

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

PADAGIS US LLC,

Petitioner, Case Nos. IPR2025-00464

vs. IPR2025-00465

NEURELIS, INC., IPR2025-00466

Patent Owner.

_____/

VOLUME I

DEPOSITION OF MAUREEN DONOVAN, PH.D.

CHICAGO, ILLINOIS

WEDNESDAY, DECEMBER 10TH, 2025

REPORTED BY:

DEBORAH HABIAN, RMR, CRR, CLR

JOB NO.: 11547

December 10, 2025

9:12 A.M. CST

Deposition of MAUREEN DONOVAN, PH.D.,
testifying at the law offices of Polsinelli
P.C., 150 North Riverside Plaza, Suite 3000,
Chicago, Illinois, 60606, USA, pursuant to
notice, appearing in person before Deborah
Habian, an Illinois Certified Shorthand
Reporter, Registered Merit Reporter, and
Certified Realtime Reporter.

A P P E A R A N C E S

ON BEHALF OF THE PETITIONER

POLSINELLI, P.C.

BY: MARK T. DEMING, ESQ.

150 North Riverside Plaza

Chicago, Illinois, 60606

(312) 819-1900

mdeming@polsinelli.com

ON BEHALF OF THE PATENT OWNERS

McDERMOTT WILL & SCHULTE LLP

BY: TIMOTHY BEST, PH.D., ESQ.

2049 Century Park East, Suite 3200

Los Angeles, California 90067-3206

(310) 277-4110

tbest@mwe.com

-and-

McDERMOTT WILL & SCHULTE LLP

BY: HANNAH HURLEY, ESQ.

650 Live Oak Avenue, Suite 300

Menlo Park, California 94025-4885

(650) 815-7400

hhurley@mwe.com

I N D E X

WITNESS: PAGE

MAUREEN DONOVAN, PH.D.

Examination by Mr. Best 7

INSTRUCTIONS AND REQUESTS OF COUNSEL

(none)

WITNESS CERTIFICATE 201

REPORTER CERTIFICATE 202

1 INDEX OF EXHIBITS

2 EXHIBITS TO MAUREEN DONOVAN, PH.D. DEPOSITION

3	NUMBER	DESCRIPTION	PAGE
---	--------	-------------	------

4	Exhibit 2100	USP document	38
---	--------------	--------------	----

6	Exhibit 2101	Cartt '784 Application	172
---	--------------	------------------------	-----

7		Publication No. US2008/0279784	
---	--	--------------------------------	--

10 PREVIOUSLY MARKED EXHIBITS

11	NUMBER	DESCRIPTION	PAGE
----	--------	-------------	------

12	Exhibit 1001-414	U.S. Patent 11,241,414	31
----	------------------	------------------------	----

14	Exhibit 1001-546	U.S. Patent 8,895,546	196
----	------------------	-----------------------	-----

16	Exhibit 1001-786	U.S. Patent 11,793,786	192
----	------------------	------------------------	-----

18	Exhibit 1008	Provisional Patent	179
----	--------------	--------------------	-----

19		Application, Administration	
20		of Benzodiazepine Compositions	

22	Exhibit 1009	International Publication	48
----	--------------	---------------------------	----

23		No. WO2009/120933	
----	--	-------------------	--

(CONTINUING)

PREVIOUSLY MARKED EXHIBITS

NUMBER	DESCRIPTION	PAGE
Exhibit 1010	Meezan et al. Application Publication No. US 2006/0046962	88
Exhibit 1012	Osborne et al. article	182
Exhibit 1016	Handbook of Pharmaceutical Excipients, 4th Edition, edited by R.C. Rowe, et al.	158
Exhibit 1026	Excerpt from Sigma Chemical Company book, 1988, titled Biochemical and Organic Compounds for Research and Diagnostic Reagents	150
Exhibit 1058	Sharma, et al. article	182
Exhibit 1062	Declaration of Maureen Donovan, Ph.D. re '786	50

1 (Oath administered at 9:12 a.m. CST.)

2 MR. BEST: Good morning, Dr. Donovan.

3 THE WITNESS: Good morning.

4 MR. BEST: Just to note for the record,
5 I'm joined by my colleague Hannah Hurley from
6 McDermott, and we may have another colleague who
7 is counsel in the case, David Tobin, who may
8 join us telephonically just to listen in.

9 I'd also note, by agreement of counsel,
10 this depo is being taken concurrently for three
11 different IPR proceedings, doing them all at
12 once, numbers IPR2025-00464, -465 and -466.

13

14 MAUREEN D. DONOVAN, PH.D.,
15 called as a witness herein by the patent owner,
16 having been first duly sworn, was examined and
17 testified as follows:

18 EXAMINATION

19 BY MR. BEST:

20 Q. Would you please state your full name
21 and your current mailing address for the record.

22 A. Maureen Donovan, and my mailing address
23 is 1607 Blain, B-L-A-I-N, Cemetery, all Es,
24 Road, Swisher, S-W-I-S-H-E-R, Iowa, 52338.

25 Q. Are you on any drugs or for any other

1 reason that you could think of that you would be
2 unable to give your best testimony today?

3 A. No.

4 Q. You've been deposed before, correct?

5 A. Yes, I have.

6 Q. So all the same admonitions apply. I
7 won't repeat them. I will just say that if
8 there's anything about one of my questions that
9 you find confusing or would like further
10 explanation, please ask. Otherwise, I'll assume
11 that you understood the question as asked.
12 Okay?

13 A. Um-hum.

14 Q. And you were retained to offer expert
15 testimony in these matters, correct?

16 A. I was retained to both consult on the
17 considerations and potentially offer testimony.

18 Q. You are a Professor at the School of
19 Pharmacy at the University of Iowa; is that
20 right?

21 A. Yes.

22 Q. I take it your education was also in
23 pharmacy and pharmaceuticals; is that right?

24 A. Yes.

25 Q. So studying pharmacy and pharmaceuticals,

1 is it fair to say that you had a substantial
2 instruction in organic chemistry?

3 A. I had a reasonable instruction, yes.

4 Q. How would you characterize your
5 instruction in organic chemistry?

6 A. You know, on par with, oh... I mean, I
7 have the kind of standard undergraduate
8 preparation in organic chemistry. As in my
9 pharmacy studies, we moved into -- it wasn't a
10 synthesis related kind of chemical reaction
11 based medicinal chemistry approach in pharmacy
12 education and I certainly haven't had that kind
13 of approach in the rest of my pharmaceuticals
14 education outside of chemical kinetics, for
15 example, and so that's why I sort of hesitate.

16 A typical organic chemist would have
17 far greater experiences, even at the bachelor's
18 level probably, in synthesis and mechanism than
19 I had in my education.

20 I have learned when I've needed to
21 learn more specifics about certain compounds, so
22 I have, you know, a reasonable understanding and
23 ability to use organic chemistry, but I wouldn't
24 say that I have the equivalent of a Ph.D. in
25 organic chemistry based on the work I've done.

1 Q. Got it. Thank you.

2 Did you -- even if it wasn't a focus,
3 did you conduct any organic synthesis during the
4 course of your education or training?

5 A. In laboratories, I did standard
6 sophomore level organic chemistry laboratory,
7 and probably nothing significant since then.

8 Precipitating a free base form is
9 probably about as far as we go. Otherwise, I
10 usually try to collaborate with chemists who are
11 far better prepared and have the right equipment
12 to do anything that we might need to do.

13 Q. Fair enough. You lead a research
14 program at Iowa or at least have led; is that
15 correct?

16 A. Yes.

17 Q. And do you still lead it?

18 A. Yes.

19 Q. What is the nature of the research your
20 group performs?

21 A. We -- I mean, my research interests are
22 in understanding mechanisms of drug absorption
23 and the interplay between those mechanisms and
24 formulations and how we can use formulations and
25 materials to optimize absorption from a

1 particular site.

2 I typically focus on mucosal sites of
3 delivery, but I've done some work that's been
4 oriented towards topical delivery also, topical
5 to the skin delivery.

6 Q. So when you say "site," you're
7 referring to the location of the body at which
8 the drug is administered; is that fair?

9 A. Yeah, that's fair.

10 Q. Have you an understanding of what a
11 small molecule is in the context of
12 pharmaceuticals?

13 A. Yes.

14 Q. What is the understanding you would
15 convey in that regard?

16 A. Typical small molecule is both -- you
17 can somewhat define it by molecular weight, but
18 molecular weight plus structure. It doesn't
19 necessarily have an amino acid sequence or a
20 derivative of an amino acid sequence that at the
21 higher molecular weights, above a thousand or
22 so, you would start referring to those as
23 peptides. Peptide mimics are going to be a
24 little on the -- in the gray area.

25 But, otherwise, small molecule,

1 something typically less than about 800 in
2 molecular weight. Molecular weights keep
3 creeping up in the small molecule world. But in
4 organic chemical, usually that is intended to
5 likely act at a receptor or influence a cell or
6 something is our -- is the definition or the
7 genre of sort of small molecule drug design or
8 drug use.

9 Q. You mentioned that molecular weights
10 are creeping up in the small molecule world.
11 Would you say that the scope of a small molecule
12 in 2008 or 2009 is the same as now, lower than
13 800, as you say, or something else?

14 A. I think the small -- the common-use
15 small molecule phrase is -- I don't know that
16 it's really changed that much in the last
17 fifteen years, but I'm trying -- because
18 Lipinski's Rule showed up in the early 2000s.
19 Yeah, even then, I think people have seen
20 success with organically-synthesized molecules
21 with an identified target that are, you know, in
22 the certainly above 500 and maybe even above 750
23 range that have been successful.

24 So they've opened up that -- the
25 definition, and I think even in 2009, that was

1 probably fair to say.

2 Q. So it'd be fair to say it was about the
3 same in 2008, 2009 as now; is that --

4 A. Probably, because again it's gray. It
5 depends on the actual chemical structure. If
6 it's intended to mimic a protein structure or a
7 segment of a protein, or now a nucleotide
8 structure, that puts you sometimes into a
9 different consideration outside of merely
10 molecular weight.

11 Q. Does your research group perform its
12 work -- withdrawn.

13 Does your research work focus its work
14 on small molecules?

15 A. We've certainly worked with more small
16 molecules than we have with proteins and
17 peptides. A lot of that's cost driven, that
18 they're just -- proteins and peptides are more
19 expensive to use, and they may not have been the
20 appropriate type of molecule for the
21 investigations we were trying do into
22 mechanisms.

23 We did look at protein and peptide
24 metabolism in the nasal cavity many, many years
25 ago. So we've worked with those. Even as a

1 graduate student, I've looked at proteins and
2 their absorption, and we've probably -- you
3 know, we've looked at glucagon off and on.

4 So I would say we're not exclusively a
5 small molecule lab, but it's whatever molecule
6 is suitable to use as something to, you know,
7 drive the mechanistic understanding that we're
8 trying to approach.

9 Q. So it's fair to say your lab works on
10 small molecules but doesn't limit its work to
11 small molecules? Is that fair?

12 A. I think that's fair, yes.

13 Q. You referred to peptides and nucleic
14 acids. Would you consider those to be large
15 molecules, macromolecules? Is there some way
16 you would refer to them?

17 A. I think peptides is where it's gray. I
18 think it's still -- with the nucleosides, I
19 would still consider those macromolecules, but,
20 you know, there's probably somebody that's got
21 an SRA sub thing that it might start approaching
22 a small molecule. I just don't keep that close
23 a tab on that.

24 But, you know, there's -- even within
25 the protein and peptide world, people are --

1 have a pretty spectrum-based definition
2 depending on which side -- you know, if they're
3 in the antibody world, they're going to view
4 sort of a molecular weight of when you start
5 protein structure to be different than people
6 who are in the protein mimic and smaller subunit
7 protein world.

8 So, you know, I don't know that I can
9 give you a definition of where one starts and
10 where the other ends. It's in the eye of the
11 beholder.

12 Q. Fair enough. In your role as a
13 Professor at Iowa, it looks like from your CV
14 you've taught a fair number of classes; is that
15 right?

16 A. Yes, I have.

17 Q. Is organic chemistry a part of the
18 curriculum you teach in any of those classes or
19 have taught?

20 A. Not specifically organic chemistry. I
21 have taught ionic equilibria and the functional
22 group analyses of the drug compounds that our
23 students would likely see in their practices or
24 even our graduate students should know about,
25 and so that's both the functional group analysis

1 and the more ionic equilibria, yes. But, again,
2 from a chemical synthesis, SAR is not something
3 I teach.

4 Q. Now, the proceedings for which Padagis
5 asked you to consult and offer opinions concern
6 three patents you've looked at, right?

7 A. Yes.

8 Q. And the claims on those patents which
9 you've offered opinions all cover pharmaceutical
10 solutions, fair?

11 MR. DEMING: Objection to form.

12 THE WITNESS: I mean, the -- at least
13 pharmaceutical solutions.

14 BY MR. BEST:

15 Q. Those solutions include a number of
16 components, including alkyl glycosides, correct?

17 A. I'm not sure that all of them are
18 specific to or specifically identify alkyl
19 glycosides, but they -- but several of them do
20 specifically identify alkyl glycosides.

21 Q. And when you say "specifically
22 identify," what do you mean by that?

23 A. That the word "alkyl glycoside" appears
24 in the text.

25 Q. Got it. Some of the claims you believe

1 state "alkyl glycoside" as such and others
2 doesn't say that; is that your point?

3 A. I mean, that's partially what I was
4 trying to communicate. I think if we're going
5 to talk about details of those patents, it'd be
6 best I have them front of me so I can be as
7 accurate as possible.

8 Q. Fair enough. And more generally, you
9 should feel free to look at anything today that
10 you want to in answering any of my questions. I
11 want your best testimony.

12 You have encountered alkyl glycosides
13 in the course of your own research, correct?

14 A. Yes.

15 Q. And at a high level, would it be fair
16 to characterize an alkyl glycoside as
17 components, an alkyl and a glycoside component?

18 A. I believe that's actually how one of
19 the specification describes them.

20 Q. Fair enough. I'd like to focus first
21 on the alkyl component. You're familiar with
22 alkyl groups and alkanes more generally,
23 correct?

24 A. Familiar enough, yeah.

25 Q. What is your understanding of what an

1 alkane is?

2 A. An alkane is -- this is going to be
3 probably even unacceptable in an organic
4 chemistry course, but a saturated carbon-carbon
5 linked system. So it's a -- in the context of
6 these patents, the alkyl chain is a -- it's a
7 carbon-carbon-carbon length of, you know,
8 approaching 10 maybe or more carbons, and I'd
9 actually have to go back and review when they --
10 what the -- when they saturate- -- when
11 saturated and unsaturated, the name changes
12 slightly. I just don't remember exactly the
13 nomenclature.

14 Q. Okay, when you say "saturated," do you
15 refer to carbon-carbon double or triple bonds?

16 A. Yes.

17 Q. So as you understand it, an alkane
18 would be a chain of carbon-carbon single --
19 withdrawn.

20 As you understand it, alkanes would be
21 compounds that have carbon-carbon bonds that are
22 always single bonds and something else?

23 A. No, that's -- I mean, that's my
24 understanding because alkenes are the
25 double-bonded analogs. And after that, I'd need

1 to refer to my organic chemistry textbook
2 because naming, nomenclature standards is not
3 something that I focus on.

4 Q. In general, I reckon you're familiar
5 with the notion in nomenclature of alkanes where
6 you name the alkane in coordination with the
7 number of carbons that are in the alkane; is
8 that fair?

9 A. There's, yeah, some situations where
10 that's generally done, yes.

11 Q. So, for example, you would append the
12 Greek prefix penta to a 5 carbon alkane, right?

13 A. Yes.

14 Q. And hexa for 6, hepta for 7, and so
15 forth?

16 A. Yes.

17 Q. The information we've been discussing
18 about alkanes, would it be fair to say that was
19 known to a person of ordinary skill in the art
20 in 2008 and 2009?

21 MR. DEMING: Objection to form.

22 THE WITNESS: So what an alkane is and
23 the kind of nomenclature regarding number of
24 carbons in the chain?

25

1 BY MR. BEST:

2 Q. Yes.

3 A. Yes.

4 Q. Alkanes -- withdrawn.

5 An alkyl group is an alkane that's been
6 appended to some other moiety, correct?

7 A. I guess I'll accept that as a starting
8 definition.

9 Q. Fair enough. Alkanes and alkyl groups
10 can isomerize, correct?

11 A. Well, they can appear in isomeric
12 forms, yes.

13 Q. Okay. And what is your understanding
14 of what an isomer is in terms of alkanes and
15 alkyl groups?

16 A. That it relates to the stereochemistry
17 around the carbon, that the mirror images are
18 not super impose-able. And beyond that, I
19 usually go and make sure I'm using the terms
20 correctly.

21 Q. And is it fair to say another form of
22 isomerization is whether an alkane is branched
23 or unbranched?

24 A. Again, now I'd need to go and refer to
25 something that describes the correct terminology

1 for isomers to answer that question.

2 Q. Fair enough. But you would accept that
3 an alkane of a given number of carbons can be
4 either linear or branched, fair?

5 A. Yeah. Yes.

6 Q. And, in fact, assuming there are enough
7 carbons, there could be multiple branches in a
8 carbon-carbon -- withdrawn.

9 In fact, there could be multiple
10 branches in an alkane of the same number of
11 carbons as a linear alkane, correct?

12 A. You know, I'm not sure. I don't know
13 how who to answer that. I haven't thought about
14 that and the nomenclature systems.

15 Q. Okay. If I use the term "structural
16 isomer" to refer to the notion that an alkane of
17 a given number of carbons could be either linear
18 or branched in one of various ways, will that
19 make sense to you as in my questioning?

20 A. Could you repeat what you're going to
21 use as your definition.

22 Q. Structural isomer.

23 A. Okay, but repeat what you're saying a
24 structural isomer is.

25 Q. Sure. For example, octane is an

1 8-carbon alkane, correct?

2 A. That's my understanding, yes.

3 Q. And octane could be linear, correct?

4 A. Yes.

5 Q. Or octane could be branched, let's say,
6 carbon-carbon, and then that -- the third carbon
7 is connected to two different carbons which then
8 terminate, correct?

9 A. I'm not sure at this point.

10 Q. Okay. Different isomers of a given
11 compound can have different chemical and
12 physical properties, fair?

13 A. I mean, they can certainly have
14 different crystal packings, which lead to
15 different physical properties, disparate
16 chemical properties. They certainly have
17 different biochemical properties.

18 How likely it is that their chemical
19 properties are going to be significantly
20 different I think is a little bit more dependent
21 on exactly what the isomeric change is.

22 Q. When you say the biochemical properties
23 can differ, what do you mean by that?

24 A. Well, often, especially at -- in
25 enzyme-based reactions, the ability of one

1 isomer versus another to actually interact well
2 with an enzyme, it may be influencing -- it may
3 not, but there are times where the enzyme will
4 only process one of the forms.

5 Q. And then enzyme is a protein --
6 withdrawn.

7 How would you define an enzyme?

8 A. An enzyme is a biological molecule that
9 is -- it works -- its working action is
10 typically to cause a chemical change in an
11 endogenous or exogenous substance or the
12 advantage of the body -- or to clear and as a
13 safety protection, a whole bunch of different
14 reasons why the body would want to chemically
15 change a material that either it produced or
16 that has been brought into it.

17 Q. And if I understood your testimony
18 correctly, the reason why an enzyme might
19 interact with different isomers differently
20 relates to some amount of shape specificity to
21 the interaction between them; is that fair?

22 A. Yes, that's fair.

23 Q. Is that a general principle where
24 different substances having different structures
25 tend to interact with proteins differently?

1 A. Please can you repeat that.

2 Q. Sure. Is it a general principle in
3 your experience that different isomers of a
4 given substance will interact with different
5 proteins in a different fashion?

6 MR. DEMING: Objection to form.

7 THE WITNESS: I think that entirely
8 depends on what the protein-drug interaction
9 really is.

10 BY MR. BEST:

11 Q. So it would depend on the protein in
12 question and the substance in question; is that
13 fair?

14 A. Yes.

15 Q. Would you agree with me that a larger
16 alkane or alkyl group can form more different
17 isomers than a shorter alkane or alkyl group?

18 A. So longer and shorter context is more
19 number of carbons and less number of carbons?

20 Q. Exactly.

21 A. Well, the increasing the number of
22 carbons increases statistically the chances of
23 an isomeric form.

24 Q. When you say "increases statistically
25 the chances of different isomeric forms," what

1 do you mean by that?

2 A. Well, just that, depending on the
3 molecule, if you've got more carbons and you
4 have more -- other functional groups being
5 attached to those carbons or other structure
6 around those carbons, you increase the
7 likelihood that you will also have isomeric
8 forms.

9 So it's just a matter of more carbons
10 and more chances that one of those carbons or
11 the new carbon or however you want to call that
12 could possess -- could be an isomeric form.

13 Q. Got it. Is it fair to say the
14 information we, you and I, have discussed about
15 isomerization and the different structures that
16 a given compound can have and how they interact
17 either the same or differently with proteins was
18 knowledge available to a person of ordinary
19 skill in 2008 and '9?

20 MR. DEMING: Objection to form.

21 THE WITNESS: Yes, I mean, there was --
22 there would be ready access to textbook-level
23 information about all of those concepts.

24 BY MR. BEST:

25 Q. As I mentioned -- withdrawn.

1 As we agreed, at least some of the
2 claims recite alkyl glycosides, the claims of
3 the patents-in-suit. I'd like now to focus on
4 the other portion, the glycoside portion of the
5 molecule. Withdrawn.

6 What is your understanding of what a
7 glycoside is?

8 A. Again, it's -- my initial, not
9 equivalence, but it's going to be something in
10 the saccharide family.

11 The -- again, the specification does a
12 nice job of defining -- specification and
13 probably Meezan, one of the references I cited,
14 does a nice job of describing what -- their
15 terminology regarding alkyl glycosides and the
16 glycosidic portion and so forth.

17 And if I can take a look at that, I
18 can -- I was happy to adopt that definition in
19 my use. It was entirely consistent with my
20 understanding, but much more well written than I
21 would have done it at the time.

22 Q. Fair enough. And we, I assure you,
23 will be reviewing that in the fullness of time.

24 Is it fair to characterize -- you
25 said -- withdrawn.

1 You said "saccharides." Do you mean by
2 that a form of carbohydrate?

3 A. It could be -- again, the nomenclature
4 around carbohydrate, saccharides,
5 polysaccharides, I -- there's a mixture of
6 convention, there's a mixture of chemical
7 accuracy, there's a -- yeah, I need something in
8 writing in some text to make sure that I'm
9 actually expressing the correct terminology for
10 those if we're naming them.

11 Q. Fair enough. And I'm really speaking
12 in generalities at this point.

13 Is it fair to say that glycosides or
14 saccharides can either be cyclized or not
15 cyclized?

16 A. Well, they're certainly --
17 monosaccharides are drawn cyclized or
18 noncyclized.

19 I'm not sure about a linear saccharide
20 sequence in a molecule being called a
21 saccharide, but -- I'd be willing to accept that
22 if I was provided a text that was of, you know,
23 reasonable quality, but it's just not something
24 that off the top of my head I think about.

25 Q. Sure. Fair enough. But you would

1 agree that glycosides or saccharides certainly
2 can be cyclic, fair?

3 A. Yes.

4 Q. And that means that they have a ring
5 structure, fair?

6 A. Yes.

7 Q. And a saccharide could have or a
8 glycosides could have more than one ring as a
9 portion of the glycosides or saccharide,
10 correct?

11 A. Yes, polysaccharides.

12 Q. Yeah. There are many types of
13 saccharides or glycosides known to chemists,
14 right?

15 A. Well, many different structures with
16 many different names that would fall into the
17 general category of a saccharide or
18 polysaccharide, yes.

19 Q. Is it correct to say a glycoside or
20 saccharide can have different isomeric forms,
21 for instance, different stereoisomers, as you
22 referred to earlier?

23 A. Yeah, it's -- yes, it's my
24 understanding that it can.

25 Q. Often they're called D- or L-glycosides

1 or saccharides, right?

2 A. I think that's a -- an older naming
3 convention now, but yes.

4 Q. And we'll skip what that stands for.

5 A. Dexter and laevus.

6 Q. Indeed. Sinister and rectus.

7 Are you also familiar with the concept
8 of alpha and beta in the context of glycosides
9 and saccharides?

10 A. I'm familiar with the use of those
11 terms, yeah. With saccharides, yes.

12 Q. And the concept of alpha and beta is
13 sometimes referred to as anomers or anomerism;
14 is that right?

15 A. That, I'd have to check it. I know the
16 term, but I would have to look that definition
17 up.

18 Q. Fair enough.

19 Okay, is it fair to say that glycosides
20 or saccharides can be substituted with
21 heteroatoms, for example, sulfur?

22 A. Substituted where?

23 Q. Let's say for an oxygen atom that's
24 otherwise a part of the saccharide.

25 A. Okay. Yes, there are times where I've

1 seen that chemical change, yes.

2 Q. So what would be a glycoside could be
3 called a thioglycoside in that circumstance,
4 fair?

5 A. I'll accept that. Seems reasonable.

6 Q. Yeah. And the discussion we've had of
7 glycosides and saccharides, this is all
8 information that was available to a person of
9 ordinary skill in 2008, 2009 just as today,
10 fair?

11 A. Yeah, there would have been textbook
12 descriptions of those characteristics, yes.

13 Q. We've spent a fair amount of time now
14 discussing alkyl glycosides. I would like to
15 move on to a different portion of the
16 pharmaceutical compositions that are the subject
17 of some of the claims in this case. Okay?

18 A. Okay.

19 Q. So at least some and perhaps all of the
20 claims that you've reviewed require one or more
21 alcohols, correct?

22 MR. DEMING: Objection to form.

23 THE WITNESS: Some or all of the
24 compositions in the claims?

25 MR. BEST: Yes.

1 THE WITNESS: Of the claims. Yeah, I
2 don't know that I looked at the claims in that
3 light. So if I see the claims, I could tell you
4 whether I thought nearly all of them included
5 that.

6 MR. BEST: We can look at one of them
7 if it's helpful. It's already marked.

8 BY MR. BEST:

9 Q. I'll hand you what's already been made
10 part of the record in this proceeding as
11 Exhibit 1001. And I'll note it's Exhibit 1001
12 in the -465 proceeding, so I'll refer to it as
13 "1001-414" because it's the '414 patent, if that
14 makes sense to you.

15 A. It does. And if somebody can provide
16 me a pen, I can write that so I don't always
17 have to say: You mean the '414 patent, right?

18 Q. Fair enough.

19 MR. DEMING: Not sure what color you
20 want.

21 THE WITNESS: I'm going to be
22 traditional. This is black.

23 You're going to refer to this
24 (indicating to document) as 1001-414?

25 MR. BEST: Yes.

1 THE WITNESS: Okay.

2 BY MR. BEST:

3 Q. And you can turn to the last page of
4 the patent, which I believe contains the claims.

5 A. (Witness complying.)

6 Q. Feel free to take your time to look at
7 them, but I'll ask you about alcohols.

8 A. (Reviewing document.)

9 Okay, want to re-ask the question?

10 Q. Of course. My only question is that at
11 least some and perhaps all of the claims that
12 you've reviewed require one or more alcohols,
13 correct?

14 A. Well, Claim 1 identifies ethanol and
15 benzyl alcohol, and those would be understood to
16 be defined as alcohols. And all of the rest of
17 the claims are dependent on Claim 1 or another
18 claim that's dependent on Claim 1, so all of the
19 claims refer to that ethanol and benzyl alcohol
20 description in Claim 1.

21 Q. Well, what is your understanding of
22 what defines what an alcohol is?

23 A. Oh, it's a beginning-level definition.
24 It has a hydroxyl group associated with it.
25 Just because it has a hydroxyl group doesn't

1 necessarily mean it will be identified as an
2 alcohol.

