

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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INTAS PHARMACEUTICALS LTD.,  
Petitioner,  
v.

ATOSSA THERAPEUTICS, INC.,  
Patent Owner.

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PGR2023-00043  
Patent 11,572,334 B2

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Record of Oral Hearing  
Held: October 30, 2024

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Before SHERIDAN K. SNEDDEN, TINA E. HULSE, and JAMIE T. WISZ,  
*Administrative Patent Judges.*

APPEARANCES:

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The above-entitled matter came on for hearing on Wednesday,  
October 30, 2024, commencing at 1:00 p.m. ET, via videoconference.

P R O C E E D I N G S

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MS. LOTT: Good morning, all. We are now here to start our hearing on today for PGR2023-0043.

Judge Hulse, it is now in your hands.

JUDGE HULSE: Thank you, Ms. Lott. Hello, everyone. As Ms. Lott said, this is the final hearing in PGR2023-00043, U.S. Patent Number 11,572,334. Petitioner is Intas Pharmaceuticals, Ltd., and Patent Owner is Atossa Therapeutics, Inc. I'm Judge Hulse. I'm joined by Judge Snedden and Judge Wisz.

I'd like to start with appearances, please. Beginning with Petitioner, please introduce yourself and whoever's with you virtually or in person.

MR. MAHON: Good afternoon, Your Honor. Ben Mahon, M-A-H-O-N of McAndrews, Held & Malloy. With me is my associate, Bradley Loren, who will be doing part of the presentation as part of the LEAP program, as well as lead counsel, Alejandro Menchaca, who are both in the room with me.

MS. KRUMPLITSCH: Good afternoon. Good afternoon, everyone. This is Susan Krumplitsch of DLA Piper on behalf of Patent Owner Atossa. With me is Mossa -- excuse me, Melissa Harwood. And we also have Derek Gretkowski and Emma Holland in the room with me.

JUDGE HULSE: Welcome, everyone. Thank you all for being here. As we stated in our hearing order, each party will have 60 minutes of time to present their arguments. But because Petitioner has notified us of their LEAP practitioner participating in today's argument, Petitioner will have an extra 15 minutes of argument time. Petitioner will open the argument, and

1 you may reserve up to 30 minutes of rebuttal time. Patent Owner will then  
2 respond to Petitioner's arguments and may (inaudible) we have available to  
3 us on our computers along with your demonstratives so you are welcome to  
4 point us to any document in the record that you may need to point us to, and  
5 we can pull that up as needed.

6 We have also received the parties' objections to each other's  
7 demonstratives. Those objections are all noted, but denied, as the Panel is  
8 able to decide for ourselves whether the demonstratives are misleading or  
9 contain new arguments.

10 Please note that this proceeding is being streamed online to enable  
11 public attendance. But just a reminder to everyone that recording of any  
12 PTAB proceeding is prohibited. The court reporter will provide a transcript  
13 of the hearing that the Board will enter into the record when it becomes  
14 available.

15 And to ensure that the transcript of this hearing is clear, please speak  
16 clearly and identify specific slide numbers when referring to your  
17 demonstratives. Also, please mute yourself when you're not speaking. And  
18 if you encounter any technical difficulties, please let us know immediately.

19 Does anyone have any questions? No? Hearing none, Petitioner,  
20 would you like to reserve any rebuttal time?

21 MR. MAHON: Yes, Your Honor, we'd like to reserve 25 minutes for  
22 rebuttal.

23 JUDGE HULSE: Great. Okay. Then that would leave, doing the  
24 math here, 50 minutes for your opening. You may proceed when you're  
25 ready.

26 MR. MAHON: May I share my screen, Your Honors?

1           Good afternoon, Your Honors. Ben Mahon, M-A-H-O-N, on behalf  
2 of the Petitioner Intas Pharmaceuticals. I'll obviously address any issue  
3 Your Honors wish to address in any order you want to address them. But  
4 unless directed otherwise, I just wanted to give you an overview of what we  
5 plan to talk about, give a quick background, just to refamiliarize Your  
6 Honors with the issues in this case.

7           Then I'm going to hand it over to my associate, Dr. Loren, who's  
8 going to address grounds 1 and 2 specifically. The only real issue in those  
9 grounds, the enablement of 90 percent (Z)-endoxifen. Dr. Loren has a Ph.D.  
10 in organic chemistry and worked closely with our expert, so I'm sure he can  
11 answer any questions you have on those grounds. He'll do an excellent job.

12           I'll take it back. And I'll address grounds 3 through 5, which we  
13 view as presenting similar issues, that they are routine formulation  
14 modifications to Ahmad to either use the enteric-coated capsule of Cole, to  
15 use the intrinsically enteric capsule of Benameur, and to use standard  
16 excipients as taught in Stegemann and the Handbook of Pharmaceutical  
17 Excipients. And then we'll turn to ground 6, talk about the dosing claims  
18 and the pharmacokinetic claims, which as Petitioner's views that those are  
19 the natural and inherent results of dosing a patient with 90 percent (Z)-  
20 endoxifen enteric-coated capsules as taught in Ahmad. And then I'll finally  
21 address the objective indicia.

22           Just briefly on the background, Your Honor, endoxifen is a known  
23 active metabolite of tamoxifen. So tamoxifen is a commercially available  
24 drug used to treat breast cancer. It was understood in the art that through  
25 metabolic pathways it was converted into endoxifen. Thus, it was  
26 understood in the art that endoxifen was a promising treatment for breast

1 cancer, including for those for whom tamoxifen could not be used because  
2 they had metabolic issues.

3 It was further understood that endoxifen can be found in two  
4 isomeric forms, the E form and the Z form, with the Z form being more  
5 active at the estrogen receptor. That's taught, for example, in Liu. And as  
6 Dr. Loren will address in more detail, it was known in the art how to  
7 synthesize highly pure (Z)-endoxifen. For example, Liu teaches forming  
8 endoxifen with isomeric purity of (Z)-endoxifen of 99 percent.

9 It was understood that endoxifen was sensitive to acid, was acid  
10 labile, and thus must be protected from stomach acids when given to  
11 patients. So Ahmad teaches delivering the endoxifen in enteric-coated  
12 capsules. Other references, such as Ahmad 2010, use enteric-coated tablets.  
13 But again, it was understood that enteric protection was necessary to prevent  
14 the drug from being degraded a stomach acid.

15 Just briefly on the '334 patent, Dr. Loren will address the priority  
16 dates, but we're talking in the time range of 2017 or 2018 and it's not  
17 dispositive whether either of those dates are used. So Dr. Loren will address  
18 that on the one reference it applies to.

19 I do want to talk about the claims and the definition of a person  
20 skilled in the art, Your Honor. I think it's very important to note the claims  
21 here are not directed to a method of synthesis. They are not directed solely  
22 to chemistry. They're directed to oral formulations wherein endoxifen is  
23 encapsulated in an enteric capsule. So we think it's very important that a  
24 person of skill in the art is defined to include knowledge of formulations of  
25 pharmacokinetics and formulation issues, not simply chemistry.

1           Certainly we're not asking you to exclude Dr. Davies' testimony and  
2 especially in regards to chemistry knowledge that is well within his  
3 knowledge. We're simply asking that you weigh the testimony of the  
4 experts accordingly when it comes to issues related to enteric formulations,  
5 pharmaceutical dosing issues, pharmacokinetics; that Dr. McConville is an  
6 undisputed expert in formulation issues and pharmacokinetics, whereas Dr.  
7 Davies only identified experience as being the CEO of companies in which  
8 he had to overview -- excuse me, oversee formulation issues, but he  
9 certainly doesn't identify research in terms of pharmaceutical dosage forms  
10 or pharmacokinetics.

11           And I do want to briefly address one argument --

12           JUDGE HULSE: I'm sorry, can we go back to the person of ordinary  
13 skill in the art definition? Do you think that we should revise our definition  
14 as set forth in the DI?

15           MR. MAHON: Yes, Your Honor. And just to be clear, I think Patent  
16 Owner calls us a new definition that we provided on reply. But in our  
17 petition at page 9, we clearly stated we believed a person of skill could have  
18 experience in research related to pharmaceutical dosage forms or three to  
19 five years practical experience in formulating drugs. We think that is  
20 important to the definition of a POSA. We certainly have no objection if  
21 Your Honors want to broaden the definition of a POSA to include both that  
22 formulation knowledge and chemistry knowledge. But we certainly think  
23 that the POSA here cannot merely be an expert in chemistry, but should be  
24 an expert in pharmaceutical dosage forms, if that's what is claimed.

25           JUDGE HULSE: So on page 8 of our DI, I think it says both  
26 definitions. We basically said that we didn't discern a substantive difference

1 between the parties' definitions. And we said both definitions provide for a  
2 highly skilled POSA with experience in formulating drugs. So is that not  
3 sufficient?

4 MR. MAHON: That is sufficient, Your Honor. I think we just  
5 wanted to be clear that that is required.

6 JUDGE HULSE: Thank you.

7 MR. MAHON: Just briefly, Your Honors, on the prosecution history,  
8 or rather the lack thereof, there's very, very little prosecution in the parent  
9 '151 patent. Those claims were allowed with the Examiner stating the key to  
10 the instant claims is the polymorph of Form I, the limitation that's not found  
11 in the '334 patent. And then there were no rejections for the '334 patent. So  
12 Your Honors are really assessing patentability on a blank slate here. There's  
13 no Examiner findings on the prior art to defer to.

14 And with that, we'll turn to grounds 1 and 2, addressing claims 1, 2,  
15 4, 15, and 20 to 22. There's no dispute between the parties that Ahmad  
16 teaches each and every limitation of each of these claims. Their only  
17 argument is the enablement of 90 percent (Z)-endoxifen limitation. So just  
18 briefly, there's no dispute that Ahmad teaches compositions where endoxifen  
19 is encapsulated in enteric capsules. There's no dispute that it teaches (Z)-  
20 endoxifen with 90 percent purity. I'll address the free base and claim  
21 construction issue later because it only addresses objective indicia. Because  
22 there is no dispute that Ahmad teaches a free base, including the free base  
23 formula recited in the claims.

24 No dispute that Ahmad teaches a delayed release formulation  
25 wherein the enteric capsule comprises an enteric coating. No dispute that  
26 Ahmad teaches administering these capsules or these dosage forms for



1 treating breast cancer, including hormone-dependent breast disorders or  
2 benign breast disorders. And no dispute that Ahmad teaches that endoxifen  
3 would be able to be effective for patients for whom tamoxifen is not  
4 effective, I mean, tamoxifen-refractory or tamoxifen-resistant patients.

5 With that, I'm going to turn it over to my associate, Dr. Loren to  
6 address the enablement issue.

7 DR. LOREN: Thank you, Your Honors. As my colleague, Mr.  
8 Mahon, already stated, there's no dispute here that Ahmad teaches  
9 formulations comprising 90 percent or greater than 90 percent (Z)-  
10 endoxifen. The only dispute here is the enablement of Ahmad.

11 But the first point I want to make is that Ahmad does more than just  
12 state or just teach compositions that comprise greater than 90 percent (Z)-  
13 endoxifen. Ahmad also teaches methods by which such compositions can be  
14 obtained. In particular, Ahmad teaches that several purification approaches,  
15 including crystallization as well as chromatography, including standard  
16 liquid chromatography as well as high pressure liquid chromatography, also  
17 known as HPLC, are methods by which mixtures of (E)- and (Z)-endoxifen  
18 can be purified to ultimately produce pure and certainly greater than 90  
19 percent pure (Z)-endoxifen.

20 There's also no dispute that these methods were well known in the  
21 prior art, and in particular these methods were well known in the prior art for  
22 purifying this exact mixture. For example, Liu, which I'll discuss in some  
23 more detail in a little bit, describes a crystallization approach whereby crude  
24 mixtures of (E)- and (Z)endoxifen can be crystallized and successively  
25 recrystallized in order to obtain (Z)-endoxifen with 99 percent isomeric  
26 purity. Fauq is another reference which teaches a chromatography method

1 whereby HPLC was used to separate mixtures of (E)- and (Z)-endoxifen and  
2 ultimately purify (Z)-endoxifen from that mixture.

3 Now, one point about Fauq I want to address regarding an argument  
4 Patent Owner makes is that Fauq teaches a smaller scale purification  
5 approach. First, the claims here are not directed to a method of synthesis,  
6 and they are certainly not directed to a commercial scale or large-scale  
7 synthetic method. Fauq teaches a method by which mixtures of (E)- and  
8 (Z)-endoxifen can be purified at an over 200 milligram scale. The only  
9 claim at issue here that even relates to scale in some way is claim 14, which  
10 describes dosage forms or doses, excuse me, with an upper limit of 200  
11 milligrams. But even for that claim, Fauq expressly teaches that its method  
12 can be used to purify greater than 200 milligrams from a mixture.

13 Now, Patent Owner's primary argument here appears to be a  
14 misunderstanding of the law. Now, first, Patent Owner argues that it is  
15 improper to consider other prior art references to demonstrate enablement of  
16 a prior art reference, but the law on enablement -- or the law on enablement  
17 of prior art is clear. Other references may be used to establish the  
18 enablement of what is already taught in a prior art reference. And that is the  
19 situation we have here. Petitioner is not relying on Liu or Fauq to teach any  
20 claim limitations. Ahmad already teaches greater than 90 percent (Z)-  
21 endoxifen, Liu, Fauq, as well as the Milroy reference simply teach and  
22 establish that that teaching was enabled to a person of ordinary skill in the  
23 art.

