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Transcript of Graham Buckton, Ph.D.

Date: September 26, 2023

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

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CELGENE 2050
APOTEX v. CELGENE
IPR2023-00512

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

- - - - - x

APOTEX, INC., :
Petitioner, :
v. : Case No. IPR2023-00512
CELGENE CORPORATION, : U.S. Patent No.
Patent Owner. : 8,846,628

- - - - - x

Videotaped Deposition of GRAHAM BUCKTON, PH.D.
New York, New York
Tuesday, September 26, 2023
8:47 a.m.

Job No.: 506502
Pages: 1 - 161
Reported By: Anita M. Trombetta, RMR, CRR

Transcript of Graham Buckton, Ph.D.
Conducted on September 26, 2023

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1 Videotaped deposition of Graham Buckton, Ph.D.,
2 held at the offices of:

3
4 Steptoe & Johnson LLP
5 1114 Avenue of the Americas
6 35th floor
7 New York, NY 10036
8 212.506.3900
9

10 Pursuant to notice, before Anita M. Trombetta,
11 RMR, CRR, Notary Public in and for the State of
12 New York.
13
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15
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22

1 A P P E A R A N C E S

2
3 ON BEHALF OF PETITIONER AND THE WITNESS:

4 VISHAL C. GUPTA, ESQUIRE

5 TYLER DOH, Ph.D., ESQUIRE

6 MICHAEL I. GREEN, ESQUIRE (via
7 teleconference)

8 STEPTOE & JOHNSON LLP

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10 New York, New York 10036

11 (212) 506-3900
12

13 ON BEHALF OF PATENT OWNER:

14 HEATHER PETRUZZI, ESQUIRE

15 LAURA MACRO, ESQUIRE, Ph.D.

16 GABRIEL ROSANIO, ESQUIRE, Ph.D.

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18 2100 Pennsylvania Avenue NW

19 Washington, DC 20037

20 (202) 663-6000
21

22 (Appearances continued on next page.)

A P P E A R A N C E S C O N T I N U E D

ALSO PRESENT:

Bo Han, BMS (via teleconference)

Enrique Casas, Videographer

Muskaan Zaidi, Planet Depo

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-----I N D E X-----

WITNESS	EXAMINATION BY	PAGE
Graham Buckton, Ph.D.	Ms. Petruzzi	7
	Mr. Gupta	147
	Ms. Petruzzi	156

-----E X H I B I T S-----

EXHIBIT	DESCRIPTION	PAGE
None		

INFORMATION REQUESTED

	Page	Line
Dr. Berkland's report	157	1

QUESTIONS INSTRUCTED NOT TO ANSWER

	Page	Line
None		

Transcript of Graham Buckton, Ph.D.
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P R O C E E D I N G S

THE VIDEOGRAPHER: Here begins Media No. 1
in the videotaped deposition of Graham Buckton,
Ph.D., in the matter of Apotex Inc. vs. Celgene
Corporation PTAB, in the United States Patent and
Trademark Office, Case Number IPR 2023-00512.

Today's date is September 26, 2023. And
the time on the video monitor is 8:47 a.m.

Today -- the videographer today is Enrique
Casas representing Planet Depos. This video
deposition is taking place at 1114 Avenue of the
Americas, New York, New York.

Would counsel please voice identify
themselves and state who they represent.

MS. PETRUZZI: Heather Petruzzi from
WilmerHale representing the patent owner Celgene
Corporation and BMS. I'm joined by my colleagues
Laura Macro and Gabriel Rosanio, also from
WilmerHale and Bo Han from BMS.

MR. GUPTA: Vishal Gupta from the law firm
of Steptoe & Johnson. I'm joined by Tyler Doh
from my firm and at some point, potentially,

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Transcript of Graham Buckton, Ph.D.
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1	Michael Green may call in.	08:48:23
2	THE VIDEOGRAPHER: The court reporter	08:48:26
3	today is Anita Trombetta representing Planet	08:48:27
4	Depos.	08:48:30
5	The witness will now be sworn in.	08:48:30
6	G R A H A M B U C K T O N, P H.D.,	
7	called as a witness, having been duly	
8	sworn by a Notary Public, was examined and	
9	testified as follows:	
10	EXAMINATION BY	
11	MS. PETRUZZI:	
12	Q Good morning, Dr. Buckton.	08:48:44
13	A Good morning.	08:48:45
14	Q Thank you for being here today.	08:48:45
15	Do you understand why you're being deposed	08:48:46
16	today?	08:48:48
17	A Yes.	08:48:48
18	Q And what is that understanding?	08:48:49
19	A To explain my evidence in relation to this	08:48:50
20	case for the patent brought.	08:48:54
21	Q Okay. And you've submitted a declaration	08:48:57
22	in connection with IPR 2023-00512, correct?	08:48:59

Transcript of Graham Buckton, Ph.D.
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1	A I haven't memorized the number, but that	08:49:05
2	sounds right, yes.	08:49:07
3	Q Okay. Have you been deposed before?	08:49:08
4	A Yes.	08:49:10
5	Q How many times have you been deposed?	08:49:10
6	A Quite a few. I don't know exactly, maybe	08:49:12
7	20 or more.	08:49:16
8	Q Okay. Do you understand that your	08:49:17
9	testimony here is given under oath?	08:49:19
10	A Yes.	08:49:21
11	Q Is there any reason that you cannot	08:49:21
12	provide complete and accurate testimony here	08:49:23
13	today?	08:49:25
14	A No.	08:49:26
15	Q Did you bring anything with you to the	08:49:26
16	deposition today?	08:49:29
17	A No, there's a report here, which I didn't	08:49:30
18	technically bring, but that is an unmarked copy of	08:49:33
19	my report.	08:49:36
20	Q Okay. So you have next to you an unmarked	08:49:36
21	copy of your report?	08:49:39
22	A I do.	08:49:39

1	Q Okay. Thank you. Anything else with you	08:49:40
2	today?	08:49:43
3	A No.	08:49:43
4	Q Okay. You are an expert in formulations,	08:49:44
5	right?	08:49:49
6	A Yeah, amongst other things, yes.	08:49:49
7	Q Okay. Have you ever formulated	08:49:52
8	5-azacytidine before?	08:50:24
9	MR. GUPTA: Objection to form.	08:49:57
10	You can answer.	08:49:59
11	A I don't believe so, but in my company	08:49:59
12	we've formulated a lot of things. I don't believe	08:50:01
13	it was this compound, but it may have been. I	08:50:04
14	don't think so though.	08:50:09
15	Q Have you personally worked with	08:50:09
16	5-azacytidine before?	08:50:13
17	A Same answer.	08:50:13
18	Q In your declaration you attached a copy of	08:50:15
19	your CV; is that right?	08:50:18
20	A Yes.	08:50:19
21	Q Your CV does not describe any research you	08:50:20
22	completed concerning 5-azacytidine, correct?	08:50:22

1	A	No. Inevitably, an academic CV covers	08:50:27
2		nonproprietary things, and you talk about other	08:50:31
3		stuff than the drug substance.	08:50:34
4	Q	Had you heard of 5-azacytidine before your	08:50:36
5		work on this case?	08:50:40
6	A	I'd heard of it as a drug, yes.	08:50:41
7	Q	In what context have you heard of it?	08:50:43
8	A	As an anticancer drug.	08:50:44
9	Q	When did you first heard of 5-azacytidine?	08:50:47
10	A	I don't know the date. It's just a drug	08:50:50
11		name that I happen to know. I don't know the	08:50:52
12		date.	08:50:54
13	Q	Okay. Were you familiar with the	08:50:55
14		literature on 5-azacytidine before your work on	08:51:01
15		this case?	08:51:04
16	A	By literature, you mean prior art of this	08:51:05
17		patent, as it were. I wasn't familiar with the	08:51:09
18		literature particularly.	08:51:12
19	Q	Your CV notes that you're an emeritus	08:51:13
20		professor of pharmaceuticals; is that right?	08:51:18
21	A	Emeritus, yes.	08:51:20
22	Q	What does that mean?	08:51:23

1	A	It essentially means that I have retired,	08:51:24
2		but I have an honorary position at the university.	08:51:26
3	Q	When did you retire from the university?	08:51:29
4	A	2015.	08:51:31
5	Q	You're currently working; is that correct?	08:51:32
6	A	I am largely retired, and I have over the	08:51:39
7		last year or so kind of been stepping down from	08:51:44
8		other things that I do. So I have some expert	08:51:46
9		witness work, and outside of that, largely	08:51:48
10		retired.	08:51:50
11	Q	Okay. And so how much of your work is	08:51:50
12		related to being an expert witness at this point?	08:51:53
13	A	Just about all of it is, but the amount of	08:51:55
14		my time that's work is, thankfully, rather small.	08:51:58
15	Q	How much of your time are you spending	08:52:01
16		working right now?	08:52:04
17	A	Well, this week isn't very good because	08:52:05
18		I've been working more than I've been golfing, for	08:52:07
19		example, but other weeks are rather better in	08:52:09
20		terms of the golf-work balance. But it isn't	08:52:11
21		consistent. It varies. There could be months I	08:52:13
22		will do nothing, like several months when I will	08:52:17

1	do nothing. And then there could be months when I	08:52:19
2	do something, I work quite a lot. So it varies	08:52:21
3	quite a lot.	08:52:26
4	Q I'm going to hand you what's previously	08:53:01
5	been marked as Exhibit 1002 in this proceeding.	08:53:03
6	A You can take that one away.	08:53:09
7	Q Do you recognize this document?	08:53:12
8	A Yes, yes, I do.	08:53:15
9	Q What is it?	08:53:16
10	A It is the report I submitted with my CV	08:53:18
11	attached at the end of it.	08:53:22
12	Q And this is concerning Celgene patent	08:53:24
13	8,846,628, correct?	08:53:29
14	A I don't recognize -- I haven't memorized	08:53:33
15	the number, but the last three digits are right.	08:53:36
16	Q Okay. It's right on the first page -- on	08:53:39
17	the cover page of your declaration there.	08:53:42
18	Do you see it?	08:53:44
19	A I really don't.	08:53:45
20	Q U.S. patent number?	08:53:49
21	A Oh, yeah, it's in the middle. I've got	08:53:50
22	it.	08:53:52

1	Q You see it?	08:53:52
2	A Yes, I've got it now.	08:53:53
3	Q Great. If I refer to it the '628 patent,	08:53:54
4	you'll know what I mean?	08:53:57
5	A I was there already on the '628.	08:53:58
6	Q Perfect. We're on the same page.	08:54:00
7	Did you review the '628 patent in its	08:54:02
8	entirety before submitting your declaration?	08:54:05
9	A Yes, I did.	08:54:06
10	Q About how many times did you do that?	08:54:07
11	A I don't think I reviewed it in its	08:54:09
12	entirety more than once probably. I would have	08:54:10
13	looked at that time in its entirety and then	08:54:13
14	looked in further detail at sections that are	08:54:16
15	relevant to what I was considering.	08:54:19
16	Q Okay. All right.	08:54:20
17	Your declaration contains Section 4, which	08:54:24
18	starts at Page 13. Turn to that: Documents.	08:54:30
19	Do you see that?	08:54:36
20	A Sorry, what was that? Page 14.	08:54:38
21	Q Page 13 of page -- starts with:	08:54:41
22	Documents.	08:54:44

1	A Yes.	08:54:44
2	Q The section starts with: Documents.	08:54:44
3	Do you see that?	08:54:46
4	A Yes.	08:54:46
5	Q And these are the documents that you	08:54:47
6	considered in forming your opinions in this	08:54:49
7	declaration; is that right?	08:54:51
8	A That's right.	08:54:52
9	Q Does Section 4 represent the full set of	08:54:53
10	materials you considered in forming your opinions	08:54:56
11	contained in the declaration?	08:54:59
12	A I think so. I may have -- yeah, there may	08:55:01
13	be kind of standard textbooks that maybe I have an	08:55:05
14	opinion based on, but I haven't got in here. I	08:55:08
15	don't know. But there's nothing that I've written	08:55:10
16	in my opinion -- there's nothing I've written in	08:55:12
17	my opinion in terms of what's in this report, of	08:55:16
18	anything else other than these.	08:55:19
19	Q Okay. In forming your opinions for this	08:55:19
20	declaration, did you search for any literature	08:55:25
21	yourself?	08:55:27
22	A I don't think I searched for literature	08:55:30

1	myself. I knew of literature myself, but I don't	08:55:32
2	know if I searched for anything.	08:55:34
3	Q How did you know of the literature	08:55:36
4	yourself?	08:55:38
5	A A quite a bit of literature is related to	08:55:38
6	aspects relating to formulation, and I would have	08:55:42
7	known about aspects relating to formulation, for	08:55:45
8	example.	08:55:47
9	Q Okay. So for example, you cite	08:55:48
10	Remington's as a reference?	08:55:50
11	A Yes.	08:55:53
12	Q And Remington's is a common textbook that	08:55:54
13	you would have been aware of?	08:55:57
14	A I certainly was aware of Remington's	08:55:57
15	before this, yes.	08:56:00
16	Q Did you talk to anyone other than counsel	08:56:04
17	for Apotex in forming your opinions in this	08:56:07
18	declaration?	08:56:10
19	A No.	08:56:10
20	Q Your report cites the -- Dr. Batchelor's	08:56:11
21	declaration, correct?	08:56:16
22	A It does.	08:56:17

Transcript of Graham Buckton, Ph.D.
Conducted on September 26, 2023

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1	Q Did you speak with Dr. Batchelor before	08:56:18
2	signing your declaration?	08:56:19
3	A Not about this, no.	08:56:21
4	Q Do you know Dr. Batchelor?	08:56:22
5	A Yes.	08:56:27
6	Q Did you talk to her about this case at all	08:56:28
7	before forming your opinions in this declaration?	08:56:31
8	A No.	08:56:33
9	Q Have you talked to her about this case at	08:56:34
10	all?	08:56:36
11	A No.	08:56:36
12	Q Did you consult with a clinician in	08:56:37
13	forming your opinions in the declaration?	08:56:45
14	A No, I had no need to do that. My opinions	08:56:47
15	are my opinions without the need to talk to anyone	08:56:50
16	else about them.	08:56:53
17	Q Did you review Dr. Batchelor's deposition	08:56:54
18	transcript in preparing for today's deposition?	08:56:59
19	A Yes, I did.	08:57:02
20	Q In preparing for your deposition, did you	08:57:03
21	review the Court's claim construction order from	08:57:07
22	the district court litigation?	08:57:10

1	A	No, I don't think so.	08:57:12
2	Q	Did you review Celgene's preliminary	08:57:14
3		response filed in this IPR proceeding?	08:57:19
4	A	I don't believe so. If I'm wrong about	08:57:21
5		any of this, I apologize, but my memory is no.	08:57:26
6	Q	Okay. Did you review Dr. Berkland's	08:57:29
7		declaration submitted in support of Celgene's	08:57:32
8		preliminary response in this proceeding?	08:57:35
9	A	Yes, I did.	08:57:37
10	Q	When did you review that?	08:57:37
11	A	I reviewed it, I think pretty soon after	08:57:40
12		it was submitted, whatever date that was, and then	08:57:44
13		I believe I've not looked at it in its entirety,	08:57:48
14		but probably looked at in part over the last few	08:57:50
15		days.	08:57:53
16	Q	Did it change any of your opinions?	08:57:54
17	A	No.	08:57:55
18	Q	Did you review the board's institution	08:57:56
19		decision for this IPR proceeding?	08:57:59
20	A	Yes, I did.	08:58:00
21	Q	When did you do that?	08:58:01
22	A	Pretty much when it came out.	08:58:03

Transcript of Graham Buckton, Ph.D.
Conducted on September 26, 2023

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1	Q Did it change any of your opinions?	08:58:04
2	A No.	08:58:07
3	Q When did you review Dr. Batchelor's	08:58:08
4	deposition transcript?	08:58:12
5	A I think on the plane coming over here.	08:58:13
6	Q When was that?	08:58:16
7	A When was that?	08:58:17
8	Q Yes.	08:58:18
9	A It was Sunday. No, was it? No, it was	08:58:18
10	Saturday. Saturday, yes.	08:58:21
11	Q Did it change any of the opinions that you	08:58:23
12	offered in your declaration?	08:58:25
13	A No.	08:58:26
14	Q Did you review any other materials in	08:58:27
15	preparation for your deposition besides the	08:58:31
16	materials listed in your documents-considered list	08:58:34
17	on -- starting on Page 13 of your declaration?	08:58:36
18	A I don't know. I haven't checked whatever	08:58:40
19	I've reviewed against what's on the list, if I'm	08:58:43
20	honest, but I read -- yes, I did. Actually, the	08:58:46
21	answer is yes, I've looked at a few papers which	08:58:48
22	were cited by Dr. Berkland, although I can't	08:58:51

Transcript of Graham Buckton, Ph.D.
Conducted on September 26, 2023

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1	honestly remember the names of them just now, just	08:58:55
2	a few of those which I haven't seen before.	08:58:57
3	Q Can you describe those papers that you	08:58:59
4	reviewed?	08:59:00
5	A Not terribly well, not really, no, but I	08:59:01
6	did read some papers from his declaration.	08:59:06
7	Q Okay. And why did you do so?	08:59:09
8	A Because I was trying to understand what he	08:59:13
9	was talking about. And see whether I agreed with	08:59:14
10	what he was talking about or not.	08:59:18
11	MS. PETRUZZI: Counsel, I'd ask you to	08:59:19
12	provide a list of the papers Dr. Buckton reviewed	08:59:20
13	in connection with his preparation for this	08:59:24
14	deposition that are not included in the	08:59:28
15	documents-considered list.	08:59:29
16	MR. GUPTA: He just reviewed the Berkland	08:59:30
17	declaration, whatever was cited in there, like I	08:59:33
18	don't -- I don't think your -- I'll take it under	08:59:36
19	advisement.	08:59:39
20	MS. PETRUZZI: Thank you.	08:59:40
21	BY MS. PETRUZZI:	08:59:39
22	Q Did you review all of the documents	08:59:39

1	considered in Dr. Berkland's declaration?	08:59:42
2	A No. Just a couple.	08:59:45
3	MS. PETRUZZI: Counsel, we'd like to know	08:59:48
4	the list of what he considered, please.	08:59:51
5	MR. GUPTA: I'll take it under	08:59:54
6	advisement -- I'll take your request under	08:59:56
7	advisement. I don't know if I agree with it.	09:00:00
8	BY MS. PETRUZZI:	09:00:08
9	Q Dr. Buckton, you've worked in	09:00:08
10	pharmaceutics and pharmaceutical formulations for	09:00:17
11	a long time, right?	09:00:20
12	A Yes.	09:00:22
13	Q Okay. When did you begin your work in	09:00:22
14	pharmaceutics and pharmaceutical formulations?	09:00:24
15	A So my Ph.D. started in '82, 1982.	09:00:27
16	Q And you've been working in the field ever	09:00:32
17	since?	09:00:35
18	A Yes.	09:00:35
19	Q You've considered -- strike that.	09:00:36
20	In your experience working in	09:00:44
21	pharmaceutics and pharmaceutical formulations,	09:00:47
22	you've considered the things that one would need	09:00:50

1	to consider when developing a pharmaceutical	09:00:53
2	formulation, correct?	09:00:55
3	A That's a very wide question, isn't it, so	09:00:56
4	specifically to an individual task, I would	09:00:59
5	consider what was necessary to that individual	09:01:03
6	task, yes.	09:01:05
7	Q And part of the individual task is	09:01:06
8	ensuring that the pharmaceutical formulation that	09:01:08
9	you develop can administer therapeutically	09:01:11
10	effective amount of the drug to a patient?	09:01:13
11	A Part of the task would be delivering a	09:01:16
12	therapeutic and effective amount, correct.	09:01:18
13	Q You agree that the stability of an active	09:01:21
14	ingredient is an important consideration in a	09:01:23
15	pharmaceutical formulation, right?	09:01:26
16	MR. GUPTA: Objection to form. Scope.	09:01:27
17	Relevance.	09:01:30
18	You can answer.	09:01:31
19	A Stabilities, well, every drug substance	09:01:32
20	that we know degrades. I don't know of a drug	09:01:36
21	substance that we have that doesn't degrade. The	09:01:39
22	vast majority of them degrade by hydrolysis; some	09:01:41

1	of them degrade by oxidation. So I would consider	09:01:44
2	those aspects in relation to a specific type of	09:01:48
3	formulation and how important they may or may not	09:01:50
4	be.	09:01:52
5	Q You mentioned degradation in your answer,	09:01:53
6	correct?	09:01:59
7	A I think I did, yes. I haven't memorized	09:01:59
8	it, but I think I -- yeah.	09:02:02
9	Q If there is degradation, that's loss of	09:02:03
10	the active ingredient, right?	09:02:07
11	MR. GUPTA: Objection to form.	09:02:08
12	You can answer.	09:02:10
13	A Well, degradation of a drug substance	09:02:11
14	through shelf life is an inevitability and that's	09:02:14
15	why we have a shelf life on all of our drug	09:02:17
16	products, and degradation is, as I was talking	09:02:19
17	about it, loss of some of the drug substance, over	09:02:24
18	shelf life, for example. But that's an example.	09:02:30
19	You know, but we're talking in very	09:02:34
20	generalizations, but that's an example. And that	09:02:36
21	happens with every product. That's why we set a	09:02:38
22	shelf life for every product.	09:02:40