3 Q. Got it. Ethanol or ethyl alcohol,
4 which you referred to a moment ago, is a
5 commonly-referred to alcohol, right?

6 A. Yes.

7 Q. Including in our cocktails at 5:00,
8 perhaps.

9 One of the characteristics of ethanol
10 is that it mixes well with water, correct?

11 A. It's known to be miscible with water,
12 yes.

13 Q. And when you say "miscible," what do
14 you mean by that?

15 A. That it's mixable in all proportions.

16 Q. Is one of the consequences of ethanol
17 being miscible with water that it's very hard to
18 remove all of the water from a solution of
19 ethanol and water?

20 MR. DEMING: Objection to form.

21 THE WITNESS: I don't know that I would
22 agree with the cause and effect there, but it is
23 true that it is difficult, with distillation
24 separation in particular, to separate ethanol
25 from water.

1 BY MR. BEST:

2 Q. Is it correct that ethanol is often
3 referred to in terms of proof?

4 A. In non-pharmaceuticals, it -- more
5 typically, but even in pharmaceutical
6 descriptions sometimes. But you will see the
7 ethanol concentrations described as proofs
8 outside of the pharmaceutical realm in the
9 alcohol -- in the ingestible alcohol realm
10 pretty frequently.

11 Q. Is it correct that a proof number is
12 roughly twice the percentage of ethanol that
13 would be in the composition that includes
14 ethanol?

15 A. That's the standard working definition
16 I'm familiar with.

17 Q. Okay. And in general -- withdrawn.

18 In the course of your research, do you
19 purchase ethanol from suppliers such as Sigma or
20 the like?

21 A. Purchase ethanol?

22 Q. Yes.

23 A. I'm trying to actually remember. The
24 source changed. The University of Iowa has a
25 unique, or at least I think it's unique, way of

1 distributing alcohol or ethanol on campus.

2 My unit is actually responsible for all
3 of the absolute ethanol storage, distribution,
4 documentation on campus, and so, no, I don't
5 have to order it from Sigma. But I'm trying to
6 remember if the lower proofs -- I just don't
7 remember whether we actually get them from
8 off-campus suppliers or whether that's all
9 locally supplied, contained and documented. I
10 just don't remember.

11 Q. Locally supplied in the sense that
12 there's a fair amount of corn, and therefore,
13 distilleries locally or --

14 A. Well, no, not necessarily, but just if
15 we -- if my unit is the holder of all absolute
16 ethanol on campus, I don't know whether other
17 associated units also are sort of the on-campus
18 suppliers. We have restricted purchasing on my
19 campus.

20 Q. Yeah.

21 A. And so I -- there's nothing -- I'm not
22 trying to say you couldn't buy it from Sigma.
23 I'm saying I might not be able to buy it from
24 Sigma.

25 Q. Yeah, fair enough. I think most

1 campuses have strict limitations on buying
2 absolute ethanol for some obvious tax and other
3 reasons.

4 A. Um-hum.

5 Q. I know that mine did when I was doing
6 this sort of thing.

7 A. Yeah, and even anything that's not
8 denatured.

9 Q. Yeah. When you say "absolute ethanol,"
10 what do you mean by that?

11 A. I mean that it is what USP describes as
12 dehydrated ethanol. So it is the -- as close to
13 100 percent ethanol as possible, sometimes
14 viewed as 100 percent. It can have a slightly
15 lower percentage than that.

16 Q. And what makes up the balance of the
17 percentage if it has less than 100 percent?

18 A. It's typically water, but it may be
19 other substances also.

20 Q. Is absolute ethanol referred to as
21 "200 proof"? Is that another way of referring
22 to it?

23 A. I think in the alcoholic beverage
24 world, yes, but I have never really checked to
25 make sure.

1 Q. Fair enough. Is it correct to say that
2 the discussion we've had about ethanol and ethyl
3 alcohol and its composition was known to a
4 person of ordinary skill in 2008 and '9, just as
5 today?

6 A. It certainly -- the terms were known.
7 The specific definitions around those terms
8 changed slightly, especially in the
9 pharmaceutical world. And so I -- and I'm not
10 aware of whether there has been a slight change
11 to the terminology definitions, percentages of
12 alcohol or ethanol in that system in the U.S.,
13 Europe and Japan, Australia, wherever, since
14 2009. I don't keep track of the official
15 changes.

16 Q. Fair enough. Feel free to review the
17 claims, if that's helpful, but in addition to
18 the alkyl glycosides we've discussed and
19 alcohols we've discussed, at least some, and
20 perhaps all, of the claims require some form of
21 tocopherols, for example, Vitamin E, correct?

22 A. Yes, because Claim 1 describes what a
23 more natural or synthetic tocopherols or
24 tocotrienols and the percentage range, and since
25 the rest of the claims are dependent on Claim 1,

1 they all describe something that contains a
2 tocopherol.

3 Q. You're familiar with tocopherols in
4 Vitamin E through the course of your training
5 and experience, right?

6 A. Yes.

7 MR. BEST: Can we see what I'm going to
8 have marked as Exhibit 2100. This will have to
9 be marked.

10 (Exhibit 2100 was marked for
11 ID.)

12 BY MR. BEST:

13 Q. I'll note for the record that this
14 document was marked Exhibit 1066, but it was
15 only marked in the '786 proceeding, which I
16 think is -466. So to make it of record for
17 purposes of the deposition which covers all the
18 proceedings, I'm going to give it a new number,
19 2100.

20 A. Okay.

21 Q. This is a document that you referred to
22 as the -- as I think colloquially called "USP,"
23 correct?

24 A. Yes.

25 Q. And you reviewed and referred to this

1 document in the course of forming your opinions
2 in this case, right?

3 A. Yes.

4 Q. Can I ask you to turn in this document
5 to page -- what would be marked in the original
6 book as 1631.

7 A. All right.

8 Q. And I'd direct your attention to the
9 top of the right-hand column of this page.

10 Do you see that?

11 A. Yes.

12 Q. There's a notation here concerning
13 "Vitamin E," correct?

14 A. Yes.

15 Q. And does -- withdrawn.

16 Do you understand this to refer to the
17 Vitamin E and tocopherol we were discussing a
18 few moments ago?

19 A. It's certainly part of that group, yes.

20 Q. Fair enough.

21 I'd direct your attention to the note
22 that says "Packing and Storage" -- "Packaging
23 and Storage."

24 Do you see that?

25 A. Okay.

1 Q. It says that Vitamin E should quote --
2 withdrawn.

3 It says that one should "preserve in
4 tight containers."

5 Do you see that?

6 A. Yes.

7 Q. And it also says to quote -- withdrawn.

8 It also says that one should keep it
9 "protected from light."

10 Do you see that?

11 A. As part of that sentence, yes.

12 Q. And it also says that one should
13 protect tocopherol "with a blanket of an inert
14 gas."

15 Do you see that?

16 A. Yes. Or alpha -- the D and L --
17 DL-alpha-tocopherol, yes.

18 Q. Got it. Do you have an understanding
19 as to why the USP directs one to undertake these
20 actions with respect to Vitamin E?

21 A. I have a presumption about why. I
22 would look at some additional chemical details
23 about tocopherol and DL-alpha-tocopherol to
24 confirm, but my working estimation is that it's
25 because the DL-alpha-tocopherol and other

1 tocopherols may be subject to oxidation.

2 Q. And by "oxidation," you mean the oxygen
3 and air can have a chemical reaction with it; is
4 that right?

5 A. That's one way that oxidation can
6 happen, yes.

7 Q. Fair enough. And apparently, light
8 could also have an effect on those chemicals; is
9 that right?

10 A. Again, it -- light sometimes catalyzes
11 oxidation reactions.

12 Q. Would other compounds than oxygen if
13 mixed with tocopherol also potentially have
14 chemical reactions with it?

15 A. There --

16 MR. DEMING: I'm sorry, objection to
17 form.

18 THE WITNESS: There's certainly a
19 possibility that chemical interactions will
20 happen between compounds in mixtures.

21 BY MR. BEST:

22 Q. How would one of ordinary skill assess
23 the effect of mixing a compound with tocopherol,
24 Vitamin E as it's listed here?

25 A. Assess what?

1 Q. Whether or not there was a reaction,
2 and if so, what kind of reaction?

3 MR. DEMING: Objection to form.

4 THE WITNESS: Sometimes visual
5 observation is enough to indicate. If you
6 are -- you desire to have a quantitative
7 estimate, you can perform chemical assays
8 oftentimes on the mixture. You can perform
9 those over the course of time to determine
10 whether the two -- two or more, whichever
11 substances were in the mixture to start with,
12 whether their concentration is changing, whether
13 there's an appearance of additional substances
14 that weren't in the original mixture is
15 typically how from -- at least from a
16 pharmaceutical standpoint one would first try to
17 determine or -- I mean, and there are others.
18 There are DSC methods and other methods that
19 might be used as an initial evaluation of
20 potential interactions.

21 BY MR. BEST:

22 Q. When you say "DSC," is that
23 differential scanning calorimetry?

24 A. Yes.

25 Q. Were the methods you just discussed

1 known generally to a person of ordinary skill in
2 the art as of 2008 or 2009?

3 A. Well, the methods themselves were
4 known. Specific applications of those methods
5 to specific chemicals or mixtures may or may not
6 have been.

7 Q. Is the -- withdrawn.

8 Another component -- you can set that
9 document aside.

10 A. (Witness complying.)

11 Q. Another component of the claims you've
12 reviewed is a benzodiazapine or in some cases
13 particularly diazepam, correct?

14 A. Well, again, I'll use the 1001-414
15 patent specifically about this Claim 1 describes
16 diazepam as a component of the pharmaceutical
17 solution.

18 Q. Now, earlier today we discussed the
19 concept of a small molecule. Do you recall that
20 testimony?

21 A. Yes.

22 Q. Would you consider diazepam a small
23 molecule?

24 A. I would consider it a small organic
25 molecule, yes.

1 Q. And would a person of ordinary skill
2 believe the same, let's say, in 2008 or '9?

3 A. Yes.

4 Q. One characteristic of diazepam is that
5 it is lipophilic, correct?

6 A. As the -- as the un-ionized form, most
7 people would characterize it as lipophilic. It
8 has a sufficiently high Log P value to usually
9 be characterized as lipophilic.

10 Q. When you say "Log P," is that the
11 octanol-water partition coefficient?

12 A. Experimentally, initially, it started
13 out as that. Now typically use some sort of
14 algorithm-based predictor to calculate it, but,
15 yes, a relative octanol solubility to relative
16 water solubility was the starting definition for
17 Log P.

18 Q. Is that concept sometimes referred to
19 as "the partition coefficient"?

20 A. Yes.

21 Q. And at least in theory, a higher
22 number -- withdrawn.

23 The higher Log P value means a
24 substance is relatively more soluble in octanol
25 or other nonpolar solvents versus water; is that

1 fair?

2 A. That's a reasonable description, yes.

3 Q. And so nonionized diazepam is poorly
4 soluble in water, right?

5 A. I think that's well reported and well
6 accepted regarding, you know, most definitions
7 of solubility ranges, that it's poorly soluble
8 in water.

9 Q. And I think you mentioned earlier today
10 you've studied in particular absorption of
11 compounds at the nasal mucosa, right?

12 A. I've studied compound absorption at
13 multiple mucosal sites, but I have studied
14 absorption across the nasal mucosa, yes.

15 Q. You would agree that there's evidence
16 that would have been available to someone with
17 ordinary skill in 2008 or '9 and today, for that
18 matter, that absorption through the nasal mucosa
19 increases with increasing partition coefficient
20 rather than with increasing molecular weight,
21 correct?

22 A. I don't think that that would be
23 correct in most people's estimation, that
24 the -- you're linking -- or your mutually
25 exclusive molecular weight versus partition

1 coefficient evaluations for absorption
2 likelihood, it doesn't work as well in the nasal
3 cavity as it does at other mucosal surfaces.

4 Q. When you say "mutually exclusive
5 molecular weight versus partition coefficient
6 evaluations," what do you mean by that?

7 A. Well, I mean that the -- you said
8 partition -- the higher the partition
9 coefficient value, the great the absorption in
10 the nasal mucosa and I think it was like
11 compared to molecular weight, which you were
12 implying that the higher the molecular weight,
13 the lower the absorption, I suspect, and that's
14 not as absolutely true as it is or it has been
15 observed at other sites of drug transfer.

16 Q. Okay, I think I understand, and I
17 appreciate your response. My question was a
18 little different. So I'll try it may be a
19 little different way.

20 A. Okay.

21 Q. Withdrawn.

22 You would agree with me that there was
23 evidence available to a person of ordinary skill
24 in 2008 or '9 as well as today that absorption
25 through the nasal mucosa increases as partition

1 coefficient increases, fair?

2 A. Up to a point, yes.

3 Q. And you would agree with me that, all
4 else equal, meaning for constant molecular
5 weight or reasonably constant molecular weight
6 compounds, that general trend, the notion that
7 more lipophilic compounds traverse the mucosa,
8 the nasal mucosa, the better is true, correct?

9 A. It's true under controlled
10 circumstances. So that as long as your
11 delivery -- or, you know, as long as what that
12 substance of varying -- or the substances of
13 varying partition coefficient are, as long as
14 they're in -- being presented to the epithelial
15 surface in the same media, in the same way, that
16 would likely be true.

17 Q. Now, the discussion we've had about
18 diazepam and its characteristics and partition
19 coefficients, that was all information available
20 to a person of ordinary skill in 2008 or 2009,
21 correct?

22 A. Yes, there were monographs about
23 diazepam that would report that, that keep that
24 information.

25 MR. BEST: We've been going for roughly

1 an hour. We can keep going or we can take a
2 short break at your discretion.

3 THE WITNESS: Why don't we take a short
4 break.

5 (Recess taken from 10:07 a.m.
6 to 10:18 a.m.)

7 BY MR. BEST:

8 Q. So I'm handing you what has already
9 been marked in this proceeding as Exhibit 1009.
10 I'll give you a moment to take a look.

11 A. (Reviewing document.)

12 Q. Ready?

13 A. Sure.

14 Q. This is a document that, if I direct
15 your attention to the upper right-hand corner,
16 is labeled "WO2009/120933."

17 Do you see that?

18 A. I see that.

19 Q. And Item No. 22, it has an
20 international filing date of 27 March 2009. Do
21 you see that?

22 A. Yes.

23 Q. And it states a priority date and
24 document a couple lines below that of 28
25 March 2008. Do you see that?

1 A. I see that.

2 Q. It's listed as having inventors -- I
3 have been given to understand that he pronounces
4 his name Gary "Gavoosh" is the first one,
5 G-W-O-Z-D-Z, Andrew Loxley is the second one,
6 and Mark Mitchnick is the third one.

7 Do you see those?

8 A. I see those.

9 Q. And there's a title at the bottom, Item
10 No. 54 "Pharmaceutical Solutions and Methods for
11 Solubilizing Therapeutic Agents."

12 Do you see that?

13 A. I do.

14 Q. This is a document with which you're
15 familiar, correct?

16 A. I have seen this document, yes.

17 Q. This is one of the documents you relied
18 on in formulating your opinions for this case,
19 correct?

20 A. I believe it is, but I'd like to see my
21 report to make sure. There's a number of
22 documents with similar inventor names and titles
23 and whatnot, and so just to make sure.

24 Q. I certainly don't object. If we can
25 have 1062-414.

1 A. And is there a number you're referring
2 to this as?

3 Q. Yes. So this document that you've been
4 handed is marked as -- previously marked as
5 Exhibit 1062. I will refer to it as "1062-786"
6 because it is, I believe, your declaration from
7 the '786 patent proceeding.

8 A. And as I look at it, yes, it is.

9 Q. If you look at the signature page at
10 the back, does that appear to be your signature?

11 A. Yes, it is.

12 Q. And so I think you've said, you believe
13 this to be a correct copy of your declaration,
14 correct?

15 A. Yes. Based on my initial review, yes.

16 Q. Okay. So going back to Exhibit 1009,
17 this is a document on -- which you reviewed and
18 relied on in forming your opinions in these
19 proceedings, correct?

20 A. Yes.

21 Q. And I think that your declarations
22 typically refer to it as Gwozdz. Does that
23 sound right?

24 A. Often, yes.

25 Q. Could I ask you to turn to page 1 of

1 Exhibit 1009. By "1," I'll refer to the numbers
2 at the top of the page.

3 A. Okay.

4 Q. I'll direct your attention to a portion
5 of this document entitled "Background of the
6 Invention."

7 Do you see that?

8 A. Yes.

9 Q. Could I ask you to read the first
10 sentence of that into the record?

11 A. "A vast number of potential therapeutic
12 agents are discovered each year, many of which
13 are water insoluble or poorly water soluble."

14 Q. You would agree that that's a fair
15 assessment of the art at the time, correct?

16 A. Yes.

17 Q. And this document goes on to identify
18 even in the next paragraph diazepam as one of
19 the agents to which it's referring, right?

20 A. Yes.

21 Q. Now, if you go to the bottom of page 1,
22 roughly line 32, you see that there's a
23 discussion that says "For therapeutic agents
24 that cannot be formulated as an aqueous
25 solution, emulsions have oftentimes provided a

1 cost-effective and therapeutically-acceptable
2 alternative."

3 Do you see that?

4 A. I see that.

5 Q. So the Gwozdz PCT -- the Exhibit 1009,
6 I'll refer to it as either "Gwozdz PTC" or
7 "1009," but I mean the same document. Okay?

8 A. Fine.

9 Q. The Gwozdz PTC discloses that one prior
10 art approach to addressing the problem of
11 solubility we discussed a moment ago and that
12 you've read was to formulate an agent as an
13 emulsion, fair?

14 A. That is one general approach, yes.

15 Q. And is emulsion -- withdrawn.

16 You're familiar with emulsions in the
17 context of your work in pharmaceuticals, right?

18 A. Yes.

19 Q. How would you define an emulsion in
20 that context?

21 A. An emulsion is a multiphasic system,
22 typically an -- either an oil phase disbursed in
23 a water phase or a water phase disbursed in an
24 oil phase or two immiscible phases, be they what
25 they are, and usually a stabilizer to assure

1 that there's at least some time constant where
2 that emulsion stays formed.

3 Q. Thank you.

4 Reading further in at the bottom of
5 page 1 and the top of page 2, is it fair to say
6 that one problem that the Gwozdz PTC identifies
7 with emulsions is that it is difficult to render
8 emulsions sterile and/or endotoxin-free for
9 intravenous injection?

10 A. I mean, that is an issue that Gwozdz
11 identifies. I -- I'm not sure that I would
12 agree, but he does identify that.

13 Q. When you say you're not sure you would
14 agree, what is the source of your disagreement?

15 A. Knowledge of multiple ways to sterilize
16 parenteral systems.

17 Q. So would you agree it's important to
18 maintain the sterility of an emulsion?

19 A. It's important to maintain the
20 sterility of an emulsion intended for
21 intravenous or intramuscular injection post
22 manufacturing and pre first use.

23 Q. Do nonaqueous solutions or other
24 nonaqueous mixtures suffer from this challenge
25 of needing to be sterilized?

1 A. Under certain circumstances. Depends
2 on what the requirements for the dosage form
3 that they are developed as, whether it would
4 need to be sterile or not.

5 Q. When you say it depends on the
6 requirements of the dosage form, what
7 requirements did you have in mind?

8 A. Well, if sterility is a requirement of
9 the dosage form for commercial supply or even
10 practical use, then it would need to be
11 sterilized. If sterility is not a requirement,
12 then it does not need to be sterile.

13 Q. So this would be a requirement imposed
14 by regulatory authorities and commercial
15 considerations; is that fair?

16 A. Well, there's certainly regulatory
17 requirements. There could also be best practice
18 for, say, compounding pharmacists, for example,
19 that there -- they may still have regulatory
20 compliance, but there may be situations where
21 there's not a specific regulation. Then they
22 are using their best professional judgment and
23 best practices.

24 Q. So in general for a nonaqueous solution
25 or the like, it is important to maintain

1 sterility where there is a requirement that's
2 been imposed by, let's say, regulatory
3 authorities to do so?

4 A. Prior to the first use, yes.

5 Q. Okay. Is that normal in your
6 experience, that there would be such a
7 requirement for a commercially-used product?

8 A. So nonaqueous systems --

9 Q. Yes.

10 A. -- needing to be sterile as a product?

11 Again, if they're intended for
12 intravenous or intramuscular or other injectable
13 type application, yes.

14 Q. In your view, would a nonaqueous system
15 that's intended for intranasal use require
16 sterilization?

17 A. Not necessarily.

18 Q. What would make the difference? You
19 say "not necessarily." So it could or could
20 not?

21 A. Well, it's -- the U.S.-based
22 regulations do not require nasal products to be
23 sterile.

24 Q. Got it.

25 A. They require -- they're required to

1 meet specific bioburden testing, and depending
2 on the choice of the manufacturer, they may
3 choose to manufacture a sterile system.

4 Q. So for a nonaqueous solution intended
5 for intranasal use in the U.S., sterilizing it
6 is not an important consideration; is that
7 essentially correct?

8 A. Low bioburden is an extremely important
9 consideration. It has to meet the standards for
10 the presence of specified -- at least bacteria.
11 I don't remember the specifications on fungi,
12 but I think there are a couple.

13 But, anyway, it has to meet at least
14 that level of limited -- limited presence of
15 potentially infective materials. And
16 oftentimes, those systems sometimes have some
17 sort of antimicrobial and other preservatives
18 included in them.

19 Q. When you referred to bioburden, are you
20 distinguishing that concept from sterility?

21 A. Yes.

22 Q. What is the distinction you're drawing?

23 A. The distinction is the regulatory
24 standards give you the ability to have a certain
25 number of colony-forming units in your

1 preparation as long as you meet the other
2 standards for that type of preparation.
3 Sterility would be the assumption that you have
4 zero colony-forming units.

5 Q. Got it. So is it less -- withdrawn.

6 Is it in your view a lower requirement,
7 meaning easier to meet, to meet the standard of
8 low bioburden that you've discussed versus
9 sterility?

10 A. I don't know that it would necessarily
11 be easier. It depends on the components, it
12 depends on the formulation, it depends on the
13 manufacturing methods.

14 Q. Okay. All right, going to page 4 of
15 this document, Exhibit 1009, I would direct your
16 attention to the section entitled "Detailed
17 Description of the Invention."

18 A. Okay.

19 Q. The first rather long sentence
20 discusses how "The present invention is directed
21 to the use of one or more tocopherols and/or
22 tocotrienols and one or more alcohols and/or
23 glycols as pharmaceutically-acceptable solvents
24 for solubilizing therapeutic agents, in
25 particular, hydrophobic or lipophilic

1 therapeutic agents."

2 Do you see that?

3 A. Yes.

4 Q. So here the Gwozdz PTC is disclosing a
5 way to solve the problem that it identified
6 previously of dissolving water in soluble
7 therapeutic agents like diazepam, right?

8 A. Yes, with the previous description that
9 the hydrophobic and lipophilic therapeutic
10 agents in context have low water solubility.

11 Q. Right. And the answer that Gwozdz
12 supplies here is to dissolve the drug in "one or
13 more tocopherols and/or tocotrienols and one or
14 more alcohols and/or glycols," correct?

15 A. Yes.

16 Q. Now, if we page forward to page 7 of
17 the Gwozdz PTC, I would direct your attention to
18 line 3, et seq., starting with "In
19 accordance..."

20 Do you see that?

21 A. Yes.

22 Q. And here the Gwozdz PTC says that one
23 advantage of its tocopherol/alcohol solutions is
24 that "hydrophobic or lipophilic therapeutic
25 agents provide increased bioavailability of the

1 therapeutic agent."

2 Do you see that?

3 A. Well, that they're used in
4 solubilization and thereby provide decreased
5 bioavailability, yes.

6 Q. If you look back to page 5 of this
7 document, we'll call it roughly line 2, there's
8 a sentence that begins "Moreover..."

9 Do you see that?

10 A. Yes.

11 Q. This certainly describes that another
12 advantage of the tocopherol and alcohol systems
13 that it discloses is that they "are more
14 tolerable than pure alcohol solutions."

15 Do you see that?

16 A. Yes.

17 MR. DEMING: Objection.

18 BY MR. BEST:

19 Q. When it says "Less irritating to the
20 skin and/or mucous membranes than pure alcohol
21 solutions," what do you understand them to be
22 referring to?

23 A. Well, that either by some measurement
24 of irritation or report of or an observation of
25 irritation that a pure alcohol solution is

1 associated with a greater amount than the
2 alcohol or glycol when combined with a
3 tocopherol.

4 Q. In your experience in intranasal
5 therapeutics, is reducing or eliminating
6 irritation an important consideration?

7 A. It depends on the purpose of the
8 materials and the potential drug and dosage form
9 that are being considered.

10 Q. So if I understand your testimony
11 correctly, you would say there are circumstances
12 where irritation is not an important
13 consideration? Is that what you're testifying?

14 A. That -- I think irritation is always a
15 consideration. Its level of importance relative
16 to other factors may not always be of the utmost
17 importance.

18 Q. Got it.

19 Going forward in the same sentence I
20 was referring to on page 5 of Exhibit 1009,
21 lines 6 and 7, another advantage that the Gwozdz
22 PTC describes for its solvent system is that it
23 "generally provides higher loading of a
24 therapeutic agent than emulsions, liposomes,
25 encapsulations or cyclodextrins."

1 Do you see that?

2 A. I see that.

3 Q. And so by "higher loading," would you
4 agree that the Gwozdz PTC is referring to a
5 higher concentration of a drug in a given
6 solvent?

7 A. It could be interpreted as that. It
8 could also be potentially just the actual drug
9 load within the disbursed phase for an emulsion
10 or a liposome or whatever it's encapsulated in.
11 Sometimes that's what the -- but then that
12 material is put into the volume. So it's kind
13 of a fine-line definition. They will get you to
14 the -- likely the same end point. The actual
15 numerical value might be different.

16 Q. Got it. Different ways of looking at
17 the concept of concentration because the system
18 is in one system the solution and in the other
19 instance potentially an encapsulation or
20 emulsion or et cetera?

21 A. Right.

22 Q. And is it fair to say that the higher
23 concentration solutions that the Gwozdz PTC
24 identifies would also tend to promote higher
25 bioavailability of the dissolved pharmaceutical

1 agent?

2 A. As long as those higher concentration
3 systems also led to higher activity of the drug,
4 then yes.

5 Q. When you say "also led to higher
6 activity of the drug," what do you mean by that?

7 A. I mean thermodynamic activity.

8 Q. And say more what you mean by that.

9 A. Okay. Well, we like to simplify mass
10 transfer in terms of concentration difference
11 across a barrier. The concentration as the
12 mass-to-volume concentration description isn't
13 adequate really to describe what the driving
14 force is.

15 The driving force is the thermodynamic
16 activity of the substance between or within and
17 then ability to move across a barrier. So the
18 activity oftentimes in very dilute solutions is
19 nearly equal to the concentration, but not in
20 all systems and not always in pharmaceutical
21 systems.

22 Q. In general, highly concentrated
23 solutions would provide higher activity,
24 correct?

25 A. Not necessarily.

1 Q. In general?

2 A. It's pretty hard to generalize that.
3 It's -- those systems are -- can be very
4 different from one another, they can have
5 self-association and a number of other things.
6 So it's -- I can't agree with a generalization.

7 Q. At least here, the Gwozdz PTC is
8 disclosing that by dissolving the agents it
9 describes in the solvent system, it describes
10 that leads to a higher loading of the agent,
11 correct?

12 A. But loading in this case may be
13 different than concentration -- well, it's going
14 to be different than activity.

15 Q. I appreciate that, but that's not my
16 question.

17 My question was: The Gwozdz PTC
18 discloses that by dissolving the agents it
19 describes in the solvent system, it describes
20 that will lead to a higher loading of the
21 therapeutic agent, correct?

22 MR. DEMING: Objection to form.

23 THE WITNESS: That it -- it generally
24 provides a higher loading, yes.

25

1 BY MR. BEST:

2 Q. If we go forward to page 8 -- and I
3 direct your attention to lines 25, et. seq --
4 I'd ask you to read that paragraph to yourself,
5 and then I'm going to ask you some questions
6 about it.

