into this, what other structures could I
4 create that might make some of these hydrogen bonds in exactly the right
5 way.

6 It's going to position my phenoxyphenyl in just the right way. We
7 give patents for successful completions of the search.

8 They have no answers to the questions. Your Honor, Marcotte
9 doesn't provide them and the modeling doesn't provide them.

10 The modeling doesn't tell you what's going to work. They still
11 don't tell you what's going to work.

12 We showed on slide 46. They didn't respond to this either. We
13 asked their expert, what are the common structural features and what did he
14 give us? More functions, hydrogen bonds, position things right.

15 And they admit at the sur-reply on page 5 those are functions, not
16 structures, because they have no common structural features.

17 Your Honor asked a very pointed question, what are the structural
18 features?

19 I'm glad you did because I've been knowledgeable about that for
20 the last 18 months too.

21 What are these structural features that they say they have? And
22 what he said was, he said they're the ones in the claim.

23 He said they're the ones in the claim, the phenoxyphenyl and the
24 warhead and the Z'.

25 But the problem is that's not enough because the Z' is a vast set of

1 structures, billions of them.

2 Most of them don't work. He said, what's the evidence that they
3 don't work?

4 Well, first of all when we looked at their own structures, they
5 didn't work.

6 Even the few that they identified, E2, E3, E4, those don't work.
7 The ones we looked at from the prior art, those don't work either, Exhibit
8 2055 and Exhibit 2033.

9 And their own expert agreeing that there are billions of structures
10 said, well, it's probably more than hundred amongst the ones that work.

11 He didn't say it's exactly hundreds. I'll give him thousands. I'll
12 give him ten thousand, and you're still looking at every one out of 100,000
13 molecules is going to work.

14 This isn't looking for hay in a stack of needles. This is looking for
15 a needle in a haystack.

16 And even if it were a coin flip, even if it were true that half of the
17 structures will work and there's no evidence whatsoever to support any sort
18 of proposition.

19 It's not enough because it doesn't tell you what structures will work
20 and what structures won't work.

21 The Idenix case I would submit is the most on point case of all
22 because there as here, you have some structures fixed in the claim.

23 Most of the substituents in Idenix were fixed. The only ones that
24 weren't were the two down and the three down.

25 And that wasn't enough. They could've said in Idenix, well, the

1 structural features are all the ones that are fixed, just like we heard now.

2 And look, you can just do something at two up and three up. And
3 that will be -- or sorry, two down and three down.

4 And there you have it. That's enough structure. And the Federal
5 Circuit said no.

6 And by the way, it said no as a matter of law, reversing a jury
7 verdict finding of written description.

8 And they said necessarily as a matter of law. That can't be. Why?

9 Because you don't disclose in your specification what will work
10 and what will not.

11 And they don't disclose it in the specification here. They don't
12 even argue that they do, which of the Z' would work and which ones don't.

13 And they clearly don't disclose it anywhere in the prior art either.

14 What they have instead is, well, give me something that works.
15 Give me something that's going to bind, that it's going to look good, and it's
16 going to somehow fit in this structure.

17 But there is no answer to the question of which of those structures
18 would work and which ones don't.

19 This is Alonzo all over again. They have tried to identify a method
20 to identify what will work as opposed to identifying structures as the written
21 description requirement requires that will work.

22 Now Your Honor, Judge Hulse asked, what's your best case? And
23 the answer was Ajinomoto.

24 I might not be pronouncing it right. But in Ajinomoto, I would
25 submit that the answer also was there.

1 The prior art provided an answer. What it said was -- it didn't say,
2 go do something that's going to work and try to find something that will
3 make hydrogen bonds.

4 Those are goals. Those are functions. And Ajinomoto, the prior
5 art guidance was make modifications to the sequence that made it closer to
6 the consensus.

7 That's a structural guidance from the prior art. That's a structural
8 limitation that says, you are going to make certain mutations from the native
9 sequence to the consensus sequence that will increase the commonality
10 between those sequences.

11 And those will be the ones that will work in the claim. That's
12 identifying structure in the prior art.

13 What are they doing here is identifying functions and identifying
14 models that could help predict whether those functions will be discharged by
15 various structures that are nowhere disclosed other than in someone's mind
16 and that we invented years later.

17 They have no case is the real answer here to Your Honor's
18 question.

19 No case in which structures are nowhere disclosed in the prior art,
20 nowhere disclosed in the specification even close to commensurate with the
21 scope of the claim.