1	Q And as you lose some of the drug substance	09:02:48
2	during degradation, the product becomes less	09:02:53
3	efficacious; is that right?	09:02:57
4	MR. GUPTA: Objection to form.	09:02:58
5	You can answer.	09:02:59
6	A No, that's not right, because within a	09:03:00
7	regulatory consideration, you would be -- your	09:03:02
8	shelf life would be something where it remained	09:03:07
9	efficacious. So it was still just fine. If it's	09:03:09
10	gone outside of its shelf life it means it's no	09:03:12
11	longer sufficiently efficacious. So then you have	09:03:15
12	a problem. But in terms of normal use, there	09:03:17
13	would be an acceptable amount of drug loss over a	09:03:21
14	shelf life, and every product will have drug loss	09:03:24
15	over the shelf life, and that won't affect	09:03:28
16	therapeutic performance. Otherwise, it wouldn't	09:03:30
17	be allowed to be on the market.	09:03:33
18	Q Okay. So the shelf life defines how long	09:03:34
19	enough of the drug substance is available to be	09:03:37
20	efficacious. Is that correct?	09:03:37
21	(Court reporter clarification.)	09:03:37
22	Q Strike that. Why don't I just ask it	09:03:37

1	again.	09:03:37
2	I said, so the shelf life defines how long	09:03:50
3	enough of the drug substance is available to be	09:03:55
4	efficacious; is that right?	09:03:57
5	A In part. The shelf life defines how long	09:03:58
6	you maintain safety, quality, and efficacy of a	09:04:02
7	drug product in terms of what you're going to	09:04:06
8	administer to a patient. That's a standard	09:04:08
9	regulatory position.	09:04:12
10	Q You mentioned that every drug degrades; is	09:04:22
11	that right?	09:04:44
12	A I don't know of any, sitting here just	09:04:44
13	now, that don't. So there may be, I don't know,	09:04:47
14	if I went away and thought about it I could	09:04:52
15	probably find an example that doesn't degrade over	09:04:55
16	time. I've got one. I'll tell you what. I'll	09:04:58
17	give you one that doesn't. Medical gases don't	09:04:59
18	degrade over time. There you go. Outside of	09:05:00
19	that, I think everything else degrades over time,	09:05:02
20	yes.	09:05:04
21	Q And so you agree that degradation must be	09:05:24
22	taken into account when formulating drug	09:05:28

1	substances, correct?	09:05:31
2	MR. GUPTA: Objection to form.	09:05:31
3	You can answer.	09:05:35
4	A I think we would always consider	09:05:36
5	degradation in terms of defining a shelf life or	09:05:42
6	defining a formulation for every drug substance.	09:05:46
7	I agree.	09:05:48
8	Q Now, in your declaration, you reference	09:05:55
9	Dr. Batchelor's declaration, correct?	09:06:00
10	A Yes.	09:06:03
11	Q In Dr. Batchelor's declaration she	09:06:03
12	discusses how pH can affect degradation.	09:06:07
13	Do you recall that?	09:06:10
14	A I haven't reviewed it for a long time. So	09:06:10
15	I don't recall it particularly, but I suspect she	09:06:12
16	probably does.	09:06:15
17	Q Okay. Do you know if pH can affect the	09:06:16
18	formulation of an active ingredient?	09:06:19
19	A I don't understand the question. Can you	09:06:22
20	give me a more specific question?	09:06:24
21	Q Sure. Do you know if the pH can affect	09:06:25
22	how you formulate a drug?	09:06:29

1	MR. GUPTA: Objection to form. And scope.	09:06:32
2	You can answer.	09:06:36
3	A I still don't understand the question.	09:06:37
4	Can you -- I don't understand -- well, in relation	09:06:39
5	to what formulation, what type of thing, how does	09:06:43
6	it -- I don't -- I don't understand it as a	09:06:47
7	general question.	09:06:50
8	Q Do you consider pH when formulating a drug	09:06:50
9	substance?	09:06:54
10	A You would, as part of a fleet of	09:06:56
11	preformulation studies, consider pH. I think	09:07:00
12	that's a reasonable thing to do when formulating a	09:07:03
13	drug substance, in terms of understanding its	09:07:06
14	properties, yes.	09:07:10
15	Q Do you know whether degradation processes	09:07:11
16	can occur faster depending on pH?	09:07:13
17	MR. GUPTA: Objection to form, scope, and	09:07:15
18	relevance.	09:07:18
19	You can answer.	09:07:19
20	A I'd say different drug substances can	09:07:20
21	degrade at different rates at different pHs.	09:07:26
22	That's a usual thing we would consider, yes.	09:07:29

1	Q All right. By 2008, the degradation	09:07:33
2	contents -- strike that.	09:07:40
3	By 2008, the degradation constants for	09:07:41
4	5-azacytidine hydrolysis in aqueous --	09:07:46
5	(Court reporter clarification.)	09:07:46
6	Q By 2008, the degradation constants for	09:07:55
7	5-azacytidine hydrolysis in a aqueous buffer	09:08:00
8	solutions at 37-degree celsius were known,	09:08:04
9	correct?	09:08:07
10	MR. GUPTA: Objection to form.	09:08:07
11	You can answer.	09:08:09
12	A I think they were known for some pH values	09:08:09
13	in terms of studying long-term stability of a	09:08:15
14	liquid formulation, I believe.	09:08:18
15	Q Okay. Did you review those degradation	09:08:20
16	rate constants in preparing your declaration?	09:08:29
17	A I may have looked at them. I don't know.	09:08:32
18	Are they on my materials considered? I don't	09:08:32
19	know. If they're on there, maybe I did. If	09:08:34
20	they're not on there, maybe I didn't. I don't --	09:08:37
21	I don't need to -- well, let's -- let's -- if	09:08:39
22	they're on there, let's have a look at them.	09:08:41

1	We'll look at them anyway. Whatever you prefer.	09:08:43
2	Q All right. If you will turn to your	09:08:55
3	declaration, please, at Page 56. The top of the	09:08:58
4	page is the end of paragraph 119. Let me know	09:09:03
5	when you're there.	09:09:11
6	A Okay.	09:09:13
7	Q And here there is -- we see part of a	09:09:13
8	sentence, but essentially at the top of the page	09:09:16
9	talks about the bioavailability when accounting	09:09:20
10	for the level of degradation of 5-azacytadine in	09:09:22
11	the stomach.	09:09:24
12	Do you see that?	09:09:25
13	A On top of the -- I'm not in the right	09:09:25
14	place, though. Okay. What page are you on?	09:09:27
15	Q Sure. I'm on Page 56.	09:09:28
16	A Yes, so am.	09:09:30
17	Q And at the very top of the page.	09:09:30
18	A Oh, second line.	09:09:32
19	MR. GUPTA: Hold on. Let me get there.	09:09:33
20	A Okay. Okay.	09:09:35
21	What was the question?	09:09:40
22	Q Okay. And you see there, you talk about	09:09:40

1	when accounting for the level of degradation of	09:09:44
2	5-azacytidine in the stomach, and cite the	09:09:47
3	Batchelor declaration at paragraphs 34 to 36,	09:09:50
4	correct?	09:09:55
5	A Yes, I do.	09:09:55
6	Q Okay. I'm going to hand you what's	09:09:56
7	previously been marked as Exhibit 1003 in this	09:10:18
8	proceeding.	09:10:21
9	Are you familiar with this document?	09:10:28
10	A I haven't looked at it in a while, but I	09:10:30
11	think it's her declaration. I think it is her	09:10:33
12	declaration.	09:10:38
13	Q This is the declaration of Dr. Batchelor	09:10:39
14	that you relied upon in forming the opinions in	09:10:43
15	your declaration, correct?	09:10:46
16	A Correct.	09:10:48
17	Q And if we turn to paragraphs 34 through	09:10:48
18	36, which -- to help you out -- begin on Page 15.	09:10:55
19	A Okay.	09:10:58
20	Q Are you there?	09:10:59
21	A Yes.	09:11:05
22	Q Okay. Great.	09:11:05

1	MR. GUPTA: Hold on. Okay. Thanks.	09:11:06
2	MS. PETRUZZI: Sure.	09:11:06
3	BY MS. PETRUZZI:	09:11:09
4	Q All right. So starting at paragraph 34,	09:11:09
5	the second sentence says: "The degradation rate	09:11:13
6	constants for 5-azacytidine hydrolysis in aqueous	09:11:16
7	buffer solution at 37 degrees celsius were	09:11:21
8	reported for various pH values between 4.5 and	09:11:23
9	8.0."	09:11:27
10	Do you see that?	09:11:27
11	A I do.	09:11:28
12	Q And is that -- when you were saying that	09:11:29
13	certain rate constants were known, is this what	09:11:30
14	you were referring to?	09:11:33
15	A I believe so. I didn't say certain rate	09:11:34
16	constants, then did I, but, anyway, in relation to	09:11:40
17	the previous question, this is what I was talking	09:11:42
18	about, yes.	09:11:45
19	Q Great. And if we turn the page in	09:11:45
20	paragraph 35, which you cite in your declaration,	09:11:51
21	there is a chart there.	09:11:53
22	Do you see that?	09:11:54

1	A I do.	09:11:54
2	Q And so it was known that the amount of	09:11:55
3	degradation of 5-azacytidine increased as the pH	09:12:01
4	values became more acidic from a pH of 7 to a pH	09:12:07
5	of 5.6, right?	09:12:11
6	MR. GUPTA: Objection to form.	09:12:12
7	You can answer.	09:12:13
8	A Can you just repeat the question, please?	09:12:13
9	MS. PETRUZZI: Of course. Can you read it	09:12:16
10	back.	09:12:17
11	(Record read.)	09:12:17
12	MR. GUPTA: So I object to form and scope	09:12:30
13	of the expert report.	09:12:32
14	But you can answer.	09:12:33
15	A So in terms of the number of 5.6, it is	09:12:35
16	faster degradation than at seven. Was that the	09:12:42
17	question?	09:12:45
18	Q Yes. Thank you.	09:12:45
19	A Yeah.	09:12:47
20	Q And further, in paragraph 35, which you	09:12:48
21	rely on in your declaration, it says that it was	09:12:52
22	known that the degradation -- the amount of --	09:12:56

1	strike that.	09:12:56
2	And in paragraph 35, which you rely on in	09:13:03
3	your declaration, it was known that the amount of	09:13:06
4	degradation increased as the pH values became more	09:13:09
5	acidic from a pH of 5.6 to a pH of 4.5, right?	09:13:12
6	A Where was that in my declaration? I'm	09:13:18
7	sorry.	09:13:20
8	Q We looked at where you cited paragraphs 34	09:13:20
9	through 36.	09:13:23
10	A Okay. So it's in my declaration.	09:13:24
11	MR. GUPTA: Hold on. Objection to form.	09:13:27
12	MS. PETRUZZI: Okay.	09:13:29
13	MR. GUPTA: For the last question.	09:13:30
14	BY MS. PETRUZZI:	09:13:32
15	Q Let me --	09:13:32
16	A Repeat the question.	09:13:33
17	Q Okay. It was known that the amount of	09:13:34
18	degradation increased as the pH values became more	09:13:42
19	acidic from a pH of 5.6 to 4.5 for azacitidine,	09:13:45
20	correct?	09:13:52
21	A That wasn't the previous question, was it?	09:13:52
22	Is that what you're asking now?	09:13:54

1	Q Yes.	09:13:55
2	A Was that the previous question?	09:13:55
3	Q That's my question.	09:13:58
4	A Forget the previous question.	09:13:58
5	Q Okay.	09:14:00
6	MR. GUPTA: Okay. I object to form.	09:14:01
7	A So you said -- can you just say that again	09:14:05
8	because I got confused by the two questions.	09:14:07
9	Q Yes. This is the question.	09:14:10
10	A Yeah.	09:14:12
11	Q It was known for 5-azacytidine that the	09:14:13
12	amount of degradation increased as the pH values	09:14:19
13	became more acidic from 5.6 to 4.5, correct?	09:14:22
14	MR. GUPTA: Objection to form.	09:14:27
15	You can answer.	09:14:29
16	A Okay. So the rate of degradation from	09:14:30
17	these data seem to be faster at 4.5 than 5.6.	09:14:35
18	Q Would a person of skill in the art, in	09:14:42
19	2008, looking at the degradation contents --	09:14:55
20	strike that.	09:14:55
21	I keep saying contents instead of	09:15:01
22	constants -- strike that.	09:15:03

1	Would a person of skill in the art in 2008	09:15:06
2	looking at these degradation constants for	09:15:09
3	5-azacytidine expect that the amount of	09:15:13
4	degradation would further increase as the pH	09:15:15
5	values became more acidic than 4.5?	09:15:18
6	MR. GUPTA: Objection to form.	09:15:21
7	A You would do the test. So you -- if you	09:15:23
8	wanted to explore that, you would do the test.	09:15:28
9	Q And what would the test be?	09:15:30
10	A Well, you said the degradation that other	09:15:32
11	pH values. If you want to know the degradation at	09:15:35
12	other pH values, do the test.	09:15:37
13	Q As a person of skill in the art in 2008,	09:15:39
14	would you have any guess as to what the	09:15:49
15	degradation would be of 5-azacytidine at a pH more	09:15:55
16	acidic than 5.5?	09:16:05
17	MR. GUPTA: Objection to form and scope.	09:16:07
18	A You do the test. If you wanted to find	09:16:09
19	out anything else, you would do the test. These	09:16:12
20	are the data that's been used and these are the	09:16:21
21	data of the calculations that Dr. Batchelor has	09:16:23
22	undertaken a base on. There's other data that	09:16:25

1	exist.	09:16:28
2	Q Have you done a test to assess the	09:16:29
3	degradation constants in your work as a	09:16:33
4	formulator?	09:16:36
5	A I'm sorry?	09:16:37
6	Q Have you done these tests in your work as	09:16:37
7	a formulator?	09:16:39
8	A Tests --	09:16:41
9	MR. GUPTA: Objection to form. And scope.	09:16:42
10	A I'm sorry, could you run it again?	09:16:43
11	Q Sure. Of course.	09:16:45
12	You said you would do the test and my	09:16:46
13	question is: Have you done these tests to assess	09:16:48
14	the degradation constants at various pH values in	09:16:51
15	your work as a formulator?	09:16:55
16	A So if the question is: The study of a	09:16:57
17	degradation rate in solution as a function of pH,	09:17:02
18	yes.	09:17:04
19	Q Okay. Thank you.	09:17:05
20	A Like I said, everything degrades. So you	09:17:10
21	would look at degradation in solution.	09:17:13
22	Q In forming the opinions in your	09:17:15

1	declaration, you opined on obviousness; is that	09:17:57
2	right?	09:18:04
3	A Yes.	09:18:04
4	Q And you opined on whether it would have	09:18:04
5	been obvious for a person of skill in the art in	09:18:06
6	2008 to formulate 5-azacytidine as a	09:18:09
7	nonenteric-coated tablet, correct?	09:18:13
8	A I'm sorry. Can you -- I didn't quite hear	09:18:16
9	it.	09:18:18
10	Q Sure. You opined as to whether it would	09:18:19
11	have been obvious for a person of skill in the art	09:18:22
12	in 2008 to formulate 5-azacytidine as a	09:18:24
13	nonenterically-coated tablet, correct?	09:18:28
14	A Broadly speaking, that's correct.	09:18:32
15	Q Okay. And in part of forming that	09:18:34
16	opinion, you considered or -- strike that.	09:18:36
17	In forming your opinion, did you consider	09:18:39
18	what a person of skill in the art in 2008 would	09:18:42
19	have -- would have thought about when considering	09:18:46
20	oral formulations?	09:18:49
21	A Could you do that again? I'm sorry. It	09:18:52
22	was quite a long question. I didn't quite follow	09:18:54

1 the whole thing. 09:18:56

2 Q Yeah, so in forming your opinions, did you 09:18:57
3 consider what a person of skill in the art in 2008 09:19:01
4 would have thought about when formulating an oral 09:19:04
5 formulation? 09:19:08

6 A I don't entirely understand the question. 09:19:10
7 I've talked about aspects relating to formulation, 09:19:13
8 but I don't really understand what you mean by 09:19:17
9 what would I have thought about. 09:19:19

10 Q Okay. Well, a person of skill in the art 09:19:20
11 in 2008 would have taken into account what was 09:19:23
12 known about 5-azacytidine when evaluating how to 09:19:24
13 formulate it, right? 09:19:27

14 A Aspects of it. You would take into 09:19:29
15 account those things which are relevant to you as 09:19:32
16 a formulator. I think that's reasonable, on 09:19:34
17 balance, but you would probably get your own data 09:19:40
18 to be sure that, you know, you were formulating 09:19:42
19 correctly. 09:19:45

20 Q What data would you get to ensure that you 09:19:46
21 were formulating correctly? 09:19:55

22 MR. GUPTA: Objection to form. 09:19:56

1	A If you are starting a formulation	09:19:58
2	exercise, you would characterize the drug	09:20:03
3	substance in terms of understanding about the drug	09:20:05
4	substance as best you reasonably can.	09:20:07
5	This is an unusual case we have here	09:20:10
6	because the drug substance is very old. Very old	09:20:12
7	has a mixed blessing because you have some stuff	09:20:15
8	which is old which is probably not credible and	09:20:18
9	you have stuff which perhaps is credible, so you	09:20:22
10	may want to obtain your own information to	09:20:24
11	determine what's credible and what's not credible.	09:20:26
12	Q What information would you want to obtain?	09:20:29
13	MR. GUPTA: Objection to form.	09:20:32
14	You can answer.	09:20:34
15	A For what?	09:20:34
16	Q You said that you would want to obtain	09:20:35
17	your own information to determine what's credible	09:20:38
18	and not credible, correct?	09:20:40
19	A Yeah, we've got to do it in relation to	09:20:43
20	something. So give me a context, and then we can	09:20:45
21	talk about what information I might want to	09:20:48
22	obtain.	09:20:50

1	Q What information would you want to obtain	09:20:50
2	with respect to 5-azacytidine?	09:20:54
3	A For what?	09:20:55
4	MR. GUPTA: Objection to form.	09:20:57
5	A For what?	09:20:59
6	MR. GUPTA: Yeah, if you could just give	09:20:59
7	me, like, a moment.	09:21:01
8	THE WITNESS: Sure.	09:21:02
9	A To do what?	09:21:04
10	Q I understood what you were saying was that	09:21:06
11	you would want to obtain information about	09:21:18
12	5-azacytidine to determine what was credible or	09:21:20
13	not credible when considering how to formulate it;	09:21:22
14	is my understanding correct?	09:21:25
15	A That's generally correct. And then in	09:21:26
16	terms of what information, it depends what the	09:21:29
17	question is that I'm looking to address. So that	09:21:32
18	was my response was "for what"? Can you tell me	09:21:34
19	specifically what for? Then I will tell you what	09:21:38
20	information I might conceivably want.	09:21:40
21	Q Okay. For an oral formulation.	09:21:43
22	A Which formulation?	09:21:44

1	Q For an oral formulation of 5-azacytidine.	09:21:45
2	A That's very wide.	09:21:47
3	Q What information would you want?	09:21:48
4	A That's very wide. So any particular type	09:21:49
5	of oral formulation?	09:21:52
6	Q No, let's just talk about oral	09:21:52
7	formulations, generally.	09:21:54
8	MR. GUPTA: Objection to form.	09:21:56
9	A I think that's -- that's a very unreal	09:21:57
10	situation because you would never have a scenario	09:22:01
11	where you're formulating for a normal formulation.	09:22:04
12	You would have a scenario where you're formulating	09:22:07
13	for a tablet or for a solution, for example, but	09:22:09
14	you wouldn't start with the notion, I'm going to	09:22:12
15	formulate for something. It would always be: I'm	09:22:15
16	going to formulate -- and if it was -- just to be	09:22:18
17	clear, if it was a default position where someone	09:22:21
18	says, you know, just formulate what's the best	09:22:23
19	thing to start formulating it, that would be a	09:22:27
20	tablet.	09:22:29
21	So we could start with a tablet if you	09:22:30
22	like, because that would be your -- 90 percent of	09:22:32

1	all doses are tablets, so you would probably start	09:22:34
2	with a tablet. We could start there if you like.	09:22:36
3	Whatever you want.	09:22:39
4	Q Okay.	09:22:40
5	Go ahead.	09:22:40
6	A So for a tablet --	09:22:41
7	MR. GUPTA: Hold on. Objection to form.	09:22:43
8	You can answer.	09:22:45
9	A The question is: What would I want to	09:22:46
10	know in terms of formulating for a tablet; is that	09:22:49
11	right?	09:22:52
12	Q Of 5-azacytidine, correct.	09:22:52
13	A Of 5-azacytidine -- yeah, that's good	09:22:54
14	point.	09:22:56
15	MR. GUPTA: Okay. Objection to form.	09:22:57
16	A So formulating for a tablet for this	09:22:59
17	particular drug substance, I would want to	09:23:01
18	understand what are sensible and reasonable	09:23:05
19	aspects of stability, as we talked about, rather	09:23:12
20	than relying on hearsay or whatever else. That	09:23:16
21	would be a reasonable thing to do.	09:23:23
22	I would probably want to know things about	09:23:25

1	its physical properties, which I don't know are	09:23:28
2	terribly relevant to our discussion here, but I	09:23:31
3	want to know things about it.	09:23:35
4	I'd want to know its solubility. Those	09:23:37
5	would be the major things I would want to know.	09:23:44
6	Q Would you want to know about its	09:23:46
7	permeability?	09:23:48
8	MR. GUPTA: Objection to form.	09:23:49
9	You can answer.	09:23:50
10	A I would subsequently want to know about	09:23:51
11	its permeability. I would not necessarily have to	09:23:53
12	know about its permeability in terms of making it	09:23:56
13	an initial formulation, but permeability would be	09:24:00
14	a significant factor as the formulation was	09:24:02
15	developed and going to be used.	09:24:05
16	As it happens, you know, we aren't in a	09:24:07
17	vacuum and we have data already, so I know for	09:24:11
18	sure it's got permeability, so it's slightly	09:24:13
19	strange situation. So permeability sounds good,	09:24:16
20	but yes, ultimately you need to know it, but we	09:24:20
21	know it does -- it has permeability.	09:24:25
22	Q And how do you know that 5-azacytidine has	09:24:29