24 Patent Owner also argues that Liu and Fauq post-date Ahmad's  
25 effective filing date. This is true, but really legally irrelevant. The Federal  
26 Circuit has made clear, for example, in the *Bristol-Myers* case that later

1 references may be used to establish enablement of a prior art reference so  
2 long as those references are themselves prior art to the challenged patent.  
3 And I have a timeline slide coming up in a little bit that shows this, I think,  
4 more clearly. But there's no dispute here that Liu and Fauq are both prior art  
5 to the '334 patent.

6 And again, Petitioner is not relying on Liu and Fauq and Milroy to  
7 fill any gaps in the prior art. Ahmad teaches these compositions and Liu and  
8 Fauq simply demonstrate that obtaining those compositions were within the  
9 skill of a person of ordinary skill in the art.

10 Patent Owner also argues that it was improper for Petitioner to  
11 introduce evidence of enablement of Ahmad on reply. But as the Federal  
12 Circuit explained in the *Apple* case, it would be error for the Board not to  
13 consider evidence introduced on reply regarding the enablement of a prior  
14 art reference. And that is because prior art is presumed enabling and must  
15 be addressed only once Patent Owner has raised an enablement argument, as  
16 we have here.

17 Patent Owner also cites to the incorrect law addressing whether a  
18 challenged patent itself complies with the Section 112 requirements. For  
19 example, Patent Owner relies on the *Amgen* case to argue that Liu and Fauq  
20 cannot be utilized to demonstrate the enablement of Ahmad because Liu and  
21 Fauq post-date Ahmad. But as I said, *Amgen* deals with enablement under  
22 Section 112. And *Amgen* is not contrary to the *Bristol-Myers* case because  
23 Liu and Fauq are both prior art to the '334 patent.

24 Patent Owner also cites to the *ALZA* case, which is another case that  
25 addresses enablement under Section 112. But here, unlike in the *ALZA* case,

1 there's ample evidence, such as Liu and Fauq, that the teachings of Ahmad  
2 were enabled to a person of ordinary skill in the art.

3 And I mentioned earlier that I had a timeline slide and that's what I'm  
4 showing here on slide 31. And all I want to demonstrate here is that Liu and  
5 Fauq are both prior art to the '334 patent. There can be no dispute of that.  
6 Milroy, I mentioned in my reference that my colleague mentioned earlier has  
7 a date that is within the year between the provisional and the non-provisional  
8 application. But Milroy won't -- not necessary to show enablement. We  
9 believe that Liu and Fauq sufficiently established enablement of the greater  
10 than 90 percent limitation. Milroy is yet another way that I'll describe in a  
11 little bit that a POSA could have used to obtain greater than 90 percent of the  
12 endoxifen compositions.

13 I want to turn now to Dr. Bihovsky's declaration. One thing Patent  
14 Owner argues is that Petitioner didn't provide any expert testimony  
15 regarding the enablement of Ahmad, but this is demonstrably incorrect. Dr.  
16 Bihovsky explained how a POSA could use the teachings of Ahmad,  
17 including the synthesis of Ahmad as well as the purification of Liu to obtain  
18 greater than 90 percent (Z)-endoxifen. Alternatively, a POSA could employ  
19 the synthesis teachings of Liu to synthesize a crude mixture of (E)- and (Z)-  
20 endoxifen and then follow the purification approach of Liu to obtain greater  
21 than 90 percent Z. And yet another way a POSA could have conducted this  
22 is using the synthesis teachings of either Ahmad or Liu and conducting the  
23 chromatography purification methods as taught by Fauq.

24 So there were multiple ways that a POSA could have obtained  
25 greater than 90 percent (Z)-endoxifen. But the important point here is that it

1 was well known and a POSA -- it was well known how to obtain these  
2 compositions and would have been well within the skill of a POSA.

3 And the next thing I want to address, while certainly not at all  
4 necessary to establish enablement of Ahmad, Dr. Bihovsky actually  
5 conducted experiments in his laboratory and conclusively demonstrated that  
6 Liu's teachings can be employed to obtain greater than 90 percent (Z)-  
7 endoxifen. In particular, Dr. Bihovsky conducted both of Liu's purification  
8 pathways which include a recrystallization approach from a mixture of crude  
9 (E)- and (Z)-endoxifen to obtain pure (Z)-endoxifen as well as an  
10 isomerization approach whereby (E)-endoxifen is subjected to an  
11 isomerization reaction followed by successive recrystallizations to obtain  
12 (Z)-endoxifen. In both cases, Dr. Bihovsky obtained well over 90 percent  
13 (Z)-endoxifen.

14 I know that Patent Owner is going to argue that Dr. Bihovsky  
15 deviated from Liu. I'll address that more fully on rebuttal once Patent  
16 Owner has made their arguments. I note that some of the arguments, as we  
17 understand them from their slides, we think are new arguments, but  
18 nevertheless I'll address them on the merits on rebuttal. But the point here is  
19 that Dr. Bihovsky's experiments were not necessary to demonstrate  
20 enablement, but are yet just another piece of evidence demonstrating that  
21 Ahmad is enabled in terms of teaching greater than 90 percent (Z)-  
22 endoxifen.

23 I mentioned Milroy earlier. Milroy is a third way by which that was  
24 known in the prior art for obtaining pure (Z)-endoxifen. Milroy teaches a  
25 stereo selective synthesis whereby Milroy was able to obtain (Z)-endoxifen  
26 with greater than 99 percent isomeric purity. And so Milroy conducted a

1 synthesis whereby the reactions themselves were selective to the particular Z  
2 isomer without further need for purification, such as taught by Liu and Fauq.  
3 So Milroy is just another way by which a POSA could have obtained pure  
4 (Z)-endoxifen.

5 Patent Owner simply dismisses Milroy as post-dating the '334 patent.  
6 And I'm not going to spend a lot of time on this because it's not necessary to  
7 have a third piece of prior art demonstrating enablement of Ahmad. But  
8 Patent Owner never antedated Milroy. Patent Owner never introduced the  
9 provisional application and demonstrated its alleged priority. So Petitioner  
10 believes that Milroy is prior art and should be considered as additional  
11 evidence of enablement of Ahmad.

12 So just to summarize, Ahmad teaches each and every limitation of  
13 the claims in ground 2 and achieving greater than 90 percent (Z)-endoxifen  
14 was within the public's possession at the time of invention. And  
15 additionally, Ahmad renders these claims obvious because a POSA certainly  
16 would have been motivated to employ the teachings of Ahmad and would  
17 have had a reasonable expectation of success in obtaining greater than 90  
18 percent (Z)-endoxifen.

19 With that, unless Your Honors have any questions, I'll hand it back  
20 over to Mr. Mahon.

21 JUDGE HULSE: I do have some questions. So, Counsel, you agree  
22 that it's Petitioner's burden to show that Ahmad is enabling, right?

23 DR. LOREN: It is. So it's Petitioner's burden to show that Ahmad is  
24 enabling. The prior art -- excuse me, is presumed enabling -- enabled. But  
25 once Patent Owner has made an argument or that Ahmad is not enabled, it is  
26 then the burden shifts to Petitioner to establish that Ahmad is enabled. And

1 that's precisely why it was proper for Petitioner to introduce evidence on  
2 reply as to the enablement of Ahmad.

3 JUDGE HULSE: All right. So then if that's the case, then why did  
4 Petitioner not address the *Wands* factors?

5 DR. LOREN: May I concur with co-counsel briefly?

6 JUDGE HULSE: Absolutely.

7 DR. LOREN: Because here the prior art teaches explicitly how to  
8 obtain greater than 90 percent (Z)-endoxifen, there would not be anything  
9 outside of routine experimentation needed because Liu, Fauq, as well as  
10 Milroy teach explicit and particular protocols for how to obtain greater than  
11 90 percent (Z)-endoxifen. There would not be the need, for example, for an  
12 iterative trial-and-error process such as was acknowledged in the ALZA case  
13 that Patent Owner cites.

14 JUDGE HULSE: Thank you.

15 DR. LOREN: Unless Your Honors, I have further questions, I'll  
16 hand it back to Mr. Mahon.

17 MR. MAHON: Thank you, Brad. Turning to ground 3, ground 3 is  
18 the obviousness of claims 5 through 8 and 16 and 17 over Ahmad in view of  
19 Cole. There's again no dispute that Ahmad and Cole teach each and every  
20 limitation. There's no dispute that Ahmad teaches the enteric capsules  
21 recited in claim 1. And there's no dispute that Cole teaches a specific  
22 enteric-coated capsule with specific data that meets the limitations of each of  
23 claims 5, 6, 17, and 18.

24 I did want to briefly address an argument that we did not address the  
25 claim construction of the Board on enteric capsule. We disagree. We  
26 simply didn't understand what Patent Owner was arguing must further be

1 shown, given that there's, again, no dispute Ahmad teaches enteric capsules  
2 and no dispute that Cole teaches the specific enteric-coated capsule,  
3 achieving each of the claimed dissolution profiles.

4 So I think it's clear Cole teaches, you know, no release of drug at a  
5 low pH. So for over two hours no drug is released. And as I've shown here  
6 on slide 41, no dispute that Cole teaches slow release over time, over many  
7 hours once the drug reaches the more neutral and basic conditions of the  
8 small intestine and large intestine, respectively.

9 So the only dispute here appears to be motivation to combine and  
10 reasonable expectation of success. But as Dr. McConville explained, there  
11 was a clear motivation for a person of skill in the art to employ the enteric-  
12 coated capsule teachings of Cole with Ahmad's formulation. Ahmad teaches  
13 that enteric protection is necessary and to use an enteric-coated capsule.  
14 Cole teaches that very enteric-coated capsule and teaches that drug can be  
15 successfully delivered to the small intestine or the large intestine as  
16 necessary. So there's a clear motivation to use Cole's teachings with Ahmad.  
17 And a person of skill would have had far more than a reasonable expectation  
18 of success because success was already demonstrated by Cole.

19 Patent Owner's arguments in ground 3 are really that there were  
20 potential challenges. There's no evidence of any actual challenges that a  
21 person of skill would have expected or encountered, but that there could  
22 have been. So, as I've shown on slide 44 at Patent Owner's response at 63,  
23 they say that there were "potential interactions between (Z)-endoxifen,  
24 HPMC, and the enteric coating material." But they have no evidence that a  
25 person of skill would expect there to be any interactions or that any of these  
26 materials would cause degradation of (Z)-endoxifen.



1           So, for example, here they say that Dr. Davies explained that the  
2 "POSA would understand that enteric coatings and pharmaceutical  
3 compositions would interact," citing paragraph 166, which I've reproduced  
4 on the next screen. But Dr. Davies says nothing of the sort. He simply says  
5 a person of skill "must consider potential interactions between enteric  
6 coatings and pharmaceutical compositions," but he identifies no evidence  
7 that any interactions were expected or that this was a concern a person of  
8 skill would have had in applying Cole's teachings to Ahmad.

9           In fact, as Dr. McConville explained, such concerns would have  
10 been unfounded because the coating does not interact directly with the drug.  
11 In the manufacturing process a person of skill takes the drug, puts it in the  
12 capsule, and then the coating is applied. So there is no direct interplay  
13 between the coating and the active ingredient. So there had been no basis  
14 for such concern.

15           In their surreply at page 19, Patent Owner seems to acknowledge that  
16 this is correct and doesn't refute Dr. McConville's testimony that the enteric  
17 coating is applied after filling, which I think is common sense. But instead  
18 they present a new argument that was not presented in the Patent Owner  
19 response that heat was the problem. So they cite to Benameur, which is  
20 Exhibit 1010, and they say heat is applied. A POSA would know that high  
21 temperatures, above 40 degrees, can degrade sensitive active ingredients.  
22 Again, this is a new argument that Dr. McConville did not have a chance to  
23 address.

24           But in any event, this is, again, an unfounded concern. Benameur is  
25 not addressing (Z)-endoxifen or concerned with (Z)-endoxifen. There's no  
26 evidence in the record that a person of skill would have been concerned that

1 Cole, in Cole's teachings would have caused degradation of (Z)-endoxifen.  
2 And to be clear, Cole does not teach heating the capsule to 40 degrees. As  
3 Petitioner -- excuse me, as Patent Owner identified in the surreply, Cole on  
4 page 86 teaches that the temperature used in the coating pan can be 25 to 27  
5 degrees Celsius, which is room temperature. And I believe it does teach that  
6 it can be dried at 30 degrees Celsius, but well below the 40 degrees here that  
7 Benameur is talking about. But, again, there's simply no evidence in the  
8 record that a person of skill would have been concerned that the heating  
9 conditions described in Cole would have caused degradation of (Z)-  
10 endoxifen or been any sort of concern.

11 Next, turning to the alleged concern that (Z)-endoxifen could interact  
12 with HPMC, the material that comprises the capsule itself. But the record of  
13 evidence shows that HPMC is actually understood and preferred because it  
14 is not reactive with materials. It is compatible with a much wider range of  
15 drugs and excipients than traditional gelatinous capsules. That's clear in the  
16 in the Majee paper that we cited, Exhibit 1026, as well as other papers: Al-  
17 Tabakha, Exhibit 1028, and Honkanen, Exhibit 1029.