7 A. And this is lines 25 through 32?

8 Q. Yes, through 31.

9 A. Okay. (Reviewing document.)

10 Okay.

11 Q. So in this paragraph, the Gwozdz PTC is
12 describing the use of suspensions of therapeutic
13 agents in the solvent system it discloses,
14 correct?

15 A. That's both my recollection of this
16 section of the document and, in specific,
17 there's a description in the last sentence about
18 "finely divided suspension of the agent."

19 So, yes, in this paragraph, there's --
20 I believe he is describing behaviors in a
21 suspension.

22 Q. And what is your understanding of what
23 a suspension is in this context?

24 A. A suspension is a mixture where there
25 is solid solute present in equilibrium with

1 solute dissolved in the carrier phase.

2 Q. Now, would you agree that at the time
3 this document was generated, that a person of
4 ordinary skill would have known that creating a
5 suspension of a therapeutic agent was "a
6 strategy for developing drug formulations that
7 are poorly soluble in aqueous media"?

8 A. It certainly was known as a method for
9 delivery of low-solubility drug compounds. I'm
10 trying -- can you repeat the beginning part of
11 your question? Because I think what you might
12 have been asking is something that I want to
13 clarify in my answer.

14 Q. I suspect your question is about the
15 timing, and so I'll ask it in a slightly
16 different way.

17 Would you agree that in 2008 or 2009,
18 it was understood by a person of ordinary skill
19 that an option for delivering a therapeutic
20 agent that's poorly soluble in aqueous media was
21 a suspension?

22 A. It wasn't -- it's an option. It's not
23 an option for every possible application or use
24 of a drug and an attempt to deliver it as
25 desired or designed, but under some

1 circumstances, yes, it's an option.

2 Q. Okay. And you say it was not an option
3 necessarily for all type of agents. But the
4 Gwozdz PTC discloses in a previous paragraph
5 that this was an option for "exemplary
6 hydrophobic or lipophilic therapeutic agents"
7 like diazepam, correct?

8 MR. DEMING: Objection to form.

9 THE WITNESS: Are you -- I'm trying to
10 find -- did you quote something about --

11 BY MR. BEST:

12 Q. Line 6.

13 A. (Reviewing document.)

14 Okay, but in that paragraph, Gwozdz is
15 referring to the tocotrienol-alcohol-glycol
16 composition. The discussion of suspensions
17 comes later.

18 So I'm not sure what you're trying to
19 combine there or what the question is outside
20 of, yes, it says that.

21 Q. So line 25, et seq., the original
22 paragraph we were looking at on page 8 discusses
23 the present invention as "the tocopherol and/or
24 tocotrienol and alcohol and/or glycol solvent
25 system," correct?

1 MR. DEMING: Objection to form.

2 THE WITNESS: Yes, in the -- in the
3 description of the present -- of the present
4 invention, yes.

5 BY MR. BEST:

6 Q. Right. And it goes further to say that
7 "In this embodiment, the solution acts as a
8 transport phase through partial solubilization
9 to increase the bioavailability of the
10 amphophobic therapeutic agent from a
11 finely-divided suspension of the agent."

12 Do you see that?

13 A. Yes.

14 Q. Okay. And one of the compounds that
15 Gwozdz states is "an exemplary hydrophobic
16 lipophilic agent which can be solubilized in
17 accordance with the present invention," which as
18 you pointed out is -- the
19 tocotrienol-tocopherol-alcohol-glycol solvent
20 system is diazepam, correct?

21 MR. DEMING: Objection to form.

22 THE WITNESS: Correct, but the
23 paragraph starting at line 25 is an add-on. It
24 also provides for -- so, yes, it describes that
25 diazepam could be as a suspension and it could

1 be completely solubilized in accordance with the
2 present invention as described earlier.

3 BY MR. BEST:

4 Q. That makes sense. So let's discuss the
5 components of the composition that the Gwozdz
6 PTC is disclosing. One of those components is
7 an alcohol or a glycol, correct?

8 A. Yes.

9 Q. Is it fair to say that the Gwozdz --
10 withdrawn.

11 If you turn back a couple pages to
12 page 6, if you start at line 16, there's a
13 discussion of "Examples of alcohols for use in
14 the present invention" and then at line 8 and
15 line 19 to 20 "Examples of glycols for use in
16 the present invention."

17 Do you see those?

18 A. I see those.

19 Q. As between alcohols and glycols,
20 there's no preference expressed as to which
21 might be used in the solution, correct?

22 MR. DEMING: Objection to form.

23 THE WITNESS: (Reviewing document.)

24 Can you restate the question?

25 MR. BEST: Sure.

1 BY MR. BEST:

2 Q. As between alcohols and glycols, the
3 Gwozdz PTC expresses no preference as to whether
4 to use alcohols or, on the other hand, glycols,
5 correct?

6 A. Okay. Well, by chemical definition,
7 glycols are actually alcohols. The Gwozdz
8 decides to classify them in two different
9 categories, and I am fine with reading this
10 patent in that sense. And in that sense, he --
11 there does not appear to be a preference for his
12 group of things defined as alcohols and others
13 that are defined as glycols.

14 Q. Got it. Now, amongst the alcohols, if
15 you go forward in this paragraph, line, let's
16 say, 24, et seq., a preference is expressed for
17 the use of "an ethanol that is biocompatible in
18 the sense that it is not toxic and does not
19 cause any physiological or pharmacological
20 effects. In this regard, the ethanol is
21 desirably 180 to 200 proof ethanol, i.e., in the
22 range of 90 to 100% ethanol."

23 Do you see that?

24 A. I see that.

25 Q. And so the Gwozdz PTC does express a

1 preference towards a particular alcohol as
2 opposed to potentially other alcohols, right?

3 MR. DEMING: Objection to form.

4 THE WITNESS: Well, it's -- the way I
5 read this, these statements is that Gwozdz is
6 describing the embodiment where the alcohol is
7 ethanol and then went on to describe preferred
8 types of ethanol for use.

9 BY MR. BEST:

10 Q. And in an embodiment -- I'm not sure
11 I'm understanding the distinction you're
12 drawing. Withdrawn.

13 When you say -- withdrawn.

14 There's no embodiment here disclosed
15 that uses a different alcohol than ethanol,
16 correct?

17 A. Do you mean in the entire 1009
18 document?

19 Q. Sure.

20 A. And there's not an embodiment disclosed
21 that uses -- that uses either -- that discloses
22 propyl alcohol, butyl alcohol, pentanol, benzyl
23 alcohol or any isomers thereof. There are uses
24 of those other alcohols described.

25 Q. So if I understood your testimony, it's

1 that there's no embodiment disclosed that uses
2 an alcohol other than ethanol. Is that much
3 correct?

4 A. No, I don't -- that's not what I meant
5 to say.

6 Q. Well, let me ask the question directly.
7 Withdrawn.

8 Do you see an embodiment in the Gwozdz
9 PTC that employs an alcohol other than ethanol?

10 MR. DEMING: Objection to form.

11 THE WITNESS: (Reviewing document.)

12 Well, I'll agree that when Gwozdz gives
13 a more specific example of a preparation or a
14 composition, the only alcohol specifically
15 described is ethanol, but he also always leaves
16 open the statement about "one or more alcohols
17 and/or glycols" when describing those
18 embodiments.

19 BY MR. BEST:

20 Q. When you say "the statement," an
21 example of that statement would be on, say,
22 page 6, lines 16 through 19? Is that what
23 you're referring to?

24 A. (Reviewing document.)

25 Well, I'm referring to the -- within

1 that paragraph, the statement at line 23 that
2 starts "In one embodiment of the present
3 invention, the alcohol's ethanol..."

4 There is -- (reviewing document) -- a
5 nonlimiting example at -- on page 7 at line 12
6 that also identifies ethanol, but also is in
7 keeping with the -- that specific embodiment
8 with ethanol, but the solutions and composition
9 of the invention are always referred to as "one
10 or more alcohols and/or glycols."

11 Q. So if I understand your testimony
12 correctly, you agree with me there's no specific
13 embodiment disclosed in the Gwozdz PTC that
14 employs any alcohol other than ethanol, but that
15 more generally the Gwozdz PTC would disclose
16 that, in an embodiment of the invention that it
17 discloses, one could use one or more alcohols,
18 at least the ones that are named, and one or
19 more glycols, at least the ones that are named;
20 is that fair?

21 A. I think that's correct, but I think
22 more simply stated that if Gwozdz gives a
23 specific example of the composition with a --
24 with a specific drug that those specific
25 examples contained ethanol as the portion of the

1 "one or more alcohols and/or" -- let me state
2 that correctly -- (reviewing document).

3 Yes, "one or more alcohols and/or
4 glycols" --

5 Q. Got it.

6 A. -- used as part of the composition.

7 Q. Got it.

8 If you'd look, and maybe they're
9 already, at page 7 which you referred to a
10 moment ago, I'd like to look at the nonlimiting
11 example you referred to beginning at line 12.

12 Once you've read that paragraph to
13 yourself, let me know --

14 A. Okay.

15 Q. -- and I'll ask you a couple of
16 questions about it.

17 A. (Reviewing document.)

18 Okay.

19 Q. This paragraph discloses dissolving
20 diazepam, in particular, in ethanol and
21 ethanol-tocopherol solvent systems, right?

22 A. Yes.

23 Q. And part of what this paragraph
24 discloses is that a 70 percent tocopherol,
25 30 percent ethanol mixture will provide an

1 8 percent diazepam solution, correct?

2 MR. DEMING: Object to the form.

3 THE WITNESS: Greater than or equal to
4 8 percent is what the concentration was
5 described as.

6 BY MR. BEST:

7 Q. Fair enough. At least 8 percent,
8 right?

9 A. Yes.

10 Q. So I think you noted this in your
11 declaration. Gwozdz does not specify whether
12 this is a weight-weight or a weight-volume
13 percentage, correct?

14 A. That's correct.

15 Q. But in your view, the distinction
16 between those, at least in this context, is
17 relatively immaterial; is that fair?

18 A. I -- in my opinion, the numbers
19 don't -- the absolute concentration terms would
20 not change significantly enough to have an
21 impact on this invention.

22 Q. It would not change if what Gwozdz
23 actually meant was weight-weight or
24 weight-volume?

25 A. Yes.

1 Q. Now, if you'd turn a couple of pages
2 forward to page 10, lines 3 through 16, that
3 paragraph -- I'd ask you to read that paragraph
4 to yourself, and then I'll ask you a couple of
5 questions on it.

6 A. (Reviewing document.)

7 Okay.

8 Q. This section of the Gwozdz PTC is an
9 embodiment on which you relied in rendering your
10 opinions in this case, correct?

11 A. I discuss this section in my
12 declaration.

13 Q. And when you discussed this section,
14 you focused on this concept of penetration
15 enhancers that are included in this embodiment,
16 right?

17 MR. DEMING: Objection to form.

18 THE WITNESS: Well, I believe there's
19 some specific discussion of penetration
20 enhancers in the paragraph, but other parts of
21 the declaration, if not in the same paragraph
22 that's being discussed, talk about Gwozdz
23 teaching that other materials that are
24 frequently included in formulations to
25 accomplish the final desired composition may be

1 used with the invented tocopherol "one or more
2 alcohols and/or glycols" system.

3 BY MR. BEST:

4 Q. Let me see if I can unpack that a bit
5 because there was a lot there.

6 You've referred to "other part of the
7 declaration, if not in the same paragraph"
8 that's being discussed about Gwozdz.

9 Are you talking about your
10 declaration -- the first question is simply:
11 Are you talking about your declarations or are
12 you talking about Gwozdz?

13 A. Well, I'm going to find the --

14 Q. Sure.

15 A. -- section that you initially asked
16 about which was where I particularly made
17 statements about penetration enhancers. And if
18 you want to point me to that, that'd be great.
19 If not, I will look around until I find it.

20 Q. I'm not a hundred percent certain I
21 can, but maybe if we're both searching, we'll
22 get there faster. (Reviewing document.)

23 A. (Reviewing document.)

24 Q. Yeah, so I'm referring to -- I think
25 you're in 1062-786, and you might look at

1 paragraph -- like the top of page 54. Bottom of
2 53, top of 54, that's your discussion.

3 A. (Reviewing document.)

4 MR. DEMING: Do you mind if I also make
5 a suggestion?

6 MR. BEST: Sure.

7 MR. DEMING: I think also on page 57,
8 paragraph 109.

9 THE WITNESS: And I'm going to add in
10 page 45, paragraph 87.

11 I lost my place. The paragraph you
12 pointed to?

13 BY MR. BEST:

14 Q. Was paragraph 50 -- sorry,
15 paragraph 104.

16 A. Okay.

17 Q. And when you're done reviewing, let me
18 know, and I'll ask a clean question.

19 A. (Reviewing document.)

20 Okay, so I've finished reading
21 paragraph 104 and I'm scanning a few others.

22 Q. All right. And you're ready for more
23 questions?

24 A. Yes.

25 Q. So my question I'm asking you pertains

1 to the Gwozdz PTC, and I'm focused in particular
2 on the passage I asked you about before on
3 page 10, lines 3 through 16. So let me know
4 when you're back to that.

5 A. I'm there.

6 Q. Okay. So my question to you is, first,
7 this is an embodiment on which you've relied to
8 explain why a person of ordinary skill in your
9 view would have been led to incorporate a
10 penetration enhancer in the Gwozdz solution
11 system, correct?

12 MR. DEMING: Objection to form.

13 THE WITNESS: Well, this is a
14 description of ways in which the invented
15 tocopherol plus alcohol plus glycols composition
16 could be treated and additional agents that
17 could be added into a pharmaceutical solution.

18 You initially stated "embodiment," but
19 this doesn't strike me as an embodiment
20 paragraph.

21 BY MR. BEST:

22 Q. However it strikes you, you relied on
23 this paragraph to explain why in your view a
24 person of ordinary skill would have been
25 encouraged to add a penetration enhancer to the

1 solvent system with Gwozdz, correct?

2 MR. DEMING: Objection to form.

3 THE WITNESS: Yes, the paragraph
4 starting at line 3 on page 10 teaches one of
5 ordinary skill that one could add penetration
6 enhancers to the invention.

7 BY MR. BEST:

8 Q. Right. And it says as much. It says
9 "penetration enhancers," right?

10 A. It does say "penetration enhancers"
11 there, yes.

12 Q. This particular embodiment is a "a
13 pharmaceutical solution comprising a therapeutic
14 agent, one or more tocopherols or tocotrienols
15 and/or one or more alcohols or glycols" which
16 "can also be formulated into a pharmaceutical
17 formulation for injection by combining the
18 instant pharmaceutical solution with, e.g.,
19 saline solution or water," and it goes on.

20 Do you see that?

21 A. Yes.

22 Q. So this paragraph discloses the use of
23 the invention that is disclosed combined
24 explicitly with saline solution or water,
25 correct?

1 A. Well, my read of this is if one were to
2 desire to use this, the tocopherol-one or more
3 alcohol-one or more glycol composition, and use
4 that for injection, a POSA would likely
5 recognize that what was meant was intravenous
6 injection or potentially a few other sites
7 were -- yeah, we'll go with intravenous
8 injection, that you would need -- that you
9 couldn't directly inject the Vitamin E, alcohol
10 and glycol mixture and that would need to be
11 diluted.

12 The rest of the paragraph also teaches
13 that compositions of the invention can contain
14 other additives because some of these other
15 additives are unlikely to be included in
16 formulations intended for intravenous injection.

17 Q. Well, what it, the document, actually
18 says on line 9 is "such pharmaceutical
19 compositions may further contain," correct?

20 A. Those are the words, yes.

21 Q. And the "such pharmaceutical
22 compositions," the only English way to read that
23 is by referring to the compositions that are
24 previously discussed in that paragraph, correct?

25 A. It is -- it's also read in light of the

1 knowledge of a POSA.

2 Q. Well, thank you for that, but that
3 wasn't my question.

4 My question was: The "such
5 pharmaceutical compositions" to which this
6 paragraph refers on lines 9 and 10 are the
7 compositions that are disclosed on lines 3
8 through 9, correct?

9 MR. DEMING: Objection to form.

10 THE WITNESS: (Reviewing document.)

11 Well, I think the composition is
12 initially described in lines 1 through 4, "the
13 instant pharmaceutical solutions comprising a
14 therapeutic agent, one or more tocopherols
15 and/or tocotrienols and one or more alcohols
16 and/or glycols," and then they "can also be
17 formulated into a pharmaceutical composition for
18 injection" is an additional -- or additional
19 case for the invented composition.

20 BY MR. BEST:

21 Q. That's right, I agree you. And it's
22 those compositions that were formulated in the
23 fashion you just disclosed that are the "such
24 pharmaceutical compositions" which "may further
25 contain other pharmaceutically-acceptable

1 additives," correct?

2 A. I'm not sure because, again, as a POSA
3 reading the list of materials that are suggested
4 that -- or taught that can be added, some of
5 those are unlikely to be added to an injection
6 for -- or intravenous injection system.

7 So a POSA would read this as that "such
8 pharmaceutical compositions" are about the
9 instant pharmaceutical solution comprising "the
10 therapeutic agent, one or more tocopherols, one
11 or more tocotrienols and one or more alcohols
12 and/or glycols."

13 Q. So your testimony is that you don't
14 know whether "such pharmaceutical compositions"
15 refers to the composition that is disclosed on
16 lines 3 through 9, correct?

17 MR. DEMING: Objection to form.

18 THE WITNESS: No, my understanding as a
19 POSA is that it could be used for other
20 pharmaceutical compositions containing the
21 pharmaceutical solution described comprising
22 "the therapeutic agent, one or more tocopherols
23 and/or tocotrienols and/or one or more alcohols
24 and/or glycols."

25 And a subset of that could be

1 compositions for injection, and knowing that if
2 intravenous injection were intended, one would
3 need to treat that solution differently before
4 administration, and Gwozdz is giving us
5 direction on how to do that, dilute it with
6 water and add a solubilizing agent such as
7 premafor.

8 BY MR. BEST:

9 Q. Exactly. And it's those pharmaceutical
10 compositions which are the "such pharmaceutical
11 compositions" which are further described in
12 this paragraph, correct?

13 A. Again, as a POSA, there are materials
14 that would be unlikely to be included in an IV
15 solution, and so that, as a POSA, I read this
16 that the "such pharmaceutical compositions" are
17 describing the instant pharmaceutical solution
18 comprising the therapeutic agent, the
19 combination of tocopherols and ethanol -- or
20 alcohols and glycols.

21 Q. And as you yourself identified, this
22 paragraph does not require IV solution, correct?

23 A. It says --

24 Q. IV -- sorry. Withdrawn. Let me
25 restate it.

1 As you yourself identified, this
2 paragraph does not require IV injection. It's
3 merely "injection," correct?

4 A. The paragraph itself says "injection,"
5 but a POSA would also understand that the type
6 of formulation described by the pharmaceutical
7 solution composition, the therapeutic agent,
8 tocopherols, alcohol and glycols, may have the
9 ability to be used either directly or may need
10 to be changed in a different manner than the
11 saline solution and Vitamin E solubilizing agent
12 directed based on the requirements of that
13 administration site.

14 So it's clear that for an intravenous
15 injection, the saline solution or water and
16 Vitamin E solubilizing agent is in keeping with
17 how one would treat this for intravenous
18 injection.

19 But for intramuscular injection, that
20 is probably unlikely to be the case or
21 subcutaneous injection or interarterial
22 injection. There would be different ways that
23 one would approach making that formulation
24 appropriate for administration at those sites.

25 Q. Okay. And you would agree that

1 "injection" here then could be either
2 subcutaneous or intramuscular or intravenous or
3 potentially other options, correct?

4 MR. DEMING: Objection to form.

5 THE WITNESS: I agree that the term
6 "injection" could mean multiple sites of
7 injection into the body.

8 The additional information provided
9 about dilution and solubilizing the Vitamin E is
10 particularly important for an intravenous
11 injection and may or may not be appropriate for
12 other sites for injection.

13 BY MR. BEST:

14 Q. Okay, I think I understand your
15 testimony.

16 Could I ask you to look on page 9 --
17 actually, it's at the -- starting at the bottom
18 of page 8, lines 32, et seq., through the top of
19 page 10, line 2. Just look through that
20 briefly, and then I'll ask you some questions
21 about it.

22 A. (Reviewing document.)

23 Okay.

24 Q. So fair to say this is the passage of
25 the Gwozdz PTC that describes the use of the

1 solvent system it discloses in the invention
2 that is disclosed for nasal purposes, correct?

3 MR. DEMING: Objection to form.

4 THE WITNESS: Yes, in this paragraph,
5 intranasal administration is included in the
6 list of possible administration sites.

7 BY MR. BEST:

8 Q. And the paragraph on page 9 beginning
9 on line 19 specifically focuses on intranasal
10 administration, correct?

11 A. The paragraph starting on line 19
12 highlights the nasal mucosa or lungs as an i.e.,
13 as an example of other formulations being
14 administered to mucosal membranes.

15 Q. It's fair to say that no other part of
16 the Gwozdz PTC specifically addresses intranasal
17 use of the disclosed invention other than the
18 passage I identified beginning at the bottom of
19 page 8 and ending at the top of page 10, right?

20 A. I'm not certain. Let me check
21 something.

22 Q. Sure. And just for the record, what
23 are you looking at?

24 A. I am looking at my 1062-786 declaration
25 and I am in the section at -- it is in the

1 Summary of Prior Art references.

2 Q. Thank you.

3 A. (Reviewing document.)

4 All right. And I'm looking at
5 paragraph 88. There are a couple of other
6 places in Gwozdz that describe something about
7 intranasal administration in addition to the,
8 i.e., nasal or lungs description about mucosal
9 membranes.

10 Q. And in paragraph 88, you refer to
11 passages of the Gwozdz PTC on page 9, lines 19
12 to 25 and line -- page 10, lines 1 to 2,
13 correct?

14 A. That's what I'm referring to, yes.

15 Q. So you would agree to me that aside
16 from the passage I identified of the Gwozdz PTC
17 beginning on page 8, lines 32 through page 10,
18 line 2, no other part of the Gwozdz PTC
19 specifically identifies intranasal applications
20 of the disclosed invention, correct?

21 A. That's my recollection.

22 Q. Okay, thank you.

23 MR. BEST: May I suggest we go off the
24 record and maybe break for lunch, if that's
25 possible, or at least take a break.

1 THE WITNESS: Taking a break is fine.

2 (Recess taken from 11:32 a.m.
3 to 12:15 p.m.)
4

5 CONTINUING EXAMINATION

6 BY MR. BEST:

7 Q. Welcome back, Doctor.

8 A. Thank you.

9 Q. I would like to move on to
10 Exhibit 1010. I'll give you a moment to look at
11 it.

12 A. (Reviewing document.)

13 Yeah, this is -- okay.

14 Q. This is a document that you reviewed in
15 forming your opinions in this case, right?

16 A. Yes, it is.

17 Q. And I think you often refer to it as
18 "Meezan." Is that right?

19 A. That's right.

20 Q. If on the first page we look at the
21 upper right-hand corner, it's a document
22 identified as a Publication No. 2006/0046962.

23 Do you see that?

24 A. Yes.

25 Q. And it's entitled on the left-hand side

1 Item No. 54, "Absorption Enhancers for Drug
2 Administration."

3 Do you see that?

4 A. Yes.

5 Q. I'd ask you to turn to page 1 of the
6 document. Again, I'll use the page numbers at
7 the top.

8 A. (Witness complying.)

9 Q. I would direct your attention to the
10 section entitled "Field of Invention."

11 A. Okay.

12 Q. Here, Meezan discloses "The invention
13 relates generally to nonirritating and nontoxic
14 compositions providing enhanced bioavailability
15 and more specifically to alkyl glycoside or
16 saccharide alkyl ester compositions for delivery
17 of therapeutic agents to a subject."

18 Do you see that?

19 A. Yes.

20 Q. So in this paragraph, Meezan discloses
21 both alkyl glycoside and saccharide alkyl ester
22 compositions, correct?

23 A. That's correct.

24 Q. Alkyl glycosides are generally
25 considered non-ionic surfactants, right?

1 A. Yes.

2 Q. And one of the purposes Meezan proposes
3 that these compounds serve is providing enhanced
4 bioavailability, correct?

5 A. Yes.

6 Q. You relied on Meezan for its disclosure
7 of alkyl glycosides, right?

8 MR. DEMING: Objection to form.

9 THE WITNESS: (Reviewing document.)

10 BY MR. BEST:

11 Q. For the record, what are you referring
12 to, please?

13 A. Well, I'm looking at my prior art
14 summaries in Meezan to refresh my memory of the
15 number of things that I was taught by Meezan.

16 (Reviewing document.)

17 Okay, could you state the question
18 again?

19 Q. Sure. And before I do, were you
20 referring to paragraphs 89 through 94 of
21 Exhibit 1062-786?

22 A. Yes.

23 Q. Okay, thank you.

24 My question is: You relied on Meezan
25 for its disclosure of alkyl glycosides, correct?

1 A. I mean, Meezan did teach and I relied
2 on that teaching regarding my discussion of
3 alkyl glycosides in this section and other
4 sections in my report.

5 Q. So fair to say that's a yes, right?

6 A. It depends on -- "relied upon" is, I've
7 learned, a more legal term than what I generally
8 use "relied upon" as. If you have some other
9 meaning to that, I'm not necessarily going to
10 agree.

11 I used Meezan to support my
12 declaration. I learned about alkyl glycosides,
13 more specifics potentially in some of Meezan. I
14 was familiar with alkyl glycosides before
15 reading Meezan.

16 Q. You relied on Meezan as prior art, at
17 least in part, because it discloses alkyl
18 glycosides, right?

19 A. For -- yes.

20 Q. And in your view, a person of ordinary
21 skill at the time Meezan was prepared would have
22 believed such compounds to be useful as
23 absorption enhancers, correct?

24 A. Prior to reading Meezan? Or...

25 Q. Let's start with that, prior to reading

1 Meezan.

2 A. And I don't remember the timeline of
3 the introduction of the alkyl glycosides. I
4 certainly knew of them being described as
5 absorption promoters in the 2000s, but I just
6 don't remember the year and the timeline
7 relative to 2006, whether -- I suspect that
8 there was -- there were literature reports
9 before 2006 regarding alkyl glycosides as
10 absorption promoters.

11 Q. Okay, fair enough. And certainly once
12 the person of ordinary skill had Meezan in hand,
13 is it fair to say you would agree that the
14 person of ordinary skill would have believed
15 alkyl glycosides to be useful as absorption
16 enhancers?

17 A. They certainly -- yeah, a POSA would
18 consider them to -- or as potential absorption
19 enhancers in various formulations for various
20 reasons.

21 Q. All right, you say "potential
22 absorption enhancers." Are you suggesting there
23 was uncertainty once Meezan was in hand in a
24 person of ordinary skill's mind whether the
25 alkyl glycosides would be absorption enhancers?

1 A. No, what I'm trying to communicate is
2 that how you want to describe "absorption
3 enhancers," how much they increase enhancement
4 is accomplished, a number of other things that
5 one person at one delivery site might look for
6 in an absorption enhancer might be different
7 than another formulator looking for an
8 absorption for a different molecule at a
9 different site.

10 So under the conditions that Meezan
11 describes, a POSA would understand that these
12 act as absorption promotion -- promoters.

13 Q. Do you mean to make a distinction
14 between absorption enhancers and absorption
15 promoters?

16 A. Not specifically, no.

17 Q. Okay. If you look again at paragraph 2
18 which we looked at a moment ago, is it fair to
19 say that Meezan expresses no preference as
20 between the use of alkyl glycosides, on the one
21 hand, and saccharide alkyl esters, on the other
22 hand?

23 A. Well, I read this to communicate not
24 necessarily a preference, that there's an
25 opportunity for alkyl glycosides and saccharide

1 alkyl ester compositions to enhance the delivery
2 of therapeutic agents.

3 So I don't think there was an intention
4 on preferring one or the other or -- I mean,
5 there's multiple compounds within all of the
6 groups described. So paragraph 2 doesn't drill
7 down into a specific preferred.