1	permeability?	09:24:33
2	A In my report I talk about a dog study	09:24:35
3	which had -- probably go to the page, it would be	09:24:39
4	more sensible, but it was a very high percentage	09:24:43
5	bioavailability. I'm going to say about	09:24:45
6	80 percent, but the numbers in my report where we	09:24:48
7	could find --	09:24:50
8	Q Okay.	09:24:50
9	A -- find the number, which means a dog is a	09:24:51
10	good model for human oral dosing. If you have	09:24:54
11	80-odd percent -- don't hold me to the 80 percent,	09:24:59
12	you understand -- bioavailability in a dog, you	09:25:03
13	are going to expect to have good bioavailability	09:25:05
14	in a human. So permeability is not an issue.	09:25:08
15	Q Is there anything else that you would want	09:25:14
16	to consider when formulating an oral tablet of	09:25:19
17	5-azacytidine tablet?	09:25:24
18	MR. GUPTA: Objection to form. Objection	09:25:26
19	to scope of the expert report.	09:25:28
20	A At this moment in time I can't think of	09:25:31
21	anything, but if we have a discussion and	09:25:34
22	something comes up, I will let you know.	09:25:36

1	Q Great. Thank you.	09:25:38
2	If it was known in 2008 that 5-azacytidine	09:25:40
3	was susceptible to acid hydrolysis in the stomach,	09:25:45
4	would a person of ordinary skill in the art want	09:25:54
5	to take that into account when formulating an oral	09:25:56
6	tablet?	09:26:00
7	MR. GUPTA: Okay. Objection to form.	09:26:00
8	A Inevitably, you consider stability when	09:26:03
9	formulating a new product, and you consider the	09:26:07
10	fact that everything will have some element of	09:26:11
11	hydrolysis. So there's nothing in the information	09:26:14
12	I know so far that would cause me any concern with	09:26:18
13	respect to formulating this drug substance. If	09:26:21
14	anything else comes up, fine, but I would not be	09:26:26
15	concerned about formulating it.	09:26:28
16	Q So acid hydrolysis is something that you	09:26:31
17	would consider in creating an oral formulation?	09:26:36
18	MR. GUPTA: Same objection.	09:26:40
19	You can answer.	09:26:42
20	A To the extent that it would be significant	09:26:44
21	over the duration that something is in the	09:26:49
22	stomach, which is a very short period of time, you	09:26:51

1 would -- may consider it, but not to the extent 09:26:55
2 that it would deter you from trying a 09:26:57
3 nonenteric-coated formulation, because you would 09:27:01
4 have an expectation of success in getting 09:27:04
5 bioavailability, not least because of the dog 09:27:06
6 study that I just told you about. 09:27:09

7 It had a very fast Tmax, was absorbed very 09:27:12
8 quickly, very full absorption, very high 09:27:17
9 percentage bioavailability. You would not be 09:27:20
10 deterred by the notion of hydrolysis, because 09:27:23
11 that's a common occurrence, and you would be 09:27:26
12 encouraged and you would actually have an 09:27:28
13 expectation of success. 09:27:32

14 Q Are you familiar with enteric coatings? 09:27:36

15 A Yes. 09:29:13

16 Q What is an enteric coating? 09:29:13

17 A An enteric coat is a substance that's 09:29:15
18 added to a solid dosage form in order to prevent 09:29:19
19 its dissolution within the stomach and potentially 09:29:25
20 to prevent its dissolution in the early part of 09:29:30
21 the intestinal tube. 09:29:35

22 Q Do you know when enteric coatings are used 09:29:36

1	by formulators?	09:29:41
2	MR. GUPTA: Objection to form.	09:29:42
3	You can answer.	09:29:44
4	A I think the simple answer is: If you have	09:29:45
5	to would be a good answer. Enteric coating is	09:29:49
6	very much a second choice. So if you're unable to	09:29:54
7	achieve your goals, having tried, for example,	09:29:58
8	immediate-release formulation, you would consider	09:30:03
9	enteric coating as a second choice. It wouldn't	09:30:08
10	be your preferred choice, but it's an alternative	09:30:12
11	which is reasonable.	09:30:15
12	Q And the reason you would use an enteric	09:30:16
13	coating if a nonenteric coating didn't achieve	09:30:20
14	your goals -- strike that.	09:30:26
15	Why would you use an enteric coating if a	09:30:30
16	nonenteric coating didn't achieve your goals, in	09:30:32
17	your opinion?	09:30:35
18	MR. GUPTA: Objection to form and scope.	09:30:35
19	You can answer.	09:30:39
20	A Could you just say the question again?	09:30:41
21	Q Yes. You mentioned that you would use an	09:30:45
22	enteric coating and -- if a nonenteric coating	09:30:56

1	didn't achieve your goals; is that right?	09:31:00
2	A Yes, I did.	09:31:03
3	Q And why would you use an enteric coating	09:31:03
4	if a nonenteric coating didn't achieve your goals?	09:31:06
5	MR. GUPTA: Same objection.	09:31:09
6	But you can answer.	09:31:11
7	A If there was a way in which the enteric	09:31:12
8	coating would allow you to achieve a goal, a goal	09:31:15
9	would be a reasonable -- reproducibility in terms	09:31:24
10	of producing something which potentially could be	09:31:27
11	efficacious. That would be a goal. If you're	09:31:30
12	unable to produce something which could be	09:31:33
13	efficacious, and that would mean you tried and	09:31:35
14	failed, if you were able to -- if you're able to	09:31:40
15	achieve something that was efficacious, you would	09:31:46
16	not move on to enteric coating, but if you weren't	09:31:48
17	able to produce something that was efficacious,	09:31:51
18	you would move on to enteric coating. I guess	09:31:53
19	that's a high level view of it.	09:31:57
20	Q Okay. If it was known in 2008 that	09:32:00
21	5-azacytidine was susceptible to enzymatic	09:32:14
22	degradation in the stomach, would a person of	09:32:19

1	skill in the art have taken that into account when	09:32:20
2	formulating it?	09:32:23
3	MR. GUPTA: Objection to form.	09:32:27
4	You can answer.	09:32:29
5	A Well, not if it was known that it was	09:32:30
6	susceptible to enzymatic degradation in the	09:32:34
7	stomach and the intestine and the plasma. It	09:32:36
8	doesn't become a meaningful consideration in that	09:32:39
9	context. So I don't think it's significant. So I	09:32:41
10	think you would start on the assumption that	09:32:50
11	things are going to be fine, and, again, if things	09:32:52
12	turned out not to be fine, you maybe would	09:32:54
13	contemplate it, but it certainly wouldn't be	09:32:56
14	something that would deter you at the outset.	09:32:59
15	Q Earlier you mentioned that 5-azacytidine	09:33:02
16	is a little bit different because it's an old	09:33:13
17	drug.	09:33:17
18	Do you recall that?	09:33:17
19	A I do.	09:33:18
20	Q Okay. And there's -- you mentioned that	09:33:19
21	there's a lot of literature about 5-azacytidine	09:33:21
22	because it's an old drug.	09:33:24

1	Do you recall that?	09:33:26
2	A I do.	09:33:27
3	Q And you said you have to distinguish	09:33:28
4	between hearsay and what's accurate; is that	09:33:30
5	correct?	09:33:37
6	A As best you can. I think you should try	09:33:37
7	and do that, and I think to some extent chronology	09:33:40
8	will help, but you would hope that people would	09:33:44
9	get more informed with time, but that isn't	09:33:47
10	inevitably true. People can just repeat stuff	09:33:52
11	that was historical without thinking about it.	09:33:56
12	Q How did you, in forming the opinions in	09:33:58
13	your declaration, determine what peer review	09:34:03
14	literature was hearsay and what was true?	09:34:10
15	A So in forming my opinions, I looked at the	09:34:12
16	documents that are cited and assessed what they	09:34:17
17	had to say, but equally looked at the more recent	09:34:20
18	documents.	09:34:25
19	Ionescu is the one that I talk about in	09:34:28
20	terms of an anticipatory document, and very	09:34:29
21	clearly, the document doesn't consider some of the	09:34:34
22	issues that were perceived to be issues in the	09:34:39

1 historical past as being issues that should be 09:34:42
2 considered now. 09:34:45

3 Q And you also relied on Dr. Batchelor's 09:34:46
4 declaration in forming your opinions, correct? 09:34:55

5 A Correct, it gives you a good encouragement 09:34:57
6 that things are going to turn out well, so it 09:35:01
7 gives you motivation and an expectation of 09:35:04
8 success, at least. 09:35:06

9 Q Dr. Batchelor's declaration also relied on 09:35:08
10 literature, correct? 09:35:12

11 A Yes. 09:35:14

12 Q Do you know how or if -- strike that. 09:35:15

13 Do you know if Dr. Batchelor distinguished 09:35:20
14 between peer review literature that was hearsay 09:35:23
15 and that which was true? 09:35:25

16 MR. GUPTA: Objection to form. 09:35:27

17 A Well, you should ask Dr. Batchelor. 09:35:29
18 That's the reasonable thing to do. 09:35:32

19 Q Okay. Okay. So we were talking about 09:35:34
20 enteric coatings. 09:36:39

21 Do you remember that? 09:36:40

22 A Not specifically, but if we could start 09:36:40

1	again.	09:36:43
2	Q Okay. Let's talk about enteric coatings,	09:36:43
3	shall we?	09:36:46
4	A Very good.	09:36:48
5	Q And we were talking about when formulators	09:36:52
6	use enteric coatings.	09:36:55
7	Do you recall that?	09:37:01
8	A Yes.	09:37:01
9	Q And one of the reasons why a formulator	09:37:02
10	may use an enteric coating is to prevent drug	09:37:06
11	release in the stomach to address issues such as	09:37:10
12	drug instability in the stomach; is that correct?	09:37:13
13	MR. GUPTA: Objection to form.	09:37:15
14	You can answer. And object to the form	09:37:17
15	and scope.	09:37:21
16	You can answer.	09:37:21
17	A One reason to use enteric coating is if	09:37:23
18	you have found yourself unable to formulate	09:37:27
19	because of an instability issue, but I don't	09:37:30
20	believe that's the case here, as I've explained,	09:37:32
21	but that is one reason you would do it.	09:37:34
22	Q So just to make sure that I understand.	09:37:37

1	A Yes.	09:37:41
2	Q Formulators use enteric coatings if there	09:37:42
3	is an issue with drug instability in the stomach?	09:37:48
4	MR. GUPTA: Same -- same objection.	09:37:52
5	BY MS. PETRUZZI:	09:37:55
6	Q Is that correct?	09:37:55
7	A Same answer I gave, that if you're unable	09:37:56
8	to have an immediate-release product, which would	09:37:59
9	be your preferred choice, and you try that and you	09:38:01
10	don't believe that is successful because you don't	09:38:05
11	have bioavailability, for example, then you can	09:38:08
12	use enteric coating to deal with an instability in	09:38:13
13	the stomach. But it, as I said, isn't necessary	09:38:17
14	to do that here.	09:38:19
15	Conceptually, you could for drug	09:38:20
16	substances where that is necessary.	09:38:23
17	Q Okay.	09:38:25
18	MS. PETRUZZI: Let's take a quick break.	09:39:05
19	THE WITNESS: Okay.	09:39:06
20	THE VIDEOGRAPHER: Stand by. We are going	09:39:07
21	off the record. The time is 9:39 a.m.	09:39:09
22	(Recess.)	09:39:13

1	THE VIDEOGRAPHER: We are back on the	09:52:13
2	record. The time is 9:52 a.m.	09:52:16
3	BY MS. PETRUZZI:	09:52:17
4	Q Welcome back.	09:52:19
5	A Thank you. I don't know if it helps or	09:52:20
6	not, but just in the break the thing I was talking	09:52:21
7	to you about in terms of percentage	09:52:24
8	bioavailability that I guessed the number is on	09:52:26
9	Page 26 of my report, and it's 67 percent	09:52:28
10	bioavailability.	09:52:31
11	Q On Page 26?	09:52:32
12	A So I guessed the number earlier which was	09:52:33
13	inevitably wrong. But the actual correct number	09:52:35
14	is 67 percent with a Tmax of 15 minutes.	09:52:37
15	Q Okay. And this is when you were talking	09:52:40
16	about it's 80 percent bioavailability, but it	09:52:41
17	might not be exactly --	09:52:44
18	(Multiple speakers.)	09:52:45
19	A Yes.	09:52:45
20	Q It might not be being exactly 80 percent.	09:52:46
21	You found it at Page 26 at paragraph 49.	09:52:48
22	A Yeah, it's 67 percent, just to put the	09:52:51

1	record straight.	09:52:54
2	Q Thank you. I appreciate that.	09:52:55
3	THE VIDEOGRAPHER: Counsel, I think the	09:53:00
4	fan is blowing on the mic.	09:53:01
5	THE WITNESS: Let's cut the fan.	09:53:04
6	MS. PETRUZZI: Can we go off the record?	09:53:06
7	THE VIDEOGRAPHER: We are going off the	09:53:08
8	record. The time is 9:53 a.m.	09:53:09
9	(An off-the-record discussion was held at	09:53:09
10	this time.)	09:53:28
11	THE VIDEOGRAPHER: We are back on the	09:53:47
12	record. The time is 9:53 a.m.	09:53:56
13	BY MS. PETRUZZI:	09:53:58
14	Q Dr. Buckton, during the break, did you	09:53:58
15	have any substantive conversations about your	09:54:03
16	testimony with counsel?	09:54:05
17	A No.	09:54:05
18	Q All right. Before the break we were	09:54:06
19	talking about enzymes that are -- strike that.	09:54:10
20	You mentioned that if an enzyme is present	09:54:16
21	in the stomach, intestine, and plasma, it's not	09:54:19
22	something that you would consider in formulating	09:54:22

1	an active ingredient.	09:54:25
2	Is my understanding correct?	09:54:27
3	A I'm not sure -- I'm not entirely sure what	09:54:28
4	the question and my complete answer were, but	09:54:32
5	let's start with the questions, and then we can --	09:54:34
6	Q Sure. So my question is: If it was known	09:54:39
7	in 2008 that 5-azacytidine was susceptible to	09:54:49
8	enzymatic degradation, a person of skill in the	09:54:53
9	art would have taken that into account when	09:54:56
10	formulating the drug, right?	09:54:59
11	A Right. Okay. I got the question. Okay.	09:55:00
12	MR. GUPTA: Okay. Objection to form.	09:55:03
13	Well, hold on. Is there a question	09:55:05
14	pending?	09:55:08
15	MS. PETRUZZI: That is my question.	09:55:08
16	A Okay.	09:55:10
17	Q Let's start over. Strike it. We're going	09:55:11
18	to start over.	09:55:13
19	If it was known in 2008 that 5-azacytidine	09:55:14
20	was susceptible to enzymatic degradation, a person	09:55:18
21	of skill in the art would have taken it into	09:55:21
22	account when formulating the drug, correct?	09:55:23

1	MR. GUPTA: Objection to form.	09:55:27
2	You can answer.	09:55:29
3	A I think as I said before, if you have an	09:55:30
4	enzyme which is ubiquitous -- I might not have	09:55:35
5	said it exactly like this before, then in terms of	09:55:39
6	formulation, I don't know. There's a lot to be	09:55:42
7	taken into account, but it depends what type of	09:55:47
8	formulation you're doing. And I'm assuming we're	09:55:50
9	talking about the nonenteric-coated tablet.	09:55:52
10	There is no immediate reason to take it	09:55:55
11	into account, not least because, you know, the	09:55:59
12	modern references and Ionescu don't take it into	09:56:02
13	account.	09:56:06
14	Q Okay. So when you say an enzyme is	09:56:07
15	ubiquitous, do you mean that the enzyme is present	09:56:12
16	in the stomach, intestine, and plasma?	09:56:15
17	A Correct, it seems to be everywhere, yes.	09:56:18
18	Q Okay. And so for an oral formulation, the	09:56:21
19	drug would encounter the enzyme in the stomach,	09:56:26
20	correct?	09:56:30
21	MR. GUPTA: Objection to form. Scope.	09:56:30
22	You can answer.	09:56:35

1 A Well, for an oral formulation, it would 09:56:37
2 encounter the enzyme, I think pretty much 09:56:39
3 everywhere in the body. The lion's share of that 09:56:42
4 is going to be in the plasma, and that's nothing 09:56:44
5 you can do about it. So a modest exposure 09:56:47
6 elsewhere doesn't sound to be like a major 09:56:51
7 contributor. 09:56:54

8 Q Just to make sure I'm clear, for an oral 09:56:55
9 formulation, the drug would encounter the enzyme 09:56:59
10 in the stomach, the intestine, and the plasma. 09:57:03

11 Is that your testimony? 09:57:05

12 MR. GUPTA: Objection to form. 09:57:07

13 You can answer. 09:57:07

14 A When in solution, it would encounter the 09:57:09
15 enzyme, is my understanding. So yes, and wherever 09:57:13
16 it's in solution in the body, the vast majority of 09:57:19
17 the time is going to be in the plasma, it will 09:57:21
18 encounter the enzyme. 09:57:24

19 Q Okay. And for an IV formulation, it would 09:57:25
20 only be exposed to the enzyme in the plasma; is 09:57:33
21 that correct? 09:57:38

22 A Inevitably, an IV formulation is injected 09:57:38

1 directly into a vein, but much the same as I said 09:57:42
2 for the previous answer, in that case it's all of 09:57:47
3 its time is in the plasma. Whereas for an oral 09:57:50
4 product, the vast majority of its time it's in the 09:57:53
5 plasma. It really doesn't make a lot of 09:57:55
6 difference one way or the other. 09:57:59

7 Q Okay. In your declaration, you rely on 09:58:02
8 Ionescu; is that correct? 09:58:06

9 A That's correct. 09:58:07

10 Q I'm handing you what's been previously 09:58:29
11 marked as Exhibit 1004, Ionescu, in this 09:58:32
12 proceeding. 09:58:37

13 A Thank you. 09:58:37

14 MR. GUPTA: Thanks. 09:58:38

15 BY MS. PETRUZZI: 09:58:42

16 Q Okay. Dr. Buckton, are you familiar with 09:58:42
17 this document? 09:58:49

18 A Yes, I am. 09:58:50

19 Q What is it? 09:58:51

20 A It's a patent in the name of Ionescu, 09:58:52
21 which describes the -- which is the basis for my 09:58:58
22 analysis in my report. That's probably enough to 09:59:06

1	start with.	09:59:11
2	Q All right. If you look at the title,	09:59:12
3	which is at Line 54 on the first page.	09:59:17
4	Do you see that?	09:59:20
5	A I do.	09:59:21
6	Q The title of Ionescu is: "Forms of	09:59:22
7	5-azacytidine"; is that right?	09:59:25
8	A That's correct.	09:59:26
9	Q At the bottom under Line 57 do you see	09:59:27
10	where it says: "Abstract"?	09:59:31
11	A I do.	09:59:32
12	Q Can you read that to yourself and let me	09:59:32
13	know when you finish?	09:59:34
14	A (Document review.)	09:59:35
15	Yes, I've read that.	09:59:40
16	Q Great. The abstract says: "The invention	09:59:42
17	provides novel polymorphic and pseudo polymorphic	09:59:47
18	crystalline forms of 5-azacytidine."	09:59:52
19	Right?	09:59:54
20	A That's the first little bit of it, yes.	09:59:56
21	Q Do you have an understanding of what a	09:59:58
22	polymorphic crystalline form of 5-azacytidine is?	10:00:01

1	A Yes, I do.	10:00:04
2	Q What is it?	10:00:04
3	A Polymorphic --	10:00:06
4	MR. GUPTA: Objection to form. Scope.	10:00:06
5	Relevance.	10:00:08
6	You can answer.	10:00:09
7	A Polymorphic forms are different crystal	10:00:10
8	packing geometries of the same substance.	10:00:13
9	Q Okay. Do you have an understanding of	10:00:16
10	what a pseudo polymorphic crystalline form of	10:00:25
11	5-azacytidine is?	10:00:29
12	MR. GUPTA: Objection. Form, scope	10:00:30
13	relevance.	10:00:32
14	A Yes, I do.	10:00:33
15	Q What is it?	10:00:33
16	A It's a slightly -- well, let's just use it	10:00:37
17	as the terminology exists. It would be largely	10:00:41
18	described as a sulfate or hydrate.	10:00:44
19	Q Do polymorphic forms -- do you know if	10:01:03
20	polymorphic forms of a drug substance affect	10:01:06
21	solubility?	10:01:12
22	MR. GUPTA: Objection to form. And scope	10:01:14

1	and relevance.	10:01:15
2	You can answer.	10:01:16
3	A Yes, I do.	10:01:17
4	Q Do polymorphic forms of a drug -- strike	10:01:18
5	that.	10:01:18
6	Do you agree that polymorphic forms of a	10:01:26
7	drug substance may affect solubility?	10:01:29
8	MR. GUPTA: Same objections.	10:01:31
9	A Absolutely not.	10:01:32
10	Q Can you please turn to Page 1 of Ionescu.	10:01:36
11	And under -- do you see where it says:	10:01:46
12	"Background of the invention"?	10:01:49
13	A Yes.	10:01:49
14	Q There is a first paragraph there that ends	10:01:50
15	at, maybe, line 27.	10:01:52
16	Do you see that?	10:01:53
17	A Yes.	10:01:54
18	Q Can you read that paragraph to yourself,	10:01:54
19	please, and let me know when you're finished.	10:01:56
20	A (Document review.)	10:01:58
21	Yes, I've read that.	10:02:14
22	Q And starting around line 22, Ionescu says:	10:02:15

1 "Polymorphic and pseudo polymorphic forms of the
2 drug substance, also known as the active
3 pharmaceutical ingredient, API, as administered by
4 itself or formulated as a drug product, also known
5 as the final or finished doses form or as a
6 pharmaceutical composition, are well-known and may
7 affect, for example, the solubility, stability,
8 flowability, fractibility, and compressibility of
9 drug substances and the safety and efficacy of
10 drug products."