18 As they point out, HPMC's only known incompatibility is oxidizing  
19 agents. And there's no argument or evidence here that (Z)-endoxifen is an  
20 oxidizing agent or would expect it to be -- have any sort of negative  
21 interaction with HPMC. So as Dr. McConville explained, not only would a  
22 person not have been led away from using an HPMC capsule such as taught  
23 in Cole, they would have been motivated to use Cole precisely because  
24 HPMC was understood to be widely applicable.

25 Patent Owner next makes an argument that charge could impact  
26 stability of the (Z)-endoxifen. There is, again, no evidence that this charge

1 is a problem. The only evidence they cite for the, you know, even existence  
2 of charge was questions posed to Dr. McConville during his deposition. But  
3 as Dr. McConville explained, he did not testify that HPMC carries a positive  
4 charge. It is not an ionic material. It's a non-reactive compatible material.  
5 What he was referring to is during the filling of capsules with powders, you  
6 can get a little bit of static such that the powder sticks to the sides of the  
7 capsules. But this is a well-known concern in the industry. It's well-  
8 characterized. It is routine to fill capsules under conditions to limit the static  
9 so that you don't get that sticking.

10 And as Dr. McConville also explained, there's no evidence that this  
11 small triboelectric charge would cause any sort of degradation of (Z)-  
12 endoxifen or that a person of skill would have been concerned about this  
13 charge. There's simply, again, no evidence on the record of such a concern.

14 And the final thing I want to point out on ground 3 here in this  
15 argument is that the patent, the '334 patent, doesn't describe these problems,  
16 describe overcoming these problems, or describe solutions to these  
17 problems. And, in fact, the '334 patent does not even measure the (Z)-  
18 endoxifen content after it has been placed in the capsule. So if a person of  
19 skill was, as Patent Owner seems to allege, would have been so concerned  
20 about interactions with the coating or the capsule or charge, then presumably  
21 they would have measured to see whether the (Z)-endoxifen degraded after it  
22 was put in the capsule. But they did not. So again, as Dr. McConville  
23 explains, the '334 patent doesn't describe a problem, it doesn't describe a  
24 solution to these problems because there's simply no evidence that they  
25 existed.

1           The final thing on ground 3, Your Honor, is Patent Owner makes an  
2 argument that you could have gotten -- or a person of skill would have  
3 believed they might get a different release profile using (Z)-endoxifen or salt  
4 or free base. I don't quite understand the salt or free base argument, but  
5 there would have been a variation in release profiles or a person of skill  
6 wouldn't have expected to get the same desired characteristics in terms of  
7 that release, bypassing the stomach and releasing the small intestine.

8           But, again, I think this goes to Dr. Davies' lack of expertise in  
9 formulations. Because an enteric-coated capsule and enteric capsules, the  
10 release is not dependent on the active ingredient inside the capsule. The  
11 active ingredient is a passive participant. It's inside the capsule. What  
12 controls the release is the coating on the exterior of the capsule, how thick  
13 that coating is, how quickly it degrades, and when it degrades. So as Dr.  
14 McConville explained, it's immaterial what salt form you have inside the  
15 capsule. And a person of skill would understand that Cole can be applied to  
16 (Z)-endoxifen with the same expected release profile.

17           So, in sum, as Dr. McConville explained, a person of skill would  
18 have been motivated to apply Cole's teachings to Ahmad. This would have  
19 been a routine combination and a person of skill would have expected  
20 success in making that combination.

21           Turning to ground 4, I won't repeat everything that I think applies  
22 from ground 3. But, again, there's no dispute that Ahmad teaches enteric-  
23 coated capsules. And there's no dispute that Benameur teaches achieving  
24 those same results, the full enteric protection, but without the use of coating.  
25 So as Dr. McConville explained, a person of skill would have been  
26 motivated to modify Ahmad and instead of using an enteric-coated capsule,

1 using the intrinsically enteric capsule taught by Benameur for the very  
2 reasons that Benameur highlights: this avoids the need for a coating step. It  
3 simplifies the drug development process.

4 And to the extent heat is a concern, which again, we don't think heat  
5 is a concern here, you avoid that heating step. So as Dr. McConville  
6 explains, it would have been a routine design choice at the very least to use  
7 the intrinsically enteric capsule of Benameur, which Benameur reports, you  
8 know, obtains the same full enteric protection as traditional coated capsules  
9 such as those taught in Cole.

10 And again, the only real argument, aside from the unsupported  
11 interaction argument that I've already addressed in ground 3, is that while  
12 Benameur doesn't explicitly mention (Z)-endoxifen or teach that its capsules  
13 can be applied with (Z)-endoxifen, but as Dr. McConville explains, a person  
14 of skill in the art reading Benameur would not read it as limited to the  
15 particular compound used in Benameur. To the contrary, Benameur  
16 describes the EMT it uses as a model compound, as a model acid labile or  
17 acid-sensitive compound, and that a person of skill would have understood  
18 that Benameur can be used with any acid-sensitive compound.

19 And Benameur itself makes this clear, as Dr. McConville points out  
20 that Benameur describes its technology as being applicable to labile entities,  
21 including wide ranges, including peptides, nucleotides, live  
22 biopharmaceutical products, and vaccines. So there's certainly nothing in  
23 Benameur that is limited to any particular compound or that would have led  
24 away from a person of skill in the art applying it to Ahmad for the purposes  
25 of protecting (Z)-endoxifen from the stomach acids.

1           As Dr. McConville explained, a person of skill in the art would have  
2 expected success in using Benameur just the same way they would have  
3 expected success in using Cole. It would have been a routine formulation  
4 process to fill Benameur's capsules with (Z)-endoxifen, as is done every day  
5 all over the world in manufacturing facilities.

6           Turning to ground 5, there's again no dispute that the excipients here  
7 were well known in the art. They were well known for the use in capsules.  
8 You know, fillers and disintegrates and lubricants are common, everyday  
9 excipients that a formulator uses all the time, that that's taught in Stegemann,  
10 the "Capsugel" article, Exhibit 1011, which is specifically addressing  
11 capsules, as well as the Handbook of Pharmaceutical Excipients, which is a  
12 more general text.

13           So as Dr. McConville explains, a person of skill in the art would  
14 have been motivated to use these standard and routine excipients for their  
15 standard and routine purposes. I won't go through each and every one of  
16 them, but a person of skill would have been motivated to use a filler for  
17 precisely the same reason persons of skill use fillers for other formulations:  
18 to make the ingredients easier to process, stabilize them, or make it a  
19 appropriate size.

20           Again, Patent Owner's argument is really quite similar to the  
21 arguments in ground 3 or 4 that there were potential interactions. But there's  
22 no evidence of any specific concerns or any teaching that a person of skill  
23 would have expected any excipients to be incompatible with (Z)-endoxifen.  
24 As Dr. McConville explains, you know, the selection of excipients was  
25 routine and predictable in the art precisely because of books such as the  
26 HPE, the Handbook of Pharmaceutical Excipients, which I've reproduced on

1 the next page, Exhibit 1032. So one can simply look up the excipient, look  
2 at its incompatibilities. For example, talc here states that it's incompatible  
3 with quaternary ammonium compounds. A person of skill would see that  
4 there is no expected incompatibility with a drug like (Z)-endoxifen and  
5 would have no reason to believe that talc cannot or should not be used with  
6 (Z)-endoxifen. Again, as Dr. McConville explains, the relevant time period  
7 in 2017, all of these excipients were well known. It was a standard and  
8 routine practice to select the excipients.

9 And again, the '334 patent does not describe anything unique about  
10 these excipients. They do not describe any -- excuse me, the '334 patent  
11 does not describe any compatibility testing of (Z)-endoxifen with these  
12 excipients. It provides no teaching that these excipients work with (Z)-  
13 endoxifen unexpectedly. In fact, there's no teaching at all of working  
14 examples using these excipients. It simply states the excipients can be used.  
15 So that does not impart novelty, Your Honor, the use of routine and typical  
16 excipients.

17 And I think that, you know, Patent Owner's arguments have been  
18 rejected by the Federal Circuit, which has made clear, you know, the mere  
19 possibility of failure does not mean there's not a reasonable expectation of  
20 success because the law does not require an absolute guarantee that there  
21 will be no challenges, but simply that a person of skill would reasonably  
22 expect success.

23 Turning to ground 6, addressing claims 14, 18, and 19, I don't think  
24 there's any dispute that it was known to treat prior art endoxifen  
25 compositions well within this incredibly broadly claimed range of 0.01  
26 milligrams to 200 milligrams. For example, Ahmad teaches that

1 formulations can be provided between 1 milligram to 10 milligrams. Ahmad  
2 2010 and Ahmad 2012 are running clinical trials at these ranges between 1  
3 and 10 milligrams. Ahmad 2010 and 2012 teach that 4 milligrams to 8  
4 milligrams is expected to be efficacious based on what's known with the  
5 drug tamoxifen, which was dosed at 20 milligrams per day. So again, as Dr.  
6 McConville explained, a person of skill would have routinely selected  
7 dosage forms well within the broad range of 0.01 milligrams to 200  
8 milligrams, you know, specifically around the range of 4 to 8 milligrams  
9 because that is the approximate amount that was expected to be efficacious.  
10 Maybe not exactly 4 to 8 milligrams they would have experimented with  
11 below that and above that, but well within this broad range.

12 Patent Owner's argument appears to be, well, a person of skill  
13 wouldn't know that -- what the exact safe and efficacious dose would be.  
14 But again, the claims here are to an oral formulation, not the safe and  
15 efficacious dose, and it's an incredibly broad range of .01 milligrams to 200  
16 milligrams. Certainly the patent does not demonstrate that that entire range  
17 is a safe and efficacious dose. But as Dr. McConville explained, a person of  
18 skill would have been motivated to make capsules with dosages well within  
19 this range for further experimentation.

20 And again, as Dr. McConville explained, it was understood that (Z)-  
21 endoxifen was expected to be more efficacious, but that would not have led  
22 a person of skill in the art away from using the approximate dosage ranges  
23 taught at Ahmad 2010 and 2012, and certainly not outside of this broad  
24 range. As Dr. McConville said, and I think it's common sense, it would have  
25 been shocking if the efficacious and safe dosage amount for the (Z)-  
26 endoxifen capsules taught in Ahmad was outside of this very broad range.



1           Finally, Your Honor, I want to spend some time on the  
2 pharmacokinetic claims because I think there was some misunderstanding  
3 about what Petitioner's argument is with regard to pharmacokinetic claims.  
4 Our position is that the pharmacokinetic claims are the natural and inherent  
5 results of dosing a patient with a 90 percent (Z)-endoxifen capsule, an  
6 enteric-coated capsule, as taught in Ahmad, as we have addressed in the  
7 other grounds and the other claims. So as Dr. McConville explained, it's  
8 simply the inherent results of giving a patient what is taught in Ahmad.

9           Dr. McConville clarified on reply to the extent there was any  
10 ambiguity or misunderstanding, he was not opining that a 90 percent (Z)-  
11 endoxifen enteric-coated capsule, as Ahmad teaches, would have the exact  
12 same pharmacokinetic profile as what is taught in Ahmad 2010 and Ahmad  
13 2012, which are using endoxifen citrate tablets. It's that what is claimed  
14 here is simply what a person of skill would obtain if they followed Ahmad's  
15 teachings and dosed a patient with 90 percent (Z)-endoxifen capsules.

16           And again, that's, as Dr. McConville explained, that's made clear in  
17 the '334 patent. The '334 patent is simply dosing patients with neat (Z)-  
18 endoxifen. So "neat" means no excipients. So there's nothing in the  
19 formulation that was used to modify the pharmacokinetics or change the  
20 pharmacokinetics or otherwise, you know, obtain unique pharmacokinetics.  
21 It's simply giving a patient 90 percent (Z)-endoxifen capsules and measuring  
22 the results.

23           And I just want to remind Your Honors that the cases we cited on  
24 these points that that is a proper use of inherency. Refer Your Honors to the  
25 *King Pharmaceuticals* case and the *In re Huai-Hung Kao* cases we cited in  
26 our reply at page 23. In those cases, the prior art taught the use of particular

1 drugs with food. The patent at issue claims increased bioavailability that  
2 occurs when these drugs were given with food. The Federal Circuit in both  
3 cases affirmed that the claims were inherently anticipated or inherently  
4 obvious because they did no more than claim the natural results of what  
5 flows from the prior art and because a contrary holding would essentially  
6 remove from the public a teaching that is already out there in the art.

7 JUDGE HULSE: Then, Counsel, why in your petition did you cite  
8 the data, the PK data from Ahmad 2010?

9 MR. MAHON: For two reasons, Your Honor.

10 JUDGE HULSE: Sorry, I was just citing the page number, on pages  
11 55 and 56 of your petition.

12 MR. MAHON: Yes, Your Honor, and I apologize for the confusion.  
13 What we were attempting to show was two things. It's first of all that it was  
14 routine to dose a patient with drug and then measure these pharmacokinetics.  
15 The second reason we identified them was simply to show that there's  
16 nothing unexpected or surprising about the range of AUC and C-max that  
17 are claimed here; that it was understood that these pharmacokinetics were  
18 achieved in the prior art and were expected to be efficacious because one  
19 could compare the pharmacokinetics to tamoxifen. So that's all we were  
20 trying to show with Ahmad 2010 and 2012. So, again, I apologize if we  
21 created confusion, but we were not saying that the results would be the exact  
22 same as what they achieved, but simply that they demonstrate the known  
23 pharmacokinetic targets, which I actually have a slide on that in a second.

