

1 UNITED STATES PATENT AND TRADEMARK OFFICE  
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3  
4 INTAS PHARMACEUTICALS LTD.,  
5 Petitioner, Case PGR2023-00043  
6 vs. Patent 11,572,334  
7 ATOSSA THERAPEUTICS, INC.,  
8 Patent Owner.

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13 REMOTE DEPOSITION OF STEPHEN G. DAVIES, D. PHIL.

14 GREAT BRITAIN

15 WEDNESDAY, SEPTEMBER 18TH, 2024

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23 REPORTED BY:

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September 18, 2024

8:03 A.M. CST

Remote deposition of STEPHEN G.  
DAVIES, D. PHIL., appearing at Great Britain,  
pursuant to agreement, appearing remotely before  
Deborah Habian, an Illinois Certified Shorthand  
Reporter, Missouri Certified Court Reporter,  
Registered Merit Reporter, Certified Realtime  
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I N D E X

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INSTRUCTIONS AND REQUESTS OF COUNSEL  
(NONE)

INDEX OF EXHIBITS

PETITIONER EXHIBITS TO DR. DAVIES DEPOSITION

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Exhibit 1	Bihovsky notebook	37
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REVIOUSLY MARKED PETITIONER EXHIBITS

NUMBER	DESCRIPTION	PAGE
Exhibit 1030	Expert Declaration of Ron Bihovsky, Ph.D.	19
Exhibit 2029	Davies Supplemental Report	6



1 THE REPORTER: Good morning. Today's  
2 date is September 18th, 2024, and the time is  
3 8:03 a.m. Central Standard Time.

4 Professor Davies, would you raise your  
5 right hand, please.

6 THE WITNESS: (Complying.)

7 (Oath administered remotely.)

8 THE WITNESS: I do.

9 THE REPORTER: Thank you so much.  
10 You may proceed.

11 MR. MAHON: Good morning, Dr. Davies.  
12 You have a clean copy of your supplemental  
13 report, which is Exhibit 2029, in front of you?

14 MS. KRUMPLITSCH: Hey, Ben, I'm sorry,  
15 should we announce ourselves on the record?  
16 Sorry to interrupt.

17 THE WITNESS: Yes, I do.

18 MS. KRUMPLITSCH: Sorry, Dr. Davies.  
19 Let's get this out of the way.

20 Susan Krumplitsch for Atossa and the  
21 witness, and with me are my colleagues Melissa  
22 Harwood, Emma Holland, and Derek Gretkowski.

23 MR. MAHON: Ben Mahon, McAndrews Held &  
24 Malloy on behalf of the Petitioner. With me is  
25 my colleague Brad Loren.



1                   STEPHEN G. DAVIES, D. PHIL,  
2   called as a witness herein by the Petitioner,  
3   having been first duly sworn remotely, was  
4   examined and testified as follows:

5                                   EXAMINATION

6   By MR. MAHON:

7           Q.   All right, I threw up Exhibit 2029 in  
8   the chat too if you want to have a digital copy,  
9   but you, I believe, confirmed you have a paper  
10   copy in front of you.

11                   So can we start at paragraph 3 of your  
12   supplemental report?

13           A.   Okay.

14           Q.   And you say that you're an expert in  
15   the field of organic chemistry and medicinal  
16   chemistry, correct?

17           A.   That's correct.

18           Q.   You do not identify yourself as an  
19   expert in formulation sciences?

20           A.   It's -- formulation sciences is a part  
21   of organic chemistry, medicinal chemistry. I  
22   have been involved in a number of formulation  
23   processes, the compounds that my companies have  
24   produced.

25           Q.   Let's go to paragraph 4 for a second on



1 the next page.

2 A. Okay. I have it, yes.

3 Q. And so is it your opinion in the  
4 definition -- in Atossa's definition of a POSA  
5 includes medicinal chemistry, that medicinal  
6 chemistry would cover formulation sciences?

7 A. It can do. It's part of chemistry.

8 Q. Now, in the second paragraph that  
9 you're quoting from Atossa, it says: "A POSA  
10 would have worked with a team of professionals  
11 with training in related disciplines such as  
12 pharmacology, pharmacokinetics formulation, drug  
13 discovery and/or drug development as of the date  
14 of claimed inventions," correct?

15 A. That's what it says, yes.

16 Q. So I'm just trying to understand, is  
17 formulation, experience in formulation part of  
18 Atossa's definition of a POSA or is it a related  
19 discipline?

20 MS. KRUMPLITSCH: Objection, calls for  
21 legal conclusion.

22 THE WITNESS: I'd say that's a legal  
23 definition, but formulation involves chemistry.  
24 Drug discovery involves medicinal chemistry and  
25 chemistry. Drug development involves chemistry,





1 but there are people who -- chemists that  
2 specialize in one area or in another.

3 BY MR. MAHON:

4 Q. And do you specialize in formulation?

5 A. As I said, I have been involved in  
6 formulation processes working with the compounds  
7 my companies have developed.

8 Q. Yeah, but that's not my question,  
9 though. My question is do you specialize in  
10 formulation?

11 A. I wouldn't say I specialize in it, but  
12 I'm a general organic chemist who's been  
13 involved in such processes.

14 Q. Do you believe that experience with  
15 formulations such as capsules is required to be  
16 a POSA in regards to the '334 patent?

17 A. It depends on how the material ends up  
18 being formulated. It's not whether you can  
19 formulate. You can deliver rather than  
20 formulate, one way you can deliver medicine.

21 Q. So let me ask the question a different  
22 way. The claims here -- give me one second. I  
23 want to make sure I accurately read it.

24 Claim 1, for example, begins: "An oral  
25 formulation comprising an Endoxifen composition



1       encapsulated in an enteric capsule."

2           A.   Okay.

3           Q.   So would you agree with me that a POSA  
4       in regards to the '334 patent should have  
5       experience with oral formulations such as  
6       enteric capsules?

7           A.   Well, one member of the team would have  
8       experience, yes.

9           Q.   But in your opinion a person of skill  
10      in the art in regards to the '334 patent could  
11      have absolutely no experience with oral  
12      formulations such as enteric capsules?

13           MS. KRUMPLITSCH:  Objection, form.

14           THE WITNESS:  Well, if you look at the  
15      definition of a POSA, then it's a team, one of  
16      which would be experienced in formulation.  So  
17      it would have experience with enteric-coated  
18      capsules.

19       BY MR. MAHON:

20           Q.   In your opinion is the alleged novelty  
21      of the claims of the '334 patent the chemistry  
22      or the formulation?

23           MS. KRUMPLITSCH:  Objection, it's  
24      outside the scope of the expert report.

25



1 BY MR. MAHON:

2 Q. I'm sorry, Dr. Davies, you still need  
3 to answer.

4 A. Okay. Could you repeat the question?

5 Q. Yes. In your opinion is the novelty of  
6 the claims of the '334 patent in the chemistry  
7 or the formulation?

8 MS. KRUMPLITSCH: Same objection.

9 Sorry, excuse me, Dr. Davis.

10 This deposition is limited to the  
11 opinions he offered in his supplemental  
12 declaration.

13 MR. MAHON: And he's offering an  
14 opinion about a definition of a POSA, is he not?

15 MS. KRUMPLITSCH: Novelty of the '334  
16 patent claims is not anywhere in his  
17 supplemental declaration. If you would point us  
18 to a paragraph, I would appreciate that.

19 MR. MAHON: Yes, well, I would say that  
20 the novelty of the claims has everything to do  
21 with what a POSA is here. So unless you're  
22 going to instruct him not to answer on the basis  
23 of privilege, I'm going to ask that he answer  
24 the question.

25 MS. KRUMPLITSCH: So I'll let you ask



1 this question, but, again, this deposition is  
2 limited to the opinions of his supplemental  
3 declaration.

4 And if you can point us to a paragraph  
5 where your question is focused on, I would  
6 appreciate it. If you can't, I'll let you ask  
7 this question and move on. Otherwise, we'll get  
8 the Board on the phone.

9 MR. MAHON: Paragraph 4 where he's  
10 offering his opinion about POSA, I think this  
11 goes directly to his opinions about what a POSA  
12 is, and I think I'm entitled to ask the  
13 question.

14 MS. KRUMPLITSCH: Your question was  
15 novelty, not a POSA definition.

16 MR. MAHON: It relates directly to what  
17 a POSA is.

18 MS. KRUMPLITSCH: Okay. Well, I'll let  
19 you ask this one question, but if we keep going  
20 down this path, we'll get the Board on the  
21 phone.

22 MR. MAHON: Okay.

23 THE WITNESS: You'll have to repeat the  
24 question again.

25



1 BY MR. MAHON:

2 Q. Sure. In your opinion is the novelty  
3 of the claims of the '334 patent in the  
4 chemistry or in the formulation?

5 MS. KRUMPLITSCH: Same objections.

6 THE WITNESS: The novelty is the claim.  
7 What the claim says is what the court would  
8 interpret as the novelty of the invention.

9 BY MR. MAHON:

10 Q. You're not offering any opinion that  
11 Dr. McConville is not a POSA in the '334 patent,  
12 correct?

13 A. I haven't looked at my previous reports  
14 or Dr. McConville's expertise for quite awhile,  
15 so I wouldn't have prepared that for this  
16 deposition.

17 Q. So that's not an opinion that you're  
18 offering in your supplemental report, correct?

19 A. I don't believe I mentioned  
20 Dr. McConville in my supplemental report.

21 Q. In paragraph 5 you say that:  
22 "Petitioner's reply now asserts that a POSA  
23 should have experience in formulating dosage  
24 form," and at the end of the paragraph you  
25 called that a "new definition of a POSA." Do



1     you see that?

2             A.   Yes.

3             Q.   What is your basis for saying that's a  
4     new definition?

5             A.   Where do I use the word "new"?

6             Q.   In the very last line on page 2.

7             A.   (Reviewing document.)

8                     Okay, so can you repeat the question  
9     again?

10            Q.   Yes.  What is your basis for saying  
11     this definition is new?

12            A.   Well, it's not the same definition as  
13     in paragraph 4.

14            Q.   You understand that paragraph 4 is  
15     Atossa's definition and Atossa is the patent  
16     owner, right?

17            A.   This is one of the definition that I  
18     would use.

19            Q.   And paragraph 5 is about Petitioner.  
20     And you're saying Petitioner's definition is  
21     new, and I'm trying to understand why you're  
22     saying that Petitioner's definition is new?