10:02:19

10:02:23

10:02:25

10:02:28

10:02:30

10:02:33

10:02:35

10:02:39

10:02:42

10:02:45

11 Do you see that?

10:02:46

12 A I do.

10:02:47

13 Q Do you agree with that statement in

10:02:48

14 Ionescu?

10:02:50

15 A I think it's oversimplistic. So as I said
16 already, solubility can't change between different
17 polymorphic forms. It's something which we would
18 describe as apparent solubility, which
19 conceptually can change. So it may be just being
20 simplistic in its language, but what I said is
21 correct, solubility can't change.

10:02:50

10:02:53

10:02:56

10:02:59

10:03:02

10:03:06

10:03:08

22 Q Okay.

10:03:08

1	(Multiple speakers.)	10:03:08
2	A Solubility can't change. Apparent	10:03:13
3	solubility can change, but that is a concept which	10:03:14
4	we don't need to discuss here. It isn't	10:03:16
5	particularly relevant.	10:03:18
6	Q Well, I was going to ask you, what is	10:03:19
7	apparent solubility?	10:03:20
8	MR. GUPTA: Objection to form. Scope, and	10:03:21
9	relevance.	10:03:23
10	You can answer.	10:03:23
11	A If you have a polysoluble drug substance,	10:03:25
12	which we don't have here, but if you had a	10:03:30
13	polysoluble drug substance, the rate at which it	10:03:33
14	dissolves can give rise to a transient elevation	10:03:35
15	in concentration, which can be deemed to be an	10:03:39
16	apparent increase in solubility, but it will be	10:03:42
17	transient and will subsequently return to the	10:03:45
18	correct solubility. And that is of significance	10:03:48
19	for polysoluble drug substances.	10:03:51
20	It isn't of any significance for a soluble	10:03:54
21	drug substance, because there will be no transient	10:03:56
22	improvement in solubility. They will all be the	10:04:01

1	same value, essentially.	10:04:03
2	Q Do you agree that polymorphic forms of a	10:04:07
3	drug substance may affect stability?	10:04:10
4	MR. GUPTA: Objection to form. And	10:04:13
5	relevance and scope.	10:04:16
6	You can answer.	10:04:19
7	A So in terms of solid-state stability, it	10:04:23
8	is conceptually possible that different	10:04:26
9	polymorphic forms can affect solid-state	10:04:29
10	stability, and that is not something that I	10:04:33
11	understand that we are considering here.	10:04:35
12	It clearly can't affect anything other	10:04:40
13	than the solid-state stability, but that isn't	10:04:44
14	something that I understand we're considering	10:04:46
15	here.	10:04:48
16	Q If you flip to the back of Ionescu, there	10:04:49
17	are eight figures.	10:04:58
18	Do you see those?	10:04:59
19	A Yes.	10:05:00
20	Q Okay. And all of them are X-ray powder	10:05:01
21	diffraction patterns; is that correct?	10:05:05
22	A That's correct.	10:05:07

1	Q Do you have an understanding of what an	10:05:08
2	X-ray powder diffraction pattern is?	10:05:11
3	A Yes, I do.	10:05:13
4	Q What is it?	10:05:14
5	A It is the result of putting a sample of	10:05:16
6	powder onto an X-ray diffractometer. You can get	10:05:20
7	diffraction of X-rays.	10:05:24
8	Q And why is it used?	10:05:26
9	A It is used to identify different crystal	10:05:27
10	structures.	10:05:31
11	Q Do you generate X-ray pattern diffraction	10:05:33
12	patterns in your work as a formulator?	10:05:37
13	MR. GUPTA: Objection to relevance.	10:05:39
14	You can answer.	10:05:41
15	A We extensively study physical form in my	10:05:42
16	company, which I've sold now, but while I was in	10:05:45
17	my company, we used to study physical form of drug	10:05:48
18	substance on a regular basis, and would do X-ray	10:05:52
19	crystallography as part of that characterization,	10:05:55
20	yes, but they would be polysoluble drug	10:05:58
21	substances; not what we have here.	10:06:02
22	Q All right. And if we turn to Page 15, of	10:06:03

1	Ionescu -- let me know when you're there.	10:06:15
2	A I am.	10:06:25
3	Q Do you see at the top of the page it says:	10:06:26
4	"Examples"?	10:06:28
5	A I do.	10:06:29
6	Q And Ionescu discloses eight examples in	10:06:30
7	this section; is that correct?	10:06:35
8	A I must have missed one. Let me try again.	10:06:52
9	Q Sure. Take your time.	10:06:56
10	A Yes, I've got it, yes, eight examples.	10:07:10
11	Q Did you review these eight examples when	10:07:13
12	considering Ionescu in forming the opinions that	10:07:16
13	are in your declaration?	10:07:19
14	A I looked at them initially, but I didn't	10:07:22
15	consider them in forming my opinions because the	10:07:24
16	bit of the abstract that we didn't talk about,	10:07:26
17	talks about the invention being related to the	10:07:29
18	pharmaceutical composition, comprising these	10:07:31
19	forms, and I concentrated my analysis on the	10:07:34
20	pharmaceutical composition aspects of Ionescu. So	10:07:37
21	I didn't, after an initial look at the examples,	10:07:40
22	consider them any further.	10:07:42

1	Q Do you know whether any of the eight	10:07:43
2	examples in Ionescu disclose formulating an oral	10:07:50
3	formulation of 5-azacytidine?	10:07:55
4	MR. GUPTA: Objection to form.	10:07:59
5	You can answer.	10:08:00
6	A The examples specifically talk about	10:08:02
7	crystal form. The claims relate to crystal form	10:08:06
8	and their compositions, but the examples just talk	10:08:09
9	about crystal form.	10:08:12
10	Q Okay. Example eight, on Page 20, can you	10:08:13
11	turn to example eight on Page 20, please.	10:08:18
12	A Yes, I will.	10:08:20
13	Q Thank you.	10:08:22
14	A Okay.	10:08:29
15	Q Example eight on Page 20 is entitled:	10:08:30
16	"Polymorphic form conversion of 5-azacytidine."	10:08:33
17	Do you see that?	10:08:35
18	A Yes.	10:08:36
19	Q All right. And it continues on to Page 21	10:08:37
20	and 22.	10:08:43
21	Do you see that?	10:08:45
22	A Yes.	10:08:46

1	Q I would like to turn your attention to the	10:08:46
2	bottom of Page 21.	10:08:49
3	A Okay.	10:08:52
4	Q Example eight refers to the administration	10:08:52
5	of 5-azacytidine in suspension or slurry.	10:08:57
6	MR. GUPTA: Excuse me, Ms. Petruzzi. I	10:09:00
7	just wanted to let you know or state for the	10:09:02
8	record that there's highlighting on this document,	10:09:04
9	so it's not a plain -- it's not a plain document	10:09:06
10	of Ionescu.	10:09:09
11	THE WITNESS: Where is it highlighted?	10:09:12
12	MS. PETRUZZI: Do you have highlighting on	10:09:15
13	your version, Dr. Buckton?	10:09:16
14	THE WITNESS: Which page is it highlighted	10:09:18
15	on?	10:09:20
16	MR. GUPTA: 13.	10:09:20
17	THE WITNESS: Let me have a look. Yes, I	10:09:22
18	do.	10:09:25
19	MS. PETRUZZI: Is that the only page with	10:09:26
20	highlighting?	10:09:28
21	MR. GUPTA: You guys should check it, but	10:09:28
22	I'd like to state for the record this is not the	10:09:30

Transcript of Graham Buckton, Ph.D.
Conducted on September 26, 2023

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1	same copy of Ionescu. It appears to be the copy	10:09:32
2	of Ionescu, but it has highlighting on it.	10:09:35
3	THE WITNESS: Yes, I have highlighting.	10:09:37
4	Talking about tablets for oral use is highlighted.	10:09:39
5	MS. PETRUZZI: Okay. Thank you. Can we	10:09:44
6	go off the record for a moment.	10:09:47
7	THE VIDEOGRAPHER: Stand by. We are going	10:09:49
8	off the record. The time is 10:09 a.m.	10:09:50
9	(An off-the-record discussion was held at	10:09:50
10	this time.)	10:10:51
11	THE VIDEOGRAPHER: We are back on the	10:10:51
12	record. The time is 10:10 a.m.	10:10:53
13	MS. PETRUZZI: Okay.	10:11:07
14	BY MS. PETRUZZI:	10:11:08
15	Q So we were on Ionescu at the bottom of	10:11:08
16	Page 21.	10:11:15
17	Are you there?	10:11:16
18	A I am.	10:11:16
19	Q Okay. Thank you.	10:11:17
20	Example eight of Ionescu refers to the	10:11:18
21	administration of 5-azacytidine suspension or	10:11:21
22	slurry in an NCI investigation, correct?	10:11:25

1	A Yes.	10:11:30
2	Q The slurry that was administered to	10:11:31
3	patients in the NCI investigation was for a	10:11:33
4	subcutaneous injection, correct?	10:11:38
5	MR. GUPTA: Objection to form.	10:11:46
6	A It doesn't actually say what it was, does	10:11:59
7	it?	10:12:01
8	Q Do you know what the formulation of the --	10:12:01
9	strike that.	10:12:01
10	Do you know how the suspension or slurry	10:12:10
11	was administered to patients in the NCI	10:12:13
12	investigation?	10:12:15
13	A No. Sorry. If you wanted to object.	10:12:16
14	MR. GUPTA: Yeah, objection to form,	10:12:18
15	scope, and relevance.	10:12:20
16	BY MS. PETRUZZI:	10:12:21
17	Q If you turn to Page 9 of Ionescu, at	10:12:21
18	line -- starting at line 11, there is a discussion	10:12:29
19	of the NCI investigation.	10:12:32
20	Do you see that?	10:12:34
21	MR. GUPTA: Hold on, let me -- please, let	10:12:35
22	me get there. One second.	10:12:37

1	MS. PETRUZZI: Yes.	10:12:38
2	MR. GUPTA: Okay.	10:12:42
3	BY MS. PETRUZZI:	10:12:46
4	Q Dr. Buckton, do you see that?	10:12:46
5	A I do see that.	10:12:47
6	Q And here it says that the 5-azacytidine	10:12:48
7	suspension or slurry was administered by	10:12:56
8	subcutaneous injection, correct?	10:12:59
9	A Yes.	10:13:04
10	Q The slurry was not a formulation for oral	10:13:06
11	formulation; is that right?	10:13:12
12	A In this example it's -- it says	10:13:15
13	subcutaneous injection of an aqueous suspension,	10:13:17
14	correct.	10:13:23
15	Q Besides the injectable slurry, do you know	10:13:27
16	if Ionescu has another example where a patient is	10:13:32
17	administered 5-azacytidine?	10:13:35
18	MR. GUPTA: Objection to form.	10:13:38
19	You can answer.	10:13:40
20	A Not examples. There's the description	10:13:41
21	that describes the different dosage form types	10:13:45
22	including the nonenteric-coated tablet, but I	10:13:48

1 don't see an example of it being administered as 10:13:50
2 such. 10:13:53

3 Q Does Ionescu provide any data establishing 10:13:53
4 that a patient was orally administered 10:14:03
5 5-azacytidine? 10:14:05

6 A I don't believe there are any data on 10:14:09
7 administering the drug at all, but I don't think 10:14:14
8 that's necessary in terms of it disclosing the 10:14:16
9 nonenteric-coated tablet. 10:14:19

10 Q Does Ionescu provide any data showing that 10:14:21
11 5-azacytidine was administered in a 10:14:38
12 therapeutically effective amount to treat AML? 10:14:40

13 A Well, he used what data again. It 10:14:46
14 describes that it would be used for treating 10:14:49
15 conditions, and it describes how much is in a 10:14:52
16 tablet, for example. But it doesn't provide data 10:14:54
17 in terms of consequence of administering that 10:14:57
18 tablet to a patient. But it does talk about 10:15:00
19 therapeutic use. 10:15:03

20 Q And I used the term AML. 10:15:04

21 Are you familiar with that term? 10:15:07

22 A Yes. 10:15:07

1	Q Okay. And if I use AML instead of acute	10:15:08
2	myelogenous leukemia, you'll know what I mean?	10:15:13
3	A Absolutely.	10:15:15
4	Q Thank you.	10:15:16
5	Are you also familiar with the term MDS?	10:15:17
6	A MDS. Give me some context. I probably	10:15:21
7	am, but it's --	10:15:24
8	Q Sure. If I refer to myelodysplastic	10:15:26
9	syndrome as MDS, will you understand what I mean?	10:15:29
10	A Okay. I'm less familiar with that	10:15:32
11	condition. I've heard it, but yes, that's fine.	10:15:34
12	Q Okay. And Ionescu -- do you know whether	10:15:36
13	Ionescu provides any data showing that	10:15:41
14	5-azacytidine was administered in a	10:15:43
15	therapeutically effective amount enough to treat	10:15:45
16	MDS?	10:15:49
17	MR. GUPTA: Objection to form.	10:15:51
18	A So what was the question again?	10:16:05
19	Q Do you know if Ionescu provides any data	10:16:11
20	showing that an oral formulation of 5-azacytidine	10:16:13
21	was administered in a therapeutically effective	10:16:15
22	amount to treat MDS?	10:16:19

1	A I don't know of any data, but the	10:16:21
2	description says it is.	10:16:23
3	Q If we turn to Page 12 of Ionescu, there is	10:16:27
4	the section heading: "Pharmaceutical	10:16:33
5	formulations."	10:16:35
6	Can you let me know when you get there.	10:16:35
7	A Yes, I'm there.	10:16:37
8	Q And this section of pharmaceutical	10:16:39
9	formulations continues from Page 12 to Page 14,	10:16:45
10	correct?	10:16:50
11	A Yes.	10:16:55
12	Q This pharmaceutical formulation section of	10:16:55
13	Ionescu describes different ways to formulate	10:17:01
14	drugs; is that accurate?	10:17:05
15	MR. GUPTA: Objection to form.	10:17:08
16	You can answer.	10:17:10
17	A I think it describes potentially different	10:17:12
18	routes of administration and different types of	10:17:14
19	formulation, correct.	10:17:17
20	Q Did Ionescu teach a person of skill in the	10:17:18
21	art in 2008 that 5-azacytidine could be	10:17:25
22	administered to a patient in a therapeutically	10:17:29

1 effective amount in all of the ways described in 10:17:35
2 the pharmaceutical formulation section from Pages 10:17:37
3 12 to 14? 10:17:40

4 MR. GUPTA: Objection. Objection to form. 10:17:42

5 You can answer. 10:17:46

6 A So it's not something that I've considered 10:17:48
7 in terms of all of the formulation options, but it 10:17:52
8 describes various formulation options, and I have 10:17:54
9 concentrated my analysis on tablet formulations in 10:17:56
10 terms of what Ionescu tells you about tablet 10:18:01
11 formulations, but it describes a range of others, 10:18:04
12 I agree. 10:18:08

13 Q So in forming the opinions in your 10:18:09
14 declaration, you did not consider whether Ionescu 10:18:18
15 tells a person of skill in the art whether 10:18:22
16 5-azacytidine could be administered in all of the 10:18:27
17 ways disclosed in a pharmaceutical formulation 10:18:30
18 section in -- 10:18:34

19 MR. GUPTA: Objection to form. 10:18:36

20 MS. PETRUZZI: I'm sorry. I wasn't 10:18:38
21 finished. 10:18:39

22 BY MS. PETRUZZI: 10:18:37

1	Q -- on Pages 12 to 14.	10:18:37
2	MR. GUPTA: Okay. Objection to form.	10:18:41
3	You can answer.	10:18:43
4	A Well, it does describe a range of	10:18:44
5	administration routes, and I see no reason why	10:18:45
6	within some consideration of those routes they're	10:18:48
7	not viable. You'd have to consider them in a way	10:18:51
8	that I haven't done just yet, but it describes in	10:18:53
9	more detail the tablet route, for example.	10:18:59
10	It tells you about making the thing, about	10:19:02
11	how to granulate the thing, about how to sugar	10:19:04
12	coat the thing. So it seems to me the detail is	10:19:07
13	skewed very much towards a nonenteric-coated	10:19:11
14	tablet and its method of manufacture, which is not	10:19:15
15	the case for the other forms that are there.	10:19:17
16	Q Okay. So let's turn to Page 12.	10:19:32
17	A Okay.	10:19:43
18	Q And there is a section, it's the last	10:19:43
19	paragraph: "Examples of suitable excipients	10:19:46
20	include."	10:19:49
21	A Yes.	10:19:49
22	Q Do these -- are these excipients only	10:19:50

1	excipients for oral tablets?	10:19:54
2	MR. GUPTA: Objection to form.	10:19:57
3	You can answer.	10:19:58
4	A The majority of them are, but they're not	10:19:59
5	only. Some are not. Oh, I don't know. I mean,	10:20:02
6	potentially, they could all be, I suppose. Let me	10:20:06
7	have a look.	10:20:09
8	Emulsifying agents are not, for example.	10:20:11
9	So suspending agents are not, so they're not	10:20:13
10	exclusively for tablets. The majority of them are	10:20:18
11	tablets excipients, but not all of them.	10:20:21
12	Q If we turn to Page 14, the first full	10:20:35
13	paragraph on that page: "In the event."	10:20:39
14	A Yes.	10:20:44
15	Q And this section talks about parenteral	10:20:45
16	administration; is that right?	10:20:48
17	MR. GUPTA: I'm sorry, let me just --	10:20:49
18	where are you?	10:20:50
19	A Yes, it does. I'm sorry, hang on a	10:20:55
20	minute.	10:20:58
21	MR. GUPTA: I'm sorry, what line number	10:21:00
22	are you?	10:21:02

1	MS. PETRUZZI: I'm in the first full	10:21:02
2	paragraph, which is line -- let's call it, it	10:21:03
3	starts at five, so it's a little bit confusing,	10:21:06
4	but it's, you know, four lines down.	10:21:09
5	MR. GUPTA: There you go. Pardon me. Go	10:21:10
6	ahead. Okay. Go ahead.	10:21:13
7	BY MS. PETRUZZI:	10:21:17
8	Q Are you familiar with the term	10:21:17
9	chemotherapeutic agents?	10:21:32
10	A Yes.	10:21:35
11	Q Is 5-azacytidine a chemotherapeutic agent?	10:21:36
12	A Yes, I think it would be called that.	10:21:41
13	Q On -- does Ionescu teach a person of skill	10:21:43
14	in the art in 2008 that 5-azacytidine could be	10:21:56
15	administered to a patient in a therapeutically	10:21:59
16	effective amount in a lozenge formulation.	10:22:02
17	MR. GUPTA: Objection to form.	10:22:12
18	You can answer.	10:22:13
19	A A lozenge is in the list of potential	10:22:14
20	formulations. I suspect it wouldn't be the most	10:22:19
21	commonly used -- well, isn't the most commonly	10:22:24
22	used of dosage forms. So I suspect the tablet	10:22:26

1 would be the route of choice. Would you use a 10:22:29
2 lozenge? You would use a tablet in preference, 10:22:35
3 I'm sure. 10:22:39

4 Q Does Ionescu teach a person of skill in 10:22:41
5 the art in 2008 that 5-azacytidine could be 10:22:45
6 administered to a patient in a therapeutically 10:22:49
7 effective amount as an lozenge? 10:22:53

8 MR. GUPTA: Objection to form. 10:22:56

9 You can answer. 10:22:57

10 A It's listed as an option, yes. So 10:22:59
11 conceptually, it's listed as an option. I don't 10:23:04
12 think it would be the one that most people would 10:23:07
13 use. I think it's listed as an option. Let me 10:23:09
14 just check. Correct, it is listed as an option, 10:23:12
15 yes. 10:23:16

16 Q Ionescu also lists buccal as an option. 10:23:16

17 Do you see that? 10:23:21

18 A Yes. 10:23:21

19 Q What is buccal? 10:23:22

20 A That would be administering a drug through 10:23:24
21 the buccal mucosa. 10:23:28

22 Q Does Ionescu teach a person of skill in 10:23:30

1	the art that 5-azacytidine could be administered	10:23:33
2	to a patient in a therapeutically effective amount	10:23:36
3	as a buccal formulation?	10:23:39
4	MR. GUPTA: Same objection.	10:23:41
5	A It isn't something I've considered in	10:23:43
6	relation to a nonenteric-coated tablet, but it's	10:23:46
7	listed there. And if someone wanted to explore	10:23:49
8	it, they could explore it based on the teaching	10:23:52
9	here.	10:23:54
10	Q You see that Ionescu discloses paper?	10:23:55
11	A On a different page --	10:24:07
12	Q Same page. Right after buccal lozenge on	10:24:09
13	paper?	10:24:12
14	A I was on the page of buccal and lozenge	10:24:13
15	either. Paper, yes.	10:24:16
16	Q Do you have an understanding of what paper	10:24:18
17	means here?	10:24:19
18	A Realistically, no. I mean, in terms of it	10:24:21
19	being different to sachet, I don't really see what	10:24:26
20	it would be. I think it's really a synonym for	10:24:30
21	sachet.	10:24:35
22	Q Okay. Does Ionescu disclose film	10:24:37

1	coatings?	10:24:53
2	A Yes.	10:24:54
3	Q Where --	10:24:55
4	A Sorry. Film coatings?	10:24:56
5	Q Film coatings.	10:24:59
6	A I apologize. Let's start that again.	10:25:00
7	Q Sure. Let me ask the question again.	10:25:02
8	Does Ionescu disclose film coatings?	10:25:04
9	A Okay. So Ionescu discloses sugar coating,	10:25:07
10	which are, if you like the precursor for film	10:25:12
11	coatings, which are not the replacement for sugar	10:25:19
12	coatings. So specifically it mentions sugar	10:25:22
13	coatings, but a person of ordinary skill in the	10:25:24
14	art would understand that would follow on to the	10:25:26
15	use of film coatings beyond sugar coating.	10:25:29
16	Q So you agree that film coatings largely	10:25:32
17	replaced sugar coatings by the 1970s, right?	10:25:34
18	MR. GUPTA: Objection to form.	10:25:38
19	A '70s maybe not, but at some stage, yes.	10:25:39
20	Q If you turn back to your declaration on	10:25:45
21	Page 24.	10:25:50
22	A Yes.	10:25:51