24 But before I get there, I did want to just address one what we feel is a  
25 new and unsupported surreply argument that Patent Owner makes, is they  
26 say, well, if a person of skill followed the synthesis of Ahmad, they might

1 have a different impurity profile than the embodiments that are described in  
2 the specification of the '334 patent. And these different impurities could  
3 impact the resulting pharmacokinetics. Again, this is a new argument. It  
4 was not presented in the Patent Owner response. Dr. McConville has not  
5 had a chance to address it. You know, they fault Dr. McConville for not  
6 addressing it. He had no opportunity to because it wasn't raised.

7 But there's also no evidence that impurity profiles would be expected  
8 to impact pharmacokinetics. So I'll just note, for example, on the screen the  
9 surreply on slide 90, what's cited in the surreply at 24 is Exhibit 2029,  
10 paragraphs 28 to 29. That is the surreply declaration of Dr. Davies. As you  
11 may recall, they were authorized to serve a surreply declaration to address  
12 the enablement arguments or enablement opinion testimony provided by Dr.  
13 Bihovsky. Those paragraphs do not address pharmacokinetics or ground 6  
14 whatsoever. So I've reproduced paragraphs 28 and 29 on the screen, but  
15 they are addressing enablement of Liu and Dr. Bihovsky's laboratory work.  
16 They are not addressing pharmacokinetics -- pharmacokinetic profiles.

17 So, again, there's simply no evidence that alleged different impurity  
18 profiles would lead to different pharmacokinetics. And there's no evidence  
19 in the record rebutting Dr. McConville's testimony that the claimed  
20 pharmacokinetics are simply the inherent and natural result of dosing a  
21 patient with 90 percent (Z)-endoxifen.

22 And I just again note, you know, Dr. McConville is an undisputed  
23 expert in pharmacokinetics. He teaches classes on pharmacokinetics. He  
24 studies pharmacokinetics and dosage forms. And so, you know, we really  
25 feel he's the only expert in this case who is an expert on these issues. But in  
26 any event, Dr. Davies did not rebut that testimony anyway.

1           And as I mentioned, Your Honor, just -- I already touched on this,  
2     but the reason we cited Ahmad 2010, 2012, was just to demonstrate  
3     pharmacokinetic target was known. So it was understood that these types of  
4     pharmacokinetics or at least pharmacokinetic data within these broad ranges  
5     were expected to be efficacious. So, and again, just to point that out, Ahmad  
6     2010 is not only disclosing pharmacokinetics within the claimed ranges, but  
7     stating that they're expected to be efficacious because they should be  
8     comparable to tamoxifen.

9           Finally, Your Honor, I just want to address the objective indicia.  
10    The problem Patent Owner has is that its alleged objective indicia are not  
11    commensurate in scope with what is claimed. First of all, many of their  
12    objective indicia arguments relate to a free base. But as Your Honor has  
13    discussed in the Institution Decision at page 10, there is nothing in the  
14    claims or the specification limiting the claims to the free base. The claims  
15    do not recite free base. They recite a compound of Formula (III). And the  
16    specification, Exhibit 1001, 12:48 to 59, makes unmistakably clear that  
17    compound, including compound of Formula (III), includes the salt forms or  
18    other polymorphic forms. The specification is simply unambiguous that  
19    Formula (III) includes the salt forms. So the claims are not limited to a free  
20    base.

21           But again, that's irrelevant even if you find otherwise, Your Honor.  
22    There's no dispute that Ahmad teaches a free base, that Liu teaches synthesis  
23    of a free base, et cetera. And even if we are to, you know, entertain Patent  
24    Owner's argument that the claims are limited to a free base, it is not limited  
25    to any particular free base. It's not limited to a free base made by any  
26    particular method. It's not limited to a free base with any particular purity or

1 stability profile. It covers any and all free bases, including the free bases  
2 taught in the prior art, such as by Liu or Ahmad or Fauq or Milroy.

3 Even if we --

4 JUDGE HULSE: And so do you -- I'm sorry. Given Patent Owner's  
5 arguments with respect to secondary considerations, do you agree that we  
6 need to construe the compound of Formula (III) in our final written  
7 decision?

8 MR. MAHON: That's an interesting question, Your Honor. I would  
9 agree that you do. Well, I think even if you find without actually deciding  
10 that the claims would cover or are limited to a free base, it still would not be  
11 -- the claim still would not be commensurate in scope of the objective  
12 indicia for the reason I'm addressing. So I don't know that you actually have  
13 to formally construe the claims.

14 I guess the easiest option would be to simply construe the claims.  
15 But we think you should find that even if the claims are construed to be  
16 limited to a free base, you know, the alleged improved free base is not  
17 commensurate in scope of the claims because the claims cover prior art, free  
18 bases, et cetera. And again, even if we ignore that, there's simply no  
19 evidence that what was achieved here is an improvement over the prior art.  
20 As Dr. McConville explains, the '334 patent describes the stability profile of  
21 the (Z)-endoxifen free base it achieves in one of the embodiments, but it  
22 doesn't compare that to any prior art free bases. It doesn't, for example,  
23 compare it to Liu's free base and any sort of stability profile of Liu.

24 The same thing with pharmacokinetics, Your Honor. I think their  
25 argument is that the specific embodiments allegedly described in the '334  
26 patent exhibit better bioavailability than the prior art. But the claims, again,

1 expressly cover the pharmacokinetics achieved in the prior art. So, you  
2 know, alleged improved bioavailability or alleged improved  
3 pharmacokinetics simply can't be commensurate in scope with the claims  
4 that expressly cover prior art.

5         And finally, Your Honor, just the last point I want to make is they  
6 make a teaching away argument. And I should be more clear. By "they," I  
7 mean Patent Owner. Patent Owner's argument is that other drugs use salt in  
8 this class. But the Federal Circuit has been very clear, Your Honor, that the  
9 use of alternatives in the prior art is not a teaching away. That disclosure  
10 does not criticize, discredit, or otherwise discourage the solution. So the fact  
11 that, you know, Petitioner's commercial drug is a salt or other prior art drugs  
12 which is in a salt form, is not a teaching away from using the free base,  
13 which is explicitly taught in Ahmad. And again, Liu teaches a free base.

14         So there's simply no evidence in the record teaching away from the  
15 combination here. There's no nothing in the record teaching away from  
16 using free base. There's nothing in the record teaching away from using (Z)-  
17 endoxifen enteric-coated capsule taught in Cole. There's nothing in the art  
18 teaching away from using the intrinsically enteric capsule taught in  
19 Benameur. There's nothing in the art teaching away from using the standard  
20 and routine excipients disclosed in Stegemann and the Handbook of  
21 Pharmaceutical Excipients. And so you know, each and every limitation  
22 here is undisputably disclosed in the prior art.

23         Again, we think Ahmad anticipates the vast majority of the claims.  
24 And the claims that are not anticipated would have been routine  
25 modifications to Ahmad. And so we ask that you find each and every claim  
26 of the '334 patent unpatentable.

1 Unless you have any questions, I'll reserve any remaining time for  
2 rebuttal.

3 JUDGE HULSE: Thank you. I apologize for not giving you a  
4 warning, but you have one minute left. So I'll add that to your rebuttal.

5 MR. MAHON: Thank you, your Honor.

6 JUDGE HULSE: Patent Owner, would you like to reserve time?

7 MS. KRUMPLITSCH: Yes, Your Honor, I would like to reserve 20  
8 minutes of the 60 minutes for rebuttal.

9 JUDGE HULSE: Great. Thank you. You may begin when you're  
10 ready.

11 MS. KRUMPLITSCH: Okay, great. We start with slide 2, please. So  
12 the '334 patent, Your Honors, claims solid oral dosage forms of at least 90  
13 percent pure (Z)-endoxifen and methods of delivering those formulations to  
14 patients. The claimed oral formulations are in clinical development for new  
15 treatments of hormone-dependent breast cancer for which there's an  
16 undisputed unmet need. And Atossa has raised over \$200 million to develop  
17 this new therapeutic.

18 Now, we've depicted independent claim 1 on this slide. As you can  
19 see, the claims themselves depict the endoxifen free base, not an endoxifen  
20 salt and not an endoxifen solvate. And we'll come back to this when we  
21 discuss claim construction. But I do want to point out that all of the experts  
22 in this case agree that a salt or solvate would be depicted with additional  
23 atoms and additional chemical bonds from what is depicted in the claims.

24 Now, Petitioner's touched on very lightly the chemistry in this case.  
25 And I want to start with the two isomeric forms of endoxifen: Z and E.  
26 Chemistry here is key to this case. It's really important. And so I apologize

1 we're going to get a little bit technical, but I think that's really important to  
2 understanding Patent Owner's arguments.

3         So E and Z exist as isomers. And these are a special category of  
4 isomer called diastereomers. And as Dr. Davies explained in his declaration,  
5 diastereomers are difficult to separate and purify because they can have  
6 similar but not identical properties. Now, Petitioner never took Dr. Davies'  
7 deposition with respect to the declarations he submitted in support of Patent  
8 Owner's response. And his declaration testimony stands unchallenged on  
9 that point. I would just point out that he describes this at Exhibit 2020 at  
10 pages 26 and 27. You can go to slide 7. Thank you.

11         Now, endoxifen is known to be unstable and the E and Z isomers can  
12 interconvert under certain conditions, which means they can switch back and  
13 forth from Z to E under certain conditions, such as acidic or aqueous  
14 conditions. And as Dr. Davies and Dr. Bihovsky, Petitioner's expert, have  
15 explained, the rate of isomerization can increase under elevated  
16 temperatures. So this is important to understand. Even if a POSA is able to  
17 make a 90 percent pure (Z)-endoxifen, if that compound is then  
18 subsequently subjected to acid or aqueous conditions, it will no longer be a  
19 90 percent Z. It will isomerize to a mixture of E and Z and heat would  
20 increase that rate of isomerization.

21         This point is significant because Ahmad, Petitioner's primary  
22 reference here, teaches that the preferred embodiment for formulation is to  
23 formulate in acid, which would result in a roughly 1-to-1 E-to-Z mixture. So  
24 you would no longer have a 90 percent pure Z. So it doesn't matter if you  
25 use Liu, Fauq, Milroy or any other background art in an attempt to purify  
26 (Z)-endoxifen. And we'll talk about why that's not a feasible method. But



1 even if you're somehow able to do that, once you apply the formulation  
2 teachings of Ahmad, you would end up back with a roughly 1-to-1 E-to-Z  
3 mixture, not a 90 percent (Z)-endoxifen. So again, the chemistry here is  
4 really key.

5 Now, in addition to Ahmad's teachings about formulating in acid, the  
6 state of the art that existed as of the time of the '334 patent is primitive and  
7 confusing. And this complicated state of the chemistry is best demonstrated  
8 by the petition itself. Petitioner identified two pieces of prior art as  
9 exemplifying the state of the art. And they asserted in the petition and their  
10 declarant, Dr. McConville, stated in his declaration that two pieces of prior,  
11 Liu, Exhibit 1004, and Song, Exhibit 1005, both of those teach a method of  
12 making highly pure (Z)-endoxifen.

13 Now, you didn't hear Petitioner mention Song at all in their  
14 argument. They shied away from that. But in the petition, both Petitioner  
15 and its expert must have believed that Song taught how to make highly pure  
16 (Z)-endoxifen. But Petitioner and Dr. McConville were flat wrong. Song  
17 actually teaches making highly pure (E)-endoxifen, the less active isomer.  
18 The fact that Song actually teaches making (E)-endoxifen, not (Z)-  
19 endoxifen, only came to light in this proceeding when Atossa's expert Dr.  
20 Davies studied Song and discovered that Song's NMR data misidentified as  
21 isomer. Now, Petitioner's own chemistry expert Dr. Bihovsky testified that  
22 he also considered Song and followed the Song experimental protocols to  
23 make a highly pure (Z)-endoxifen. But he also eventually realized that he  
24 made highly pure (E)-endoxifen.

25 So it's undisputed in this proceeding that one of the two references  
26 on which the petition relies to show enablement of Ahmad is completely

1 wrong. A POSA following the teachings of Song would never make 90  
2 percent (E)-endoxifen. And this is even more problematic because Song's  
3 publication date is 2012. It predates Ahmad. So a POSA looking at Ahmad  
4 at the time of Ahmad would look to Song for the teaching of how to purify,  
5 not to Liu. Liu post-dates Ahmad and we'll talk about that in a minute. But  
6 the fact that even -- that Petitioner and Petitioner's expert were mistaken in  
7 2023 in what Song teaches is strong evidence that the state of the art at the  
8 time of the '334 invention was confusing, unpredictable, and fraught with  
9 errors. Go to slide 6 please. Great, thanks.

10 Now, again, we're going to stick with the chemistry here. As Dr.  
11 Davies has explained, it's difficult to separate the E and Z isomers. And this  
12 is important because the difficult and unpredictable nature of separating the  
13 isomers from each other means that a POSA would have little expectation of  
14 success in achieving the 90 percent pure (Z)-endoxifen based on Ahmad.  
15 We'll talk about this more in a minute. And Petitioner touched on the fact  
16 that there are two ways Ahmad discloses a purifying endoxifen isomer:  
17 crystallization and chromatography. But both of those purification protocols  
18 require very precise conditions.