22 And that somehow, we are supposed to engage in some research
23 project to find all the compounds that are somehow going to bind within
24 Marcotte's modeling, again, also nowhere disclosed in the specification.

25 And however successfully finds that, well, guess what. Now

1 you're within the scope of our patent.

2 That's not how the written description requirement works. That is
3 preempting the future.

4 That is attempting to obtain a patent for a research plan, a research
5 plan with a medicinal chemist, a research plan with modelers that their own
6 modelers and their own experts cannot tell you what the common structural
7 features are.

8 They actually had some structural features in their patent. I would
9 submit the common structural feature that they have and they show and was
10 all over the art was, for example, the amino substituent.

11 That's a common structural feature. They could've put that in their
12 claim.

13 Of course, they didn't because we don't use that amino. So instead,
14 they say, okay, we'll take that out.

15 We'll take that out. We'll keep in the phenoxyphenyl because that's
16 in zanubrutinib.

17 We'll keep the warhead, that's in zanubrutinib. And everybody
18 else, we'll just say, okay, 5:6 bond.

19 Of course, everything we disclose is aromatic. Everything
20 essentially that works in the prior art that's disclosed for BTK like Exhibit
21 2027, that's aromatic too.

22 But we're not going to do that, of course, because then we wouldn't
23 capture zanubrutinib.

24 So we'll make it non-aromatic. Ignore the fact that we don't
25 disclose non-aromatic BTK inhibitors.

1 There is no disclosure anywhere in the prior art of non-aromatic
2 BTK inhibitors that are within the scope of their claim.

3 And they still don't identify what those structures are that actually
4 work.

5 They give you a goal, not a written description of the structures.
6 And it just doesn't work.

7 Two minutes on written -- on non-enablement if I may which is
8 that the problem with their theory of you would just look at the modeling
9 and then you could just cut it down and it'd be very easy is that they don't
10 identify from their experts any action to do that.

11 What they do instead is their experts agree that you neither look at
12 the whole molecule.

13 You can't just cut out substituents and throw them overboard. You
14 have to look at the whole molecule and you have to model it.

15 And you have to do that in an iterative process working with
16 medicinal chemists, working with other members on the team.

17 And this is a research project. You make something. You model
18 it.

19 You say, okay, now I'm going to make something else and I'm
20 going to model it.

21 This is exactly what people were doing for years in these
22 programs.

23 And a few people succeeded. Our client succeeded. Most didn't.

24 But the notion that this is all very easy and you can just come up
25 with any structure you want and you think it's going to inhibit BTK, that's

1 not how it works.

2 The fact is the only ones that are non-biaryl that they identified in
3 their patent owner response, you can look at it at 64 and 65 and you can look
4 at their slide 78 in their presentation.

5 All they have is biaryl compounds, compounds that are not Z', not
6 within the scope, and two non-biaryl compounds.

7 And they don't work. They don't work. So this magical system
8 that they have, oh, we'll just model it and we can, again, go home and be
9 home by 5:00 for dinner because it's all easy.

10 And the computer tells us that's not right. If they thought it was
11 that easy, why wouldn't they have modeled E2, E3, E4?

12 And why would they have included them in their specification if
13 they realized that they don't work?

14 What we heard today was, well, I'll throw those overboard. That
15 shows modeling works.

16 So no one would bother with E2, E3, E4. And then they criticize
17 us for not figuring out which substituents to put on E2, E3, E4.

18 The absence of guidance is not our problem. It's theirs. That's
19 why there's no written description.

20 We use the exact substituents they told us to use, and they didn't
21 work.

22 And there's no dispute they didn't work. They never refuted it or
23 put it in a declaration or sought to do so to the contrary.

24 I see I'm out of time. Happy to answer any questions. Otherwise,
25 I'll --

1 (Simultaneous speaking.)

2 JUDGE HULSE: I have a quick question.

3 MR. BERL: Yes, Your Honor.

4 JUDGE HULSE: You didn't address the Board's construction of
5 therapeutically effective amounts. Do you maintain your prior construction
6 or do you accept ours?

7 MR. BERL: I don't think it's necessary. We'll accept the Board's
8 construction of that. It's not germane necessarily for us to prevail on 112.