23            A.   I don't remember seeing it before.

24            Q.   Did you read the petition?

25            A.   I don't recall.  I haven't looked at



1 what I've read previously other than what's in  
2 this report.

3 Q. So you don't recall one way or the  
4 other whether this definition of a POSA was in  
5 the petition?

6 A. I don't recall.

7 Q. Okay. I'm going to drop into the chat  
8 the petition, which is Paper 1 in this  
9 proceeding. Let me know when you have it open.  
10 Or if it's easier, I can share my screen.

11 A. It's probably easier if you'd share  
12 your screen.

13 Q. Sure. (Complying.)

14 All right, can you see my screen?

15 A. Yes.

16 Q. And you see page 9 of the petition?

17 A. Yes.

18 Q. And you see section D says "Person of  
19 ordinary skill in the art"?

20 A. Yes.

21 Q. And it states: "A POSA for purposes of  
22 the '334 patent is someone with a Ph.D. in  
23 pharmaceutical sciences or a closely related  
24 field and experience and research related to  
25 pharmaceutical dosage forms or someone with at



1     least a Bachelor's or Master's degree in  
2     pharmaceutical sciences and three to five years  
3     of practical experience in formulating drugs."

4             Did I read that correctly?

5             A.   I believe so.

6             Q.   So do you agree with me then that  
7     Petitioner's position that a POSA should have  
8     experience in formulating dosage forms is not a  
9     new opinion?

10            A.   Well, that's a different definition to  
11    the one that the Board adopted.

12            Q.   But you agree with me that Petitioner's  
13    definition of a POSA requiring experience in  
14    pharmaceutical dosage forms or formulating drugs  
15    is not new, right?  It was in the petition.

16            A.   Well, I can't remember the dates of all  
17    of these things when they came up.

18            Q.   Well, I just read the petition to you,  
19    right?

20            A.   Yes, but "new" in paragraph 4, it was  
21    produced after this.

22            Q.   You understand the petition is the  
23    first filing of this case, right?

24                    I'll withdraw the question.  I'll  
25    withdraw the question and move on.





1 Do you perform any research on  
2 pharmaceutical dosage forms such as capsules?

3 A. We have --

4 MS. KRUMPLITSCH: Object to form.

5 THE WITNESS: I have experience --

6 MS. KRUMPLITSCH: Sorry.

7 THE WITNESS: I have experience in  
8 formulating new compounds in the context of the  
9 compounds that my companies has produced.  
10 BY MR. MAHON:

11 Q. Has any of that experience involved  
12 capsules?

13 A. One of them has involved enteric-coated  
14 capsules, yes.

15 Q. And did you have any day-to-day role in  
16 the selection of the enteric-coated capsules?

17 A. Sorry, I didn't catch that question,  
18 the beginning.

19 Q. Did you have any day-to-day role in the  
20 selection of the enteric-coated capsules?

21 A. I believe I was the person who  
22 suggested it.

23 Q. Did you ever personally perform  
24 research on capsules?

25 A. I personally haven't done so, no.



1 Q. Moving on to paragraph 6 of your  
2 report.

3 A. Okay.

4 Q. And here you're beginning to discuss  
5 Dr. Bihovsky's laboratory work, correct?

6 A. Well, I say that he "attempted to  
7 perform synthetic and purification methods of  
8 Liu," yes.

9 Q. You didn't perform any laboratory work  
10 in this case, correct?

11 A. I did not, no.

12 Q. You did not attempt to carry out the  
13 teachings of Liu?

14 A. I wasn't asked to.

15 Q. And you didn't ask anyone to attempt to  
16 carry out the teachings of Liu, correct?

17 A. I did not, no.

18 Q. Can you pull out Liu Exhibit 1004 in  
19 this case as well as Dr. Bihovsky's reports?

20 A. Well, I have his reports on the  
21 experimental and his lab notebook and his NMR  
22 spectra.

23 Q. Let me clarify that a little bit. Can  
24 you pull up -- and I apologize. I used the term  
25 "report." I meant declaration.

1 Can you pull out the expert declaration  
2 of Ron Bihovsky, Ph.D.?

3 A. I have that, yes.

4 Q. And could you pull out -- it should be  
5 a Patent WO/2017070651 which I will refer to as  
6 "Liu."

7 A. I have that, yes.

8 Q. Okay. And can you go to page 13 of Liu  
9 and let me know when you're there?

10 A. Yeah, I'm there.

11 Q. In paragraph 61, example 1, Liu is  
12 testing different crystallization conditions on  
13 one-to-one mixtures of (Z)- and (E)-Endoxifen,  
14 correct?

15 A. He's working on the 50/50 mixture of  
16 those two compounds.

17 Q. And let me back up and ask a question.  
18 You're familiar with Liu, correct?

19 A. Yes.

20 Q. And going to page 14, in Example 2 Liu  
21 is teaching the synthesis -- and for the  
22 purposes of the court reporter I will call it a  
23 methanone intermediate -- is that fair?

24 A. In the time that I've had to look this  
25 over this page, that's what it says, yes.



1 Q. If you go to the next page,  
2 Example 3 --

3 A. Yes.

4 Q. -- Liu is forming a -- what I'll call a  
5 phenol intermediate; is that fair?

6 A. It is a phenol derivative in Example 3,  
7 yes.

8 Q. And in Example 4, beginning on page 16,  
9 Liu is converting that phenol derivative into a  
10 mixture of (E)- and (Z)-Endoxifen?

11 A. He is, yes.

12 Q. Is it fair to refer to Examples 2  
13 through 4 as "the synthesis of Liu"?

14 A. That's fair enough.

15 Q. In paragraph 70 on page 17, he reports  
16 the results of that synthesis, and it's  
17 Endoxifen with an E-Z isomer ratio of 51 to 47?

18 A. He made that synthesis here, yes,  
19 that's correct.

20 Q. So fair to say the synthesis of Liu  
21 results in a relatively even mixture of (E)- and  
22 (Z)-Endoxifen?

23 MS. KRUMPLITSCH: Objection, form.

24 THE WITNESS: They're close numbers.

25 It's roughly 50/50. The way it's written 51/47,



1 normally you'd have it adding up to a hundred.

2 BY MR. MAHON:

3 Q. Can you pull your report back out.

4 A. Okay.

5 Q. In paragraphs 8, 9 and 10 you're  
6 referring to Dr. Bihovsky's laboratory notebook,  
7 and you offer the opinion that "Dr. Bihovsky  
8 modified several steps of the Liu procedure."

9 A. He did, yes.

10 Q. In your opinion is it common for a  
11 person of skill in the art to modify a procedure  
12 when they carry it out?

13 MS. KRUMPLITSCH: Objection, form.

14 THE WITNESS: If you're given a  
15 procedure that you understand works, you would  
16 not expect to modify.

17 BY MR. MAHON:

18 Q. So if one of your students came back  
19 and said I blindly followed this reference  
20 exactly as written and I didn't get the same  
21 results, you would conclude that that reference  
22 is not successful?

23 A. I'd tell them to go do it again,  
24 actually.

25 Q. And would you instruct them to make



1 commonsense modifications?

2 MS. KRUMPLITSCH: Object to form.

3 THE WITNESS: No, I would expect it to  
4 work. That's the whole point of publishing  
5 experimental procedures in papers is you expect  
6 people to be able to report -- to repeat them.

7 BY MR. MAHON:

8 Q. And, now, you agree Dr. Bihovsky  
9 performed the synthesis of Liu at a smaller  
10 scale, correct?

11 A. A very small scale, about 1000 to 2000  
12 times smaller.

13 Q. Because Liu is an industrial scale,  
14 correct?

15 A. Yeah, it's a large scale. It could be  
16 used on industrial, yeah.

17 Q. And so the person of skill who is  
18 conducting Liu at a smaller scale, you would  
19 expect them to have to make some minor  
20 modifications, right?

21 A. Well, you'd expect them to have to try  
22 and do as close as possible to Liu.

23 Q. In paragraph 10 you refer to  
24 Dr. Bihovsky increasing the heat to 75 degrees  
25 as a deviation from Liu, right?



1           A. Well, I don't -- well, I believe he  
2     got -- he didn't get the reaction of the  
3     temperatures that Liu suggested, and therefore,  
4     had to increase the temperature. So temperature  
5     shouldn't make a difference between two things  
6     reacting.

7           Q. You agree with me that one way to drive  
8     a reaction to completion is to increase the  
9     temperature?

10          A. It depends. So I agree that if it was  
11     a simple reaction, you increase the temperature  
12     by 10 degrees, you double the rate roughly. But  
13     that doesn't mean that it works all the time  
14     because if your reaction has other products that  
15     could be made, you also increase the amount of  
16     byproducts you produce by increasing the  
17     temperature.

18          Q. Do you agree with me the reaction that  
19     Dr. Bihovsky was performing was exothermic?

20          A. I'd have to check his notebook to see  
21     what he said.

22          Q. Let me direct you to something. In  
23     paragraph 9, you're quoting paragraph 62 of Liu  
24     and you say "phosphorus tribromide was added via  
25     an addition funnel over a period of 2.5 hours at



1 a rate as to keep temperature below 50 degrees  
2 Celsius."

3 Do you see that?

4 A. That's what it says, yes.

5 Q. A POSA would understand that he is  
6 adding phosphorus tribromide to keep the  
7 temperature below 50 degrees because the action  
8 is exothermic, correct?

9 A. That's correct.

10 Q. And a POSA would understand that the  
11 effects of an exothermic reaction are larger --  
12 at a larger scale; is that fair?

13 MS. KRUMPLITSCH: Objection, form.

14 THE WITNESS: They're harder to control  
15 than -- the amount of heat that is generated per  
16 mol is different from whatever scale you're  
17 doing it on. But if you're doing it on a  
18 smaller scale, then the heat can be dissipated  
19 much faster than it could doing it on a very  
20 large scale.

21 BY MR. MAHON:

22 Q. So if the reaction was not proceeding,  
23 heating would be a commonsense modification to a  
24 POSA at small scale, right?

25 MS. KRUMPLITSCH: Objection, form.





1 THE WITNESS: It depends on the  
2 reaction. So phosphorus tribromide is very  
3 reactive, so you expect it to react at any  
4 temperature above room temperature.

