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Transcript of Hannah K. Batchelor, Ph.D.

Date: September 19, 2023

Case: Apotex Inc. -v- Celgene Corporation (PTAB)

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CELGENE 2049
APOTEX v. CELGENE
IPR2023-00512

1 UNITED STATES PATENT AND TRADEMARK OFFICE

2 BEFORE THE PATENT TRIAL AND APPEAL BOARD

3 - - - - - x

4 APOTEX, INC., :

5 Petitioner, : Case No. IPR2023-00512

6 v. : U.S. Patent No.

7 CELGENE CORPORATION, : 8,846,628

8 Patent Owner. :

9 - - - - - X

10
11
12 Videotaped Deposition of

13 HANNAH K. BATCHELOR, Ph.D.,

14 Conducted Virtually

15 Tuesday, September 19, 2023

16 8:07 a.m. EDT

17
18
19
20 Job No.: 507038

21 Pages 1 - 190

22 Reported by: Debra A. Whitehead

1 Videotaped Deposition of HANNAH K. BATCHELOR,
2 Ph.D., conducted virtually.

3
4
5 Pursuant to notice, before Debra Ann Whitehead,
6 E-Notary Public in and for the State of Maryland.

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C O N T E N T S

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EXHIBITS MARKED IN TODAY'S SESSION

(Attached to the Transcript)

PATENT OWNER CELGENE EXHIBIT	PAGE
Exhibit 2048 Paper, "Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict In Vivo Performance and Bioequivalence of Generic Drugs in Pediatric Populations: A Carbamazepine Case Study," by Pawar, et al.	155

EXHIBITS MARKED IN PRIOR SESSIONS

(Not attached)

PETITIONER APOTEX EXHIBIT	PAGE
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Exhibit 1003	2/10/23 Declaration of Hannah K. Batchelor, Ph.D.	12
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Exhibit 1014	Chen Reference	130
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Exhibit 1027	GastroPlus Manual	61	09:50:18
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Exhibit 1042	IARC Monographs on the	82	10:31:32
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Evaluation of Carcinogenic Risks	10:31:34
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To Humans, Volume 50	10:31:36
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10:31:36

P R O C E E D I N G S

08:07:15

VIDEO SPECIALIST: Here begins the remote video deposition of Hannah Batchelor in the matter of Apotex, Inc., V Celgene Corporation, in the Patent Trial and Appeal Board of the United States Patent and Trademark Office; Case Number IPR2023-00512.

08:07:15

08:07:28

08:07:32

08:07:37

08:07:42

08:07:47

Today's date is September 19, 2023. The time on the video monitor is 8:07 a.m. eastern standard time. The remote videographer today is Brendon Skipper, representing Planet Depos. All parties of this video deposition are attending remotely.

08:07:51

08:07:54

08:07:58

08:08:02

08:08:05

08:08:07

Would counsel please voice-identify themselves and state whom they represent.

08:08:09

08:08:13

MS. MACRO: My name is Laura Macro. I represent Patent Owner Celgene and BMS. I'm joined by my colleagues today Heather Petruzzi, also from WilmerHale, and Gabriel Rosanio, also from WilmerHale. And today we also have Bo Han, in-house counsel for Patent Owner Celgene and BMS.

08:08:13

08:08:18

08:08:23

08:08:28

08:08:31

08:08:37

MR. GUPTA: Hi. This is Vishal Gupta

08:08:42

1	from the law firm of Steptoe & Johnson. I	08:08:47
2	represent Apotex in this litigation. With me	08:08:50
3	today is Tyler Doh, also from Steptoe & Johnson.	08:08:52
4	And from time to time Michael Green may also be	08:08:55
5	present, he's another associate at my firm.	08:08:57
6	I also represent the witness.	08:09:00
7	VIDEO SPECIALIST: The court reporter	08:09:03
8	today is Debbie Whitehead, representing Planet	08:09:03
9	Depos.	08:09:03
10	The witness will now be sworn.	08:09:05
11	HANNAH K. BATCHELOR, Ph.D.,	08:09:05
12	having been duly sworn, testified as follows:	08:09:14
13	EXAMINATION BY COUNSEL FOR PATENT OWNER	08:09:14
14	BY MS. MACRO:	08:09:14
15	Q Hi, Dr. Batchelor. Can you please state	08:09:27
16	your name, for the record.	08:09:29
17	A Yeah. It's Hannah Batchelor.	08:09:31
18	Q How are you today?	08:09:33
19	A Well, thank you.	08:09:37
20	Q And can you hear me okay?	08:09:38
21	A Yes.	08:09:41
22	Q Great. Thank you for taking the time to	08:09:42

1	be here today.	08:09:48
2	Do you have an understanding of why	08:09:49
3	you're being deposed?	08:09:50
4	A Yes, I do.	08:09:53
5	Q And what is that understanding?	08:09:54
6	A It's based on the declaration that I've	08:09:59
7	written, and I understand that I'll be questioned	08:10:02
8	on the declaration and the contents of it.	08:10:05
9	Q And you submitted that declaration in	08:10:08
10	connection with IPR2023-00512. Correct?	08:10:14
11	A Yes.	08:10:22
12	Q Have you been deposed before?	08:10:22
13	A No.	08:10:26
14	MR. GUPTA: And, Ms. Macro, just for the	08:10:28
15	record, Dr. Batchelor has an unmarked copy of her	08:10:30
16	declaration in paper with her. She doesn't have	08:10:35
17	other documents.	08:10:38
18	MS. MACRO: Okay. Thanks. I'll ask	08:10:43
19	Dr. Batchelor that question.	08:10:44
20	Q So did you bring any documents or notes	08:10:45
21	with you to today's deposition?	08:10:47
22	A No, apart from the unmarked copy I have.	08:10:49

1	I just prefer a paper copy sometimes.	08:10:53
2	Q And so just to confirm, you have a paper	08:10:55
3	copy of your declaration with you?	08:10:57
4	A Correct.	08:11:02
5	Q And you don't have any notes or anything	08:11:02
6	on it?	08:11:03
7	A Correct.	08:11:04
8	Q No markings on it?	08:11:04
9	A No markings.	08:11:08
10	Q And did you bring anything else with you	08:11:09
11	to today's deposition?	08:11:11
12	A No.	08:11:12
13	Q I want to briefly just go over some	08:11:12
14	ground rules. As you know, the deposition is	08:11:23
15	being transcribed by the court reporter. So it's	08:11:25
16	important that you answer with an audible response	08:11:29
17	rather than nodding or shaking your head.	08:11:33
18	Does that make sense?	08:11:35
19	A Yes.	08:11:36
20	Q And we should also try not to talk over	08:11:36
21	each other.	08:11:41
22	Does that make sense?	08:11:42

1	A	Yes.	08:11:44
2	Q	If I ask you a question and you don't	08:11:44
3		understand the question, can you please tell me	08:11:48
4		and I'll rephrase the question?	08:11:51
5	A	Yeah.	08:11:55
6	Q	Unless you tell me that you don't	08:11:55
7		understand the question, I'll assume that you do.	08:11:57
8		Is that fair?	08:11:59
9	A	Yes, that's fair.	08:12:01
10	Q	If you need a break at any time please	08:12:02
11		just ask, and we'll take a break. The only rule	08:12:06
12		is that we cannot take a break while a question is	08:12:09
13		pending.	08:12:11
14		Do you understand?	08:12:13
15	A	Yes. I'm quite keen to make breaks short	08:12:15
16		where possible just due to the time differences so	08:12:18
17		that I'm alert and giving you a best possible	08:12:21
18		response.	08:12:24
19	Q	Okay. Do you understand that your	08:12:24
20		testimony here today is given under oath?	08:12:28
21	A	Yes.	08:12:31
22	Q	And do you have any reason you cannot	08:12:31

1	provide complete and accurate testimony today?	08:12:35
2	A No reason.	08:12:39
3	Q I am going to introduce the first	08:12:39
4	exhibit.	08:12:45
5	MS. MACRO: So, Jack, that's going to be	08:12:49
6	Exhibit 1003.	08:12:51
7	(Exhibit 1003, previously marked, not	08:12:54
8	attached.)	08:14:14
9	(Discussion off the record with the A/V	08:14:14
10	technician.)	08:14:17
11	Q Dr. Batchelor, can you just let me know	08:14:25
12	when you see it on your end.	08:14:28
13	A Yeah, I can see that.	08:14:31
14	Q Do you recognize the document?	08:14:33
15	A I do, yes.	08:14:38
16	Q What is it?	08:14:39
17	A It's the copy of my declaration dated	08:14:42
18	February the 10th, 2023.	08:14:46
19	Q And so this is the expert declaration	08:14:50
20	that you filed in connection with IPR2023-00512	08:14:52
21	for Celgene Patent 8,846,628. Correct?	08:14:59
22	A That's correct.	08:15:05

1	Q	Will you understand if I refer to the	08:15:05
2		patent 8,846,628 as the '628 patent?	08:15:11
3	A	Yes, I will.	08:15:16
4	Q	I have some questions about the materials	08:15:16
5		you considered in forming your opinions in this	08:15:22
6		matter.	08:15:25
7		Do you have that in mind?	08:15:26
8	A	The materials I considered. Do you mean	08:15:31
9		the documents that are listed in the -- in the	08:15:33
10		report?	08:15:36
11	Q	Yes. So your declaration contains	08:15:38
12		Section IV on Pages 6 to 8.	08:15:40
13	A	Yeah.	08:15:45
14	Q	Listing the materials you considered in	08:15:45
15		forming your opinions. Correct?	08:15:46
16	A	Yes.	08:15:48
17	Q	Does the documents in Section IV	08:15:48
18		represent the materials you considered in forming	08:15:56
19		your opinions contained in the declaration?	08:15:58
20	A	Yes, the documents that I reviewed are	08:16:10
21		the ones that I reviewed and relate to my	08:16:12
22		declaration are all listed here.	08:16:14

1 Q And did you consider anything other than 08:16:15
2 the materials included in Section IV? 08:16:22

3 A So putting myself in the position of sort 08:16:27
4 of a person skilled in the art at the time, I 08:16:30
5 obviously considered the general knowledge around 08:16:34
6 that time. And when I was provided with the task 08:16:36
7 by my counsel, that we spoke about the patent as 08:16:41
8 well, '628. 08:16:49

9 Q Have you reviewed the patent? 08:16:50

10 A I didn't need to review it in detail to 08:16:54
11 undertake the task that I was asked to do. 08:16:58

12 Q So have you reviewed it? 08:17:00

13 A In terms of the definition of "review," I 08:17:08
14 haven't reviewed it because I didn't need to for 08:17:10
15 the task I was given to do. I'm aware of the 08:17:14
16 overview of the context, but I haven't reviewed 08:17:17
17 it. 08:17:19

18 Q Have you ever seen a copy of the '628 08:17:19
19 patent? 08:17:26

20 A I haven't reviewed it independently. I 08:17:40
21 may have seen parts of it in my discussions with 08:17:43
22 counsel. 08:17:45

1 Q Are there any other materials that you've 08:18:01
2 seen parts of that aren't listed in Exhibit 4? 08:18:05

3 MR. GUPTA: Objection, to the extent it 08:18:11
4 calls for privileged information. 08:18:13

5 Dr. Batchelor, all that I caution you is 08:18:14
6 not to reveal discussions between counsel. 08:18:18

7 You can answer. 08:18:21

8 A I think this refers a little bit to my 08:18:26
9 earlier answer, when as an expert I've seen a lot 08:18:28
10 of materials and I had to put myself in the 08:18:33
11 position of someone skilled in the art at the 08:18:35
12 time. 08:18:37

13 So there's materials that would be 08:18:38
14 generally known that I've used to form this 08:18:40
15 declaration that I didn't need to list. The ones 08:18:42
16 that I listed here are the ones I specifically 08:18:45
17 refer to in the declaration. 08:18:47

18 Q Other than the '628 patent, is there any 08:18:57
19 other document you can identify that you 08:19:02
20 considered in forming your opinions, other than 08:19:08
21 the ones in Section IV? 08:19:11

22 A The ones listed in Section IV are the 08:19:18

1 ones that I've referred to in my declaration, so
2 they would be the ones I would consider pertinent
3 to what's written in this declaration and the
4 opinion laid out in it.

5 Q Have you reviewed the claims of the '628
6 patent?

7 A I haven't reviewed the patent, so I
8 haven't specifically reviewed the claims, no.

9 Q Have you ever seen the claims of the '628
10 patent?

11 A I don't recall seeing them as during the
12 preparation of this report. I was given a task to
13 undertake, and that's really what this report
14 focuses on. That was the task I was given.

15 Q Do you have an understanding of what the
16 claims of the '628 patent are?

17 A My understanding was that I was given the
18 task to look at the overall pharmacokinetics of
19 azacitidine and that the patent referred to the
20 oral azacitidine. So that's my understanding.

21 Q Did you review the court's -- strike
22 that. I'll start again.

08:19:20

08:19:23

08:19:27

08:19:28

08:19:35

08:19:37

08:19:40

08:19:43

08:19:45

08:19:50

08:19:57

08:20:02

08:20:07

08:20:09

08:20:11

08:20:15

08:20:22

08:20:25

08:20:32

08:20:34

08:20:41

08:21:01

1	Have you ever reviewed a claim	08:21:03
2	construction order from a district court	08:21:06
3	litigation related to this matter?	08:21:07
4	A No.	08:21:12
5	Q Did you review Celgene's patent owner	08:21:13
6	preliminary response?	08:21:25
7	A Sorry, I didn't hear the last part of	08:21:25
8	that question.	08:21:27
9	Q Did you review Celgene's patent owner	08:21:28
10	preliminary response?	08:21:33
11	A No, it's not listed in the documents that	08:21:39
12	I reviewed, so I didn't review it.	08:21:41
13	Q Did you review Dr. Buckton's declaration?	08:21:43
14	A Again, it's not listed in the documents I	08:21:50
15	reviewed, so I didn't review it.	08:21:53
16	Q Did you ever speak with Dr. Buckton?	08:21:54
17	A I did not. So I know Professor Buckton,	08:22:01
18	but I did not speak to him about this case.	08:22:05
19	Q How do you know Dr. Buckton?	08:22:09
20	A When I did my Ph.D., Professor Buckton	08:22:14
21	worked at the same institution, which was	08:22:18
22	pre-2000.	08:22:23

1 Q And which institution was that? 08:22:24

2 A It was the School of Pharmacy, University 08:22:26
3 of London. 08:22:29

4 Q So you were a student at the London 08:22:29
5 School of Pharmacy at the same time Dr. Buckton 08:22:38
6 worked at that institution. Correct? 08:22:41

7 A That's correct. 08:22:43

8 Q What type of relationship? Did you have 08:22:43
9 any relationship with him? 08:22:49

10 A The laboratory I was working in was 08:22:56
11 shared with some of his students, so I would know 08:22:58
12 him to say hello to, and our professional paths 08:23:00
13 have crossed over the years. I wouldn't say I 08:23:05
14 have a strong relationship with him. But we know 08:23:07
15 each other. 08:23:09

16 Q Okay. Did you review Dr. Berkland's 08:23:12
17 declaration? 08:23:23

18 A I didn't quite catch the name. Sorry. 08:23:24

19 Q Dr. Berkland, B-E-R-K-L-A-N-D? 08:23:26

20 A No. Again, it's not listed in the list 08:23:33
21 of documents. 08:23:35

22 Q Did you review the board's Institution 08:23:36

1	Decision for this IPR?	08:23:42
2	A It's not listed in the documents. No.	08:23:47
3	Q Did you review the Iyanowski (phonetic)	08:23:49
4	reference which is Exhibit 1004?	08:24:02
5	A Again, it's not listed in the documents,	08:24:05
6	so I didn't review it.	08:24:06
7	Q Did you review the Atadja reference,	08:24:07
8	A-T-A-D-J-A, Exhibit 1005?	08:24:14
9	A No, it's not listed in the documents, so	08:24:24
10	I didn't review it.	08:24:26
11	Q Did you review the Gibson reference,	08:24:27
12	Exhibit 1006?	08:24:29
13	A No. Again, it's not listed.	08:24:35
14	Q Did you review the Pharmion press	08:24:37
15	release, Exhibit 1010?	08:24:42
16	A The documents that I did review are	08:24:49
17	listed, and those are the ones necessary to	08:24:51
18	conduct the task. So it's not listed, so I didn't	08:24:54
19	review it.	08:24:57
20	Q Were you familiar with the 5-azacitidine	08:24:57
21	before working on this matter?	08:25:02
22	A Just -- I'm just going to repeat. I	08:25:12

1 struggled to hear again. Did you ask if I was 08:25:14

2 familiar with the 5-azacitidine or working on it? 08:25:18

3 Q Yeah, I'll repeat the question. The 08:25:20

4 question was, were you familiar with 5-azacitidine 08:25:22

5 before working on this matter? 08:25:25

6 A So my expertise is in pharmacokinetics 08:25:27

7 and broadly pharmaceutical development, so I'm 08:25:42

8 aware of a great number of drugs, including 08:25:44

9 azacitidine. 08:25:47

10 Q So you were aware of 5-azacitidine before 08:25:47

11 working on this matter. Correct? 08:25:51

12 A In the way that I'm aware of a great 08:25:57

13 number of drugs that I use in my teaching, I would 08:26:00

14 have had knowledge of drug names, passing 08:26:03

15 knowledge. 08:26:06

16 Q So other than a passing knowledge of the 08:26:08

17 drug name of 5-azacitidine, do you have any other 08:26:12

18 knowledge on 5-azacitidine before working on this 08:26:16

19 matter? 08:26:19

20 A My expertise for this matter is really 08:26:21

21 about the pharmacokinetic modeling and 08:26:24

22 interpretation, and I have expertise on this that 08:26:28

1 can be applied to all small molecules, including 08:26:31

2 5-azacitidine. 08:26:34

3 Q What did you know about 5-azacitidine 08:26:36

4 before working on this matter? 08:26:47

5 A In terms of the task that I was asked to 08:26:54

6 do, I'm just trying to work out where that is in 08:26:56

7 the declaration, my prior knowledge of the drug. 08:27:02

8 Q You can take a minute to look at your 08:27:08

9 declaration, that's fine. Let me know when you're 08:27:10

10 done. 08:27:12

11 A So in the declaration the part that I 08:27:25

12 think is relevant is about the person -- the POSA. 08:27:27

13 And it's saying, really, the expertise and the 08:27:31

14 skills that they would have would be experiencing 08:27:34

15 candidate drug selection clinical use, and it's in 08:27:38

16 Paragraph 16. And that's the expertise I've 08:27:42

17 applied to this. So you can apply it to any 08:27:45

18 candidate drug. 08:27:49

19 Q Did you say cancer drug or candidate 08:27:51

20 drug? 08:28:12

21 A It says candidate drug. 08:28:12

22 Q Okay. 08:28:14

1	A	And candidate drug selection.	08:28:16
2	Q	Before working on this matter, have you	08:28:18
3		ever worked on 5-azacitidine?	08:28:39
4	A	In providing the expert opinion, I needed	08:28:54
5		to do a task that required me to have worked on	08:28:57
6		pharmacokinetic predictions for candidate drugs,	08:29:00
7		and I have experience on that, without needing to	08:29:03
8		have direct experience on 5-azacitidine.	08:29:06
9	Q	Have you ever done pharmacokinetic	08:29:10
10		predictions for 5-azacitidine before working on	08:29:13
11		this matter?	08:29:15
12	A	I had done numerous pharmacokinetic	08:29:21
13		simulations and predictions, but prior to working	08:29:24
14		on this I had not considered 5-azacitidine.	08:29:25
15	Q	And in your prior work have you	08:29:27
16		considered 5-azacitidine in any other context?	08:29:34
17	A	So my prior work is extensive. It may	08:29:46
18		well have featured in part my teaching activities	08:29:48
19		when discussing the range of drugs.	08:29:51
20	Q	Do you remember an instance where you	08:29:54
21		taught about 5-azacitidine in your teaching	08:30:19
22		activities?	08:30:22

1	A	I didn't review all my teaching materials	08:30:28
2		as part of the declaration. I would have to go	08:30:30
3		back and review them to see what --	08:30:32
4	Q	But sitting here today -- sorry. Sorry.	08:30:36
5		Do you want to finish? I'm sorry. I didn't mean	08:30:38
6		to cut you off.	08:30:41
7	A	No. I think I had finished. It's okay.	08:30:42
8	Q	Sitting here today, you can't think of a	08:30:44
9		particular instance of teaching about	08:30:50
10		5-azacitidine. Correct?	08:30:54
11	A	So my teaching career spanned over 23	08:30:58
12		years on various courses, with multiple lectures.	08:31:01
13		I'm unable to recall every -- the context of it	08:31:04
14		all.	08:31:07
15	Q	Did you review any documents that are not	08:31:07
16		on your documents considered list in preparing for	08:31:15
17		the deposition today?	08:31:19
18	A	The documents that I've reviewed are	08:31:21
19		listed in the -- in the Section IV of the	08:31:24
20		declaration.	08:31:28
21	Q	All right. Besides the modeling done to	08:31:29
22		generate the results reported in your declaration,	08:31:45

1	did you perform any other modeling of	08:31:48
2	5-azacitidine?	08:31:51
3	A All the modeling that I conducted is	08:31:55
4	contained within this declaration.	08:31:56
5	Q You ran the model twice. Correct?	08:31:59
6	A I ran -- I don't know where -- where does	08:32:08
7	it say I ran the model twice? I'm not completely	08:32:11
8	sure I understand the question.	08:32:14
9	Q You ran the model once for a	08:32:16
10	200-milligram dose. Correct?	08:32:20
11	A That's correct. So I developed the	08:32:23
12	model, and then applied the model based on a 200-	08:32:25
13	and 400-milligram dose.	08:32:28
14	Q So you applied the model once for a	08:32:30
15	200-milligram dose. Correct?	08:32:47
16	A Yes.	08:32:49
17	Q And you applied the model once for a	08:32:49
18	400-milligram dose. Correct?	08:32:54
19	A Yes.	08:32:55
20	Q And those two were the only times you	08:32:55
21	applied the model. Correct?	08:33:00
22	A Yes.	08:33:02

1	Q	So just to confirm, you only ran the	08:33:02
2		model -- sorry. Withdraw.	08:33:11
3		To confirm, you only applied the model	08:33:14
4		twice. Correct?	08:33:17
5	A	Yes, all of the modeling is contained	08:33:23
6		within the declaration.	08:33:26
7	Q	You said you developed the model. Can	08:33:27
8		you explain what you mean by that?	08:33:30
9	A	So the description of how the model was	08:33:34
10		built is in the declaration. It requires certain	08:33:37
11		inputs that we put into the model. Once those	08:33:42
12		inputs are there for a drug, you can apply it to	08:33:45
13		dosing scenarios. So the same model was used.	08:33:49
14		The input that changed was the dose.	08:33:55
15	Q	You provide no opinion on whether any	08:33:56
16		claims of the '628 patent are obvious. Correct?	08:34:07
17	A	I'm just reviewing the declaration.	08:34:18
18		I didn't refer to the claims in my	08:34:21
19		declaration.	08:34:24
20	Q	But you don't have an opinion of whether	08:34:27
21		the claims of the '628 patent are obvious.	08:34:30
22		Correct?	08:34:32

1	A	Having not reviewed the patent, I don't	08:34:36
2		know the specifics of the claims, so I don't know	08:34:39
3		that I can provide an opinion.	08:34:41
4	Q	And I'm going to ask the same question	08:34:43
5		about anticipation. So you provide no opinion on	08:34:46
6		whether any claims of the '628 patent are	08:34:53
7		anticipated. Correct?	08:34:56
8	A	As I've not reviewed the patent, I can't	08:35:01
9		form an opinion on the contents of it.	08:35:03
10	Q	The modeling in your declaration was	08:35:06
11		performed using GastroPlus Version 5.2. Correct?	08:35:11
12	A	Yes.	08:35:18
13	Q	So you decided to use GastroPlus Version	08:35:18
14		5.2 to complete the modeling?	08:35:25
15	A	I did as part of my task as a person	08:35:32
16		skilled in the art at that time.	08:35:35
17	Q	Why did you select GastroPlus Version	08:35:36
18		5.2?	08:35:42
19	A	So I put myself back to the time, the	08:35:46
20		dates of relevance in this case, and recalled the	08:35:50
21		softwares that were available at the time where	08:35:56
22		GastroPlus was the preferred software for this	08:35:59

1	type of analysis at that time, and 5.2 was the	08:36:02
2	version available at the time.	08:36:08
3	Q What other programs did you consider?	08:36:11
4	A At that time there were two major	08:36:19
5	commercial programs, Simcyp and GastroPlus. So I	08:36:20
6	considered Simcyp as an alternative, but	08:36:26
7	GastroPlus at that time would be superior for this	08:36:30
8	type of analysis because it's based on the	08:36:35
9	gastrointestinal system, the gastro part, so it	08:36:39
10	would be the most suitable to use at that time for	08:36:43
11	this type of analysis.	08:36:49
12	Q Can you just spell the name of the other	08:36:50
13	program?	08:36:53
14	A It's Simcyp. It's S-I-M, which is short	08:36:54
15	for simulation, and then cyp is C-Y-P, which	08:36:59
16	relates to cytochrome P450.	08:37:06
17	MS. MACRO: Sorry. There's a noise in	08:37:24
18	this room.	08:37:25
19	(A discussion was held off the record.)	08:37:40
20	Q How did you obtain GastroPlus Version	08:37:40
21	5.2?	08:37:57
22	A Access was arranged via Steptoe.	08:37:58