8 Q. And when you say as "doesn't drill down
9 into a specific preferred," are you referring to
10 does not identify any particular compounds that
11 would be preferred, doesn't identify that alkyl
12 glycosides versus saccharide alkyl esters would
13 be preferred or both?

14 A. There -- nothing that I read in
15 paragraph 2 communicates anything about
16 preferred materials within the alkyl glycoside
17 or saccharide alkyl ester description in the
18 field of the invention.

19 Q. Got it. Now, if you move forward to
20 paragraph 8, you'll be in a section titled
21 "Summary of the Invention."

22 Do you see that?

23 A. Yes.

24 Q. And, actually, let's step back to
25 paragraph 4.

1 A. (Complying.)

2 Q. We're still in a section entitled
3 "Summary of the Invention," right?

4 A. Okay.

5 Q. And read paragraph 4 to yourself for a
6 moment, and then I'll ask you a couple of
7 questions on it.

8 A. Okay. (Reviewing document.)

9 Okay.

10 Q. So paragraph 4 of Meezan also refers to
11 the invention that it discloses as pertaining to
12 alkyl glycosides or saccharide alkyl esters,
13 correct?

14 A. Yes, along with "the therapeutic
15 agent."

16 Q. And, once again, this paragraph does
17 not disclose any preference for alkyl glycosides
18 over saccharide alkyl esters, fair?

19 A. Correct.

20 Q. Nor does this paragraph express a
21 preference for any particular compound within
22 those two broad categories, right?

23 A. That's correct.

24 Q. So now if we move forward to
25 paragraph 8, I would ask you to read it, and

1 then I'll ask a couple questions.

2 A. (Reviewing document.)

3 Okay.

4 Q. Is it also the case in your view that
5 paragraph 8 expresses no preference as to
6 whether one employs alkyl glycosides versus
7 saccharide alkyl esters or any particular one of
8 the compounds in those broad categories?

9 A. Well, paragraph 8 leaves open the -- or
10 describes the surfactant as "an alkyl joined by
11 a linkage to a hydrophilic saccharide."

12 And looking at Meezan's definition for
13 alkyl saccharides and saccharide esters, but
14 I -- my recollection of his point is that it's
15 in keeping with both.

16 Q. So you would agree that paragraph 8, by
17 leaving open the option, expresses no preference
18 for alkyl glycosides versus saccharide alkyl
19 esters or for any particular individual member
20 of those categories, correct?

21 A. Correct.

22 MR. DEMING: Objection to form.

23 BY MR. BEST:

24 Q. Thank you. Could we look at
25 paragraph 49 on page 3?

1 A. (Witness complying.)

2 Q. And let me know when you've had a
3 chance to review it.

4 A. Okay. (Reviewing document.)

5 Okay.

6 Q. This is going to sound familiar. Would
7 you agree with me that paragraph 49 expresses no
8 preference as between alkyl glycosides --
9 withdrawn.

10 Would you agree with me that
11 paragraph 49 expresses no preference as between
12 alkyl glycosides or saccharide alkyl esters or
13 any particular members of those two categories?

14 A. (Reviewing document.)

15 And paragraph 49 starts with the -- a
16 quote of the term "therapeutic composition," and
17 in paragraph 48, the therapeutic composition is
18 defined and in paragraph 48 includes both "at
19 least one alkyl glycoside and/or at least one
20 alkyl saccharide ester" and with no statements
21 regarding preference for which type.

22 Q. And so you would agree that
23 paragraph 49, by virtue of the explanation you
24 identified in paragraph 48, identifies no
25 preference as to either of those categories or

1 any individual member of those categories,
2 correct?

3 A. Right, it does not describe a
4 preference for alkyl glycosides over saccharide
5 alkyl esters.

6 Q. Or any individual member of those
7 categories?

8 A. Right.

9 Q. Could we look at paragraph 56 on
10 page 4?

11 A. (Witness complying.)

12 Q. And again take a moment -- it's a long
13 paragraph -- and then I'm going to ask some
14 questions about it.

15 A. (Reviewing document.)

16 Okay.

17 Q. Paragraph 56 of Meezan discloses a very
18 large number of compounds that the disclosed
19 invention includes, correct?

20 A. It discloses, I think, large -- well,
21 multiple groups and multiple individual entities
22 within those groups.

23 Q. And when you say "multiple groups," do
24 you mean multiple alkyl groups?

25 A. No, I mean multiple things -- multiple

1 groups such as the alkyl thiomaltosides, for
2 example.

3 Q. So, according to this paragraph, the
4 "alkyl" portion of the alkyl glycoside that
5 Meezan discloses can be any alkyl group from one
6 containing 8 carbon atoms to one containing 18
7 carbon atoms, right?

8 MR. DEMING: Objection to form.

9 THE WITNESS: The statement prior --
10 well, part of the first sentence is that they
11 can include, but are not limited to that octyl
12 to octyl decyl bracketing. So they can be
13 between 8 and 18. They could be others.

14 BY MR. BEST:

15 Q. Even broader?

16 A. (Nodding.)

17 Q. And those alkyl groups could be linear
18 or branched, right?

19 A. Yeah, there's -- there is nothing that
20 indicates the -- any specifics about arrangement
21 of the alkyl chain.

22 Q. So it could be linear or branched,
23 fair?

24 A. Again, as we discussed earlier, I'm not
25 certain of the nomenclature standards on that,

1 but I will certainly accept, not necessarily
2 based on the naming convention, that linear or
3 branched probably would fit in with -- within
4 the description groups.

5 Q. Fair enough. And would you equally
6 accept under the same caveats the notion that
7 the alkyl groups could be branched in one
8 location or in multiple locations or it could be
9 linear?

10 A. Yes, that could be the case.

11 Q. Yeah. Now, if you look at roughly
12 line 5 -- 4 and 5 or so of this -- let's say 4
13 to 6 of this paragraph, there's a discussion of
14 "either alpha or beta glycosides."

15 Do you see that?

16 A. "were attributed to different alpha or
17 beta forms," yes.

18 Q. Are we looking at the same thing? So
19 I'm reading -- and maybe it's the same thing --
20 "Alkyl glycosides of the present invention can
21 include, but are not limited to" various options
22 "and octyl decyl, alpha or beta D-maltoside,
23 glycoside or sucroside."

24 Do you see that?

25 A. Yes.

Q. Is it fair to say this paragraph, therefore, mentions the notion of anomeric -- withdrawn.

Is it fair to say that this paragraph expresses no preference as between the alpha or the beta anomer of the alkyl glycoside it discloses?

A. No, it just leaves open the opportunity for either.

Q. Now, paragraph 56 also discloses that the glycoside portion of the alkyl glycoside can be various options, correct?

MR. DEMING: Objection to form.

MR. BEST: Sorry, on what basis, Counsel?

MR. DEMING: I think you're mischaracterizing paragraph 56 and what it discloses.

MR. BEST: In what fashion?

MR. DEMING: There was a -- I'm not going to count them all, but there's a number of different references that are cited in this paragraph, and I think for you to accurately say what paragraph 56 discloses, you'd have to ask for judgment as to what each one of those

1 references was also disclosing.

2 MR. BEST: Fair enough.

3 MR. DEMING: So I think you
4 mis-summarized or mischaracterized paragraph 56.

5 MR. BEST: Okay, thank you, Counsel.

6 BY MR. BEST:

7 Q. You may answer the question.

8 A. (Reviewing document.)

9 Okay, can you remind me of the
10 question?

11 Q. Sure. Withdrawn.

12 You would agree with me that
13 paragraph 56 discloses various options for the
14 "glycoside" portion of the alkyl glycosides that
15 it talks about, right?

16 A. Yes, it does.

17 Q. And some of the options it discloses
18 are maltosides, glycosides or sucrosides,
19 correct?

20 A. Yes.

21 Q. It also discloses
22 heteroatom-substituted glycosides such as alkyl
23 thiomaltosides, alkyl thioglycosides, alkyl
24 thiosucrosides, correct?

25 A. Yes.

1 Q. It also discloses as additional options
2 alkyl maltriose- -- let me try that one again.
3 Withdrawn.

4 It also discloses as an option alkyl
5 maltotriocides, correct?

6 A. Yes.

7 Q. It discloses as options derivatives of
8 palatinose and isomaltomine, correct?

9 A. What spot again?

10 Q. We'll call it a third of the way up
11 from the bottom of the paragraph.

12 A. (Reviewing document.)

13 Yes.

14 Q. And as you pointed out, the paragraph
15 begins by noting that the alkyl glycosides that
16 the paragraph is going to discuss can include,
17 but are not limited to, those options, correct?

18 A. Yes.

19 Q. Now, let's look at paragraph 57. And
20 once you've had a moment to look at it, I'll ask
21 you a couple of questions.

22 A. (Reviewing document.)

23 Okay.

24 Q. So paragraph 57, as we've seen before,
25 does not specify any particular alkyl glycoside

1 or saccharide alkyl ester or a preference as to
2 alkyl glycosides versus saccharide alkyl esters,
3 fair?

4 A. That -- it does not specify.

5 Q. It does specify a preference toward a
6 certain range of what it calls "HLB numbers,"
7 correct?

8 A. Yes. And it also gives the formula by
9 which the inventors calculate that HLB value.

10 Q. And that formula requires identifying
11 both the hydrophobic portion, which in context
12 would be the alkyl portion, and the hydrophilic
13 portion, which in context would be the
14 saccharide or glycoside portion, correct?

15 A. At the most simplistic, but it -- not
16 to be offensive, but there --

17 Q. I'm not offended.

18 A. -- could be plenty of functional groups
19 of various types associated with each of those
20 characteristic portions of the molecules that
21 would have to be interpreted regarding their
22 impact on the hydrophobicity or hydrophilicity.

23 Q. And just to understand your testimony,
24 you're suggesting, I think, that if in fact the
25 alkyl portion or the glycoside/saccharide

1 portion or both had some form of chemical
2 modification, that factor would have to be taken
3 into account in calculating the HLB number; is
4 that fair?

5 A. That's my understanding, yes.

6 Q. Okay, great. The HLB number is a ratio
7 between the hydrophobic and the hydrophilic
8 portion, effectively, correct?

9 A. I'm not sure that I agree. The
10 equation given in the paragraph describes it as
11 "a ratio."

12 There are other ways of calculating an
13 HLB value, and I am not sure sitting here
14 whether all of them are simple ratios.

15 Q. Okay. Limited to the formula that is
16 described in paragraph 357, that formula, at
17 least, describes the calculation as a ratio
18 between the hydrophobic and hydrophilic
19 portions, correct?

20 A. Yes.

21 Q. No particular alkyl group sizes are
22 disclosed as preferred in this paragraph,
23 correct?

24 A. That's correct.

25 Q. Nor any particular alkyl group

1 structures?

2 A. That's correct.

3 Q. Nor any particular glycoside or
4 saccharide structures, correct?

5 A. Correct.

6 Q. Nor any particular stereochemistry,
7 right?

8 A. That's correct.

9 Q. Nor any particular anomeric structure
10 insofar as that differs from stereochemistry,
11 correct?

12 A. Correct.

13 Q. Let's look at the next paragraph,
14 paragraph 58. I'll ask you to take a look, and
15 then I'll ask you a couple of questions.

16 A. (Reviewing document.)

17 Okay.

18 Q. Would you agree with me that
19 paragraph 58 also does not describe a preference
20 as between alkyl glycosides versus saccharide
21 alkyl esters or any particular individual
22 compound falling within either of those
23 categories?

24 A. (Reviewing document.)

25 Well, the paragraph describes some

1 preferred alkyl chain characteristics and gives
2 example of several preferred glycosides, but
3 there isn't a single preferred agent or -- yeah,
4 there isn't a single preferred agent described
5 or identified.

6 Q. Nor is there a preference shown between
7 alkyl glycosides versus saccharide alkyl esters,
8 correct?

9 A. Not specifically, no.

10 Q. You alluded to some preferences that
11 are disclosed, and I'd like to talk about those.
12 There is, for example, a range disclosed between
13 9 -- about 9 and about 24 carbon atoms, correct?

14 A. Yes.

15 Q. And another what it calls "even more
16 preferred range from about 9 to about 16 or
17 about 14 carbon atoms."

18 Do you see that?

19 A. That's what it states.

20 Q. Once again, paragraph 58 -- withdrawn.

21 Paragraph 58 discloses no preference as
22 to the structure that any particular alkyl group
23 should have, correct?

24 A. Not specifically, no.

25 Q. And paragraph 58 identifies certain

1 preferred glycosides, but, again, does not
2 disclose any preference as between those
3 glycosides, correct?

4 A. It does not describe any preference
5 between those groups.

6 Q. Nor does it describe any preference as
7 to the stereochemistry or anomeric
8 configuration, correct?

9 A. Correct.

10 Q. Let's go to paragraph 61.

11 A. (Witness complying.)

12 Q. Take a look, and then I'll ask you a
13 few questions.

14 A. (Reviewing document.)

15 Okay.

16 Q. Paragraph 61 of Meezan, once again,
17 does not specify as between alkyl glycosides, on
18 the one hand, or saccharide alkyl esters, on the
19 other, correct?

20 A. (Reviewing document.)

21 Can you -- can you state that again?

22 Q. Sure. Paragraph Meezan -- withdrawn.

23 Paragraph 61 of Meezan does not specify
24 a preference as between alkyl glycosides, on the
25 one hand, or saccharide alkyl esters, on the

1 other, correct?

2 A. (Reviewing document.)

3 No, it -- I mean, it lists some
4 preferred characteristics, but -- of preferred
5 glycosides and some examples in keeping with the
6 9 and now 16 carbon atoms.

7 Q. But it expresses no preference as
8 between the two broad categories I articulated,
9 correct?

10 A. Not specifically.

11 Q. And it does not identify as preferred
12 any particular compound falling within either of
13 those categories, right?

14 A. Correct.

15 Q. The paragraph discloses that the
16 chemical linkage between the alkyl portion and
17 the glycoside or saccharide portion "can
18 include" one of various options, correct?

19 A. Yes.

20 Q. And one of those options, for example,
21 is a glycosidic bond, right?

22 A. Yes.

23 Q. And the other options that are stated
24 include thioglycosidic, amide, ureide, or ester
25 bonds, right?

1 A. Correct.

2 Q. And it expresses no preference between
3 those options, correct?

4 A. That's right.

5 Q. Paragraph 70, next page.

6 A. (Reviewing document.)

7 Okay.

8 Q. Paragraph 70 specifies nothing in
9 particular about the structure of the alkyl
10 glycoside or the alkyl saccharide esters that it
11 suggests employing, correct?

12 A. It does not speak to the structure.

13 Q. Nor does it specify between alkyl
14 saccharides -- withdrawn.

15 It does not specify between alkyl
16 glycosides nor saccharide alkyl esters
17 generally, correct?

18 THE REPORTER: I'm sorry.

19 MR. BEST: No problem.

20 THE REPORTER: It does not specify...?

21 MR. BEST: Withdrawn. Clean question.

22 BY MR. BEST:

23 Q. Paragraph 70 specifies nothing in
24 particular about whether one should employ, on
25 the one hand, alkyl glycosides or, on the other,

1 saccharide alkyl esters, correct?

2 A. No, it leaves open the opportunity for
3 both.

4 Q. Thank you. Paragraph 74.

5 A. (Reviewing document.)

6 Okay.

7 Q. Would you agree with me that
8 paragraph 74 specifies no preference as between
9 alkyl glycosides and saccharide alkyl esters?

10 A. Well, paragraph 74 is focused on the
11 pharmaceutically acceptable carriers for the
12 therapeutic compositions being described, and as
13 we discussed previously, when "therapeutic
14 composition" is defined in paragraph 48, that
15 paragraph does not highlight one or the other,
16 the alkyl glycosides or the saccharide alkyl
17 esters, in any preferred way.

18 Q. So it sounds like you agree with me
19 that 74 does not express any preference, by
20 virtue of referring back to paragraph 48, as to,
21 on the one hand, alkyl glycosides and, on the
22 other, saccharide alkyl esters, correct?

23 A. Yes. Based on paragraph 48, yes.

24 Q. And paragraph 74 also expresses no
25 preference for any particular compound falling

1 within either of those broad categories,
2 correct?

3 A. That's correct.

4 Q. If you'd look at the next paragraph,
5 paragraph 75.

6 A. (Reviewing document.)

7 Okay.

8 Q. Now, would you agree with me that
9 paragraph 75 expresses no preference as between
10 alkyl sacc- -- alkyl glycosides or salkyl -- I'm
11 getting a little tired of it too. Withdrawn.

12 Would agree with me that paragraph 75
13 also expresses no preference as between alkyl
14 glycosides or saccharide alkyl esters or any
15 particular compound falling within either of
16 those categories?

17 A. Well, paragraph 75 actually changes the
18 terminology a bit and it's referring to "alkyl
19 saccharides or saccharide alkyl esters," but
20 does not indicate any preference of -- between
21 those or any specific one of either category.

22 Q. Fair enough. Paragraph 75 does express
23 a -- the notion that "hetera" -- withdrawn.

24 Paragraph 75 does express the notion
25 that one could have heteroatom substitution of

1 the sugar portion of the molecule, right?

2 A. I read that as suggesting substitution
3 within the drug, not within the alkyl saccharide
4 or saccharide alkyl ester.

5 Q. Well, the discussion here states "...to
6 decrease susceptibility of alkyl saccharides or
7 saccharide alkyl esters to hydrolytic cleavage
8 of the drug, various oxygen atoms within the
9 drugs can be substituted for by sulfur."

10 Do you see that?

11 A. Yes.

12 Q. And you're suggesting you read "drug"
13 in that sentence to mean a compound other than
14 the alkyl glycoside or the saccharide alkyl
15 ester?

16 A. In keeping with the way those words are
17 used in the beginning portion of that sentence,
18 they're distinct. The drug is not the
19 saccharide alkyl or saccharide alkyl ester.

20 Q. Okay. But the next sentence says "For
21 example, the heteroatom of the sugar ring can be
22 either oxygen or sulfur, or the linkage between
23 monosaccharides in a oligosaccharide can be
24 oxygen or sulfur."

25 Do you see that?

1 A. I see that.

2 Q. So the saccharide alkyl esters and the
3 alkyl glycosides of the invention all have
4 either monosaccharides or oligosaccharide
5 portions, correct?

6 A. Yes.

7 Q. And the --- either the oxygen atom
8 within the ring or the oxygen atom between the
9 rings, if there are multiple sugar rings as a
10 part of the oligosaccharide, could be
11 substituted by sulfur. That's what this
12 paragraph discloses, right?

13 A. Well, I beg -- that sentence in the
14 center of the paragraph describes that. The
15 second one that you read describes that. I
16 don't agree that that's the only thing that this
17 paragraph says.

18 Q. Fair enough. And another thing that
19 the paragraph says is that the oligosaccharides
20 can have either alpha or beta anomeric
21 configuration, correct?

22 A. That's correct.

23 Q. And that's in keeping with the
24 discussion we had about paragraph 56 a few
25 moments ago, correct?

1 A. Yes.

2 Q. Let's go to paragraph 92 on page 8.

3 A. (Reviewing document.)

4 Okay.

5 Q. Paragraph 92 does focus on alkyl
6 glycosides, particularly alkylmaltosides, and
7 more specifically, "dodecylmaltoside (DDM) and
8 tetradodecylmaltoside (TDM)," correct?

9 A. Correct.

10 Q. Now, is it fair to say nothing is
11 disclosed in paragraph 92 about the structure of
12 the alkyl group on the DDM or TDM other than the
13 number of carbons they contain?

14 A. Well, certainly as named here, they
15 only named dodecylmaltoside and
16 tetradodecylmaltoside. Yet, again, from a
17 naming standpoint, I'm unsure sitting here what
18 the -- its terms -- what the recognized -- what
19 this name is then recognized regarding
20 structure.

21 So if, for example, I searched
22 "dodecylmaltoside" in PubChem, would it only
23 tell me that the structure associated with the
24 word "dodecylmaltoside" is recognized as a
25 single structure or hold open the possibility of

1 it being multiple structures.

2 My sense is it's a single structure,
3 but I'd have to -- I'd have to check that.

4 Q. Okay. There's certainly nothing stated
5 in the paragraph that specifies anything about
6 the structure other than the number of carbons
7 that those alkyl chains have?

8 A. Well, it specifies the name of a
9 chemical substance, and one could ascertain the
10 structure or structures based on that name.

11 Q. And in particular, if somewhere Meezan
12 actually said something about the structure,
13 correct?

14 A. Potentially. Otherwise, there are
15 other ways of discerning what the structure of a
16 chemical described by name is.

17 Q. So fair to say nothing is disclosed
18 about the stereochemistry of the DDM or TDM
19 discussed in paragraph 92, correct?

20 A. Nothing about the stereochemistry is
21 described.

22 Q. Nor is there anything about the
23 anomeric structure described, correct?

24 A. That's correct.

25 Q. Paragraph 92 discloses that the DDM and

1 TDM it discusses "stabilize insulin in solution
2 and prevent aggregation of the peptide."

3 Do you see that?

4 A. Yes.

5 Q. And that function -- withdrawn.

6 What is your understanding of the
7 utility of that function?

8 A. That in the particular formulation used
9 in the publication cited, that the insulin
10 structure stayed sufficiently stable to be able
11 to provide the same pharmacologic response as
12 the structure did before it was exposed to the
13 formulation, including the TDM or DDM.

14 Q. Is that potential -- withdrawn.

15 Tacit, I think, in your response is the
16 notion that the structure of insulin could
17 change under certain circumstances; is that
18 fair?

19 A. Well, starting with what we're
20 necessarily referring to as "insulin." So
21 insulin, it is a multimer, and I believe it's a
22 4 or 6 mer. I can't remember now.

23 And how -- what's being referred to as
24 the peptide versus aggregation, is it
25 aggregation into the desired multimer, is it

1 aggregation of the multimers? I would have to
2 read the report to understand exactly what is
3 being communicated in this paragraph.

4 Q. And is there a general reason why you
5 would be -- would seek to stabilize the
6 structures of a peptide such as insulin in
7 solution and prevent aggregation?

8 A. Sure. Because we don't want chemical
9 instability of any of the drug agents we're
10 formulating, and their -- the aggregation of
11 compounds, peptides included, often time leads
12 to their inactivation.

13 Q. Can I ask you to look at paragraph 149,
14 please.

15 A. (Witness complying.)

16 Q. Let me know when you've read it.

17 A. (Reviewing document.)

18 Okay.

19 Q. Paragraph 149 discusses, once again,
20 dodecylmaltoside, DDM, and
21 tetradodecylmaltoside, TDM, correct?

22 A. Yes.

23 Q. And paragraph 149 discusses something
24 about the DDM and TDM's structure, correct?

25 A. It at least mentions branching of the

1 alkyl chain.

2 Q. Read into the record the first sentence
3 of paragraph 149.

4 A. "Stability of the alkyl glycoside
5 depends, in part, on the number of carbon atoms,
6 or branching of the alkyl chain, with
7 tetradecylmaltoside (TDM) having the greatest
8 effect; but other highly branched alkyl chains
9 including DDM also have stabilizing effects."

10 Q. Thank you. So here, Meezan discloses
11 that the dodecylmaltoside it talks about has
12 "highly branched alkyl chains," correct?

13 A. It describes something about branching
14 of the alpha chain of the TDM.

15 Q. Paragraph 149 describes that the DDM it
16 discloses has highly branched alkyl chains,
17 correct?

18 A. As a -- as something that has achieved
19 the greatest effect, yes. Or has stabilizing
20 effect, sorry, yes.

21 Q. And so the answer to my question is
22 yes --

23 MR. DEMING: Objection.

24 BY MR. BEST:

25 Q. -- correct?

1 A. Well, the paragraph does describe some
2 positive aspects of branched alkyl chains for
3 both TDM and DDM.

4 Q. Right. And the DDM it describes in
5 Meezan it describes as having highly branched
6 alkyl chains, correct?

7 MR. DEMING: Objection, form.

8 THE WITNESS: Yes, in this example.

9 BY MR. BEST:

10 Q. Okay. Are you aware of any other
11 example in the patent application that discloses
12 anything specific about the structure of the
13 alkyl chain of the DDM or the TDM or any other
14 alkyl chain?

15 MR. DEMING: Objection to form.

16 THE WITNESS: I could... let's see. I
17 did not put that to memory, so I'd have to look
18 at the other examples to make sure of that.

19 BY MR. BEST:

20 Q. Sitting here right now, you're unaware
21 of any such disclosure?

22 A. That's correct.

23 Q. Okay. Now, Meezan says that branched
24 compounds are preferred because they have "the
25 greatest effect," correct?

1 MR. DEMING: Objection to form.

2 THE WITNESS: (Reviewing document.)

3 The greatest effect regarding stability
4 is what that sentence is referring to.

5 BY MR. BEST:

6 Q. And the first -- withdrawn.

7 The person of ordinary skill would
8 identify tetradecylmaltoside as having "the
9 greatest effect," correct?

10 A. Well, that's what the inventors are
11 reporting.

12 Q. Now, although Meezan discloses highly
13 branched -- withdrawn.

14 So I can go on or we can take a break
15 at your discretion.

16 A. If you're getting ready to finish up a
17 series of questions on Meezan, we can go for
18 longer. If you think it's going to be another
19 hour of similar questions, probably taking a
20 break would be a good idea.

21 MR. BEST: Let's take a break.

22 THE WITNESS: Okay.

23 (Recess taken from 1:20 p.m.
24 to 1:40 p.m.)

25

1 BY MR. BEST:

2 Q. Can I ask you to turn back in Meezan to
3 paragraph 92 which we discussed earlier.

4 A. (Witness complying.)

5 Q. And earlier we had discussed the
6 stabilizing effect and talked about it at the
7 beginning of the paragraph. Do you recall that
8 testimony?

9 A. Yes.

10 Q. I'd like to focus on a later portion of
11 the paragraph. Could I ask you to look at the
12 bottom, the sentence that begins on -- it's
13 basically the penultimate line and the last
14 line.

15 "Yet, in a related study, Hovgaard et
16 al. (1996) demonstrated when DDM-insulin was
17 orally administered to animals in vivo,
18 bioavailability of the complex was weak (e.g.
19 0.5 to 1% bioavailability)."

20 Do you see that?

21 A. I see that.

22 Q. Do you understand this passage to
23 discuss an attempt to use DDM as disclosed in
24 Meezan as an enhancer of bioavailability?

25 Withdrawn. That was a bad question.

1 Let me try it a different way.

2 Do you understand the passage I just
3 read to reflect results from an evaluation of
4 the ability of DDM, as disclosed in Meezan,
5 to -- on bioavailability of, in this case,
6 insulin?

7 MR. DEMING: Objection to form.

8 THE WITNESS: (Reviewing document.)

9 Well, based on these paragraphs,
10 without having read the two -- at least two or
11 more publications that the sentences were -- are
12 describing, you know, the bioavailability was an
13 endpoint calculation or determination, but it's
14 not clear to me whether that was made by the
15 authors of the publications or whether that
16 calculation and determination was made by the
17 inventors writing this. And so I'm -- without
18 reviewing those publications, I'm not sure in
19 what context they're using the term, and I also
20 have no idea what kind of formulation was also
21 associated with the studies.

22 BY MR. BEST:

23 Q. Fair enough. You know something about
24 the formulation, that it involved insulin,
25 correct?

1 A. Yes.

2 Q. And you know that the observation by
3 whoever made it, whether it's Hovgaard and his
4 colleagues or Meezan and his colleagues, was
5 that the effect on bioavailability was as
6 they -- as whoever described it "weak," correct?

7 MR. DEMING: Objection to form.

8 THE WITNESS: Well -- and, again,
9 that's in the writer's description. There are
10 circumstances where 1% bioavailability is a
11 great bioavailability, and so I don't know what
12 do with that statement without reading the
13 publications and drawing my own conclusion.

14 BY MR. BEST:

15 Q. Fair enough. But a person of ordinary
16 skill reading the paragraph would read the words
17 that I stated, correct?