1	Q	Let me know when you're there.	10:26:01
2	A	Yes.	10:26:02
3	Q	Paragraph 47.	10:26:03
4	A	Yes.	10:26:04
5	Q	In your declaration, you cite Gibson,	10:26:05
6		Exhibit 1006; is that right?	10:26:08
7	A	Yes.	10:26:10
8	Q	And Gibson states, and you quote: "Sugar	10:26:11
9		coating was the most commonly used method until	10:26:14
10		the 1970s when it was largely superseded by film	10:26:16
11		coating."	10:26:20
12		Do you see that?	10:26:21
13	A	Yes.	10:26:21
14	Q	Do you agree with that statement?	10:26:21
15	A	I think before the '70s it was used	10:26:23
16		exclusively. I guess I'm discussing the	10:26:25
17		transition period. I think the previous question	10:26:27
18		was superseded by the '70s or something like that,	10:26:30
19		largely superseded, I will go with.	10:26:33
20		Film coating was catching on, sugar	10:26:35
21		coating -- they would have dovetailed, if you	10:26:39
22		like, for a period of time, but after this period	10:26:41

1 of time, then, sugar coating would have been 10:26:43
2 replaced by film coating. 10:26:49

3 Q So by 2008, a person of skill in the art 10:26:50
4 would have understood that film coatings largely 10:26:56
5 would have replaced sugar coating? 10:26:59

6 MR. GUPTA: Objection to form. 10:27:01

7 A That's correct. In most pharmaceutical 10:27:03
8 contexts, sugar coating is still used, but it's 10:27:06
9 trivial compared to film coating. I agree. 10:27:09

10 Q If you turn to Page 14 of your 10:27:17
11 declaration, back to the documents-considered 10:27:22
12 table. 10:27:25

13 A Okay. 10:27:27

14 Q And we just talked about Gibson, which is 10:27:28
15 Exhibit 1006. 10:27:34

16 Do you see that? 10:27:34

17 A Yes. 10:27:35

18 Q You considered Gibson Chapter 11: "Oral 10:27:36
19 solid dosage forms" in developing the opinions 10:27:39
20 that are in your declaration; is that right? 10:27:43

21 A I refer to Gibson. I don't think I needed 10:27:46
22 Gibson to do that, but I did refer to Gibson in 10:27:50

1 relation to that, yes, and I have cited to Gibson 10:27:53
2 in relation to that. 10:27:55

3 Q Chapter 11 is the only portion of Gibson 10:27:56
4 cited in your documents-considered list? 10:27:59

5 A Yes, I think so. 10:28:01

6 Q Do you know if Chapter 7 -- strike that. 10:28:05

7 Do you know if Chapter 11 of Gibson 10:28:10
8 discloses 5-azacytidine? 10:28:12

9 A Well, Gibson a textbook on pharmaceutical 10:28:15
10 formulation, and as such would not talk about drug 10:28:18
11 substances. So I would be very surprised if it 10:28:21
12 talked about, other than a few example 10:28:24
13 formulations, about any drug substances, as with 10:28:26
14 any textbook. 10:28:30

15 Q So Chapter 11 of Gibson does not disclose 10:28:31
16 5-azacytidine? 10:28:35

17 A For the reasons I just said, you wouldn't 10:28:36
18 expect it to disclose individual drug substances, 10:28:39
19 apart from a few, kind of, very famous examples of 10:28:41
20 things which they would mention. Other than that, 10:28:46
21 you wouldn't expect it. 10:28:49

22 Q So the answer to my question is no? 10:28:50

1	MR. GUPTA: Objection to form.	10:28:55
2	A I've given you a detailed answer. You can	10:28:56
3	use it as you wish, but I've given you the	10:28:59
4	detailed answer.	10:29:01
5	Q I'm handing you what's been previously	10:29:02
6	marked as Exhibit 1006 in this proceeding.	10:29:35
7	A Thank you.	10:29:38
8	Q Are you familiar with this document?	10:29:39
9	A Yes, I am.	10:29:55
10	Q What is this document?	10:29:55
11	A A chapter by Peter Davidson in the Gibson	10:29:57
12	textbook.	10:30:02
13	Q This is the Gibson Chapter 11 that you	10:30:02
14	relied on in forming the opinions that are in your	10:30:04
15	declaration, correct?	10:30:08
16	A Yes.	10:30:08
17	Q Does Chapter 11 of Gibson disclose	10:30:09
18	5-azacytidine?	10:30:12
19	A I just answered that. Didn't I just talk	10:30:14
20	to you about that? Didn't you just ask me about	10:30:18
21	Gibson disclosing that?	10:30:22
22	Q My question is yes or no, does Gibson	10:30:23

1	Chapter 11 disclose 5-azacytidine?	10:30:26
2	A I've already answered that for the reasons	10:30:27
3	that I gave you before. Drug substances are	10:30:30
4	generally not included in this. I wouldn't expect	10:30:32
5	it to, and therefore you wouldn't expect to see	10:30:34
6	many drug substances, other than a few kind of	10:30:37
7	very famous examples. You wouldn't expect it to	10:30:39
8	be there.	10:30:45
9	Q Is 5-azacytidine in Chapter 11 of Gibson?	10:30:46
10	MR. GUPTA: Objection to form.	10:30:50
11	A That's the same question, same answer.	10:30:51
12	It's -- you wouldn't expect drug substances to be	10:30:54
13	there, so you wouldn't look to see it, and	10:30:56
14	therefore, yeah, you wouldn't see hardly any drug	10:30:59
15	substances that have been made into solid or	10:31:02
16	dosage forms are going to be listed in a textbook,	10:31:04
17	so you wouldn't expect it to be.	10:31:07
18	Q I'm sorry. I'm just trying to make sure I	10:31:09
19	understand. I understand that you wouldn't expect	10:31:14
20	5-azacytidine to be in this, but you mentioned	10:31:15
21	that there are some example drugs that are in	10:31:19
22	textbooks.	10:31:22

1	A Yes.	10:31:22
2	Q Correct? And so my question is: Is	10:31:23
3	5-azacytidine listed in Chapter 11 anywhere?	10:31:25
4	MR. GUPTA: Same -- same objection.	10:31:28
5	A Same answer. It isn't one of the example	10:31:29
6	questions as -- example drugs, as far as I know,	10:31:31
7	that have been used in the standard textbook.	10:31:35
8	Q If we turn back to your declaration, let's	10:31:37
9	go back to Page 14, which is the documents	10:31:44
10	considered.	10:31:47
11	Let me know when you're there.	10:31:54
12	A I'm there.	10:31:55
13	Q Great.	10:31:56
14	MR. GUPTA: Hold on.	10:31:58
15	Q In forming the opinions in your	10:32:10
16	declaration, you considered -- you considered	10:32:11
17	Exhibit 1005 to Atadja; is that correct?	10:32:14
18	A Yes.	10:32:18
19	Q If I call 1005 Atadja, will you understand	10:32:20
20	what I mean?	10:32:24
21	A I will.	10:32:25
22	Q All right. Can you turn to Page 19 of	10:32:26

1	your declaration, please.	10:34:14
2	A Okay.	10:34:21
3	Q And here you include a chart that says:	10:34:21
4	"Prior art examples describing the oral	10:34:28
5	administration of 5-azacytidine"; is that right?	10:34:30
6	A That's right.	10:34:34
7	Q Can we turn the page. You list Pharmion	10:34:35
8	PR, Exhibit 1010.	10:34:40
9	Do you see that?	10:34:44
10	A Yes.	10:34:44
11	Q And the Pharmion PR is the reference that	10:34:44
12	you rely on as part of ground 3 in your	10:34:47
13	declaration; is that correct?	10:34:51
14	A Specifically named in ground 3, correct.	10:34:52
15	Q It's not relied upon in ground 1?	10:34:55
16	A It is -- ground 1 is anticipation of	10:35:00
17	Ionescu, and other documents are only there for	10:35:05
18	expectation of success or -- yeah, they're not	10:35:08
19	there as an anticipation reference. So it's not	10:35:14
20	there for that, but, you know, certain documents	10:35:16
21	I've looked at for a motivation to combine or	10:35:19
22	expectation for success, and I'm not going to say	10:35:23

1	it's excluded from those. I don't need motivation	10:35:26
2	to combine for Ionescu. That's anticipation.	10:35:34
3	Forget that little bit there.	10:35:36
4	But in terms of the obviousness, I'm not	10:35:37
5	going to exclude it. In terms of anticipation,	10:35:39
6	Ionescu is what it is. But I've used it in --	10:35:43
7	it's a long way around, rather badly saying, I've	10:35:47
8	used it in various places as a supportive	10:35:49
9	document, but in ground 3 as part of the main	10:35:52
10	consideration.	10:35:55
11	Q Okay.	10:35:57
12	A Is probably the better answer that I tried	10:35:58
13	to do in the first instance.	10:36:00
14	Q All right. And looking at the chart	10:36:02
15	describing Exhibit 1010, the Pharmion PR, you do	10:36:07
16	not state here the type of oral dosage formulation	10:36:13
17	used, correct?	10:36:19
18	A That's correct. Well, tablet, but I don't	10:36:21
19	say there, but it is a tablet. But I don't state	10:36:26
20	anything more than that elsewhere.	10:36:30
21	Q Okay. I'm handing you what's previously	10:36:32
22	been marked as Exhibit 1010 in this proceeding.	10:37:17

1	Are you familiar with this document?	10:37:24
2	A Yes.	10:37:26
3	Q What is it?	10:37:27
4	A It is a Document 1010, I believe, which is	10:37:27
5	the press release.	10:37:33
6	Q And this is the Pharmion press release	10:37:34
7	that you rely on in your declaration for ground 3,	10:37:38
8	correct?	10:37:43
9	A Yes.	10:37:44
10	Q The Pharmion PR does not state whether a	10:37:45
11	tablet was used in this study, correct?	10:37:50
12	A It says oral dosage form, correct.	10:37:53
13	Q So it doesn't -- Pharmion PR does not	10:38:22
14	state whether a tablet was used in this study,	10:38:27
15	right?	10:38:29
16	MR. GUPTA: Objection to form.	10:38:29
17	A It says oral formulation. It doesn't	10:38:32
18	specifically say tablet, I believe. I can't see	10:38:35
19	tablet there. No, it says oral dosage form.	10:38:42
20	Q Right. If we look at the title of the	10:38:44
21	press release, it says: "Clinical data presented	10:38:54
22	on pilot pharmacokinetic study of oral	10:39:00

1	azacitidine."	10:39:05
2	Do you see that?	10:39:05
3	A Yes, I do.	10:39:06
4	Q Do you know what a pilot pharmacokinetic	10:39:06
5	study is?	10:39:09
6	MR. GUPTA: Objection to form and	10:39:10
7	relevance.	10:39:12
8	You can answer.	10:39:13
9	A It's an early pharmacokinetic study.	10:39:15
10	Q Do you agree that a pilot pharmacokinetic	10:39:20
11	study reports preliminary results?	10:39:27
12	A Yes.	10:39:31
13	Q The pilot study, would you agree that the	10:39:32
14	pilot study results may not be confirmed on full	10:40:01
15	analysis of the detailed results of a trial?	10:40:05
16	MR. GUPTA: Objection to form. Scope, and	10:40:08
17	relevance.	10:40:10
18	You can answer.	10:40:11
19	A Well, in terms of context, in the press	10:40:12
20	release they are extremely excited about this as	10:40:15
21	an opportunity. So they obviously don't regard it	10:40:18
22	as insignificant or trivial.	10:40:20

1 In terms of your question, are the data 10:40:24
2 from an early study going to be identical to data 10:40:28
3 of a later study? That's why you do a later 10:40:32
4 study, to confirm whether they're the same or 10:40:35
5 different when things get -- how they look with a 10:40:37
6 bigger study is an important extra bit of 10:40:40
7 information. 10:40:49

8 Q In your experience, are you aware -- 10:40:50
9 strike that. 10:40:50

10 In your experience, are you aware of drugs 10:40:52
11 that show some bioavailability in preliminary 10:40:54
12 studies but ultimately were not approved and 10:40:57
13 available to patients? 10:41:00

14 MR. GUPTA: Objection to form, scope, and 10:41:01
15 relevance. 10:41:05

16 You can answer. 10:41:08

17 A Yes, but not for the lack of 10:41:09
18 bioavailability. I mean, conceptually, I mean, 10:41:11
19 you can have perfectly bioavailable product which 10:41:15
20 doesn't demonstrate adequate efficacy or safety. 10:41:18
21 That is possible and that's why the larger scale 10:41:21
22 clinical trials are carried out. And it doesn't 10:41:24

1	go from being bioavailable to being not	10:41:29
2	bioavailable. But that bit is going to carry on.	10:41:31
3	Q Okay. If you turn to Page 2, I mean,	10:41:36
4	there is not a page number but the back side.	10:41:46
5	A Okay.	10:41:49
6	Q And if you look at the bottom, there is a	10:41:49
7	safe harbor statement, do you see that section?	10:41:57
8	A I do.	10:41:59
9	Q The second sentence reads: "Such	10:42:00
10	statements are based on current expectations and	10:42:07
11	involve a number of known and unknown risks and	10:42:10
12	uncertainties that could cause the final results	10:42:13
13	to differ significantly from the results	10:42:15
14	summarized by such statements."	10:42:18
15	Do you see that?	10:42:19
16	A I do.	10:42:20
17	Q You agree that Pharmion, the Pharmion	10:42:22
18	press release is telling its readers that final	10:42:27
19	results after additional trials could differ	10:42:34
20	significantly from the preliminary results, right?	10:42:40
21	MR. GUPTA: Objection to form. And scope.	10:42:43
22	You can answer.	10:42:47

1	A I think it comes down to what	10:42:48
2	difference -- the issue we talked about before.	10:42:56
3	You're not going to go from something which is	10:42:58
4	bioavailable here to something which is not	10:43:00
5	bioavailable. That isn't going to change, but you	10:43:03
6	might go from extremely exciting to rather less	10:43:06
7	exciting or even more exciting. That could	10:43:08
8	change. So it's going to be about safety and	10:43:10
9	efficacy, not about bioavailability.	10:43:12
10	Q Okay. In your declaration, you discuss	10:43:16
11	cytidine deaminase inhibitors, right?	10:43:37
12	A Conceptually and generally and	10:43:42
13	specifically in some discussion there, yes.	10:43:44
14	Q Do you know what a cytidine deaminase	10:43:46
15	inhibitor is?	10:43:49
16	A Yes.	10:43:49
17	Q What is it?	10:43:50
18	MR. GUPTA: Objection to form.	10:43:51
19	Go ahead.	10:43:52
20	A It is exactly what it says. I don't know	10:43:53
21	what else you can say.	10:44:01
22	Q Why is a cytidine deaminase inhibitor	10:44:02

1	used?	10:44:05
2	MR. GUPTA: Same objection.	10:44:06
3	A Well, it would be -- if it were used, it	10:44:10
4	would be used to block certain enzyme -- enzyme	10:44:13
5	pathways, if it were used. So it would -- by	10:44:19
6	interfering with the enzyme process, you're	10:44:25
7	affecting things that happen in the body, that if	10:44:28
8	you don't have that there, you wouldn't be	10:44:30
9	affecting things that happen in the body.	10:44:32
10	Q Do you know what types of enzyme pathways	10:44:39
11	are blocked?	10:44:52
12	MR. GUPTA: Objection to form and scope	10:44:53
13	and relevance.	10:44:55
14	You can answer.	10:44:56
15	A So I haven't considered, for example, the	10:44:57
16	THU, the breadth of its enzyme blocking in the	10:44:59
17	human body in terms of which pathways it blocks.	10:45:05
18	I haven't considered that because it isn't	10:45:08
19	relevant to my consideration for the formulation	10:45:12
20	of this product. So I -- but it can interfere	10:45:13
21	with enzyme pathways, inevitably, that's what its	10:45:19
22	function is. And I haven't looked at how broadly	10:45:23

1	that would be true.	10:45:27
2	Q You mentioned THU, which is one type of	10:45:27
3	cytidine deaminase inhibitor.	10:45:30
4	That was known by 2008; is that right?	10:45:33
5	A That's right.	10:45:35
6	Q Are there other cytidine deaminase	10:45:35
7	inhibitors that were known in 2008?	10:45:37
8	A It's not something I considered. I've	10:45:40
9	considered it in relation to whether that one --	10:45:42
10	well, indeed, whether any inhibitor should be	10:45:45
11	included in the formulation, but specifically that	10:45:47
12	one should be included in the formulation, and I	10:45:49
13	haven't considered other inhibitors.	10:45:52
14	Q So you don't know whether any other	10:45:56
15	cytidine deaminase inhibitors were known in 2008	10:46:01
16	besides THU?	10:46:04
17	MR. GUPTA: Objection to form.	10:46:07
18	A I would be surprised if there were none.	10:46:08
19	I haven't looked to see what they are or which	10:46:11
20	ones would be viable to use in any particular	10:46:13
21	circumstance. I've considered whether it's viable	10:46:16
22	or sensible to use any or, specifically, THU in	10:46:19

1	this circumstance. I've concluded that it's not.	10:46:25
2	Q Okay. In your declaration you also	10:46:28
3	discuss cytosine arabinoside, AraC.	10:46:30
4	Do you recall that?	10:46:36
5	A Can you take me to where in my	10:46:36
6	declaration.	10:46:38
7	Q Yes. It's at Page 65 in paragraph 138.	10:46:39
8	A Okay. I'll have a look. Okay. Paragraph	10:46:46
9	what?	10:46:54
10	Q Paragraph 138.	10:46:54
11	A Not paragraph 65, Page 65.	10:46:58
12	Q Oh, on Page 65.	10:47:00
13	A Thought that didn't quite add up. Very	10:47:02
14	good, paragraph 138. All right.	10:47:05
15	Q You discuss cytosine arabinoside, which is	10:47:07
16	AraC, correct?	10:47:12
17	A I'm just reading through.	10:47:13
18	Yes, I do discuss that.	10:47:14
19	Q What is AraC?	10:47:17
20	A So I'm not entirely sure of the mechanism	10:47:24
21	by which it works, but the discussion -- the	10:47:54
22	statement here that I put in talks about it's	10:47:59

1	administration of AraC either in 2008, to the	10:49:33
2	extent it was administered to patients?	10:49:38
3	A I don't know.	10:49:40
4	MR. GUPTA: Hold on, hold on. Objection	10:49:41
5	to form.	10:49:42
6	You can answer.	10:49:43
7	A I suspect if I were to go back and look at	10:49:45
8	these references that were cited, which I haven't	10:49:48
9	been back to look at, it would tell me the way it	10:49:50
10	was administered to patients, and also be able to	10:49:53
11	read more about what it was as a compound, but I	10:49:55
12	don't know, just now, how it was administered to	10:50:00
13	patients.	10:50:02
14	Q Are you aware of any oral drugs where --	10:50:03
15	strike that.	10:50:03
16	Are you aware of any oral drugs where	10:50:24
17	introducing a cytidine deaminase inhibitor was	10:50:27
18	effective as of 2008?	10:50:31
19	MR. GUPTA: Hold on. Objection. Form,	10:50:34
20	scope, and relevance.	10:50:37
21	You can answer.	10:50:40
22	A I'm not aware of any, no.	10:50:41

1	Q Are you aware of any drugs administered by	10:50:43
2	injection where introducing a cytidine deaminase	10:51:03
3	inhibitor was effective as of 2008?	10:51:07
4	A I haven't considered it and haven't looked	10:51:10
5	to see if it's true or not. So sitting here	10:51:15
6	today, I'm not, but that's because I haven't	10:51:18
7	considered it.	10:51:20
8	Q Let's turn to your declaration at Page 86,	10:51:21
9	paragraph 176.	10:51:58
10	A I'll try and get it right this time.	10:52:00
11	Page 86, paragraph 176. Very good.	10:52:08
12	Q All right. You agree that 5-azacytidine	10:52:12
13	was known to cause side effects, particularly at	10:52:16
14	high doses, right?	10:52:19
15	A When administered by injection, yes.	10:52:21
16	Q A person of skill in the art in 2008 --	10:52:24
17	strike that.	10:52:24
18	Would a person of skill in the art in 2008	10:52:43
19	understand that side effects could also interfere	10:52:46
20	with oral administration of a drug?	10:52:49
21	MR. GUPTA: Objection to form and scope.	10:52:51
22	You can answer.	10:52:56

1	A As a general statement, and I can't think	10:52:58
2	in a minute of examples where side effects	10:53:07
3	interfere with oral administration of the drug,	10:53:10
4	but it depends in what context. It depends how	10:53:13
5	you're administering the drug, over what period of	10:53:25
6	time. So it would depend on a lot of parameters	10:53:29
7	as to whether it panned out that side effects	10:53:32
8	interfered with the oral administration of a drug.	10:53:34
9	Conceptually, well, I'm sure it could. I	10:53:37
10	just can't think of an example, sitting here in	10:53:39
11	the minute, across the broad spectrum. But I'm	10:53:42
12	sure it could.	10:53:45
13	Q Okay. And so a person of skill in the art	10:53:46
14	would conduct a dose-escalation study to determine	10:53:54
15	the maximum therapeutically effective amount of a	10:53:58
16	drug?	10:54:05
17	A By some particular route of administration	10:54:08
18	you would do a dose-escalation study, correct. If	10:54:10
19	it was an oral tablet for example, you would do a	10:54:14
20	dose-escalation study on an oral tablet.	10:54:17
21	Q So without a dose-escalation study, a	10:54:25
22	person of skill in the art wouldn't know the	10:54:28