9

10 JUDGE HULSE: Thank you.

11 MR. BERL: Thank you, Your Honors.

12 JUDGE SNEDDEN: Thank you.

13 MR. FRAZIER: Can I have slide 5 from our presentation?

14 MS. CORN: Oh, I'm so sorry.

15 MR. FRAZIER: All right. So I just want to go back to the claim 1
16 itself and remind everybody.

17 To hear the Petitioner's presentation here, you would think that the
18 whole claim -- and I'm on slide 5 -- that the whole claim was just Z'.

19 That's all they're talking about. But why are they using -- why
20 does their compound have phenoxyphenyl?

21 Why does the claim have phenoxyphenyl? It's because that's
22 where you determine the selectivity.

23 That's what's being held constant by adding that phenoxyphenyl
24 moiety.

25 Why does their claim -- why doesn't their molecule have a warhead

1 and why is that warhead incorporated into the claim?

2 Because the warhead is critically important to achieving the
3 function here.

4 These are elements that are critical to creating the function and
5 structure of correlation that's necessary in order to carry out the method in
6 the claim.

7 They want to focus just on Z' in a vacuum as though somehow
8 there was no description around that.

9 But they're ignoring these structural features which are very
10 important which they've incorporated into their own molecule for reasons
11 that, as I said, to me seem facially apparent because they're useful attributes
12 that convey an important function onto that molecule which is why they've
13 been co-opted by the Petitioner here.

14 And then within the Z' itself, these are generic characteristics that
15 are also found ibrutinib.

16 So ibrutinib itself has the 5:6 ring. It has the scattering of -- it has
17 nitrogens in places frankly that are sufficient to allow it to mimic the role of
18 adenine in the active site.

19 And we see now they said multiple times. They've said it over and
20 over again in their papers that zanubrutinib is not an adenine mimetic.

21 They seem to be running away from that today. But if we go to
22 our slide 38, this is on the right-hand side of slide 38.

23 The critically important point which as you look at the actual
24 residues, this is -- again, this is the furthest thing from the Idenix Gilead
25 case.

1 This is -- everybody knows exactly what you need to -- the types
2 of things you need to make, the types of connections you need to make, and
3 which moieties are able to make them.

4 And that's what's here in this chart on the right-hand side. So
5 adenine was making what they referred to as GK plus 3 which happens to be
6 methionine 477 in BTK.

7 And it has a ring nitrogen that's acting as a hydrogen bond
8 acceptor.

9 The other -- and then there's one that's two amino acids over at
10 Guo 475.

11 And there they have a hydrogen bond acceptor. So they know how
12 hydrogen bonds work.

13 They know the moieties that can either be acceptors or donors.
14 And they know the corresponding amino acids that are there in that spot on
15 the -- in BTK to create those hydrogen bond interactions.

16 So this is the furthest thing from an Idenix situation where
17 essentially there's just no guidance as to why would you want flooring up,
18 why would you want flooring down. Nobody knows.

19 Here, you know exactly what you're looking for. And again, it's
20 not just Z' that's in this claim.

21 This is a claim that was drafted based on the preferred embodiment
22 that was shown all the way through the level of clinical testing.

23 So the ibrutinib testing went as far as you can go, show the clinical
24 effect.

25 It's a clinical method that's claimed showing that actually --

1 through occupancy that that's actually a result of carrying out this type of
2 inhibition.

3 And then we take the main structural features of ibrutinib, put them
4 into a claim, and say, you know what you can do is as long as you maintain
5 the 5:6 heterocycle in the middle of it, you can have -- you can adjust it a
6 little bit in that middle section.

7 And everybody knows that because it's well known that the middle
8 section binds to the hinge region.

9 And that's the most well-known part of BTK and frankly of all the
10 kinases.

11 And so you can make known interactions by adding substitutions
12 as necessary to put in those hinges.

13 This is not a research plan. This is describing -- we said these are
14 5:6 heterocycles.

15

16 And you simply use those and you fit them into place. And you
17 visualize them in the appropriate condition.

18 And if you need to add a substitution, you can do so. And I would
19 note again you go back to Dr. Showalter's declaration in the initial petition.

20 He was able to jot down 1,700 structures that actually fit this in
21 terms of being 5:6 rings.

22 So this is not a question again of nobody of skill would know what
23 we're talking about.

24 It's not like an antibody where you say, I know what the first
25 antibody is.

1 But then unless I'm doing something that essentially has the same
2 amino acid sequence or something that's closely conserved, I have no idea
3 what to do next.