18 A. The words are there.

19 MR. DEMING: Objection -- sorry.

20 BY MR. BEST:

21 Q. And could I ask you to turn to
22 paragraph 130 on page 11.

23 A. (Witness complying.)

24 Q. Take a look and let me know when you're
25 done, and I'll ask you a few questions.

1 A. Okay. (Reviewing document.)

2 Okay.

3 Q. Would you agree with me that
4 paragraph 130 of Meezan discloses nothing about
5 a preference as to, on the one hand, alkyl
6 glycosides or, on the other hand, saccharide
7 alkyl esters or any particular compound falling
8 within either of those categories?

9 A. Paragraph 130 is speaking to the types
10 of therapeutic agents included in the present
11 invention and is describing characteristics of
12 peptides, proteins and small molecules for
13 inclusion in the invention.

14 Q. And in doing so, you would agree that
15 paragraph 130 says nothing about preferring in
16 the present invention, on the one hand, alkyl
17 saccharide -- withdrawn.

18 You would agree with me that
19 paragraph 130 says nothing about a preference as
20 to alkyl glycosides or saccharide alkyl esters
21 or any particular compound falling within either
22 of those categories, correct?

23 A. It does not express any preference. It
24 does not even express anything about the alkyl
25 glycoside or alkyl -- saccharide alkyl esters.

1 Q. Thank you. Could I ask you to turn to
2 paragraph 150.

3 A. (Witness complying.)

4 Q. And you may as well also read 151. And
5 when you've done so, let me know.

6 A. (Reviewing document.)

7 Okay.

8 Q. Paragraphs 150 and 151 discuss an
9 experiment using tetradecylmaltoside in a
10 formulation of Miacalcin, correct?

11 A. Yes.

12 Q. Miacalcin is a polypeptide or protein,
13 right? Withdrawn.

14 Miacalcin is a formulation that
15 contains a polypeptide or protein like salmon
16 calcitonin, correct?

17 A. Yes, I think it's more accurately
18 described as a peptide, but regardless, yes,
19 it's an amino acid structure drug compound.

20 Q. Fair enough. Is it fair to say you see
21 nothing in paragraphs 150 and 151 discussing the
22 use of dodecylmaltoside?

23 A. That's correct, there's nothing
24 discussing dodecylmaltoside in those two
25 paragraphs.

Q. The two paragraphs refer to Figure 1 of the patent application. Do you see that?

A. Yes.

Q. And if you look at Figure 1, which I believe is on the second page of the document, there's no discussion there either of dodecylmaltoside, correct?

A. (Reviewing document.)

In the key of the figure, no. I am looking for the -- is there a section with the -- with figure captions in this application?

Q. That there is. Let's see if I could help you.

A. Oh, there they are, page 3. (Reviewing document.)

Okay. And, no, either in the figure caption or in the figure or the key to the figure, it only says "alkyl glycoside concentration."

Q. And to understand what alkyl glycoside is being used, one must refer then to paragraph 150 and 151 which refers to tetradodecylmaltoside, correct?

A. Yes.

Q. Okay. So looking now -- withdrawn.

1 Could I ask you to look in the next
2 example, Example 3, paragraph 156.

3 A. (Reviewing document.)

4 Okay.

5 Q. And, I'm sorry, you might as well look
6 at 158 as well before I ask you questions.

7 A. Okay. (Reviewing document.)

8 Okay.

9 Q. Starting with 158, the paragraph
10 discusses the use of two different
11 alkylmaltosides, dodecylmaltoside and
12 tridecylmaltoside, correct?

13 A. Yes.

14 Q. And both of those components are used
15 in formulations that contain insulin, correct?

16 A. Yes.

17 Q. And those insulin compositions are, in
18 the experiment here, administered I believe
19 ocularly to rats; is that correct?

20 A. I thought... (reviewing document.)

21 Q. I was looking at the end of the
22 paragraph.

23 A. Yeah, I know it says rats at the end of
24 the paragraph. I'm just trying to remember and
25 find in these multiple paragraphs --

1 Q. There's a lot.

2 A. -- where they switched animals.

3 Q. If it's helpful, paragraph 158 refers
4 to Table 1. Table 1 specifies rat, if it's
5 helpful.

6 A. (Reviewing document.)

7 Okay. And where my confusion was is
8 they're using porcine insulin. That's where I
9 got the species confused. So, yes, in rats.

10 Q. And the paragraph discloses nothing
11 about the particular structure of the alkyl
12 glycosides that are used in this experiment,
13 right?

14 A. It does not.

15 Q. Table 1 discloses effects of eye drops
16 containing the dodecylmaltoside described in
17 paragraph 158 administered to rats, correct?

18 A. Based on the table heading, yes.

19 Q. And the dodecylmaltoside was
20 administered at four different concentrations;
21 is that correct?

22 A. That's correct.

23 Q. 0.125%, 0.25%, 0.375% and 0.5%; is that
24 right?

25 A. That's what's listed in the table.

1 Q. Now, paragraph 158 a few lines above
2 Table 1 states that "Whereas, 0.5% and 0.375%
3 dodecylmaltoside appear equally effective in
4 achieving systemic absorption of insulin and
5 reduction of blood glucose levels, 0.25% has a
6 smaller and more transient effect and 0.125% is
7 ineffective."

8 Do you see that?

9 A. I see that.

10 Q. And then if you look at -- withdrawn.
11 The composition -- we may have gotten
12 to this already, but I'm going to ask you again
13 in case we didn't. Withdrawn.

14 The compositions here have been
15 administered ocularly, meaning eye drops, in the
16 rats, correct?

17 A. Yes.

18 Q. So the 0.25% DDM was disclosed as
19 having a smaller and more transient effect,
20 right?

21 A. That's what the paragraph states.

22 Q. Whereas, tridecylmaltoside at 0.25% had
23 an effect that was "of the absorption enhance is
24 sustained for the two hour time course of the
25 experiment." Do you see that?

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

2 Q. So setting aside the questionable
3 English, does it appear that tridecylmaltoside
4 was more effective at 0.25% of the composition
5 than was dodecylmaltoside?

6 A. I'm -- I don't know because it's -- I'm
7 looking at Figure 2, and it's stating that
8 that's the -- those are the results for the
9 0.25% TDM, looks like one animal tested.

10 And then looking at the data in
11 Table 1, that -- if these were described as
12 decreased from baseline or something else, it
13 would be easier to compare and evaluate the
14 statement you made, but as the data are
15 presented, I'm sitting here having a difficult
16 time making a comparison between the very --
17 between how the blood glucose decreases across
18 these groups. And how the data are presented
19 don't really help me.

20 Q. So, perhaps, we can clear some of this
21 up. If you look -- you referred to looking at
22 Figure 2, correct?

23 A. Yes.

24 Q. If you look at Example 6 on page 16,
25 paragraph 167 -- and actually paragraph 168 gets

1 there too -- Figure 2 refers to results with
2 tetradecylmaltoside, correct?

3 A. Yes, that's what the figure caption
4 indicates.

5 Q. All right. Not tridecylmaltoside,
6 correct?

7 A. Oh, okay. So I can just ignore
8 Figure 2 as telling me anything about this.

9 Q. I think so.

10 A. Thank you for that.

11 And -- but it still holds that Table 1
12 is giving me values of the blood glucose values
13 which have some differences between the groups
14 even prior to the insulin exposure.

15 So I'm having a difficult time looking
16 at the data and deciding whether there really is
17 a transient or not to describe something about
18 what's happening. I believe your question
19 was -- it was at about 0.25%.

20 Q. I don't want to interrupt your answer,
21 but are you completed?

22 A. Okay, but you could -- maybe it would
23 be helpful for to restate the question.

24 Q. Sure. Happy to.

25 At a minimum, you would agree that the

1 person of ordinary skill reading paragraph 158
2 would see that the authors of this document
3 described the effect of tridecylmaltoside at
4 0.25% as "sustained for the two hour time course
5 of the experiment," but the effect of
6 dodecylmaltoside at 0.25% as "has a smaller and
7 more transient effect," correct?

8 MR. DEMING: Objection to form.

9 THE WITNESS: And while those are --
10 you know, yes, I mean, that -- you've summarized
11 what's stated there.

12 BY MR. BEST:

13 Q. Okay.

14 A. And there would be some other things
15 that would be useful to know in comparison
16 between tridecylmaltoside and dodecylmaltoside
17 to actually understand chemically what
18 differences might be occurring between those
19 concentrations.

20 So the simple tridecylmaltoside at
21 0.25% works better than dodecylmaltoside at
22 0.25% without any context regarding of what the
23 insulin concentration was, of what the pH is, a
24 few other things is -- you know, the numbers are
25 the numbers, but the interpretation needs --

1 could use some additional information to be much
2 more assured that the tridecylmaltoside is
3 indeed under some circumstances better.

4 Q. So in your view, a person of ordinary
5 skill would require more information than is
6 conveyed in Meezan to understand the effects
7 that Meezan is describing for the various alkyl
8 glycosides that it's discussing?

9 MR. DEMING: Objection to form.

10 THE WITNESS: No, I think the person
11 evaluating these would be -- and selecting among
12 them and selecting an appropriate concentration
13 would benefit from, you know, information about
14 the therapeutic agent that's being used, the
15 concentration of the therapeutic agent, the
16 other characteristics of the vehicle before
17 immediately drawing the conclusion only about
18 one material in the formulation.

19 BY MR. BEST:

20 Q. And if I understand your testimony
21 correctly, it's your view that it would be
22 useful to a person of ordinary skill to have
23 data about the therapeutic agent that's being
24 used in an experiment and experimental data
25 about how that agent was employed in order to be

1 able to evaluate the quality of the experiment
2 in connection with use of alkyl glycosides,
3 correct?

4 A. No, I wasn't saying anything about the
5 quality of the experiment. I -- what I'm saying
6 is being asked to immediately presume that the
7 changes were only due to the change from
8 dodecylmaltoside to tridecylmaltoside without
9 knowing what else is going on in the mixture
10 is -- may be premature.

11 Q. There's no information that Meezan
12 conveys showing differences between what is in
13 the two mixtures other than the identity of the
14 alkyl glycoside, correct?

15 A. Correct, that there is no indication
16 that there were any differences.

17 Q. Fair. Could I ask you to look at
18 paragraph 147, which is on page 13.

19 A. (Witness complying.)

20 Q. Oh, scratch that. That's a -- never
21 mind.

22 Could I ask you, instead, to look at
23 paragraph 159, which is right after where we
24 were.

25 A. Okay.

Q. And when you've had a chance to look at it, I'll ask you a few questions.

A. (Reviewing document.)

Okay.

Q. Paragraph 159 describes an experiment using dodecylsucrose and decylsucrose as absorption enhancers for insulin, correct?

A. Yes.

Q. And here, the dodecyl -- withdrawn.

First off, these are alkyl glycosides having a sucrose-glycoside moiety rather than maltoside, correct?

A. Correct.

Q. And the dodecylsucrose was examined at 0.125%, 0.25% and 0.375%, correct?

A. Yes.

Q. And what the author discloses is that "... dodecylsucrose, "at those percentages, "also shows a dose-dependent effect in producing ocular absorption of insulin and reduction in blood glucose levels. This effect was observed even at 0.125%," correct?

A. That's correct.

Q. So here, there's a disclosure that alkyl sucrose is effective in producing an

absorption-enhancing effect even at 0.125%,
correct?

A. That's correct.

Q. Later in the paragraph, the penultimate
sentence -- it's sort of a long one, but it
discusses dodecylactose.

Do you see that?

A. (Reviewing document.)

Yes.

Q. And the sentence reads "The absorption
enhancing abilities of alkyl saccharides with
two distinct disaccharide moieties suggests that
it is the physiochemical properties of the
compounds which are crucial to their activity
and that other alkyl saccharides, e.g.,
dodecylactose, have the right balance of
properties to be equally or more effective as
absorption enhancers while retaining the
metabolic and nontoxic properties of the
alkylsaccharide enhancing agents."

Do you see that?

A. Yes.

Q. So here, the authors of Meezan are
proposing to the reader that lactose would be an
equally or more effective glycoside portion as

1 would the other glycoside moieties that have
2 been examined in the discussion we've had
3 previously of this document, correct?

4 A. That's what is stated. They're -- they
5 must have some -- they must be using some data
6 about the physiochemical properties of
7 dodecylmaltose to help them make that
8 determination, but that's not clearly stated in
9 the paragraph.

10 Q. Fair enough. Could I ask you to look
11 at paragraphs 167 through 169.

12 A. (Reviewing document.)

13 Okay.

14 Q. Those paragraphs discuss results from
15 experiments using tetradodecylmaltoside with
16 insulin to observe TDM's effect on
17 bioavailability, correct?

18 A. Yes.

19 Q. These paragraphs disclose nothing about
20 dodecylmaltoside, correct?

21 A. No, I believe everything described in
22 this experiment is with TDM.

23 Q. And nothing in these paragraphs
24 discloses the structure of the alkyl group on
25 the TDM that is employed, correct?

1 A. So the specifics of whether it was
2 branching or not?

3 Q. Correct.

4 A. No, there's nothing included.

5 Q. Similarly, going back to paragraph 159
6 which we looked at a moment ago, you can look at
7 it, but my question would be that you agree that
8 this paragraph also discloses nothing about the
9 structure of the alkyl groups aside from the
10 number of carbons that they have?

11 A. (Reviewing document.)

12 Okay, yes, in paragraph 159, there is
13 no specific additional information about the
14 structure of the alkyl chain.

15 Q. And, again -- sorry to ask you to do
16 this, but if you'd go back to paragraph 158, I'm
17 going to ask you the same question.

18 A. (Reviewing document.)

19 Similarly, in that paragraph, there is
20 no additional detail about the branched or
21 unbranched structure of the alkyl chain.

22 Q. And is the same true of paragraph 156?

23 MR. DEMING: Objection to form.

24 THE WITNESS: (Reviewing document.)

25 And in paragraph 156, they describe

1 using dodecyl-beta-D-maltoside and
2 decyl-beta-D-maltoside and provide no further
3 description of either compound.

4 BY MR. BEST:

5 Q. And paragraphs 150 and 151, which we
6 also looked at earlier, is it the case that
7 there's nothing disclosed in those paragraphs
8 about the structure of the alkyl groups aside
9 from the number of carbons that they contain?

10 A. (Reviewing document.)

11 Paragraph 150 describes a study with
12 miacalcin, including TDM, but doesn't describe
13 anything in addition about that. Paragraph 149
14 has some discussion of branching, at least.

15 Q. Yeah, sorry, I may have misspoke. I
16 meant paragraphs 150 and 151.

17 A. Okay, so 150 I described.

18 Q. Yeah.

19 A. It doesn't include any additional
20 information about the TDM. And let me look at
21 151. (Reviewing document.)

22 And in paragraph 151, they merely
23 describe it as the alkyl glycoside, and they're
24 referring to TDM.

25 Q. So no discussion of the structure of

1 the alkyl group?

2 A. That's correct.

3 Q. So going I guess it's forward --
4 withdrawn.

5 More generally, you have reviewed the
6 examples in Meezan in the course of your work to
7 form opinions in this case; is that fair?

8 A. Yes.

9 Q. And you would agree that none of the
10 examples test the effect of an alkyl glycoside
11 or a saccharide alkyl ester as an absorption
12 enhancer for a small molecule, correct?

13 MR. DEMING: Objection to form.

14 THE WITNESS: All of the examples
15 starting on page 13 and beyond I believe are
16 focused on -- (reviewing document) -- either
17 involved studying usual blood glucose decrease
18 after administration of insulin or miacalcin
19 concentration or the concentration of salmon
20 calcitonin, likely.

21 BY MR. BEST:

22 Q. And both of those compounds, insulin
23 and salmon calcitonin, are not small molecules
24 whatever they might otherwise be, fair?

25 A. They are not considered to be small

1 molecules.

2 Q. Okay. Am I correct in understanding
3 that none of the examples -- withdrawn.

4 Am I correct in understanding that,
5 because these are -- whether they're peptides,
6 proteins, polypeptides, whatever word one would
7 describe, they all employ an aqueous medium, at
8 least in part?

9 A. (Reviewing document.)

10 Well, miacalcin does. I know that. I
11 don't necessarily recall specific information
12 about the vehicle in any of the rest of the
13 experimental descriptions. Let's see.

14 (Reviewing document.)

15 Example 5 -- Example 3, I'm sorry,
16 indicates they're using phosphate buffered
17 saline, which is aqueous. (Reviewing document.)

18 Example 4 describes administered to
19 rats, as previously described. I believe they
20 used phosphate saline buffer there. (Reviewing
21 document.)

22 And I stand corrected. Example 5 is
23 about Glucagon even though it says insulin, but
24 I'm not seeing anywhere where it states about
25 the vehicle.

1 Example 6... (reviewing document.)

2 Example 6 is a little unclear because it's not
3 clear to me whether they started with Humalog
4 and added 0.25% tetradodecylmaltoside to that
5 product or if, instead, they've started with a
6 2.5 -- or 0.25% tetradodecylmaltoside in some
7 vehicle and added the insulin component of
8 Humalog to that.

9 Example 7... (reviewing document.)

10 Example 7 is Exendin rather than insulin. It
11 describes using saline as a control, but doesn't
12 describe specifically the vehicle that was used
13 for the drug-containing solutions.

14 Q. And when you discussed Exendin and
15 Glucagon, those are also peptides, proteins?

16 A. Yes, they are peptides.

17 Q. Okay. Not small molecules?

18 A. Yes.

19 Q. So if you'd look at the claims that
20 were included in this patent application on
21 pages 17 and 18 -- you should take a look at
22 them, but the question I'm going to ask you is
23 whether you agree that the only compound that
24 is -- withdrawn.

25 The question I was going to ask you is

1 whether the only alkyl glycoside that is
2 disclosed specifically in the claims is
3 tetradodecylmaltoside?

4 A. (Reviewing document.)

5 MR. DEMING: Objection to form.

6 THE WITNESS: Okay, so Claim 45 and 46,
7 they specifically are limiting to
8 tetradodecylmaltoside, but Claim 45 depends on
9 Claim 1, and Claim 1 describes "a surfactant
10 composition comprising at least one alkyl
11 glycoside or at least one saccharide alkyl
12 ester, and Claim 46 depends on Claim 45 which
13 depends on Claim 1.

14 So while those two later claims are
15 specific to the tetradodecylmaltoside, Claim 1
16 is open regarding the "at least one alkyl
17 glycoside or at least one saccharide alkyl
18 ester."

19 BY MR. BEST:

20 Q. So if I understand your testimony
21 correctly, you would agree with me that Claim 1
22 is -- expresses no preference as between the use
23 of alkyl glycosides or saccharide alkyl esters;
24 is that fair?

25 MR. DEMING: Objection to form.

THE WITNESS: Claim 1 leaves open the possibility of using one or other or combinations thereof one or more of each number of possibilities.

BY MR. BEST:

Q. It doesn't focus on any particular -- withdrawn.

Claim 1 doesn't focus on any particular alkyl glycoside or saccharide alkyl ester, fair?

A. It does not state in particular "alkyl glycoside" or "saccharide alkyl ester."

Q. And the only claims that you have identified of the Meezan reference that state a particular alkyl glycoside or saccharide alkyl ester are Claims 45 and 46 which state "tetradodecylmaltoside;" is that a fair summary?

A. Yes.

Q. Thank you.

Would you turn back to paragraph 130 which we looked at a hundred hours ago.

A. Okay.

Q. Now, paragraph 130, the final sentence states that "The methods of the invention also anticipate the use of small molecules, for example, an organic compound that has a

1 molecular weight of less than 3 kilodaltons, or
2 less than 1.5 kilodaltons."

3 Do you see that?

4 A. Yes.

5 Q. Is it fair to say that less than 3
6 kilodaltons or less than 1.5 kilodaltons
7 embraces a very large number of potential small
8 molecules as to a person of ordinary skill in
9 2008 or 2009?

10 A. It does, yes.

11 Q. Is it fair to say that you are unaware
12 of any evidence in Meezan that the inventors
13 actually tried to use the invention they
14 disclosed with any small molecule?

15 A. They don't appear, at least in their
16 examples, to use small molecules; yet there's
17 plenty of information about their understanding
18 of mucosal delivery and of absorption
19 enhancement, which the absorption enhancer may
20 be therapeutic agent independent in its action
21 or it may be therapeutic agent dependent in its
22 action. And so whether or not they provide an
23 example with a small molecule as compared to
24 their examples with large molecules, their
25 absorption enhancers may be able to act

1 independently of the molecule, and as a result,
2 would work on both small and large, which is
3 exactly what paragraph 130 is teaching.

4 Q. Let me unpack that just a little bit.

5 It's fair to say you have not
6 identified any data showing the use of the alkyl
7 glycosides or saccharide alkyl esters that
8 Meezan discloses to enhance the absorption of
9 any small molecule, fair?

10 MR. DEMING: Objection to form.

11 THE WITNESS: I haven't personally
12 looked for that because I was aware of these
13 agent as absorption enhancers. I don't remember
14 whether I was ever aware of them or the specific
15 molecules that were used in information that I
16 had seen regarding them, but I also knew of
17 the -- at least one of the proposed mechanisms
18 of action which is compound independent and
19 would do the same thing whether the therapeutic
20 agent was a large molecule or a small molecule.

21 And so it -- Meezan is clearly
22 describing that these could be used for large
23 molecules and for small molecules, that was in
24 keeping with my understanding of the materials,
25 and so I didn't go try to find an example.

1 BY MR. BEST:

2 Q. So it's fair to say that, at least as
3 you sit here right now, you are unaware of any
4 data presented by Meezan showing the use of the
5 alkyl glycosides or the saccharide alkyl esters
6 that Meezan discloses in conjunction with a
7 small molecule, correct?

8 A. Could you restate that?

9 Q. Sure. It's fair to say that, as you
10 sit here right now, you are unaware of any data
11 presented by Meezan showing the use of an alkyl
12 glycoside or a saccharide alkyl ester with a
13 small molecule?

14 A. In this patent application, I do not
15 see any examples regarding the use of these
16 alkyl glycosides or saccharide alkyl esters
17 working in small molecules; yet the description
18 provided in the specification about their
19 actions and the teaching of at least
20 paragraph 130 are sufficient for me to learn
21 that these enhancers will work both for large
22 molecules, as demonstrated by the examples, but
23 should certainly work for small molecular weight
24 molecules also.

25 Q. You have not identified any reference

1 in Meezan to diazepam, correct?

2 A. Let me make sure. (Reviewing
3 document.)

4 No, there's -- there -- I don't -- I
5 didn't see anything specifically regarding
6 diazepam in this patent application.

7 Q. It's also the case that you saw nothing
8 in particular about benzodiazepines in Meezan,
9 correct?

10 A. That's correct.

11 Q. Nor did you see anything specific about
12 tocopherol or tocotrienol or Vitamin E in this
13 application, correct?

14 A. (Reviewing document.)

15 While not stated explicitly in
16 paragraph 74, the inventors describe therapeutic
17 compositions containing pharmaceutically
18 acceptable carriers, and they go on to describe
19 and identify a couple of pharmaceutically
20 acceptable carriers.

21 They state that pharmaceutically
22 acceptable carriers are well known in the art,
23 and a person of skill in the art would recognize
24 Vitamin E as a pharmaceutically acceptable
25 carrier for some administration sites.

1 Q. So to my question: You saw nothing
2 specific about tocopherol, tocotrienol or
3 Vitamin E in this application? You would answer
4 yes?

5 A. I don't believe the words "tocopherol,"
6 "Vitamin E," or "tocotrienol," right, appear in
7 the specification.

8 Q. Okay, thank you?

9 MR. BEST: I'm ready to move on to
10 another document, so I suspect it's a good time
11 for another break.

12 THE WITNESS: Okay.

13 (Recess taken from 2:53 p.m.
14 to 3:06 p.m.)

15 BY MR. BEST:

16 Q. I'm going to hand you what's been
17 marked in these proceedings as 1026. This is an
18 excerpt from the Sigma Chemical Company book
19 entitled "Biochemical and Organic Compounds for
20 Research and Diagnostic Reagents."

21 Do you see that?

22 A. Yes.

23 Q. And this particular edition is dated
24 1988. Do you see that?

25 A. Um-hum. Yes.

1 Q. I reckon you're familiar with the Sigma
2 catalog from the context or research?

3 A. Back in the days when it was a catalog,
4 yes.

5 Q. Could I ask you to turn to the second
6 page of the document, page 2.

7 A. Okay.

8 Q. Do you see here a table of contents,
9 correct?

10 A. Yes.

11 Q. This document that you have in your
12 hand is an excerpt of a much larger book having
13 at least 1800 pages, right?

14 A. Yes.

15 Q. I guess by the very name "catalog" --
16 well, withdrawn.

17 One could purchase all the compounds
18 that are disclosed in the Sigma catalog to a
19 first approximation, correct?

20 A. Potentially, yes.

21 Q. Yeah.

22 A. Hopefully.

23 Q. And there are circumstances where, for
24 example, they don't have it, I guess. Is that
25 fair?

1 A. Those prepared by Sig- -- or prepared
2 for Sigma compounds sometimes were rare, but in
3 general, you could -- most of the compounds you
4 could obtain, yes.

5 Q. Now, if you look forward in this
6 document to page 19, according to the numbers in
7 the lower right-hand corner, we're at a section
8 entitled "Biological Detergents."

9 Do you see that?

10 A. Yes.

11 Q. And this is a document you've reviewed
12 in the course of forming your opinions in this
13 case, right?

14 A. Yes.

15 Q. So including this page, page 19, is it
16 fair to say there are six pages of chemical
17 compounds presented as detergents?

18 A. (Reviewing document.)

19 Q. In the internally numbered pages 316 to
20 321.

21 A. Yes.

22 Q. As page 19 discloses at the top, what
23 is presented here are "A wide range of
24 detergents useful to the biochemist for the
25 solubilization of proteins and membrane

1 components."

2 Do you see that?

3 A. Yes.

4 Q. Is it the case that compounds that tend
5 to solubilize proteins and membrane components
6 also tend to increase the permeability of
7 membranes?

8 A. In many cases, yes.

9 Q. Where such a compound increases the
10 permeability of the membrane, that compound
11 could function as an absorption enhancer in
12 maybe some circumstances, right?

13 A. Certainly could. It may actually be
14 too effective and negatively alter the cell
15 membrane, but -- but, yes, those -- anything
16 that can induce change in that structure
17 potentially could act as an absorption enhancer.

18 Q. Are you aware of any evidence that the
19 detergents that are listed on these six pages of
20 the Sigma catalog would not have acted as
21 absorption enhancers?

22 A. Again, I'm aware of... (reviewing
23 document.)

24 Well, I think all of these have -- they
25 certainly have the potential. It's definitely a

1 concentration-dependent potential.

2 Some of the materials, even at
3 extremely low concentrations, are too toxic to
4 serve as absorption or permeation enhancers.
5 Others would need to be at much higher
6 concentrations or they... (reviewing document.)

7 They just have more complicated
8 behaviors. And I think, again, the -- I think
9 on a number of them that they're -- the issue
10 with them is that they wouldn't be considered as
11 absorption enhancers due to toxicity, due to
12 issues with either obtaining a low enough
13 concentration or a high enough concentration for
14 them to be effective as absorption enhancers.

15 Q. And these are concerns that a person of
16 ordinary skill would be attentive to; is that
17 fair?

18 A. Should be, yes.

19 Q. And would have known in the 2008
20 timeframe?

21 A. Would have known to be attentive to
22 those?

23 Q. Would -- I'll do it more cleanly.
24 Withdrawn.

25 A person of ordinary skill in the

1 2008-2009 timeframe would have known about the
2 concerns you've articulated about some of the
3 compounds?

4 A. They would have known about the
5 concerns. They might not necessarily know about
6 the likelihood for any of the -- among these
7 which concerns might be significant.

8 Q. For a person of ordinary skill to
9 discern the ability for one of these compounds
10 to be an absorption enhancer, would that person
11 have to conduct an experiment to figure that out
12 in 2008 or 2009?

13 A. I think yes, because the -- there are
14 hypotheses regarding how some of these may act
15 or behaviors and solution or whatever. Not all
16 of them translate to an effective absorption
17 enhancement in vivo.