1	Q	Did Steptoe send you the GastroPlus	08:38:02
2		Version 5.2 software?	08:38:17
3	A	The access was arranged by a temporary	08:38:28
4		license for remote access.	08:38:31
5	Q	And who was the temporary license from?	08:38:35
6	A	Do you mean the supplier of the software?	08:38:45
7	Q	Yes.	08:38:48
8	A	So Simulations Plus are the owners of the	08:38:52
9		software.	08:38:55
10	Q	And so Steptoe arranged access to	08:39:00
11		GastroPlus Version 5.2 with Simulations Plus.	08:39:10
12		Is that right?	08:39:14
13	A	They own the software, Simulations Plus,	08:39:19
14		they're the software owners.	08:39:21
15	Q	And then you were given access to that	08:39:23
16		software?	08:39:29
17	A	I was given access, remote access to the	08:39:29
18		software, to run the simulation.	08:39:32
19	Q	And you said Steptoe arranged that access	08:39:33
20		to the Simulations Plus software?	08:39:45
21	A	Yes, that's correct.	08:39:47
22	Q	And so did Steptoe communicate with	08:39:49

1	Simulations Plus?	08:39:52
2	A My part of it was to run the software	08:40:00
3	remotely.	08:40:03
4	Q Maybe -- I think did you communicate	08:40:06
5	directly with Simulations Plus?	08:40:08
6	A No; access was arranged by Steptoe.	08:40:11
7	Q Did anyone help you develop the	08:40:13
8	GastroPlus model?	08:40:32
9	A No.	08:40:35
10	Q Besides the software, did you receive any	08:40:35
11	documents from Simulations Plus about the	08:40:41
12	software?	08:40:44
13	A So within the software there's a user	08:40:51
14	manual. But I've used GastroPlus, I'm familiar	08:40:52
15	with the software.	08:40:57
16	Q If you look at your declaration on Page	08:40:58
17	7, do you see a reference to Exhibit 1027,	08:41:13
18	GastroPlus Version 5.2 manual?	08:41:16
19	A Yes.	08:41:19
20	Q Where did you get the copy of the manual	08:41:19
21	from?	08:41:30
22	A It's embedded within the versions of the	08:41:34

1	software, so it was downloaded as a PDF to use.	08:41:36
2	Q You downloaded it from the software once	08:41:41
3	you had access to the software.	08:41:44
4	Is that right?	08:41:45
5	A I was provided it alongside access from	08:41:46
6	Steptoe.	08:41:49
7	Q Before preparing for this declaration,	08:41:55
8	had you ever used GastroPlus Version 5.2 before?	08:41:58
9	A So whilst I was at AstraZeneca I was	08:42:07
10	using GastroPlus, which was back in 2008. So,	08:42:11
11	yes. And in terms of the version number,	08:42:19
12	AstraZeneca would have had the latest version. So	08:42:23
13	I'm confident I used Version 5.2, but it's not	08:42:26
14	always the thing that you remember. When you're	08:42:31
15	using software you use the version in front of you	08:42:33
16	without -- without looking at the numbers.	08:42:36
17	Q So -- withdraw that.	08:42:42
18	Before December 5th, 2008, you had used	08:42:48
19	GastroPlus. Correct?	08:42:53
20	A Yeah, my date starting at AstraZeneca I	08:42:56
21	think was January of that year, so ...	08:42:59
22	Q And was that -- withdraw.	08:43:02

1 Had you used GastroPlus before working at 08:43:08
2 AstraZeneca? 08:43:11

3 A Prior to working at AstraZeneca, I had 08:43:18
4 used other physiologically-based pharmacokinetic 08:43:21
5 software, but I don't recall using GastroPlus 08:43:27
6 before that date. 08:43:30

7 Q And then when did you finish working at 08:43:31
8 AstraZeneca? 08:43:34

9 A That's listed in my CV as part of the 08:43:38
10 declaration. I was there for three years, so I'm 08:43:41
11 just going to double-check the dates so I'm 08:43:46
12 accurate in the response. 08:43:48

13 Yes. I finished in January 2011. 08:43:53

14 Q After finishing AstraZeneca in January 08:43:56
15 2011, did you ever use GastroPlus? 08:44:05

16 A Yes; I used it as part of my research. 08:44:08

17 Q While you were working at AstraZeneca, 08:44:13
18 what did you use GastroPlus for? 08:44:22

19 A My role at AstraZeneca related to 08:44:28
20 predicting the pharmacokinetics of small drug 08:44:33
21 molecules, so I used GastroPlus to predict the 08:44:37
22 pharmacokinetics of candidate drugs. 08:44:41

1	Q	And then after working at AstraZeneca	08:44:47
2		what did you use GastroPlus for?	08:44:49
3	A	As part of my research I look at the	08:44:54
4		interplay of formulations in the gastrointestinal	08:44:58
5		tract and the consequences on the	08:45:02
6		pharmacokinetics. So in that capacity I used	08:45:05
7		GastroPlus.	08:45:08
8	Q	So at any time before December 5th, 2008,	08:45:14
9		did you ever use GastroPlus to generate an in	08:45:22
10		silico model of an oral tablet dosage or based on	08:45:30
11		in vivo IV pharmacokinetic data?	08:45:34
12	A	Yes.	08:45:39
13	Q	And were those oral tablet dosage forms	08:45:40
14		immediate release?	08:45:48
15	A	Yeah, the portfolio of AstraZeneca at	08:45:54
16		that time was broad, but the majority of the	08:45:57
17		products I was working were immediate-release	08:45:59
18		tablets.	08:46:01
19	Q	Prior to December 5th, 2008, did you ever	08:46:01
20		use GastroPlus to generate an in silico model for	08:46:26
21		a nonimmediate-release oral tablet dosage form	08:46:31
22		based on in vivo IV pharmacokinetics data?	08:46:35

1	A	At that time all the projects I was	08:46:51
2		working on were immediate release, so it was only	08:46:53
3		immediate-release oral products that I was looking	08:46:57
4		at.	08:47:01
5	Q	I'm going to turn to your declaration,	08:47:02
6		Page 13, Paragraph 29. Just read the paragraph	08:47:17
7		and let me know when you're done.	08:47:25
8	A	Just Paragraph 29?	08:47:37
9	Q	Yes.	08:47:39
10	A	Yeah, I've read that.	08:47:46
11	Q	You applied the model to 200-milligram	08:47:47
12		and 400-milligram doses. Correct?	08:47:55
13	A	Yes.	08:47:59
14	Q	You -- withdraw that.	08:47:59
15		How did you select 200 and 400 milligrams	08:48:09
16		as the dosage model?	08:48:13
17	A	I was asked to undertake a task, and that	08:48:17
18		task was to do the modeling on those two doses.	08:48:21
19		So those doses were given to me as part of my	08:48:23
20		task.	08:48:27
21	Q	Do you know why those dosages were	08:48:30
22		selected as the two doses model?	08:48:34

1	A	I didn't -- I didn't ask that question at	08:48:41
2		the time, so, no, I don't know why.	08:48:44
3	Q	And you didn't consider any other doses.	08:48:46
4		Right?	08:48:51
5	A	The task I was given was to look at those	08:48:54
6		two doses, so those are the only ones I	08:48:56
7		considered.	08:48:59
8	Q	Do you -- sorry, there was some	08:48:59
9		background noise. You provide -- sorry. Withdraw	08:49:15
10		that.	08:49:22
11		You provide no opinion on what doses a	08:49:26
12		person of skill in the art as of 2008 would have	08:49:28
13		expected to use for a nonenteric-coated tablet	08:49:32
14		formulation of 5-azacitidine. Correct?	08:49:39
15	A	I don't think that was important for the	08:49:48
16		task that I was given. I was given a specific	08:49:50
17		task to look at those two doses.	08:49:52
18	Q	So you haven't formed an opinion on	08:49:55
19		whether a particular dose would have been used by	08:50:14
20		a person of skill in the art for a	08:50:20
21		nonenteric-coated tablet formulation of	08:50:27
22		5-azacitidine. Correct?	08:50:30

1 A So my understanding of a person skilled 08:50:33
2 in the art would be a -- one, an expert in 08:50:36
3 pharmacokinetics looking at drug development. So 08:50:43
4 in terms of dose selection, that wouldn't be part 08:50:48
5 of their skill set. So I don't think it's 08:50:50
6 important to undertake this task. 08:50:58

7 Q Can you point me to anywhere in your 08:51:28
8 declaration where you discuss what doses a person 08:51:30
9 of skill in the art as of 2008 would have used for 08:51:35
10 a nonenteric-coated tablet formulation of 08:51:38
11 5-azacitidine? 08:51:43

12 A I don't think that's of relevance to the 08:51:51
13 task that I was given, so I don't know that it 08:51:55
14 exists in my declaration. But I'm happy for you 08:51:58
15 to point out to me if I've missed that. 08:52:02

16 Q When you generate in silico models for an 08:52:04
17 oral dosage form, is it typical to apply the model 08:52:16
18 to only two doses? 08:52:18

19 A In this case the task that I was given 08:52:34
20 was to apply it to only two doses, so I was really 08:52:36
21 focused on the task for this declaration. For the 08:52:41
22 more broader context, I'd need to know more about 08:52:44

1 what the model is being used for to understand how 08:52:47
2 many doses one might apply it to. But this task 08:52:51
3 was just for the two doses. 08:52:53

4 Q Thinking back to your work at 08:53:02
5 AstraZeneca, can you think of a time when you 08:53:04
6 generated an in silico model for an oral dosage 08:53:06
7 form and applied it to more than two doses? 08:53:10

8 A In the context of the application of 08:53:23
9 models, you use them to solve an issue. In this 08:53:24
10 case the issue was relating to two doses, so I 08:53:28
11 applied it to two doses. The issues that I was 08:53:32
12 looking to solve on other occasions are not 08:53:34
13 especially relevant to this case, so I don't think 08:53:37
14 it brings anything to the declaration. 08:53:41

15 Q Yeah, I'm just trying to understand your 08:53:51
16 prior experience. 08:53:53

17 So have there been times when you've 08:53:56
18 generated an in silico model for an oral dosage 08:53:58
19 form and applied it to more than two doses? 08:54:02

20 A Yeah, in the past where the task 08:54:09
21 necessary -- I can't say the words -- necessitated 08:54:12
22 multiple doses, I've generated models and applied 08:54:15

1	them to multiple doses. But normally I'm very	08:54:17
2	task-focused, so I use the model to complete the	08:54:22
3	task.	08:54:26
4	Q What circumstances -- withdraw that.	08:54:26
5	Under what circumstances might you in	08:54:56
6	silico model more than two doses?	08:55:02
7	MR. GUPTA: Objection.	08:55:11
8	Hold on.	08:55:11
9	Objection. Form. Relevance.	08:55:12
10	You can answer, Dr. Batchelor.	08:55:14
11	A Yeah, my pause was again, I was	08:55:18
12	considering how it relates to my declaration.	08:55:21
13	The cases that may necessitate modeling	08:55:26
14	multiple doses could be many-fold. One of the	08:55:30
15	benefits of modeling that we used in AstraZeneca	08:55:40
16	was scenario planning. So we could scenario plan	08:55:43
17	a range of situations to explore how the	08:55:50
18	pharmacokinetics may be influenced by dose,	08:55:57
19	exploration of dose linearity, if that was	08:56:01
20	required. Though there were many reasons. I	08:56:03
21	don't know -- I don't feel they're relevant to	08:56:08
22	this particular example where my task was to model	08:56:09

1	two specific doses, which I've done and the	08:56:13
2	reports are listed here.	08:56:19
3	Q So I'd like to turn to the summary of	08:56:20
4	your modeling results. They're on Pages 8 to 9 of	08:56:32
5	your declaration. Let me know when you're there.	08:56:36
6	A Yeah, I can see them on the screen.	08:56:47
7	They're being shown to me.	08:56:51
8	MS. MACRO: Yeah, can you just scroll	08:56:54
9	down a little more, please? Kind of split. I	08:56:55
10	just want to look at the table that's kind of	08:56:57
11	split over Pages 8 and 9. Thank you. All right.	08:57:00
12	Q This table presents the results of your	08:57:06
13	modeling. Correct?	08:57:08
14	A Yes.	08:57:11
15	Q And -- withdraw that.	08:57:11
16	These results show that AUC, Cmax, and Tmax	08:57:25
17	results of your modeling for 200-milligram or	08:57:30
18	400-milligram oral doses. Correct?	08:57:36
19	A Yeah, it shows the simulation result for	08:57:40
20	modeling, yeah.	08:57:43
21	Q And the results in this table are AUC,	08:57:44
22	Cmax, and Tmax. Correct?	08:57:50

1	A	Yeah, correct.	08:57:52
2	Q	And just so I understand, the only thing	08:57:53
3		that was different in the model between the	08:58:00
4		200-milligram and 400-milligram modeling was the	08:58:04
5		dose. Correct?	08:58:08
6	A	Yeah. So the two simulations that were	08:58:13
7		run on the model, one was 200 and the other one	08:58:16
8		was 400. And the only input that changed between	08:58:19
9		those was the input dose of the 200 or the 400	08:58:22
10		milligrams.	08:58:25
11	Q	Okay. So let's look at Cmax first. Your	08:58:26
12		results show that 200-milligram dose has an	08:58:33
13		estimated Cmax of 105.3 nanograms per milliliter.	08:58:42
14		Correct?	08:58:50
15	A	That's what the simulation predicted,	08:58:51
16		yes.	08:58:53
17	Q	And your simulation predicted that for a	08:58:54
18		400-milligram dose, the estimated Cmax is 210.6	08:59:00
19		nanograms per liter. Correct?	08:59:07
20	A	Nanograms per milliliter, yes, correct.	08:59:12
21	Q	210.6 is close to double 105.5. Right?	08:59:14
22	A	Yeah. Yeah, the numbers are. Uh-huh.	08:59:26

1	Q	The numbers are close to double.	08:59:29
2		Correct?	08:59:38
3	A	Yeah. Yes.	08:59:38
4	Q	Changing the dose -- sorry, withdraw	08:59:39
5		that.	08:59:48
6		Changing the dose would change the Cmax	08:59:53
7		predicted by GastroPlus. Correct?	08:59:56
8	A	So the results from the model show that	09:00:01
9		when we predicted at 200 milligrams, yeah, we got	09:00:02
10		the Cmax of just over a hundred. And when we	09:00:07
11		simulated the run at 400 milligrams, we got the	09:00:11
12		dose that was approximately double, at 200.	09:00:14
13	Q	Is it correct to say that your modeled	09:00:24
14		Cmax values are proportional to the dose that you	09:00:29
15		used in the modeling?	09:00:33
16		MR. GUPTA: Objection to form.	09:00:36
17	A	So the results of the modeling that I	09:00:43
18		undertook are shown here. I only took modeling on	09:00:45
19		these two doses, and those are the results that	09:00:50
20		show.	09:00:53
21	Q	According to the results that you show,	09:00:55
22		the relationship between dose and Cmax is linear.	09:01:13

1	Correct?	09:01:17
2	MR. GUPTA: Objection to form.	09:01:19
3	A So the only modeling that was undertaken	09:01:27
4	is that that's presented here, which was the two	09:01:30
5	doses. I think it -- interpretation beyond these	09:01:32
6	two doses, two simulations that are presented, is	09:01:39
7	something I haven't done. Only these two	09:01:43
8	conditions were modeled, so these are the data	09:01:46
9	that I've got. I wouldn't really want to	09:01:50
10	speculate beyond that.	09:01:52
11	Q Okay. But for the two doses that you did	09:01:55
12	model, the relationship between dose and Cmax is	09:02:00
13	linear. Right?	09:02:05
14	MR. GUPTA: Objection to form.	09:02:07
15	A I'm going to refer to my previous answer.	09:02:11
16	But when there's only two data points and you join	09:02:14
17	them, it's a dangerous place to be. I wouldn't do	09:02:18
18	it.	09:02:23
19	Q In general in your experience and in	09:02:25
20	silico modeling, do you agree that there can be a	09:03:19
21	nonlinear relationship between Cmax and dose?	09:03:21
22	MR. GUPTA: Objection to form. And	09:03:27

1	relevance.	09:03:30
2	You can answer.	09:03:31
3	A I think that in silico modeling and its	09:03:39
4	applications are so broad, I would need more	09:03:43
5	context to be able to provide an answer.	09:03:45
6	Otherwise it's speculation that I don't really --	09:03:49
7	that I don't want to do, as I'm here really to	09:03:52
8	talk about the declaration instead of speculation.	09:03:55
9	Q Is Cmax always linearly correlated with	09:04:04
10	dose?	09:04:09
11	MR. GUPTA: Same objection.	09:04:10
12	A In the declaration I presented, only	09:04:13
13	two -- only two doses were simulated, so it's	09:04:16
14	impossible to really -- the data for those two is	09:04:19
15	presented. And anything outside of that isn't	09:04:25
16	considered.	09:04:27
17	Q I mean, I'm just trying to understand	09:04:27
18	from your experience as a pharmacokinetics expert.	09:04:31
19	In your experience, is Cmax always	09:04:37
20	linearly correlated with dose?	09:04:41
21	MR. GUPTA: Same objection.	09:04:45
22	A If you're asking me about the	09:04:55

1 azacitidine, the only data that I've got are the 09:04:59
2 data that's presented here, and that's -- that's 09:05:02
3 not sufficient for me to answer the question. 09:05:04

4 Q I'm not asking about 5-azacitidine. I'm 09:05:07
5 just asking in general are you aware of any time 09:05:12
6 when Cmax has not been linearly correlated with 09:05:17
7 dose? 09:05:20

8 MR. GUPTA: Same objection. 09:05:25

9 A If we take this away from azacitidine, 09:05:27
10 then there's so much pharmacokinetic data out 09:05:32
11 there, there are -- there would be examples. But 09:05:37
12 that's outside and beyond the work that's within 09:05:40
13 this declaration. 09:05:43

14 Q And taking it back to 5-azacitidine, you 09:05:54
15 don't know one way or another whether Cmax is 09:05:58
16 linearly correlated with dose. Right? 09:06:01

17 MR. GUPTA: Objection to form. 09:06:06

18 A The modeling that's presented in the 09:06:08
19 declaration considers the dose of 200 and 400 09:06:10
20 milligram, and the results relating to those doses 09:06:17
21 are shown here. 09:06:20

22 Q And you don't provide an opinion on 09:06:21

1	whether Cmax and dose are linearly correlated in	09:06:33
2	your declaration. Right?	09:06:41
3	A My declaration provides the results of	09:06:51
4	the modeling at 200 and 400 milligrams. I don't	09:06:54
5	recall mentioning linearity. But if it's in the	09:07:03
6	declaration, please -- please point me to it, and	09:07:06
7	I can reread that section.	09:07:09
8	Q Okay. Turning to the AUC results. Your	09:07:10
9	results show that a 200-milligram dose results in	09:07:26
10	an estimated AUC of 264.72 nanogram hours per mL.	09:07:31
11	Correct?	09:07:42
12	A Yes.	09:07:43
13	Q And your results show that for a	09:07:43
14	400-milligram dose, your estimated AUC is 529.46	09:07:49
15	nanogram hours per mL. Correct?	09:07:56
16	A Yeah, those are the values reported.	09:07:59
17	Q And 529.46 is close to double 267.72.	09:08:01
18	Correct?	09:08:18
19	A So, yeah, close to double the 264.72.	09:08:22
20	Q Oh, sorry.	09:08:26
21	A Yeah.	09:08:28
22	Q I will do this again. I apologize for	09:08:29

1	the record.	09:08:32
2	529.46 is close to double 264.72.	09:08:34
3	Correct?	09:08:43
4	A Yeah. Mathematically, yeah.	09:08:46
5	Q Your estimated AUC for the 400-milligram	09:08:49
6	dose is about double the estimated AUC for the	09:08:59
7	200-milligram dose. Correct?	09:09:02
8	A So the results that are presented, yeah,	09:09:07
9	the numbers -- the numbers tell that story.	09:09:10
10	Q And in this instance changing the dose	09:09:13
11	changed the AUC that was predicted by GastroPlus.	09:09:21
12	Correct?	09:09:25
13	A So the results that are shown are the	09:09:27
14	results from the 200- and the 400-milligram	09:09:29
15	simulation. So you can see that the values are	09:09:32
16	presented in the declaration.	09:09:35
17	Q And those values show that when you	09:09:36
18	change the dose, the AUC number predicted by	09:09:40
19	GastroPlus changed. Right?	09:09:44
20	A The results that are shown show that.	09:09:50
21	Q In your general experience, is AUC always	09:09:54
22	linearly correlated with dose?	09:10:34

1	MR. GUPTA: Objection. Form. Relevance.	09:10:38
2	Scope. Outside of her report.	09:10:43
3	You can answer.	09:10:45
4	A So simulations run in this case were just	09:10:48
5	run for 200 and 400 milligrams, and the results of	09:10:51
6	the AUC are shown.	09:10:55
7	Q But again I'm asking about your	09:10:59
8	experience as a pharmacokinetics expert.	09:11:02
9	So outside of 5-azacitidine, is AUC	09:11:08
10	always linearly correlated with dose?	09:11:14
11	MR. GUPTA: Objection. Form. Relevance.	09:11:17
12	Scope.	09:11:20
13	You can answer.	09:11:21
14	A Again, pharmacokinetics is very broad.	09:11:26
15	Outside of azacitidine, I would have to consider	09:11:32
16	the case and the scenario to provide an answer.	09:11:36
17	It's -- it could be too broad to answer in the	09:11:40
18	abstract.	09:11:44
19	Q So AUC is always linearly correlated with	09:11:45
20	dose.	09:12:00
21	Is that right?	09:12:01
22	MR. GUPTA: Same objection.	09:12:02

1	A	The results that are shown are the	09:12:06
2		results for a 200- and 400-milligram dose here for	09:12:09
3		azacitidine. If we're talking outside	09:12:15
4		azacitidine, it's really important to put context	09:12:18
5		in to give an answer that would be meaningful.	09:12:23
6		But if it's outside azacitidine, I'm unsure how it	09:12:29
7		relates to my declaration.	09:12:34
8	Q	In your prior experience, has it been the	09:12:35
9		case that AUC is always linearly correlated with	09:12:55
10		dose?	09:13:00
11	MR. GUPTA:	Objection. Form. Relevance.	09:13:02
12		Scope.	09:13:06
13		You can answer.	09:13:06
14	A	My experience is broad. In	09:13:15
15		pharmacokinetics there can be examples of all	09:13:24
16		sorts of attributes that I'd need to know more	09:13:29
17		details to really answer.	09:13:32
18	Q	One example of a pharmacokinetic	09:13:45
19		attribute that could exist is a nonlinear	09:13:52
20		relationship between AUC and dose. Right?	09:13:57
21	MR. GUPTA:	Objection. Same objections.	09:14:02
22		You can answer.	09:14:06

1 A I'm just trying to work out. I don't 09:14:12

2 know in the declaration where this is or ... 09:14:19

3 Q I'm just trying to ask about general 09:14:22

4 principle of pharmacokinetics. So generally 09:14:24

5 speaking, can a drug have a nonlinear relationship 09:14:28

6 between area under the curve and dose? 09:14:37

7 MR. GUPTA: Again. Same objections to 09:14:41

8 the same question. 09:14:43

9 You can answer. 09:14:44

10 A If we're talking outside this case and 09:14:49

11 outside of azacitidine, then I know of examples 09:14:52

12 are -- that there are examples I could draw up, if 09:14:54

13 that's useful; but I'm unclear on the relevance. 09:15:01

14 Q You don't provide an opinion on whether 09:15:09

15 AUC and dose are linearly correlated in your 09:15:55

16 declaration. Right? 09:15:58

17 A My declaration includes the results from 09:16:03

18 the simulations that were conducted for the 200- 09:16:08

19 and the 400-milligram dose. But I don't recall 09:16:10

20 any other factors being reported. I simulated 09:16:22

21 those two doses and presented the data from those, 09:16:27

22 those two, which was the task I had been asked to 09:16:30

1	do.	09:16:34
2	MS. MACRO: Okay. Let's take a break,	09:16:34
3	please. Thank you.	09:16:36
4	MR. GUPTA: All right. Let's take five	09:16:38
5	minutes then.	09:16:40
6	VIDEO SPECIALIST: We are going off	09:16:40
7	record. The time is 9:16.	09:16:41
8	(A recess was taken.)	09:17:08
9	VIDEO SPECIALIST: We're back on record.	09:24:26
10	The time is 9:24. Please proceed.	09:24:35
11	BY MS. MACRO:	09:24:38
12	Q Dr. Batchelor, can you please turn to	09:24:39
13	Page A-5 of your declaration?	09:24:44
14	Are you there?	09:25:00
15	A Yes.	09:25:04
16	Q This appendix shows PKPlus models from IV	09:25:05
17	PK Data. Correct?	09:25:13
18	A At Page A-5, yes, it's the IV data with	09:25:14
19	the -- with the simulation overlaid.	09:25:17
20	Q You use data from Exhibit 1017, the	09:25:19
21	Marcucci reference. Right?	09:25:32
22	A Yes, that's correct, the IV data came	09:25:34

1	from Marcucci.	09:25:36
2	Q On this page you indicate a dose from	09:25:37
3	Marcucci of 142.5 milligrams. Right?	09:25:46
4	A Yes, that's the dose that was used in the	09:25:54
5	simulation.	09:25:56
6	Q And you got that dose by calculating the	09:25:56
7	dose of 75 milligrams per meters squared from	09:26:02
8	Marcucci by the 1.9 meters square average weight	09:26:08
9	of the patient of Marcucci. Right?	09:26:12
10	A I think it's listed in the Marcucci	09:26:21
11	paper. Are we able to open that and look?	09:26:23
12	Q Yeah. We can introduce Exhibit 1017,	09:26:25
13	please.	09:26:34
14	(Petitioner Apotex Exhibit 1017,	09:26:34
15	previously marked, not attached.)	09:26:48
16	Q And, Dr. Batchelor, please let us know	09:26:48
17	once you see it on your end.	09:26:51
18	I'd like to introduce Exhibit 1017,	09:27:05
19	Marcucci reference. Can you please turn to Page	09:27:08
20	599, which is PDF Page 3.	09:27:19
21	A I don't have it in the SharePoint yet.	09:27:25
22	MR. GUPTA: Yeah, I don't either yet.	09:27:27