5 BY MR. MAHON:

6 Q. But would you agree with me that if  
7 your reaction is not proceeding on a small  
8 scale, one thing a POSA would think to do would  
9 be to increase the temperature to drive the  
10 reaction to completion?

11 A. Well, the increase in the temperature  
12 Liu has suggest is not a good idea. That's why  
13 he keeps it below 50 degrees.

14 Q. And next you refer to a calcium  
15 chloride drying tube?

16 A. Where is that? I see, in paragraph 10.  
17 Okay.

18 Q. Correct?

19 A. Yes.

20 Q. What is a calcium chloride drying tube?

21 A. It's a tube you put on the exit part of  
22 your apparatus that contains calcium chloride,  
23 and it's there to stop moisture ingress from the  
24 atmosphere.

25 Q. And is it a commonly-used piece of



1 equipment?

2 A. It's commonly used if you want to keep  
3 moisture out of your reaction mixture. But  
4 there are many reactions where small amounts of  
5 water make the reaction go, and putting on the  
6 calcium chloride drying tube would actually stop  
7 the reaction.

8 Q. So you said it's commonly used if you  
9 want to keep moisture out of your reaction  
10 mixture?

11 A. That's right.

12 Q. Would you agree that you typically want  
13 to keep moisture out of your reaction mixture  
14 when you have moisture-sensitive materials?

15 MS. KRUMPLITSCH: Objection, form.

16 THE WITNESS: Not necessarily because,  
17 as I've just said, you may want a small amount  
18 of water in there, which in this case would  
19 generate a small amount of acid and you might  
20 want that to actually catalyze the reaction to  
21 go.

22 BY MR. MAHON:

23 Q. So you might want that or you might not  
24 want that, right?

25 A. Well, I don't believe Liu says put

1 moisture control on the apparatus.

2 Q. Zinc bromide, which Liu is using, is  
3 known to be water sensitive, right?

4 A. Slightly, yes.

5 Q. Would you agree with me it would be  
6 routine to run a reaction using zinc bromide  
7 with the calcium chloride drying tube?

8 A. No. I've just said it depends on the  
9 reaction.

10 Q. So do you disagree that calcium  
11 chloride drying tubes are commonly used with  
12 moisture-sensitive materials such as zinc  
13 bromide?

14 A. I said it depends on the reaction. And  
15 Liu does not suggest that you need to do that,  
16 and so it may well be that Bihovsky started to  
17 get the reaction to go to the tube, so not  
18 allowing a bit of water to get in.

19 Q. And Dr. Bihovsky ultimately got the  
20 reaction to go, right?

21 A. Sorry?

22 Q. Dr. Bihovsky ultimately got the  
23 reaction to go?

24 A. Yes. At a lower yield, yes.

25 Q. And you don't offer any opinion that an

1 ordinary person of skill in the art could not  
2 have made the modifications that Dr. Bihovsky  
3 did, do you?

4 A. I say a person of ordinary skill would  
5 not expect to have to make such modifications,  
6 and if it's not stated in Liu, it may well be  
7 that you need a bit of moisture in there.

8 Q. You don't offer the opinion that  
9 anything that Dr. Bihovsky did was beyond the  
10 ordinary skill in the art, do you?

11 A. I'm saying he didn't follow Liu's  
12 procedures, and therefore, didn't get the  
13 yields, et cetera that Liu managed to optimize  
14 his reaction to get.

15 Q. I understand that, but you're not  
16 answering the question that I'm asking.

17 You're not offering any opinion that  
18 anything that Dr. Bihovsky did was beyond the  
19 ordinary skill in the art. Are you?

20 A. Well, a person of ordinary skill could  
21 do those types of experiments with those  
22 modifications, but I'm not sure they'd be  
23 motivated to do so.

24 Q. When you say "Finally, Dr. Bihovsky  
25 purified the reaction product by chromatography

1 on silica gel" and that "Liu does not disclose  
2 this" --

3 A. Whereabouts is that?

4 MS. KRUMPLITSCH: Sorry, what paragraph  
5 are we at?

6 MR. MAHON: Paragraph 10 still. I  
7 apologize.

8 MS. KRUMPLITSCH: Thank you.

9 THE WITNESS: (Reviewing document.)

10 BY MR. MAHON:

11 Q. I believe it's the third sentence.

12 A. Liu does not suggest you should use  
13 silica gel chromatography in his reaction.

14 Q. Liu does at a later step teach using  
15 chromatography on silica gel to purify, right?

16 A. I believe so, yes.

17 Q. So Dr. Bihovsky simply performed this  
18 purification step twice, correct?

19 A. No, he performed it on a completely  
20 separate reaction.

21 Q. Would you agree with me that it's  
22 common for a person skilled in the art to purify  
23 a reaction after every stage?

24 MS. KRUMPLITSCH: Objection, form.

25 THE WITNESS: Not if you want to



1 maximize the yield. What you actually want to  
2 try and do is called telescoping. What you want  
3 to do is to avoid trying to purify at every step  
4 because your yield will go down. So to maximize  
5 the yield through a process, you try to move  
6 stuff on with a minimum of purification.

7 BY MR. MAHON:

8 Q. If you perform more purification steps,  
9 you're going to increase the purity at those  
10 stages, but decrease the yield; is that fair?

11 A. Not always.

12 MS. KRUMPLITSCH: Objection.

13 THE WITNESS: Not always because if you  
14 can purify to the required standard at the end,  
15 it didn't matter whether you purified or not on  
16 the intermediate steps. That's the whole point  
17 of trying to get a telescope set of reactions,  
18 so that you can go quickly from one to the other  
19 without the need to purify on Liu's material.

20 BY MR. MAHON:

21 Q. Let's turn to paragraph 11 of your  
22 report.

23 A. Okay.

24 Q. And you say: "Further modifications  
25 including using a nitrogen bubbler, oven-drying

1 the zinc bromide starting material at 230  
2 degrees Celsius, and filtering the reaction  
3 mixture over Celite, right?

4 A. Yes.

5 Q. And you say: "These modifications are  
6 neither taught nor suggested by Liu."

7 A. They're not.

8 Q. And you agree it's common to place  
9 reactions involving moisture-sensitive materials  
10 under nitrogen using a nitrogen bubbler?

11 MS. KRUMPLITSCH: Objection, form.

12 THE WITNESS: It's an alternative to  
13 calcium chloride drying tubes, and so my  
14 comments are going to be the same, that it  
15 depends on your reaction. You only do that if  
16 you need it.

17 Liu doesn't suggest you need it. And  
18 as I've said already, that a small amount of  
19 water can catalyze reactions and actually make  
20 them go better.

21 BY MR. MAHON:

22 Q. If you can pull Liu back up.

23 A. Okay.

24 Q. If you can turn to page 13,  
25 paragraph 61.

1 A. Okay.

2 Q. I apologize. Paragraph 60.

3 A. Okay.

4 Q. And he says: "The reagents and  
5 solvents used were commercially anhydrous  
6 grade," right?

7 A. That's correct.

8 Q. And would you agree with me that  
9 oven-drying zinc bromide starting material at  
10 230 degrees Celsius would help ensure that it  
11 was anhydrous?

12 A. You're going to have to -- I mean, zinc  
13 bromide will react with water to give you zinc  
14 oxide and hydrogen bromide. If you heat it to  
15 230 degrees, you will drive up the hydrogen  
16 bromide, not the water. And if your reaction is  
17 actually catalyzed, then that will stop the  
18 reaction going.

19 Q. You'll agree you would use anhydrous  
20 reagents to prevent water from being introduced,  
21 right?

22 MS. KRUMPLITSCH: Objection, form.

23 THE WITNESS: Well, what it does is  
24 limit the amount of water. Water can come in  
25 other ways.





1 BY MR. MAHON:

2 Q. Well, by teaching that you should use  
3 anhydrous materials, Liu is teaching the person  
4 of ordinary skill in the art to avoid the  
5 introduction of water, isn't he?

6 A. He leaves off the nitrogen bubblers and  
7 calcium chloride, so he's not worried about the  
8 ingress of water, small amounts of water from  
9 the atmospheric air.

10 Q. Do you agree with me that a person of  
11 skill in the art would consider oven drying zinc  
12 bromide to -- let me withdraw the question and  
13 start again.

14 Do you agree with me that a person of  
15 skill in the art would understand that the  
16 purpose of oven-drying zinc bromide was an  
17 attempt to make it anhydrous?

18 A. I just said I don't think it would be.  
19 It would be hydrated anyway. What you're doing  
20 is removing HBR, hydrogen bromide. It's a gas.  
21 You'd be removing that.

22 Q. In paragraph 11 you say that  
23 Dr. Bihovsky refers to filtering the reaction  
24 mixture over Celite, C-E-L-I-T-E.

25 A. Yes.



1 Q. What is Celite?

2 A. It's an inorganic material that's very  
3 fine and you can use it as a filtering agent, it  
4 stops -- stop coating and you could filter your  
5 reaction mix using Celite.

6 Q. And Liu teaches filtering the material,  
7 right?

8 MS. KRUMPLITSCH: Objection, form.

9 THE WITNESS: You'd have to show me  
10 where that is for this particular reaction too.  
11 BY MR. MAHON:

12 Q. Sure. If you go to paragraph 61.

13 A. Yeah. (Reviewing document.)

14 Okay, so he filters, which would be  
15 through an obvious sort of source. It's  
16 actually a mechanical filter.

17 If you use Celite, then again you  
18 lose -- you'll end up losing materials. It goes  
19 through the Celite. You coat the Celite with  
20 the material.

21 Q. You agree with me Liu is teaching to  
22 filter and Dr. Bihovsky used Celite to filter,  
23 right?

24 A. It's a different way of doing it. It  
25 doesn't necessarily make it a better way.

1 Q. Sure, I'm just -- you're describing it  
2 as a deviation.

3 A. It is a deviation because you're mixing  
4 your material up with Celite and then filtering  
5 out with more Celite, the way it's normally  
6 done, and you risk losing yield.

7 Q. Do you know what way Liu used the  
8 filter?

9 MS. KRUMPLITSCH: Objection.

10 THE WITNESS: Well, he doesn't say with  
11 Celite. If he added something, it would be --  
12 he would say so.

13 BY MR. MAHON:

14 Q. But you don't know what material he  
15 used to filter?

16 A. I would expect him to use a Cidlite  
17 (phonetic) based on that grade.

18 Q. But you don't know that?

19 A. Well, if he used anything else, by  
20 adding something like silica gel, Celite,  
21 alumina, he would say so.

22 Q. Let's go to paragraph 13.

23 A. Okay.

24 Q. In here you're addressing Example 3  
25 from Liu for the second step of the synthetic



1 method?