18 Q. Fair enough. So to have a reasonable
19 expectation that one of these compounds would
20 act as an absorption enhancer, a person of
21 ordinary skill would have conducted the
22 experiment?

23 A. Or they could have been convinced by
24 literature evidence, but something more than
25 knowing that it's a surfactant.

1 Q. Okay. Is there a distinction in your
2 mind between surfactant and detergent? I only
3 ask because you changed up the language there.

4 A. Okay. And only because I was looking
5 at the page. No, in my utilization, I think of
6 detergents and surfactants as being the same
7 kind of structural entities.

8 I think there might be the possibility
9 that there may be detergents that aren't
10 surfactants, but I -- that's not usually what we
11 think in the biological detergents world or in
12 my understanding of biological detergents. I
13 think all of them are surfactants to some extent
14 of their behaviors.

15 Q. Got it. Is it fair to say that to test
16 whether any of these compounds would act as a
17 surfactant, say, in the context of the
18 diazepam-tocopherol-alcohol compositions of
19 Gwozdz, one would have had to make the solution
20 containing those three components plus the
21 surfactant or detergent?

22 A. Well, I'm not convinced that the
23 material needs to be acting as a surfactant in
24 the composition of Gwozdz.

25 But if one wanted to determine

1 whether -- well, it's which surfactant behaviors
2 that you want to characterize. I suspect you'd
3 need to do an experiment. There would be
4 several different characteristics that you might
5 want to characterize and say something about a
6 surfactant activity, I guess.

7 Q. Is there any reason in your mind to
8 believe that these detergents listed in this
9 excerpt of the Sigma catalog could not have been
10 mixed with the composition of diazepam,
11 tocopherol and alcohols of Gwozdz to then test
12 their characteristics?

13 A. Solubility is always a concern in any
14 system, and so the -- if the -- whichever of
15 these would have to be soluble in whatever
16 combination of solvents identified for the
17 compositions of Gwozdz in order for them to be
18 active. So that would be -- and I'm not -- I
19 have no idea whether any of them would be
20 sufficiently soluble or all of them would be at
21 concentrations that would enable them to serve
22 as a permeation enhancer.

23 Q. Are you aware of any specific data or
24 evidence that would have been available to a
25 person of ordinary skill in the 2008-2009

1 timeframe that any of these compounds in the
2 Sigma catalog excerpt you're looking at would
3 not have been able to be mixed with the
4 composition of Gwozdz?

5 A. I'm not aware of any evidence at that
6 time that would indicate whether they -- any of
7 them were sufficiently soluble or were insoluble
8 and what kinds of material interactions might
9 have taken place in that composition which would
10 have either allowed them to act as permeation
11 enhancers or not.

12 Q. For the moment, you can set that aside.

13 A. (Witness complying.)

14 Q. I'll hand you another document, 1016,
15 and this is a document entitled Handbook of
16 Pharmaceutical Excipients, 4th Edition, edited
17 by Raymond C. Rowe, et al., correct?

18 A. Yes.

19 Q. This is one of the documents you
20 reviewed in the course of forming your opinions
21 in this case, right?

22 A. Yes.

23 Q. Can I ask you to turn in this document
24 to page 3?

25 A. (Witness complying.)

1 Q. This is the -- an excerpt of a larger
2 book -- withdrawn.

3 The document that's front of you is an
4 excerpt of a larger book containing information
5 about various chemical compounds, correct?

6 A. Various frequently-used pharmaceutical
7 excipients, yes.

8 Q. And one of the frequently-used
9 pharmaceutical excipients that it addresses is
10 alcohol or what we discussed earlier as ethanol
11 or ethyl alcohol, correct?

12 A. Yes.

13 Q. And that's what's depicted on pages 3,
14 4 and 5 of the document, right?

15 A. Yes.

16 Q. So this excerpt that discusses alcohol
17 states various general categories of information
18 numbered 1 through 22.

19 Do you see that?

20 A. Um-hum. Yes.

21 Q. And I would like to focus first on
22 Item No. 6 "Functional Category."

23 Do you see that?

24 A. Yes.

25 Q. What is the first of the functional

1 characteristics Rowe discloses ethanol to have?

2 A. It discloses it as an antimicrobial
3 preservative.

4 Q. And what is the second of those
5 functions?

6 A. Disinfectant.

7 Q. So if you look at section -- the next
8 section, Section 7, "Applications in
9 Pharmaceutical Formulation or Technology," you
10 see a table labeled "Uses of Alcohol," correct?

11 A. Yes.

12 Q. What is the first and second of the
13 uses that are listed in that table?

14 A. "Antimicrobial preservative" and
15 "disinfectant," but it looks to me like the
16 table and the list are in alphabetical order.

17 Q. It may well be. Now, to have the
18 function of being an antimicrobial preservative,
19 the composition must have greater than or equal
20 to 10 percent ethanol, correct?

21 A. That's what the table states, yes.

22 Q. And the composition of Gwozdz that we
23 looked at earlier had greater than 10 percent
24 ethanol, correct? I believe on page 7.

25 A. Let me find it. (Reviewing document.)

1 So are you referring to about line 9 or
2 10?

3 Q. In Gwozdz, I would point you to page 7,
4 lines 12 through 17.

5 A. Okay, about the solubility of diazepam
6 in ethanol?

7 Q. That subject matter is discussed in
8 those lines.

9 A. Okay. But that's where you were
10 pointing me towards?

11 Q. It is.

12 A. Okay. And what was your question?

13 Q. My only question was: You would agree
14 with me that those compositions of Gwozdz PTC
15 describe compositions of greater than 10 percent
16 ethanol, correct?

17 A. Yes.

18 Q. Okay. If you go back to Rowe,
19 Exhibit 1016, Typical Properties, Item No. 10,
20 what is the first of the properties that is
21 addressed?

22 A. "Antimicrobial activity," yes, in the
23 list of several things.

24 Q. And on the next page, page 4 of the
25 document, there's a discussion that states

1 "Antimicrobial activity is enhanced in the
2 presence of Edetic acid or edetate --"

3 A. Edetate.

4 Q. Yeah. "-- salts."

5 Do you see that?

6 A. Yes.

7 Q. Another term for Edetic acid would be
8 EDTA, right?

9 A. That's a synonym, yes.

10 Q. And Edetic acid salts are salts of
11 EDTA, right?

12 A. Yes.

13 Q. EDTA and its salts are chelating
14 agents, correct?

15 A. They can be, yes.

16 Q. Often are?

17 A. Yes.

18 Q. And can be permeation enhancers,
19 correct?

20 A. They've been reported to be -- have
21 some activity, yes.

22 Q. Now, the fact that EDTA enhances
23 antimicrobial activity would have encouraged a
24 person of ordinary skill to add EDTA to a
25 pharmaceutical solution that that person wanted

1 to maintain as sterile or to reduce the
2 biological burden, correct?

3 A. Not necessarily.

4 Q. Well, the goal of decreasing biological
5 burden or rendering a solution sterile is to
6 remove microbes, correct?

7 A. State that again.

8 Q. Sure. You discussed a concept earlier
9 today, I think you said "biological burden." Is
10 that --

11 A. Yes.

12 Q. And to render -- I think we
13 discussed -- withdrawn.

14 I think we discussed the concept that
15 it would be useful in at least some
16 circumstances to reduce the biological burden or
17 to render a solution sterile, correct?

18 A. Yes, for sites of administration that
19 shouldn't be administering large amounts of
20 bacteria into.

21 BY MR. BEST:

22 Q. Including the nasal membranes, correct?

23 A. Including nasal membranes, yes.

24 Q. Okay. So one of the ways that Rowe
25 suggests the antimicrobial activity of a

1 solution would be -- that contains ethanol would
2 be to add EDTA to that solution, correct?

3 A. (Reviewing document.)

4 Only maybe. It depends on the
5 circumstances. If you look at the reference
6 that that statement is generalizing, it's
7 describing the potentiating effects of EDTA on
8 the bacteriocidal activity of lower
9 concentrations of ethanol or -- a slight typo
10 there.

11 And that's in keeping with my
12 understanding is that ethanol's really
13 bacteriocidal, not -- and it's -- whether you
14 need an additional antimicrobial enhancement
15 agent or a different antimicrobial preservative
16 system in a system with low concentrations of
17 alcohol very much depends on whatever else is in
18 that system and also on how you're going to be
19 administering it and what the likely microbes
20 that are going to be encountered is.

21 And so this general statement
22 "antimicrobial activity," I don't know, is that
23 against gram negatives, against gram positives,
24 against any particular species, whatever was in
25 that particular reference. When you're

1 designing a preservative system, there's a lot
2 more thought and understanding of the
3 formulation, the chemical characteristics of the
4 preservative and the both site of application
5 and likelihood for continued biological ingress
6 into the product that you entertain simply --
7 there's no indication of concentration of the
8 edetate salts here to increase that activity.
9 There are just a -- there's a lot of mixture
10 there and likely would not be the first
11 antimicrobial agent a formulator would select
12 when developing a preservative system for
13 something that contains ethanol.

14 MR. BEST: Okay, thank you for that.
15 It doesn't really respond to my question, so
16 I'll move to strike it. And I'm going to ask
17 again.

18 BY MR. BEST:

19 Q. My question is as follows: You would
20 agree with me that one way that Rowe suggests
21 enhancing the antimicrobial activity of a
22 solution containing ethanol would be to add EDTA
23 or EDTA salts to that solution, correct?

24 MR. DEMING: Objection to form.

25 THE WITNESS: No, Rowe simply states a

1 summary of a paper that he -- that is referenced
2 in this. And it's not even Rowe. It is -- who
3 wrote this? (Reviewing document.)

4 S.C. Owen is the author of this
5 monograph. And it simply states "antimicrobial
6 activity is enhanced in the presence of edetate
7 acid or edetate salts" with the reference. And
8 a POSA would know to go read this reference
9 regarding what antimicrobial effects it had on
10 which microbes under what conditions. So I
11 don't think Owen is teaching us what you
12 suggest.

13 BY MR. BEST:

14 Q. You disagree that Rowe teaches
15 "Antimicrobial activity is enhanced in the
16 presence of edetate acid or EDTA salts" in
17 solution containing ethanol of greater than
18 10 percent content?

19 A. I believe Rowe is teaching that
20 statement "antimicrobial activity is enhanced in
21 the presence of edetate acid or edetate salts"
22 under the conditions described in the reference.

23 Q. Okay. Now, there's also a discussion
24 in the next sentence that says "Ethanol is
25 inactivated in the presence of non-ionic

1 surfactants and is ineffective against bacterial
2 spores."

3 Do you see that?

4 A. I see that.

5 Q. So adding a non-ionic surfactant to a
6 solution containing greater than 10 percent
7 ethanol would, according to Rowe, render it
8 inactivated in terms of its ability to -- and
9 ineffective in terms of its ability to kill,
10 let's say, bacterial spores, correct?

11 A. That statement in isolation, a POSA
12 would know that -- you know, non-ionic
13 surfactants there's a tremendous number of
14 non-ionic surfactants. They have different
15 solubilities, different solution behaviors. And
16 so a broad brush generalization about all
17 non-ionic surfactants, you need to know about
18 what concentration the non-ionic surfactant has
19 to be at to reduce the effectiveness of ethanol,
20 especially against bacterial spores.

21 And so this is certainly an indication
22 that the formulator should investigate, whether
23 that non-ionic surfactant is appropriate or not,
24 but it's a very general statement without any
25 specifics and without any reference support, and

1 it's simply -- it's a statement. It's there.
2 It would teach a POSA to evaluate whether the
3 specific non-ionic surfactant of interest would
4 indeed reduce the effectiveness of ethanol as an
5 anti- -- or as a -- what does he say --
6 antimicrobial agent if they were using ethanol
7 as the antimicrobial agent in their formulation.

8 Q. Thank you for that. Rowe says none of
9 what you said in that answer except "ethanol is
10 inactivated in the presence of non-ionic
11 surfactants and is ineffective against bacterial
12 spores" in that circumstance, correct?

13 MR. DEMING: Objection, argumentative.

14 THE WITNESS: The sentence as written
15 is "ethanol is inactivated in the presence of
16 non-ionic surfactants and is ineffective against
17 bacterial spores."

18 BY MR. BEST:

19 Q. Okay.

20 A. But --

21 Q. You're ending your quote, right?

22 A. I'm ending my quote. I'm not ending my
23 answer.

24 Q. Okay.

25 A. But the Handbook of Pharmaceutical

1 Excipients is a monograph text intended for use
2 by pharmaceutical formulators and potentially
3 some others, and it is written to inform
4 individuals who know about these materials, know
5 something about these systems.

6 And so isolated individual sentences
7 are oftentimes a signal to the formulator. If
8 that is going to have impact on their form- --
9 on their formulation, they need to seek further
10 details to determine whether that case holds for
11 their formulation.

12 MR. BEST: I move to strike that answer
13 as nonresponsive, everything following the word
14 and including the word "but."

15 Let's press on.

16 BY MR. BEST:

17 Q. Going back to page 3 of this document,
18 the Section 6 "Functional Category" -- you
19 there?

20 A. Yes.

21 Q. What is the third of the functions that
22 Rowe discloses ethanol possesses?

23 A. "Disinfectant."

24 Q. What is the next one?

25 A. Oh, I'm sorry, that's not the third

1 word. Third category: "Skin Penetrant."

2 Q. That's another word of saying an
3 absorption enhancer, right?

4 A. Yes.

5 Q. Let's go forward to page 9.

6 A. (Witness complying.)

7 Q. This is the entry in Rowe for benzyl
8 alcohol, correct?

9 A. That's correct.

10 Q. I'd like to focus on the functional
11 category discussion again, Item No. 6 once
12 again.

13 This states that benzyl alcohol has the
14 effects of antimicrobial preservative and
15 disinfectant, correct?

16 A. Along with solvent, yes.

17 Q. As well as solvent, that's right.

18 Now, as with the entry on ethanol,
19 Item No. 10 discusses the typical properties of
20 the benzyl alcohol.

21 Do you see that?

22 A. Yes.

23 Q. Midway through the passage under
24 "Antimicrobial Activity," there's a sentence
25 which reads "Antimicrobial activity is reduced

1 in the presence of non-ionic surfactants such as
2 polysorbate 80," and it goes on.

3 Do you see that?

4 A. It says that, yes.

5 Q. So, once again, Rowe discloses that
6 benzyl alcohol's ability to be an antimicrobial
7 is reduced by the addition of non-ionic
8 surfactants, correct?

9 A. Yes, without any further information
10 about what concentration that surfactant might
11 be at.

12 Q. A person of ordinary skill in 2008 or
13 '9 would have had to have actually made up the
14 solution that contains benzyl alcohol and other
15 components and whichever non-ionic surfactant
16 one wanted at whatever concentration one sought
17 and would have had to test whether that solution
18 maintained the antimicrobial activity that Rowe
19 discloses benzyl alcohol as having, correct?

20 A. Most likely, yes.

21 Q. And all of the caveats that you
22 described with respect to ethyl alcohol's entry
23 in this document pertain to the entries for
24 benzyl alcohol, meaning it's a monograph, one of
25 ordinary skill would know to look more deeply,

1 et cetera, correct?

2 MR. DEMING: Objection to form.

3 THE WITNESS: Again, depending on
4 whether the comment is referenced, depending on
5 the amount of information that's actually
6 provided within the monograph itself.

7 BY MR. BEST:

8 Q. This is a document you selected for use
9 in supporting your opinions, right?

10 A. Yes.

11 Q. We didn't select it, Neurelis?

12 A. No.

13 Q. Let's move to another document. This
14 will be Cartt '784.

15 I'm handing you a document which was
16 made of record in the -466 proceeding as
17 Exhibit 1064, but because it's not of record in
18 the other two proceedings, I'm re-marking it for
19 purposes of this deposition as Exhibit 2101.

20 (Deposition Exhibit 2101 was
21 marked for ID.)

22 BY MR. BEST:

23 Q. This document is a patent application
24 that you reviewed in the course of forming your
25 opinions in this case, right?

1 A. Yes.

2 Q. And if you look at the publication
3 number at the upper right-hand corner it is
4 US2008/0279784, correct?

5 A. Correct.

6 Q. It is entitled "Nasal Administration of
7 Benzodiazepines," correct?

8 A. Yes.

9 Q. With inventors listed as Steve Cartt
10 and David Medeiros?

11 A. That's what it says.

12 Q. I'll call this Cartt '784 to
13 distinguish the document from the individual
14 inventor.

15 A. Okay.

16 Q. If I could ask you to look at the
17 abstract that is on the cover page.

18 A. (Reviewing document.)

19 Q. I think it would be back on the cover
20 page.

21 A. Oh, sorry.

22 Q. Read that to yourself for a moment and
23 then I'll ask a couple questions about it.

24 A. Okay.

25 Q. The inventors describe the invention

1 here as "particulate formations of
2 benzodiazepines such as diazepam used for nasal
3 administration," correct?

4 A. Yes.

5 Q. And by "particulate formulations," the
6 formulations are to include "small solid
7 particles of benzodiazepine such as diazepam,"
8 right?

9 A. When reading further into Cartt '784,
10 yes, that's what is intended by that.

11 Q. If I could ask you to just page forward
12 to the claims of the application.

13 Actually, before doing that, you said
14 "when reading forward into Cartt" and you said
15 other things -- withdrawn.

16 Is it fair to characterize Cartt as
17 addressing particulate formulation to
18 benzodiazepine --

19 THE REPORTER: I'm sorry, can you start
20 your question again.

21 MR. BEST: No problem.

22 THE REPORTER: Is it fair to say...?

23 BY MR. BEST:

24 Q. Is it fair to say the Cartt '784
25 describes particulate formulations of

1 benzodiazepines and not solution formulations of
2 benzodiazepines?

3 MR. DEMING: Objection to form.

4 THE WITNESS: Well, in general, Cartt
5 is describing suspension diazepam or
6 benzodiazepine formulations.

7 With a suspension, there's always a
8 component of the drug solution and then there is
9 undissolved drug particles. So the particulate
10 that he is referring to are the undissolved drug
11 particle characterization of his formulation,
12 not particles that we might think of as
13 microcapsules or something like that.

14 BY MR. BEST:

15 Q. I think we discussed that concept
16 earlier today in the context of the Gwozdz PTC,
17 this concept of suspensions. Do you recall that
18 testimony?

19 A. I recall the topic. I don't recall the
20 testimony.

21 Q. Fair enough. Would you draw any
22 distinctions between the suspensions that were
23 disclosed in Gwozdz PTC versus the suspensions
24 as you described them disclosed in Cartt '784?

25 A. I'd have to take a look a little bit

1 more closely at both.

2 Q. Okay.

3 A. (Reviewing document.)

4 Q. In any event, the -- I don't want to
5 intrude. Are you --

6 A. Well, if you would like me to answer
7 the question, I'm going to have to look at these
8 and look at Gwozdz.

9 If you'd like to move on and have a
10 different question, that's fine.

11 Q. Let's move on and have a different
12 question. So to the extent anything's pending,
13 I withdraw it.

14 Is it fair to say that all the
15 formulations that Cartt '784 describes include
16 some particulates of benzodiazepines and are in
17 no case homogenous solutions?

18 A. Only homogenous solutions because the
19 solution portion will be homogenous, but the
20 formulation will be nonhomogenous.

21 Q. I understand what distinction you're
22 drawing. Let me be clear in my question.

23 The compositions that are described in
24 Cartt '784, would you agree that all of them
25 include particulates?

1 A. Well, I'm going to -- as I start to
2 page through Cartt, I'm going to reevaluate
3 because I see some descriptions of microsphere
4 precipitates. So he must have other
5 particulates in addition to just diazepam
6 particles. So I need to refresh my memory about
7 this.

8 Q. Sure.

9 A. (Reviewing document.)

10 Okay, now I have a slightly better idea
11 of what's described in Cartt '784. To refresh
12 my memory, can you repeat the question you'd
13 asked?

14 Q. Certainly. Not as a criticism, but
15 just to make the record clear, in the eleven
16 minutes that you took to review Cartt, did you
17 identify any embodiments in Cartt of a
18 formulation that did not include particulates?

19 A. And so I didn't look through every
20 paragraph to see if there was an embodiment
21 hidden in there.

22 Looking at the examples, all of the
23 examples contained particles containing an
24 active pharmaceutical ingredient.

25 Q. Okay. Thank you.

1 MR. BEST: I'm ready to move to another
2 document. We can either proceed or break.

3 THE WITNESS: I would suggest -- I
4 would prefer continuing on.

5 MR. BEST: Very well.

6 BY MR. BEST:

7 Q. So you can set that aside.

8 A. (Witness complying.)

9 Q. And can I ask you actually to pull up
10 again Exhibit 1026, the Sigma catalog.

11 A. Okay.

12 Q. And just looking again at page 19, on
13 page 19, there are four categories of detergents
14 listed, correct?

15 A. That's what they're saying. That's how
16 they organized this, yes.

17 Q. And those four categories are anionic,
18 cationic, zwitterionic, and non-ionic, correct?

19 A. Yes.

20 Q. Amongst that last category is listed
21 "n-Dodecyl-beta-D-maltoside," correct?

22 A. Yes.

23 Q. A person of ordinary skill would
24 immediately discern that this is the same
25 compound that is included in the claims of the

1 '414 patent we looked at I think as the first
2 document today, correct?

3 A. (Reviewing document.)

4 Q. The claims are in the back.

5 A. (Reviewing document.)

6 Yes, it's the same compound listed in
7 the claims of the 1001-414.

8 Q. Thank you. It's fair to say that back
9 when the Sigma catalog was a physical object, it
10 was widely distributed amongst researchers in
11 the field, correct?

12 A. Yes.

13 Q. All right, so I'm ready to move,
14 actually, to a new document.

15 I will hand you what has been marked
16 previously as Exhibit 1008. This is a document
17 entitled "Provisional Patent Application,
18 Administration of Benzodiazepine Compositions,"
19 correct?

20 A. Yes, by title.

21 Q. And at the bottom of that page, it
22 identifies as having been electronically filed
23 on March 28th, 2008, correct?

24 A. Yeah, that's what it states.

25 Q. With inventors Steve Cartt, David

1 Medeiros, Gary Gwozdz, Andrew Loxley, and Mark
2 Mitchnick, correct?

3 A. Yes.

4 Q. So this is a document you reviewed in
5 the course of preparing your opinions in this
6 case, correct?

7 A. I believe so. (Reviewing document.)

8 Q. It may be useful to look in the table
9 of your declaration.

10 A. Oh. All right, then that's a great
11 place to start and... (reviewing document.)

12 Yeah. And I was used to seeing or
13 expecting the number and the application number
14 existed, but yes.

15 Q. So if you'd turn forward to page 30 of
16 the application by the numbering at the bottom
17 of the page.

18 A. (Witness complying.)

19 Q. I would direct your attention to
20 paragraph 150.

21 A. Okay.

22 Q. Would you please read the first two
23 sentences into the record?

24 A. "In some embodiments, the drug delivery
25 system of the invention may advantageously

1 comprise an absorption enhancer. The term
2 'enhancer', means any material which acts to
3 increase absorption across the mucosa and/or
4 increases bioavailability."

5 Q. Thank you. The remainder of the
6 paragraph describes how to determine whether a
7 given compound is an enhancer in the context
8 that it discloses, correct?

9 A. (Reviewing document.)

10 Yes, there's a section in that
11 paragraph that describes a very generalized
12 experimental protocol for determining whether
13 something has been -- the absorption's been
14 enhanced.

15 Q. If you move forward to paragraphs 151
16 and 152, please review them, and then I'm going
17 to ask you some questions about them.

18 A. Okay. (Reviewing document.)

19 Okay.

20 Q. These two paragraphs disclose what the
21 inventors state are "preferred enhancing
22 materials" or "enhancing agents," correct?

23 A. They identify some examples of in some
24 embodiments "preferred enhancing materials" or
25 "enhancing agents appropriate".

Q. And do you understand when they say "enhancing agents" or "enhancing materials," they mean the same concept of enhancer described in paragraph 150?

A. Yes.

Q. So one of the categories of enhancing agents that is described here are chelating agents such as EDTA in paragraph 152, correct?

A. Yes.

Q. Could I ask that Exhibits 1058 and 1012 be introduced. And you'll want to keep Exhibit 8 handy.

A. Yes.

Q. Exhibit 1058 is one of the documents you relied on in forming your opinions in this case, correct?

A. Correct.

Q. The same is true of Exhibit 1012, correct?

A. Yes.

Q. It's in your table?

A. Yeah.

Q. So I'd like to -- we're going to do a little bit of a compare-and-contrast. So if you start with paragraph 151 of Exhibit 8 at your

1 right hand -- or maybe it's at your left hand,
2 your other left -- the first of the preferred
3 enhancing materials that is listed is --
4 withdrawn.

5 First off, would you agree with me that
6 the various materials that are stated in
7 paragraphs 151 and 152 were all understood to be
8 absorption enhancers by a person of ordinary
9 skill as of 2008 or 2009 in both 2008 and 2009?

10 A. Well, the specific agents listed in --
11 as examples in those paragraphs all had reports
12 in the literature describing them as able to
13 enhance the permeability of some compound from
14 a -- likely a specific delivery site.

15 Q. And the review articles that, let's
16 say, collect the literature reports that you
17 described are documents 1012 and 1058 in front
18 of you, right?

19 A. Yes.

20 Q. And would it be shocking to find that
21 all of the compounds in paragraph 151 and 152 of
22 Exhibit 8 are present in Exhibits 1012, 1058, or
23 indeed both?

24 A. All of the specific individual
25 compounds in those paragraphs?

1 Q. Correct.

2 A. I would not find it shocking that they
3 were in there.

4 Q. Have you any reason to believe any of
5 the compounds listed in paragraphs 151 and 152
6 of Exhibit 8 could not have been added to the
7 formulations of diazepam, tocopherol and ethanol
8 that the -- and other alcohols the specification
9 of Exhibit 8 discloses?

10 A. Let me walk through those specific
11 compounds one-by-one. So the first being
12 Palmitoyle-DL-Carnitine - Chloride, and even
13 that, I would actually need to look at the
14 structure because I don't remember whether that
15 chloride is as a salt. If it is, I'm concerned,
16 especially being able to make it to the
17 20 percent concentration in the solvent mixture
18 described by Gwozdz.

19 And that's what mixture you want to
20 talk about, right?

21 Q. It's not. So let me try again and --

22 A. Okay.

23 Q. -- maybe it will clarify.

24 So Exhibit 100 -- withdrawn.

25 Exhibit 1008, you understand to be the

1 provisional patent application to which all of
2 the patents that you have reviewed and offered
3 opinions as to validity in this case claim
4 priority, correct?

5 A. That it's listed on the face pages as
6 being a pri- -- yes.

7 Q. And you have reviewed 1008 in the
8 course of forming your opinions in this case, as
9 we discussed earlier, right?

10 A. Yes.

11 Q. And so you understand that Exhibit 1008
12 discloses compositions of benzodiazepines,
13 including diazepam in alcohol and tocopherol,
14 correct?

15 A. Yes.

16 Q. So my question is: Have you any
17 specific reason to believe any of the compounds
18 listed in paragraph 151 or 152 could not be
19 added to those compositions of the
20 benzodiazepine, alcohol and tocopherol that are
21 described in Exhibit 1008?

22 A. Okay, and so I will go back to my
23 answer. Starting with Palmitoyle-DL-Carnitine -
24 Chloride, I would need to know something about
25 the solubility of that compound, and I can't

1 even -- I can't make an estimate without looking
2 at the structure.

3 And that's okay. I'm just going to say
4 I'm not sure, and I don't necessarily think it
5 could be included.

6 Q. That's some- -- sorry to interrupt, but
7 that's something you didn't look at when you
8 were forming your opinions in this case, fair?

9 A. Not specifically, no.

10 Q. Okay. Thanks. Please proceed.

11 A. EGTA and EDTA, I doubt that they could
12 be included. I don't think there's a monograph
13 for EDTA in the handbook, that section I
14 provided. Again, it's a solubility issue,
15 depending on the -- well, they don't have a pH
16 there. I don't know. Maybe.