1	MS. MACRO: I apologize.	09:27:33
2	(Discussion off the record with the A/V	09:27:42
3	technician.)	09:27:45
4	Q Dr. Batchelor, do you have the exhibit?	09:29:03
5	MR. GUPTA: Yes.	09:29:39
6	A Yes, I have it as well.	09:29:40
7	MR. GUPTA: Yeah, I've got it as well	09:29:42
8	now. Thank you.	09:29:44
9	Q Do you recognize this exhibit?	09:29:46
10	A Yes.	09:29:50
11	Q What is it?	09:29:51
12	A It's the Marcucci paper I've listed in	09:29:54
13	the documents I've reviewed.	09:29:58
14	Q If you turn to PDF Page 3, which is Page	09:29:59
15	599 of the exhibit. Let me know when you're	09:30:05
16	there.	09:30:20
17	A Yes.	09:30:21
18	Q Are you there, Dr. Batchelor?	09:30:21
19	A Yes.	09:30:26
20	Q Under Statistical Analysis, Marcucci	09:30:32
21	states that it uses a dose of 75 milligrams per	09:30:35
22	meter squared for both the SC dose and the IV	09:30:40

1	dose. Right?	09:30:47
2	A Yeah.	09:30:52
3	Q And if you looks at the section titled	09:30:52
4	Patients, it's split onto the next page.	09:31:03
5	A Uh-huh.	09:31:07
6	Q Marcucci states that the mean body	09:31:07
7	surface area of the patients was 1.9 plus or minus	09:31:12
8	0.2 meters squared. Right?	09:31:16
9	A Yes.	09:31:21
10	Q And -- withdraw that.	09:31:25
11	You got the dose of 142.5 milligrams in	09:31:28
12	the GastroPlus modeling by calculating 75	09:31:37
13	milligrams per meter squared by 1.9 meters squared	09:31:46
14	average weight of the patient in Marcucci.	09:31:52
15	Correct?	09:31:56
16	A Yes, that would be how the dose is	09:31:56
17	calculated.	09:31:58
18	Q Turn back to --	09:31:59
19	MS. MACRO: We can take that exhibit	09:32:03
20	down.	09:32:07
21	Q Turning back to Page A-5 of your	09:32:07
22	declaration.	09:32:10

1	PKPlus calculates an AUC based on the	09:32:27
2	Marcucci data. Right?	09:32:44
3	A I'm not seeing where you're getting the	09:32:50
4	AUC value for that.	09:32:52
5	Q Do you see where it says,	09:32:58
6	Noncompartmental Analysis of Data, and then it	09:33:01
7	says AUC equals 1.028 microgram hours per ml?	09:33:03
8	A Okay. Yes.	09:33:08
9	Q So PKPlus calculates an AUC based on the	09:33:14
10	Marcucci IV data. Right?	09:33:18
11	A So yes, the way the model is working	09:33:28
12	there, these are screen grabs from the model that	09:33:31
13	you're seeing. So there's an awful lot of	09:33:34
14	parameters on the left-hand side. So it's worth	09:33:36
15	just looking at these in sequence, because it's	09:33:41
16	like a table, the pages. But there was an AUC	09:33:44
17	value reported for this, yes.	09:33:49
18	Q So turning back to Pages 8 and 9 of your	09:33:50
19	report, which is the table with your results.	09:34:29
20	Just let me know when you're there.	09:34:34
21	A Yes.	09:34:47
22	Q You don't -- okay. Sorry. You don't	09:34:47

1	report any acceptable error for your AUC values.	09:34:49
2	Right?	09:34:54
3	A So the purpose of the simulation was to	09:35:04
4	generate a simulation. I didn't -- I didn't	09:35:05
5	report any errors there.	09:35:12
6	Q And you didn't report any errors for your	09:35:18
7	Cmax values. Correct?	09:35:22
8	A I think it really depends here what you	09:35:27
9	mean by "errors." Are you -- because the	09:35:29
10	simulation is generating a value based on the	09:35:33
11	inputs, so ...	09:35:36
12	Q And what do you understand "error" to	09:35:43
13	mean?	09:35:45
14	MR. GUPTA: Objection to form.	09:35:49
15	You can answer.	09:35:50
16	A I think I know what you're asking, but	09:35:55
17	I'm trying to answer in a really scientific way.	09:35:57
18	When you run a simulation, it's only got	09:36:06
19	one set of inputs, so it will give you one answer.	09:36:08
20	So the -- so it won't -- it will generate you an	09:36:15
21	answer that there's no variability in the inputs	09:36:20
22	as I type them into the model. But if you're	09:36:26

1	asking about general pharmacokinetic variability,	09:36:32
2	that's a slightly different question. I wasn't	09:36:36
3	sure whether that's what you're asking.	09:36:40
4	Q Do you know -- let's take a step back.	09:36:42
5	Generally speaking, in pharmacokinetic in	09:37:06
6	silico modeling, you can compare the modeled value	09:37:10
7	to a measured value. Right?	09:37:17
8	MR. GUPTA: Objection to form.	09:37:27
9	A So in silico modeling can be used in a	09:37:30
10	variety of ways. For the purposes of the	09:37:34
11	declaration, there was no oral data I was	09:37:37
12	comparing this to. I was conducting a simulation	09:37:43
13	to predict oral data. So that was what was done	09:37:45
14	in this report.	09:37:50
15	Q If there was oral data, you could compare	09:37:52
16	your simulated result to that hypothetical oral	09:38:07
17	data. Right?	09:38:13
18	MR. GUPTA: Objection to form and scope.	09:38:17
19	You can answer.	09:38:19
20	A In this case the purpose of the modeling	09:38:24
21	was to predict the pharmacokinetics, so that's	09:38:25
22	what I undertook in this study. There was no data	09:38:32

1 to compare it to, so I didn't do that. 09:38:34

2 Q I'd like to walk through and discuss the 09:38:41

3 GastroPlus Input. 09:39:12

4 A Okay. 09:39:14

5 Q So turning to Page 14 of your report, 09:39:14

6 looking at Paragraph 32. 09:39:20

7 Do you agree there are four categories of 09:39:27

8 inputs? 09:39:30

9 A So in Paragraph 32, where it says the 09:39:34

10 GastroPlus involves the input of the compound, 09:39:38

11 physiology, PK, and simulation parameters, are 09:39:40

12 they the four things that you're referring to? 09:39:45

13 Q Yes. So with that in mind, I'll try 09:39:48

14 again. 09:39:55

15 Do you agree that there are four 09:39:55

16 categories of inputs: Compound parameters, 09:39:57

17 physiological parameters, pharmacokinetic 09:40:02

18 parameters, and simulation parameters? 09:40:05

19 A Yes. 09:40:08

20 Q In Paragraph 32 you state that all of the 09:40:08

21 parameters to the simulation were known. Correct? 09:40:16

22 A The modeling that I've done has generated 09:40:27

1 the parameters required for the model to provide 09:40:29
 2 the output that's listed in the declaration, and 09:40:32
 3 that was done putting myself in the position of a 09:40:36
 4 POSA at the relevant time. 09:40:39

5 Q You just state here that all of the 09:40:43
 6 parameters of the simulation were known. 09:40:48

7 A The parameters required to run the 09:40:52
 8 simulation and generate the outputs I generated 09:40:54
 9 were known. 09:40:59

10 Q Not all of the inputs were actually 09:41:00
 11 measured inputs. Right? 09:41:10

12 A So using GastroPlus in the way that a 09:41:21
 13 POSA would have used it at the time is a 09:41:25
 14 combination of measured and simulated inputs as it 09:41:30
 15 would have been used at that time. So my task was 09:41:34
 16 to generate this data based on what was available 09:41:38
 17 at that time, so I followed the best practice, and 09:41:41
 18 the results are presented. 09:41:46

19 Q So some inputs -- withdrawn. 09:41:47

20 Some input parameters were themselves in 09:41:53
 21 silico modeled. Right? 09:41:58

22 MR. GUPTA: Objection to form. 09:42:04

1	A	The parameters required were available to	09:42:05
2		the POSA to run the model as I ran it.	09:42:11
3	Q	Right. And some of the values were in	09:42:17
4		silico modeled. Right?	09:42:21
5	A	Some of --	09:42:25
6		MR. GUPTA: Hold on.	09:42:26
7		Objection to form.	09:42:27
8		You can answer.	09:42:29
9		THE WITNESS: Sorry.	09:42:29
10	A	So in the declaration I think it tells	09:42:30
11		you how the parameters were generated and input.	09:42:37
12		So I think on Page 14 there's a Footnote 2 which	09:42:44
13		describes how they were generated.	09:42:49
14	Q	So turning to Footnote 2, it states,	09:42:55
15		"Certain relevant inputs were analyzed in the	09:43:00
16		ADMET or PKPlus modules to generate certain	09:43:02
17		parameters used by GastroPlus 5.2."	09:43:08
18		Correct?	09:43:11
19	A	Yes.	09:43:16
20	Q	So some input parameters were modeled in	09:43:17
21		the ADMET predictor model. Right?	09:43:20
22	A	Yes.	09:43:26

1	Q	And some input parameters were modeled in	09:43:26
2		PKPlus. Correct?	09:43:31
3	A	Yes.	09:43:36
4	Q	ADMET is itself an in silico model.	09:43:36
5		Right?	09:43:46
6	A	Yes.	09:43:53
7	Q	And so inputs that were analyzed in the	09:43:53
8		ADMET predictor are in silico inputs. Correct?	09:44:01
9		MR. GUPTA: Objection. Form. Objection	09:44:13
10		to form.	09:44:15
11		You can answer.	09:44:15
12	A	The inputs were generated as stated in	09:44:18
13		the declaration, which is consistent with how	09:44:21
14		someone at that time would have used the software.	09:44:23
15	Q	ADMET produces in silico modeled	09:44:30
16		parameters. Correct?	09:45:02
17		MR. GUPTA: Objection to form.	09:45:04
18	A	So in my declaration, Paragraph 33	09:45:11
19		describes how GastroPlus uses the information to	09:45:20
20		generate the physicochemical properties that can	09:45:26
21		be used in a pharmacokinetic simulation.	09:45:30
22	Q	I'm just trying to understand what ADMET	09:45:35

1	predictor is. So it's an in silico model. Right?	09:45:38
2	A So ADMET is a part of the Simulations	09:45:52
3	Plus software family, which is based on a library	09:45:59
4	and machine learning of compounds that can predict	09:46:06
5	the physicochemical properties of the drug.	09:46:10
6	Q And those physicochemical properties of	09:46:13
7	the drug are used as inputs to the pharmacokinetic	09:46:32
8	modeling. Correct?	09:46:38
9	A Yeah, those inputs are used within	09:46:40
10	GastroPlus, which will predict the pharmacokinetic	09:46:43
11	profile.	09:46:45
12	Q And so because some of the inputs used	09:46:47
13	with GastroPlus come from ADMET -- withdraw that.	09:47:06
14	The inputs used with GastroPlus that come	09:47:17
15	from ADMET are themselves predicted inputs.	09:47:20
16	Right?	09:47:27
17	A That's correct. And that's absolutely	09:47:30
18	how a POSA would have used the GastroPlus software	09:47:32
19	at the time.	09:47:36
20	Q Okay. Turning to --	09:47:42
21	MS. MACRO: Can we bring up Exhibit 1027,	09:48:07
22	please.	09:48:11

1	(Petitioner Apotex Exhibit 1027,	09:48:12
2	previously marked, not attached.)	09:48:12
3	A I've also received it here.	09:50:02
4	MR. GUPTA: I have now as well.	09:50:04
5	Q I would like to introduce what's marked	09:50:05
6	as Exhibit 1027.	09:50:07
7	Dr. Batchelor, do you recognize this	09:50:11
8	document?	09:50:13
9	A Yes. It's a GastroPlus manual that's	09:50:14
10	listed in my list of documents in the declaration.	09:50:19
11	Q Can you turn to Page 23 of the PDF, which	09:50:22
12	is Page 14 of the manual.	09:50:35
13	A Uh-huh.	09:50:48
14	Q Towards the bottom of that page do you	09:50:48
15	see the paragraph that says "Ideally"? Can you	09:50:53
16	just read that paragraph and let me know when	09:51:05
17	you're done.	09:51:07
18	A Yeah, I've read that paragraph.	09:51:32
19	Q ADMET predictor generate estimates for	09:51:33
20	GastroPlus inputs. Correct?	09:51:40
21	A Yeah, I --	09:51:50
22	MR. GUPTA: I'm sorry. Objection to	09:51:51

1	form.	09:51:52
2	You can answer.	09:51:52
3	A Yeah, it says, "ADMET Predictor, a	09:51:54
4	powerful structure-to-property prediction	09:51:57
5	application from Simulations Plus, can be used to	09:52:01
6	generate estimates for GastroPlus inputs."	09:52:05
7	Q Your report includes appendices.	09:52:08
8	Correct?	09:52:16
9	A Sorry, I didn't hear the question.	09:52:16
10	Q Your report includes appendices.	09:52:19
11	Is that correct?	09:52:21
12	A Appendices, yeah. Yeah. The report	09:52:22
13	includes appendices, yes.	09:52:25
14	Q And those include the support files for	09:52:26
15	your modeling. Right?	09:52:34
16	A With the appendices, the work done to	09:52:43
17	generate the models is within the appendices, yes.	09:52:47
18	Q All right. Can you turn -- we can take	09:52:50
19	down 1027. Can you turn to Appendix I.A.1 on Page	09:52:55
20	1.	09:53:03
21	Are you there?	09:53:03
22	A On Page A-1?	09:53:04

1	Q	Yes.	09:53:11
2	A	Yes.	09:53:16
3	Q	And this is titled ADMET Predictor	09:53:17
4		Inputs. Right?	09:53:21
5	A	Yes.	09:53:22
6	Q	How did you select these run options?	09:53:22
7	A	So I put myself back into the shoes of a	09:53:31
8		POSA at the time and followed the procedure that	09:53:34
9		would have been conducted here. So it's about	09:53:36
10		using the ADMET predictor to generate values	09:53:46
11		for -- for the drug. So we used the different	09:53:54
12		settings for GastroPlus.	09:54:00
13	Q	Why did you select pH 7.4 as the pH for	09:54:02
14		pH sensitive ADMET model?	09:54:17
15	A	pH 7.4 is the default value as the plasma	09:54:23
16		pH.	09:54:29
17	Q	And then just below that you see where it	09:54:30
18		says, "ADMET risk rules will be read from the	09:54:33
19		following file"?	09:54:36
20	A	Uh-huh.	09:54:37
21	Q	What are ADMET risk rules?	09:54:37
22	A	I didn't include those in my declaration.	09:54:51

1 If you wanted to see them, they would be within 09:54:55
2 the GastroPlus manual. I wouldn't really want to 09:54:57
3 try and remember them off the top of my head here 09:55:00
4 and read them out to you. 09:55:03

5 Q Do you know if there's a separate manual 09:55:04
6 that comes with an ADMET predictor? 09:55:20

7 A I don't know from the top of my head 09:55:26
8 whether there's a separate manual, but -- there, I 09:55:28
9 don't think it's relevant to this case. 09:55:33

10 The -- without trying to memorize it, the 09:55:39
11 ADMET risk rules are risks that a candidate won't 09:55:40
12 be a suitable drug. I just don't know the 09:55:46
13 parameters of those as into how it's -- and I 09:55:48
14 wouldn't want to speculate. 09:55:55

15 In this case I don't think it's relevant 09:55:59
16 to what we're doing. Because what is shown in the 09:56:03
17 next appendix is the ADMET predictor output, which 09:56:05
18 is the values of interest for what we're doing. 09:56:10

19 Q And where would I find information on the 09:56:12
20 ADMET risk rules? 09:56:29

21 MR. GUPTA: Objection to form. 09:56:33

22 A It's not something that was part of my 09:56:34

1	declaration.	09:56:35
2	Q On the right-hand side of this, do you	09:56:40
3	see the tab, it says, ADMET Predictor (TM)?	09:56:56
4	A Yes.	09:57:04
5	Q How did you make the selections on this	09:57:05
6	ADMET predictor tab?	09:57:07
7	A As a POSA would at the time, these were	09:57:15
8	the default values.	09:57:17
9	Q Did you select any other ADMET predictor	09:57:23
10	settings other than the ones shown in Appendix	09:57:28
11	I.A.1?	09:57:33
12	A No.	09:57:38
13	Q All right. Turning to Page A-2, that	09:57:38
14	shows ADMET Predictor Output. Correct?	09:57:46
15	A It does, yes.	09:57:50
16	Q Why are some values shown in red?	09:57:50
17	A I will try and see that on a bigger scale	09:58:01
18	so that I can read them properly, if that's okay.	09:58:03
19	Q Yeah.	09:58:07
20	A So I'm just trying to find the right	09:58:34
21	document. Here we go.	09:58:36
22	That was outside of the declaration, and	09:58:53

1	I would have to review some of the paperwork to	09:58:58
2	know exactly. So I wouldn't want to speculate	09:59:01
3	right now.	09:59:04
4	Q So sitting here today, you're not sure	09:59:05
5	why some of these are red.	09:59:10
6	Is that right?	09:59:12
7	MR. GUPTA: Objection to form.	09:59:17
8	A I don't want -- because I'm here giving a	09:59:21
9	deposition, which I take quite seriously, I would	09:59:27
10	want to be sure before I said anything, rather	09:59:30
11	than guess. So without being completely sure, I'd	09:59:34
12	rather not say right now.	09:59:41
13	Q In Footnote 5 you reference an ADMET	09:59:42
14	predictor output file, Exhibit 1053.	10:00:11
15	Do you see that?	10:00:14
16	MR. GUPTA: I'm sorry. What page?	10:00:18
17	MS. MACRO: Footnote 5 on the page we're	10:00:20
18	on.	10:00:22
19	MR. GUPTA: Oh, Footnote 5. Thanks.	10:00:28
20	Q Do you see that, Dr. Batchelor?	10:00:32
21	A Yes, I do.	10:00:34
22	Q And that output file contains more values	10:00:35

1	than is showing in the screen shots in Appendix	10:00:42
2	I.A.2. Right?	10:00:47
3	A So I think my understanding is that the	10:00:57
4	output files that were provided were also provided	10:00:59
5	as screen shots here for context to allow	10:01:02
6	discussion. I'd have to open the file to -- to	10:01:07
7	see what information there was in conjunction to	10:01:13
8	what's already on the screen, just to refresh my	10:01:16
9	memory.	10:01:23
10	Q Well, let's turn back up to the screen	10:01:29
11	shot at least.	10:01:31
12	A Uh-huh.	10:01:34
13	Q Were all of the values shown on this	10:01:35
14	screen shot used as inputs to the GastroPlus	10:01:38
15	model?	10:01:51
16	A So the inputs to the GastroPlus model are	10:01:51
17	shown in the further appendices where the data was	10:01:54
18	entered.	10:01:59
19	Q Okay. Maybe we'll get to it later then.	10:02:00
20	I'm just trying to understand which inputs came	10:02:04
21	from ADMET and which didn't. Okay.	10:02:06
22	A Okay.	10:02:10

1	Q	I'll come back to it.	10:02:11
2		Okay. Some input parameters for the	10:02:23
3		GastroPlus model were modeled in the PKPlus model.	10:02:30
4		Is that right?	10:02:33
5	A	So the input parameters that were used in	10:02:40
6		GastroPlus are detailed in the declaration, either	10:02:44
7		in the text or in the appendices as screen grabs.	10:02:50
8	Q	Let's turn to -- we were looking at it	10:02:53
9		before, Footnote -- sorry, Page 14 of your	10:03:02
10		declaration, Footnote 2.	10:03:06
11	A	Okay. I can see the paragraph.	10:03:19
12	Q	Some input parameters to the GastroPlus	10:03:31
13		model were modeled in PKPlus. Correct?	10:03:34
14	A	Yeah, certain -- certain relevant inputs	10:03:42
15		were analyzed in the ADMET or PKPlus modules.	10:03:44
16	Q	PKPlus estimates pharmacokinetic	10:03:48
17		parameters from IV plasma concentration-time data.	10:03:54
18		Correct?	10:03:59
19	A	In the case of this declaration, I used	10:04:02
20		IV data within the PKPlus to generate the	10:04:04
21		pharmacokinetic parameters.	10:04:09
22	Q	And PKPlus estimates those	10:04:10

1	pharmacokinetic parameters. Correct?	10:04:16
2	A So the PKPlus parameters and the data is	10:04:22
3	generated in the appendices, the ones from -- the	10:04:28
4	ones from I.C, in other words.	10:04:31
5	Q If you can turn back to Exhibit 1027, the	10:04:37
6	GastroPlus manual. PDF Page 209, manual Page 200.	10:04:40
7	Let me know when you're there.	10:04:51
8	A My -- my screen here is just frozen,	10:05:11
9	but -- so I'll try to read off the screen while it	10:05:16
10	reloads.	10:05:18
11	Q Do you see where it says, Appendix F:	10:05:22
12	PKPlus Module, and then there are four paragraphs?	10:05:25
13	A Uh-huh.	10:05:33
14	Q Can you read that first paragraph.	10:05:34
15	A Yes.	10:05:50
16	Q You agree that PKPlus module estimates	10:05:50
17	pharmacokinetic parameters from IV plasma	10:05:57
18	concentration-time data?	10:06:00
19	A Yes.	10:06:07
20	Q Can you go to -- is your screen working	10:06:08
21	again? PDF -- sorry. Can you turn to PDF Page	10:06:16
22	212, which is Page 203 of the manual.	10:06:23

1	Do you see where it says Model Options	10:06:32
2	under F.4.2?	10:06:35
3	A Yes. F.4.2, Model Options. Yeah, I see	10:06:39
4	that.	10:06:44
5	Q Did you use a linear kinetic solution or	10:06:44
6	a nonlinear kinetic solution when you did the PK	10:06:48
7	module?	10:07:10
8	A I used a linear.	10:07:11
9	Q How did you decide which solution to use?	10:07:13
10	MR. GUPTA: Objection. Form.	10:07:20
11	You can answer.	10:07:22
12	A This comes back to the person skilled in	10:07:28
13	the art and how you would use it. As it says	10:07:30
14	there, linear kinetics governs most drugs. So you	10:07:34
15	would use linear as a default. And if that	10:07:40
16	failed, you might explore those. In this case	10:07:46
17	linear was appropriate for azacitidine.	10:07:51
18	Q And turning to -- back to your	10:07:53
19	declaration, Exhibit A -- sorry, Page A-15 in your	10:07:59
20	appendix. Let me know when you're there.	10:08:05
21	A A-15. Yes.	10:08:08
22	Q It says here that you used Hooke & Jeeves	10:08:23

1	pattern search. Right?	10:08:36
2	MR. GUPTA: I'm sorry, could I hear that	10:08:37
3	again, because it didn't come through the	10:08:38
4	real-time.	10:08:40
5	Q On Page A-15 it says the Hooke & Jeeves	10:08:40
6	pattern search was used. Correct?	10:08:56
7	A Yeah. I need to go -- I don't want to	10:09:11
8	speculate on this now, because I'm trying to	10:09:17
9	remember what was done -- not what was done. I'm	10:09:23
10	trying to recall things that happened 18 months	10:09:28
11	ago. May need some time to refresh my memory.	10:09:32
12	Q Let's turn back to the manual, Exhibit	10:09:47
13	1027. Page 213 of the PDF, which is Page 204 of	10:09:51
14	the manual.	10:10:02
15	Do you see where it says Search Method.	10:10:07
16	There are two options. Hooke & Jeeves pattern	10:10:10
17	search and Nelder-Mead Simplex.	10:10:13
18	Do you see that?	10:10:18
19	A Yeah. I think I need to read this in its	10:10:19
20	entirety rather than just pick the parts out right	10:10:22
21	now. I'm still struggling with that, with that	10:10:25
22	one manual. It won't load on my screen. Because	10:10:28

1 I think that these may be two different sections 10:10:32
2 here. So with the -- so I would need to read it 10:10:35
3 into its entirety to give a really -- to give you 10:10:43
4 the quality answer you need for this. 10:10:46

5 MS. MACRO: Can we take a break so that 10:10:59
6 the witness can refresh the link? Let's take a 10:11:00
7 break so that Dr. Batchelor can use the manual. 10:11:05

8 VIDEO SPECIALIST: We're going off 10:11:09
9 record. The time is 10:11. 10:11:11

10 (A recess was taken.) 10:11:13

11 VIDEO SPECIALIST: We're back on record. 10:11:58
12 One moment, Counsel. Sorry. We're back on 10:12:05
13 record. The time is 10:12. 10:12:08

14 Please proceed. 10:12:09

15 BY MS. MACRO: 10:12:11

16 Q Let's turn to the manual, Exhibit 1027, 10:12:12
17 Page 213 of the PDF, which is Page 204 of the 10:12:16
18 manual. 10:12:20

19 A Yeah, so I've got it to load now. 10:12:25

20 I think previously you were looking at 10:12:28
21 the model options and to Section 4.2. Then into 10:12:30
22 the Hooke & Jeeves, it's under Section F.4.3, so 10:12:38

1 they're two different parameters. So if you
2 scroll up, the linear that I was talking about was
3 the model options. You were talking about Hooke &
4 Jeeves under the Search Method. So those are two
5 different things within the GastroPlus software.

6 Q Okay. And so for the search method,
7 there's two options. Right?

8 A So for the search method, as you can see
9 in the manual, there's the Hooke & Jeeves and
10 Nelder-Mead Simplex are the two options.

11 Q And how did you decide to use Hooke &
12 Jeeves pattern search?

13 MR. GUPTA: Objection to form.

14 You can answer.

15 A Using GastroPlus as a POSA would have
16 done at the time, we used the default settings
17 unless we had good reason not to. And the default
18 setting was the Hooke & Jeeves. It says that.

19 Q And then that -- I'm sorry. Are you --

20 A I was just saying, it says that in the
21 manual in the sentence below that. It says it's
22 the default search method for PKPlus.