2 A. It's Example 3 of Liu, yes.

3 Q. In paragraph 14, you say: "It is not  
4 specified in Dr. Bihovsky's laboratory notebook  
5 whether the zinc used was zinc dust."

6 You have no reason to believe he did  
7 not use zinc dust?

8 A. Well, he doesn't tell me. So you can  
9 have zinc dust, you can have zinc turnings, you  
10 can have zinc metal. There are several forms of  
11 commercial zinc that are used in reactions.

12 Q. But you don't know one way or the other  
13 which type of zinc he used?

14 A. I know what Liu used. I don't know  
15 what Bihovsky used.

16 Q. Fair to say you also don't know whether  
17 the dimethoxy ethane used was anhydrous?

18 A. I don't know that. He doesn't specify.

19 Q. Can you pull out Dr. Bihovsky's  
20 notebook?

21 A. Okay.

22 Q. And can you go to page 24? And I'm  
23 referring to the page numbers in the upper  
24 corners.

25 A. Okay.

1 MS. KRUMPLITSCH: I'm sorry to  
2 interrupt. Ben, this is not an exhibit. Do you  
3 want to mark it --

4 MR. MAHON: Oh, yeah.

5 MS. KRUMPLITSCH: -- and put that in  
6 the record.

7 MR. MAHON: Sorry.

8 (Davies Exhibit 1 was marked  
9 for ID.)

10 MS. KRUMPLITSCH: Sorry to interrupt.

11 MR. MAHON: No, no problem. I dropped  
12 it into the chat. And it might be easier here  
13 if I share my screen again. How you made any  
14 sense of his writing, I have no idea.

15 THE WITNESS: It's a mess.

16 BY MR. MAHON:

17 Q. Does everybody have the notebook up  
18 ready?

19 A. I do.

20 Q. Okay. And I'm going to highlight on  
21 the screen here the first full line. It says  
22 "DME."

23 A. You're not sharing your screen with me.

24 Q. Sorry. Now can you see it?

25 A. Yeah.



1 Q. All right, and the DME is dimethoxy  
2 ethane, right?

3 A. I assume so in this case because he's  
4 following Liu. Pardon me, I've seen he's  
5 following Liu.

6 Q. And this is a bit hard to read here,  
7 but do you agree with me that this says "13 mol  
8 3A sieve"?

9 A. I don't see how -- that looks like  
10 3A mol silica gel, SG, to me.

11 Q. Would you agree with me that a 3A sieve  
12 is a way to make DME anhydrous?

13 A. I don't know that that's true.

14 Q. Are you familiar with the term "3A  
15 sieve"?

16 A. I am familiar with the term 3A  
17 molecular sieves, yes, but they don't -- they  
18 absorb water in an equilibrium process and a lot  
19 of solvents, the equilibrium actually lies with  
20 the water in the solvent, particularly where the  
21 solvent has a lot of oxygen atoms, in this case  
22 two dimethoxy ethane. So I'm not sure if that  
23 would be -- if that does actually state it, but  
24 that would actually dry down the dimethoxy  
25 ethane.



1 Q. You don't have any reason to doubt that  
2 Dr. Bihovsky attempted to make the DME  
3 anhydrous, do you?

4 MS. KRUMPLITSCH: Objection, form.

5 THE WITNESS: Well, as I said, I didn't  
6 read that as saying sieve. If he put that in  
7 there, that doesn't mean he actually made it  
8 anhydrous.

9 BY MR. MAHON:

10 Q. But you just don't know one way or the  
11 other whether he made it anhydrous?

12 A. I don't know whether he's written  
13 "sieve" there. I don't know whether he's  
14 managed to make it anhydrous or just added water  
15 to it from the 3A molecular sieve.

16 Q. And you also say: "It is not clear  
17 whether Dr. Bihovsky allowed the reaction  
18 mixture to stir overnight at ambient  
19 temperature."

20 Do you see that in paragraph 14?

21 A. Ah... (reviewing document.)

22 Yeah, okay.

23 Q. Now I'm going to highlight again. It's  
24 about ten rows down in Dr. Bihovsky's notebook.  
25 It's a little bit hard to read here, but he says

1 I believe, "Set at RT," and then next line  
2 "O.N."?

3 A. Yeah.

4 Q. Do you agree with me that a plausible  
5 reading of that is set at room temperature  
6 overnight?

7 MS. KRUMPLITSCH: Object to form.

8 THE WITNESS: It could be. Not clear.

9 BY MR. MAHON:

10 Q. Turn to paragraph 16 of your report.

11 A. Okay.

12 Q. And Dr. Bihovsky acknowledged that he  
13 used centrifugation rather than filtration,  
14 correct?

15 A. Yes.

16 Q. Do you agree with me that using  
17 centrifugation rather than filtration is a  
18 reasonable modification when running a reaction  
19 at small scale?

20 A. It's one way you can do it on a small  
21 scale, but -- you can't do it on a large scale,  
22 but if you use centrifugation instead of  
23 filtration, then you are liable -- there's a  
24 different reaction profile, a different product  
25 profile because if you're filtering, to filter





1     that amount on a large scale, it takes quite  
2     awhile and the reaction is or the  
3     crystallization or whatever you're looking at  
4     will still be going on during the filtration  
5     step. If you centrifuge, it's over very  
6     quickly.

7           Q. In paragraph 16 of your report you  
8     didn't offer -- excuse me. Let me start again.

9           Paragraph 16 of your supplemental  
10    declaration, you didn't offer any opinion that  
11    using centrifugation affected Dr. Bihovsky's  
12    results, did you?

13          A. Well, the whole point of my saying that  
14    these processes are different is that they will  
15    affect the results of the experiments.

16          Q. But you didn't say that in  
17    paragraph 16, did you?

18          A. I believe it's implied throughout my  
19    whole report. The reason that these things  
20    don't work the same way is because they're done  
21    through a different process.

22          Q. And you described how centrifugation  
23    could affect results on a larger scale, right?

24          A. Well, you can't do it on a large scale.

25          Q. But Dr. Bihovsky ran it on a small

1 scale, right?

2 A. Right. Which is why he doesn't  
3 reproduce the results that were got by Liu on  
4 the larger scale.

5 Q. If you'd go back to Liu, paragraph 70.

6 A. Yep. Okay, I'm there.

7 Q. And as we talked about earlier, the  
8 conclusion of the synthesis of Liu, he obtains  
9 an easy isomer ratio of 51 to 47?

10 A. That's correct, an 87 percent yield.

11 Q. And can you pull up Dr. Bihovsky's  
12 declaration?

13 A. Okay.

14 Q. And I'll drop that in the chat as well.  
15 Can you go to paragraph 39.

16 A. It doesn't have paragraphs. Oh, so --

17 Q. Not in his notebook, sorry, in his  
18 expert declaration.

19 A. Expert declaration, 39. Okay.

20 Q. And he describes obtaining a 48 to 52  
21 ratio of (Z)- to (E)-Endoxifen, correct?

22 A. That's what he says, yeah.

23 Q. You'd agree with me that's quite close  
24 to the 51/47 E-to-Z ratio obtained by Liu?

25 A. It is. But what was the yield?



1 Q. In paragraph 39 he reports a yield of  
2 82 percent, correct?

3 A. In paragraph which one?

4 Q. In paragraph 39, the first line.

5 A. (Reviewing document.)

6 Well, yeah, that's a pre-drying yield.  
7 So you don't know what the actual final yield  
8 was.

9 Q. But you agree with me he obtained  
10 material with a similar E-to-Z ratio as Liu,  
11 correct?

12 A. At that stage, yes, if that's what his  
13 notebook says. So where in his notebook is  
14 that?

15 Q. I believe he refers to the numbers, but  
16 I don't think there's a pending question.

17 MR. MAHON: Why don't we go ahead and  
18 take a quick break here. I think we're about,  
19 hopefully, halfway without any promises.

20 THE WITNESS: Okay.

21 MS. KRUMPLITSCH: How long do you want  
22 to break for?

23 MR. MAHON: Five minutes. But if you  
24 want longer... I don't think we're going to go  
25 particularly long.



1 MS. KRUMPLITSCH: Okay, Dr. Davies,  
2 five, ten minutes, what do you prefer?

3 THE WITNESS: Five minutes is fine.

4 MS. KRUMPLITSCH: Okay. Thanks,  
5 everyone.

6 (Recess taken from 8:59 a.m.  
7 to 9:08 a.m.)

8 BY MR. MAHON:

9 Q. Let's turn to paragraph 17 of your  
10 supplemental declaration.

11 A. I'm there.

12 Q. And, now, you're referring to Example 5  
13 of Liu, right?

14 A. That's correct.

15 Q. And Example 5 is where Liu begins the  
16 purification processes?

17 A. That's correct.

18 Q. And can you pull Liu back out?

19 A. Yes.

20 Q. And Example 5 begins or consists  
21 entirely of paragraph 72 of Liu, right?

22 A. (Reviewing document.)

23 Of the 50/50 mixture, yes.

24 Q. So he begins with a 50/50 mixture and  
25 he performs a recrystallization and he reports a



1 crystalline material with an E-Z ratio of 68 to  
2 30, right?

3 A. That's what it says, yes.

4 Q. So he's removing a lot of the  
5 (E)-Endoxifen into the solid form, right?

6 MS. KRUMPLITSCH: Objection, form.

7 THE WITNESS: Well, he's only got about  
8 half of the material -- 49 -- he's got  
9 49 percent of the material. So he's certainly  
10 removing some of the E into the solid, but I  
11 wouldn't say it's a huge amount.

12 BY MR. MAHON:

13 Q. In the last sentence of paragraph 72,  
14 he's taking the filtrate and he's concentrating  
15 it to get a solid which is enriched with the  
16 Z-isomer with an E-Z ratio of 19 to 77, correct?