17 And phenylalanine enamine of ethyl
18 acetoacetate and diethylene oxymethylene
19 malonate, suitable compositions up to
20 20 percent. Again, it's a solubility issue.

21 And even for the compounds that aren't
22 specified, but the categories that contain
23 multiple compounds, which ones would be
24 appropriate for incorporation into the solvent
25 composition and which ones could not, one would

1 need additional information about their
2 solubility and the solvents included in that
3 mixture, either found in the literature or
4 easily obtained experimentally.

5 Q. And that's a general concern you would
6 have as a person of ordinary skill in 2008 or
7 2009, before incorporating a composition such as
8 those described in paragraphs 151 and 152 in the
9 alcohol-benzodiazepine-tocopherol compositions
10 of either Exhibit 1008 or the Gwozdz PTC, fair?

11 A. If I was intending on the material that
12 I was going to add to go into solution in the
13 medium I was placing it into, yes, then I would
14 either need to be aware of, have an estimate of,
15 or actually test the solubility to determine
16 whether it would go into solution at the
17 concentration that I intended.

18 Q. And the concentrations that are
19 disclosed in paragraph 152 of these components
20 is up to 20 percent weight by volume, correct?

21 A. In both paragraph 151 and 152, that
22 seems to be the high -- the upper concentration
23 limit, yes.

24 Q. So non-zero, but no higher than
25 20 percent, fair?

A. Well, it's defined as "a suitable concentration." I don't know that it's necessarily a limiting concentration, but it's the range that they identified initially as "suitable."

Q. And paragraph 151 states "a suitable concentration from 0.02 to 20 percent weight by volume," correct?

A. Yes.

Q. You can set those aside for the moment.

A. (Witness complying.)

MR. BEST: I'd like to -- I would like to take a break, actually --

THE WITNESS: Okay.

MR. BEST: -- before we proceed.

(Recess taken from 4:21 p.m.
to 4:35 p.m.)

BY MR. BEST:

Q. Could I ask you to pull out Exhibit 1001-414 which we looked at previously today.

A. (Witness complying.)

Q. And although we may have sped through this earlier, this is the '414 patent you have reviewed and offered opinions concerning the

1 validity of, correct?

2 A. Yes.

3 Q. So I would like you to turn to the
4 claims of the patent in the back.

5 A. (Witness complying.)

6 Q. I think we established earlier that at
7 least Claim 1 requires -- withdrawn.

8 We established earlier that Claim 1
9 states the compound
10 "n-Dodecyl-beta-D-maltoside," correct?

11 A. Yes.

12 Q. And you would agree with me that all
13 the claims of this patent require that compound,
14 right?

15 A. Yes, because both Claim 1 and 11
16 require n-Dodecyl-beta-D-maltoside, and those
17 are the only two independent claims.

18 Q. The claims don't state what function
19 that compound must provide in the pharmaceutical
20 solutions in the claims, correct?

21 A. Not in the claims, no.

22 Q. Are you aware of anything that requires
23 in the patent that requires -- withdrawn.

24 Are you aware of anything in the patent
25 that discloses a requirement for what

1 n-Dodecyl-beta-D-maltoside must do in this
2 composition of Claim 1 and the other claims?

3 A. I believe there's attributions to what
4 it's doing, but... (reviewing document.)

5 And the dodecylmaltoside and others
6 start being mentioned about Example 6 in the
7 specification that I can see. So your question
8 about whether -- its role in a formulation, is
9 that the question?

10 Q. Not exactly. So let me withdraw my
11 pending question and just ask it cleanly again.

12 You would agree that the patent states
13 no requirement for what
14 n-Dodecyl-beta-D-maltoside must do in the
15 formulations that are claimed, right?

16 A. What it must be doing in the
17 formulation?

18 Q. Correct.

19 A. No, there's no description of a
20 mechanism or role of the
21 n-Dodecyl-beta-D-maltoside.

22 Q. Going back to Claim 1, perhaps we've
23 tacitly established this, but you would agree
24 that it covers a pharmaceutical solution,
25 correct?

1 A. Yes.

2 Q. As do the other claims in this patent,
3 correct?

4 A. Yes, they all are limited to
5 pharmaceutical solutions.

6 Q. None of the '414 patent state any
7 particular clinical purpose for the
8 pharmaceutical solutions that are disclosed,
9 correct?

10 A. (Reviewing document.)

11 No, they do not.

12 Q. For example, there's no particular
13 requirement for any level of efficacy in any
14 particular clinical fashion required by any of
15 the '414 claims, correct?

16 A. There's no indication of a therapeutic
17 use in -- stated in the claims.

18 Q. Including any level of -- specific
19 level of clinical efficacy, right?

20 A. No indication of some measure of
21 clinical efficacy.

22 Q. Claim 1 requires diazepam as a part of
23 the composition it covers, right?

24 A. Yes.

25 Q. And the other claims of the '414 patent

1 also require diazepam, correct?

2 A. Yes.

3 Q. None of the claims of the '414 patent
4 states any particular amount of absorption or
5 bioavailability that the diazepam must have,
6 correct?

7 A. That's correct.

8 Q. Thank you.

9 I'm going to hand you what has -- it's
10 also marked Exhibit 1001, but this one is
11 1001-786.

12 And this is the '786 patent that you
13 reviewed in forming your opinions and on which
14 you've offered opinions concerning validity,
15 correct?

16 A. Yes.

17 Q. Once again, I would ask you to look at
18 the claims.

19 A. (Witness complying.)

20 Q. As with the '414 patent, the '786
21 patent covers pharmaceutical solutions, correct?

22 A. Yes.

23 Q. And as with the '414 patent, all the
24 claims of the '786 patent require
25 n-Dodecyl-beta-D-maltoside, correct?

1 A. Yes, they do.

2 Q. Do you have an understanding of what
3 that "n" prefix means in the context of
4 n-Dodecyl-beta-D-maltoside?

5 A. It's a structural arrangement indicator
6 that escapes me at the moment.

7 Q. If I told you it it's an indicator that
8 stands for "normal," would that make sense?

9 A. Oh, I -- it -- I mean, it makes sense
10 because it's in keeping that I know that what
11 "n" -- I know that's what "n" stands for, but
12 what "normal" is being attributed to is where
13 I -- I'm not willing to state that I know that
14 clearly right now.

15 Q. You don't recall what structural
16 information the "n" conveys in
17 n-Dodecyl-beta-D-maltoside; is that correct?

18 A. Not at this moment to testify to.

19 Q. Okay. And that's not an issue you
20 investigated in the course of forming your
21 opinions in this case, correct?

22 A. Not for a very long time. I probably
23 looked at a description of
24 n-Dodecyl-beta-D-maltoside and noted it, but it
25 didn't stick.

Q. Okay, fair enough. As with the '414 patent, is it -- withdrawn.

Would you agree with me that none of the claims of the '786 patent require any particular clinical purpose for the pharmaceutical solutions they cover?

A. They don't specify a specific clinical application, but they do describe "therapeutically effective amounts."

Q. All of the claims of the '786 patent require a "therapeutically effective amount of diazepam;" is that correct?

A. Yes, based on the descriptions in the independent claims, at least.

Q. And would you agree that the remainder of the claims, likewise, required "therapeutically effective amounts of diazepam"?

A. I'm con- -- I'm slightly confused by the question because there are two independent claims. They both require "a therapeutically effective amount of diazepam."

Several other of the claims still specifically state something else about the "therapeutically effective amount," but there are other claims that don't have

1 "therapeutically effective amount" expressly
2 stated in them, yet they are dependent on the
3 independent claims that do.

4 Q. And your understanding of the fact of a
5 claim being dependent is what?

6 A. That the dependent claim is encompassed
7 by the independent claim and adds oftentimes
8 more specificity for that specific -- that
9 particular claim.

10 Q. Okay. None of the claims of the '786
11 patent state any specifically-required level of
12 therapeutic efficacy, correct?

13 A. What do you mean by "level of
14 therapeutic efficacy"?

15 Q. The same thing I meant when I asked
16 about the claims of the '414 patent.

17 MR. DEMING: Objection to form.

18 THE WITNESS: Well, I may not have been
19 listening as carefully, but therapeutic efficacy
20 is -- either it's effective or it's not or it
21 could be, I guess, super effective or something.
22 There's got to be some set of levels.

23 If you're asking about different levels
24 of therapeutic efficacy -- what are you asking
25 about?

1 BY MR. BEST:

2 Q. I'm only asking: You would agree with
3 me that the claims state no particular levels of
4 therapeutic efficacy are required?

5 A. And I agree there's no additional
6 information about the type of efficacy that
7 "therapeutically effective" is describing in the
8 claims.

9 Q. The claims of the '786 patent all
10 require diazepam, correct?

11 A. Diazepam or a pharmaceutically
12 acceptable salt thereof, yes.

13 Q. Fair enough. No claim requires any
14 particular amount of absorption or
15 bioavailability of the diazepam or its
16 pharmaceutically acceptable salt, correct?

17 A. No, there's no indication of the extent
18 of absorption or percentage compared to what was
19 delivered.

20 Q. Okay. You can set that aside.

21 A. (Witness complying.)

22 Q. And I'm going to hand you what will not
23 be a surprise, Exhibit 1001-546.

24 Does this appear to be the '546 patent
25 on whose validity you've offered opinions in

1 this case?

2 A. Yes.

3 Q. Could I ask you once again to turn to
4 the claims of the patent.

5 A. (Witness complying.)

6 Q. Now, once again, the claims of the '546
7 patent cover pharmaceutical solutions, correct?

8 A. Yes, they do.

9 Q. And all of the pharmaceutical solutions
10 of the '546 patent require either "an alkyl
11 glycoside" or "dodecylmaltoside," correct?

12 A. Yes, based on the independent claim
13 requiring an alkyl glycoside, a couple of claims
14 specify dodecylmaltoside.

15 Q. The claims do not state what function
16 the alkyl glycoside or the dodecylmaltoside must
17 possess in the context of the claimed invention,
18 correct?

19 A. No, there's no specific descriptions in
20 the claims of any functional purpose of the
21 alkyl glycoside or the dodecylmaltoside.

22 Q. And are you aware of any statement of
23 required purpose in the rest of the patent for
24 the alkyl glycoside or the dodecylmaltoside?

25 A. (Reviewing document.) No. There's no

specific role indicated in the specification for the alkyl glycoside or the dodecylmaltoside.

Q. Would you agree with me that none of the claims of the '546 patent state a particular clinical purpose for the pharmaceutical solutions that are claimed?

A. All of the claims describe the solution composition but do not describe a clinical situation for use of that solution.

Q. And perhaps it's implied, but, likewise, none of the claims state any particular requirement of a level of clinical efficacy, correct?

A. That's correct.

Q. Nor do any of the claims state any particular level of absorption or bioavailability that's required of the benzodiazepine or diazepam, correct?

A. That's correct.

Q. And, I'm sorry, could you please go back to 1001-786, which is the immediately preceding document --

A. Um-hum.

Q. -- and back to the claims.

A. (Witness complying.)

1 Q. And would you agree with me that, as
2 with the other two patents, neither the claims
3 nor the specification of the '786 patent
4 requires any particular role of the
5 n-Dodecyl-beta-D-maltoside that the claims
6 require?

7 A. Yeah, the claims do not have a
8 requirement for the role of
9 n-Dodecyl-beta-D-maltoside, nor does the
10 specification -- let me just check one thing
11 first (reviewing document) -- nor does the
12 specification give or attribute a particular
13 role to n-Dodecyl-beta-D-maltoside.

14 MR. BEST: Thank you. I think this is
15 probably a good location to stop because I'm
16 going to move in a different direction.

17 THE WITNESS: Okay.

18 MR. BEST: I would only admonish you,
19 as I'm sure Mark will do, you're still on Cross,
20 so this should be treated as a break. You
21 shouldn't discuss the subject matter of your
22 questioning with your counsel between now and
23 tomorrow morning.

24 THE WITNESS: Yes.

25 MR. BEST: And you'll remain under oath

1 and all of that, and we'll reconvene tomorrow at
2 9:00.

3 MR. DEMING: Yep.

4 THE WITNESS: That's fine.

5 (Deposition adjourned at 4:58 p.m. CST to
6 be reconvened Thursday, December 11, 2025
7 at 9:00 a.m. CST.)
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

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

PADAGIS US LLC,
 Petitioner, Case Nos. IPR2025-00464
 vs. IPR2025-00465
 NEURELIS, INC., IPR2025-00466
 Patent Owner.

_____ /

VOLUME I

I hereby certify that I have read the
 foregoing transcript of my deposition given at
 the time and place aforesaid, consisting of
 pages 1 to 199, inclusive, and I do again
 subscribe and make oath that the same is a true,
 correct, and complete transcript of my
 deposition so given as aforesaid and includes
 changes, if any, so made by me.

 MAUREEN DONOVAN, PH.D.

SUBSCRIBED AND SWORN TO
 before me this _____ day
 of _____, A.D. _____.

1 REPORTER CERTIFICATE

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

5 That previous to the commencement of
6 the examination of the witness, the witness was
7 by me duly sworn in person to testify the whole
8 truth concerning the matters herein;

9 That the foregoing deposition was
10 reported stenographically by me in person and was
11 thereafter reduced to printed transcript by me,
12 and constitutes a true record of the testimony
13 given and the proceedings had;

14 That the said deposition was taken in
15 person by me at the time and place specified;

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

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

24 IN WITNESS WHEREOF, I do hereunto set
25 my hand this 17th day December, 2025.

DEBORAH HABIAN, CSR, RMR, CRR, CRC
IL CSR NO. 084-02432 (exp. 5/31/27)

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

PADAGIS US LLC,

Petitioner,

Case Nos. IPR2025-00464

vs.

IPR2025-00465

NEURELIS, INC.,

IPR2025-00466

Patent Owner.

_____/

VOLUME II

DEPOSITION OF MAUREEN DONOVAN, PH.D.

CHICAGO, ILLINOIS

THURSDAY, DECEMBER 11TH, 2025

REPORTED BY:

DEBORAH HABIAN, RMR, CRR, CLR

JOB NO.: 11548

December 11, 2025

8:57 A.M. CST

Deposition of MAUREEN DONOVAN, PH.D.,
testifying at the law offices of Polsinelli
P.C., 150 North Riverside Plaza,
Suite 3000, Chicago, Illinois, 60606, USA,
pursuant to notice, appearing in person before
Deborah Habian, an Illinois Certified Shorthand
Reporter, Registered Merit Reporter, and
Certified Realtime Reporter.

A P P E A R A N C E S

ON BEHALF OF THE PETITIONER

POLSINELLI, P.C.

BY: MARK T. DEMING, ESQ.

150 North Riverside Plaza

Chicago, Illinois, 60606

(312) 819-1900

mdeming@polsinelli.com

ON BEHALF OF THE PATENT OWNERS

McDERMOTT WILL & SCHULTE LLP

BY: TIMOTHY BEST, PH.D., ESQ.

2049 Century Park East, Suite 3200

Los Angeles, California 90067-3206

(310) 277-4110

tbest@mwe.com

-and-

McDERMOTT WILL & SCHULTE LLP

BY: HANNAH HURLEY, ESQ.

650 Live Oak Avenue, Suite 300

Menlo Park, California 94025-4885

(650) 815-7400

hhurley@mwe.com

I N D E X

WITNESS:	PAGE
MAUREEN DONOVAN, PH.D.	
Continuing Examination by Mr. Best	208
INSTRUCTIONS AND REQUESTS OF COUNSEL	
(none)	
WITNESS CERTIFICATE	296
REPORTER CERTIFICATE	297

INDEX OF EXHIBITS

PREVIOUSLY MARKED EXHIBITS

NUMBER	DESCRIPTION	PAGE
Exhibit 1001-414	U.S. Patent 11,241,414	208
Exhibit 1010	Meezan et al. Application	271
	Publication No. US 2006/0046962	
Exhibit 1019	Florida Regional Common EMS	255
	Protocols Field Guide	

(Deposition resumed at 8:57 a.m. CST.)

MAUREEN DONOVAN, PH.D.,

called further as a witness herein by the patent owner, having been previously duly sworn, was examined further and testified further as follows:

CONTINUING EXAMINATION

BY MR. BEST:

Q. Good morning again, Doctor.

A. Good morning.

Q. So you submitted written declarations in each of the three proceedings that we're here today to talk about, right?

A. Yes.

Q. And remind me, which do you have in front of you?

A. I have the 1062-786, I have...

Q. I suspect that's the only one.

A. I believe that's it.

Q. Okay, so I'm going to hand you what are going to be 1062-414 and 1062-546. And I think we've already established that the '786 you've identified as that (indicating) declaration.

If you would take up the '414

1 declaration and turn it to your signature page
2 and confirm that that's your signature?

3 A. Yes, it is.

4 Q. And does this appear to be a correct
5 copy of that declaration filed for the '414
6 patent?

7 A. It does.

8 Q. And same questions with respect to the
9 '546. Does this appear to be A correct copy of
10 your declaration and does your signature appear
11 at the end?

12 A. If the signature on -- at the end is
13 mine? (Reviewing document.)

14 Yeah, it looks like complete copy.
15 Yes.

16 Q. Thank you. Now, the declarations that
17 you have submitted in this proceeding, these
18 three proceedings, is it fair to say they're a
19 complete statement of the opinions you
20 formulated today for this case?

21 A. Yes, they are.

22 Q. And -- a yes-or-no question -- have you
23 formed any new opinions in this matter since
24 those were filed?

25 A. No.

1 Q. Thank you. Do you have any corrections
2 to offer with respect to any of the three
3 declarations?

4 A. No.

5 Q. Great. So if you'd take up the '414
6 declaration and turn -- the Exhibit 1026-414 and
7 turn to page 15.

8 A. (Witness complying.)

9 Q. You there?

10 A. Yes.

11 Q. So this is a section of your
12 declaration that sets forth what I understand to
13 be your understandings of the legal principals
14 you're applying in this case. Is that right?

15 A. Yes.

16 Q. And I believe that this section is
17 substantially identical amongst the three
18 documents, but if think there's anything
19 different, please point it out to me.

20 A. No, you are correct, they are
21 substantially identical.

22 Q. If you'd look at paragraph 26 and
23 paragraph 27.

24 A. (Witness complying.)

25 Q. Both of those paragraphs address a

1 concept called "anticipation."

2 Do you see that?

3 A. I do.

4 Q. It's correct to say you have not
5 offered an opinion that any claim of the '414
6 patent is anticipated, correct?

7 A. Yes, that's correct.

8 Q. And it's also correct that you've not
9 offered the opinion that any claim of the other
10 two patents in these proceedings is anticipated,
11 correct?

12 A. That's correct.

13 Q. If you'd look at page 17, just a couple
14 pages later, still in the Legal Understanding
15 section, paragraph 32.

16 A. (Witness complying.)

17 Q. Here, you say: "I understand that a
18 claim may be obvious in view of a single prior
19 art reference without the need to combine
20 references," and it goes on.

21 Do you see that?

22 A. I do.

23 Q. Is it fair to say you have not offered
24 the opinion that any claim of the '414 patent is
25 obvious in view of a single prior art reference?

1 A. (Reviewing document.)

2 That is correct.

3 Q. And is it also correct to say that
4 you've not offered the opinion that any claim of
5 the '546 or '786 patents is invalid as to
6 obvious over the single prior art reference?

7 A. That's correct.

8 Q. Your obviousness opinions for all three
9 patents require the combination of two or more
10 references; is that correct?

11 A. Yes.

12 Q. Okay. Would you turn to page 18, the
13 other side of the paper maybe, paragraph 33.

14 A. (Witness complying.)

15 Q. Roughly, I don't know, a third to
16 halfway down the paragraph, you have a sentence
17 that begins "Third..."

18 And it reads "Third, while many
19 combinations of the prior art might be 'obvious
20 to try', I understand that any obvious to try
21 analysis will not render a patent invalid unless
22 it is shown that the possible combinations
23 are..." and you go on to describe those
24 principals.

25 Do you see that?

1 A. I do see that, yes.

2 Q. Is it fair to say that you have not
3 offered an opinion that any claim of the '414
4 patent is obvious to try?

5 MR. DEMING: Objection, form.

6 THE WITNESS: (Reviewing documents.)

7 Well, I mean, there are certainly
8 obvious to try aspects in my opinions, but there
9 aren't any single claims where my only opinion
10 is that that claim would be or something about
11 that claim would be obvious to try.

12 BY MR. BEST:

13 Q. I'll represent to you the word "try"
14 does not appear in the remainder of this
15 declaration other than in paragraph 33 that we
16 were just looking at, and the same is true or
17 the analogous facts are true of the other two
18 declarations.

19 A. Um-hum.

20 Q. Assuming that to be true, is it fair to
21 say you did not apply the obvious to try
22 analysis to any claim of the three patents that
23 you analyzed?

24 A. Not as a single entity, yes.

25 Q. Okay. When you say "as a single

1 entity," what do you mean?

2 A. Well, I mean you're -- this indicates
3 that there is a simple -- you know, just an
4 obvious to try analysis, and "obvious to try" is
5 built into aspects of my opinions, but it's not
6 the single obvious to try analysis.

7 Q. Okay. Would you please turn to page 22
8 of your declaration.

9 A. (Witness complying.)

10 Q. There's a section here entitled
11 "Earliest Priority and Support for the '414
12 Patent Claims."

13 Do you see that?

14 A. I do.

15 Q. And if I direct your attention to
16 paragraph 41, you discuss here what you
17 understand to be a test, and perhaps in later
18 paragraphs, for establishing priority of patent
19 claims; is that correct?

20 A. Yes, that's what's described.

21 Q. And the earliest application -- I think
22 we established this yesterday. Withdrawn.

23 The earliest application to which the
24 '414 patent states a claim for priority is the
25 '558 provisional, correct?

1 MR. DEMING: Objection to form.

2 THE WITNESS: (Reviewing document.)

3 The '558 provisional?

4 BY MR. BEST:

5 Q. Yes. And I believe we looked at that
6 yesterday as Exhibit 1008, perhaps.

7 A. Yes.

8 Q. Okay, that application, the '558
9 provisional, was filed in March of 2008,
10 correct?

11 A. Yes.

12 Q. Now, you offered the opinion in your --
13 back to your declaration -- in this section to
14 which I directed your attention that the claims
15 of the '414 patent are in your view not entitled
16 to priority to the '558 provisional; is that
17 correct?

18 A. That is correct.

19 Q. Now, if you look at paragraph 52 of the
20 declaration, which I believe remains within this
21 section concerning priority date, you will see
22 discussion of your opinion concerning priority
23 dates; is that correct?

24 A. That's correct.

25 Q. In paragraph 53, you say: "It is also

1 possible that some of the claims in the '414
2 Patent may be entitled to an even later
3 effective filing date, if support for their
4 claim elements is first found in a later-filed
5 application."

6 Do you see that?

7 A. I do.

8 Q. It's fair to say you have offered no
9 opinion that any claim of the '414 patent is
10 entitled to a priority date after March 27,
11 2009, correct?

12 A. Not at this time.

13 Q. Nor have you offered an opinion that
14 any claim of the other two patents in this case
15 is entitled only to a priority date after
16 March 27, 2009, correct?

17 A. Yes, not at this time.

18 Q. Still in your '414 declaration, would
19 you please turn to page 49.

20 A. (Witness complying.)

21 Q. This is a section Roman numeral 10
22 "Motivation to Combine and Expectation of
23 Success."

24 You're there?

25 A. Yes.

1 Q. And if I direct your attention to
2 paragraph 94, you offer here the opinion that a
3 person of ordinary skill would have been
4 motivated to combine the teachings of the Gwozdz
5 PTC document and the Meezan document to pursue
6 the compositions of the '414 patent claims,
7 correct?

8 A. Yes.

9 Q. The problem you identify in the art is
10 "... the inability to administer benzodiazepine
11 drugs (e.g., diazepam) due to the limited
12 solubility of the drug compounds," correct?

13 A. That was also identified by the '414
14 patent, yes.

15 Q. Right. And you cite the '414 patent as
16 providing the discussion of the problem, right?

17 A. Yes.

18 Q. Now, if you look to the next paragraph,
19 paragraph 95, it's a two-sentence paragraph, and
20 the sentence begins "Consequently..."

21 Do you see that?

22 A. Yes.

23 Q. You say: "Consequently, a POSA was
24 motivated to identify strategies to improve the
25 solubility of benzodiazepine drugs, to allow for

1 the development of additional dosage forms that
2 would be an improvement over the known
3 shortcomings of oral, intravenous, and rectal
4 dosage forms."

5 Did I read that correctly?

6 A. Yes.

7 Q. Now, when you refer to the limited
8 solubility of benzodiazepine and diazepam, I
9 understand you to refer to the knowledge that
10 those compounds were -- had limited solubility
11 in aqueous solutions; is that right?

12 A. That's correct, and its solubility
13 relative to the dose that would -- needed to be
14 administered.

15 Q. And that notion goes back to the
16 partition coefficient discussion we had
17 yesterday concerning octanol-water ratios,
18 correct?

19 A. The solubility aspect? Or...

20 Q. The solubility aspect of
21 benzodiazepines and diazepam.

22 A. Well, certainly, because the aqueous
23 solubility is part of the typical octanol-water
24 partitioning study. You don't necessarily
25 obtain the solubility value directly from that

1 particular experiment, but it's certainly
2 related to that experiment.

3 Q. Diazepam has a relatively high
4 partition coefficient, meaning it's relatively
5 more soluble in nonpolar solvents versus polar
6 solvents like water?

7 A. It has a higher partition coefficient
8 than 1 percent, yes, where the solubilities
9 would be equal.

10 Q. So your testimony is that the partition
11 coefficient of diazepam exceeds 1?

12 A. Yes.

13 Q. Do you have a sense of what the
14 partition coefficient of diazepam actually is?

15 A. I do.

16 Q. What is that sense?

17 A. In log PC terms, the references state
18 it's, you know, about 3, um...

19 Q. Okay.

20 A. That's okay.

21 Q. That insolubility of diazepam in
22 aqueous solution was the problem a person of
23 ordinary skill was motivated to solve at the
24 priority date of these patents you reviewed,
25 correct?

1 A. Again, the solubility problem based on
2 desired dose in a particular volume for
3 administration.

4 Q. Fair enough. Thank you.

5 Could I ask you to turn to page 51,
6 still in the same section, paragraph 97.

7 A. Okay.

8 Q. Or, actually, you can -- you can skip
9 ahead to 57.

10 A. (Witness complying.)

11 Q. And I would direct your attention to
12 paragraph 110. Are you there?

13 A. Yes.

14 Q. So this is a section where perhaps the
15 title says it all: "A POSA Was Motivated to
16 Include Benzyl Alcohol in the Intranasal Spray
17 of Gwozdz Despite Any Potential Irritation."

18 Do you see that?

19 A. I do.

20 Q. You offer the opinion in this paragraph
21 that the person of ordinary skill would have
22 been motivated to select benzyl alcohol as an
23 excipient to add to the Gwozdz PTC solution,
24 correct?

25 A. Or to -- yes, to include in a solution

1 as described by Gwozdz, yes.

2 Q. Now, would you agree with me that the
3 only reason you cite for such a motivation is
4 that benzyl alcohol acts as a preservative?

5 MR. DEMING: Object to form.

6 THE WITNESS: (Reviewing document.)

7 No, I mean benzyl -- I -- the reason
8 for inclusion would be that benzyl alcohol is an
9 alcohol. Benzyl alcohol is identified by Gwozdz
10 and benzyl alcohol is -- you know, it is capable
11 of solubilizing lipophilic substances. Benzyl
12 alcohol is also used in other diazepam
13 formulations that were known. And, you know, in
14 addition, it functions as an antimicrobial
15 preservative in some cases.

16 BY MR. BEST:

17 Q. Well, thank you for reading the
18 paragraph to me. My point was different, so
19 I'll ask it, perhaps, a little differently.

20 The reason to select benzyl alcohol as
21 opposed to the other alcohols that are disclosed
22 in Gwozdz that you cite is benzyl alcohol's
23 putative function as an antimicrobial
24 preservative, correct?