1	Q	And then just turning back to Exhibit --	10:13:59
2		sorry, Page A-15 of your declaration.	10:14:01
3	A	Yes.	10:14:06
4	Q	Let me know when you're there.	10:14:06
5		It says weighting. I'm going to ask you	10:14:09
6		about the weighting parameter.	10:14:12
7		Do you see that, it says, weighting 1	10:14:14
8		over $\hat{Y}$ squared.	10:14:16
9		Do you see that?	10:14:20
10	A	Uh-huh.	10:14:21
11	Q	So you used $\hat{Y}$ over $\hat{Y}$ squared as the	10:14:24
12		objective function weighting. Correct?	10:14:31
13	A	I'm just going back to check.	10:14:33
14	Q	It's PDF Page 214 of the manual, if that	10:14:40
15		helps you.	10:14:43
16	A	Yeah.	10:14:56
17	Q	How did you decide which objective	10:14:56
18		function weighting to use?	10:14:59
19		MR. GUPTA: Objection to form.	10:15:05
20	A	Again, it's using the software as a POSA	10:15:10
21		would have used it.	10:15:13
22	Q	Okay. Turning back to your declaration,	10:15:17

1	Page A-16.	10:15:21
2	A Uh-huh.	10:15:23
3	Q This shows the model results for the	10:15:23
4	200-milligram -- sorry. This Appendix 2 shows the	10:15:29
5	model results for the 200-milligram dose.	10:15:33
6	Correct?	10:15:36
7	A So Page A-16 shows a Compound tab.	10:15:41
8	Q And that's the Compound tab for the	10:15:49
9	200-milligram dose simulation. Correct?	10:15:53
10	A Yes. So these are some of the input	10:15:54
11	values.	10:15:58
12	Q I'm going to ask you about some of these	10:15:58
13	inputs. Okay?	10:16:07
14	A Okay.	10:16:08
15	Q So do you see where it says, LogP Neutral	10:16:08
16	minus 2.3?	10:16:18
17	A Yes.	10:16:20
18	Q LogP is a value you calculated from a	10:16:20
19	measured octanol-water partition coefficient in	10:16:22
20	Exhibit 1043. Correct?	10:16:25
21	A I'm just trying to cross-refer, because	10:16:29
22	it was written in the declaration. I remember	10:16:32

1	writing that part about how the LogP was	10:16:34
2	calculated.	10:16:37
3	Q Page 18 to 19 --	10:16:42
4	A Yes.	10:16:43
5	Q -- of your declaration.	10:16:44
6	A Yeah.	10:16:46
7	Q Maybe -- okay. I'll ask the question	10:16:46
8	again. LogP is measured from a -- sorry.	10:16:48
9	Withdraw.	10:16:55
10	LogP is a value you calculated from a	10:16:57
11	measured octanol-water partition coefficient in	10:17:00
12	Exhibit 1042. Correct?	10:17:03
13	A Yeah, we used the data in Israili, the	10:17:10
14	experimental data for that LogP value.	10:17:15
15	Q Does ADMET also calculate an estimated	10:17:20
16	LogP value?	10:17:23
17	A Yes. So that would be a LogP calculated	10:17:28
18	by ADMET.	10:17:35
19	In terms of best practice, using	10:17:36
20	GastroPlus where experimental data is available	10:17:40
21	and it's robust and reliable, you build your model	10:17:43
22	using that. So I used the prior art to identify	10:17:46

1	the inputs that were experimentally available and	10:17:51
2	used them where I could to ensure the model was	10:17:55
3	robust.	10:17:58
4	Q Did you compare the measured LogP to the	10:17:58
5	estimated LogP from ADMET?	10:18:08
6	MR. GUPTA: Objection to form.	10:18:15
7	A It would have looked at the data. But	10:18:18
8	knowing how to use GastroPlus, it's important to	10:18:20
9	use experimental data where it's available.	10:18:23
10	Q Turning back to A-16. Do you see the	10:18:28
11	button that says "pKa table"?	10:19:06
12	A Yes.	10:19:12
13	Q The pKa table is used to calculate	10:19:12
14	solubility versus pH. Correct?	10:19:20
15	A Correct.	10:19:24
16	Q And then that's used as an input to the	10:19:25
17	GastroPlus model. Correct?	10:19:32
18	A Correct.	10:19:33
19	Q If you turn to Page A-17, that shows the	10:19:34
20	pKa table. Correct?	10:19:53
21	A Yes.	10:19:55
22	Q The curve showing on Page A-17 is a	10:19:55

1	theoretical pKa based solubility model of	10:20:10
2	solubility over a range of pH values. Right?	10:20:15
3	A Yes, the curve shows the solubility	10:20:23
4	versus pH based on the data that's in the table.	10:20:25
5	Q You used a reference solubility for	10:20:32
6	5-azacitidine of 28 mgs per ml at pH 1.1 as an	10:20:36
7	input to the pKa table. Correct?	10:20:42
8	A Not quite. The pKa table itself is	10:20:51
9	generated by the chemical structure and the pKas.	10:20:57
10	The graph is then drawn, and that uses the input	10:21:01
11	value which was actually in the Compound tab on	10:21:06
12	the page before, the A-16 page, where we had	10:21:10
13	listed the solubility of azacitidine as being 28	10:21:13
14	and pH 1.1.	10:21:18
15	Q Would you agree that 5-azacitidine is	10:21:20
16	highly soluble?	10:21:42
17	A So for drug to classify as highly	10:21:51
18	soluble, it's important to consider not only its	10:21:56
19	solubility but also the dose. In this case	10:21:59
20	azacitidine is highly soluble.	10:22:08
21	Q Looking at the solubility pH chart on	10:22:14
22	Page A-17. You see the round circle on that plot?	10:22:27

1	A	Yes.	10:22:37
2	Q	And that corresponds to that measured	10:22:37
3		value of 28 mgs per mL of 28.1. Right?	10:22:42
4	A	That's correct, yes.	10:22:49
5	Q	You didn't input any solubility data at	10:22:51
6		different pHs. Right?	10:22:59
7	A	To generate --	10:23:05
8	Q	Withdrawn. I'll rephrase.	10:23:06
9		MR. GUPTA: Hold on.	10:23:08
10		Objection to form.	10:23:09
11		You can answer.	10:23:10
12		Oh, you're withdrawing the question?	10:23:12
13		MS. MACRO: I'm withdrawing the question.	10:23:14
14		MR. GUPTA: Go ahead.	10:23:16
15	Q	You didn't input any solubility data at a	10:23:17
16		pH other than pH 1.1. Correct?	10:23:24
17		MR. GUPTA: Objection to form.	10:23:27
18		You can answer.	10:23:31
19	A	In doing the literature review to build	10:23:35
20		the model solubility data that I identified for	10:23:37
21		this that's listed in the declaration, was the 28	10:23:46
22		milligrams at 1.1, at the pH value of 1.1. And I	10:23:56

1	didn't think it was necessary to enter other	10:24:01
2	solubility data. This was sufficient to run the	10:24:05
3	model and generate the data outputs.	10:24:12
4	Q And if we can turn to Page A-26, please.	10:24:21
5	This is the pKa table for the	10:24:45
6	400-milligram dose. Correct?	10:24:49
7	A Yes.	10:24:55
8	Q You agree for the 400 milligram for the	10:24:56
9	azacitidine dose that 5-azacitidine is highly	10:25:02
10	soluble. Correct?	10:25:04
11	A I'm just reviewing this in terms of the	10:25:22
12	solubility to see whether I do or not.	10:25:26
13	Yes.	10:25:43
14	Q Looking -- you can turn back to A-17.	10:25:48
15	Thanks.	10:26:07
16	Looking at the pH/solubility curve on	10:26:20
17	Page A-17, you would agree that the software is	10:26:30
18	predicting the solubility of 5-azacitidine rapidly	10:26:33
19	decreases around pH 3. Right?	10:26:36
20	MR. GUPTA: Objection to form.	10:26:39
21	A The chart is showing the effect of the	10:26:48
22	pKa and the pH on solubility. So it -- the	10:26:50

1	prediction is a lower solubility after pH 4,	10:26:58
2	compared to the solubility value that's shown at	10:27:03
3	pH 1.1.	10:27:05
4	Q And that solubility above pH 4 is around	10:27:06
5	2 to 3 mgs per ml. Right?	10:27:20
6	A I didn't calculate that value, so I	10:27:25
7	wouldn't want to speculate.	10:27:30
8	Q Well, it's less than 6 mgs per mL, you	10:27:31
9	can see that from the chart. Right?	10:27:37
10	A Yes, the chart clearly shows it's less	10:27:39
11	than 6, but I haven't estimated to any greater	10:27:41
12	degree than that.	10:27:43
13	Q And turning to -- sorry to jump around,	10:27:44
14	back to A-26. Let me know when you're there.	10:27:53
15	A Yeah.	10:28:03
16	Q This shows that 5-azacitidine has a	10:28:03
17	predicted lower solubility after pH 4 compared to	10:28:11
18	the solubility value at pH 1.1. Right?	10:28:16
19	MR. GUPTA: Objection to form.	10:28:23
20	You can answer.	10:28:24
21	A This graph is the same as we've just	10:28:27
22	looked at in the other appendix.	10:28:29

1	MS. MACRO: I'd like to introduce Exhibit	10:28:36
2	1042.	10:28:37
3	(Petitioner Apotex Exhibit 1042,	10:28:38
4	previously marked, not attached.)	10:30:13
5	(Discussion off the record with the A/V	10:30:13
6	technician.)	10:30:17
7	Q Ready, Dr. Batchelor?	10:31:01
8	A Yes. Yes.	10:31:02
9	Q I'd like to introduce what's been marked	10:31:05
10	as Exhibit 1042.	10:31:08
11	Dr. Batchelor, do you recognize this	10:31:13
12	exhibit?	10:31:14
13	A Yes.	10:31:15
14	Q What is it?	10:31:16
15	A It's the one listed here.	10:31:17
16	Q And it's an IARC Monographs on the	10:31:19
17	Evaluation of Carcinogenic Risks to Humans, Volume	10:31:34
18	50. Correct?	10:31:38
19	A That's correct, yes.	10:31:39
20	Q If you turn to Page 48, which is PDF Page	10:31:41
21	5. Let me know when you're there.	10:31:49
22	A Yes.	10:31:56

1	Q	This also provides -- withdrawn.	10:31:58
2		Exhibit 1042 provides solubility for	10:32:04
3		5-azacitidine in 0.1 normal sodium hydroxide.	10:32:07
4		Correct?	10:32:15
5	A	Yes.	10:32:15
6	Q	And that solubility is 43 mgs per ml.	10:32:16
7		Correct?	10:32:22
8		MR. GUPTA: Objection.	10:32:24
9		Hold on.	10:32:25
10		Objection to form.	10:32:31
11		Go ahead.	10:32:32
12	A	That's what's listed in the exhibit, yes.	10:32:32
13	Q	So Exhibit 1042 provides solubility for	10:32:37
14		5-azacitidine in 0.1 normal sodium hydroxide at 43	10:32:40
15		mgs her ml. Correct?	10:32:48
16	A	It does. But that wouldn't be a value	10:32:50
17		that would be inputted into GastroPlus because	10:32:51
18		it's not a physiologically relevant pH.	10:32:55
19	Q	0.1 normal sodium hydroxide is pH 13.	10:33:03
20		Correct?	10:33:12
21		MR. GUPTA: I'm sorry. I didn't hear the	10:33:13
22		last part of your question.	10:33:14

1	Q	0.1 -- I'll repeat.	10:33:15
2		0.1 normal sodium hydroxide is pH 13.	10:33:21
3		Correct?	10:33:26
4	A	And stretching to reach my chemistry, but	10:33:33
5		that sounds about right. I can trust you if	10:33:35
6		it's ...	10:33:37
7		My research is mainly related to oral and	10:33:45
8		gastrointestinal, so it's a pH range of a solution	10:33:48
9		I wouldn't typically use.	10:33:56
10	Q	We can agree it's highly alkalined?	10:33:58
11	A	I can agree that for sure.	10:34:00
12	Q	If you turn back to the page A-17. Let	10:34:08
13		me know when you're there.	10:34:22
14	A	Yes.	10:34:28
15	Q	Would you agree that a solubility of 43	10:34:30
16		mgs per mL or pH 13 is order of magnitude	10:34:34
17		different from the solubility predicted in this	10:34:40
18		chart?	10:34:44
19		MR. GUPTA: Objection to form.	10:34:45
20	A	When I'm conducting modeling, which was	10:34:55
21		the task I was asked to do, there's various inputs	10:34:57
22		that you would add to a model. I would not be	10:35:01

1	considering inputs for pH values of things that	10:35:05
2	are not physiological, whereas the solubility	10:35:10
3	inputted at that pH was relevant to this model.	10:35:16
4	Q In -- could you have input the solubility	10:35:21
5	values at pH 1.1 and pH 13 into GastroPlus?	10:35:56
6	MR. GUPTA: Objection to form.	10:36:04
7	A I wouldn't have done that, because pH 13	10:36:08
8	isn't a pH of relevance for GastroPlus.	10:36:12
9	Q Can you input two values into GastroPlus	10:36:19
10	to generate the solubility versus pH curve?	10:36:59
11	MR. GUPTA: Objection to form.	10:37:04
12	A The solubility versus pH is driven by the	10:37:17
13	pKa value, so that would be the more important	10:37:22
14	value to input.	10:37:25
15	Q Sorry. The pKa is the more important	10:37:26
16	value?	10:37:35
17	A If we're looking at this pKa table here,	10:37:43
18	the graph is generated based on the pKa values	10:37:49
19	there.	10:37:54
20	Q And what does the circle represent on the	10:38:12
21	chart?	10:38:14
22	A So the circle is the solubility that was	10:38:16

1 listed, the 28 at pH 1.1. 10:38:19

2 Q And if you input the solubility at pH 13, 10:38:37

3 that would also have been shown on this chart. 10:38:44

4 Correct? 10:38:47

5 MR. GUPTA: Objection to form. 10:38:48

6 A I wouldn't input a solubility at pH 13 10:38:50

7 because it's not a relevant pH for GastroPlus. 10:38:54

8 Q Can you turn to Exhibit 1027, the manual. 10:39:02

9 Let me know when you're there. 10:39:07

10 A Yes. 10:39:09

11 Q PDF Page 27, which is Page 18 of the 10:39:11

12 manual. 10:39:14

13 So in GastroPlus you can use a file which 10:39:39

14 shows solubility to pH data. Correct? 10:39:45

15 MR. GUPTA: Objection to form. 10:39:48

16 You can answer. 10:39:49

17 A The manual is showing that this is 10:39:56

18 feasible. But I didn't do it in this work because 10:39:59

19 I didn't think it was necessary. 10:40:02

20 Q And in the example shown in the manual, 10:40:08

21 it's showing values fitted at pH 10. Correct? 10:40:13

22 MR. GUPTA: Objection to form. And 10:40:27

1	scope.	10:40:35
2	Go ahead.	10:40:35
3	A The GastroPlus manual will show a whole	10:40:41
4	wealth of things that GastroPlus can do. I didn't	10:40:44
5	do this because I didn't think it was relevant to	10:40:47
6	the task I was conducting. But in this example it	10:40:49
7	is showing a data point at pH 10.	10:40:54
8	Q Okay. So turning back to A-17. Let me	10:40:59
9	know when you're there.	10:41:14
10	If this solubility pH curve changed, you	10:41:17
11	would expect changes in the GastroPlus simulation	10:41:26
12	results. Correct?	10:41:31
13	MR. GUPTA: Objection to form, and scope.	10:41:32
14	You can answer.	10:41:36
15	A No, I wouldn't expect changes for	10:41:40
16	azacitidine, as it's highly soluble across the pH	10:41:45
17	range.	10:41:49
18	Q All right. On the table do you see the	10:41:53
19	header that says SolFactor?	10:42:03
20	A Yes.	10:42:15
21	Q Can you tell me what that is?	10:42:15
22	A It's an abbreviation of solubility	10:42:22

1	factor.	10:42:25
2	Q And what is a solubility factor?	10:42:29
3	A As before, I wouldn't want to give a	10:42:31
4	false answer, so I'd rather look it up and give a	10:42:33
5	really precise answer than speculate here.	10:42:36
6	Q Do you know if it comes from ADMET	10:42:43
7	predictor?	10:42:45
8	A Sorry, I missed the question.	10:42:46
9	Q Do you know if the solubility factor	10:42:48
10	comes from the ADMET predictor?	10:42:51
11	A I don't want to speculate, so I would	10:42:59
12	need to look it up to confirm that.	10:43:01
13	Q Okay. Turning back to Page A-16.	10:43:06
14	Do you see that white box in the top	10:43:25
15	right with some values in it?	10:43:28
16	A Do you mean the one that starts Si Trans	10:43:35
17	Time?	10:43:40
18	Q Yes. Exactly.	10:43:41
19	A Yes.	10:43:44
20	Q What are the source of the values in this	10:43:45
21	box?	10:43:50
22	A They generated as part of the simulation.	10:44:05

1 So the support -- the support files which are 10:44:07
2 listed are ones that I've listed in my 10:44:10
3 declaration. And then the data, or the 10:44:14
4 information I should say, in the white box, is 10:44:19
5 part of the whole simulation. 10:44:21

6 Q So where it says SI, which I think is 10:44:37
7 small intestine, trans time is 3.209 hours, where 10:44:49
8 does that value come from? 10:44:57

9 A It's part of the physiology of the model. 10:45:13

10 Q Is that modeled in PKPlus? 10:45:16

11 A No. The PKPlus analysis that we did was 10:45:33
12 based on intravenous data, not gastric or small 10:45:40
13 intestinal data. 10:45:46

14 Q So GastroPlus is calculating these values 10:45:49
15 based on the inputs on this screen. 10:45:55

16 Is that right? 10:45:59

17 A I think the inputs on the screen are a 10:46:06
18 function of what GastroPlus is doing. So the 10:46:07
19 physiology cap that's presented in A-18. 10:46:16

20 Q So the values in the white box -- 10:46:28
21 withdrawn. 10:46:32

22 Are the values in the white box an output 10:46:32

1	of GastroPlus model?	10:46:35
2	A I'm pausing because I'm thinking about	10:46:52
3	whether they're an output. They're a	10:46:54
4	functionality, they're a part of the modeling.	10:46:59
5	I'm trying to work out -- I normally see the	10:47:01
6	output as the pharmacokinetic data, but that's --	10:47:06
7	these are also parameters. I'm trying to work out	10:47:11
8	whether I would use the word "output" or not.	10:47:16
9	They're part of the GastroPlus program.	10:47:20
10	Q Is it fair to say that parameters	10:47:22
11	calculated by GastroPlus?	10:47:28
12	A Yeah. I'm trying to work out whether	10:47:39
13	it -- what do I mean by "calculated." I'm trying	10:47:41
14	to -- the parameters that just help -- yeah, I'm	10:47:44
15	trying to work out, really, the sort of what	10:47:49
16	the -- what the -- so I would say GastroPlus is	10:47:59
17	the output being the pharmacokinetic data. These	10:48:05
18	are parameters of GastroPlus that actually in this	10:48:07
19	case aren't that relevant to azacitidine.	10:48:11
20	Q Why do you say they aren't relevant to	10:48:18
21	azacitidine?	10:48:27
22	A The task I was given was to predict the	10:48:31

1	pharmacokinetics, and those are the outputs that	10:48:35
2	were of interest.	10:48:36
3	Q Okay. Turning back to the input.	10:48:42
4	So do you see where it says, Dose Volume	10:49:12
5	250 mls?	10:49:15
6	A (Nonverbal response.)	10:49:15
7	Q Do you see that, Dr. Batchelor?	10:49:22
8	A Oh, yes. Yes. Sorry. I nodded. I	10:49:24
9	didn't say yes.	10:49:27
10	Q That's a default -- sorry. Dose volume	10:49:27
11	of 250 mls is a default value. Correct?	10:49:31
12	A It's the -- it's used as the default	10:49:39
13	because it's the value of a glass of water. So	10:49:42
14	when clinical studies are done it's assumed	10:49:44
15	that -- in a clinical study it's observed that the	10:49:47
16	tablet would be taken with a glass of water.	10:49:49
17	Q And solubility at pH 1.1 is a measured	10:49:50
18	value. Correct?	10:50:02
19	A Yes, that's the data that we just looked	10:50:04
20	at in the exhibit.	10:50:06
21	Q Mean precipitation time of 900 seconds is	10:50:08
22	a default. Correct?	10:50:14

1	A	Correct, that's a default value.	10:50:15
2	Q	Diffusion coefficient is calculated from	10:50:18
3		molecular weight. Correct?	10:50:22
4	A	Yes.	10:50:24
5	Q	Drug particle density is a default value.	10:50:24
6		Correct?	10:50:31
7	A	Yes. Those values that -- sorry.	10:50:31
8	Q	Go ahead.	10:50:37
9	A	Because azacitidine is highly soluble,	10:50:41
10		those values there are not participating in the	10:50:44
11		model in this case.	10:50:51
12	Q	Particle radius is a default value.	10:50:56
13		Correct?	10:50:59
14	A	It is.	10:51:00
15	Q	You didn't change any of these default	10:51:00
16		values and run this simulation. Correct?	10:51:25
17		MR. GUPTA: Objection to form.	10:51:31
18	A	All of the simulation data that was run	10:51:35
19		is included in the declaration.	10:51:37
20	Q	You mentioned that some of the value --	10:51:40
21		values are not participating in the model in this	10:51:55
22		case because azacitidine is highly soluble.	10:52:00

1	Which values were you referring to when	10:52:04
2	you said that?	10:52:10
3	A The precipitation time.	10:52:18
4	Q Is that the only value?	10:52:22
5	MR. GUPTA: Objection to form.	10:52:27
6	A Yes.	10:52:40
7	Q So -- withdrawn.	10:52:40
8	Precipitation time is the only input	10:52:59
9	value on this page which you consider is not	10:53:04
10	participating in the model because azacitidine is	10:53:08
11	highly soluble.	10:53:10
12	Is that correct?	10:53:11
13	A Yes.	10:53:16
14	Q We've just -- I just lost you on my	10:53:17
15	screen. I can hear you. So I just need to go off	10:53:26
16	the record.	10:53:29
17	VIDEO SPECIALIST: We're going off the	10:53:35
18	record. The time is 10:53.	10:53:36
19	(A recess was taken.)	10:53:38
20	VIDEO SPECIALIST: We are back on record.	11:02:32
21	The time is 11:02.	11:02:37
22	BY MS. MACRO:	11:02:43

1	Q	Looking at Page A-16.	11:02:45
2		Do you see the box that says, Effective	11:02:47
3		Permeability?	11:02:59
4	A	Page A-16, yes. Effective permeability.	11:03:00
5	Q	And you used a effective permeability of	11:03:03
6		0.51 centimeters per second times 10 to the	11:03:09
7		negative 4?	11:03:16
8		Is that right?	11:03:16
9	A	Yes.	11:03:24
10	Q	What's the source of the effective	11:03:24
11		permeability value?	11:03:28
12	A	In this simulation that was one of the	11:03:35
13		values from the ADMET predictor.	11:03:37
14	Q	If you turn to Page A-2 of your	11:03:39
15		declaration. Let me know when you're there.	11:03:53
16	MS. MACRO:	Can you zoom in to the middle	11:04:13
17		of that table. A couple more zooms. Okay.	11:04:17
18	Q	Dr. Batchelor, do you have Page A-2 in	11:04:24
19		front of you?	11:04:26
20	A	Yes.	11:04:27
21	Q	Do you see there are two headings, one	11:04:27
22		that says S+Peff and next to it S+Pavg.	11:04:35

1	A	Yes.	11:04:51
2	Q	What is the S+P effective value shown	11:04:51
3		here?	11:05:00
4	A	I don't want to speculate. I would need	11:05:10
5		to look up the exact -- the exact terminology	11:05:12
6		that's used for that.	11:05:17
7	Q	Would you agree that the GastroPlus	11:05:24
8		simulation is using the S+P average value as the	11:05:26
9		effective permeability input?	11:05:33
10	A	That's the value that's being used in the	11:05:37
11		simulations, yes.	11:05:39
12	Q	And without looking it up, you don't know	11:05:47
13		what the difference is between S+P effective and	11:05:50
14		S+P average.	11:05:54
15		Is that right?	11:05:56
16	MR. GUPTA:	Objection to form.	11:05:59
17	A	I -- I'm not confident enough to be able	11:06:04
18		to say it explicitly now so that it's recorded as	11:06:09
19		part of this deposition. I would need time to	11:06:14
20		just explore that before it goes into an official	11:06:16
21		record.	11:06:20
22	Q	You didn't explain the difference between	11:06:20

1	S+P effective and S+P average in your declaration.	11:06:30
2	Right?	11:06:33
3	A I didn't think it was necessary. The way	11:06:35
4	that the GastroPlus modeling was done was as a	11:06:38
5	POSA would have done at the time of the prior art,	11:06:43
6	and I'm confident in the outputs that were	11:06:45
7	generated.	11:06:47
8	Q You agree that 5-azacitidine has low	11:06:48
9	permeability?	11:07:09
10	MR. GUPTA: Objection to form.	11:07:13
11	A It's not something I explored explicitly	11:07:18
12	in my declaration, so I would -- wouldn't want to	11:07:21
13	speculate just now.	11:07:29
14	Q But you don't have an opinion whether	11:07:34
15	5-azacitidine is -- has low permeability.	11:07:36
16	Correct?	11:07:41
17	A It wasn't part of the task that I was	11:07:43
18	asked to undertake, which was look at the	11:07:46
19	pharmacokinetics. It's not something I've	11:07:48
20	considered, and it's something I would want time,	11:07:51
21	if you really wanted my opinion on it, to look it	11:07:54
22	up.	11:07:56