1	maximum therapeutically effective dose of an oral	10:54:34
2	tablet?	10:54:39
3	MR. GUPTA: Objection to form, scope, and	10:54:39
4	relevance.	10:54:41
5	A I don't know what you mean by	10:54:41
6	maximum-therapeutic dose. I think you would	10:54:43
7	normally talk about maximum-tolerated dose, for	10:54:48
8	example.	10:54:50
9	Q Okay. So let me rephrase my question.	10:54:50
10	Without a dose-escalation study, a person	10:54:53
11	of skill in the art would not know the	10:54:59
12	maximum-tolerated dose of an oral tablet, right?	10:55:03
13	MR. GUPTA: Same objections.	10:55:10
14	THE WITNESS: What were your objections?	10:55:14
15	MR. GUPTA: I objected to form, scope, and	10:55:16
16	relevance of that question.	10:55:18
17	You can go ahead.	10:55:20
18	A Okay. Sorry, can -- I got distracted.	10:55:21
19	Can you ask the question again?	10:55:24
20	Q Sure. I'd be happy to.	10:55:26
21	Without a dose-escalation study, a person	10:55:27
22	of skill in the art would not know the maximum	10:55:30

1	tolerated dose of an oral tablet, right?	10:55:34
2	MR. GUPTA: Same objections.	10:55:42
3	You can answer.	10:55:44
4	A So you would -- you would generally get	10:55:45
5	the maximum-tolerated dose by the oral route	10:55:48
6	rather than specifically by an oral tablet.	10:55:52
7	Q Okay.	10:55:54
8	A But it would be true of the oral route,	10:55:55
9	although you wouldn't necessarily do the study on	10:55:58
10	maximum-tolerated dose with a tablet, necessarily.	10:56:01
11	Q So without a dose-escalation study, a	10:56:07
12	person of skill in the art would not know the	10:56:11
13	maximum tolerated dose of an oral formulation?	10:56:13
14	MR. GUPTA: Objection to form and scope	10:56:19
15	and relevance.	10:56:22
16	You can answer.	10:56:23
17	A I think we've refined the question now to	10:56:24
18	a point where I can agree, yes.	10:56:28
19	Q Okay. What is the maximum-tolerated dose?	10:56:30
20	A It --	10:56:36
21	MR. GUPTA: Same objection.	10:56:37
22	You can answer.	10:56:38

1	A The maximum-tolerated dose would be a	10:56:39
2	chemical definition of what is acceptable in terms	10:56:43
3	of a -- if you'd like, a risk-benefit ratio or	10:56:48
4	side-effect ratio for that drug substance for that	10:56:52
5	disease indication.	10:56:55

6	Q Okay. And so in your declaration, at	10:56:56
7	paragraph 176, you use the term, maximum-tolerated	10:57:05
8	dose, right?	10:57:09

9	A Yes.	10:57:15
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10	Q And when you use that term in your	10:57:16
11	declaration, did you apply the definition that you	10:57:18
12	just gave me?	10:57:22

13	A Can you tell me what you're asking me, if	10:57:26
14	I applied -- just so I can --	10:57:28

15	Q Yes. Of course. So when you wrote your	10:57:30
16	declaration and used the term maximum-tolerated	10:57:32
17	dose, did you mean a clinical definition of what	10:57:39
18	is acceptable in terms of, if you like, a	10:57:46
19	risk-benefit ratio or a side-effect ratio for that	10:57:48
20	drug substance and for that disease indication?	10:57:51

21	A It was a little verbose, wasn't it, but	10:57:54
22	nonetheless, broadly, yes, I think that's right.	10:57:57

1 It's what you can reasonably give before it 10:57:59
2 becomes nontolerated, unacceptable. 10:58:03

3 Q Have you ever formulated, in your 10:58:20
4 experience as a formulator, an oral dosage where 10:58:28
5 only subcutaneous or IV dosages were known? 10:58:31

6 MR. GUPTA: Objection to form and scope 10:58:39
7 and relevance. 10:58:42

8 You can answer. 10:58:43

9 A Well, largely, we would be formulating new 10:58:45
10 chemical entities. In new chemical entities you 10:58:54
11 would really only have either models or injection 10:58:58
12 data into animals, which would have been something 10:59:01
13 which would give you some indication of what your 10:59:05
14 target dose was. So I guess, yes, in that 10:59:07
15 respect. 10:59:11

16 Q In your experience, is the dose of the 10:59:11
17 active ingredient for an injection formulation 10:59:39
18 different from the dose given in an oral 10:59:44
19 formulation? 10:59:48

20 MR. GUPTA: Objection, relevance and 10:59:50
21 scope. 10:59:54

22 You can answer. 10:59:55

1	A Yes. With a whole lot of assumptions,	10:59:56
2	like you're treating the same condition, yeah,	11:00:05
3	there's a whole lot of things we haven't talked	11:00:06
4	about in there, but if like-for-like, yes.	11:00:09
5	Q How do you determine the amount of active	11:00:13
6	ingredient to include in the oral dosage form?	11:00:23
7	MR. GUPTA: Objection to form, scope, and	11:00:31
8	relevance.	11:00:32
9	You can answer.	11:00:34
10	A So if -- we should talk specifically	11:00:36
11	because it's too general a question, but if we're	11:00:39
12	talking about a nonenteric-coated tablet of this	11:00:41
13	drug substance even or a drug substance, and you	11:00:44
14	will have preclinical data and model data like	11:00:48
15	Dr. Batchelor produced, for example. And you will	11:00:54
16	ascertain a starting dose which will be used in	11:00:58
17	early clinical studies. And then early clinical	11:01:02
18	studies would subsequently go forward to later	11:01:06
19	clinical studies, and during that process the dose	11:01:08
20	will be refined.	11:01:11
21	Q Would you conduct an dose-escalation study	11:01:14
22	as part of that work?	11:01:18

1	A Yes.	11:01:19
2	Q All right. You just mentioned	11:01:30
3	Dr. Batchelor's in silico model.	11:01:37
4	You cite to Dr. Batchelor's in silico	11:01:40
5	model in your declaration, correct?	11:01:42
6	A I do.	11:01:45
7	Q Have you conducted in silico modeling	11:01:49
8	personally in your work as a formulator?	11:01:58
9	A It's a very broad question, and yes,	11:02:02
10	they're not the same type of in silico modeling	11:02:06
11	that Dr. Batchelor is doing, but I think we all	11:02:08
12	use various models for various things, but -- but	11:02:11
13	not necessarily the same that she has done.	11:02:16
14	Q Okay. So you personally haven't used	11:02:18
15	GastroPlus before to model; is that right?	11:02:20
16	A That's a more specific question, and that	11:02:24
17	is true, I haven't.	11:02:27
18	Q Would you consider yourself an expert on	11:02:28
19	in silico modeling?	11:02:30
20	MR. GUPTA: Objection to form.	11:02:33
21	You can answer.	11:02:34
22	A I would consider myself a formulation	11:02:35

1 expert, and as part of that we would base our
2 early formulations on in silico modeling. So I
3 would be -- my expertise would be in understanding
4 the use of the data rather than necessarily
5 using -- generating the data for the GastroPlus,
6 for example.

7 There's other models we might use
8 scientifically. But that's not what we're talking
9 about today.

10 Q So if I had questions about the GastroPlus
11 model that Dr. Batchelor reported on, you would
12 refer me to her to answer those questions?

13 A Yes, I've read her deposition. I know you
14 have asked -- not necessarily you. I know
15 somebody has asked her questions about her model,
16 and I've read that and I'm happy with the answers
17 that she gave, and I've got nothing extra to add
18 to that.

19 Q Do you know if Dr. Batchelor's in silico
20 modeling included an excipient?

21 MR. GUPTA: Objection to form.

22 A I don't want to answer on her modeling. I

11:02:38

11:02:41

11:02:44

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11:03:00

11:03:02

11:03:06

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11:03:23

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11:03:34

11:03:39

11:03:42

1 mean, as it happens, I don't think it did include 11:03:44
2 an excipient, but I really don't want to -- you 11:03:47
3 know, I want to use her data which are there to 11:03:54
4 give me an expectation of success and a 11:04:00
5 motivation, if you like, to go forward, which is 11:04:05
6 how they would be used in the industry. 11:04:07

7 And then also I've used her data in 11:04:09
8 relation to my analysis of obviousness. But -- 11:04:11
9 and inherency, but beyond that I don't want to 11:04:17
10 talk about her generation of the data because 11:04:25
11 that's something that you and her should discuss. 11:04:27

12 Q Okay. So you also would refer me to her 11:04:29
13 about whether her in silico modeling modeled a 11:04:32
14 sugar coated tablet correct? 11:04:37

15 A I would refer you to her about her 11:04:39
16 modeling and how it was carried out, yes. 11:04:42

17 Q Is it your understanding that 11:04:48
18 Dr. Batchelor modeled the prior art formulation in 11:04:49
19 Ionescu? 11:04:51

20 A Well, I will tell you that from my 11:04:52
21 perspective of receiving the data, if you like, 11:05:01
22 that she has modeled an immediate-release tablet 11:05:04

1 with a 200-milligram dose, which would be the 11:05:08
2 upper end of the unit dosage form in Ionescu, 11:05:13
3 which goes up to 200 milligram. 11:05:18

4 So in that respect, I view that as a model 11:05:21
5 of the immediate-release 200-milligram dosage form 11:05:24
6 by Ionescu, which has also modeled 400 milligrams 11:05:28
7 which I would take as two tablets administered 11:05:32
8 from the Ionescu teacher. 11:05:35

9 Q Okay. So earlier, do you recall we talked 11:05:39
10 about Ionescu, right? 11:05:52

11 A I'm sure we did, yes. You have to remind 11:05:55
12 me about what we talked about from Ionescu. 11:05:59

13 Q And we discussed Ionescu discloses 11:06:01
14 different polymorphic forms. 11:06:04

15 Do you recall that? 11:06:06

16 A I do. 11:06:06

17 Q And it also discloses different pseudo 11:06:06
18 polymorphic forms. 11:06:09

19 Do you recall that? 11:06:10

20 A Yes. 11:06:11

21 Q Do you know what polymorphic form of 11:06:11
22 5-azacytidine disclosed in Ionescu Dr. Batchelor 11:06:15

1	modeled?	11:06:18
2	MR. GUPTA: Objection to form.	11:06:19
3	You can answer.	11:06:20
4	A It has no relevance at all, because it is	11:06:22
5	a freely soluble drug and that has -- polymorphism	11:06:25
6	has no relevance in terms of dissolution rate for	11:06:28
7	a freely soluble drug. There is no relevance in	11:06:32
8	terms of solid-state stability, because that's not	11:06:36
9	what's being considered. So polymorphism has no	11:06:38
10	significance for the model at all.	11:06:41
11	Q So it's your position that the polymorphic	11:06:43
12	form of 5-azacytidine that Dr. Batchelor modeled	11:06:47
13	doesn't affect -- doesn't matter?	11:06:50
14	A Correct.	11:06:52
15	Q All right. You opine that Dr. Batchelor's	11:06:53
16	in silico modeling confirms that the claimed PK	11:07:10
17	limitations are inherently obvious; is that right?	11:07:14
18	A I think that's well put. I think they are	11:07:18
19	inherently obvious, just by their very nature.	11:07:20
20	So, primarily, that would be my position.	11:07:23
21	And secondary to that, the modeling also	11:07:25
22	confirms that. So your question was exactly right	11:07:29

1	in that respect.	11:07:32
2	Q Okay. What's your understanding of	11:07:33
3	inherently obvious as you applied it to your	11:07:36
4	declaration?	11:07:42
5	A Sure. So.	11:07:42
6	Q Excuse me for a moment.	11:07:44
7	A Sure. So my understanding is that by	11:07:46
8	selecting a dose to put into, for example, Claim 1	11:07:49
9	of the Patent, '628 patent, by using that dose	11:07:55
10	each and every time, you will produce something	11:08:03
11	that falls within the pharmacokinetic claim, which	11:08:05
12	means its an inherent property of a product of	11:08:11
13	Claim 1, with a specific dose. You obviously have	11:08:16
14	to choose a dose because Claim 1 is silent on the	11:08:19
15	dose that you are going to use.	11:08:22
16	MR. GUPTA: Heather, if you don't mind if	11:08:27
17	we could take a break whenever -- whenever we can.	11:08:28
18	I have to use the restroom.	11:08:31
19	MS. PETRUZZI: Sure. We can take a break	11:08:32
20	now.	11:08:33
21	THE VIDEOGRAPHER: We are going off the	11:08:34
22	record. The time is 11:08 a.m.	11:08:35

1	(Recess.)	11:08:38
2	THE VIDEOGRAPHER: We are back on the	11:26:39
3	record. The time is 11:26 a.m.	11:27:01
4	BY MS. PETRUZZI:	11:27:03
5	Q So before the break -- well, let me ask	11:27:07
6	before, did you have any substantive	11:27:12
7	communications with your counsel during the break?	11:27:15
8	A No.	11:27:16
9	Q Before the break, we were talking about	11:27:18
10	your opinions on inherent obviousness.	11:27:20
11	Do you recall that?	11:27:23
12	A Kind of.	11:27:24
13	Q Okay. Well, let's turn to your	11:27:26
14	declaration at Page 81, okay?	11:27:29
15	A Yeah.	11:27:32
16	Q All right. And I'm looking at	11:27:32
17	paragraph 167. Let me know when you're there.	11:28:00
18	A I am.	11:28:03
19	Q Great. You agree that a person of skill	11:28:04
20	in the art would have understood that AUC	11:28:07
21	typically increases with increasing dosage	11:28:10
22	amounts, right?	11:28:12

1	MR. GUPTA: Objection to form.	11:28:13
2	A Yes, I would.	11:28:17
3	Q And in the case of 5-azacytidine, would	11:28:19
4	you also expect AUC to increase with increasing	11:28:26
5	dosage amounts?	11:28:29
6	A Yes, I would -- you would want AUC to	11:28:30
7	increase with increasing dosage amounts. So when	11:28:36
8	it says: "Typically," that would be your -- what	11:28:40
9	you'd want to see happen.	11:28:42
10	Q And that's what you would expect for	11:28:43
11	5-azacytidine?	11:28:45
12	A What you'd expect and what you would want,	11:28:46
13	yes. Within a reasonable dose range.	11:28:49
14	Q All right. Can we turn back to Page 86 of	11:28:55
15	your declaration. And I'm looking at	11:29:25
16	paragraph 176. Let me know when you're there.	11:29:30
17	A I am.	11:29:32
18	Q All right. The first -- can you read the	11:29:33
19	first sentence to yourself and let me know when	11:29:44
20	you're done.	11:29:46
21	A (Document review.)	11:29:49
22	Yes.	11:29:58

1 Q Do you agree that a person of skill in the 11:30:01
2 art would understand that side effects could 11:30:04
3 interfere or alter oral administration of 11:30:08
4 5-azacytidine? 11:30:12

5 MR. GUPTA: Objection to form. And scope. 11:30:13
6 You can answer. 11:30:16

7 A It isn't a straightforward answer. It 11:30:18
8 depends on the structure of the administration, so 11:30:23
9 when things are being given, and what is being 11:30:26
10 given, multiple tablets. So it depends what is 11:30:30
11 being given and when it's being given as to what 11:30:36
12 the side effects are likely to interfere with. 11:30:39

13 Q So your statement at the top of one -- 11:30:42
14 paragraph 176 is: "As the side effects, the 11:30:46
15 studies also failed to account for known side 11:30:48
16 effects, such as vomiting and diarrhea, that could 11:30:52
17 alter or interfere with oral administration, 11:30:55
18 particularly at high dosages of 5-azacytidine." 11:30:57

19 Do you see that? 11:31:00

20 A Yes. 11:31:01

21 Q So here you're noting that side effects 11:31:01
22 could alter or interfere with oral administration, 11:31:10

1 particularly at higher dosage of 5-azacytidine; is 11:31:14
2 that right? 11:31:18

3 A For this particular study, when you're 11:31:18
4 giving a large number of entero-coated tablets for 11:31:20
5 example, it is possible. 11:31:25

6 Q And so a person of skill in the art in 11:31:27
7 2008 would want to consider whether side effects 11:31:30
8 were known because they may alter or interfere 11:31:37
9 with the oral administration of 5-azacytidine? 11:31:41

10 MR. GUPTA: Objection to form and scope. 11:31:43

11 A I'm not saying that in a standard 11:31:46
12 therapeutic administration of a single tablet, 11:31:49
13 single immediate-release tablet, for example, that 11:31:53
14 for this drug substance you would expect side 11:31:55
15 effects to interfere. 11:31:58

16 What I am saying is if you give a large 11:32:00
17 number of enteric-coated tablets simultaneously or 11:32:03
18 over a period of time, even, side effects can 11:32:07
19 interfere. So it is a specific case in relation 11:32:10
20 to administering a large number of small-dose 11:32:12
21 tablets that are enteric coated. 11:32:16

22 Q Does it also apply to nonenteric-coated 11:32:17

1	tablets?	11:32:21
2	MR. GUPTA: Same objection.	11:32:23
3	You can answer.	11:32:24
4	A I don't believe so, no.	11:32:25
5	Q So side effects such as vomiting and	11:32:32
6	diarrhea cannot interfere with oral administration	11:32:37
7	of nonenteric-coated tablets?	11:32:40
8	A I don't believe so, was my answer. So	11:32:44
9	I -- you would first of all have to trigger the	11:32:47
10	response for nausea and vomiting, which requires	11:32:50
11	you to have administered some drug for the	11:32:54
12	response to happen. Immediate-release dosage	11:32:55
13	forms would all have dissolved, I would have said,	11:32:58
14	before you triggered the response. A large number	11:33:01
15	of enteric dosage forms will not all have	11:33:04
16	dissolved. Some would be in the stomach. Some	11:33:07
17	would have passed through and been absorbed.	11:33:09
18	So what I'm saying here is, conceptually,	11:33:11
19	for a large number of enteric dose --	11:33:13
20	enteric-coated tablets with a large dose, you	11:33:16
21	could have vomiting before you have emptied from	11:33:19
22	the gastric contents all of your enteric-coated	11:33:23

1	tablets.	11:33:27
2	Q You mentioned a large number of tablets	11:33:27
3	and a large dose.	11:33:32
4	Would you still be concerned about side	11:33:39
5	effects during oral administration if you had a	11:33:44
6	large dose in one tablet?	11:33:46
7	MR. GUPTA: Objection to form and scope.	11:33:50
8	You can answer.	11:33:54
9	A I'd be concerned about side effects on a	11:33:55
10	risk-benefit ratio for a patient, just as a	11:33:58
11	general therapeutic concept, but not in terms of	11:34:01
12	interrupting the absorption of the dose, no.	11:34:04
13	Q Okay. So how many -- so how many tablets	11:34:07
14	would one need to administer?	11:34:26
15	THE WITNESS: Is she all right?	11:34:30
16	A She doesn't sound all right.	11:34:30
17	Q No, I know. She'll be okay.	11:34:34
18	A I was just distracted. I'm sorry.	11:34:35
19	Q It's fine. Thank you for your concern.	11:34:36
20	How many tablets would one need to	11:34:39
21	administer before a person of skill in the art	11:34:41
22	would take into account known side effects that	11:34:48

1	could alter or interfere with oral administration?	11:34:52
2	MR. GUPTA: Objection to form.	11:34:57
3	A So just to be clear, what I'm talking	11:34:59
4	about specifically here is the notion of vomiting	11:35:02
5	before you have cleared enteric-coated tablets,	11:35:05
6	multiple tablets, from your stomach.	11:35:08
7	There is another aspect of side effects	11:35:12
8	which is: Are the side effects tolerable, given	11:35:14
9	the dose of drug that you've given, and I'm not	11:35:17
10	entirely sure what your question relates to, but	11:35:20
11	those -- those are -- there are different things.	11:35:22
12	One is affecting absorption; the other one is just	11:35:24
13	a side effect, which you can decide whether it's	11:35:27
14	acceptable or not an acceptable side effect.	11:35:30
15	Q Okay. So there are two different types of	11:35:45
16	side effects that we're talking about here, it	11:35:57
17	sounds like?	11:35:59
18	A Well, the side effect of vomiting, for	11:36:00
19	example, is a side effect. It's a simple side	11:36:02
20	effect. What I'm talking about is, is it vomiting	11:36:05
21	after you've absorbed the drug, in which case you	11:36:08
22	can decide whether that's tolerable or not, or is	11:36:12

1 it vomiting before all the enteric-coated tablets 11:36:15
2 have left the stomach, in which case it affects 11:36:18
3 the absorption. 11:36:20

4 Q And are you saying that there wouldn't be 11:36:26
5 vomiting before all the nonenteric-coated tablets 11:36:34
6 leave the stomach to affect absorption? 11:36:40

7 A Correct, because this drug is very freely 11:36:43
8 soluble and very readily absorbed, so it will be 11:36:48
9 dissolved very quickly, absorbed very quickly, and 11:36:53
10 subsequent to that dissolving and absorption, you 11:36:56
11 will trigger the side effects, and by then it's 11:36:59
12 already gone. 11:37:01

13 Q But there is a separate situation of side 11:37:02
14 effects after absorption, and that's something 11:37:06
15 that a person of skill in the art would consider 11:37:09
16 in their risk-benefit analysis? 11:37:11

17 A A clinician would consider the 11:37:13
18 risk-benefit analysis. If you're in a 11:37:15
19 life-threatening condition, you will accept a 11:37:18
20 higher level of side effects than if you have a 11:37:21
21 trivial condition where you won't accept a very 11:37:23
22 high level of side effects. That's just, you 11:37:25