4 It's very clear what you can do. We've told you the 5:6 heterocycle
5 is the structural component and you can move the nitrogens around as
6 necessary to achieve these hydrogen bonds.

7 And the strictness of the written description and the enablement
8 standard that they are inviting you to hold here is inconsistent with cases like
9 mentioned, Ajinomoto.

10 Falko-Gunter is another one that involved poxvirus vaccines where
11 essentially they were able to show generally that you can make a vaccine by
12 taking a critical gene that was important for replicating the virus.

13

14 And again, there, it was the ability -- the attack on written
15 description was the limited disclosure of specific essential genes and
16 poxvirus.

17 And what the Federal Circuit agreed with was that written
18 description was appropriate where the art knew which essential -- what the
19 essential genes were.

20 And then you could take that broad teaching of the essential genes
21 that were in poxvirus and apply it as needed in the application or in the claim
22 method.

23 And that's the same thing we're talking about here which is to say
24 if you take this knowledge in the art.

25 We've given you the top and the bottom of the molecule and we've

1 told you the contours, the 5:6 heterocycle in the middle.

2 And then you take the knowledge in the art and you apply
3 substitutions if you need to, only if you need to.

4 But you can see that those are compounds that actually can be
5 modeled and that are useful. And I just want to go back briefly here --

6 JUDGE HULSE: Counsel, I'm sorry.

7 MR. FRAZIER: No, go ahead, please.

8 JUDGE HULSE: Could you please -- if you can address the Juno
9 case.

10 MR. FRAZIER: Well, I think Juno, again, is quite different in
11 terms of -- the real issue on Juno, Juno was a CAR T with a binding region
12 and then the membrane crossing region and a region that signals inside the
13 cell.

14 And the real dispute was about the binding region that was outside
15 the cell.

16 And I think the issue there was very much the sort of standard
17 problem that one sees with antibodies which is to say that there just wasn't a
18 description of what the different structures were that could have that binding
19 attribute that they were saying was a requirement for that part of the
20 molecule.

21 So it's essentially just saying it's, like, saying every antibody that
22 binds to hemoglobin or something like that.

23 I may know the first one that I've discovered. But I don't know the
24 rest of them.

25 It's exactly the problem that you had in Amgen Sanofi where they

1 had a small number of antibodies that they had discovered.

2 But even the Supreme Court recognized looking at that, that there
3 were many, many other possibilities that you just had no idea where to start.

4 You didn't have any guidance as to what the structures were that
5 would carry out the desired function.

6 And obviously, here that's what we keep trying to go through is
7 that this is a structural claim.

8 It has these -- we fixed the shape of the rings and all that we're
9 leaving that hasn't been described is a few substitutions.

10 And I submit that those are substitutions that you can make
11 according to the well-known rules such as are described in Ghose to create
12 these hydrogen bonds.

13 Does that answer the question? Thank you, Your Honor. I just
14 want to turn back again to slide 6 if we could.

15 And again, this is just going again to the point that I was trying to
16 make which is that under their theory of 112, it's inventive for them to
17 essentially take the primary structures of that ibrutinib compound and the
18 method that's disclosed in the ibrutinib patent about using ibrutinib in the
19 context of treating patients.

20 And to discount all of the discussion in the patent, all the teaching
21 that this is not just an ibrutinib effect but is actually a BTK inhibition effect.

22 And to discount the part of the patent that tells you that pocket
23 binding is important, warhead is important.

24 Make contact with Cys481 using this specific warhead structure.

25 Discount all of that.

1 None of that is important. And instead, they want to focus on, oh,
2 look, we have our nitrogens in slightly different spots and we have the 5:6
3 is -- half of it's not aromatic and half of it is.

4 And so that's great innovation on our part. We've really solved a
5 puzzle here.

6 And we should be out from under this '803 patent as a result. And
7 the '803 patent is clearly too broad to the extent that it covers compounds
8 like that.

9 That's the whole theory of their case. And I would just submit
10 again that what we see here with these other six molecules that we've
11 illustrated are innovative ways that one could go about solving this problem.

12 And you don't necessarily -- you could've innovated around the
13 phenoxyphenyl.

14 You could've innovated a different warhead. You could've
15 innovated a middle section that didn't fall within the -- that didn't have the
16 same 5:6 ring system that you see in ibrutinib.

17 I would submit to you that what they are asking is to apply 112 in a
18 way that encourages an endorses making close copies of disclosed molecules
19 and the way that they're used and then denying patent coverage on those
20 close copies by virtue of an overly strict reading of 112.