1	Q	And turning back to A-16. Let me know	11:07:57
2		when you're there.	11:08:23
3		Are you there, Dr. Batchelor, on Page	11:08:37
4		A-16?	11:08:40
5	A	Yes. A-16, yeah.	11:08:40
6	Q	For the 200-milligram dose, if you	11:08:43
7		changed the effective permeability, would you	11:08:51
8		necessarily get the same predicted AUC value?	11:08:54
9		MR. GUPTA: Objection to form.	11:08:57
10	A	I wouldn't change it. It wouldn't make	11:09:02
11		sense to change it for the purposes of what I was	11:09:05
12		doing.	11:09:09
13	Q	If you did change it, would you	11:09:11
14		necessarily get the same predicted AUC value for	11:09:15
15		the 200-milligram dose?	11:09:18
16		MR. GUPTA: Objection to form.	11:09:22
17	A	I wouldn't -- I wouldn't change it, so it	11:09:24
18		wouldn't make sense to change it.	11:09:30
19	Q	You can change it. Right?	11:09:36
20		MR. GUPTA: Objection to form.	11:09:38
21	A	Well, GastroPlus enables you to do --	11:09:42
22		type in a different number. But it wouldn't make	11:09:51

1	sense to do that.	11:09:54
2	Q Is the AUC value for the 200-milligram	11:09:55
3	dose permeability-dependent?	11:10:03
4	MR. GUPTA: Objection to form.	11:10:08
5	A It's not part of my declaration. My	11:10:16
6	declaration was to look at the pharmacokinetics	11:10:19
7	following a 200- and 400-milligram dose.	11:10:23
8	Q I think we went over this before.	11:10:27
9	A Yes, we did.	11:10:41
10	Q You didn't vary any of the values shown	11:10:42
11	on Page A-16 other than dose and run the	11:10:44
12	simulation. Correct?	11:10:48
13	MR. GUPTA: Objection to form.	11:10:50
14	A The modeling that was done is reported in	11:10:56
15	this declaration. And we ran the model using a	11:11:02
16	200-milligram dose and a 400-milligram dose, and	11:11:05
17	that's what's reported here.	11:11:08
18	Q Turning to Page A-19. Now I'm going to	11:11:09
19	ask you about the Pharmacokinetics tab. Just let	11:11:20
20	me know when you're there.	11:11:24
21	A A-19. Yes, I have that in front of me.	11:11:25
22	Q The values of blood plasma concentration	11:11:37

1	ratio was taken from Israeli. Correct?	11:11:42
2	A It's in the declaration. It's --	11:11:52
3	Q Yeah. So why don't you turn to Page 20	11:11:55
4	of your declaration, Paragraph 45. Let me know	11:11:57
5	when you're there.	11:12:02
6	A Yes. Yes, I've got that. And yes, it	11:12:05
7	was the Israeli reference.	11:12:08
8	Q So the value for blood plasma	11:12:09
9	concentration was taken from Exhibit 1043,	11:12:13
10	Israeli. Correct?	11:12:17
11	A Yes.	11:12:18
12	Q And the value for unbound percent in	11:12:18
13	plasma was taken from Exhibit 1043, Israeli.	11:12:24
14	Correct?	11:12:28
15	A Yes.	11:12:29
16	Q And you state that distribution and	11:12:29
17	clearance related values were generated by PKPlus	11:12:41
18	from PK data in Marcucci. Correct?	11:12:45
19	A Yes.	11:12:50
20	Q Turning back to A-19.	11:12:50
21	Can you tell me which are the	11:12:58
22	distribution and clearance-related values?	11:13:01

1 A So on A-19, in the table? The clearance
2 values are shown as renal clearance, and the CL in
3 the box below that is liters per hour. So that is
4 the clearance values. 11:13:19
11:13:29
11:13:35
11:13:42

5 And the distribution values, so, I don't
6 know. I'm not seeing it on your screen, I'm
7 seeing it on my screen. I don't know if you
8 wanted me to point it out on the -- 11:13:45
11:13:53
11:13:56
11:13:58

9 MS. MACRO: Yeah. Can you go to Page
10 A-19, which is on ... 11:14:00
11:14:02

11 A So on this table, underneath the line
12 that says "renal clearance," there's a clearance
13 CL in liters per hours of 183, per liters per hour
14 per kilo. Those are both clearance values. It's
15 just the same value but in different units. 11:14:19
11:14:22
11:14:25
11:14:30
11:14:34

16 And then distribution, so the
17 distribution of a drug relates to its volume of
18 distribution, so there's a V_c , the central volume
19 in liters per kilo, that's listed there. And
20 there's also a V_2 , which is a two-compartmental
21 model. That's the volume of the second
22 compartment. So those are some of the 11:14:36
11:14:39
11:14:42
11:14:46
11:14:50
11:14:56
11:14:58

1	distribution ones.	11:15:00
2	And then the rate constants that refer to	11:15:02
3	how the drug moves between the two compartments	11:15:05
4	are listed at K12 and K21. So those are the	11:15:08
5	values.	11:15:13
6	Q So I'm just going to take you back	11:15:20
7	through that so I have it clear for me. Okay?	11:15:22
8	A Okay.	11:15:25
9	Q Sorry. So renal clearance is estimated	11:15:25
10	value from PKPlus. Correct?	11:15:30
11	A So the --	11:15:38
12	MR. GUPTA: Hold on.	11:15:39
13	Objection to form.	11:15:40
14	You can answer.	11:15:42
15	A So the way that the model is marking as	11:15:47
16	the clearance is there in this particular screen,	11:15:51
17	it's showing you the clearance value beneath the	11:15:55
18	renal clearance.	11:15:57
19	Q Sorry. The CL in liters per hour or	11:15:59
20	liters per hour per kilogram --	11:16:07
21	A Yes.	11:16:11
22	Q -- is a value from PKPlus.	11:16:11

1	Correct?	11:16:18
2	A Yes.	11:16:19
3	Q And Vc is an estimated value from PKPlus.	11:16:19
4	Correct?	11:16:27
5	A Yes.	11:16:29
6	Q And T half is an estimated value from	11:16:29
7	PKPlus? Correct?	11:16:44
8	MR. GUPTA: Objection to form.	11:17:03
9	A The half-life here I think it is -- well,	11:17:08
10	it would be the same whether it came from PKPlus	11:17:13
11	or here because it's the clearance of the volume.	11:17:16
12	So, yeah.	11:17:21
13	Q And the rate constant K12 and then K21,	11:17:21
14	those are estimated values from PKPlus. Correct?	11:17:35
15	A Those values came from the simulation we	11:17:41
16	did in PKPlus.	11:17:43
17	Q And V2 is an estimated value from PKPlus.	11:17:46
18	Correct?	11:17:51
19	A Yes.	11:17:54
20	MR. GUPTA: Objection. Objection.	11:17:55
21	THE WITNESS: Sorry.	11:17:56
22	A Yeah, it came from the -- came from the	11:17:57

1	work we did using PKPlus. I think the values are	11:17:58
2	also listed in A-10, the appendix.	11:18:03
3	Q So you see the box on the right that	11:18:06
4	says, Observed Values?	11:18:12
5	A Yes.	11:18:13
6	Q No observed values were used. Correct?	11:18:13
7	A At the time when this was conducted,	11:18:20
8	there was no oral data that we could use to put as	11:18:22
9	observed values into the simulation.	11:18:26
10	Q No changes to The Metabolism/Transporter	11:18:32
11	Scale Factors were being made. Correct?	11:18:41
12	A Correct.	11:18:45
13	Q Looking back on the left-hand side, do	11:18:45
14	you see the box that says "First pass extraction	11:18:51
15	(if fixed) percentage"?	11:18:55
16	A Yes.	11:18:57
17	Q You did not include any first pass	11:18:57
18	extraction. Correct?	11:18:59
19	A Correct.	11:19:01
20	Q First pass extraction percentage is the	11:19:01
21	percent of drug extracted in the liver before it	11:19:08
22	passes into the systemic circulation. Correct?	11:19:10

1 MR. GUPTA: Objection to form. 11:19:16

2 A This isn't something that's covered in my 11:19:20
3 declaration in detail, or at all. I don't think 11:19:23
4 that I mentioned first pass in there. 11:19:29

5 MS. MACRO: Can you pull up Exhibit 1027, 11:19:35
6 please. And go to PDF Page 41, which is Page 32 11:19:40
7 of the manual. 11:19:50

8 Q And do you see where it's defining there 11:19:58
9 first pass extraction (if fixed) percentage, can 11:20:02
10 you read that definition and let me know when 11:20:07
11 you're done. 11:20:09

12 A I've read the paragraph. 11:20:23

13 Q First pass extraction percentage 11:20:24
14 parameter is the percent of drug extracted in the 11:20:30
15 liver before it passes into the systemic 11:20:34
16 circulation. Correct? 11:20:41

17 MR. GUPTA: Objection. 11:20:42

18 A I'm not seeing that sentence written on 11:20:42
19 the page. 11:20:44

20 Q It's -- 11:20:49

21 A Yeah, yeah. 11:20:50

22 Q I'll ask again. 11:20:51

1	First pass extraction percentage	11:20:52
2	parameter is the percent of drug extracted in the	11:20:57
3	liver before it passes into the systemic	11:21:00
4	circulation. Correct?	11:21:02
5	A Yeah, that's what it says. Yeah.	11:21:03
6	Q And if you look at the last sentence,	11:21:15
7	"First pass extraction percentage includes first	11:21:16
8	pass extraction that can take place in gut	11:21:22
9	metabolism."	11:21:22
10	Correct?	11:21:30
11	MR. GUPTA: Objection to form.	11:21:30
12	A So I've read the paragraph, and I wasn't	11:21:41
13	sure what the question was. Sorry.	11:21:42
14	Q The first pass extraction percentage	11:21:45
15	parameter includes first pass extraction that can	11:21:49
16	take place in gut metabolism. Correct?	11:21:54
17	A That -- so that's what it's saying within	11:22:04
18	the manual. It's the transporters within the gut	11:22:06
19	wall there it's talking about, the enzymes there.	11:22:10
20	Q You did not account for any first pass	11:22:12
21	metabolism in your simulation. Correct?	11:22:29
22	MR. GUPTA: Objection to form.	11:22:34

1 A The task I was given was to build a 11:22:40
2 GastroPlus model to simulate the drugs at 200 and 11:22:43
3 400 milligrams. I identified literature to build 11:22:46
4 the model. So there was no data to be included on 11:22:50
5 this. 11:23:00

6 So the model was built in a robust way to 11:23:03
7 give us the outputs that I'm confident are 11:23:06
8 reliable for what could have taken place at the 11:23:08
9 time that a person -- a POSA at the time of the 11:23:12
10 patent. 11:23:15

11 Q If you change the first pass extraction 11:23:22
12 percentage, you would not necessarily get the same 11:23:28
13 AUC value for the 200-milligram dose. Correct? 11:23:31

14 MR. GUPTA: Objection to form. 11:23:34

15 A I wouldn't change the value because there 11:23:35
16 was no meaningful input to use. 11:23:39

17 Q And if you changed the first pass 11:23:47
18 percentage, you would not necessarily get the same 11:23:54
19 AUC value for the 400-milligram dose. Correct? 11:23:56

20 MR. GUPTA: Objection to form. 11:23:59

21 A I wouldn't. I wouldn't change the value. 11:24:02
22 I'm confident in the model that was generated 11:24:05

1	being one that one would have generated at the	11:24:08
2	time of the patent.	11:24:12
3	Q 5-azacitidine is subject to first pass	11:24:15
4	extraction. Correct?	11:24:22
5	MR. GUPTA: Objection to form. And	11:24:24
6	scope.	11:24:31
7	Go ahead.	11:24:32
8	A That's outside the -- that's outside the	11:24:32
9	declaration. When I did the literature search, no	11:24:35
10	evidence came up that would justify me including a	11:24:41
11	value there.	11:24:45
12	Q In your literature search -- withdraw.	11:24:48
13	In your literature search did you	11:25:21
14	identify a reference that said 5-azacitidine is	11:25:25
15	not subject to first pass extraction?	11:25:29
16	MR. GUPTA: Objection to form.	11:25:32
17	A In my search I did not find data	11:25:37
18	following oral administration of azacitidine. And	11:25:42
19	first pass metabolism is only relevant for oral	11:25:51
20	administration.	11:25:54
21	Q Can you turn to Exhibit 1017, which is	11:25:56
22	Marcucci. Let me know when you're there.	11:26:07

1	A	Exhibit 1017. I don't think that one is	11:26:16
2		in the SharePoint. Is it?	11:26:22
3	Q	We had it up.	11:26:24
4		A/V TECHNICIAN: Yeah, it's in there.	11:26:27
5	A	Yeah, I just got it up. Okay.	11:26:29
6		Which page?	11:26:31
7	Q	Okay. So please turn to Exhibit 1017,	11:26:32
8		Marcucci, PDF Page 5.	11:26:36
9	A	Yeah.	11:26:47
10	Q	On the right-hand column more towards the	11:26:47
11		bottom do you see the paragraph that says, "The	11:26:54
12		apparent (SC) clearance."	11:26:56
13		Do you see that paragraph?	11:26:59
14	A	The apparent subcutaneous clearance.	11:27:00
15		I've read the paragraph.	11:27:32
16	Q	Marcucci states that 5-azacitidine is	11:27:33
17		metabolized. Correct?	11:27:40
18		MR. GUPTA: Objection.	11:27:46
19	A	Yes.	11:27:47
20		THE WITNESS: Sorry.	11:27:47
21		MR. GUPTA: Yeah, I objected to form.	11:27:48
22	Q	Marcucci states that the role of	11:27:50

1	metabolism in the disposition of azacitidine is	11:27:55
2	potentially quite significant. Correct?	11:28:01
3	MR. GUPTA: Objection to form.	11:28:03
4	A So the SC clearance shown by Marcucci	11:28:07
5	following the intravenous dose is due to the drug	11:28:14
6	being cleared, and it's being cleared by this	11:28:17
7	metabolism. So when we built our model using the	11:28:21
8	Marcucci data for the IV, all of this information	11:28:25
9	that's in this paper is built into that model.	11:28:27
10	Q But the Marcucci data doesn't take into	11:28:33
11	account the pass metabolism. Correct?	11:28:38
12	MR. GUPTA: Objection to form.	11:28:42
13	A The Marcucci data is based on an	11:28:43
14	intravenous or a subcutaneous dose, so neither of	11:28:45
15	which of those are oral. So -- so they don't	11:28:50
16	report anything at all on first pass metabolism.	11:28:55
17	Q Is first pass metabolism considered	11:28:58
18	nonrenal elimination?	11:29:12
19	MR. GUPTA: Objection to form. Scope.	11:29:17
20	A Yeah, I don't know how this is relevant	11:29:22
21	to the declaration.	11:29:26
22	Q Well, you're an expert, so I'm taking it	11:29:33

1	to the --	11:29:33
2	A Yeah. I mean --	11:29:41
3	Q Sorry. Go ahead.	11:29:45
4	A Although it -- I don't think it's	11:29:50
5	relevant to the azacitidine. Renal clearance is	11:29:52
6	clearance by the kidneys, and first pass is gut	11:29:58
7	wall and liver.	11:30:02
8	Q So you would agree that first pass	11:30:05
9	metabolism is a type of nonrenal elimination.	11:30:10
10	Correct?	11:30:14
11	MR. GUPTA: Objection. Form. Scope.	11:30:15
12	Relevance.	11:30:16
13	You can answer.	11:30:20
14	A Okay. If you look at the Marcucci data,	11:30:23
15	the nonrenal elimination is dictating the rapid	11:30:27
16	clearance there. So the nonrenal elimination	11:30:31
17	that's happening from the body is accounted for in	11:30:35
18	the intravenous data which was used to build the	11:30:38
19	model.	11:30:42
20	Q That's not what I asked you. Would you	11:30:46
21	agree that first pass metabolism is a type of	11:30:48
22	nonrenal elimination?	11:30:51

1	MR. GUPTA: Objection. Form. Scope.	11:30:52
2	Relevance.	11:30:55
3	A First pass metabolism is metabolism that	11:30:59
4	occurs at the gut wall or in the liver following	11:31:03
5	oral availability, so it doesn't involve the	11:31:06
6	kidneys.	11:31:11
7	Q So first pass metabolism is nonrenal.	11:31:12
8	Correct?	11:31:18
9	MR. GUPTA: Same objection.	11:31:19
10	A The kidneys aren't involved in first pass	11:31:26
11	metabolism.	11:31:29
12	Q So because the kidneys are not involved	11:31:30
13	in first pass metabolism, you would agree that	11:31:38
14	first pass metabolism is nonrenal. Correct?	11:31:42
15	MR. GUPTA: Objection. Form. Same	11:31:46
16	objections as before.	11:31:48
17	You can answer.	11:31:50
18	A Nonrenal elimination includes elimination	11:31:53
19	by metabolism in the liver, gut wall metabolism.	11:31:58
20	I don't really understand where this is relevant	11:32:07
21	to the azacitidine. I'm just getting confused.	11:32:10
22	Q Do you know whether first pass metabolism	11:32:12

1	is considered nonrenal?	11:32:24
2	MR. GUPTA: Objection. Form. Scope.	11:32:28
3	Relevance. Asked and answered.	11:32:30
4	You can -- you can answer.	11:32:32
5	A I can repeat the answer I've already	11:32:36
6	given. First pass metabolism occurs at the gut	11:32:38
7	wall and in the liver; it doesn't involve the	11:32:41
8	kidney.	11:32:43
9	Q I'm sorry, because first pass metabolism	11:32:43
10	doesn't involve the kidney, first pass metabolism	11:32:51
11	is considered nonrenal. Correct?	11:32:55
12	MR. GUPTA: Same objections.	11:32:59
13	A I've never seen first pass metabolism	11:33:03
14	described in that sort of abstract way before.	11:33:07
15	First pass metabolism involves the gut wall and	11:33:09
16	the liver; it doesn't involve the kidney.	11:33:12
17	Q Would you describe first pass metabolism	11:33:14
18	as renal elimination?	11:33:41
19	MR. GUPTA: Same objections. And	11:33:45
20	relevance.	11:33:53
21	A I describe first pass metabolism as first	11:33:56
22	pass metabolism. I don't see the need to use any	11:33:58

1	other terminology for it.	11:34:01
2	Q So that's a no then?	11:34:03
3	MR. GUPTA: Now you're being	11:34:05
4	argumentative. Objection. Argumentative. And	11:34:07
5	same objections as before.	11:34:09
6	Q Yes or no, would you describe first pass	11:34:14
7	metabolism as renal elimination?	11:34:18
8	MR. GUPTA: Objection to form. Same	11:34:22
9	objections as before.	11:34:23
10	THE WITNESS: Does that mean I need to	11:34:30
11	answer?	11:34:32
12	MR. GUPTA: Yeah. You can. You can	11:34:34
13	answer.	11:34:38
14	A I think it needs to be described clearly	11:34:42
15	in context. And in this case first pass	11:34:44
16	metabolism doesn't involve the kidneys. But I	11:34:51
17	feel that in isolation we've got to discuss this	11:34:54
18	as a whole of the declaration of azacitidine.	11:34:59
19	Q Can you turn to Page A-18.	11:35:07
20	Do you see the box that says, Enzyme And	11:35:44
21	Transporter Regional Distributions?	11:35:47
22	A Yeah, I can see the box.	11:35:52

1	Q	GastroPlus 5.2 allows a user to scale	11:35:54
2		back to the gut enzymes each compartment.	11:36:02
3		Correct?	11:36:05
4	A	It incorporates the gut wall enzymes, so	11:36:07
5		those that are present in the enterocytes of the	11:36:10
6		gut wall.	11:36:16
7	Q	Can you turn to Exhibit 1027, GastroPlus	11:36:18
8		manual, PDF Page 217. Page 208 of the manual.	11:36:31
9		Do you see that?	11:37:02
10	A	Yes.	11:37:03
11	MR. GUPTA:	I'm sorry. Please let me get	11:37:03
12		there. One second.	11:37:05
13	THE WITNESS:	Sorry.	11:37:07
14	MR. GUPTA:	Okay. Thanks.	11:37:18
15	Q	Actually, can you turn to PDF Page 218,	11:37:21
16		which is Page 209.	11:37:36
17		Do you see where it says Enzymes Table?	11:37:43
18	A	In G.4.	11:37:58
19	Q	Yeah.	11:38:00
20		You didn't adjust any of the scale	11:38:06
21		factors for gut enzymes in your GastroPlus model.	11:38:14
22		Correct?	11:38:22

1 MR. GUPTA: Objection to form. 11:38:22

2 A I didn't think it was necessary to do 11:38:28
3 that for the task I was asked to do. 11:38:30

4 Q And if you can turn to Page 28 of the 11:38:32
5 PDF, which is Page 19 of the manual. And read the 11:38:49
6 very last paragraph at the bottom. And let me 11:38:52
7 know when you're done. 11:38:55

8 A The paragraph starting "For gut enzymes." 11:39:01
9 I've read the paragraph. 11:39:35

10 Q The enzyme distribution factors are built 11:39:36
11 into the Physiology tab are for enzymes 3A4 and 11:39:43
12 2D4 family. Correct? 11:39:50

13 MR. GUPTA: Objection to form. 11:39:54

14 A So in the manual it says that the 11:40:02
15 built-in enzyme distribution factors for the 11:40:04
16 gut -- this is just relating to the gut wall 11:40:07
17 enzymes -- the ratios of the amounts relative to 11:40:09
18 the amounts in an 1800-gram liver and provided 11:40:17
19 only for 3A4 and 2D6. 11:40:21

20 Q Okay. You can turn back to Page A-18 of 11:40:28
21 your report. Let me know when you're there. 11:40:34

22 A Yeah, I have that in front of me. 11:40:45

1	Q	For the Compartment Data you used human	11:40:46
2		physiology in the fasted state as the model.	11:40:58
3		Correct?	11:41:00
4	A	Yeah, that's the sort of standard way of	11:41:01
5		operating GastroPlus that you would have used at	11:41:03
6		this time.	11:41:06
7	Q	You used a default compartment data	11:41:06
8		associated with that model. Correct?	11:41:14
9	A	Yes.	11:41:17
10	Q	You used the optimized logD model for	11:41:17
11		calculating the absorption scale factor. Correct?	11:41:24
12	A	Yes.	11:41:30
13	Q	Can you turn back to Exhibit 1027, the	11:41:31
14		manual, PDF Page 40, Page 31 of the manual.	11:41:36
15		I think my citation is wrong. Okay. I'm	11:42:23
16		referring to Exhibit 1027. Please turn to PDF	11:42:29
17		Page 14 and look at the top. It says, Notes.	11:42:34
18		Do you see that? And can you just read	11:42:42
19		that paragraph. Read that paragraph and let me	11:42:44
20		know when you're done.	11:42:46
21	A	Yeah, I've read that paragraph.	11:43:03
22	Q	The manual states that the opt logD model	11:43:06

1 is a general absorption model for compounds where 11:43:13

2 no better information is available. Correct? 11:43:20

3 MR. GUPTA: Objection to form. 11:43:23

4 A It says, the default simulation, Plus Opt 11:43:24

5 logD module, incorporates that. The scale factors 11:43:27

6 are used as a general absorption model where no 11:43:33

7 better information is available. That's what it 11:43:35

8 says in the manual. 11:43:37

9 Q It says that it is not exact for any one 11:43:38

10 drug but is the best compromise over a set of 11:43:43

11 drugs. Correct? 11:43:50

12 A That's what the manual says. It also 11:43:55

13 says it's the default file. So when you're a 11:43:56

14 person -- a POSA at the time of the patent, it's 11:44:01

15 the -- it's the option you would select for a drug 11:44:05

16 at that time. 11:44:10

17 Q The optimized logD model is not exact for 11:44:13

18 5-azacitidine. Correct? 11:44:18

19 MR. GUPTA: Objection to form. 11:44:20

20 A My task was to undertake a simulation to 11:44:25

21 predict the pharmacokinetics of azacitidine 200 11:44:28

22 and 400 milligrams as someone could have done at 11:44:33

1 the time of the patent and the prior art. So I 11:44:35
2 used the tools available in the best possible way 11:44:39
3 to get to those predictions. And that's what's in 11:44:43
4 the declaration. 11:44:47

5 Q Is the optimized logD model exact for 11:44:48
6 5-azacitidine? 11:44:56

7 MR. GUPTA: Objection to form. 11:44:57

8 A The task was to use the tools that would 11:45:07
9 be available at the time of the patent to predict 11:45:10
10 the pharmacokinetics of azacitidine. This is the 11:45:12
11 default option. It's the best -- best possible 11:45:18
12 model that could have been conducted at that time. 11:45:24
13 It's the very best way of undertaking this 11:45:26
14 modeling. It's the most robust way. 11:45:28

15 Q Well, the manual says that the opt logD 11:45:31
16 module is not exact for any one drug. Correct? 11:45:38

17 MR. GUPTA: Objection to form. And 11:45:42
18 scope. 11:45:46

19 A Yeah, if you read the paragraph in 11:45:50
20 isolation, you can say that it's the default 11:45:52
21 option. It's the -- these factors are used where 11:45:57
22 there's no better information available. And 11:46:02

1 then -- and then it says that it's the most 11:46:05
 2 suitable to use for the modeling I undertook for 11:46:08
 3 the purposes of this declaration. 11:46:11

4 Q The manual says that you may need to 11:46:14
 5 calibrate the absorption scale factors for your 11:46:18
 6 drug. Correct? 11:46:22

7 MR. GUPTA: Objection to form. 11:46:25

8 A The manual says you may need to. It -- 11:46:29
 9 we didn't -- you know, for azacitidine, I was 11:46:35
 10 asked to undertake the modeling as a POSA would at 11:46:38
 11 the time of the patent, and that's what's reported 11:46:41
 12 in the declaration, using the best -- to the 11:46:43
 13 best -- the best tools that would be available at 11:46:47
 14 the time to give the most robust output. 11:46:49