1	know, life over a drug administration.	11:37:29
2	Q So what is it about enteric -- this large	11:37:32
3	number of enteric-coated tablets that would	11:37:51
4	trigger -- strike that.	11:37:54
5	What is it about the administering of a	11:38:29
6	large amount of enteric-coated tablets that could	11:38:34
7	trigger vomiting before the drug is absorbed?	11:38:37
8	A Okay.	11:38:41
9	MR. GUPTA: Objection to form and scope.	11:38:42
10	A So if you take one enteric-coated tablet,	11:38:45
11	it has either left the stomach or it has not left	11:38:48
12	the stomach. If it leaves the stomach it will	11:38:51
13	then dissolve and absorb, not a problem. If you	11:38:54
14	take, for example, ten enteric-coated tablets, one	11:38:57
15	of them will leave the stomach. It will dissolve	11:39:00
16	and absorb, nine are still in the stomach. The	11:39:03
17	second one will leave the stomach, it will	11:39:06
18	dissolve and absorb. Eight are still in the	11:39:09
19	stomach, and if you have the nausea and vomiting	11:39:11
20	induced partway through that process, the vomiting	11:39:15
21	will clean out the ones that remain in the	11:39:19
22	stomach. It won't all empty at the same time.	11:39:22

1	Q You're saying multiple enteric-coated	11:39:25
2	tablets will not empty from the stomach at the	11:39:27
3	same time?	11:39:30
4	A Correct.	11:39:30
5	Q All right. I would like to introduce	11:39:31
6	what's been previously marked in this proceeding	11:40:39
7	as Exhibit 1005, Atadja.	11:40:41
8	A Thank you.	11:40:53
9	Q Do you recognize this document?	11:40:54
10	A Yes.	11:40:59
11	Q What is it?	11:41:00
12	A It's what I refer to as Atadja in my	11:41:03
13	declaration.	11:41:08
14	Q And Item 54 on Atadja says: "Title."	11:41:09
15	Do you see that?	11:41:14
16	A Yes.	11:41:15
17	Q What is the title of Atadja?	11:41:18
18	A "Combination of histone deacetylase	11:41:22
19	inhibitors with chemotherapeutics agents."	11:41:27
20	Q Do you see the abstract at Item 57?	11:41:30
21	A I do.	11:41:33
22	Q Can you please read the abstract to	11:41:34

1	yourself and let me know when you finish?	11:41:37
2	A (Document review.)	11:41:41
3	Okay.	11:42:00
4	Q Okay. And so Atadja is related to a	11:42:01
5	combination of chemotherapeutic agents and histone	11:42:09
6	deacetylase inhibitors, right?	11:42:16
7	A Yes.	11:42:16
8	Q If we turn to Page 3 of Atadja, and the	11:42:17
9	three is on the top of the page.	11:42:26
10	A Yes.	11:42:28
11	Q On Page 3, we see a list from one to ten.	11:42:29
12	Do you see that?	11:42:37
13	A Yes.	11:42:38
14	Q And this is a list that describes	11:42:39
15	chemotherapeutic agents, correct?	11:42:47
16	A Yes.	11:42:51
17	Q And some numbers disclose more than one	11:42:51
18	type of chemotherapeutic agents.	11:43:05
19	Do you see that?	11:43:08
20	A Yes.	11:43:09
21	Q How many, approximately, types of	11:43:09
22	therapeutic -- chemotherapeutic agents are listed	11:43:11

1	here?	11:43:16
2	MR. GUPTA: Objection to form.	11:43:18
3	You can answer.	11:43:19
4	A Well, there's more than ten, but some of	11:43:20
5	them will list multiple ones.	11:43:24
6	Q More than 20?	11:43:26
7	A Oh, I don't know. It's more than ten.	11:43:30
8	Q You can take time to count it if you want.	11:43:33
9	A I'm good. It's more than ten.	11:43:37
10	Q All right. And then after this list,	11:43:39
11	there are several pages that give examples of the	11:43:46
12	specific types of chemotherapeutic drugs, right?	11:43:49
13	A Correct.	11:43:55
14	Q Do you know how many different	11:43:56
15	chemotherapeutic agents are listed in Atadja?	11:43:59
16	A No.	11:44:02
17	Q More than 20?	11:44:11
18	A It looks like it.	11:44:13
19	MR. GUPTA: Objection to form.	11:44:14
20	A Sorry.	11:44:16
21	MR. GUPTA: Objection to form.	11:44:16
22	You can answer.	11:44:17

1	A	It looks like a reasonably long list. So	11:44:18
2		I would say more than 20, yes.	11:44:20
3	Q	5-azacytidine is one example of a	11:44:22
4		chemotherapeutic agent disclosed in Atadja; is	11:44:26
5		that right?	11:44:30
6	A	That's right.	11:44:30
7	Q	If we turn to Page 9, let me know when you	11:44:30
8		get there.	11:44:37
9	A	Okay. I'm there.	11:44:41
10	Q	All right. Atadja discloses DNA	11:44:42
11		demethylating agent -- strike that.	11:44:59
12		Atadja discloses DNA demethylating agents	11:44:56
13		such as 5-azacytidine and decitabine.	11:45:00
14		Do you see that?	11:45:02
15	A	I do.	11:45:02
16	Q	Are you familiar with decitabine?	11:45:04
17	A	Not particularly. It is an alternative	11:45:06
18		demethylating agent.	11:45:10
19	Q	Have you ever studied decitabine?	11:45:12
20	MR. GUPTA:	Objection to form. Objection	11:45:17
21		outside the scope. Objection, relevance.	11:45:18
22		You can answer.	11:45:20

1	A	No, I haven't.	11:45:21
2	Q	Have you read literature about decitabine?	11:45:22
3	MR. GUPTA:	Same objections.	11:45:25
4	A	Not outside of the fact that it is	11:45:27
5		included in some of the literature that I've	11:45:31
6		reviewed in relation to this case.	11:45:33
7	Q	Do you know if decitabine was orally	11:45:35
8		formulated for patients in the 2003-2004 time	11:45:42
9		period that Atadja was written?	11:45:47
10	MR. GUPTA:	Objection, relevance, and	11:45:50
11		scope.	11:45:52
12		You can answer.	11:45:53
13	A	I haven't looked at that, so I've not made	11:45:54
14		an assessment of that.	11:45:57
15	Q	Do you know if decitabine was orally	11:45:58
16		formulated for patients in 2008?	11:46:01
17	MR. GUPTA:	Same objections.	11:46:03
18		You can answer.	11:46:05
19	A	Same answer.	11:46:06
20	Q	All right. We talked about what a	11:46:07
21		chemotherapeutic agent was earlier today.	11:46:37
22		Do you recall that?	11:46:40

1 A Generally, yes. 11:46:41

2 Q Do you know what chemotherapeutic agents 11:46:42
3 are used to treat? 11:46:44

4 A Well, generally speaking, they use 11:46:47
5 chemotherapeutic agents in relation to cancer, but 11:46:49
6 to be fair it's a term that really could be 11:46:52
7 applied anywhere, but it is generally used in 11:46:54
8 relation to cancer. 11:46:57

9 Q Do you know whether all of the 11:46:58
10 chemotherapeutic agents disclosed in Atadja could 11:47:01
11 be formulated as a tablet and administered to a 11:47:04
12 patient in a therapeutically effective amount in 11:47:07
13 2008? 11:47:10

14 A It's not something I've looked at. It's 11:47:12
15 not an exercise I've been through. 11:47:14

16 Q Looking through the list, are you aware of 11:47:17
17 any chemotherapeutic agents in Atadja that were 11:47:23
18 available as a tablet? 11:47:27

19 MR. GUPTA: Objection to form. Objection, 11:47:30
20 scope, and relevance. 11:47:33

21 You can answer. 11:47:34

22 A Well, there are chemotherapeutic agents 11:47:35

1	which are available as tablets. I haven't done	11:47:38
2	the exercise of looking to see whether the ones	11:47:41
3	listed in here are the ones available as tablets.	11:47:44
4	Q Are you familiar with the drug letrozole?	11:47:47
5	A It doesn't ring a bell, no.	11:47:53
6	Q Are you familiar with the drug	11:47:55
7	anastrozole?	11:47:58
8	A I've heard of it, but familiar in terms of	11:47:59
9	I've heard of it, yes.	11:48:02
10	Q Do you know whether it can be administered	11:48:03
11	to a patient in a therapeutically effective amount	11:48:06
12	as a tablet?	11:48:09
13	MR. GUPTA: Objection. Objection to this	11:48:10
14	whole line of questioning under relevance, and	11:48:12
15	outside the scope of the expert report.	11:48:14
16	You can answer.	11:48:16
17	A It's not something I've considered. I	11:48:17
18	haven't looked at drug substances, other than the	11:48:18
19	drug substance that we're considering here.	11:48:20
20	Q Is it your opinion that Atadja teaches a	11:48:49
21	person of skill in the art in 2008 that	11:48:52
22	5-azacytidine could be administered in a	11:48:56

1 therapeutically effective amount to treat patients 11:48:58
2 as a tablet? 11:49:01

3 A So on Page 27 of Atadja, starting towards 11:49:27
4 the end of the large paragraph at the top of the 11:50:16
5 page, it talks about: "5-azacytidine as 11:50:19
6 administered, and it gives the range of doses 11:50:25
7 under which it's administered, in one or two doses 11:50:28
8 daily, preferably the compounds" -- and I'll skip 11:50:32
9 the salts bit -- "are administered as an oral 11:50:35
10 formulation in the form of a tablet and then also 11:50:39
11 potentially capsule, syrup, and as an alternative 11:50:41
12 or as parenteral injections, if appropriate." 11:50:48

13 So on the basis of that, I would say 11:50:51
14 Atadja does teach that 5-azacytidine can be 11:50:55
15 administered in those doses, and there's a tablet. 11:50:58

16 Q Is it your opinion that Atadja teaches a 11:51:02
17 person of skill in the art in 2008 that 11:51:08
18 5-azacytidine could be administered in a 11:51:11
19 therapeutically effective amount as a tablet 11:51:13
20 capsule, syrup, or parenteral injection? 11:51:17

21 MR. GUPTA: Objection to form. 11:51:21

22 A Yes, it has -- it talks about 11:51:24

1 therapeutically -- yeah, so it's got doses. And 11:51:26
2 it talks about a wide range of doses, and it does 11:51:30
3 describe tablet, capsule, or syrup, as well as a 11:51:32
4 parenteral injection. So you would need to 11:51:37
5 suitably formulate those, and then I would suggest 11:51:39
6 that that's a viable thing to do. 11:51:44

7 Q Do you know whether all of the 11:51:46
8 chemotherapeutic agents disclosed in Atadja could 11:51:47
9 be formulated as a capsule and administered to a 11:51:50
10 patient in a therapeutically effective amount in 11:51:53
11 2008? 11:51:55

12 MR. GUPTA: Objection to form, scope, and 11:51:56
13 relevance. 11:51:59

14 A As I said before, I haven't done an 11:52:01
15 analysis of other drugs, other than the one we're 11:52:03
16 considering today. So I can't do that now. 11:52:06

17 Q Do you know whether any of the 11:52:08
18 chemotherapeutic agents listed in Atadja were 11:52:14
19 available as a capsule in the 2003-2004 time 11:52:17
20 period of Atadja's? 11:52:21

21 MR. GUPTA: Objection to form, scope, and 11:52:25
22 relevance. 11:52:28

1	You can answer.	11:52:29
2	A Same answer. The analysis I've done is in	11:52:30
3	relation to this drug substance.	11:52:33
4	Q Do you know whether any of the	11:52:35
5	chemotherapeutic agents listed in Atadja were	11:52:40
6	available as a capsule in 2008 and were admin --	11:52:42
7	could be administered to a patient in a	11:52:50
8	therapeutically effective amount?	11:52:52
9	MR. GUPTA: Same objection.	11:52:54
10	A Same answer.	11:52:56
11	Q You're not aware?	11:52:57
12	A Well, it's not an analysis I've done. So	11:52:59
13	I would need to do the analysis.	11:53:02
14	Q Okay. Do you know whether all of the	11:53:04
15	chemotherapeutic agents disclosed in Atadja could	11:53:06
16	be formulated as a syrup and administered to a	11:53:12
17	patient in a therapeutically effective amount in	11:53:15
18	2008?	11:53:18
19	MR. GUPTA: Same objection.	11:53:18
20	You can answer.	11:53:19
21	A Same answer.	11:53:20
22	Q You don't know whether any of the	11:53:21

1	chemotherapeutic agents listed in Atadja were	11:53:27
2	available as a syrup in 2008; is that right?	11:53:31
3	MR. GUPTA: Objection to form, scope,	11:53:37
4	relevance.	11:53:39
5	You can answer.	11:53:40
6	A I don't think it's relevant whether it was	11:53:41
7	available as a syrup or not. This is teaching you	11:53:44
8	what you can do. And as I said, I've looked at it	11:53:47
9	in relation to the drug substance we're	11:53:49
10	considering here. And that's my -- that's what my	11:53:51
11	opinion is based on for the drug substance that	11:53:55
12	we're considering here.	11:53:57
13	Q But you don't know whether any of the	11:53:58
14	chemotherapeutic agents listed in Atadja were	11:54:01
15	available as a syrup?	11:54:04
16	MR. GUPTA: Objection to form.	11:54:06
17	BY MS. PETRUZZI:	11:54:07
18	Q Correct?	11:54:07
19	MR. GUPTA: Objection to form, scope, and	11:54:10
20	relevance.	11:54:12
21	You can answer.	11:54:13
22	A I haven't done an analysis of any of the	11:54:14

1	other chemotherapeutic agents in Atadja, as I said	11:54:16
2	in the answer to the previous questions.	11:54:19
3	Q Are you familiar with the drug Celebrex?	11:54:22
4	A I've heard of it.	11:54:24
5	Q Do you know if Celebrex was available as a	11:54:26
6	tablet in 2003, 2004?	11:54:32
7	MR. GUPTA: Objection to relevance, form,	11:54:34
8	and scope.	11:54:38
9	You can answer.	11:54:38
10	A I can't remember which drugs are available	11:54:39
11	in which dosage forms, sitting here today. So it	11:54:43
12	isn't something I can give an opinion on without	11:54:47
13	just very easily looking it up, but I can't give	11:54:49
14	an opinion sitting here now.	11:54:52
15	Q All right. Let's just turn to Page 8.	11:54:54
16	A Of what?	11:54:57
17	Q Of Atadja. I'm sorry.	11:54:58
18	A Okay.	11:55:01
19	Q And Page 8 at the top is talking about	11:55:05
20	cycloogenics inhibitors -- cyclooxygenase	11:55:09
21	inhibitors, excuse me, correct?	11:55:14
22	A Yes.	11:55:16

1	Q And cyclooxygenase inhibitors are	11:55:17
2	chemotherapeutic agents, correct?	11:55:20
3	A Yes.	11:55:22
4	Q And the first one is Celebrex.	11:55:22
5	Do you see that?	11:55:24
6	A Yes.	11:55:24
7	Q Do you know if Celebrex was available as a	11:55:25
8	tablet?	11:55:30
9	MR. GUPTA: Objection to form, scope,	11:55:32
10	relevance.	11:55:34
11	You can answer.	11:55:36
12	A Same answer. Yeah, I haven't done the	11:55:37
13	analysis. Same answer.	11:55:41
14	Q The next drug is Vioxx.	11:55:42
15	Do you see that?	11:55:45
16	A Yes, I do.	11:55:45
17	Q Are you familiar with the drug Vioxx?	11:55:46
18	A I've heard of it.	11:55:48
19	Q Do you know if Vioxx was available as a	11:55:49
20	tablet?	11:55:54
21	MR. GUPTA: Same objection.	11:55:54
22	A I don't remember. I have not done the	11:55:57

1	analysis.	11:55:59
2	Q Do you know if Vioxx was available as a	11:55:59
3	syrup?	11:56:02
4	MR. GUPTA: Same objection.	11:56:03
5	You can answer.	11:56:04
6	A Same answer. I haven't analyzed what	11:56:05
7	dosage form any of these drug were present in the	11:56:07
8	market today. Not that that affects my opinion in	11:56:10
9	any way in relation to the drug substance that	11:56:13
10	we're talking about here.	11:56:14
11	Q When were you first approached about	11:56:16
12	working on this matter?	11:57:15
13	A I don't know. I can't remember. No, I	11:57:17
14	don't remember.	11:57:24
15	Q Can you give me a ballpark?	11:57:24
16	A No, I don't remember.	11:57:25
17	Q Okay. Who reached out to you?	11:57:26
18	A I don't remember that either, sorry.	11:57:35
19	Q Is it someone from Steptoe & Johnson?	11:57:37
20	A I would think it would be. That's the	11:57:42
21	logical thing. I guess, it's one of the guys	11:57:45
22	sitting here, but I don't remember.	11:57:47

1 Q Did you write the first draft of your 11:57:49
2 declaration? 11:58:24

3 A I've wrote -- 11:58:26

4 MR. GUPTA: I just object to the extent 11:58:28
5 that -- on the basis of privilege. I just caution 11:58:31
6 you not to disclose any discussions directly 11:58:34
7 between attorneys and yourself. Otherwise you can 11:58:37
8 answer generally. 11:58:39

9 Go ahead. 11:58:40

10 A I've wrote parts of it. Other people 11:58:40
11 drafted other parts of it, and then I then changed 11:58:43
12 things and got to a position that I was 11:58:49
13 comfortable with this being my report and my 11:58:51
14 opinions. 11:58:54

15 Q How much time did you spend drafting your 11:58:54
16 declaration? 11:58:56

17 A That's tricky because I don't remember 11:58:58
18 that either, but I don't know ballpark-wise. I 11:59:00
19 don't know. I think there were quite a lot of 11:59:03
20 iterations. It would have been a reasonable 11:59:05
21 amount of time, but I -- I can't tell you exactly 11:59:06
22 what it was, even vaguely what it was, if I'm 11:59:11

Transcript of Graham Buckton, Ph.D.
Conducted on September 26, 2023

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1	honest. I don't remember.	11:59:15
2	Q A reasonable amount of time is 20 hours?	11:59:16
3	A I don't know. I mean, I don't want to	11:59:18
4	mislead you by giving you a number. If I say it's	11:59:20
5	20 and it's 40, that sounds bad, doesn't it? I	11:59:23
6	don't know what it was. Or if I say it was 20 and	11:59:26
7	it was ten, that's bad. I think it would be more	11:59:29
8	than ten. Quite a few iterations, and we had to	11:59:30
9	get to words that were my opinions and that I was	11:59:34
10	comfortable with. And that's what we've done in	11:59:36
11	the end.	11:59:40
12	Q You signed your declaration on	11:59:40
13	February 10, 2023, correct?	11:59:45
14	A Yes.	11:59:47
15	Q When did you draft it?	11:59:51
16	A Well, finished being drafted at that time.	11:59:54
17	I don't have any memory of it sitting around	11:59:59
18	waiting to be used. I think it was pretty much	12:00:01
19	just before we submitted it that we finished	12:00:08
20	the -- the iterations and the drafting. So I	12:00:12
21	would have signed it when it was done.	12:00:14
22	Q Did you start drafting it before the new	12:00:16

1	year last year?	12:00:18
2	A I don't know. I don't know. If it was, I	12:00:20
3	don't suppose it would have been much before, but	12:00:26
4	I don't know.	12:00:28
5	Q Did you talk to anybody from Apotex during	12:00:28
6	the preparation of your declaration?	12:00:41
7	A No.	12:00:42
8	Q Did you talk to anyone besides counsel	12:00:43
9	from Steptoe & Johnson?	12:00:49
10	A No. Sorry. I interrupted your question.	12:00:51
11	Did you get that?	12:00:53
12	The answer is no.	12:00:54
13	Q How much time did you spend reviewing your	12:00:56
14	declaration in preparation for your deposition	12:01:00
15	today?	12:01:02
16	A My declaration?	12:01:03
17	Q Yes.	12:01:05
18	A Maybe an hour or so.	12:01:06
19	Q Without revealing any privileged	12:01:11
20	information, I'm not looking for that, did you	12:01:16
21	prepare for your deposition today?	12:01:19
22	A Yes.	12:01:21

Transcript of Graham Buckton, Ph.D.
Conducted on September 26, 2023

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1	Q Did you meet with anyone?	12:01:22
2	A Yes.	12:01:26
3	Q Who did you meet with?	12:01:27
4	A These two guys, and also Michael.	12:01:28
5	Q How long did you meet with them?	12:01:33
6	A So we met yesterday and Sunday and	12:01:37
7	probably for maybe six or seven hours each day,	12:01:42
8	something like that.	12:01:49
9	Q At the beginning you talked about the fact	12:01:50
10	that in preparation for your deposition, you	12:02:01
11	reviewed some of the documents cited by	12:02:04
12	Dr. Berkland.	12:02:07
13	Do you remember that?	12:02:09
14	A Yes.	12:02:10
15	Q Do you have any recollection of what those	12:02:10
16	documents were?	12:02:12
17	A No. I don't remember the names of them or	12:02:12
18	particular exhibit numbers or anything like that,	12:02:16
19	but I looked at a couple of them, yes.	12:02:18
20	Q Do you remember what they were about?	12:02:20
21	A I think they were documents that he was	12:02:22
22	talking about stability. So I just looked to see	12:02:26

1 whether the documents made sense in relation to 12:02:29
2 what he was saying. 12:02:32

3 Q Did you have any impressions of those 12:02:33
4 documents? 12:02:35

5 A I think generally I thought they didn't 12:02:36
6 make sense in terms of my opinion, that they were 12:02:38
7 of no value and shouldn't be weighed seriously. 12:02:41

8 Q And why is that? 12:02:45

9 A I would have to look at the documents. So 12:02:46
10 that's not very helpful because I can't tell you 12:02:48
11 what you they are, but either they were documents 12:02:50
12 from a totally wrong animal model, like mouse 12:02:53
13 study or something, or they -- you know, they were 12:02:57
14 irrelevant because they were looking at some other 12:03:01
15 application. So I can't remember exactly. I 12:03:03
16 haven't looked at them over the last, you know, 12:03:06
17 recent moments, so I can't recall what they were 12:03:10
18 called. 12:03:15