17 A. That's what he says, yes.

18 Q. Then turning to Example 6, Example 6 is  
19 an isomerization reaction, right?

20 A. That's correct.

21 Q. What does isomerization mean?

22 A. You equilibrate to isomers. So it's a  
23 reaction to equilibrate the E- and Z-isomers in  
24 this case.

25 Q. In paragraph 73, he begins with



1 Endoxifen with an E-Z ratio of about 70 to 30,  
2 right?

3 A. That's what it says, yes.

4 Q. So that's similar to the first solid  
5 material that he removed in Example 5, right?

6 A. That's correct.

7 Q. And he heats that material, and he now  
8 has an E-Z ratio of approximately 1 to 1, right?

9 A. That's what he says, yes.

10 Q. So he has converted some of that  
11 (E)-Endoxifen into (Z)-Endoxifen?

12 A. And vice versa until he reaches an  
13 equilibrium mixture which is roughly 1 to 1.

14 Q. But if the starting material was  
15 70 percent E and the ending material is  
16 50 percent E, there's been a net conversion of  
17 E to Z, right?

18 A. Overall, that's what you see.

19 Q. And then he crystalizes out the  
20 E-isomer?

21 A. Some of it.

22 Q. Some of the E-isomer, leaving mother  
23 liquor which then evaporates, retaining material  
24 with a Z content of 73 percent?

25 A. That's what he says, yes.



1 Q. And he repeats the process twice. So  
2 he gets two more batches of material with the  
3 Z-isomer content of 71 percent and 69 percent in  
4 paragraph 74?

5 A. That's what he says, yes.

6 Q. So both Examples 5 and 6 obtain  
7 materials that are enriched in Z-isomer but not  
8 yet 90 percent pure Z, right?

9 MS. KRUMPLITSCH: Objection, form.

10 THE WITNESS: (Reviewing document.)

11 They're enriched in E-Z because he's  
12 taken out some of the E.

13 BY MR. MAHON:

14 Q. But in Example 5 he obtained a sample  
15 that was 77 percent Z, right?

16 A. Well, he has an E-to-Z ratio of 19 to  
17 87 -- to 77.

18 Q. (Inaudible.)

19 A. I think you're on mute.

20 Q. Apologies.

21 And in Example 6, he has made different  
22 batches of Z-enriched Endoxifen, right?

23 MS. KRUMPLITSCH: Objection, form.

24 THE WITNESS: Well, he's repeating the  
25 experiment and crystalizing out some E.



1 BY MR. MAHON:

2 Q. Let me ask the question a different  
3 way. The Z-enriched material that he obtains in  
4 Example 5 which we said had an E-to-Z ratio of  
5 19 to 77, he's not using that material in  
6 Example 6, right?

7 MS. KRUMPLITSCH: Objection, form.

8 THE WITNESS: He's not, no.

9 BY MR. MAHON:

10 Q. So at the conclusion of Example 6, Liu  
11 has generated a material that has an E-to-Z  
12 ratio of 19 to 77, which you got from Example 5,  
13 and then he's got the three different batches  
14 that he describes making in Example 6, right?

15 MS. KRUMPLITSCH: Objection, form.

16 THE WITNESS: (Reviewing document.)

17 Well, he's doing two -- he's doing both  
18 crystallization in Example 5, and then he's  
19 doing the isomerization and crystallization in  
20 paragraphs 73, 74 and 75 and gets different  
21 results for each of them, all of which are  
22 enhanced in the Z.

23 BY MR. MAHON:

24 Q. Examples 5 and 6 are two different  
25 pathways to obtain Z-enriched Endoxifen, right?





1           A. I don't know what you mean by  
2     "different pathways" because Example 5 starts on  
3     a 50/50 mixture and Example 6 generates a 50/50  
4     mixture to start with and then you repeat the  
5     same process as in Example 5.

6           Q. But you'd agreed with me, right, that  
7     the enriched (Z)-Endoxifen from Example 5 is not  
8     used in Example 6?

9           A. Well, the partially enriched one -- no,  
10    because he's using the E-enriched material, yes,  
11    but he ends up -- the first step is to make a  
12    50/50 mixture again, so the purification is the  
13    same as the last step in Example 5.

14          Q. But Example 5 generated an Endoxifen  
15    material that was Z-enriched with an E-to-Z  
16    ratio of 19 to 77?

17          A. That's correct.

18          Q. And Example 6 takes the left-overs from  
19    Example 5 and generates a new batch of  
20    Z-enriched Endoxifen, right?

21                 MS. KRUMPLITSCH: Objection, form.

22                 THE WITNESS: I think that  
23    mischaracterizes what he's doing. What he does  
24    is turns the E-enriched material into a 1-to-1  
25    mixture, so he's back to the same starting point



1 as he was in Example 5.

2 BY MR. MAHON:

3 Q. Turning to Example 7 of Liu, he's  
4 recrystallizing the Endoxifen mixture that is  
5 enriched in Z-isomer, correct?

6 A. That's what he says.

7 Q. And he begins with material that has an  
8 E-to-Z ratio of approximately 30 to 70, right?

9 A. That's what he says.

10 Q. Now, that material could be the  
11 material he generated in Example 6, right?

12 MS. KRUMPLITSCH: Give me time.

13 Objection, form.

14 THE WITNESS: (Reviewing document.)

15 You can't tell exactly the same measure  
16 or not exactly the same measure.

17 BY MR. MAHON:

18 Q. But a person of skill in the art would  
19 also understand from Liu that you could take a  
20 19 to 77 E-to-Z ratio material if you generate  
21 it in Example 5 and enrich that or recrystallize  
22 that following Example 7, right?

23 MS. KRUMPLITSCH: Objection, form.

24 THE WITNESS: I don't think that's an  
25 experiment that Liu describes.



1 BY MR. MAHON:

2 Q. Let's come back to that. Can you pull  
3 Dr. Bihovsky's expert declaration back up.

4 A. Okay.

5 Q. Can you turn to page 28.

6 A. Okay.

7 Q. And Section 2 is titled Sequential  
8 Recrystallizations, right?

9 A. That's correct.

10 Q. And in paragraph 41 he describes  
11 following paragraph 72 of Liu, right?

12 A. (Reviewing document.)

13 Sorry, could you repeat that question?

14 Q. Yes. In paragraph 41, Dr. Bihovsky  
15 says: "I then dissolved this precipitate in  
16 refluxing isopropyl acetate with stirring for  
17 one hour then cooled slowly then stored at  
18 23 degrees C for six hours Id at paragraph 72."  
19 Right?

20 A. Yes, that's what he says.

21 Q. And what he means by that is that he is  
22 following paragraph 72 of Liu, right?

23 MS. KRUMPLITSCH: Objection, form.

24 THE WITNESS: Well, Liu doesn't say how  
25 long he heated the mixture to start with before



1 cooling it for six hours.

2 BY MR. MAHON:

3 Q. Would you agree with me in paragraph 41  
4 Dr. Bihovsky is replicating what is taught in  
5 Liu paragraph 72?

6 A. Well, Liu doesn't say he let it sit for  
7 an hour. He just says dissolved it at  
8 88 degrees.

9 Q. Fair. So Dr. Bihovsky has to take the  
10 time for dissolving it, right, because Liu does  
11 not specify a time?

12 MS. KRUMPLITSCH: Object to form.

13 THE WITNESS: Well, Dr. Bihovsky  
14 doesn't say what was going on during that hour.  
15 Did he take an hour to dissolve or did he just  
16 heat it for an hour?

17 BY MR. MAHON:

18 Q. What does refluxing mean?

19 A. Heat at boiling point.

20 Q. And do you agree that the boiling point  
21 of isopropyl acetate is approximately  
22 88 degrees?

23 A. It's about that, yeah.

24 Q. And then Dr. Bihovsky cools slowly and  
25 stores at 23 degrees C and keeps it for six



1 hours, right? And that's what's taught in Liu,  
2 paragraph 72?

3 A. I would say --

4 MS. KRUMPLITSCH: Objection -- sorry,  
5 Dr. Davies.

6 Objection, form.

7 THE WITNESS: The second bit is that he  
8 described the cooling and kept for six hours,  
9 but the first bit, there's no time. So you  
10 don't know what difference that's going to make  
11 because we know that these things aren't  
12 summarized, and yet he put -- (reviewing  
13 document.)

14 BY MR. MAHON:

15 Q. Now, turning to paragraph 42,  
16 Dr. Bihovsky describes drying the filtrate he  
17 obtained from paragraph 41 and suggesting that  
18 recrystallization is taught by Liu, Example 7,  
19 right?

20 A. So where's that in Bihovsky's report?

21 Q. Page 289, paragraph 42.

22 A. (Reviewing document.)

23 That's what he says, yes.

24 Q. So in the sequential recrystallization  
25 experiment, Dr. Liu carries out Example 5 of



1 Liu, takes the Z-enriched Endoxifen and subjects  
2 it to Example 7 of Liu, correct?

3 A. (Reviewing document.)

4 Q. And just to clarify the record, let me  
5 ask the question again. I think I said Dr. Liu  
6 instead of Bihovsky.

7 In the sequential recrystallization  
8 experiment described in paragraphs 40, 43 of  
9 Dr. Bihovsky's declaration, he is carrying out  
10 Example 5 of Liu, taking the Z-enriched  
11 Endoxifen that he gets and subjecting it to  
12 Example 7 of Liu, correct?

13 A. (Reviewing document.)

14 That appears to be what he's doing.

15 Q. Turning to page 30 of Dr. Bihovsky's  
16 declaration.

17 A. Okay.

18 Q. And in Section 3, Dr. Bihovsky is  
19 describing performing the isomerization  
20 reactions taught in Liu, right?

21 A. I think he's doing an isomerization  
22 reaction again, yes.

23 Q. In paragraph 45, he says he takes the  
24 crystalline -- last sentence -- "the crystalline  
25 precipitate enriched in (E)-Endoxifen provided



1 from Liu's process taught in paragraph 72 was  
2 subjected to the isomerization procedure taught  
3 by Liu's Example 6." Right?

4 A. (Reviewing document.)

5 Where does he say Example 6?

6 Q. At the very last line on page 30.

7 A. Oh, yes. (Reviewing document.)

8 Okay, that's what he says.

9 Q. In paragraphs 46 and 47 he describes  
10 the isomerization reactions?

11 A. (Reviewing document.)

12 He seems to get the same ratio after  
13 the end as he does at the start. Because he  
14 starts at 5 to 95 Z to E and ends up with 5 to  
15 95 Z to E. That's no isomerization at all, is  
16 it?

17 Q. Well, that's not quite my question. So  
18 let me ask it a different way.

19 We agreed in paragraph 45 that he says  
20 he's carrying out the isomerization procedure  
21 taught by Liu's Example 6, right?