15 Q You didn't calibrate the absorption scale 11:46:56
 16 factors for 5-azacitidine. Correct? 11:47:01

17 MR. GUPTA: Objection to form. 11:47:04

18 A I didn't need to. The task that I was 11:47:05
 19 given was to model the pharmacokinetics as someone 11:47:08
 20 could have done at the time that's relevant in 11:47:13
 21 this case based on a POSA, and that's the task 11:47:17
 22 that's presented in this declaration. It wasn't 11:47:19

1	necessary.	11:47:27
2	Q Because you didn't need to, you didn't	11:47:27
3	calibrate the absorption scale factors of	11:47:29
4	5-azacitidine. Correct?	11:47:33
5	MR. GUPTA: Objection to form.	11:47:34
6	A It wasn't necessary to do that.	11:47:35
7	Q We've been looking at the appendices for	11:47:48
8	the 200-milligram dose. Except for changing the	11:47:51
9	dose -- sorry. Let me withdraw that.	11:47:59
10	We've been looking at the parameters for	11:48:02
11	the Physiology tab of the 200-milligram dose.	11:48:05
12	Except for changing the dose, the parameters of	11:48:13
13	the simulation were the same for the 400-milligram	11:48:17
14	dose. Correct?	11:48:20
15	MR. GUPTA: Object.	11:48:21
16	THE WITNESS: Sorry.	11:48:23
17	MR. GUPTA: I'm sorry. I'm just waiting	11:48:24
18	for the real-time to come in. Just give me a	11:48:25
19	second.	11:48:28
20	Objection to form.	11:48:31
21	Go ahead.	11:48:33
22	A The Physiology tab for the 200-milligram	11:48:34

1	dose is shown on Page A-18. And the Physiology	11:48:39
2	tab for the 400-milligram dose is shown on Page	11:48:42
3	A-27. So they're both within the declaration.	11:48:46
4	Q You didn't change any parameters on the	11:48:50
5	Physiology tab between the 200-milligram dose and	11:49:12
6	the 400-milligram dose. Right?	11:49:15
7	MR. GUPTA: Same objection.	11:49:18
8	A In both cases the data shown in the	11:49:26
9	declaration, there was no need to change the	11:49:29
10	Physiology tab between the two doses. The only	11:49:32
11	thing of interest you were looking at was the	11:49:38
12	different dose.	11:49:40
13	Q Can you please turn to your declaration,	11:49:41
14	Exhibit 1003, Page 16, specifically Paragraph 34.	11:50:05
15	A Paragraph 34.	11:50:40
16	Q You state that the hydrolysis rate for	11:50:43
17	5-azacitidine reported in the literature for pH	11:51:05
18	values between 4.5 and 8 aqueous 37 degrees.	11:51:08
19	Is that right?	11:51:16
20	A Yes.	11:51:16
21	Q And you base that on the Chan paper,	11:51:18
22	which is Exhibit 1014. Correct?	11:51:21

1 A Yeah, the literature I referred to is the 11:51:24
2 Chan paper. 11:51:27

3 Q You are aware that 5-azacitidine is known 11:51:28
4 to be acid labile. Correct? 11:51:33

5 MR. GUPTA: Objection to form. 11:51:38

6 A When conducting the search to build the 11:51:42
7 model, I was really interested in data that would 11:51:45
8 be used to feed into the model. And this was the 11:51:48
9 most relevant paper that I identified. 11:51:53

10 Q So based on your literature search, you 11:51:56
11 were aware that 5-azacitidine was 90 acid labile. 11:52:24
12 Correct? 11:52:31

13 MR. GUPTA: Objection to form and scope. 11:52:32
14 Go ahead. 11:52:34

15 A The literature used for the model was the 11:52:36
16 Chan data that's reported here in the declaration. 11:52:39

17 Q And Chan shows that 5-azacitidine is acid 11:52:46
18 labile. Correct? 11:52:50

19 MR. GUPTA: Objection to form. 11:52:51

20 A Chan reported, as is shown in Paragraph 11:52:54
21 35 of my report, degradation with rate constants 11:52:58
22 over a range of pH was from 4.5 to 8. 11:53:03

1	Q	And that degradation rate constant shown	11:53:14
2		in Chan shows that 5-azacitidine is acid labile.	11:53:18
3		Correct?	11:53:26
4		MR. GUPTA: Objection to form.	11:53:27
5	A	So the data in Chan shows the degradation	11:53:34
6		rate constants at a range of pHs.	11:53:38
7	Q	You agree that the pH of a stomach in the	11:54:03
8		fasted state is a pH of about 1.1. Correct?	11:54:08
9		MR. GUPTA: Objection to form.	11:54:12
10	A	The pH of the stomach I think is shown in	11:54:15
11		sort of the appendices of what was used in the	11:54:21
12		GastroPlus model.	11:54:27
13	Q	Why don't you look at Page 18 of your	11:54:28
14		declaration, Paragraph 41.	11:54:30
15	A	Page 18, Paragraph 41. Yes.	11:54:37
16	Q	You say that the pH for the reference	11:54:40
17		solubility was set at pH 1.1 to reflect the pH of	11:54:43
18		the stomach acid.	11:54:43
19	A	Yes.	11:54:43
20	Q	And the solubility at that pH 1.1 was	11:54:43
21		utilized.	11:54:50
22		Do you see that?	11:54:50

1	A	Yes.	11:54:52
2	Q	Do you agree that the pH of the stomach	11:54:52
3		in the fasted state is about pH 1.1. Correct?	11:54:55
4	A	Yes.	11:55:03
5	Q	You agree that in the fasted state	11:55:03
6		gastric juices have a pH of about 1.1.	11:55:07
7		Correct?	11:55:13
8		MR. GUPTA: Objection to form.	11:55:13
9	A	That is not something that was considered	11:55:14
10		within the declaration. So the ...	11:55:16
11	Q	Do you know what the pH of gastric juice	11:55:45
12		is in the fasted state, approximately?	11:55:48
13	A	It wasn't something I looked at in	11:55:57
14		preparing this declaration, so it's not something	11:55:58
15		I'd want to pick out of the air. I would have to	11:56:00
16		look it up.	11:56:04
17	Q	Would you agree that gastric juice in the	11:56:05
18		fasted state is acidic?	11:56:12
19	A	I think it probably depends on how you're	11:56:17
20		defining "gastric juice." I think you can say	11:56:19
21		there that the pH of stomach acid is 1.1.	11:56:25
22	Q	How do you define gastric juice?	11:56:29

1	MR. GUPTA: Objection. Form. Scope.	11:56:35
2	Relevance.	11:56:36
3	A I would look at a definition of gastric	11:56:45
4	juice. But in the context of this declaration, I	11:56:47
5	don't think it -- it's important. GastroPlus	11:56:52
6	accounts for the pH of the stomach, and beyond	11:57:00
7	that I don't think it's important.	11:57:04
8	Q So generally speaking as a	11:57:11
9	pharmacokinetic expert, you don't have a	11:57:14
10	explanation of what gastric juice is that comes to	11:57:16
11	mind right now.	11:57:19
12	Is that correct?	11:57:20
13	MR. GUPTA: Objection. Form. Scope.	11:57:21
14	And relevance.	11:57:22
15	A I've never felt it necessary in my career	11:57:31
16	to date to define gastric juice.	11:57:33
17	Q You modeled a nonenteric-coated tablet	11:57:36
18	formulation of 5-azacitidine. Correct?	11:58:37
19	MR. GUPTA: Objection to form.	11:58:41
20	A The task that I was asked to conduct was	11:58:51
21	based on an immediate-release oral formulation of	11:58:55
22	azacitidine.	11:59:01

1	Q	Can you turn to Page 13 and look at	11:59:13
2		Paragraph 39 of your declaration.	11:59:17
3	A	Yeah. It says nonEC there, immediate	11:59:41
4		release.	11:59:45
5	Q	Do you consider nonenteric-coated tablet	11:59:46
6		to be the same as immediate release?	11:59:56
7		MR. GUPTA: Objection to form.	12:00:03
8	A	The report that I've prepared really is	12:00:10
9		just looking at the pharmacokinetics of an	12:00:12
10		immediate-release formulation here. I haven't	12:00:16
11		considered formulation attributes particularly	12:00:20
12		within this, other than immediate release.	12:00:22
13	Q	So the dosage form you selected for the	12:00:35
14		modeling was immediate-release tablet. Correct?	12:00:44
15	A	Yes, that was what was used in the	12:00:51
16		GastroPlus modeling, immediate-release tablet.	12:00:55
17	Q	How did you select that formulation to	12:00:59
18		model?	12:01:05
19	A	It was part of the original discussions	12:01:18
20		on the task that I was going to undertake.	12:01:21
21	Q	Did you decide which formulation to	12:01:36
22		model?	12:01:41

1	A	It was part of the discussion I was asked	12:01:43
2		by Steptoe to undertake, a task, it was part of	12:01:47
3		the discussion on what the task was. So the task,	12:01:53
4		it was part of those discussions.	12:01:58
5	Q	But why did you select the formulation to	12:01:59
6		model?	12:02:18
7	A	The decision on the formulation --	12:02:24
8		MR. GUPTA: Objection.	12:02:26
9		THE WITNESS: I'm sorry.	12:02:27
10		MR. GUPTA: Objection to form.	12:02:28
11		And objection to the extent you're asking	12:02:31
12		for discussions between counsel and the witness.	12:02:33
13		I just -- in your answer I just caution	12:02:36
14		you not to reveal direct discussions between	12:02:39
15		Steptoe and the attorneys and you. Otherwise you	12:02:41
16		can answer.	12:02:44
17	A	It was part of the outline of the task.	12:02:51
18	Q	What was the task that you were asked to	12:02:55
19		undertake?	12:03:01
20	A	I was asked to put myself in the position	12:03:07
21		of a POSA back at the time of the date of the	12:03:09
22		patent and use modeling to predict the	12:03:12

1 pharmacokinetics of oral azacitidine. And then 12:03:18
 2 the most obvious and simple formulation is the 12:03:26
 3 immediate-release tablet, so that's what was used 12:03:30
 4 in the model. 12:03:32

5 Q When you did your in silico modeling at 12:03:33
 6 AstraZeneca, did you ever do an in silico model of 12:04:02
 7 an oral dosage form and modify the types of 12:04:06
 8 formulations used? 12:04:09

9 MR. GUPTA: Objection. Form. Scope. 12:04:22
 10 Relevance. 12:04:23

11 You can answer. 12:04:23

12 A At AstraZeneca the most common dosage 12:04:33
 13 form we were developing were immediate-release 12:04:36
 14 tablets, so that's where the modeling was based. 12:04:38

15 Q Do you have any experience modeling 12:04:43
 16 nonimmediate-release formulations? 12:04:48

17 A The task I was asked to do here was about 12:04:58
 18 an immediate-release formulation, so I'm not -- I 12:05:00
 19 don't -- don't know what relevance it is to talk 12:05:03
 20 about other modeling that I've done. 12:05:07

21 Q I'm just trying to understand your 12:05:08
 22 background as an expert. 12:05:12

1	So have you ever -- do you have any	12:05:14
2	experience modeling nonimmediate-release	12:05:17
3	formulations?	12:05:19
4	A Yes.	12:05:25
5	Q In what context?	12:05:27
6	MR. GUPTA: Objection. Relevance.	12:05:32
7	A I think in my CV there's some papers that	12:05:40
8	you could look at where I've done some modeling of	12:05:44
9	nonimmediate-release ones, specifically	12:05:47
10	formulations that target the colon. But I don't	12:05:51
11	see those as being relevant to this case.	12:05:55
12	Q Sorry, we just went blank again. Give me	12:06:02
13	one moment.	12:06:20
14	MR. GUPTA: Ms. Macro, when you get to a	12:06:20
15	good point in the next few minutes, if we could	12:06:23
16	stop for a break, that would be great.	12:06:25
17	MS. MACRO: We might have to do that now.	12:06:29
18	MR. GUPTA: Okay. Is it -- okay. That's	12:06:33
19	fine.	12:06:35
20	MS. MACRO: I think we have to go off the	12:06:36
21	record because I can't see anyone. We can take a	12:06:38
22	break for lunch now.	12:06:40

1	MR. GUPTA: Sure.	12:06:41
2	VIDEO SPECIALIST: We are going off the	12:06:42
3	record. The time is 12:06.	12:06:43
4	(A recess was taken.)	12:06:45
5	VIDEO SPECIALIST: We're back on record.	12:42:08
6	The time is 12:42.	12:42:18
7	BY MS. MACRO:	12:42:23
8	Q Dr. Batchelor, did you have any	12:42:24
9	communications with counsel while you were on	12:42:25
10	lunch break?	12:42:27
11	A Yes.	12:42:31
12	Q Did you discuss the substance of your	12:42:31
13	testimony?	12:42:37
14	A No. He was just checking in that I was	12:42:38
15	okay for food and drink, and small talk.	12:42:41
16	MS. MACRO: Can we enter Exhibit 1014.	12:42:48
17	(Petitioner Apotex Exhibit 1014,	12:42:53
18	previously marked, not attached.)	12:44:59
19	Q Dr. Batchelor, do you recognize Exhibit	12:44:59
20	1014?	12:45:02
21	A Yes, I do.	12:45:03
22	Q And what is it?	12:45:04

1 A It's the paper by Chan where we got the 12:45:08
2 degradation data. 12:45:15

3 Q And if you look at your declaration at 12:45:17
4 Paragraph 34 on Page 15, you reference Exhibit 12:45:21
5 1014, Chan, at Pages 810 Table 2; Page 811 and 12:45:28
6 Figure 8. 12:45:35

7 Is that right? 12:45:35

8 A Yes. 12:45:45

9 Q Can you please turn to PDF Page 5 of 12:45:45
10 Chan. Do you see Figure 8? 12:45:56

11 A Yes. 12:46:03

12 Q You used data from Figure 8 of Chan to 12:46:03
13 determine the 5-azacitidine hydrolysis rate. 12:46:10

14 Correct? 12:46:17

15 MR. GUPTA: Objection to form. 12:46:20

16 A We -- we took the data from Chan and 12:46:22
17 inserted the data from this paper into our model. 12:46:26

18 Q And the data you took from Chan is shown 12:46:30
19 in Figure 8 of Chan. 12:46:40

20 Is that right? 12:46:41

21 A Yes. 12:46:42

22 Q Sorry, did you answer? I didn't hear. 12:46:44

1	A	Sorry. I said yes.	12:48:01
2	Q	Okay. Sorry.	12:48:03
3	A	I was waiting for you. Sorry.	12:48:04
4	Q	All right. No worries.	12:48:06
5		And you used the data for the 37 degree	12:48:09
6		Celsius values. Correct?	12:48:18
7	A	Yes.	12:48:21
8	Q	And can you turn to Table 2 of Chan,	12:48:21
9		which is on Page -- PDF Page 4.	12:48:29
10	A	Yes.	12:48:33
11	Q	This is -- withdrawn.	12:48:33
12		You used the data in Table 2 of Chan to	12:48:45
13		determine the hydrolysis rate. Correct?	12:48:50
14	A	Yes.	12:48:55
15		MR. GUPTA: Objection. Objection to	12:48:56
16		form.	12:48:57
17		Go ahead.	12:48:58
18	A	Yeah, I don't know to wait for the	12:49:05
19		question or pre-empt whether it's about the	12:49:07
20		temperature being 30 degrees on the table which I	12:49:10
21		felt was a mistype in the paper.	12:49:14
22	Q	Okay. That was my question.	12:49:16

1	So this table shows that the rate	12:49:18
2	constant is at 30 degrees? Correct?	12:49:26
3	A The table does read 30 degrees.	12:49:31
4	Q And that's different from the 37 degrees	12:49:34
5	shown for Figure 8. Correct?	12:49:39
6	MR. GUPTA: Objection to form.	12:49:41
7	A The figure says 37 degrees, and the table	12:49:47
8	says 30 degrees in the paper.	12:49:49
9	Q The hydrolysis measurements in Chan could	12:49:51
10	have been performed at 30 degrees. Right?	12:50:02
11	MR. GUPTA: Objection to form.	12:50:04
12	A I -- I considered the 30 degrees in the	12:50:09
13	table to be a mistype, as in the methodology they	12:50:13
14	say 37 and in the figure they say 37, and 37 is a	12:50:18
15	temperature that's physiologically relevant. So I	12:50:22
16	think it was 37, and there's a mistype in the	12:50:25
17	paper.	12:50:29
18	Q Chan doesn't include any degradation rate	12:50:29
19	data for pH below 4.5. Correct?	12:50:44
20	MR. GUPTA: Objection to form.	12:50:50
21	Go ahead.	12:50:52
22	A The data I used from the Chan paper were	12:50:56

1	the values in the table from pH 4.5 to pH 8.	12:51:00
2	Q There are no values in the table from	12:51:05
3	Chan below pH 4.5. Correct?	12:51:22
4	A In Table 2, the lowest pH is 4.5.	12:51:28
5	Q Can you turn to Page A-3 of your	12:51:33
6	declaration.	12:52:08
7	A Page 3. Yes, I have that in front of me.	12:52:15
8	Q And this is the degradation rate data	12:52:27
9	file derived from the Chan data. Correct?	12:52:34
10	A Yes.	12:52:42
11	Q GastroPlus interpolates the degradation	12:52:42
12	rate at the pH in each compartment from this input	12:52:52
13	table of degradation rate. Correct?	12:53:01
14	A That's my understanding of how GastroPlus	12:53:06
15	uses the data, yes.	12:53:09
16	Q And Chan shows that increasing the	12:53:10
17	temperature increased the degradation rate.	12:53:18
18	Correct?	12:53:22
19	MR. GUPTA: Objection to form.	12:53:23
20	A In the declaration I was only interested	12:53:29
21	in the 37 degree data. I didn't really look at	12:53:31
22	the data at the temperatures.	12:53:34

1	Q	Can you go back to Exhibit 1014, Chan,	12:53:37
2		Page 5. We'll look at Figure 8, please.	12:53:42
3		Figure 8 shows that the degradation rate	12:53:53
4		for 5-azacitidine is higher at a higher	12:53:59
5		temperature. Correct?	12:54:05
6	A	When we're looking at the match pH, yes.	12:54:11
7	Q	So going back to Exhibit A-3.	12:54:17
8		When GastroPlus interpolates the	12:54:27
9		degradation rate at the pH of each compartment,	12:54:30
10		does it use the lowest pH measurement as a	12:54:38
11		constant?	12:54:42
12	A	It's my understanding that GastroPlus	12:54:51
13		will use the pH value where there is a measure if	12:54:55
14		it's within that compartment or the nearest pH	12:54:59
15		value.	12:55:02
16	Q	Okay. So I'm just trying to understand.	12:55:06
17		Sorry. Actually, why don't we -- if you look at	12:55:10
18		A-18, GastroPlus uses a pH of 1.3 for the stomach.	12:55:20
19		That's correct?	12:55:27
20	A	Yes.	12:55:28
21	Q	Okay. And so then what degradation rate	12:55:28
22		would GastroPlus use for the stomach compartment?	12:55:39

1 MR. GUPTA: Objection to form. 12:55:43

2 A Based on my understanding of GastroPlus, 12:55:51

3 the interpolation would direct the system to use 12:55:54

4 the pH which is nearest. So it would use the data 12:55:57

5 from pH 4.5 for any pH lower than that. 12:56:00

6 Q And if you can go back to Exhibit 1014, 12:56:50

7 Chan, PDF Page 5, Figure 8. Let me know when 12:56:59

8 you're there. 12:57:03

9 A Yes, I'm there. 12:57:08

10 Q Chan shows the hydrolysis rate of 12:57:09

11 5-azacitidine increases as you move from a neutral 12:57:16

12 pH to a more acidic pH. Correct? 12:57:21

13 MR. GUPTA: Objection to form. 12:57:25

14 A The data of Chan shows the values at each 12:57:32

15 of the pH measures -- measurements taken. 12:57:36

16 Q And the degradation rate at pH 4.5 is 12:57:40

17 more than the degradation rate at around pH -- 12:57:50

18 sorry, withdrawn. 12:57:54

19 The degradation rate at pH 4 reported in 12:57:55

20 Chan is more than the degradation rate at pH 7 12:57:58

21 reported in Chan. Correct? 12:58:03

22 MR. GUPTA: Objection to form. 12:58:11

1 A The data from Chan was used because it 12:58:12
2 was the most robust data to feed into the 12:58:17
3 GastroPlus model, so that the pattern of 12:58:20
4 degradation that was available in it was 12:58:24
5 integrated into the model in the best way. 12:58:26

6 Q Okay. Yeah, I understand that that was 12:58:29
7 what you used in the model. I was just trying to 12:58:33
8 understand what Figure 8 of Chan is showing. 12:58:35

9 So just with that in mind, Figure 8 of 12:58:41
10 Chan shows that the degradation rate for 12:58:46
11 5-azacitidine at pH 4 is more than the degradation 12:58:48
12 rate at pH 7. Correct? 12:58:52

13 MR. GUPTA: Same objection. 12:58:55

14 A The values that are shown are in the 12:58:58
15 table, and you can see the differences in the 12:59:01
16 value from the table or the figure. The values 12:59:03
17 are different where they're at 4.5 is a higher 12:59:09
18 number than that at pH 7. 12:59:16

19 Q If you change the hydrolysis rate of 12:59:21
20 5-azacitidine, you would not necessarily get the 12:59:25
21 same AUC result predicted from your modeling. 12:59:29

22 Correct? 12:59:35

1	MR. GUPTA: Objection to form.	12:59:35
2	A I wouldn't -- I wouldn't make a change to	12:59:39
3	the model, because everything that I used in the	12:59:42
4	model was what I felt was the best data at the	12:59:44
5	time when it would be conducted. So I wouldn't	12:59:48
6	make that change.	12:59:50
7	And due to the very rapid transit through	12:59:53
8	the stomach, the results would be about the same	12:59:57
9	in any case, I think.	13:00:00
10	Q You just don't know for certain if	13:00:03
11	they're the same because you didn't model a	13:00:13
12	different degradation rate. Right?	13:00:15
13	MR. GUPTA: Objection to form.	13:00:17
14	A I incorporated degradation into the model	13:00:23
15	using the most robust data that was available at	13:00:27
16	the time. I didn't need to make any changes. I'm	13:00:31
17	confident that the results are robust. And due to	13:00:34
18	the rapid transit, any change would mean the	13:00:40
19	results are about the same anyway.	13:00:42
20	Q Does GastroPlus model the enzyme	13:00:44
21	azacitidine deaminase as a default?	13:00:55
22	MR. GUPTA: Objection to form.	13:01:01

1 A I would need to read very precisely, but 13:01:14
2 I don't think it was necessary in this case to 13:01:17
3 include in the model. I included all the 13:01:20
4 necessary parameters and undertook the model as 13:01:23
5 someone would have done at the time. So I'm 13:01:27
6 confident in the outputs. 13:01:29

7 Q Okay. Let's pull up the manual again, 13:01:32
8 Exhibit 1027, Page 40 of the manual, PDF Page 149. 13:01:43
9 And while we get there, just to follow up on that 13:02:12
10 last question. 13:02:15

11 You didn't discuss azacitidine deaminase 13:02:26
12 in your declaration. Correct? 13:02:34

13 MR. GUPTA: Objection to form. 13:02:35

14 A I didn't think it was necessary, the 13:02:37
15 declaration for the task at hand I undertook. So 13:02:41
16 I don't remember it being in there. And if you're 13:02:51
17 saying it's not, I'm sure it's not in the 13:02:53
18 declaration. 13:02:55

19 Q All right. So do you have Page 149 of 13:02:55
20 the manual in front of you? 13:03:10

21 A I have PDF 149. Sorry. 13:03:13

22 Q Yeah, to be clear, we're looking at 13:03:16

1	Exhibit 1027, Page 140 of the manual, PDF Page	13:03:18
2	149.	13:03:22
3	Do you see it there, Running a Parameter	13:03:22
4	Sensitivity Analysis?	13:03:25
5	A Yes, I do see it.	13:03:27
6	Q Can you read that first paragraph under	13:03:28
7	the heading.	13:03:38
8	A Yes, I've read that paragraph.	13:03:50
9	Q GastroPlus -- withdrawn.	13:03:51
10	The GastroPlus manual recognizes that	13:03:58
11	some of the input values for in silico predictions	13:04:01
12	will be estimates that do not correlate perfectly	13:04:05
13	with in vivo values. Correct?	13:04:09
14	MR. GUPTA: Objection to form.	13:04:12
15	A So the manual says that often input	13:04:16
16	values for some of the physicochemical properties	13:04:19
17	of a compound will be estimates, perhaps from an	13:04:22
18	in silico model or from in vitro methods that do	13:04:25
19	not correlate perfectly with in vivo values.	13:04:30
20	Q And in in silico modeling, parameter	13:04:33
21	sensitivity analysis is used to assess the effects	13:04:37
22	of different values for critical parameters.	13:04:41

1	Correct?	13:04:44
2	MR. GUPTA: Objection to form.	13:04:44
3	A So for the task that I was asked to	13:04:56
4	undertake, which is about predicting based on the	13:04:58
5	prior art --	13:05:00
6	MR. GUPTA: Excuse me one second. I just	13:05:01
7	want to make sure my objection was noted.	13:05:02
8	(A discussion was held off the record.)	13:05:02
9	A So I think I was saying that the task	13:05:24
10	that I was given was to predict the	13:05:26
11	pharmacokinetics based on the prior art. And in	13:05:28
12	solving the shoes of a POSA from the right time,	13:05:32
13	that didn't require parameter sensitivity	13:05:37
14	analysis, so I didn't do it.	13:05:42
15	Q And if you look at the next paragraph,	13:05:45
16	after the one we were looking at, Parameter	13:05:50
17	Sensitivity Analysis.	13:05:55
18	Do you see that?	13:05:56
19	A Yes.	13:05:57
20	Q Just let me know when you've read it.	13:05:57
21	Just, like, generally speaking, you agree that	13:06:00
22	parameter sensitivity analysis is used to assess	13:06:04