19 There are almost an unlimited number of conditions that could be  
20 varied and Ahmad provides no guidance or working examples on which  
21 conditions to choose. Modifying any of these conditions, such as solvent  
22 type, solvent ratio, temperature, there's so many variables to be modified that  
23 Ahmad does not provide any guidance on, if you modify any of those  
24 conditions, the purification would be unsuccessful. So it is undisputed.  
25 Petitioner's experts have agreed that Ahmad provides no guidance on how to

1 perform either chromatography or crystallization or under what conditions.

2 Ahmad just simply says you can do it.

3 Now, a POSA would have to engage in undue experimentation to  
4 find the right conditions to separate the isomers. And as I just explained,  
5 even if a POSA somehow able to purify to 90 percent, once they apply the  
6 teachings of Ahmad with respect to formulation and they formulate that 90  
7 percent (Z)-endoxifen in acid, that 90 percent (Z)-endoxifen will isomerize  
8 back to a mixture that's closer to 1-to-1. Petitioner's simplistic view of the  
9 complex chemistry in this case infects its enablement argument. And with  
10 this background, I'd like to address Petitioner's argument that forming the 90  
11 percent Z was in the public's possession prior to the '334 Patent.

12 JUDGE HULSE: Counsel, before you move on, could you please  
13 clarify something for me? I heard you just say that you could apply the  
14 crystallization of Liu, but even if you did, based on Ahmad's formulation in  
15 acidic conditions, it would isomerize back. Is that right?

16 MS. KRUMPLITSCH: That's right.

17 JUDGE HULSE: So, but I understand what Petitioner's argument is is  
18 that you would start with Ahmad even if it were in acidic conditions, which  
19 is -- I guess was like a 50-50 mixture of E and Z. So if you were to put that  
20 through the crystallization process of Liu, then would that remove the acidic  
21 conditions and I guess obviate that worry?

22 MS. KRUMPLITSCH: Yes, that's a great question and the answer is  
23 no. So Liu does not provide any formulation guidance. So what you would  
24 -- I think what Petitioner is suggesting a POSA would do is that you use  
25 Ahmad to come up with this crude -- we call it a crude mixture of 1-to-1 E-  
26 to-Z. Then you would take that crude mixture and somehow use Liu to

1 purify. But then once you get that purified 90 percent Z, you still have to  
2 formulate it back into the enteric capsule, which Ahmad provides no  
3 guidance of doing. But Ahmad does suggest that the formulation, so once  
4 you have that 90 percent Z is formulated in acid, in glacial acetic acid, which  
5 is examples 5 and 6 of Ahmad. So you need to go back to Ahmad for the  
6 formulation limitation.

7 JUDGE HULSE: Thank you.

8 MS. KRUMPLITSCH: So let's talk about Liu, Fauq, and I guess now  
9 Milroy. And I want to address, before we dive into the chemistry, I just  
10 want to address Milroy first. We, of course, objected to this argument as a  
11 new argument. And I want to point out that Milroy is only discussed in  
12 Petitioner's papers at -- in the petition at page 37 and they're quoting Milroy  
13 for the proposition that endoxifen is unstable in acid. Then at paper 10 in  
14 response to our Patent Owner's preliminary response where we point out that  
15 Milroy is dated later, they point out that Milroy is just background art. It's  
16 not statutory prior art. So it's that -- and that is the most they have said about  
17 Milroy in their papers.

18 So now I heard Petitioner's argument and they seem to be implying  
19 that a POSA could use Liu, Fauq, or Milroy to purify (Z)-endoxifen. And  
20 we would argue that Milroy is a new argument. We would also argue that  
21 Fauq is a new argument, but we'll get to Fauq in a second, so let's spend our  
22 time talking about Liu.

23 So as I've stated the crux of Petitioner's argument is that a POSA  
24 would follow Ahmad's methods to make this crude 1-to-1 mixture of Z and  
25 E, then rely on background knowledge as exemplified by Liu, perhaps Fauq  
26 and Milroy, to purify that crude mixture and achieve the 90 percent Z

1 without undue experimentation. But, again, I just want to remind the Board  
2 that the petition itself and Petitioner and Petitioner's expert argued that this  
3 background knowledge of purification was supposed to come from Liu or  
4 Song, but they got Song completely wrong. So a POSA looking at the state  
5 of the art at the time Ahmad was filed would look to Song and go down the  
6 wrong path and make the completely wrong isomer.

7 It's also worth noting that Liu, Song, and Ahmad were submitted  
8 during prosecution and cited by the Examiner in the file history. But no  
9 matter using Liu, Fauq, Milroy, or any other background art, none of this  
10 solves the enablement problem of Ahmad.

11 I first want to, you know, hit on the fact that Liu postdates Ahmad  
12 and cannot be used to show enablement of Ahmad as of Ahmad's filing date.  
13 Petitioners cite *Bristol-Myers Squibb v. Ben Venue* and *In re Donahue*.  
14 Neither of those cases support what they say, what they're arguing here.  
15 Both *Donahue* and *BMS*, *Donahue* came first, *BMS* cites *Donahue* and  
16 they're consistent, stand for the proposition that an anticipatory prior art  
17 reference can be enabled by a later dated reference, even if the anticipatory  
18 reference did not actually make the invention. So -- but that's only if the  
19 disclosure in that first reference would allow a POSA to make and use the  
20 invention. This isn't in dispute.

21 In *Donohue* and *BMS*, the later dated references are used to confirm  
22 the teachings in that earlier reference. But here we have Ahmad that doesn't  
23 provide any teaching of how to get to a 90 percent Z. That's not disputed.  
24 There's a single sentence that says -- a single prophetic statement saying,  
25 you know, one object of the invention is to get 90 percent Z. Ahmad does  
26 not provide any guidance on how to use chromatography or crystallography

1 to purify to the 90 percent Z. There's just a single sentence. Liu provides a  
2 completely different synthetic pathway than Ahmad.

3 JUDGE HULSE: Counsel, can we go back and talk about that *BMS*  
4 case?

5 MS. KRUMPLITSCH: Sure.

6 JUDGE HULSE: So my understanding is that the prior art reference  
7 did not disclose the limitation or the claim limitation whereas here Ahmad  
8 does teach the claim limitation of 90 percent purity. Correct?

9 MS. KRUMPLITSCH: So I guess I would quibble a little bit with the  
10 use of "teach." There's a prophetic object saying one object of the invention  
11 is to achieve 90 percent purity. I don't think that's a -- that could be properly  
12 characterized as a teaching.

13 JUDGE HULSE: But it discloses it then?

14 MS. KRUMPLITSCH: That statement is in the specification, yes.  
15 Yes, but there's no -- it would be one thing -- there's no indication anywhere  
16 in Ahmad that Ahmad ever knew how to get to 90 percent. So it would be  
17 one thing if the Petitioner -- I mean, sorry, if Ahmad, the specification said  
18 one object of the invention is to get to 90 percent. You can use  
19 chromatography or crystallization to get there. Here are the types of -- here  
20 are the solvents that you would use and here are the ratios that you would  
21 use and here's the temperatures that you would use. I think *BMS* and  
22 *Donahue* stand for the point that the -- Ahmad did not actually have to make  
23 the 90 percent, but he could have laid out the groundwork for how to get  
24 there.

25 But here, if you look at the passage of the specification that describes  
26 the conditions that could be used for chromatography and crystallization,

1 there are I think it's 19 different solvents there. The solvents could be in any  
2 ratio, you know, any ratio specified. The specification also says you could  
3 use a solvent that's not listed. There's no guidance provided about  
4 temperature, any other reaction conditions. There's just no indication that  
5 Ahmad ever -- like those teachings could ever be used to enable a POSA to  
6 make 90 percent Z.

7 JUDGE HULSE: Well, is it your position that Ahmad has to be  
8 enabled as of the effective filing date of Ahmad?

9 MS. KRUMPLITSCH: Yes. Yes.

10 JUDGE HULSE: But doesn't the *BMS* reference teach otherwise?

11 MS. KRUMPLITSCH: Well, I think the *BMS* reference is that you  
12 can use later dated art to show that at the time of the filing date, the inventor  
13 of that anticipatory prior art was enabled. But what *BMS* does not stand for  
14 is that you can't use a later filed publication to fill in the gaps. Here. The  
15 purification, the ability to purify.

16 JUDGE HULSE: Okay. I may come back to this later, but please  
17 proceed.

18 MS. KRUMPLITSCH: Okay. That's fine. I think Petitioner's  
19 argument seems to be grounded in this concept that it's irrelevant whether  
20 the synthetic pathway of Ahmad, Liu, or the '334 patent are different. And  
21 that's just incorrect. While different synthetic pathways might be able to  
22 achieve a 90 percent (Z)-endoxifen, the claims here are limited to a  
23 formulation. So there are limits as to what types of solvents you could use,  
24 what types of impurities might be present. Those are inherent. It's a  
25 pharmaceutical formulation. So, for example, you could not use benzene as

1 a solvent. So the synthetic pathway does matter and I just want to make that  
2 point.

3 But I want to take -- turn a little bit to how Petitioner has tried to  
4 demonstrate enablement of Ahmad, and that is through Dr. Bihovsky's  
5 testimony and his experimental work. So I think it's important to remind us  
6 all that Dr. Bihovsky never attempted to carry out the synthetic method of  
7 Ahmad, never tried it. Instead he carried out the synthetic method of Liu  
8 from the very beginning to the purification step. But the enablement of Liu  
9 is not at issue here. With respect to taking the crude mixture of Ahmad and  
10 then applying Liu's purification schema, which is, I think, what Petitioner is  
11 suggesting a POSA would do, Dr. Bihovsky testified, that's not what I did  
12 and that's not what Liu did. And that's exhibit -- his deposition at Exhibit  
13 2027 at page 56.

14 Dr. Bihovsky testified that he was given, when he was first engaged  
15 in this matter, he was given a number of patent publications including Liu  
16 and Ahmad. And he was asked by Petitioner to synthesize endoxifen and  
17 purify it. This was back in June of 2023 before the petition was filed,  
18 according to Dr. Bihovsky. He said he chose Liu over Ahmad because Liu  
19 had sufficient detail in terms of the synthesis, but also detail in terms of the  
20 separation of isomers. And then I'm paraphrasing, some of the others were  
21 not as good as Liu because Dr. Bihovsky found them to be less practical or  
22 possibly not having sufficient detail. So he did not try to synthesize -- he did  
23 not try to follow the synthetic method of Ahmad and then purify, because  
24 Ahmad didn't have sufficient detail. And that's his deposition, Exhibit 2027  
25 at page 62, line 18 to 66:4. And that's key. Dr. Bihovsky couldn't do it.



1           In addition to Dr. Bihovsky, I think, trying to show that Liu is  
2 enabled, he made numerous modifications to Liu's purification protocol.  
3 Some of these were disclosed in his expert declaration. Some of his  
4 modifications came to light in his subsequent deposition. And some of these  
5 modifications we only learned about after we had to request a copy of his lab  
6 notebook that Petitioner did not include as an exhibit in this proceeding. So  
7 Patent Owner didn't have an opportunity to conduct a second deposition to  
8 question Dr. Bihovsky about the contents of his lab notebook.

9           Nevertheless, we have the lab notebook, and we can see the  
10 modifications that he made. And we summarized those in the next three  
11 slides. So we'll start with -- and just to ground us all, because I know we are  
12 talking, again, about a lot of chemistry. Liu's examples 5, 6, and 7 are the  
13 ones that Petitioner identified. And so we'll go through some of the change  
14 that Dr. Bihovsky made to Liu. And this is important because Dr. Bihovsky  
15 couldn't just pick up Liu. You know, even though he thought it had  
16 sufficient detail, he had to modify it to get it to work.

17           So Petitioner's kind of glossing over all the chemistry, saying that it's  
18 so easy that a POSA would just easily be able to manufacture a crude  
19 endoxifen using Ahmad and then applying Liu's purification protocol and,  
20 bam, you get the claimed invention. That's far from what actually happened  
21 here. So slide 30 here, these are the changes that Dr. Bihovsky made to  
22 example 5 of Liu. And we have Dr. Davies' description of the impact of  
23 those changes.

24           Now, Dr. Bihovsky agreed that he performed his experiments on a  
25 scale over 1,000 times smaller than Liu. He also testified that about the  
26 starting material, the endoxifen starting material had a different Z-to-E ratio

1 than Liu did. And that's in his testimony and in his expert reports at the  
2 citations on the slide.

3 Dr. Davies pointed out that a POSA would know that reactions on a  
4 small scale are not useful models to predict the same reactions on a large  
5 scale. And when you're crystallizing stuff on a large scale, that's very  
6 different. Dr. Davies was deposed on his surreply testimony, and this is  
7 what he said in his deposition. If you can go to the next slide, please.

8 So, again, these are the changes that Dr. Bihovsky made to Liu  
9 example 6, which is the isomerization of E to Z. And again, he changed the  
10 heating times. He dried precipitates and concentrated the filtrates of each  
11 step. Now, this is complex chemistry and I don't think we need to get too far  
12 down in the weeds, but we just want to point out that Dr. Bihovsky  
13 fundamentally changed what Liu suggested was the correct purification  
14 schema. And again, Dr. Davies' reaction said, you know, even slight  
15 changes in a methodology can lead to different results and different synthetic  
16 pathways can result in different stability and impurity profiles. And this is  
17 really important. And if you can go to slide 32, please.