22 MS. KRUMPLITSCH: Objection to form.

23 THE WITNESS: Well, he's trying to,  
24 yeah.

25



1 BY MR. MAHON:

2 Q. And he's trying to carry out that  
3 process we described, how he's trying to carry  
4 out that process in paragraphs 46 and 47, right?

5 A. (Reviewing document.)

6 That's what he's trying to do, yeah,  
7 I'll give you that.

8 Q. And at the end of paragraph 46 he  
9 describes "NMR indicated a 69-to-31 ratio of  
10 Z-to-E Endoxifen," right?

11 A. That's what he says.

12 Q. And paragraph 47 he repeats the  
13 isomerization procedure two times as taught by  
14 Liu's paragraph 74?

15 A. That's what he says.

16 Q. And in paragraphs 48 he describes  
17 combining the materials he "obtained from the  
18 evaporation of the filtrates from the two  
19 isomerization reactions and subjects the mixture  
20 to recrystallization from acetone to produce a  
21 material further enriched in (Z)-Endoxifen as  
22 taught by Liu's Example 7," right?

23 A. That's what he's saying.

24 Q. So in the Section 3, the isomerization  
25 section, Dr. Bihovsky describes following Liu's





1 Examples 6 and 7, correct?

2 MS. KRUMPLITSCH: Objection, form.

3 THE WITNESS: It appears that he's  
4 trying to follow those procedures.

5 BY MR. MAHON:

6 Q. And in paragraph 49 he shows the  
7 purification scheme that he used that's taught  
8 by Liu, and he provides a chart in paragraph 33,  
9 right, on page 33?

10 A. There is a chart there, yes.

11 MS. KRUMPLITSCH: Object to form.

12 BY MR. MAHON:

13 Q. And that chart shows two different  
14 procedures, right?

15 A. What do you mean by two procedures?  
16 What he's doing is showing different routes for  
17 the products of one reaction.

18 Q. Sure. So he shows two different  
19 routes, right?

20 A. Well, you're taking different starting  
21 materials, so they're two different processes.

22 Q. And the process on the left is what he  
23 refers to as "the sequential recrystallization  
24 process," right?

25 A. Where does he say it's a sequential



1 process? Oh, yes, I've got it okay. (Reviewing  
2 document.)

3 So that's his sequential one, yes.

4 Q. And on the right he is showing what he  
5 referred to as "the isomerization process,"  
6 right?

7 A. So there it summarizes the mostly  
8 E form and then does a recrystallization.

9 Q. So there were two different processes  
10 that he performed, and both of them resulted in  
11 (Z)-Endoxifen at a ratio of greater than  
12 90 percent, right?

13 MS. KRUMPLITSCH: Objection, form.

14 THE WITNESS: They're not two different  
15 processes. They're the same process because  
16 he's making the 69 to -- well, 70/30 mixture,  
17 roughly, in both of those processes.

18 BY MR. MAHON:

19 Q. So Dr. Bihovsky identifies the  
20 materials at the different stages of each of  
21 those processes using a numbering system  
22 beginning with 15 dash other numbers, right?

23 A. The numbers on the left, yes.

24 Q. And you understand that those refer to  
25 numbers that are in his notebook, right?

1           A. I believe so, yes. They're not  
2       separate processes. When you say they're two  
3       processes, it's the same process.

4           Q. What would be your preferred term for  
5       referring to these two different paths that are  
6       taken?

7           A. They're not two different paths because  
8       they all start from roughly a 1-to-1 mixture.

9           Q. I guess I'm little confused because I  
10      referred to them as "two routes." I believe you  
11      said -- well, you're talking different starting  
12      materials, so there's two different processes,  
13      and now you're saying they're not different  
14      processes. So I'm confused. Can you clarify?

15          A. Well, there's an additional step, which  
16      is the isomerization, but that just turns the  
17      material back to what you started with, the  
18      crude Endoxifen at the top.

19          Q. So Dr. Bihovsky begins with crude  
20      Endoxifen. That's shown at the top of the  
21      flowchart, right?

22          A. Yeah. Yes.

23          Q. He performs an acetone  
24      recrystallization, right?

25          A. Yes.

1 Q. And that generates precipitate

2 15-331P --

3 A. Yes.

4 Q. -- right?

5 A. Yes.

6 Q. And he performs an isopropyl acetate  
7 recrystallization?

8 A. He says "isomerization."

9 Q. I'm referring to "takes precipitate  
10 15-331P" --

11 A. And then --

12 Q. -- and then he subjects that as shown  
13 on the left to isopropyl acetate  
14 recrystallization, right?

15 A. That's correct.

16 Q. And that yields two different  
17 materials, right? There's a filtrate which is  
18 enriched in Z --

19 A. Yes.

20 Q. -- and there's a precipitate that is  
21 enriched in E, correct?

22 A. Yes.

23 Q. And then he does two different things,  
24 right? On the one hand, he takes that filtrates  
25 and subjects the Z-enriched filtrate to



1 sequential recrystallization, right?

2 A. Well, he does the same thing three  
3 times.

4 Q. So what's shown on the left of this  
5 diagram, right, is that he's taking the  
6 filtrates and performing sequential  
7 recrystallization, right?

8 A. He is there, yes.

9 Q. And that results in a precipitate that  
10 is 100 percent (Z)-Endoxifen, right?

11 A. Nothing is a hundred percent, so I  
12 don't -- I haven't seen any evidence that states  
13 a hundred mil.

14 Q. It states there 100 to zero, right?

15 A. But I haven't seen it. What I have  
16 seen is NMR that doesn't toll it makes 100/0.

17 Q. And on the right-hand portion of the  
18 diagram he's taking the precipitate from his  
19 isopropyl acetate recrystallization and he's  
20 subjecting that to isomerization?

21 A. He is, yes.

22 Q. And then he recrystallizes that and he  
23 ends up with a different precipitate from what's  
24 shown on the left-hand of the diagram? It's a  
25 different precipitate that he reports as having

1 an E-to-Z ratio of 93-to-7, right?

2 A. That's what he's got on his diagram,  
3 but the filtrate that's labeled on the left-hand  
4 side is no different to the filtrates on the  
5 right-hand side.

6 Q. But you agree with me he made two  
7 different (Z)-Endoxifen materials, right, one  
8 that was -- he reports being 100 percent  
9 (Z)-Endoxifen and one he reports as being  
10 93 percent (Z)-Endoxifen, right?

11 A. He does that, yes, but they're not  
12 different processes.

13 Q. And so I'm trying to understand what's  
14 the term you would prefer to use for the two  
15 different -- the left-hand part of the diagram  
16 and the right-hand part of the diagram?

17 A. (Reviewing document.)

18 The only difference is how you end up  
19 with a roughly 67-to-30-grade mixture of the  
20 two. One is on the left-hand side, but the  
21 isomer precipitate to give you the filtrate on  
22 the left which is the same as the three  
23 filtrates on the right.

24 Q. Let's go to page 20 of your report --  
25 excuse me -- of your supplemental declaration.



1           A.   Okay.

2           Q.   And you say:  "Notably, Dr. Bihovsky  
3   attempted to repeat the crystallization  
4   experiments of Examples 5, 6 and 7 of Liu over  
5   15 times, often using conditions not described  
6   in Liu; e.g., bearing temperatures and times."  
7   Right?

8           A.   Yes.

9           Q.   You don't offer any opinion that these  
10   experiments use conditions not described in  
11   Liu -- scratch that.  Let me withdraw that  
12   question.

13           You say:  "For example, Dr. Bihovsky  
14   took the crude material he obtained by the  
15   methods of Example 4 of Liu and dissolved this  
16   crude Endoxifen in isopropyl acetated reflux,  
17   cooled the solution to 47 degrees C for one hour  
18   followed by step-wise cooling at 25 degrees C  
19   and then 15 degrees C over one and a half  
20   hours."  Right?

21           A.   Where were you reading that from?

22           Q.   The second sentence of paragraph 20 of  
23   your supplemental declaration.

24           A.   (Reviewing document.)

25           That's correct.



1 Q. So this is not the crystallization  
2 experiment he describes in his declaration,  
3 correct?

4 A. Why is it different?

5 Q. I'm sorry, I couldn't hear your answer  
6 in my realtime feed.

7 A. I said: Why is it different? He tries  
8 these experiments in his notebook.

9 Q. So what you're saying is in his  
10 notebook he tried experiments that differed from  
11 Liu, right?

12 A. He did, yes.

13 Q. But in his declaration, he followed the  
14 experiments of Liu, right?

15 A. (Reviewing document.)

16 Well, he didn't follow them in the  
17 sense that the scale is 1000 to 2000 times  
18 smaller, so any cooling processes and  
19 recrystallizations are going to be different.

20 Q. Let's go to paragraph 21 of your  
21 supplemental declaration.

22 A. Yes.

23 Q. And you say: "Dr. Bihovsky reports  
24 that he obtained (Z)-Endoxifen with 100 percent  
25 isomeric purity" in paragraph 43?



1 A. Yes.

2 Q. And you say that he deviates from the  
3 method disclosed by Liu?

4 A. I say that, yes.

5 Q. And you say: "Liu recrystallized the  
6 crude Endoxifen by (subparagraph 1)  
7 recrystallizing an acetone by heating to  
8 65 degrees C followed by slow cooling to 20  
9 degrees C degrees for 19 hours and then negative  
10 10 C for four days."

11 A. Yes.

12 Q. If you go to paragraph 40 of  
13 Dr. Bihovsky's declaration, that's what he  
14 describes doing, right?

15 MS. KRUMPLITSCH: Objection, form.

16 THE WITNESS: We're on a different  
17 scale here.

18 BY MR. MAHON:

19 Q. I'll help you out. In paragraph 22,  
20 subparagraph 1, you say: "Dr. Bihovsky  
21 recrystallized the crude Endoxifen by following  
22 subparagraph 1, recrystallizing acetone as  
23 described above," right?

24 A. Okay. (Reviewing document.)

25 Okay.



1 Q. You then say in paragraph 21,  
2 subparagraph 2 that: "Liu then teaches  
3 subparagraph 2, recrystallizing the material of  
4 subparagraph 1 in isopropyl acetate at 85 degree  
5 for two hours followed by cooling to 15 degrees  
6 C," right?