1	the effects of different values for critical	13:06:07
2	parameters. Correct?	13:06:10
3	MR. GUPTA: Objection. Form. And scope.	13:06:13
4	Relevance.	13:06:16
5	You can answer.	13:06:18
6	A So if we looked at this Section 5.3.7	13:06:23
7	within the manual holistically, it really relates	13:06:27
8	to whether a compound has a poor predicted	13:06:30
9	fraction absorbed or a poor F bioavailability.	13:06:34
10	The purpose of my task was to predict those	13:06:38
11	values. And I didn't know whether they would be	13:06:42
12	good or bad because there was no oral data to	13:06:44
13	compare it to, which is why I didn't do parameter	13:06:46
14	sensitivity analysis.	13:06:49
15	If you've got nothing to compare it to,	13:06:52
16	it's not useful in this case. So it's not	13:06:56
17	something I considered.	13:07:01
18	Q Can you look at your declaration, Pages 8	13:07:08
19	to 9. Again, this is -- I just want to bring up	13:07:39
20	the AUC results and the Cmax and Tmax results.	13:07:54
21	Okay.	13:08:00
22	Your declaration doesn't describe a	13:08:02

1	comparison of your AUC simulated values to any in	13:08:05
2	vivo AUC values obtained from orally administering	13:08:11
3	a nonenteric-coated 5-azacitidine tablet.	13:08:20
4	Correct?	13:08:23
5	MR. GUPTA: Objection to form.	13:08:25
6	A I was asked -- I was asked to predict the	13:08:33
7	pharmacokinetics, and at the time I didn't have	13:08:35
8	any data to compare it to, so it's not within the	13:08:39
9	declaration.	13:08:43
10	Q Since submitting your declaration, have	13:08:47
11	you compared your AUC simulated values to any in	13:08:51
12	vivo AUC values obtained from orally administered	13:08:56
13	nonenteric-coated 5-azacitidine tablets?	13:09:00
14	A No, I haven't. I was asked to do this as	13:09:08
15	a -- as a task. I did my task and I delivered the	13:09:11
16	task, and then I moved down my task list to other	13:09:14
17	tasks, rather than doing something that wasn't	13:09:18
18	required.	13:09:21
19	Q Okay. I'm going to ask you the same two	13:09:25
20	questions about Cmax and Tmax. Okay?	13:09:28
21	So your declaration doesn't describe a	13:09:30
22	comparison of your Cmax simulated values to any in	13:09:48

1	vivo Cmax values obtained from orally administering	13:09:54
2	a nonenteric-coated 5-azacitidine tablet.	13:09:57
3	Correct?	13:10:00
4	MR. GUPTA: Same objection.	13:10:01
5	A When I was asked to do the task, I was	13:10:07
6	asked to predict the pharmacokinetics of	13:10:09
7	azacitidine, either the 200- or 400-milligram	13:10:12
8	dose. I was not asked to compare it to anything,	13:10:18
9	I didn't find any data, so it's not in the	13:10:21
10	declaration.	13:10:30
11	Q And you haven't done that comparison	13:10:30
12	since submitting the declaration?	13:10:32
13	A I didn't do the comparison, therefore	13:10:33
14	it's not in the declaration.	13:10:35
15	Q Your declaration does not compare your	13:10:37
16	simulated Tmax values to any in vivo Tmax values	13:10:41
17	obtained from orally administered	13:10:45
18	nonenteric-coated 5-azacitidine tablet. Correct?	13:10:48
19	MR. GUPTA: Same objection.	13:10:52
20	A The task was to generate the	13:10:59
21	pharmacokinetic parameters for azacitidine	13:11:01
22	following a 200- and 400-milligram dose. I was	13:11:04

1	not tasked with comparing it to data. I didn't	13:11:08
2	see it was necessary for the task and for the	13:11:12
3	declaration, so it's not within the declaration.	13:11:15
4	Q And since submitting your declaration,	13:11:16
5	you haven't done that comparison. Correct?	13:11:22
6	A Correct.	13:11:26
7	Q You -- sorry. Withdrawn.	13:11:26
8	Are you aware of any in vivo AUC values	13:11:34
9	obtained from orally administered	13:11:38
10	nonenteric-coated 5-azacitidine tablets before	13:11:40
11	December 2008?	13:11:45
12	A No, I'm not aware of that.	13:11:53
13	Q Are you aware of any in vivo Cmax values	13:11:58
14	obtained from orally administered	13:12:01
15	nonenteric-coated 5-azacitidine tablets before	13:12:03
16	2008?	13:12:08
17	A I probably should caveat, I assume you're	13:12:13
18	talking about oral administration. So no, I	13:12:15
19	wasn't aware of that.	13:12:18
20	Q Are you aware of any in vivo Tmax values	13:12:19
21	obtained from orally administered	13:12:27
22	nonenteric-coated 5-azacitidine tablets before	13:12:29

1	December 2008?	13:12:32
2	A No, I'm not.	13:12:37
3	Q Are you aware of any in vivo	13:12:38
4	pharmacokinetic values obtained from orally	13:12:43
5	administered nonenteric-coated 5-azacitidine	13:12:45
6	tablets before December 2008?	13:12:49
7	MR. GUPTA: I object to this line of	13:12:54
8	questioning as outside the scope.	13:12:55
9	You can answer.	13:12:56
10	A I think that was just a repeat of one of	13:13:04
11	the previous questions. I didn't get anything new	13:13:06
12	from it. Sorry.	13:13:09
13	Q I was asking about the Tmax rather than	13:13:11
14	the Cmax. So let me give it to you again.	13:13:14
15	A Oh.	13:13:16
16	Q Are you aware of any in vivo Tmax values	13:13:16
17	obtained from orally administered	13:13:20
18	nonenteric-coated 5-azacitidine -- oh, sorry. I	13:13:23
19	think I did that one, too. All right. Withdrawn.	13:13:26
20	I think I got them all. Right? I'm	13:13:33
21	sorry.	13:13:37
22	A That's okay.	13:13:38

1	Q	I see where I was. I was asking about	13:13:39
2		any pharmacokinetic values. All right. Let me	13:13:43
3		give it to you again.	13:13:45
4		Are you aware of any in vivo	13:13:46
5		pharmacokinetic values obtained from orally	13:13:51
6		administered nonenteric-coated 5-azacitidine	13:13:53
7		tablets before December 2008?	13:13:57
8		MR. GUPTA: Same objection. I object to	13:14:01
9		this line as outside the scope and for relevance.	13:14:03
10		Go ahead, Dr. Batchelor.	13:14:06
11	A	My declaration relates to the task that I	13:14:14
12		was given, which was to use the data in the prior	13:14:17
13		art and conduct modeling to predict the	13:14:21
14		pharmacokinetics following oral dosing. I	13:14:23
15		searched for the information that I've required	13:14:30
16		and undertook the modeling as a POSA would have	13:14:33
17		done at that date. So it wasn't necessary for me	13:14:36
18		to include in the declaration, so it's not there.	13:14:38
19	Q	Can you turn to your declaration at Page	13:14:41
20		13, Paragraph 38.	13:14:59
21	A	Paragraph 28?	13:15:12
22	Q	Paragraph 28. Sorry. I said 38. I'm	13:15:14

1	sorry. Yes. I apologize. Can you look at your	13:15:27
2	Exhibit 1003, your declaration, Page 13, Paragraph	13:15:36
3	28.	13:15:41
4	A Uh-huh.	13:15:43
5	Q Do you see it says, "Prior to testing	13:15:43
6	known compositions such as 5-azacitidine in	13:15:50
7	humans, a POSA would have been motivated to obtain	13:15:53
8	data on in silico modeling, for example, from	13:15:56
9	others of skill in the art that a POSA may have	13:16:00
10	collaborated with using GastroPlus 5.2 based on at	13:16:02
11	least reduced time and cost considerations."	13:16:06
12	Do you see that?	13:16:09
13	A Yes.	13:16:10
14	Q So -- withdraw.	13:16:10
15	Do you agree that after in silico	13:16:15
16	modeling, it would be routine to test compositions	13:16:19
17	in vivo?	13:16:27
18	MR. GUPTA: Objection as outside the	13:16:34
19	scope of the report. And relevance.	13:16:37
20	A The question asked is a very broad	13:16:47
21	question. Again, to go back to my task for this	13:16:49
22	declaration, my task was to conduct the in silico	13:16:52

1 modeling in isolation of any program. So in this 13:16:57

2 case I can't answer the question. 13:17:01

3 Q What did you mean when you wrote, "Prior 13:17:05

4 to testing known compositions such as 13:17:08

5 5-azacitidine in humans"? 13:17:11

6 A In this part of the declaration I'm 13:17:23

7 referring to how GastroPlus was used based on my 13:17:30

8 experience of working at AstraZeneca, which would 13:17:35

9 be similar to a person skilled in the art at that 13:17:38

10 time point. 13:17:42

11 Q And how would GastroPlus be used? 13:17:43

12 MR. GUPTA: Objection to form. 13:17:55

13 You can answer. 13:18:00

14 A So I think the emphasis for Paragraph 28 13:18:02

15 here is that prior to conducting a study in 13:18:08

16 humans, you would -- you would use GastroPlus to 13:18:17

17 inform that study. 13:18:23

18 Q And so after using GastroPlus, you might 13:18:30

19 test the compositions of 5-azacitidine in vivo. 13:18:47

20 Is that fair to say? 13:18:53

21 MR. GUPTA: Objection to form and scope 13:18:54

22 of the expert report. 13:18:59

1	You can answer.	13:19:00
2	Sorry. And relevance.	13:19:07
3	You can answer.	13:19:08
4	A In relation to the azacitidine task I	13:19:11
5	did, this is -- this has no relevance. Whilst	13:19:13
6	based on my experience outside of this, before any	13:19:20
7	clinical study is conducted in a human population,	13:19:25
8	there are many measures that are pulled together	13:19:30
9	to make sure that that study is a valuable use of	13:19:32
10	resources and time. GastroPlus is certainly one	13:19:35
11	that would have been used at that time.	13:19:40
12	MS. MACRO: Can we take a short break.	13:20:01
13	Five minutes, please.	13:20:03
14	MR. GUPTA: Okay.	13:20:05
15	VIDEO SPECIALIST: We are going off	13:20:07
16	record. The time is 13:20.	13:20:09
17	(A recess was taken.)	13:20:11
18	VIDEO SPECIALIST: We're back on record.	13:30:08
19	The time is 13:30.	13:30:19
20	BY MS. MACRO:	13:30:24
21	Q Dr. Batchelor, earlier we were talking	13:30:25
22	about the permeability of 5-azacitidine.	13:30:27

1	Do you have that in mind?	13:30:34
2	A Permeability.	13:30:37
3	Q Yeah.	13:30:46
4	Do you agree that permeability of a	13:30:46
5	compound plays a major role in its absorption	13:30:48
6	after oral administration?	13:30:52
7	MR. GUPTA: Objection. Form. Scope.	13:30:57
8	And relevance.	13:30:59
9	You can answer.	13:30:59
10	A So in the task that I did, permeability	13:31:03
11	was incorporated into the model for azacitidine.	13:31:06
12	Q And the model incorporates permeability	13:31:25
13	because permeability of a compound plays a major	13:31:27
14	role in the absorption of -- absorption after oral	13:31:32
15	administration. Correct?	13:31:40
16	MR. GUPTA: Objection. I lodge the same	13:31:41
17	objections to this question.	13:31:44
18	You can answer.	13:31:45
19	A GastroPlus incorporates those values in	13:31:56
20	making the predictions that were part of my task.	13:32:00
21	So I included the data that was necessary to	13:32:04
22	conduct the task and provide the -- what's within	13:32:09

1 the declaration. 13:32:13

2 Q Would you disagree with the statement 13:32:14

3 that permeability of a compound doesn't play a 13:32:19

4 major role in its absorption after oral 13:32:24

5 administration? 13:32:27

6 MR. GUPTA: Same objections. Again, you 13:32:35

7 can answer. 13:32:36

8 A For azacitidine, the GastroPlus model 13:32:37

9 incorporated the permeability values as derived 13:32:42

10 within the declaration. 13:32:46

11 Q And why does GastroPlus incorporate 13:32:50

12 permeability when modeling oral administration of 13:32:53

13 a compound? 13:33:01

14 A Yes. 13:33:05

15 MR. GUPTA: Objection. Objection to 13:33:05

16 form. Objection. Relevance. 13:33:07

17 You can answer. 13:33:10

18 A GastroPlus is a specific software that's 13:33:18

19 designed to predict pharmacokinetics based on a 13:33:22

20 range of inputs. Permeability is an input that it 13:33:25

21 uses, as I used for modeling azacitidine in the 13:33:29

22 case that's in the declaration. 13:33:32

1 Q And so why did you use permeability in 13:33:37
2 the input? 13:33:41

3 A Yeah, GastroPlus is designed to predict 13:33:46
4 pharmacokinetic from a range of inputs, of which 13:33:50
5 permeability is one. It's a holistic piece of 13:33:53
6 software. Permeability is a part of that. 13:33:57

7 Q Do you consider it a major part of the 13:34:15
8 GastroPlus model, the permeability factor? 13:34:21

9 MR. GUPTA: Objection. Form and scope. 13:34:26
10 You can answer. 13:34:30

11 A GastroPlus incorporates a range of input 13:34:37
12 parameters. I think we reviewed those earlier 13:34:46
13 from the manual, those four. Permeability comes 13:34:48
14 into the compound, it's is part of the inputs, 13:34:58
15 but ... 13:35:12

16 Q In your modeling, if any input values are 13:35:12
17 inaccurate to 5-azacitidine, that inaccuracy will 13:35:31
18 be incorporated into the ultimate pharmacokinetic 13:35:36
19 results generated by GastroPlus. Correct? 13:35:40

20 MR. GUPTA: Objection. Objection to 13:35:43
21 form. 13:35:45

22 You can answer. 13:35:46

1 A The task that I was given was to use the 13:35:51
2 available data to generate the modeling GastroPlus 13:35:53
3 to predict pharmacokinetics of azacitidine. I did 13:36:01
4 that using the most appropriate inputs for this 13:36:02
5 scenario, and the outputs are presented in the 13:36:07
6 declaration. 13:36:12

7 Q So if those most appropriate inputs are 13:36:20
8 inaccurate, that inaccuracy is incorporated into 13:36:25
9 the ultimate pharmacokinetic result generated by 13:36:28
10 GastroPlus. Correct? 13:36:34

11 MR. GUPTA: Objection to form. 13:36:34

12 A When using best practice to model, you 13:36:44
13 find the most robust data to put into the software 13:36:48
14 and you undertake the simulation. In this case I 13:36:51
15 took a step back in time and did it as a POSA at 13:36:57
16 the time of the priority date and ran the model as 13:37:01
17 I think someone would have at that time, to 13:37:07
18 provide the outputs that are presented in the 13:37:09
19 declaration. 13:37:11

20 MS. MACRO: Okay. I would like to 13:37:16
21 introduce an exhibit that's not been marked 13:37:17
22 before. So, Jack, that's going to be X20XX, Pawar 13:37:24

1 and Batchelor. And I will mark -- I'll give it a 13:37:38
2 number once we have it up. Jack, you can mark it 13:37:41
3 as Exhibit 2048, please. 13:37:44

4 (Patent Owner Celgene Deposition Exhibit 13:37:44
5 2048 marked for identification and is attached to 13:37:44
6 the transcript.) 13:38:57

7 MR. GUPTA: Hold on. Before you share, I 13:38:57
8 would like to -- I just need a moment to review 13:38:59
9 the exhibit. It hasn't come up on mine. 13:39:01

10 Okay. So I object to Exhibit 2048 on the 13:39:40
11 grounds of relevance; 403, prejudice outweighing 13:39:43
12 the probative value. Hearsay. 13:39:54

13 And that's what I can tell from my 13:40:00
14 initial read of this document. I reserve my 13:40:02
15 rights to supplement in the future. 13:40:04

16 You can go ahead, Ms. Macro. 13:40:07

17 MS. MACRO: I'd like to introduce as 13:40:11
18 Exhibit 2048 the Pawar, et al., paper. 13:40:13

19 Q Dr. Batchelor, do you recognize this 13:40:27
20 document? 13:40:29

21 A Yeah. Yes, I recognize it. 13:40:32

22 Q Can you tell me what it is? 13:40:37

1 A It's a publication that resulted from a 13:40:43
2 collaboration with the FDA, specifically looking 13:40:45
3 at pediatric populations, and derisking the use of 13:40:49
4 generics in pediatric populations was the broader 13:41:02
5 project. 13:41:07

6 Q And as part of this paper did you do in 13:41:09
7 silico pharmacokinetic modeling? 13:41:16

8 A I'm just going to look. So the whole 13:41:27
9 project is really familiar to me. I just need to 13:41:29
10 recall what was written in this specific paper. 13:41:31

11 Q Take your time. 13:41:35

12 A Yes, this reports some of the 13:41:41
13 pharmacokinetic modeling that was done as part of 13:41:42
14 that project. 13:41:44

15 Q And can you turn to PDF Page 4, which is 13:41:47
16 Page 67 of the reference. 13:41:58

17 Do you see that section that starts CBZ 13:42:01
18 PBPK Model? 13:42:12

19 Do you see that? 13:42:13

20 A Yes. 13:42:14

21 MR. GUPTA: Hold on. Let me just get 13:42:15
22 there myself. 13:42:16

1 Okay. I'm there. Thank you. 13:42:23

2 Q And then turning to Page 5, I want to 13:42:27
3 draw your attention to the paragraph that starts, 13:42:30
4 "Model prediction." 13:42:32

5 Can you read that and let me know when 13:42:35
6 you're done. 13:42:36

7 A Yeah, I've read that paragraph. 13:43:05

8 Q In this paper you report that you 13:43:08
9 validated model predictions using published 13:43:15
10 clinical PK studies. Correct? 13:43:22

11 A Yeah, the first sentence -- 13:43:30

12 MR. GUPTA: Hold on. 13:43:32

13 Objection to form. Objection to outside 13:43:33
14 the scope of the expert report. 13:43:34

15 You can answer. 13:43:36

16 A So, yeah, this piece of work is a project 13:43:41
17 that I did. And the first sentence is correct. 13:43:44
18 But I'm struggling to see where this relates to 13:43:48
19 the declaration that's in front of me. 13:43:53

20 Q Okay. And if we -- you go down, I'm in 13:43:55
21 the same column, the very last two lines you see 13:44:02
22 where it says, "The CBZ model was validated in 13:44:05

1	adults by calculating the prediction error	13:44:09
2	percentage"? Can you read that paragraph that	13:44:13
3	goes into the next column, and just let me know	13:44:15
4	when you're done.	13:44:17
5	MR. GUPTA: I'm sorry, Ms. Macro, I'm	13:44:22
6	just trying to follow along with you myself.	13:44:24
7	Could you please direct me to the paragraph again?	13:44:26
8	MS. MACRO: Sorry. Page 5, first column,	13:44:29
9	the last two lines. The CBZ model.	13:44:32
10	MR. GUPTA: Okay. Got it. "The CBZ	13:44:37
11	model was validated in adults," that one?	13:44:40
12	MS. MACRO: Yeah, that paragraph, please.	13:44:44
13	MR. GUPTA: Okay.	13:44:45
14	Q And just let me know when you're ready,	13:44:47
15	Dr. Batchelor.	13:44:49
16	A I have read that paragraph.	13:45:11
17	Q So your paper states that you validated	13:45:17
18	your model by calculating prediction error	13:45:21
19	percentage fold error. Correct?	13:45:27
20	MR. GUPTA: Objection. Form. Relevance,	13:45:35
21	and scope of the expert report.	13:45:39
22	A The task that I was asked to do for the	13:45:53

1 azacitidine was to make a prediction. And you 13:45:55
2 asked me before about comparing it to existing 13:45:59
3 data. This paper is a different project because 13:46:01
4 this is very much about comparing the model 13:46:09
5 outputs to existing data. So they're two very 13:46:11
6 different pieces of work. 13:46:14

7 Q In this work -- 13:46:21

8 MR. GUPTA: Excuse me. Just for the 13:46:24
9 record, I don't know if I had stated it above. 13:46:25
10 But one of the objections that I have to Exhibit 13:46:28
11 2048 is that it's outside the scope of Dr. 13:46:30
12 Batchelor's report. That's it. I'm just stating 13:46:33
13 it for the record. You can go ahead. 13:46:34

14 Sorry, Ms. Macro. 13:46:37

15 Q In this work in Exhibit 2048, you did 13:46:39
16 validate your predicted model values by 13:46:49
17 calculating the prediction error percentage fold 13:46:55
18 error. 13:47:01

19 Is that right? 13:47:03

20 MR. GUPTA: Objection. Relevance. 13:47:06
21 Scope. And form. 13:47:09

22 A So the statement in the paper tells you 13:47:20

1	to pause longer.	13:49:04
2	MR. GUPTA: If you could, thank you.	13:49:06
3	Yeah. So objection to form. That's it.	13:49:08
4	A My answer was, no, I wouldn't agree.	13:49:16
5	Q And why don't you agree with that	13:49:19
6	statement?	13:49:21
7	MR. GUPTA: Okay. Same objections as	13:49:23
8	before.	13:49:24
9	You can answer, Dr. Batchelor.	13:49:25
10	A I just might need the question repeated.	13:49:29
11	Sorry.	13:49:31
12	Q Would you agree that even if your	13:49:33
13	predictions are not an accurate representation of	13:49:41
14	real-world 5-azacitidine oral tablets, they're	13:49:45
15	still useful?	13:49:50
16	MR. GUPTA: Objection to form.	13:49:52
17	A I'm just trying to interpret the	13:50:06
18	question.	13:50:07
19	The task that I was given was to predict	13:50:08
20	the pharmacokinetics based on the available	13:50:12
21	information from the prior art at the time of the	13:50:15
22	priority date. The model -- the model accounts	13:50:18

1 for all the necessary factors, and the outputs are 13:50:24
2 presented. 13:50:31

3 Q So I was just trying to understand if you 13:50:36
4 think your model is useful based on how it -- how 13:50:43
5 accurate it is compared to the real-world data. 13:50:56

6 With that in mind, would you agree that 13:51:01
7 your model in your declaration is only useful if 13:51:07
8 it's an accurate representation of real-world oral 13:51:13
9 5-azacitidine tablets? 13:51:20

10 MR. GUPTA: Again, objection to form. 13:51:21
11 Scope. And relevance. 13:51:24

12 A I was tasked with creating a model that 13:51:34
13 would predict the pharmacokinetics based on the 13:51:37
14 prior art. I delivered a model that would predict 13:51:45
15 the pharmacokinetics based on the prior art, which 13:51:49
16 I think is useful. 13:51:51

17 Q But you don't have any idea on how that 13:51:52
18 relates to any real-world 5-azacitidine values. 13:51:56

19 Correct? 13:52:01

20 MR. GUPTA: Objection to form. 13:52:01

21 A The task that I was requested to do was 13:52:05
22 to predict the pharmacokinetics based on the prior 13:52:08

1 art at the time. I was not asked to compare it to 13:52:12
2 clinical data. There was no clinical data to 13:52:22
3 compare it to. So the model that I've provided is 13:52:23
4 what a POSA would have delivered to predict the 13:52:29
5 pharmacokinetics of 5-azacitidine at that time, 13:52:33
6 based on the prior art. 13:52:35

7 Q So I think I was asking you this morning 13:52:38
8 do you have a value in mind for how much error is 13:53:01
9 acceptable between a predicted value and a 13:53:06
10 real-world value in order for them to be 13:53:13
11 considered acceptable? 13:53:20

12 MR. GUPTA: Objection, form. Objection, 13:53:22
13 scope. Objection, relevance. 13:53:25

14 A That wasn't something I was requested to 13:53:33
15 do as part of my declaration, so it's not within 13:53:35
16 the declaration. 13:53:41

17 Q If the AUC for the 200-milligram dose of 13:53:46
18 oral 5-azacitidine in the real world was 50 13:53:59
19 percent more than your modeled value, would you 13:54:04
20 consider your modeled value an accurate prediction 13:54:06
21 of the real-world value? 13:54:13

22 MR. GUPTA: Objection. Form. Scope. 13:54:15

1 And relevance. 13:54:17

2 A That wasn't something I was asked to do 13:54:21

3 as part of my task. 13:54:23

4 Q You don't have an opinion on whether a 50 13:54:34

5 percent difference in AUC value would be 13:54:36

6 considered an accurate prediction? 13:54:41

7 MR. GUPTA: Same objection. 13:54:45

8 A It wasn't something that was part of my 13:54:52

9 task. I was asked to generate a model, not 13:54:54

10 compare it to data. 13:54:59

11 Q If you got 50 percent error rates in your 13:55:03

12 published manuscript, Exhibit 2048, would you have 13:55:08

13 considered your predictions there to be an 13:55:11

14 accurate representation of the real-world 13:55:14

15 pharmacokinetics of the compound? 13:55:22

16 MR. GUPTA: Objection. Relevance. 13:55:25

17 Scope. And form. 13:55:28

18 A This is outside what I've considered for 13:55:46

19 this declaration, so I'd have to review and 13:55:48

20 consider many aspects to give you a quality answer 13:55:55

21 that's required for this deposition. 13:56:00

22 Q I think I'm just trying to get an 13:56:07

1	understanding of your experience in being able to	13:56:11
2	apply in silico model data. So with that in mind,	13:56:18
3	you know how to calculate prediction error	13:56:37
4	percentages from comparing in silico model data	13:56:44
5	and real-world data. Correct?	13:56:48
6	MR. GUPTA: Objection. Relevance and	13:56:50
7	scope.	13:56:54
8	You can answer.	13:56:55
9	A I wasn't required to make those	13:57:00
10	calculations to the azacitidine case. Other	13:57:02
11	experience that calculated in the paper, we just	13:57:12
12	said that, but --	13:57:14
13	Q So you know how to do it?	13:57:17
14	MR. GUPTA: Objection.	13:57:22
15	A Yes.	13:57:22
16	MR. GUPTA: To form.	13:57:24
17	A I know how to do it, but it wasn't	13:57:24
18	necessary for this declaration.	13:57:26
19	Q And I'm just trying to understand like,	13:57:31
20	generally speaking, are there, like, numbers that	13:57:34
21	you can put around what an acceptable error is,	13:57:36
22	just, you know, as a person of skill in the art?	13:57:39