18 This is example 7 again, additional changes that Dr. Bihovsky made  
19 to Liu's purification schema. Again, Dr. Bihovsky increased the cooling  
20 time to allow for more isomerization. He omitted a step completely. And  
21 again, Dr. Davies testified that when you change the recrystallization  
22 parameters, you get a different output. So, again, this is important because  
23 Petitioner's argument is that you would take Ahmad, apply Liu, and then you  
24 get the claimed invention, and that a POSA would know how to do that  
25 without undue experimentation. But Petitioner's expert, Dr. Bihovsky, A,  
26 couldn't start with Ahmad. He said there wasn't enough detail provided

1 about purification. When he got to Liu, he had to make a number of  
2 modifications to get to the claimed 90 percent pure Z.

3 So, in summary, with respect to Liu, Petitioners failed to explain  
4 how a POSA would use Liu to purify the crude endoxifen of Ahmad. Again,  
5 Dr. Bihovsky did not even try to do the experiment. And again, even if a  
6 POSA somehow got all the way through to the end and made it to the end of  
7 Liu and ended up with a 90 percent pure (Z)-endoxifen, the minute they  
8 turned back to Ahmad for the teachings of formulating an acid that 90  
9 percent pure (Z)-endoxifen would isomerize back to a mixture of E to Z at a  
10 roughly 1-to-1 ratio. And again, Petitioner provides no explanation at all as  
11 to why a POSA would follow Liu and disregard Song, which teaches the  
12 completely wrong outcome.

13 So I want to spend a minute and talk about Fauq, which is another --  
14 a new reference cited for the first time in Petitioner's reply. And Fauq  
15 supports a new argument that a POSA would know how to use reverse phase  
16 high performance liquid chromatography to purify the crude endoxifen  
17 mixture of Ahmad. But Fauq should be disregarded. It was not identified in  
18 the petition. Petitioner never advanced the argument that a POSA would  
19 look to the background art teaching reverse phase HPLC to purify Ahmad's  
20 crude endoxifen. Again, in the petition Petitioner relied on Ahmad and  
21 Song, but Fauq and HPLC was not mentioned.

22 Now, even -- I'm sorry, and I point the Board to *Intelligent*  
23 *Biosystems v. Illumina*, the Federal Circuit case from 2016, that where the  
24 Fed Circuit found that the reply brief and the declaration exceeded the  
25 proper scope because they set a new prior references not relied on in the  
26 petition to support unpatentability, and we would argue that that standard

1 should apply here. But even if Fauq is considered, the Petitioner never  
2 explains how a POSA would use the knowledge of Fauq to enable Ahmad.

3 So Fauq separated a mixture -- a 1-to-1 mixture of Z to E using  
4 reverse phase HPLC. But Fauq's yield is minuscule. Dr. Bihovsky, excuse  
5 me, agreed that the two -- let me take a step back. Fauq produced 200  
6 milligrams total of 90 percent (Z)-endoxifen. Dr. Bihovsky agreed and he  
7 testified that 200 milligrams produced by Fauq is not even enough to dose a  
8 single patient, let alone formulate into a formulation as required by the  
9 claims.

10 More importantly, though, a POSA would understand that HPLC  
11 specifically and chromatography more generally should be avoided for  
12 purification. Dr. Bihovsky testified in his deposition, and I'm going to read  
13 it, he testified that HPLC is not an efficient process and he said, "Generally  
14 purifying by preparative HPLC is to be avoided. Crystallization is much  
15 more practical on a large scale. A person of ordinary skill in the art would  
16 try to avoid chromatography if possible." And that's Exhibit 2027 at pages  
17 48 through 50. Again --

18 JUDGE HULSE: What is your response to Petitioner's argument  
19 earlier that the claims don't recite a particular scale?

20 MS. KRUMPLITSCH: Right, but they do -- the claims do -- are to a  
21 pharmaceutical formulation. So a POSA would never look to a method of  
22 purifying that resulted in only 200 milligrams if they're trying to make a  
23 pharmaceutical formulation.

24 I'd like to point out that Milroy, which is the reference that Petitioner  
25 now seems to rely on, also teaches that HPLC should be avoided because the  
26 yields are so small. And Liu, Petitioner's other referent, also states that some

1 procedures in the art separate E and Z isomers via methods which are  
2 expensive and difficult to perform on a large scale, such as preparative  
3 HPLC. So you have Dr. Bihovsky saying a POSA would never do it. You  
4 have the other art cited by Petitioner saying that no one would ever -- you  
5 know, a POSA would never look to HPLC to purify here.

6 And again, even if a POSA was able to somehow use Fauq to take  
7 the crude endoxifen from Ahmad, apply HPLC purification techniques, and  
8 get sufficient product to formulate, the minute they took that 200 milligrams  
9 of (Z)-endoxifen and put it back into a formulation as taught by Ahmad, you  
10 would get back to the 1-to-1 mixture. Ahmad teaches -- again, Ahmad does  
11 not teach -- contain any teaching about the instability of the Z isomer.

12 Okay. I next want to turn to enablement generally and the *Wands*  
13 factors. As I've said ad nauseam, Ahmad does not enable a POSA to make  
14 and use the invention as claimed by the '334 without undue experimentation.  
15 And Ahmad's single recitation of 90 percent Z is that sentence up on your  
16 screen on slide 21. There's no other disclosure in Ahmad of 90 percent Z,  
17 whether free base or salt.

18 So the *Wands* factors provide the framework with which to evaluate  
19 enablement and whether undue experimentation is required. And we've  
20 identified that in our Patent Owner response. Petitioner, as Your Honor  
21 pointed out, did not address the *Wands* factors, but I'd like to go through  
22 them, a few of them anyways, that are particularly applicable to here.

23 The unpredictability of the prior art. The state of the art regarding  
24 the synthesis and purification of a 90 percent (Z)-endoxifen is confusing and  
25 unpredictable. It's so confusing that Petitioner and Dr. McConville got it  
26 wrong. I don't think you could show the art being any more unpredictable

1 than that. They got it completely wrong by asserting that Song teaches how  
2 to make 90 percent pure Z. Boards have previously found the field of  
3 organic chemistry is difficult and unpredictable. That's the *Impax Labs v.*  
4 *Aventis* case. That's the Fed. Circuit in 2008. That's a *Boston Scientific v.*  
5 *J&J* case. Sorry, that's a District of Delaware case in 2010. The Federal  
6 Circuit has also found that the science of separating stereoisomers, and  
7 remember the Z and E isomers are stereoisomers and they're difficult to  
8 separate, the Federal Circuit has found that separating those, the science of  
9 separating those is also difficult and unpredictable. That's *Forest Labs v.*  
10 *Ivax*. That's a Fed. Circuit case from 2007. And the *Sanofi-Synthelabo v.*  
11 *Apotex*, and that's 2008. And I have all the citations there, but they're also in  
12 our papers.

13 JUDGE HULSE: Counsel, but those are cases from 10 years prior to  
14 the effective filing date of this case, right? (Inaudible)?

15 MS. KRUMPLITSCH: They are older cases. That's true. That's true.  
16 But even in 2023, the Petitioner couldn't figure out which of the prior art  
17 taught making (Z)-endoxifen and (E)-endoxifen. So I'd argue that while  
18 those cases are older, the unpredictability of the prior art remains, as  
19 evidenced by the petition and Dr. McConville's declaration.

20 JUDGE HULSE: Is it really that they got confused about Song? Is  
21 that really a matter of unpredictability or is that just a matter of, for lack of a  
22 better word, carelessness on their part?

23 MS. KRUMPLITSCH: I don't -- I can't comment on whether they  
24 were careful or careless. However, a POSA looking at that art at the time,  
25 especially at the time of Ahmad, because this is back in 20 -- Song is 2012  
26 and Ahmad is shortly after that. At that time I don't think would have had

1 any reason to suspect that Song was wrong. And they would -- they could  
2 have followed the procedure of Song. They could have characterized their  
3 compound, compared it to the NMR data in Song and would have  
4 concluded, oh, look, I made a 90 percent pure Z, when, in fact, they didn't.

5 JUDGE HULSE: But if we apply -- let's say we disagree with you  
6 that Ahmad needs to be enabled as of Ahmad's filing date, and we apply the  
7 date of one year prior to the effective filing date, which here would be  
8 September 11, 2016, then how does that affect your arguments?

9 MS. KRUMPLITSCH: You know, honestly, it doesn't. Ahmad is not  
10 enabled even today. I mean, there's no -- there's just no teaching in Ahmad  
11 of how to get to -- well, putting aside the '334 patent, there's no teaching in  
12 Ahmad of how to get to 90 percent pure Z. There's just no way to do it  
13 using the synthetic pathway of Ahmad. Dr. Bihovsky tried. He looked at it  
14 and said, no, this is too tough, I'm not going to do it. There's not enough  
15 detail provided on how to purify. So he chose the easier path of going with  
16 Liu from start to finish.

17 JUDGE HULSE: Right. But if it was well known in the art how to  
18 purify these isomers, then does it have to be disclosed or taught expressly in  
19 Ahmad?

20 MS. KRUMPLITSCH: I would argue that it's not well known to  
21 purify the -- sorry, let me start over. The synthetic pathway that's used to  
22 create the isomers would include different impurities, different solvents, and  
23 things like that. So an impurity purification schema that works for the '334  
24 patent may or may not work for Ahmad or the purification schema for a  
25 different synthetic pathway that we haven't talked about may or may not  
26 work for Liu. You can't just mix and match these like they're Lego blocks

1 that click together. The purification schema is important because the  
2 chemistry here is very, very complex. And the Z, excuse me, isomer is very,  
3 very unstable. So I don't think you could say even today that it's the science  
4 of purifying the Z and E isomers is easy or well known. I think it would still  
5 require a tremendous amount of experimentation.

6 JUDGE HULSE: But if the level of skill in the art as it is here is very  
7 high, then is it not within that level to determine which solvents should be  
8 used or which conditions should be applied, et cetera?

9 MS. KRUMPLITSCH: So, mm-hmm, I think, one, I'm not saying it's  
10 impossible, but it would certainly require an extensive amount of  
11 experimentation. And again, I would -- you know, I deposed Dr. Bihovsky.  
12 He's a very credible organic chemist. He did not want to try Ahmad. So he  
13 said there's not enough detail, it would take too long, it would be too  
14 complex to try and figure out how to do this on my own. Right? I think that  
15 shows that even a person of ordinary skill, let's see, that was 2023 last  
16 summer, would not have been able to take the teachings of Ahmad and come  
17 up with a purified (Z)-endoxifen.

18 JUDGE HULSE: Thank you.

19 MS. KRUMPLITSCH: Okay. So I'm going to continue marching  
20 through the *Wands* factors quickly, mindful of my time. One of the *Wands*  
21 factors is the presence or absence of working examples. It's undisputed  
22 there are no working examples of how to purify 90 percent pure Z in  
23 Ahmad.

24 Again, the quantity of experimentation necessary is undisputed that  
25 Ahmad synthetic pathway examples 1 through 4 results in a 1-to-1 E-to-Z  
26 ratio. And all the experts here agree with that. That's not disputed.



1           It's not disputed that Ahmad does not teach the isomeric ratio exactly  
2   what that crude endoxifen mixture is. Dr. Davies came up with that by  
3   looking at other art. But Ahmad certainly doesn't teach that. It's undisputed  
4   that Ahmad synthetic pathway is different than what's in the '334 patent.  
5   And Dr. Bihovsky again testified that crystallization, which is what a POSA  
6   would do to try and purify the crude endoxifen, is frequently -- now, again,  
7   this is another quote of his, "Crystallization is frequently very empirical,  
8   which is to say trial and error. So I just emphasize again, it's a trial-and-  
9   error process to determine what you would call a different solubility in  
10   certain solvents. He emphasized the trial-and-error nature of trying to use  
11   crystallization to purify throughout his deposition, Exhibit 2027 at pages 117  
12   to 120.

13           The next *Wands* factor --

14           JUDGE HULSE: You have five minutes.

15           MS. KRUMPLITSCH: Okay, thank you. The next *Wands* factor, the  
16   amount of direction or guidance provided. Again, it's undisputed that that  
17   single line in the specification at column 12, lines 14 to 17, is the only  
18   mention of 90 percent pure (Z)-endoxifen in the entire patent. And again,  
19   Ahmad does not contain any guidance on how to purify other than to  
20   aspirationally suggest using crystallization or chromatography. And again,  
21   as we've discussed, Ahmad provides a laundry list of solvents and ratios, but  
22   does not provide any specific teachings.

23           And just I want to go back to this point about Ahmad teaching  
24   formulation in acid. If you look at the specification, column 12, 14 to 17,  
25   contains the prophetic sentence regarding the 90 percent pure Z. The very  
26   next sentence states that another object of the invention is to provide

1 solubilized endoxifen and aqueous acid. Ahmad does not teach to avoid an  
2 acidic pH. And examples 5 and 6 of Ahmad teach formulating, excuse me,  
3 in glacial acetic acid, which again, as Dr. Davies has testified, would result  
4 in isomerization back to that 1-to-1 ratio.