7 A. That's correct.

8 Q. Now, you don't cite where Liu teaches  
9 this, do you?

10 A. I don't give a cite there, no.

11 Q. Could we go to paragraph 73 of Liu.

12 A. Okay.

13 Q. That's what you're describing in your  
14 supplemental declaration paragraph 21,  
15 subparagraph 2?

16 A. That's what I'm describing, yes.

17 Q. And this is Example 6 of Liu?

18 A. That's in Example 6.

19 Q. And when you say "recrystallizing the  
20 material of subparagraph 1," what are you  
21 referring to?

22 A. What Liu starts with, which is a ratio  
23 he gives 70/30.

24 Q. In paragraph 45 Dr. Bihovsky's  
25 supplemental declaration, he describes following



1 Liu's Example 6, right?

2 MS. KRUMPLITSCH: Objection, form.

3 THE WITNESS: (Reviewing document.)

4 Well, at 45 he started from 48/52  
5 mixture, whereas Liu starts with 70/30. So  
6 they're different.

7 BY MR. MAHON:

8 Q. Let's go to paragraph 46 of  
9 Dr. Bihovsky's report -- or excuse me -- his  
10 supplemental declaration.

11 A. Okay.

12 Q. "He dissolved the Endoxifen precipitate  
13 in refluxing isopropyl acetate for four hours,  
14 the mixture was slowly cooled and kept at  
15 15 degrees C for two days," right?

16 A. That's what he said.

17 Q. Now, in your paragraph 21,  
18 subparagraph 2, that's what you say Liu does  
19 right, recrystallizing the material in isopropyl  
20 acetate, and you say "for two hours followed by  
21 cooling slowly at 15 C."

22 That's what Dr. Bihovsky does in  
23 paragraph 46 except that he does it for four  
24 hours, right? Excuse me, he does the reflux for  
25 four hours?

1 A. Well, that's different.

2 Q. But he does carry out what is taught in  
3 Liu's Example 6, right?

4 A. On a smaller scale, which is not  
5 representative of the large-scale reaction and  
6 for different time.

7 Q. In paragraph 22 of your report, you  
8 say: "By contrast, Dr. Bihovsky recrystallized  
9 the crude Endoxifen by first recrystallizing the  
10 acetone as described above to recrystallizing  
11 the material (subparagraph 1) in isopropyl  
12 acetate reflux for an unspecified amount of time  
13 followed by cooling to 23 degrees C for one hour  
14 and allowing the solution to stand at 23 degrees  
15 C for six hours and then, three, recrystallizing  
16 the material to two times in acetone, first in  
17 acetate reflux followed by cooling at 4  
18 degrees C for a total of 64 hours filtration and  
19 washing the solid with cold acetone, and second,  
20 in acetone followed by cooling at 4 degrees C  
21 for at total of 50 hours and filtering the  
22 drying solid," right?

23 A. Yes.

24 Q. You don't cite which paragraphs of  
25 Dr. Bihovsky's declaration you're referring to,

1 do you?

2 A. I don't cite it there, no.

3 Q. So you don't make clear whether you're  
4 referring to Dr. Bihovsky's sequential  
5 recrystallization experiments or his  
6 isomerization experiments, do you?

7 A. Well, I'm sure we can find it.

8 Q. I'm asking you a question, though. Do  
9 you clarify that here?

10 MS. KRUMPLITSCH: I'm sorry.

11 Objection, form. What's the question?

12 MR. MAHON: I'm asking him if in  
13 paragraph 22 he identifies which of the two  
14 experiments Dr. Bihovsky performed he's  
15 referring to.

16 THE WITNESS: Well, obviously, one of  
17 the recrystallizations he did.

18 MR. MAHON: Let's take a quick break.  
19 I think we're pretty close to wrapping up. 10  
20 minutes.

21 MS. KRUMPLITSCH: That sounds great.  
22 Thanks.

23 (Recess taken from 10:00 a.m.  
24 to 10:11 a.m.)  
25



1 BY MR. MAHON:

2 Q. Let's go back to paragraph 21 of your  
3 report.

4 A. Okay.

5 Q. And you were quoting Dr. Bihovsky's  
6 paragraph 43, right?

7 A. That's correct.

8 Q. Would you pull Dr. Bihovsky's report  
9 up.

10 A. (Witness complying.)

11 Q. Paragraph 43 is the last paragraph in  
12 the sequential recrystallization section, right?

13 A. I am there. I'm on paragraph 43.

14 Q. And you agree with me that that's the  
15 last paragraph in his sequential  
16 recrystallization section?

17 A. (Reviewing document.)

18 It is, yes.

19 Q. And if you go to paragraph 22 of your  
20 supplemental declaration --

21 A. Okay.

22 Q. -- you say: "Dr. Bihovsky  
23 recrystallized crude Endoxifen by  
24 recrystallizing in acetone as described above"?

25 A. I say that, yes.



1 Q. And if you go back to Dr. Bihovsky's  
2 supplemental declaration, that's what your --  
3 that's what he's describing in paragraph 40,  
4 correct?

5 A. (Reviewing document.)

6 That's correct.

7 Q. Back to your supplemental declaration,  
8 on page 11, subparagraph 2, paragraph 22, you  
9 describe that "Dr. Bihovsky was recrystallizing  
10 the material of one in isopropyl acetated reflux  
11 for an unspecified amount of time followed by  
12 cooling to 23 degrees C for one hour and  
13 allowing the solution to stand at 23 degrees C  
14 for six hours."

15 And you were referring -- you don't  
16 provide a citation, but what you were referring  
17 to is paragraph 41 of Dr. Bihovsky's  
18 declaration, right?

19 A. That's correct.

20 Q. And back to page 11 of your  
21 supplemental declaration, subparagraph 3,  
22 paragraph 22. You refer to "recrystallizing the  
23 material of two, two times acetone."

24 And, again, no citation, but what you  
25 were referring to is paragraph 42 of

1 Dr. Bihovsky's declaration, right?

2 A. (Reviewing document.)

3 That's correct. 40 hours plus 24 hours  
4 is 64 hours.

5 Q. Paragraphs 40 --

6 A. And 50 hours is later on in that  
7 paragraph, yes.

8 Q. And you agree with me paragraphs 40,  
9 41, 42 and 43 you've got Dr. Bihovsky's  
10 sequential recrystallization experiments, right?

11 A. I note there the material -- that's  
12 subjected to those materials, one after the  
13 other, yes.

14 Q. So in paragraph 22 of your reports you  
15 do not ever refer to what Dr. Bihovsky did in  
16 his isomerization experiment described in  
17 paragraph 44 and beyond in his report, correct?

18 MS. KRUMPLITSCH: Objection, form.

19 THE WITNESS: Well, I don't need to  
20 because everything starts with the 1-to-1  
21 mixture, and the isomerization takes it back to  
22 1-to-1.

23 BY MR. MAHON:

24 Q. In your supplemental declaration you do  
25 not address the Fauq, F-A-U-Q, reference, do





1     you?

2           A.   Not in this declaration, I don't  
3     believe I do.

4           Q.   In your supplemental declaration you do  
5     not address the Milroy reference, correct?

6           A.   I don't believe I do. My declaration  
7     is describing -- discussing the experiments done  
8     by Bihovsky.

9           MR. MAHON: All right, that's all I  
10    have.

11          MS. KRUMPLITSCH: Okay, I have a few  
12    questions. We can get start.

13

14                               EXAMINATION

15    BY MS. KRUMPLITSCH:

16          Q.   Dr. Davies, do you stand by the  
17    opinions in your supplemental declaration?

18          A.   I do, yes.

19          Q.   So I have a couple of specific  
20    questions, just a few.

21                You've referenced a few times the  
22    difference in scale of the experiments between  
23    Liu and Bihovsky. Do you recall that?

24          A.   Yes.

25          Q.   Why is the difference in scale between

1 Liu and Bihovsky important for your opinions?

2 MR. MAHON: Objection, scope.

3 Objection, leading.

4 THE WITNESS: Because there's a big  
5 difference between doing something on a  
6 multi-kilogram scale as to doing something on a  
7 grand or left scale so that the conditions the  
8 reaction is occurring under is very different.

9 Whenever you try and mix things on a  
10 big scale, it's very hard. It's very easy on a  
11 small scale. Whenever you try to cool things on  
12 a large scale, it's very hard; whereas, on a  
13 small scale, it's very easy.

14 For example, everybody knows if you  
15 have a hot cup of coffee, it cools quite quickly  
16 so you can drink it. But if you have a hot  
17 bathtub full of water, then it cools a lot  
18 slower. It's just a case of scale and how fast  
19 heat could transfer.

20 And when you're crystalizing stuff on a  
21 large scale, that's very different to on a small  
22 scale. So on a large scale, you can get the  
23 nucleation in different parts of the reactor  
24 going at different rates. That gives you  
25 concentrations gradients, a large scale acting



1 very differently with impurity profiles, isomer  
2 ratios than you would have on a small scale.

3 That's why, obviously, the company  
4 spent so much time trying to develop large scale  
5 processes to make large amounts of material.  
6 You can't take what was done on a small scale  
7 and hope to get it immediately on a big scale.

8 BY MS. KRUMPLITSCH:

9 Q. If you could turn to page 33 of  
10 Bihovsky's expert declaration, there's that flow  
11 chart that we were discussing -- you were  
12 discussing with counsel. I'll give you a second  
13 to get there.

14 A. Yes, I'm there.

15 Q. Okay. And do you recall in the bottom  
16 left corner of that flowchart Dr. Bihovsky  
17 represents that he got 100 percent  
18 (Z)-Endoxifen?

19 A. I do. And I don't see any evidence for  
20 that number. I saw his NMR spectra which --

21 MR. MAHON: I'll object as  
22 nonresponsive, outside the scope of his Direct  
23 and trying to produce new opinions into the  
24 record.

25 THE WITNESS: The hundred mil, as I

1 said earlier, there's no such thing as a hundred  
2 mil. But you have to look at what the method of  
3 the use to determine that number was. And  
4 looking at Bihovsky's NMR spectra, there's no  
5 way you can conclude 100/0 because an NMR  
6 spectra process is not very sensitive. I don't  
7 see any ratios on a lot of the peaks, but there  
8 are carbon, which is -- you're making the  
9 protons, but they're attached to carbon. Most  
10 of carbons are carbon 12, so you get signal  
11 peaks, but 1.1 percent of carbon, natural carbon  
12 is carbon 13 which is NMR active. So  
13 1.1 percent actually gives you a doubler, split  
14 the signal, for example, is a doubler, it gives  
15 you double for a couple peaks and they occur  
16 either side of the carbon 12 peak. And because  
17 it's a doubler, you get .55 percent.