1 Are there rough numbers around the 13:57:43

2 acceptable error, is all I'm trying to understand? 13:57:46

3 MR. GUPTA: Objection. Form. Scope. 13:57:51

4 And relevance. 13:57:54

5 A For the azacitidine, my task was to 13:58:03

6 generate a model. There was no data that I 13:58:06

7 compared it to. So talk about differences or 13:58:10

8 errors is irrelevant of this declaration. 13:58:15

9 Q When you were working on your -- on 13:58:25

10 Exhibit 2048 and you were deciding what was an 13:58:45

11 acceptable error rate there, how did you go about 13:58:48

12 that? 13:58:50

13 MR. GUPTA: Objection. Form. Scope. 13:58:53

14 And relevance. 13:58:57

15 A The Exhibit 2048 is an entirely different 13:59:08

16 project to the azacitidine. So although I can 13:59:11

17 talk about that, I don't see the relevance for 13:59:18

18 this declaration here. 13:59:20

19 Q Well, I would like you to talk about it, 13:59:25

20 that's why I'm asking. 13:59:27

21 Can you tell me, when you were working on 13:59:32

22 Exhibit 2048, separate from the azacitidine, how 13:59:34

1 did you decide what was an acceptable error rate 13:59:39

2 in that work? 13:59:43

3 MR. GUPTA: Objection. Outside the scope 13:59:46

4 of the expert report. And objection, relevance. 13:59:49

5 A The decisions that were made in that 14:00:09

6 paper were made between all of the authors and all 14:00:10

7 of the parties, based on their -- the data sets 14:00:12

8 that we had at our disposal. 14:00:17

9 Q And when you were working on Exhibit 2048 14:00:33

10 separate from the azacitidine work, what did you 14:00:44

11 consider as an acceptable error rate in this work? 14:00:47

12 MR. GUPTA: Objection. Objection. Form. 14:00:53

13 Scope, relevance. And 403. 14:01:00

14 You can answer. 14:01:03

15 A I can reread the paper to see what we 14:01:05

16 listed in the paper, if that would help answer the 14:01:07

17 question. 14:01:13

18 Q Yes. Yeah, that will be -- so why don't 14:01:13

19 you go to PDF Page 6, under Evaluation of 14:01:17

20 Predictability of the PBPK Model. 14:01:24

21 In the middle of the left-hand column you 14:01:31

22 say, "In this study, we considered a PE value of 14:01:33

1	less than 20 percent, confirming good	14:01:38
2	predictability of the model."	14:01:43
3	Do you see that?	14:01:45
4	A Yeah, I can see that line.	14:01:51
5	Q And so you agree in this instance in	14:01:54
6	Exhibit 2048 that a prediction error of less than	14:02:01
7	20 percent between the in silico data and the in	14:02:13
8	vivo data confirms good predictability of the in	14:02:18
9	silico model.	14:02:22
10	Is that right?	14:02:22
11	MR. GUPTA: Objection. Scope.	14:02:24
12	Relevance. 403.	14:02:27
13	A For this particular study using	14:02:40
14	carbamazepine, the existing data bank of clinical	14:02:44
15	data against the backdrop of all of the material	14:02:48
16	that went into this, we used the value as stated	14:02:52
17	there of less than 20 percent for this particular	14:02:55
18	model under those circumstances.	14:02:59
19	Q When were you first approached about	14:03:01
20	working on this matter?	14:03:08
21	A The carbamazepine or the case at hand?	14:03:15
22	Q I'm sorry, yes. Let me clarify.	14:03:18

1	When were you first approached about	14:03:20
2	working on your -- on the 5-azacitidine matter?	14:03:22
3	A I don't recall the exact date, but I'm	14:03:34
4	going to say two years ago-ish.	14:03:36
5	Q So sometime in 2021.	14:03:42
6	Is that fair to say?	14:03:46
7	A To the best of my memory, yes.	14:03:52
8	Q And who retained you?	14:03:54
9	A Steptoe.	14:04:02
10	Q And who first reached out to you?	14:04:05
11	A I don't recall exactly who from Steptoe	14:04:13
12	first reached out.	14:04:18
13	Q But it was someone from Steptoe.	14:04:22
14	Correct?	14:04:30
15	A Yes.	14:04:30
16	Q Have you ever spoken to anyone from	14:04:30
17	Apotex?	14:04:32
18	A Not in relation to this matter.	14:04:36
19	Q From the time of your retention until	14:04:38
20	today, what have you done in connection with	14:04:50
21	preparing your declaration?	14:04:54
22	A Do you mean a breakdown of the tasks that	14:05:03

1 I have done? 14:05:05

2 Q At a high level can you describe the 14:05:06
3 types of tasks you did in connection with 14:05:10
4 preparing your declaration? 14:05:11

5 A I've spent -- initially I spent some time 14:05:22
6 in discussions until I understood what task I had 14:05:27
7 been given. And then I did some sort of 14:05:35
8 literature searching in order to prepare the 14:05:41
9 materials in the declaration that culminated, if 14:05:44
10 you like, in running the simulations that I 14:05:51
11 reported here in the model. And then drafting and 14:05:54
12 writing the report. 14:05:57

13 Is that the level of detail that's 14:06:03
14 needed? 14:06:06

15 Q Yes. Thank you. 14:06:06

16 In connection with drafting and writing 14:06:09
17 your report, did you meet with counsel? 14:06:11

18 MR. GUPTA: Dr. Batchelor, you can answer 14:06:20
19 that question without revealing specifics of 14:06:22
20 communications between counsel and yourself. So 14:06:24
21 you can answer that with a yes or no. 14:06:29

22 A Yes. 14:06:36

1 Q Who did you meet with in connection with 14:06:38
2 drafting and writing your report? 14:06:44

3 A The names of the people who I met with 14:06:50
4 from Steptoe, is that what you want? 14:06:53

5 Q Yes, please. 14:06:56

6 THE WITNESS: I'm checking. Am I allowed 14:07:00
7 to give them? Yes. 14:07:01

8 A Vishal, who's on the call. Tyler Doh, 14:07:03
9 who's on the call. Michael Green, who's also on 14:07:07
10 the call. And John -- Molina? If I mispronounce 14:07:10
11 his name, I'm not sure. 14:07:17

12 Q And generally speaking, what was the 14:07:24
13 process for preparing your declaration? 14:07:25

14 MR. GUPTA: Again, Dr. Batchelor, I 14:07:31
15 object on the grounds of privilege. I give you 14:07:33
16 the same instruction not to reveal the specifics 14:07:36
17 of, you know, back-and-forth discussions with 14:07:38
18 counsel. 14:07:40

19 You can answer generally. 14:07:41

20 A The report is mine, it's my opinion. I 14:07:50
21 needed some help and assistance with the 14:07:53
22 formatting. It's not a style of writing I am used 14:07:56

1	to formatting in this way. I'm used to writing	14:08:00
2	scientific papers. So counsel helped me with the	14:08:03
3	formatting of the document.	14:08:12
4	Q How much of your declaration would you	14:08:13
5	say you wrote?	14:08:24
6	A They're my words, they're my opinions.	14:08:27
7	It's -- it's mine.	14:08:30
8	Q And did you write all of the words that	14:08:33
9	are in the declaration?	14:08:43
10	A They're my words. It's all my opinion.	14:08:53
11	I couldn't say which words I typed directly, yeah.	14:08:57
12	Q How much time did you spend drafting your	14:09:02
13	declaration?	14:09:05
14	A I have it logged somewhere, but I don't	14:09:13
15	have it to hand.	14:09:15
16	Q And when did you begin drafting the	14:09:16
17	declaration?	14:09:19
18	A Quite some time ago.	14:09:33
19	Q So the files are from April 2022, and the	14:09:41
20	declaration is signed in February of 2023. So	14:09:45
21	with that in mind, can you tell me when you did	14:09:49
22	the modeling?	14:09:58

1	A	So the modeling was conducted on the	14:10:03
2		dates of the files in April 2022.	14:10:06
3	Q	And then sometime between April 2022 and	14:10:10
4		February of 2023 you started working on the	14:10:14
5		declaration.	14:10:18
6		Is that right?	14:10:18
7	A	I'm trying to remember because it's quite	14:10:28
8		some time ago. Prior to doing the modeling I	14:10:31
9		would have been preparing ultimately for this. So	14:10:34
10		there may have been some work prior to the	14:10:44
11		modeling.	14:10:46
12	Q	And when you say "work," do you mean	14:10:53
13		drafting of the declaration prior to April 2022?	14:10:55
14	A	Well, I would have had to collect the	14:11:10
15		information to put into the model in a form. I	14:11:12
16		can't remember whether I was writing it as part of	14:11:20
17		the declaration or collating that data.	14:11:23
18	Q	And I'm not looking for attorney-client	14:11:42
19		privileged communication here. Can you describe	14:11:47
20		at a high level how you prepared for your	14:11:48
21		deposition today?	14:11:50
22		MR. GUPTA: So same privilege objection.	14:11:52

1 Don't disclose specific communications between 14:11:54
2 counsel and yourself. You can answer generally. 14:11:57

3 A I've previously done similar expert 14:12:09
4 witness trial in the UK, so we had some 14:12:12
5 conversations about differences in procedures and 14:12:15
6 practices between the UK and the US. And then 14:12:17
7 some of the logistics just to get me up to 14:12:21
8 speed -- I'm not an expert in, like, the US legal 14:12:26
9 system. So to make sure I understood, like, the 14:12:30
10 processes and how things work. 14:12:32

11 Q So you met with counsel to prepare for 14:12:36
12 your deposition. Correct? That's what I was 14:12:43
13 really asking. 14:12:46

14 You had a meeting with Steptoe to prepare 14:12:47
15 for your deposition. Correct? 14:12:49

16 A Yes. This is something I take quite 14:12:53
17 seriously, so I wanted to make sure that I was 14:12:56
18 properly prepared for the procedural side of how, 14:12:59
19 what's going to happen. 14:13:03

20 Q And did you review your declaration in 14:13:04
21 preparation for your deposition today? 14:13:06

22 A Yeah. I think that's an important part 14:13:09

1 of -- a useful way -- if I'm going to spend my 14:13:12

2 time, I want it to be constructive and useful. 14:13:16

3 Q Do you know roughly how much time you 14:13:18

4 spent reviewing your declaration? 14:13:21

5 A I was already pretty familiar with it, 14:13:27

6 with the contents. But as this project has been 14:13:31

7 ongoing and I have other projects, I needed to 14:13:34

8 refresh my mind. So probably a few hours through 14:13:38

9 reading it. 14:13:43

10 Q And how long did you meet with counsel 14:13:43

11 for in preparing for your deposition today? 14:13:46

12 A I don't recall the exact times. 14:13:52

13 Q Was it two days, three days, four days, 14:13:56

14 one day? 14:14:00

15 A We met on two occasions. 14:14:10

16 Q And do you recall when those occasions 14:14:15

17 were? 14:14:17

18 A We met -- I'm trying to think what day it 14:14:24

19 is today. We met yesterday. 14:14:27

20 Q And then I presume one time before 14:14:31

21 yesterday? 14:14:34

22 A Yes. 14:14:35

1	Q	And who did you meet with?	14:14:36
2	A	The combination of Vishal, Tyler, and	14:14:46
3		Michael.	14:14:50
4	Q	You can answer this yes or no. Did you	14:14:57
5		review any documents in that meeting?	14:15:03
6	A	Yes.	14:15:12
7	Q	Did you review any documents other than	14:15:13
8		your declaration when you met with counsel to	14:15:20
9		prepare for your deposition?	14:15:22
10	A	We reviewed my declaration, and the	14:15:25
11		points referred to some of the documents that I	14:15:30
12		refer to in my declaration. So to refresh my	14:15:32
13		memory on the Marcucci paper, for example.	14:15:34
14	Q	You mentioned that you had testified in a	14:15:37
15		UK proceeding before.	14:15:46
16		Is that right?	14:15:48
17	A	Yes.	14:15:49
18	Q	And how many times have you testified?	14:15:49
19	A	Only once in person, but I have written	14:15:54
20		paperwork.	14:15:58
21	Q	When you say you've "written paperwork,"	14:16:01
22		was that for a different case from where you	14:16:03

1	testified or the same case?	14:16:07
2	A Different cases.	14:16:08
3	Q So how many cases approximately have you	14:16:11
4	worked on?	14:16:15
5	A I think I've written four, four expert	14:16:16
6	witness reports, and once I've appeared in court.	14:16:22
7	Q And were they all patent litigation cases	14:16:25
8	or patent-related cases?	14:16:27
9	A Yes, they were.	14:16:30
10	MR. GUPTA: I object to this line	14:16:30
11	under -- under no relevance.	14:16:34
12	You can answer.	14:16:36
13	Q And what case was it in which you	14:16:41
14	testified?	14:16:47
15	A I'm not sure I'm allowed to share the	14:16:49
16	details.	14:16:54
17	MR. GUPTA: Okay. So then I object on	14:17:02
18	the grounds of -- to the extent this falls under a	14:17:04
19	confidentiality agreement where she can't disclose	14:17:07
20	the answers, you know, Dr. Batchelor, I would ask	14:17:10
21	you to refer to those agreements to the extent	14:17:15
22	you're not allowed to talk about them.	14:17:17

1	Q	Did you testify in court in the UK?	14:17:21
2	A	Yes.	14:17:28
3	Q	But you're just not sure whether that was	14:17:32
4		public.	14:17:36
5	A	When I was asked to be an expert witness,	14:17:37
6		I was told that I shouldn't disclose what I was	14:17:50
7		doing to others. I don't recall whether now that	14:17:54
8		it's complete I can or not.	14:17:59
9	MS. MACRO:	I'm just going to take a five	14:18:07
10		minute, probably less than, break.	14:18:09
11	MR. GUPTA:	Okay.	14:18:12
12	VIDEO SPECIALIST:	We are going off the	14:18:13
13		record. The time is 14:18.	14:18:14
14		(A recess was taken.)	14:18:17
15	VIDEO SPECIALIST:	We are back on record.	14:34:41
16		The time is 14:34.	14:34:49
17	MS. MACRO:	I have no further questions.	14:34:53
18	MR. GUPTA:	Okay. I might have a few	14:34:57
19		questions, but I need to take -- I need to take a	14:34:59
20		few-minute break myself then. I didn't realize	14:35:02
21		you were going to stop now.	14:35:05
22		Okay. Let's go off the record. I need	14:35:07

1	at least five minutes.	14:35:10
2	VIDEO SPECIALIST: We're going off the	14:35:12
3	record. The time is 14:35.	14:35:13
4	(A recess was taken.)	14:35:18
5	VIDEO SPECIALIST: We're back on record.	14:50:05
6	The time is 14:50.	14:50:13
7	EXAMINATION BY COUNSEL FOR PETITIONER	14:50:16
8	AND THE WITNESS	14:50:16
9	BY MR. GUPTA:	14:50:16
10	Q Good evening, Dr. Batchelor. I just have	14:50:16
11	a few questions for you. Okay?	14:50:19
12	A Yeah.	14:50:22
13	Q Earlier in the deposition you used the	14:50:22
14	phraseology "about the same" in the context of PK	14:50:27
15	parameters.	14:50:32
16	Do you remember that?	14:50:32
17	A I'm sure I used it. I don't remember the	14:50:39
18	specific occasion. But, yeah, I can move forward	14:50:41
19	with it.	14:50:44
20	Q So generally in the field of	14:50:44
21	pharmacokinetics, when would you consider two PK	14:50:48
22	values to be considered about the same?	14:50:52

1 MS. MACRO: Objection. 14:50:55

2 Q Go ahead. 14:50:59

3 A So pharmacokinetics data is subject to 14:51:04

4 quite a lot of variability due to the natural 14:51:06

5 variability between people. So quite high 14:51:10

6 coefficients of variation are often accepted. Up 14:51:14

7 to 30 percent coefficient of variation is a 14:51:18

8 measure that's often applied to things that we say 14:51:23

9 are about the same. 14:51:27

10 Q Earlier in the deposition you were asked 14:51:28

11 about azacitidine deaminase related degradation. 14:51:30

12 Do you remember that? 14:51:37

13 A I do. 14:51:38

14 Q Does your model account for degradation 14:51:39

15 to azacitidine deaminase? 14:51:42

16 A So the way the model is constructed using 14:51:47

17 the intravenous data from Marcucci, the Marcucci 14:51:49

18 data measured -- the word is gone now -- 14:51:56

19 azacitidine levels in the blood, and those levels 14:52:05

20 were incorporated into the model. 14:52:07

21 So any degradation that would have 14:52:11

22 happened prior to those levels is already 14:52:13

1 incorporated into the model within the elimination 14:52:14

2 that's -- that's there. 14:52:18

3 Q And if you somehow had -- if you somehow 14:52:20

4 had additional azacitidine deaminase data, would 14:52:28

5 you expect your calculated PK parameters to be 14:52:33

6 about the same? 14:52:35

7 MS. MACRO: Objection. Form. Scope. 14:52:38

8 Q Sorry. Go ahead. 14:52:45

9 A So the model originally incorporates the 14:52:46

10 level of degradation that's taking place in the 14:52:54

11 blood in the IV measurements. So I would expect 14:52:56

12 those to be the same. 14:52:59

13 Q Okay. And you were asked about Exhibit 14:53:04

14 2048. 14:53:11

15 Do you recall that? 14:53:13

16 A That was the paper that was new. 14:53:16

17 Q Yeah. It was -- this was -- Exhibit 2048 14:53:19

18 is a paper entitled, Integration of Biorelevant 14:53:22

19 Pediatric Dissolution Methodology into PBPK 14:53:28

20 Modeling to Predict In Vivo Performance and 14:53:33

21 Bioequivalence of Generic Drugs in Pediatric 14:53:36

22 Populations -- 14:53:39

1	A	Yeah.	14:53:40
2	Q	-- Carbamazepine Case Study.	14:53:40
3		Do you remember that?	14:53:46
4	A	Yes.	14:53:51
5	Q	Would -- do you still have that in your	14:53:52
6		OneDrive?	14:53:55
7	A	Yes.	14:53:55
8	Q	If you could open that up, I'd appreciate	14:53:56
9		it.	14:53:58
10	A	Sure.	14:54:00
11	Q	And we could go to the first page.	14:54:08
12	A	Yeah.	14:54:10
13		MS. MACRO: Can you give me one moment?	14:54:11
14		Okay, I'm ready.	14:54:12
15	Q	Okay. Dr. Batchelor, now when is this	14:54:21
16		paper from?	14:54:29
17	A	2023 it was accepted for publication.	14:54:34
18	Q	Is that significantly after the 2008	14:54:37
19		date, the priority date in this case?	14:54:41
20	A	Yes.	14:54:43
21		MS. MACRO: Objection. Form.	14:54:45
22		THE WITNESS: Oh, sorry. Keep going too	14:54:47

1	fast.	14:54:50
2	Q Now, Dr. Batchelor, what was the drug	14:54:50
3	being studied in this paper?	14:54:52
4	A Carbamazepine.	14:55:07
5	Q Is that a different drug than	14:55:07
6	azacitidine?	14:55:09
7	A Yes, it is.	14:55:09
8	Q Just generally speaking, what was the	14:55:10
9	goal of the study?	14:55:20
10	MR. GUPTA: Objection. Scope.	14:55:27
11	A The purpose of this paper was to	14:55:32
12	understand more about pediatric populations, and	14:55:36
13	specifically dissolution methodology that could be	14:55:45
14	used and integrated into PBPK models for pediatric	14:55:50
15	populations, to compare those to existing clinical	14:55:56
16	data on carbamazepine.	14:56:00
17	Q Was your goal to analyze a pediatric	14:56:04
18	population in the azacitidine work that you did in	14:56:08
19	this case?	14:56:13
20	MR. GUPTA: Objection. Form. Scope.	14:56:13
21	A The modeling that I undertook for my	14:56:22
22	declaration was based on an adult physiology, not	14:56:28

1	pediatric.	14:56:32
2	Q What, if any, relevance does the 2023	14:56:33
3	paper have on your opinions for this case related	14:56:35
4	to azacitidine?	14:56:38
5	MR. GUPTA: Objection. Form.	14:56:41
6	A This paper has no -- no connection to the	14:56:49
7	azacitidine declaration.	14:56:52
8	MR. GUPTA: Okay. I have no further	14:56:57
9	questions.	14:56:59
10	MS. MACRO: Can we take a quick break,	14:57:02
11	please. Five minutes.	14:57:04
12	VIDEO SPECIALIST: We're going off the	14:57:07
13	record. The time is 14:57.	14:57:08
14	(A recess was taken.)	14:57:11
15	VIDEO SPECIALIST: We are back on record.	15:02:45
16	The time is 15:02.	15:02:53
17	EXAMINATION BY COUNSEL FOR PATENT OWNER	15:02:57
18	BY MS. MACRO:	15:02:57
19	Q I just have a couple of followup	15:02:58
20	questions on Marcucci. The data in Marcucci is --	15:03:00
21	withdraw that.	15:03:13
22	The data that you used for Marcucci was	15:03:14

1	administration by IV. Correct?	15:03:18
2	A Yeah.	15:03:25
3	Q 5-azacitidine administered intravenously	15:03:34
4	doesn't travel through your stomach. Correct?	15:03:38
5	MR. GUPTA: Objection to form.	15:03:41
6	You can answer, Dr. Batchelor.	15:03:46
7	A Correct, an intravenous dose is	15:03:51
8	administered. The only way it can get to the	15:03:53
9	stomach is if it -- if it goes that way from the	15:03:57
10	blood into the stomach rather than the stomach --	15:04:00
11	or the intestine into the blood.	15:04:03
12	Q 5-azacitidine administered intravenously	15:04:06
13	isn't initially absorbed through the stomach.	15:04:14
14	Is that right?	15:04:16
15	MR. GUPTA: Same objection. Objection to	15:04:17
16	form.	15:04:19
17	You can answer.	15:04:21
18	A I agree with the statement that	15:04:25
19	5-azacitidine administered intravenously is	15:04:27
20	directly administered to the bloodstream not via	15:04:31
21	the gastrointestinal tract.	15:04:35
22	Q In that case, the Marcucci IV data	15:04:41

1	doesn't account for any degradation that would	15:05:01
2	happen to 5-azacitidine if it was administered via	15:05:07
3	the gastrointestinal tract. Correct?	15:05:12
4	MR. GUPTA: Objection to form.	15:05:15
5	You can answer.	15:05:20
6	A So the intravenous data captures the	15:05:33
7	intravenous profile of azacitidine following	15:05:38
8	administration where any elimination in the blood	15:05:43
9	is occurring, and that was built into the model.	15:05:47
10	And that was where the model was built for the --	15:05:54
11	sorry, I couldn't remember the second part of the	15:06:00
12	question.	15:06:01
13	Q The Marcucci IV data doesn't account for	15:06:03
14	any degradation that would happen to 5-azacitidine	15:06:10
15	if it was administered via the gastrointestinal	15:06:14
16	tract. Correct?	15:06:18
17	MR. GUPTA: Same objection.	15:06:21
18	A Within the model, I used the most robust	15:06:31
19	data that I had, to the very rapid transit through	15:06:35
20	the intestinal tracts would mean that any	15:06:40
21	degradation that was happening there would make	15:06:43
22	the outputs about the same. So I didn't need to	15:06:47

1	consider that in the model.	15:06:49
2	MS. MACRO: I have no further questions.	15:07:17
3	MR. GUPTA: Okay. Nothing further from	15:07:20
4	our end. Thank you, Dr. Batchelor.	15:07:21
5	VIDEO SPECIALIST: If there's nothing	15:07:25
6	further everyone stand by, and I'll read us off	15:07:28
7	the video record.	15:07:32
8	This marks the end of the deposition of	15:07:33
9	Hannah Batchelor. We're going off the video	15:07:34
10	record at 15:07.	15:07:37

11 (Off the record at 3:07 p.m. EDT.)

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ACKNOWLEDGMENT OF DEPONENT

I, HANNAH K. BATCHELOR, Ph.D., do hereby
acknowledge that I have read and examined the
foregoing testimony, and the same is a true,
correct and complete transcription of the
testimony given by me, and any corrections appear
on the attached Errata sheet signed by me.

(DATE)

(SIGNATURE)

C E R T I F I C A T E

I, Debra Ann Whitehead, E-Notary Public in and for
the State of Maryland, do hereby certify:

That HANNAH K. BATCHELOR, Ph.D., the
witness whose deposition is hereinbefore set forth,
was duly sworn by me before the commencement of such
deposition and that such deposition was taken
virtually and is a true record of the testimony
given by such witness.

I further certify that the adverse party,
APOTEX, INC., was represented by counsel at the
deposition.

I further certify that the deposition of
HANNAH K. BATCHELOR, Ph.D., occurred virtually, on
Tuesday, September 19, 2023, from 8:07 a.m. to 3:07
p.m. EDT.

1 I further certify that I am not related to
2 any of the parties to this action by blood or
3 marriage, I am not employed by or an attorney to any
4 of the parties to this action, and that I am in no
5 way interested, financially or otherwise, in the
6 outcome of this matter.

7
8 IN WITNESS WHEREOF, I have hereunto set my
9 hand this 20th day of September, 2023.

10
11 My commission expires:

12 April 30th, 2027

13 A circular notary seal for Hannah K. Batchelor, Ph.D., Notary Public, State of Maryland. The seal contains the text "Hannah K. Batchelor, Ph.D.", "NOTARY PUBLIC", and "STATE OF MARYLAND".

14 Hannah K. Batchelor

15 E-NOTARY PUBLIC IN AND FOR THE
16 STATE OF MARYLAND

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