5 Real quickly, I think the POSA definition, Dr. Davies testified, it's  
6 not just in his declaration. He testified that chemistry was important and  
7 chemistry is part of formulation. And he certainly has the relevant  
8 experience in formulation to provide the opinions in this case. And that's all  
9 in our papers. I'll rest on that.

10 The claim construction. The compound of Formula (III) is the  
11 endoxifen. Again, I can spend some of my time on rebuttal talking about  
12 claim construction, but I do want to point the Board to our papers where the  
13 first thing we need to do is look at the structure that is in claim 1 and claim  
14 15. And that's the structure of a free base. And again, it's undisputed. The  
15 experts here all agree that that structure is not a salt or a solvate.

16 The passage that the Board pointed to with respect to the broader  
17 construction, respectfully, is a passage that describes the scope of  
18 embodiments. And consistent with that passage, the specification does  
19 describe different embodiments, including the free base, polymorph and  
20 crystalline forms, salt forms, and solvate forms. Those are described in the  
21 specification. But that does not mean that the claims themselves should be  
22 broad enough to encompass all of those.

23 JUDGE HULSE: So that passage from the specification on column  
24 12, I don't know if you have a slide for this, but it does say a compound such  
25 as Compounds of Formula (III) include the polymorphic salt, free base,  
26 cocrystal, and solvate forms. And it points to Formula (III), which is the, as

1 you say, is the free base form. So how can the compound of Formula (III),  
2 that particular molecular structure, be a salt or a cocrystal or, you know, any  
3 of the other things that you say, if the molecular structure is different?

4 MS. KRUMPLITSCH: So the polymorph and crystal forms have the  
5 same atoms and the same chemical formula. They're just in a different  
6 spatial -- they're oriented different in space. So the structure as you draw it  
7 on the paper would look the same. But the first part of that passage is that  
8 embodiments include Formula (III). So we read that as it's describing the  
9 scope of embodiments.

10 JUDGE HULSE: I mean, if you read further, it says, "Thus  
11 appearances of the phrase 'a compound', compound of Formula (I)," blah,  
12 blah, blah, "compounds of Formula (III) include the free base and/or the  
13 gluconate salt as described herein." So again, it's pointing to that particular  
14 structure as including the salts.

15 MS. KRUMPLITSCH: Yes, but, I mean, I guess I would read it in  
16 conjunction with the first part. I mean, I don't want to go round and round,  
17 but with the first part of that sentence which describes the embodiments.  
18 Because if you look at the language of the rest of the spec, over 30 times the  
19 patent describes -- it uses definitional intent language like as recited here in  
20 "This means." We've put those examples on the screen. They're also in our  
21 papers. And that is different than the language that's used at this passage.  
22 So I think, you know, that we cited a bunch of case law in our papers that  
23 where the definitional intent is not clear, you can't presume that  
24 lexicography.

25 JUDGE HULSE: Okay. You are out of time unless you want to take  
26 --

1 MS. KRUMPLITSCH: Okay.

2 JUDGE HULSE: -- (inaudible) into your rebuttal time.

3 MS. KRUMPLITSCH: I will reserve. I will cover everything else on  
4 rebuttal time.

5 JUDGE HULSE: Thank you.

6 MS. KRUMPLITSCH: Thank you.

7 MR. MAHON: Sorry. Your Honor, before I begin, can I just ask a  
8 procedural question? My understanding is that our rebuttal is supposed to be  
9 limited to what they just said. They didn't get into the other grounds. So I'm  
10 just not sure how you want us to proceed here.

11 JUDGE HULSE: I mean, yes, it should be limited to what Patent  
12 Owner argued.

13 MR. MAHON: And then I believe their surrebuttal should be limited  
14 to our rebuttal. So I think if they want to address the other grounds, they  
15 should do so now and then -- but I'm happy to proceed however you want.  
16 I'm just -- it seems a little procedurally irregular to me.

17 JUDGE HULSE: Patent Owner, did you -- you did not get into the  
18 secondary considerations.

19 MS. KRUMPLITSCH: Sorry, sorry. I was muted there. Apologies.  
20 Then may I spend two minutes to talk about the pharmacokinetic claims?  
21 And then I think we can rest on our papers on the rest of the claims. I don't -  
22 - so if I can take two minutes of my rebuttal time to talk about the  
23 pharmacokinetic claims 18 and 19, I'd like to do that now and then I can pass  
24 it back over to Petitioner, if that's okay.

25 MR. MAHON: No objections.

26 JUDGE HULSE: That's fine. Great. Thank you.

1 MS. KRUMPLITSCH: Okay, thank you. Okay. So ground 6, and I  
2 want to focus on the pharmacokinetic claims at slide 42. Petitioner has not  
3 identified any teaching in Ahmad, Liu, Fauq, or any other background art  
4 that teaches the PK limitations of a 90 percent endoxifen compound.  
5 Petitioner points to Ahmad 2010 and Ahmad 2012. But those references  
6 report PK values for an 80 percent (Z)-endoxifen citrate salt. And there is  
7 no evidence in the record that an 80 percent (Z)-endoxifen citrate salt would  
8 have the same PK parameters as a 90 percent endoxifen, whether free base  
9 or salt.

10 It's also undisputed in this proceeding that the synthetic methods of  
11 Ahmad, Liu, and the '334 patent are all different, and any resulting  
12 compound, even if it was achievable, would have a different impurity  
13 profile. So I think what Petitioner is arguing here is that any 90 percent (Z)-  
14 endoxifen would have the same (inaudible) in it. For the PK limitations to  
15 be inherently obvious, any 90 percent (Z)-endoxifen would have the same  
16 PK parameters. They haven't shown that at all. So I think their inherency  
17 argument fails on that point alone. Inherency with respect to obviousness is  
18 a very high standard and you'd have to show that there's -- a POSA would  
19 have some expectation that the PK values of the 90 percent (Z)-endoxifen  
20 formulated as in the claim would have the same PK values as a 90 percent  
21 (Z)-endoxifen formulated by Ahmad applying Liu or Ahmad applying Fauq.  
22 And it's undisputed that when you do that and you apply these other  
23 synthetic pathways, you may get different impurity profiles, which will  
24 impact solubility, which will impact pharmacokinetics.

25 I also think there's some tension in Petitioner's claim construction  
26 argument that the compound of Formula (III) can be a free base or a salt.

1 Yet I think they're arguing that under that construction a free base or a salt  
2 would have the same PK values. And I don't think there's any evidence in  
3 the record showing that either. So again, for this inherency argument to  
4 work, they would have to show that there is no other possible outcome, and  
5 they haven't made that showing.

6 JUDGE HULSE: You're at two and a half minutes.

7 MS. KRUMPLITSCH: Okay, great. I have one more thing to say.  
8 The data in the '334 specification and the PK values in claims 18 and 19 are  
9 the result of dosing with a 90 percent pure endoxifen free base synthesized  
10 using the method described in the patent. And again, if the 90 percent  
11 endoxifen is administered as salt, the PK values would be different. There's  
12 no evidence showing that they would be the same. And because there are  
13 these differences, the inherency argument falls apart. There's not one  
14 inherent PK value for the administration of any 90 percent endoxifen  
15 compound, which I think is their argument.

16 So with that, I think I will save the rest of my time for rebuttal.

17 JUDGE HULSE: You'll have 17 minutes for rebuttal. Petitioner, you  
18 have 26 minutes.

19 MR. MAHON: Thank you, Your Honor. I don't think we'll use  
20 anywhere close to that.

21 I'll just briefly start on ground 6. We disagree, obviously, with their  
22 contentions. There's simply no evidence in the record that impurities would  
23 be expected to affect the pharmacokinetics. Again, Dr. McConville is the  
24 only expert who testified on this point. He testified that the claimed results  
25 are the inherent results of dosing a patient with what is taught in Ahmad 90  
26 percent (Z)-endoxifen enteric-coated capsule neat with no excipients. And

1 so again, I just direct Your Honors to the *King* case and the *In re Huai-Hung*  
2 *Kao* case where, you know, where something is simply the inherent result of  
3 what is taught in the prior art. It is not a patentable distinction.

4 And again, I just want to point out on their slide they cite to Dr.  
5 McConville's testimony to support this impurity profile argument, which is a  
6 new argument. Dr. McConville's testimony, Exhibit 2028 at 101:21 to 102:3  
7 and 120:16 to 121:3, has nothing to do with impurity profiles. And again,  
8 Dr. McConville was not allowed to address this argument because it was not  
9 raised. In that testimony that Patent Owner cited on its slide Dr. McConville  
10 is asked whether he thinks E and Z isomers or E and Z formulations would  
11 have different pharmacokinetics, and he said he did not think so. You know,  
12 they're largely similar molecules with one atom rearranged. But that's not  
13 the basis of our argument, so that testimony is simply not relevant here.

14 I did want to go back to a few things regarding enablement, and then  
15 I'll let Dr. Loren address the arguments on Dr. Bihovsky's testing. First of  
16 all, Your Honor, you're absolutely correct in your reading of *BMS*. *BMS* is  
17 clear that where all the limitations are taught in the prior art, it is entirely  
18 proper to use later references to demonstrate that what is taught is enabled.  
19 And what is taught in Ahmad and what is claimed here are oral formulations  
20 comprising 90 percent (Z)-endoxifen. No dispute that that's disclosed if they  
21 want to use that term in Ahmad. So it's entirely proper to use Liu and Fauq  
22 and Milroy to demonstrate that that was in the public's possession.

23 But you are correct. What *BMS* held is that where there's not that  
24 disclosure, you cannot rely on later references to supply a missing limitation.  
25 So in *BMS*, they found the claims to predicaments to be anticipated because  
26 the other references demonstrated the enablement of predicaments. The

1 Federal Circuit, however, held that claims to a specific predicament that  
2 were not disclosed in the prior art were not enabled by other prior references  
3 because the main -- the anticipatory prior art reference didn't teach that  
4 limitation. It didn't teach the specific predicament. But that's not the  
5 situation we have here.

6 Secondly, the *Apple* case that we cited makes very clear that we only  
7 have to address enablement once they raise an enablement issue, that Ahmad  
8 was presumed enabling for its teachings. And on reply, we were permitted  
9 to rely on Liu and Fauq and Milroy to demonstrate enablement. So, you  
10 know, as my associate Dr. Loren pointed out, in the *Apple* case, the Federal  
11 Circuit held it was error for the Board to not consider such reply evidence.

12 I do want to briefly address Song, Your Honor. There's no dispute  
13 that Song erroneously reports that it obtained 90 percent (Z)-endoxifen.  
14 They appeared to confuse their NMR data. So that wasn't our oversight. We  
15 read Song to be what Song says, that it achieves 90 percent (Z)-endoxifen.  
16 They are correct, Song was in error. Our expert quickly discovered that.  
17 But that doesn't demonstrate a lack of enablement. That wouldn't be this  
18 difficult trial and error. Okay. Song didn't work. A person of skill then can  
19 simply follow Liu or can simply follow Fauq. So it does not show undue  
20 experimentation that one prior art reference was unsuccessful.

21 JUDGE HULSE: Counsel, do you -- have any of your experts opined  
22 on the predictability or unpredictability of the art? Do they say that this art  
23 is predictable?

24 MR. MAHON: I think it'd be hard in a generic sense to say that  
25 crystallization or chromatography are highly predictable. But again, here I  
26 think Patent Owner is simply ignoring the specific teachings of Liu. So a



1 person of skill didn't have to guess at which solvents to use. Liu teaches  
2 exactly which solvents are effective. So our expert didn't get into  
3 predictability of Ahmad alone because there are more specific teachings. So  
4 there's no experimentation a person of skill has to do to experiment with  
5 different chromatographic conditions or different crystallization conditions  
6 because the teachings are there in the prior art, prior to the '334 patent.

7 JUDGE HULSE: Well, under *Wands*, we're required to look at the  
8 art, the predictability of the art as a whole, right? Not just the predictability  
9 of Ahmad. So do you have evidence that supports, you know, one way or  
10 the other? If you say it's predictable, then what does your evidence show  
11 that it's predictable?

12 MR. MAHON: Your Honor, as I said, I don't think we're arguing that  
13 in a generic sense it is predictable. But the other *Wands* factors, for  
14 example, are the state of the art. And I've never seen *Wands* applied in a  
15 case where the prior art explicitly teaches the limitation. So it's not like  
16 we're relying on a reference, you know, that simply teaches crystallization  
17 can be used generally. It's references that exactly teach using crystallization  
18 to achieve 90 percent (Z)-endoxifen. So I think it's highly predictable that a  
19 person of skill could follow Liu and obtain 90 percent (Z)-endoxifen.

20 I apologize, Your Honor. Your Honor lost video. I don't know if  
21 we've lost audio with you.

22 JUDGE HULSE: No, I'm here. Can you see me?

23 MR. MAHON: I can't see you, but I can hear you and I'm happy to  
24 proceed.

1 JUDGE HULSE: Okay. I'm not sure what's happening because I can  
2 see myself. What was I -- I lost my question. Please proceed and I'll think  
3 of it again, I'm sure.