21 I think that's what they're asking you to do here, and I would ask
22 you to not follow that. Thank you.

23 JUDGE HULSE: Are there other examples of irreversible BTK
24 inhibitors that fall within the scope of the claim that are not routine?

25 MR. FRAZIER: Yes, those did come up in the context. There

1 were other compounds that were tested.

2 Just as an example here, I think Dr. Veal even mentioned -- I
3 believe that's been in a section here.

4 Okay. Yeah, actually, so paragraph 49 then of the Showalter
5 declaration even has a number of structures that were identified that also fall
6 within the scope of the claims.

7 JUDGE HULSE: And to Petitioner's point those are all biaryl
8 structures, correct?

9 MR. FRAZIER: The ones that are mentioned there are biaryl.
10 Yes, that's right.

11 And I think our primary point on the aryl, non-aryl distinction is
12 like I said, that at the end of the day, it doesn't seem to make that big of
13 difference in terms of how the binding actually occurs and its ability to be an
14 adenine mimetic.

15 And that therefore, when you're saying -- if you're essentially just
16 saying, look, I'm using a 5:6 ring system that that's certainly on the table in
17 terms of the things that one can choose.

18 And there's nothing that tells you that was something the patent
19 wasn't contemplating when it said, look at something that will bind in this
20 region, that essentially, you're looking at all these 5:6 ring systems.

21 And that's certainly one that could be used. Again, I think the
22 other key point is there's no requirement in a genus claim like this.

23 There's no requirement that there's specific disclosure of every
24 species that falls within that genus, right?

25 That is not the test for written description. So we cited the Cordis

1 case, among others for that concept.

2 But in general, that's the case. So it's not our job to show that we
3 specifically disclose zanubrutinib in the '803 patent.

4 Rather, the '803 patent appropriately takes the characteristics of
5 ibrutinib together with the teaching in the specification and creates a genus
6 that's appropriately described.

7 And they happen to fall within that genus because they have so
8 many structural features that are set forth in the patent.

9 JUDGE HULSE: So then just to recap, Patent Owner mentioned
10 that the common structural features in this case are the 5:6 heterocyclic ring,
11 correct, and then the two fixed features, the hydrophobic moiety of the
12 linker-warhead?

13 MR. FRAZIER: And the other features that are recited in the
14 claim.

15 So essentially, the need for the nitrogens and the optional
16 substitutions, yes.

17 And the optional substitutions are important structural features
18 because as I think we're in agreement that I heard Mr. Berl say earlier that
19 those structures are used for hydrogen bonding.

20 And it's clear that a person of skill in the art understood what
21 makes a hydrogen bond and what's a donor and what's an acceptor.

22 And so those structures, while the point is to have a particular
23 function, the structure that elicits that function is known.

24 JUDGE HULSE: And so then it's Patent Owner's position that
25 anything that falls within the scope of that claim would successfully

1 inhibit -- irreversibly inhibit BTK.

2 MR. FRAZIER: I think it's our position that the -- based on the
3 record that we have, that the majority of things would -- they obviously have
4 identified a handful of counterexamples.

5 And I think that's our point with the modeling is to the extent that
6 you have counterexamples that you can identify them through modeling.

7 And that's perfectly consistent with cases like Ajinomoto that says,
8 look, all you need is a correlation.

9 It doesn't have to be perfection. Cases like Atlas Powder, Capon
10 that we cited in the brief that say that you don't have to have perfection for
11 enablement either, that it's not the job of the patent to eliminate all possible
12 nonworking embodiments from within the scope of the claim.

13 JUDGE HULSE: Thank you.

14 MR. FRAZIER: Thank you.

15 JUDGE SNEDDEN: Thank you. That will conclude our hearing
16 today.

17 Thank you very much for your helpful arguments. I'd also like to
18 thank Mr. Hoagland-Hanson, our lead practitioner for participating in our
19 LEAP program.

20 And we thank your law firm and your client for allowing you that
21 opportunity.

22 If the parties could stay and answer any questions that the court
23 reporter may have, that'll be helpful and we thank you for that.

24 With that said, the panel will take this matter under advisement.
25 The case is submitted, and we are adjourned.

PGR2024-00009

Patent 11,672,803 B2

1 (Whereupon, the above-entitled matter went off the record at 3:33
2 p.m.)

PGR2024-00009
Patent 11,672,803 B2

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