19 Q What do you mean by they were looking at 12:03:15
20 some other application? 12:03:17

21 MR. GUPTA: Objection to form. 12:03:19

22 You can answer. 12:03:20

1 A Like, for example, long-term stability or 12:03:21
2 something like that, but I don't remember exactly 12:03:25
3 what they said now. I just -- to be honest, I 12:03:27
4 looked at them to say is there anything credible 12:03:29
5 here. I came to the conclusion there is nothing 12:03:32
6 credible here at all and then dismissed them 12:03:35
7 because I wanted to know if my opinions would be 12:03:37
8 needed to be adjusted based on anything that was 12:03:40
9 there, but they clearly didn't, because there was 12:03:43
10 nothing that was credible or valuable in them. 12:03:45

11 Q Do you know Dr. Berkland? 12:03:48

12 A No. 12:03:50

13 Q Have you ever encountered his name before? 12:03:51

14 A I've heard of his name. I don't know him. 12:03:53

15 Q In what context have you heard of him? 12:03:56

16 A Pardon? 12:03:58

17 Q In what context have you heard of him? 12:03:58

18 I'm sorry. 12:04:02

19 A I think I've seen another expert report 12:04:02
20 from him in another case. 12:04:04

21 Q Do you know what case that was? 12:04:05

22 A No. 12:04:07

1	Q Have you heard of him in any other	12:04:08
2	context?	12:04:14
3	A I don't think so, no.	12:04:15
4	Q You mentioned that you've been deposed	12:04:17
5	more than 20 times; is that right?	12:04:27
6	A That was a guess. I haven't totaled them	12:04:28
7	off, but they're on my CV, so I'm sure you have	12:04:31
8	them, if you're interested, you have them.	12:04:34
9	Q Have you testified at trial?	12:04:36
10	A Yes.	12:04:37
11	Q Have you ever testified at trial for a	12:04:38
12	generic drug company?	12:04:40
13	A Yes.	12:04:41
14	Q Have you ever testified at trial for a	12:04:42
15	brand drug company?	12:04:44
16	A Yes.	12:04:45
17	Q What drug company did you testify at trial	12:04:45
18	for that was a brand drug company?	12:04:47
19	A Silvergate.	12:04:49
20	Q Any others?	12:04:55
21	A Not gone to trial, but I've provided	12:04:58
22	advice and reports for branded drug companies, but	12:05:03

1	they've all settled. They didn't go to trial.	12:05:07
2	Q Is your testimony on behalf of Silvergate	12:05:12
3	Pharmaceuticals versus Bion Pharmaceuticals?	12:05:31
4	A I think that's right. I can't remember	12:05:35
5	what the other company was, but I think that	12:05:36
6	probably is right. I don't know. I can't	12:05:38
7	remember. I know it was Silvergate. I don't	12:05:39
8	remember who the other company were.	12:05:44
9	MR. GUPTA: Just for the record, I object	12:05:45
10	to this line under irrelevant -- irrelevant.	12:05:46
11	Go ahead.	12:05:49
12	BY MS. PETRUZZI:	12:05:51
13	Q Okay. What did you opine on in Silvergate	12:05:51
14	on behalf of Silvergate Pharmaceuticals?	12:05:55
15	MR. GUPTA: Okay. Objection to the extent	12:05:59
16	that calls for information that is subject to a	12:06:01
17	confidentiality agreement that you may have.	12:06:05
18	If you don't believe that it's subject to	12:06:09
19	a confidentiality agreement, then you can answer.	12:06:10
20	A So if something's been talked about in	12:06:12
21	court, is it still confidential?	12:06:15
22	Q No, it's public.	12:06:17

1	MR. GUPTA: Was it a public hearing or	12:06:18
2	not? I don't know if it was sealed, so...	12:06:20
3	A I genuinely don't know what was sealed or	12:06:23
4	what wasn't sealed, but it's a broad overriding	12:06:28
5	view. I talked about the obviousness or not	12:06:32
6	obviousness of a particular formulation.	12:06:34
7	Q Do you recall talking about degradation	12:06:36
8	processes in your testimony on behalf of	12:06:40
9	Silvergate?	12:06:43
10	A It would be part of it, yes.	12:06:47
11	Q Do you agree -- strike that.	12:06:49
12	Does pH matter for an oral formulation	12:08:33
13	because degradation processes can occur faster or	12:08:38
14	slower depending on what the pH of the solution	12:08:41
15	is?	12:08:44
16	MR. GUPTA: Objection. Outside the scope	12:08:46
17	of the expert report. Objection, relevance.	12:08:48
18	Objection, form.	12:08:51
19	You can answer.	12:08:52
20	A But I think we already talked about that	12:08:54
21	earlier today, and I said that pH, you would study	12:08:56
22	the degradation as a function of pH. So pH, yes,	12:09:00

1 you would study degradation as a function of pH. 12:09:03

2 Q And if there is degradation of the active 12:09:12
3 ingredient, you can lose part of the active 12:09:20
4 ingredient so that the drug becomes less potent, 12:09:26
5 correct? 12:09:29

6 MR. GUPTA: Objection. Outside the scope 12:09:29
7 of the expert report, form, relevance. 12:09:31

8 You can answer. 12:09:34

9 A We talked about that already. That's the 12:09:36
10 definition of a shelf life, is there a tolerable 12:09:40
11 loss of active ingredient which happens with every 12:09:43
12 product but doesn't cause a detrimental effect on 12:09:45
13 therapeutic properties. We talked about already, 12:09:50
14 I think. So I agree, shelf life is that. 12:09:52

15 Q Are you concerned about -- strike that. 12:09:55

16 During degradation of an active 12:10:00
17 ingredient, can there be degradation products? 12:10:02

18 MR. GUPTA: Objection. Form. Scope. 12:10:05
19 Relevance. 12:10:09

20 You can answer. 12:10:11

21 A Inevitably, if you have degradation, you 12:10:12
22 have degradation products. 12:10:16

1	Q Would a person of ordinary skill in the	12:10:17
2	art in 2008 consider degradation products in	12:10:22
3	formulating an oral formulation if it was known	12:10:29
4	that the product suffered from degradation?	12:10:37
5	MR. GUPTA: Objection. Outside the scope	12:10:40
6	of the expert report, form, and relevance.	12:10:44
7	You can answer.	12:10:47
8	A So if you plan to license your product and	12:10:49
9	take it to the market, you will study the	12:10:52
10	degradation products that are produced, yes.	12:10:56
11	Q Why would you study the degradation	12:10:58
12	products that are produced?	12:11:01
13	MR. GUPTA: Same objections.	12:11:03
14	You can answer.	12:11:03
15	A Because if they are present to any	12:11:07
16	significant level, you would need to demonstrate	12:11:09
17	their properties in terms of whether they're	12:11:12
18	therapeutically active or potentially toxic. So	12:11:15
19	you would need to understand their properties.	12:11:18
20	MS. PETRUZZI: I'd like to take a short	12:11:39
21	break.	12:11:41
22	THE VIDEOGRAPHER: Stand by. We are going	12:11:42

Transcript of Graham Buckton, Ph.D.
Conducted on September 26, 2023

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1	off the record. The time is 12:11 p.m.	12:11:47
2	(Recess.)	12:12:28
3	THE VIDEOGRAPHER: We are back on the	12:22:38
4	record. The time is 12:22 p.m.	12:22:42
5	MS. PETRUZZI: I have no further	12:22:45
6	questions.	12:22:46
7	MR. GUPTA: Okay. I need to take a break	12:22:47
8	to assess. We can go off the record.	12:22:50
9	THE VIDEOGRAPHER: We are going off the	12:22:56
10	record. The time is 12:22 p.m.	12:22:58
11	(Recess.)	12:23:45
12	THE VIDEOGRAPHER: We are back on the	12:52:19
13	record. The time is 12:52 p.m.	12:52:48
14	EXAMINATION BY	12:52:48
15	MR. GUPTA:	12:52:52
16	Q Good afternoon, Dr. Buckton.	12:52:52
17	A Good afternoon.	12:52:54
18	Q Doctor, I have a few questions for you	12:52:54
19	myself, if that's all right with you.	12:52:57
20	A Okay.	12:52:58
21	Q Just before I begin, is there anything	12:52:59
22	that you wanted to clarify regarding your earlier	12:53:04

1 testimony? 12:53:06

2 A When we broke -- just before we broke, you 12:53:07
3 were talking about degradation and degredance. I 12:53:13
4 just want to be clear that we were talking about 12:53:20
5 in the product. So yeah, what happens in the 12:53:22
6 shelf life of the storage of the product. And 12:53:24
7 that's why you qualify degredance in relation to, 12:53:27
8 you know, the regulatory submissions and such 12:53:34
9 things, which is vaguely what I remember we were 12:53:35
10 talking about before we broke. 12:53:40

11 Sorry. I just didn't want that to be 12:53:42
12 unclear that we were talking about within the 12:53:44
13 product itself. 12:53:46

14 Q Now I guess that leads me to my next 12:53:49
15 question. You were asked earlier in the 12:53:51
16 deposition about stability and degradation, 12:53:53
17 generally. 12:53:57

18 Do you remember that? 12:53:58

19 MS. PETRUZZI: Objection to form. 12:53:59

20 A We talked a few times about it, so I don't 12:54:00
21 know what specifically. 12:54:04

22 Q Do you remember discussing it in the 12:54:05

1	deposition earlier?	12:54:08
2	A Yes.	12:54:09
3	Q And was there anything about 5-azacytidine	12:54:10
4	that would have affected a POSA's motivation to	12:54:14
5	pursue a nonenteric tablet of azacitidine back in	12:54:19
6	2008?	12:54:24
7	MS. PETRUZZI: Objection to form.	12:54:24
8	A No. I talked about motivation previously,	12:54:28
9	including the Batchelor in silico calculations.	12:54:32
10	That would be motivation, but also the other prior	12:54:37
11	art documents, there was nothing that would stop	12:54:41
12	me from wanting to pursue a nonenteric tablet --	12:54:46
13	enteric-coated [sic] tablet.	12:54:50
14	Q Earlier in the deposition you were asked	12:54:52
15	about potential nontablet routes and formulations	12:54:55
16	in Ionescu.	12:55:01
17	Do any of those affect your opinions	12:55:02
18	regarding the nonenteric tablet formulation	12:55:04
19	disclosed by Ionescu?	12:55:08
20	MS. PETRUZZI: Objection to form.	12:55:10
21	A No, they don't.	12:55:11
22	Q Why do you say that?	12:55:13

1 A Well, they talked about the other dosage 12:55:15
2 forms that are there, but none of those affect my 12:55:18
3 consideration of enteric-coated tablet against 12:55:23
4 nonenteric-coated tablet, for example, which is 12:55:27
5 part of the analysis that I was looking at. 12:55:30

6 The other formulation was there, they 12:55:33
7 aren't enteric coated, so they don't affect my 12:55:36
8 opinions. 12:55:40

9 Q So just so we're all clear, in total, how 12:55:41
10 do you interpret Ionescu with respect to a 12:55:46
11 nonenteric-coated tablet formulation for 12:55:49
12 5-azacytidine? 12:55:52

13 MS. PETRUZZI: Objection. Form. 12:55:53

14 A Can you just repeat your question, please? 12:55:53

15 Q Sure. In total, how do you interpret 12:55:56
16 Ionescu with respect to a nonenteric-coated tablet 12:56:00
17 formulation of 5-azacytidine? 12:56:04

18 MS. PETRUZZI: Objection. Form. 12:56:08

19 A So the best I understand the question, 12:56:10
20 Ionescu discloses tablet formulations. It 12:56:13
21 discloses excipients that you would use in tablet 12:56:19
22 formulations, describes broadly how you would make 12:56:22

1 tablet formulations, and it also talks about you 12:56:25
2 could use them in a noncoated form, which 12:56:27
3 obviously is not enteric coated, and also you 12:56:31
4 could use them as a sugar coated form, which is 12:56:34
5 obviously not enteric coated. 12:56:37

6 So you have a wide disclosure. 12:56:39

7 Q As relating to 5-azacytidine? 12:56:46

8 MS. PETRUZZI: Objection to form. 12:56:48

9 A The reference is related to 5-azacytidine, 12:56:49
10 yes. 12:56:53

11 Q I'd like to turn your attention to the 12:56:57
12 Atadja reference. If you could put that in front 12:57:05
13 of you, please. It's -- 12:57:07

14 MR. GUPTA: For the record, it is 12:57:10
15 Exhibit 1004. 12:57:12

16 MS. PETRUZZI: Counsel, I believe it's 12:57:16
17 1005. 12:57:19

18 MR. GUPTA: I'm sorry. I'm looking at 12:57:36
19 Ionescu. 12:57:37

20 BY MR. GUPTA: 12:57:37

21 Q Did I say Atadja? 12:57:37

22 A You did. 12:57:39

1	Q I apologize. Let me -- let me re-ask the	12:57:41
2	question. Please strike that.	12:57:44
3	Can I direct your attention to Ionescu,	12:57:45
4	please, which is Exhibit 1004.	12:57:49
5	Are with you me, Dr. Buckton?	12:57:55
6	A Ionescu, yes.	12:57:58
7	Q Can we go to Page 14 of Ionescu. On	12:57:59
8	Page 14, earlier in the deposition you were asked	12:58:09
9	about the paragraph that spans lines 8 through 16.	12:58:14
10	Do you remember that?	12:58:24
11	A Yes.	12:58:25
12	Q Does that paragraph affect your view	12:58:26
13	regarding -- sorry, let me re-ask the question.	12:58:30
14	Does that specific paragraph somehow	12:58:36
15	affect your opinion regarding any of the other	12:58:39
16	sections of Ionescu as applicable to	12:58:41
17	nonenteric-coated tablet formulations?	12:58:45
18	MS. PETRUZZI: Objection to form.	12:58:47
19	A No, it doesn't.	12:58:48
20	Q You were asked earlier in the -- you can	12:58:51
21	put this aside.	12:58:55
22	You were asked earlier in the deposition	12:58:57

1 about film coats. 12:59:00

2 Do you recall that? 12:59:03

3 A Generally, yes. 12:59:04

4 Q Does the existence of film coats in 2008 12:59:05

5 affect your opinion that the sugar coat 12:59:11

6 formulation disclosed in Ionescu is nonenteric? 12:59:14

7 MS. PETRUZZI: Objection to form. 12:59:18

8 A No, Ionescu discloses sugar-coated tablets 12:59:19

9 which are not enteric-coated tablets. It also 12:59:25

10 discloses uncoated tablets, which are not 12:59:29

11 enteric-coated tablets. It doesn't disclose 12:59:34

12 film-coated tablets, which was the technology 12:59:37

13 which moved to replace sugar coating. That 12:59:39

14 doesn't affect my opinion. 12:59:44

15 Q Earlier in the deposition you were asked 12:59:45

16 about dose-escalation studies. 12:59:48

17 Do you remember that? 12:59:52

18 A Yes. 12:59:52

19 Q What is your opinion regarding the routine 12:59:53

20 nature of these studies as of 2008? 12:59:55

21 MS. PETRUZZI: Objection. Form. 12:59:58

22 A I'm not sure I entirely understand, other 12:59:59

1	than they are routine. That's something you would	13:00:02
2	do which is, I think, what we discussed. It was a	13:00:04
3	routine step you would progress through.	13:00:08
4	Q Earlier in the deposition Ms. Petruzzi	13:00:10
5	discussed the reference Atadja, and potential --	13:00:19
6	I'm sorry, let me rephrase the question.	13:00:29
7	Earlier in the deposition, Ms. Petruzzi	13:00:32
8	asked you about potential compositions discussed	13:00:38
9	in Atadja.	13:00:43
10	Do you remember that?	13:00:44
11	MS. PETRUZZI: Objection. Form. Scope.	13:00:45
12	A Yes, we did.	13:00:49
13	Q Do any of the formulations that she	13:00:54
14	discussed with you affect your opinion regarding	13:00:58
15	Atadja?	13:01:00
16	MS. PETRUZZI: Objection. Form.	13:01:02
17	A No. The -- I explained the use I put	13:01:03
18	Atadja to, and I maintain that.	13:01:08
19	Q Earlier in the deposition you were asked	13:01:13
20	about the Silvergate case in which you were an	13:01:16
21	expert.	13:01:20
22	Do you recall that?	13:01:21

1	A I remember talking about it, yes.	13:01:22
2	Q Do your opinions in the Silvergate case	13:01:26
3	relate in any way to your opinions here?	13:01:33
4	MS. PETRUZZI: Objection, form.	13:01:36
5	A That was about a liquid-dosage form, not	13:01:37
6	about a tablet, and not about an enteric-coated	13:01:40
7	tablet, and it was relating to the storage	13:01:44
8	stability of a liquid product, rather than	13:01:48
9	anything else. So no, it doesn't relate to what I	13:01:52
10	am opining on here.	13:01:55
11	MR. GUPTA: Okay. I have no further	13:01:58
12	questions.	13:02:00
13	MS. PETRUZZI: I'd like to take a short	13:02:01
14	break.	13:02:03
15	THE VIDEOGRAPHER: Stand by. We are going	13:02:03
16	off the record. The time is 1:02 p.m.	13:02:05
17	(Recess.)	13:02:09
18	THE VIDEOGRAPHER: We are back on the	13:04:07
19	record. The time is 1:04 p.m.	13:04:12
20	MS. PETRUZZI: Dr. Batchelor.	13:04:18
21	THE WITNESS: Or?	13:04:22
22	MR. GUPTA: Sorry. Wrong expert.	13:04:22

Transcript of Graham Buckton, Ph.D.
Conducted on September 26, 2023

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1	MS. PETRUZZI: We said Dr. Batchelor's	13:04:24
2	name.	13:04:26
3	EXAMINATION BY	13:04:26
4	MS. PETRUZZI:	13:04:26
5	Q Dr. Buckton, apologies.	13:04:26
6	A That's all right.	13:04:26
7	Q Counsel just asked you some questions.	13:04:29
8	Do you recall that?	13:04:31
9	A Yes.	13:04:31
10	Q There was a break before he asked you	13:04:33
11	questions.	13:04:34
12	Do you remember that?	13:04:35
13	A Yes.	13:04:35
14	Q Did you discuss the substance of this case	13:04:36
15	during that break?	13:04:39
16	A No. I said as we went out there was	13:04:40
17	something I wanted to say on the record when we	13:04:42
18	came back in, but that was all I said.	13:04:44
19	MS. PETRUZZI: I have no further	13:04:47
20	questions.	13:04:49
21	Counsel, just before we go off the record,	13:04:52
22	I do want the list of the documents that he	13:04:53

1 considered from Dr. Berkland's report. 13:04:55

2 MR. GUPTA: Well, our position is that he 13:05:01

3 was provided access to Dr. Berkland's report and 13:05:03

4 the exhibits, and he's here to answer any of your 13:05:05

5 questions in that regard right now. And so you 13:05:08

6 can go exhibit by exhibit and ask him the 13:05:11

7 questions, and he's available to answer those. 13:05:13

8 I don't have -- sitting here right now, I 13:05:16

9 don't have the specifics of what he reviewed and 13:05:19

10 what he didn't, but he was certainly provided 13:05:20

11 access to the Berkland declaration. 13:05:23

12 Secondly, I would like your position on 13:05:25

13 whether you believe deposition prep is fair game 13:05:27

14 for examination of a witness. Because I would 13:05:30

15 like your position on the record on that, so that 13:05:33

16 I can -- I can assess whether you -- whether -- 13:05:36

17 whether you believe you're going into deposition 13:05:41

18 prep appropriately or not. 13:05:43

19 MS. PETRUZZI: I'm sorry, I don't 13:05:45

20 understand your question. 13:05:46

21 MR. GUPTA: You're asking him what he did 13:05:47

22 for his deposition prep, which I allowed the 13:05:49

1 questions on. Now you're asking about specific
2 documents, which he said -- which he already
3 testified that he reviewed the Berkland
4 declaration. He was provided access -- I even
5 told you what he's provided access to.

6 So it's on you to ask him the questions.
7 I'm not being deposed here. So if you don't ask
8 him the questions, you're waiving those questions,
9 but I don't have an obligation to -- beyond what
10 I've told you, I don't have -- I don't have an
11 obligation to say anything else, as far as I
12 understand. If you tell me authority otherwise or
13 you're telling me that deposition prep is not
14 privileged, I'd like your -- I'd like your view on
15 that.

16 MS. PETRUZZI: Okay. I'll take that under
17 advisement.

18 THE VIDEOGRAPHER: Off the record. Stand
19 by. This marks the end of the deposition. We are
20 going off the record. The time is 1:06 p.m.

21 (Time Noted 1:06 p.m.)
22

13:05:51

13:05:54

13:05:56

13:05:58

13:06:00

13:06:03

13:06:05

13:06:08

13:06:10

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13:06:36

13:06:38

13:06:40

ACKNOWLEDGMENT OF DEPONENT

I, GRAHAM BUCKTON, 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.

(SIGNATURE)

(DATE)

1 CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

2 I, Anita M. Trombetta, RMR, CRR, and
3 Notary Public, and E-Notary Public within and for
4 the State of New York do hereby certify: That
5 GRAHAM BUCKTON, Ph.D., the witness whose
6 deposition is hereinbefore set forth, was duly
7 sworn by me before the commencement of
8 such deposition and that such deposition was taken
9 before me and is a true record of the testimony
10 given by such witness.

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

14 I further certify that the deposition of
15 GRAHAM BUCKTON, Ph.D., occurred at the offices
16 of Steptoe & Johnson LLP, on September 26, 2023,
17 commencing at 8:47 a.m. to 1:06 p.m.

18 I further certify that I am not related to
19 any of the parties to this action by blood or
20 marriage, I am not employed by or an attorney to
21 any of the parties to this action, and that I am
22 in no way interested, financially or otherwise, in

1 the outcome of this matter.

2
3 IN WITNESS WHEREOF, I have hereunto set my

4 Hand this 27th day of September, 2023.

5 My commission expires:

6 10.07.2025

7 
8 _____

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