18 I don't see any carbon 13 satellites on  
19 Bihovsky's NMR spectra, which are an internal  
20 standard to say how accurate you're able to  
21 determine purity. So he can't determine  
22 suddenly half a percent. He can't tell what he  
23 could determine because there's no internal  
24 standards to go by. So I don't believe the  
25 100/00.



1 BY MS. KRUMPLITSCH:

2 Q. If you could turn to paragraph 39 of  
3 Dr. Bihovsky's declaration on page 27.

4 A. I'm there.

5 Q. Do you recall counsel asking you about  
6 paragraph 39?

7 A. Yes.

8 Q. Okay. So counsel asked you a question  
9 about the Z-to-E ratio that Dr. Bihovsky reports  
10 and that Dr. Bihovsky stated that he got  
11 48-to-52 ratio of Z to E. And that's in the  
12 middle of paragraph 39. Do you see that?

13 A. I see that.

14 Q. And you started to explain why you  
15 questioned that number. Did you see any NMR  
16 spectra that supported that ratio?

17 MR. MAHON: Objection, scope.  
18 Objection, leading.

19 MS. KRUMPLITSCH: Counsel, objection to  
20 form is the only objection you can make in a  
21 PTAB proceeding.

22 MR. MAHON: Well, I'm going to object  
23 to all of this because it's highly improper.

24 MS. KRUMPLITSCH: Again, object to form  
25 is all that's allowed in this proceeding.



1 THE WITNESS: In Dr. Bihovsky's  
2 declaration, he says he provides NMR spectra to  
3 back up his ratios. He does not provide NMR  
4 spectra for all of these experiments. He  
5 provides only the spectra of the end products.  
6 So I can't tell what ratio he got for any of  
7 these intermediates because I haven't seen the  
8 NMR spectra which should be able to tell because  
9 it would give me the integrations on those  
10 spectra.

11 BY MS. KRUMPLITSCH:

12 Q. Okay. And now we're going to go back  
13 to -- and thank you for your patience for  
14 flipping through all these paragraphs and  
15 papers.

16 Okay, we're going to look at Liu, the  
17 Liu patent and Dr. Bihovsky's notebook. So  
18 we're going to look at Liu page 15,  
19 paragraph 65.

20 A. Okay.

21 Q. And that spans pages 15 and 16. And in  
22 this paragraph 65, do you recall counsel asking  
23 you about this paragraph?

24 A. I do because this is the one with zinc  
25 dust in it which started it.

1           Q.   So in Liu paragraphs 65, would you  
2   agree that Liu is describing heating the mixture  
3   to reflux and stirring for one hour and then  
4   leaving that mixture overnight at ambient  
5   temperature?

6           MR. MAHON:  Objection, form.

7           THE WITNESS:  Yes, it's in the first  
8   line of page 16.

9   BY MS. KRUMPLITSCH:

10          Q.   And then:  "The reactor is cooled to  
11   5 degrees centigrade on a solution of  
12   propiophenone and 4-2 bromo ethoxy phenyl  
13   4-ydroxyphenyl methanone and anhydrous dimethoxy  
14   methane was added to the reaction class in one  
15   portion."

16          Do you see that?

17          A.   That's correct.

18          Q.   So Liu is saying you should stir  
19   overnight prior to adding the propiophenone?

20          A.   He is, yes.

21          Q.   Okay, now let's look the Bihovsky's  
22   notebook, which I believe you looked at with  
23   counsel, and it's page 24 of Bihovsky's  
24   notebook.

25          A.   Yes.



1 Q. Do you recall looking at these pages  
2 with counsel?

3 A. I did. And he didn't follow Liu in  
4 this example.

5 Q. And why do you say that?

6 A. Because he's taking zinc dio -- zinc  
7 hexane and adding titanium tetrachloride and for  
8 one hour and then cooling it and then he adds  
9 his mixture plus propiophenone, those starting  
10 materials plus propiophenone only in one drug.

11 Q. So if Bihovsky's describing -- sorry.  
12 Okay, so the --

13 A. The --

14 Q. Sorry, let me just finish my question  
15 real quick, Dr. Davies.

16 Is Dr. Bihovsky describing reflux  
17 gently for one hour, cool in an ice bath and add  
18 the mixture of starting material plus  
19 propiophenone, correct?

20 A. Yes.

21 Q. And then the line you were discussing  
22 with Counsel, which is this looks like it says  
23 "stir at RT," on this line Dr. Bihovsky is  
24 suggesting stirring the reaction overnight after  
25 adding the propiophenone solution, correct?





1 A. That's correct.

2 Q. You just described Liu teaches stirring  
3 overnight prior to adding propiophenone?

4 A. Yes. And you have to do that because  
5 the zinc is reacting with the titanium  
6 tetrachloride, and that's what that overnight  
7 stirring is for is to get that reaction done so  
8 that you could then move on to the next step,  
9 which is adding the next reagent which is going  
10 to react with the titanium that the zinc has  
11 produced.

12 Q. So this is another example of the  
13 difference between the methods of Liu and what  
14 Dr. Bihovsky did?

15 A. Absolutely.

16 MS. KRUMPLITSCH: Okay, thank you. I  
17 have no further questions.

18

19 FURTHER EXAMINATION

20 BY MR. MAHON:

21 Q. All right, Dr. Davies, you talked a lot  
22 at length on NMR in your redirect. Did you ever  
23 address NMR in your supplemental declaration?  
24 Did you ever question the NMR results obtained  
25 by Dr. Bihovsky?



1 MS. KRUMPLITSCH: Objection, form.

2 THE WITNESS: Well, I certainly say to  
3 40 to produce 100/0.

4 BY MR. MAHON:

5 Q. Can you point me to anywhere in your  
6 supplemental declaration where you suggest his  
7 NMR did not support his results?

8 MS. KRUMPLITSCH: Objection, form.

9 THE WITNESS: I don't recall, but that  
10 is the evidence he produces to support his  
11 notebook in part. Well, he relies on the NMR  
12 and I didn't see anymore produced in the rest of  
13 the reactions in notebook.

14 BY MR. MAHON:

15 Q. So to answer my question, you cannot  
16 point to anywhere in your declaration where you  
17 questioned Dr. Bihovsky's NMR results, right?

18 MS. KRUMPLITSCH: Sorry. Objection,  
19 form.

20 THE WITNESS: Well, I imply it by  
21 saying that the hundred mil is reported and he  
22 uses NMR to do that.

23 BY MR. MAHON:

24 Q. So you don't suggest anywhere that his  
25 NMR results were inaccurate, do you?



1 MS. KRUMPLITSCH: Objection, form.

2 THE WITNESS: That's implicit by my  
3 saying reported the 100 to zero.

4 MR. MAHON: All right, no further  
5 questions.

6 MS. KRUMPLITSCH: Nothing else from us.

7 MR. MAHON: Debbie, can we request the  
8 transcript by Friday?

9 THE REPORTER: Yes, no problem at all.  
10 Just a final and not a rough?

11 MR. MAHON: Right.

12 THE REPORTER: Anything for the  
13 opposing side in the way of transcript or no?

14 MS. KRUMPLITSCH: We'll take a copy, no  
15 rush. No, wait a minute, let me take that back.  
16 If they are ordering rush, we will take it the  
17 same day, but no sooner.

18 THE REPORTER: Okay, so on the same  
19 delivery date?

20 MS. KRUMPLITSCH: Yes.

21 THE REPORTER: All right, thank you.

22 (Deposition concluded at 10:30 a.m. CST.)  
23  
24  
25

1 UNITED STATES PATENT AND TRADEMARK OFFICE  
2 BEFORE THE PATENT TRIAL AND APPEAL BOARD  
3  
4 INTAS PHARMACEUTICALS LTD.,  
5 Petitioner, Case PGR2023-00043  
6 vs. Patent 11,572,334  
7 ATOSSA THERAPEUTICS, INC.,  
8 Patent Owner.  
9 \_\_\_\_\_/

10  
11 I hereby certify that I have read the  
12 foregoing transcript of my deposition given at  
13 the time and place aforesaid, consisting of  
14 pages 1 to 83, inclusive, and I do again  
15 subscribe and make oath that the same is a true,  
16 correct, and complete transcript of my  
17 deposition so given as aforesaid and includes  
18 changes, if any, so made by me.

19  
20 \_\_\_\_\_  
21 STEPHEN G. DAVIES, D. PHIL.

22  
23 SUBSCRIBED AND SWORN TO  
24 before me this \_\_\_\_\_ day  
25 of \_\_\_\_\_, A.D. \_\_\_\_\_.

\_\_\_\_\_  
Notary Public



REPORTER CERTIFICATE

I, Deborah Habian, a Certified  
Shorthand Reporter within and for the State of  
Illinois, do hereby certify:

That previous to the commencement of  
the examination of the witness, the witness was  
by me duly sworn remotely to testify the whole  
truth concerning the matters herein;

That the foregoing deposition was  
reported remotely stenographically by me, was  
thereafter reduced to printed transcript by me,  
and constitutes a true record of the testimony  
given and the proceedings had;

That the said deposition was taken  
remotely by me at the time and place specified;

That the reading and signing by the  
witness of the deposition transcript was not  
discussed within the body of this transcript;

That I am not a relative or employee of  
attorney or counsel, nor a relative or employee  
of such attorney or counsel for any of the  
parties hereto, nor interested directly or  
indirectly in the outcome of this action.

IN WITNESS WHEREOF, I do hereunto set  
my hand this \_\_\_\_ day of \_\_\_\_\_, 20\_\_.

*Deborah Habian*

DEBORAH HABIAN, CSR, RMR, CRR, CLR  
IL CSR NO. 084-02432  
MO CCR NO. 1409



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ERRATA SHEET FOR THE TRANSCRIPT OF:

Case Name: Intas Pharma v. Atossa Therapeutics  
Dep Date: September 18, 2024  
Deponent: Stephen G. Davies, D. Phil.

Pg.	Ln.	Now reads	Should Read	Reason
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Signature of Deponent

SUBSCRIBED AND SWORN BEFORE ME

THIS \_\_\_\_ DAY OF \_\_\_\_\_, 20\_\_.

\_\_\_\_\_  
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MY COMMISSION EXPIRES: \_\_\_\_\_



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