4 MR. MAHON: Sure. Dr. Loren will address this more fully. But  
5 here it was highly predictable to follow Liu's teachings, and Dr. Bihovsky  
6 did that with -- you know, so I think it's -- the question I don't think is in the  
7 abstract. With no teachings of, you know, ignoring Liu and ignoring Fauq,  
8 could a person of skill have achieved 90 percent (Z)-endoxifen? You have  
9 to consider the state of the art that those, you know, specific teachings were  
10 there.

11 JUDGE HULSE: Well, then, what is your response to Patent Owner's  
12 argument that Bihovsky didn't follow Liu? He changed certain conditions  
13 and parameters.

14 MR. MAHON: Your Honor, if I may, my associate, Dr. Loren was  
15 going to address that. Can I make my final point and then let him address  
16 that?

17 JUDGE HULSE: Sure. Apologies. I forgot about that. Thank you.

18 MR. MAHON: No problem, Your Honor. And I just want to address  
19 their last argument that I think is a new argument that I don't see presented  
20 in any paper, and I'm not even sure I fully understand it, but is that a person  
21 would have to formulate in acid after synthesizing 90 percent (Z)-endoxifen,  
22 which would cause degradation back to an equilibrium mixture. We have  
23 never argued that a person of skill would have to formulate in acid. I think  
24 what they're saying is that Ahmad, in one of its teachings, teaches that you  
25 can form the salt form. So you can take the endoxifen and then add acid to it  
26 to form a salt. But Ahmad also teaches forming a free base. And as we've

1 explained, there are many ways you could make the free base, just as in Liu.  
2 And so a person of skill would simply take that free base and add it to a  
3 capsule. There's no need to add it to acid.

4 Again, I don't believe this argument was ever made by Patent Owner,  
5 but it's simply not what we're arguing. We're arguing a person of skill would  
6 have taken free base and inserted it into the capsule.

7 Unless Your Honor has any questions, I'll let Dr. Loren address the  
8 Bihovsky testing.

9 JUDGE HULSE: Thank you.

10 DR. LOREN: Thank you, Your Honor. I just want to clear up the  
11 record related to the alleged alterations or deviations of Liu that Patent  
12 Owner brought up. Looking at Patent Owner's slide 30 -- or, excuse me, if I  
13 may share my screen. Give me a moment. Apologies. Just give us one  
14 second. Are you able to see Patent Owner slides?

15 And so first, looking at slide 30 from Patent Owner's  
16 demonstratives, which addresses Liu's recrystallization, for example, in  
17 example 5 from Liu, first, Petitioner does not dispute that Dr. Bihovsky ran  
18 his experiments at a smaller scale than what Liu describes in his examples.  
19 But as both my colleague and I have discussed today, the '334 patent claims  
20 are not directed to a method of synthesis and certainly not to a commercial  
21 multi kilogram scale method of synthesis as was conducted by Liu.

22 Second, with respect to the point regarding the starting material of  
23 example 5, first, Dr. Bihovsky did not use endoxifen here as his starting  
24 material. Dr. Bihovsky conducted the synthesis as taught by Liu to  
25 synthesize a crude mixture of (E)- and (Z)-endoxifen. Patent Owner here  
26 appears to be referring to the fact that when Dr. Bihovsky reached example 5

1 of Liu, as Dr. Bihovsky explained in paragraphs 40 to 41 of his declarations,  
2 at this stage he had a crude endoxifen mixture with 33 percent (Z)-endoxifen  
3 and 67 percent (E)-endoxifen. In other words, Dr. Bihovsky had a crude  
4 endoxifen mixture that had less percent of (Z)-endoxifen than Liu did at this  
5 stage. But despite starting with a less pure mixture, following Liu's further  
6 teachings and in the subsequent examples and teachings, Dr. Bihovsky still  
7 obtained greater than 90 percent. So if anything, this really just  
8 demonstrates the robustness of Liu's protocols.

9       Next, looking at slide 31 which relates to Liu's isomerization  
10 experiments, Patent Owner points to two alleged deviations here, which I'll  
11 note are new arguments not presented on their surreply, but I will address  
12 them on the merits. With respect to the heating for four hours as shown in  
13 red at the top of the diagram, Dr. Bihovsky explained, and this is in  
14 paragraph 46 of his declaration, that he heated this isomeric reaction --  
15 isomerization reaction, excuse me, for four hours. This is taught in Liu at  
16 paragraph 46 where Liu states that this reaction can be run anywhere from a  
17 half an hour up to four hours. So what Dr. Bihovsky conducted was within  
18 the teachings of Liu.

19       With respect to the drying of the precipitates, which is shown in red  
20 at the bottom or underneath the boxes on Patent Owner slides, Liu states in  
21 paragraph 73 from example 6, and I'll read you what Liu states. "The  
22 mother liquor (containing 71 percent Z isomer) was removed from the  
23 reactor, evaporated to provide a solid, and dried at 35 degrees Celsius to a  
24 constant weight." And then in paragraph 74 Liu states, "The above  
25 operations were repeated twice with the residual E isomer crystals in the  
26 reactor." This is exactly what Dr. Bihovsky did. This is not a deviation.

1           And the last points I want to make, which is on slide 32 of Patent  
2 Owner's demonstratives, and this is related to Liu's example 7 or the final  
3 sets of recrystallizations to produce the enriched endoxifen. On the first red  
4 note, Dr. Bihovsky did run the (inaudible) recrystallization step for 64 hours.  
5 But extending the time for crystallization is explicitly taught in Liu in  
6 paragraph 26, which indicates how one can run the crystallization anywhere  
7 from half an hour up to 10 days. As Dr. Bihovsky explained in paragraph 42  
8 of his declaration, he conducted the recrystallization initially for 40 hours,  
9 observed a lower yield than he was expecting, and allowed the  
10 recrystallization to extend for a longer period, as Liu teaches.

11           Next, Patent Owner claims that Dr. Bihovsky skipped the second  
12 recrystallization discussed in Liu's example 7. Dr. Bihovsky did not skip  
13 this step. In fact, he ran this second recrystallization exactly as Liu teaches  
14 in example 7. Patent Owner's slide incorrectly states in the fourth box from  
15 the left that Liu's second recrystallization from example 7 was for 40 hours.  
16 But Liu clearly states in paragraph 76 from example 7 that the second  
17 recrystallization was stirred for 50 hours at 1 to 5 degrees Celsius. This is  
18 exactly what Dr. Bihovsky did. And Dr. Bihovsky explains this process in  
19 paragraph 42 of his declaration.

20           Now, at this stage, Dr. Bihovsky had obtained (Z)-endoxifen with a  
21 100 percent isomeric purity. So, yes, Dr. Bihovsky did not conduct a third  
22 recrystallization because it simply was not necessary. The pure (Z)-  
23 endoxifen product was already obtained. And in any case, Liu discloses in  
24 paragraph 20 that this recrystallization step can be conducted from one to  
25 five times. So again, I think this is a little bit of a distraction because we  
26 certainly were not required to have further evidence of the enablement of a

1 mob where it is undisputed that Liu teaches a method of forming 90 percent  
2 (Z)-endoxifen, as well as Fauq and Milroy also teaching methods for  
3 obtaining 90 percent (Z)-endoxifen. But I did want to clear the record that  
4 Dr. Bihovsky did not deviate from Liu.

5 With that, unless Your Honors have any questions, I'll cede the  
6 remainder of our time.

7 JUDGE HULSE: Thank you. I have no further questions.

8 MS. KRUMPLITSCH: Do I have 17 minutes left, Your Honor?

9 JUDGE HULSE: That's correct.

10 MS. KRUMPLITSCH: Okay. I don't think I'll use all of that either. I  
11 just wanted to address a few of the points that Petitioner made in the  
12 rebuttal.

13 First, regarding Song, a POSA would not know that Song was  
14 wrong. It's not like there is one piece of prior art that a POSA would be like,  
15 oh, that's a mistake, so we know we're not going to follow that. Clearly,  
16 Petitioner and Petitioner's expert thought Song was correct all the way up  
17 until the time they filed the petition. It's included in their petition. It's  
18 included in their surreply to our Patent Owner's preliminary response where  
19 they said, we provided evidence of enablement, and they cite to Liu and  
20 Song. So a POSA at the time of Ahmad would not know that Song was  
21 wrong or that purified the E isomer. And I'll just leave that there.

22 With respect to Liu, again, Liu teaches how to purify the crude  
23 endoxifen mixture of Liu, not of Ahmad. Liu does not -- Dr. Bihovsky.  
24 Sorry. Dr. Bihovsky purified the crude endoxifen mixture of Liu. He did  
25 not even attempt to purify the crude endoxifen mixture of Ahmad. He said  
26 Ahmad didn't have enough details. He didn't know what the ratio of E to Z

1 was at the end. He said it was easier. He looked at all these references when  
2 he was setting out to do his research and said, I'm going to stick with Liu  
3 from start to finish. He never touched Ahmad.

4 So Petitioner, again, is kind of stepping away from the chemistry and  
5 running away from a little bit. But the chemistry is really important. These  
6 are not just synthetic -- you can't just take a synthetic process from one  
7 reference and tack on a purification process from another reference and  
8 expect a patent -- a practitioner would be able to combine them without  
9 undue experimentation. There's no evidence that that's the case. That's not  
10 what Dr. Bihovsky did.

11 And he did make modifications to Liu. So even there, he had to  
12 modify Liu in a number of ways stated on our slides to get the experiment to  
13 work, to purify. With respect to Petitioner's argument about  
14 pharmacokinetics, that you just take a free base, add it to a capsule, that  
15 ignores the chemistry of the isomers, and we've discussed quite a bit how  
16 unstable they are. Their argument -- they have no -- there is no support in  
17 the record to support that argument.

18 Petitioner said we've made a new --

19 JUDGE HULSE: Counsel?

20 MS. KRUMPLITSCH: Yes.

21 JUDGE HULSE: I'm sorry. Could we go back to Dr. Bihovsky's  
22 experiments again? So you're saying that he deviated. Petitioner is saying  
23 that he didn't. How do -- it sounds like what Petitioner is saying is that he  
24 may not have followed that particular example, but that the teachings of Liu  
25 provide for greater parameters such as the, what was it, the cooling time or  
26 something along those lines.

1 MS. KRUMPLITSCH: Mm-hmm.

2 JUDGE HULSE: What's your response to that?

3 MS. KRUMPLITSCH: I mean, whether I think what it shows, A, it  
4 shows that a person of ordinary skill in the art would have to play around  
5 with those parameters. You can read his deposition testimony. He said he  
6 had to play around with the parameters to get the reactions to go. And he  
7 engaged in some hindsight because he knew he was trying to achieve the 90  
8 percent and work backwards. And you can see in his lab notebook, I believe  
9 it's also in his declaration, that he refers to X-ray crystallography data that  
10 comes right from the '334 patent. So the fact, you know, whether or not --  
11 he made a number of modifications, I think that's not in dispute. And he had  
12 to do that to get the reaction to go. So I think it, again, points to the  
13 unpredictability and the inherent difficultness of the purification of these  
14 really unstable isomers.

15 JUDGE HULSE: Thank you.

16 MS. KRUMPLITSCH: I do want to point out that, again, we did not  
17 get the chance to depose Dr. Bihovsky on his notebook, and it was not  
18 attached to his declaration. And we only requested it after his deposition  
19 when it was clear that there were changes he made to the Liu experimental  
20 protocol that were not reflected in his declaration.

21 JUDGE HULSE: Has that lab notebook been entered into the record  
22 as an exhibit?

23 MS. KRUMPLITSCH: It has not. Because Petitioner wanted it to  
24 remain confidential. I think that's a question for Petitioner.

25 The last -- the Petitioner argued that the -- we are making a new  
26 argument about the effect of formulating an acid. Our Patent Owner



1 preliminary response at pages 3 and 4 clearly states that acetic acid of  
2 Ahmad results in isomerization. So this is not a new argument. And I  
3 believe Dr. Bihovsky and perhaps Dr. McConnell both agreed that if you put  
4 an unstable Z isomer in acid, it will isomerize. So that's -- it's not -- we can  
5 get you those citations.

6 JUDGE HULSE: What is your response to Petitioner's argument that  
7 Ahmad teaches the free base form and that that's -- I guess the adding the  
8 acid to the formulation is just another embodiment?

9 MS. KRUMPLITSCH: So I would say Ahmad teaches the freebase  
10 form as much as Ahmad teaches a 90 percent pure Z. It just says -- I'm  
11 sorry, Your Honor, I don't think it teaches any specific formulation of the  
12 free base. It certainly doesn't teach an enteric-coated formulation. There's  
13 no example of that in Ahmad anywhere.

14 I think I will concede the rest of my time.

15 JUDGE HULSE: Well, thank you all for your very helpful arguments  
16 today. We'd especially like to thank our LEAP practitioner, Mr. Loren, for  
17 appearing today. Hopefully your participation, you were able to gain some  
18 valuable experience today, and we thank your law firm and your client for  
19 allowing you to have this opportunity.

20 If the parties could please stay on the line and see if our court  
21 reporter has any questions for you, we would greatly appreciate that. With  
22 that said, the Panel will take the matter under advisement and issue a final  
23 written decision in due course. So thank you again. We're adjourned.

24 MS. KRUMPLITSCH: Thank you, Your Honors.

25 MR. MAHON: Thank you, Your Honors.

26 REPORTER: Thank you. We're off the record.

1           (Whereupon, the proceedings at 3:02 p.m. were concluded.)

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Patent 11,572,334 B2

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