25 MR. DEMING: Objection to form, asked

1 and answered.

2 THE WITNESS: And I don't think that's
3 what this statement in that paragraph says.
4 It's -- the statement about antimicrobial
5 preservatives is -- begins with "Moreover..."

6 So that, in addition to language that
7 it's known to function as an antimicrobial
8 preservative, not only because it was only -- it
9 was not selected directly because of its
10 antimicrobial preservative properties as one of
11 the solvents that Gwozdz identifies -- or one of
12 the alcohols that Gwozdz names.

13 BY MR. BEST:

14 Q. Gwozdz names several different
15 alcohols, correct?

16 A. Yes.

17 Q. And so the fact that Gwozdz discloses
18 those alcohols applies equally to each of those
19 alcohols, correct?

20 MR. DEMING: Objection to form.

21 THE WITNESS: As Gwozdz describes them,
22 yes, a POSA would make selections among them,
23 among those alcohols, maybe prioritizing the
24 selection of one or two or however many they
25 would like to test based on potentially other

1 knowledge about the formulation they're
2 preparing, its route of administration.

3 BY MR. BEST:

4 Q. The second reason you stated in a
5 previous answer why you believe benzyl alcohol
6 should have been selected was that it was used
7 in previous diazepam formulations.

8 Do you recall that testimony?

9 A. I do.

10 Q. The fact that -- withdrawn.

11 What about the fact that benzyl alcohol
12 had been included in a prior diazepam
13 formulation suggested to a person of ordinary
14 skill that it should be selected amongst the
15 alcohols that are disclosed in Gwozdz?

16 A. It's suggestive that benzyl alcohol --
17 and we'll use diazepam as an example, but we
18 could use lorazepam also -- that it's likely
19 chemically compatible with the drug and other
20 similar agents in the formulation.

21 This would be -- need to be, certainly,
22 verified, but it's a strongly suggestive aspect.
23 And while -- I'm not sure that it was even
24 generally accepted at the time -- at any time
25 that benzyl alcohol is only serving as an

1 antimicrobial preservative in the compositions
2 that were in the marketplace containing benzyl
3 alcohol.

4 And everybody understands that benzyl
5 alcohol is also a solvent and formulation
6 excipients can play multiple roles, whether
7 those roles are specifically identified in an
8 NDA or in the product descriptions or whatever.
9 So a POSA would also anticipate that there may
10 have been some contribution of the benzyl
11 alcohol to the solubility of the diazepam in
12 that formulation, in addition to the other
13 solvents.

14 Q. Have you any reason to believe the
15 other alcohols identified in Gwozdz are not
16 compatible with diazepam?

17 A. I have -- I have no knowledge of
18 whether those other alcohols would be chemically
19 or physically incompatible or compatible.

20 Diazepam seems to be relatively
21 compatible with low molecular weight alcohols,
22 so I might anticipate that it's likely that it
23 would be, but it just, like every combination,
24 still needs to be checked.

25 Q. Have you any reason to believe that the

1 other alcohols cited by Gwozdz would not act as
2 a solvent for diazepam to some extent?

3 A. I suspect that all of them would
4 solubilize diazepam. To what extent is unknown.

5 Q. The previous formulations of diazepam
6 to which you refer, are those IV formulations?

7 A. They were approved for, I think, IV and
8 IM administration.

9 Q. Those were aqueous formulations,
10 correct?

11 A. I believe they have a water component
12 to them.

13 Q. And they're quite a bit more dilute
14 than the formulations that Gwozdz teaches,
15 correct?

16 A. They have a lower concentration as
17 prepared, yes.

18 Q. They also -- withdrawn.

19 Okay, could I ask you to look at --
20 bear with me a moment. (Pause in proceedings.)

21 Could I ask you to turn to page 62?

22 A. (Witness complying.)

23 Q. And I'm focused on paragraph 121 which
24 is in a large section of your report entitled
25 "Grounds of Unpatentability."

1 A. Yes.

2 Q. Are you there?

3 A. Yes.

4 Q. Now, in paragraph 121, you state:

5 "... Counsel has explained to me that the
6 'consisting of' language in the claim preamble
7 requires that the claimed solution includes only
8 those components explicitly recited in the
9 claim." And you go on.

10 Do you see that?

11 A. Yes.

12 Q. No claim of the '414 patent states that
13 it includes water, correct?

14 A. That's correct.

15 Q. Nor does any claim of the '546 or '786
16 patents state that it includes water, correct?

17 A. Correct.

18 Q. So you would agree that the claims
19 exclude embodiments that include even small
20 amounts of water, correct?

21 A. Yes.

22 Q. Now, would you turn in your declaration
23 to paragraph, backwards this time, 48.

24 A. (Witness complying.)

25 Q. It should be on about page 26.

1 A. I'm there.

2 Q. So I'd like to return to your opinions
3 concerning priority date.

4 As I understand it, in your view, a
5 person of ordinary skill reading the '558
6 provisional, Exhibit 8, that we looked at
7 earlier, would have understood it as disclosing
8 "various enhancers and identifying the
9 mechanisms of enhancement by which they were
10 known to function," correct?

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

12 Q. And in particular -- let's see where it
13 says it. Um... bear with me. (Pause in
14 proceedings.) Okay, withdrawn.

15 The second sentence of paragraph 48
16 discusses what you believe a person of ordinary
17 skill would have understood, including that the
18 descriptions in paragraphs 150 to 152 of
19 Exhibit 8 are directed to "compounds which
20 increase permeability of the mucosal cell
21 membranes."

22 Do you see that?

23 A. (Reviewing document.)

24 Yes.

25 Q. At the end of paragraph 48, you go on

1 to say "The '558 Provisional discloses a vast
2 number of potential candidates in paragraph 152,
3 without any direction as to which compound
4 classes are preferred, or any guidance for
5 choosing one candidate over another."

6 Do you see that?

7 A. Yes.

8 Q. Now, is it your understanding that in
9 order to provide a written description for this
10 case, that the '558 provisional must provide an
11 identification of which compound or classes of
12 compounds are preferred?

13 A. (Reviewing document.)

14 Well, as stated in my declaration on
15 page 22, paragraph 41, that "to benefit from a
16 claim of priority to an originally filed
17 disclosure, the originally filed disclosure must
18 contain a written description of the invention
19 as claimed in the latter application, and of the
20 matter" -- or "of the manner and process of
21 making and using it, in such full, clear,
22 concise, and exact terms as to enable any person
23 of ordinary skill in the art to make and use the
24 invention as claimed."

25 Q. Thank you for that. And for the

1 record, before answering my question, you
2 consulted and read through paragraph 41; is that
3 correct?

4 A. I did, yes.

5 Q. Did you consult or read through
6 anything else?

7 A. I think, centered, I looked over
8 paragraph 40.

9 Q. Okay. So directing your attention back
10 to the end of paragraph 48, you state, as I
11 said, that the '558 provisional discloses a vast
12 number of potential candidates without any
13 direction as to which compound classes were
14 preferred or guidance for choosing one candidate
15 over another, correct?

16 A. That's correct.

17 Q. What is the weight of that --
18 withdrawn.

19 Why did you say that, since that
20 discussion is not found in paragraph 41 that you
21 reviewed a moment ago?

22 MR. DEMING: Objection to form.

23 THE WITNESS: Well, that discussion is
24 a continuation of being able to provide the
25 information that would enable a -- enable

1 someone to make, use and -- or a person of
2 ordinary skill in the art to make or use the
3 process or the manner or the invention and
4 the -- even if the patent application had
5 described something that was potentially
6 preferred or any guidance about one of the
7 extremely large number of potential classes and
8 types of reported absorption enhancers, there
9 might have been some information that could be
10 viewed as information about the manner and
11 process of making and using the invention in a
12 full and clear and concise and exact terms that
13 would enable a person of ordinary skill in the
14 art to make and use the invention.

15 BY MR. BEST:

16 Q. So there's a lot there. I'm going to
17 unpack it a bit.

18 Did the legal standard for evaluating a
19 written description that you applied require the
20 patent owner to have stated a preference as to
21 either compound classes or a particular compound
22 in the provisional application?

23 A. Again, the requirement that I
24 understand is that the written description needs
25 to provide information about the manner and

1 process of making and using the invention in
2 full, clear, concise and exact terms sufficient
3 to enable a person of ordinary skill in the art
4 to make and use the invention.

5 Q. So that's a no, correct?

6 A. That's my answer.

7 Q. Your answer is to read me paragraph 41
8 of your report again?

9 A. Yes --

10 Q. Yeah.

11 A. -- because that's my understanding of
12 the legal standard.

13 Q. Okay, so if that's your understanding
14 of the legal standard, then it's irrelevant to
15 the legal standard whether the inventor has
16 stated a preference as to the compound or the
17 compound categories, correct?

18 MR. DEMING: Objection to form,
19 argumentative.

20 THE WITNESS: I don't think it's
21 irrelevant. As I stated before, the -- that
22 statement at the end of paragraph 48 is a
23 continuation of the thought of the analysis
24 about -- and the legal standard for "written
25 description."

1 BY MR. BEST:

2 Q. Okay. So if you would look further --
3 bear with me -- to paragraph 50 in the same
4 section.

5 A. (Witness complying.)

6 Q. And I'd direct your attention to the
7 sentence that begins "Additionally..." the
8 penultimate sentence of the paragraph.

9 A. (Reviewing document.)

10 Q. Here, you say: "... it would require
11 the POSA to conduct undue experimentation to
12 determine whether any of the alkyl glycosides
13 are useful or preferred over any of the other
14 biological detergent candidates."

15 Do you see that?

16 A. Yes.

17 Q. So is it the case that part of the
18 written description standard that you applied in
19 evaluating priority in this case was to assess
20 whether the person of ordinary skill would have
21 had to conduct undue experimentation to identify
22 a preferred biological detergent candidate?

23 A. (Reviewing document.)

24 Well, I was looking to see whether in
25 the section on Legal Understanding there was

1 something that specifically used the phrase
2 "undue experimentation." And I thought there
3 was, but I don't find it.

4 Repeat the question, and I'll get ready
5 to answer it.

6 Q. I will, but could you just identify for
7 me what you consulted in your declaration before
8 responding to my question so that I can follow
9 along?

10 A. I quickly looked through Section 5,
11 Legal Understanding.

12 Q. Okay, thank you. So I'll withdraw the
13 previous question and ask it again.

14 Am I correct that part of the written
15 description standard you applied in evaluating
16 priority in this case was to assess whether the
17 person of ordinary skill would have had to
18 conduct undue experimentation to identify a
19 preferred biological detergent candidate?

20 A. (Reviewing document.)

21 Well, paragraph 50 explains my
22 evaluation process in arriving at my opinion
23 that the provisional application doesn't
24 identify with detail and particularly --
25 particularity that it is incorporating the alkyl

1 glycosides referred to in the Sigma catalog.

2 And then a few descriptions about the
3 listings in the Sigma catalog: "... it would
4 require the POSA to conduct undue
5 experimentation to determine whether any of the
6 alkyl glycosides are useful or preferred over
7 any of the other biological detergent
8 candidates."

9 I understand that there are legal
10 evaluations regarding "undue experimentation,"
11 and so I'm going to step from that particular
12 phrase so that it's clear that part of my
13 opinion and evaluation of the Sigma catalog
14 listings is that there are many, many, many,
15 many surfactants of different types and
16 different characteristics in the Sigma catalog,
17 and the provisional application does not
18 describe anything about any of them and would
19 not provide sufficient information -- let me
20 just find that -- for a person of ordinary skill
21 in the art to prepare, make, use the invention.

22 Q. Thank you. So am I correct then in
23 understanding that you applied an undue
24 experimentation analysis in evaluating the
25 written description support for the claims of

1 the challenged patents in this case?

2 A. I evaluated a number of different
3 materials and a knowledge of the types of
4 experiments that would need to be conducted to
5 identify whether any of them were useful at any
6 particular concentration for the descriptions of
7 the invention or the intention of the invention,
8 and I -- my opinion is there are a huge number
9 of surfactants, there's a large number of
10 experiments even for each surfactant that would
11 need to be conducted to actually put it into
12 practice with or in the invention as described.

13 Q. So yes or no, did you apply an undue
14 experimentation standard to evaluate priority in
15 this matter?

16 MR. DEMING: Objection to form.

17 THE WITNESS: If you would like to
18 explain to me the legal standard for "undue
19 experimentation" analysis, I can answer that
20 question. I've told you what I've done and what
21 I've considered.

22 BY MR. BEST:

23 Q. So your testimony, as I understand it,
24 is that without me explaining what "undue
25 experimentation" is to you, you don't know

1 whether you applied an undue experimentation
2 standard in evaluating priority in this case,
3 correct?

4 MR. DEMING: Objection, form.

5 THE WITNESS: I under- -- I've used the
6 term "undue experimentation." I believe I have
7 a clear understanding, and my conversations with
8 counsel have me agree that I understand what
9 "undue experimentation" is.

10 I don't have a specific description of
11 it in my Legal Understanding section.
12 Therefore, I've given you essentially my
13 understanding of the process to determine "undue
14 experimentation."

15 You're indicating there's a standard.
16 I don't know exactly what standard it is you're
17 referring to. I don't have it in my Legal
18 Understanding description. Therefore, I've
19 provided you my process of evaluation.

20 BY MR. BEST:

21 Q. When I refer to a "standard," I'm
22 asking you whether -- withdrawn.

23 When I refer to "a standard," I'm
24 asking you what standard you applied in figuring
25 out priority and the opinions about priority you

1 rendered in this case.

2 MR. DEMING: Objection, form, asked and
3 answered.

4 THE WITNESS: And I've told you that I
5 evaluated the number of surfactants and types of
6 surfactants that were provided in the Sigma
7 catalog listing and the knowledge of the number
8 of experiments regarding each specific
9 surfactant even that would need to be conducted
10 to determine whether it could be used
11 successfully in the invention described in the
12 application. And that large number of
13 experiments, I believe, would qualify as "undue
14 experimentation."

15 BY MR. BEST:

16 Q. So I think I, perhaps, understand.
17 Withdrawn.

18 You would agree with me that as you
19 understand the term "undue experimentation,"
20 that is an analysis you applied in evaluating
21 priority in this case, correct?

22 A. Well, I applied it in evaluating the
23 information provided in the Sigma catalog and
24 how a POSA would use that information regarding
25 the invention described in the application.

1 Q. For the purposes of evaluating priority
2 in this case?

3 MR. DEMING: Objection to form.

4 THE WITNESS: It -- I mean, the end
5 result is for the purpose of evaluating whether
6 there was sufficient information in the
7 application to support claims in another patent
8 and whether there was a relationship between
9 that application and those -- yeah, those other
10 claims.

11 BY MR. BEST:

12 Q. You indicated you have an understanding
13 of what the concept of -- what a concept of
14 "undue experimentation" is. What is that
15 understanding?

16 A. That it is -- I mean, it's -- in
17 context of what the experiments certainly are
18 and the level of skill in the art and what it
19 would take to accomplish those undue
20 experimentation in some senses could be two
21 experiments, but they could take a year to
22 accomplish each experiment.

23 Specifically regarding this, the "undue
24 experimentation" is you would need to reproduce
25 numerous experiments, experiments that are

1 certainly known to POSAs about how to conduct,
2 but that there are so many choices and, again,
3 levels of concentrations within the -- within
4 even the surfactants outside of the rest of the
5 elements of the invention, that someone could
6 spend years trying to evaluate which of the
7 combinations and components actually work for
8 the invention as described and which don't.

9 Q. When you say "work," what do you mean?

10 A. That they accomplish what the invention
11 tells us the invention is.

12 Q. The invention is what is stated in the
13 claims, correct?

14 A. Yes.

15 Q. What is stated in the claims is a
16 mixture of components, correct?

17 MR. DEMING: Objection to form.

18 THE WITNESS: In the '414? Or...

19 BY MR. BEST:

20 Q. Let's start with that.

21 A. In the application? Or...

22 Q. Yes, let's start with the '414 patent.
23 If you look at the claims of the '414 patent --

24 A. (Reviewing document.)

25 Q. -- what is stated in the claims is a

1 pharmaceutical composition having various
2 components, correct?

3 A. Can you say that again, please?

4 Q. Sure. The claims of the '414 patent in
5 describing what the invention is say it's a
6 pharmaceutical solution for nasal administration
7 consisting of various components, correct?

8 A. Yes, "consisting of several
9 components."

10 Q. That's the invention of certainly
11 Claim 1 and, in variations, the remainder of the
12 claims, correct?

13 A. Yes.

14 Q. And that's also true about the '786
15 patent, correct?

16 A. That's my recollection. (Reviewing
17 document.)

18 The '786 patent also requires
19 therapeutic effectiveness of this -- the
20 pharmaceutical solution, but same
21 multicomponent, multilevel potential component
22 combinations as the pharmaceutical solution.

23 Q. And the same is true of the '546
24 patent?

25 A. Yes.

1 Q. That it recites pharmaceutical
2 solutions having various components?

3 A. Yes.

4 Q. That's the invention of the claims of
5 the '546 patent?

6 A. That's what is the claimed invention,
7 yes.

8 Q. In forming your opinion that the claims
9 of the '414 patent cannot trace priority to the
10 '558 provisional, did you require that the '558
11 provisional enable a person of ordinary skill to
12 make and use the invention that the '414 patent
13 claims?

14 MR. DEMING: Objection to form.

15 THE WITNESS: (Reviewing document.)

16 I'll direct you -- I'm reading. I'm at
17 paragraph 42 in my declaration, and as stated,
18 my understanding is: "The disclosures
19 originally filed in the earlier application or
20 patent must convey with reasonable clarity to
21 those skilled in the art that the inventor was
22 in possession of the invention."

23 And then, moving on, and: "A
24 disclosure in the parent application that merely
25 renders the latter claimed invention obvious is

1 not sufficient to meet the written description
2 requirement; the disclosure must describe the
3 claimed invention with all its limitations."

4 So when you were asking whether I
5 believed that the application needs to enable
6 the -- enable the claims for the '414 in this
7 case, it, again, needs to provide the components
8 of what is included in an enablement analysis,
9 but it requires what I stated, that "The
10 disclosure must convey with reasonable clarity
11 to those skilled in the art the inventor was in
12 possession of the invention" and that and it has
13 to describe "the claimed invention with all of
14 its limitations."

15 BY MR. BEST:

16 Q. Thank you for that.

17 Before responding to my question, am I
18 correct in assuming you again consulted your
19 Legal Standard section of your declaration?

20 A. Briefly.

21 Q. Well, two or three minutes.

22 But, in any event, I don't think I got
23 a clear answer, so I'm going to ask it maybe a
24 slightly different way. Withdrawn.

25 In forming your opinions that the '414

1 patent cannot trace priority to the '558
2 provisional, did you require that the '558
3 provisional enable a person of ordinary skill to
4 make and use the invention the '414 patent
5 claims?

6 MR. DEMING: Objection to form, asked
7 and answered.

8 THE WITNESS: Again, you're using a
9 specific legal definition term that I'm aware
10 of, "enablement," but I don't have an
11 "enablement" definition in my Legal
12 Understanding section.

13 I have a working understanding of
14 "enablement," but I don't have an exacting
15 recollection of the standard and the portion
16 of -- portions of paragraph 42 that I read and
17 I -- are my opinions, speak to "enablement."

18 I just can't tell you which part of the
19 enablement standard as legally described, so I
20 can't answer the question directly about
21 "enablement" as you have stated it.

22 I understand that "enablement" is part
23 of the description that I have read and/or
24 speaks to -- this (indicating to document)
25 speaks to "enablement," but I can't answer

1 completely regarding a legal standard that I
2 don't -- I can't review at this moment.

3 BY MR. BEST:

4 Q. When you said "this" in your response,
5 are you referring to paragraph 42?

6 A. Paragraph 42. There's some sections of
7 paragraph 45 that I could also read into the
8 record that also speak to -- the patent
9 application and a description in the patent
10 application, again, as I said previously, have
11 to provide "the manner and process of making,
12 using the invention in a full, clear, concise,
13 and exact terms to enable a person of ordinary
14 skill in the art to make and use the invention
15 as claimed," which is at least I -- the enable
16 term is there. And counsel helped me prepare
17 this declaration. I am sure it's used
18 correctly.

19 Q. So you did require that the '558
20 provisional enable the invention claimed in the
21 '414 patent in order that it provide a priority
22 claim for those patent claims, correct?

23 MR. DEMING: Objection, form, asked and
24 answered.

25 THE WITNESS: My opinion is "the

1 originally filed application disclosure must
2 contain a written description of the invention
3 as claimed in the latter application and of the
4 manner and process of making and using it in
5 such full, clear, concise, and exact terms as to
6 enable any person of ordinary skill in the art
7 to make and use the invention as claimed."

8 BY MR. BEST:

9 Q. So you would agree that the standard
10 that you applied in evaluating priority required
11 that the '558 patent provide a process of making
12 and using the claimed invention of the '414
13 patent in exact terms so as to enable a person
14 of ordinary skill in the art to make and use the
15 invention as claimed, correct?

16 MR. DEMING: Objection, form, asked and
17 answered.

18 THE WITNESS: (Reviewing document.)

19 I'm going to provide the answer I
20 provided in my opinion on paragraph 41, that I
21 have been informed that "to benefit from a claim
22 of priority to originally filed disclosure, the
23 originally filed disclosure must contain a
24 written description of the invention as claimed
25 in the latter application, and of the manner and

1 process of making and using it, in such full,
2 clear, concise, and exact terms to enable any
3 person of ordinary skill in the art to make and
4 use the invention as claimed."

5 BY MR. BEST:

6 Q. Okay. Then I think we can agree that,
7 in evaluating priority for the claims of the
8 '414 patent, you required that the '558
9 application provide quote "the manner and
10 process of making and using it in such full,
11 clear, concise, and exact terms as to enable any
12 person of ordinary skill in the art to make and
13 use the invention as claimed," correct?

14 MR. DEMING: Objection, form, asked and
15 answered.

16 THE WITNESS: (Reviewing document.)

17 And I stand by my answer in
18 paragraph 41.

19 BY MR. BEST:

20 Q. I just quoted your answer in
21 paragraph 41.

22 A. And that's the statement of my opinion.

23 Q. So you agree with the fact that you
24 applied, in evaluating priority, the standard
25 that in part required that the '558 application

1 provide "the manner and process of making and
2 using it," where "it" refers to the '414 patent
3 claims "in such full, clear, concise, and exact
4 terms as to enable any person of ordinary skill
5 in the art to make and use the invention as
6 claimed," correct?

7 MR. DEMING: Objection, form, asked and
8 answered.

9 THE WITNESS: And what I did in my
10 evaluation regarding this particular topic is
11 described in paragraph 41, which states "I have
12 been informed that to be entitled to an earlier
13 priority date, each claim limitation must be
14 expressly, implicitly, or inherently supported
15 in the originally filed disclosure. I
16 understand this to mean that each element of the
17 claims has a specific priority date, based on
18 when that specific element was previously
19 supported in the '786 Patent, the '439
20 Application and/or the '558 Provisional
21 disclosures. I have also been informed that to
22 benefit in a claim of priority to an originally
23 filed disclosure, the originally filed
24 disclosure must contain a written description of
25 the invention as claimed in the latter

1 application (i.e. in the '414 Patent), and of
2 the manner and process of making and using it,
3 in such full, clear, concise, and exact terms as
4 to enable any person of ordinary skill in the
5 art to make and use the invention as claimed."

6 BY MR. BEST:

7 Q. Did I misquote you in any way when I
8 asked you the previous question I asked you?

9 A. No, but you only read a portion of that
10 paragraph, and I felt it was important to have
11 the complete paragraph in the record.

12 Q. My previous question asked whether in
13 evaluating priority, the standard you applied in
14 part required the quotation at the end of
15 paragraph 41 I rendered.

16 Do you recall that question?

17 MR. DEMING: Objection, argumentative.

18 THE WITNESS: Yes.

19 BY MR. BEST:

20 Q. Okay. So I was not asking -- I was --
21 withdrawn.

22 I was not limiting the reasons that you
23 may have had for evaluating priority to only
24 that quotation. You understand that, correct?

25 MR. DEMING: Objection.

1 THE WITNESS: I accept that, yes.

2 BY MR. BEST:

3 Q. Okay. So why could you simply not
4 answer "yes" to the question I asked since I was
5 quoting you?

6 MR. DEMING: Objection, form,
7 argumentative.

8 THE WITNESS: Because I wanted a clear
9 understanding of what that -- where that
10 statement was derived in the information I
11 provided in my opinion in my declaration.

12 BY MR. BEST:

13 Q. Okay. Would you provide the same
14 answer with respect to -- withdrawn.

15 With respect to the '546 patent and the
16 '786 patent, did you provide a standard for
17 evaluating priority that required, in part, "the
18 manner and process of making and using it" where
19 it refers to the claimed invention of those
20 patents "in such full, clear, concise, and exact
21 terms as to enable any person of ordinary skill
22 in the art to make and use the invention as
23 claimed"?

24 MR. DEMING: Objection, form.

25 THE WITNESS: (Reviewing document.)

1 All right, so I've checked to make sure
2 that the sufficiently similar paragraphs in my
3 declaration for the '546 patent, the '786 patent
4 and the '414 patent appear in my written
5 declarations, and, of course, now'd be a good
6 time to repeat the question so I make sure I
7 answer your question.

8 BY MR. BEST:

9 Q. Sure. No problem. And for the record,
10 you're referring to paragraphs 42 of your '546
11 declaration and, I guess, 42 of the '786 as
12 well; is that correct?

13 A. No, I don't think the paragraph numbers
14 are right. So it'd be paragraph 42 and 43 of
15 the '546, paragraph 42 and 43 of the '786, and
16 41 and 42 in the '414 declaration.

17 Q. Okay, thank you. Having reviewed those
18 paragraphs, I'll ask the question once again.
19 Withdrawn.

20 Is it fair to say that with respect to
21 the '546 and '786 patent claims, you, in
22 evaluating their priority date, required that
23 the '558 application disclose "the manner and
24 process of making and using it in such full,
25 clear, concise, and exact terms as to enable any

1 person of ordinary skill in the art to make and
2 use the invention as claimed," where "it" refers
3 to the claimed invention of the patents?

4 A. And as stated previously, that's --
5 I've been informed about the entitlement to
6 earlier priority date for claim limitation using
7 that standard for evaluation and, as described
8 in paragraph 43 of my '786 declaration, that
9 "The person of ordinary skill in the art would
10 recognize that the applicant possessed what is
11 claimed in the latter filed application as of
12 the filing date of the earlier filed application
13 or patent. The disclosure as originally filed
14 in the original application or patent must
15 convey with reasonable clarity to those skilled
16 in the art that the inventor was in possession
17 of the invention, that is, one skilled in the
18 art reading the original disclosure must
19 immediately discern the limitation at issue in
20 the claims. A disclosure in a parent
21 application that merely renders the latter
22 claimed invention obvious is not sufficient to
23 meet the written description requirement. This
24 disclosure must describe the claimed invention
25 with all its limitations."

1 Q. You concluded?

2 A. Yes.

3 Q. So you just read to me the paragraph of
4 one or the other of your other declarations
5 which succeeds the language I used in my
6 question, correct, immediately follows that
7 language?

8 A. Yes.

9 Q. I'm asking you about the preceding
10 paragraph and with respect to your opinions of
11 priority -- withdrawn.

12 In evaluating priority of the '546
13 patent and the '786 patent, did you require that
14 the '558 application provide "the manner and
15 process of making and using it in such full,
16 clear, concise, and exact terms as to enable any
17 person of ordinary skill in the art to make and
18 use the invention as claimed," where "it" refers
19 to the claimed invention of those patents?

20 MR. DEMING: Objection to form, asked
21 and answered.

22 THE WITNESS: And my answer is: In
23 paragraphs 42 and 43, I describe my
24 understanding of the legal requirements for
25 determination of the earliest priority and

1 support for a claim.

2 BY MR. BEST:

3 Q. So you did apply that standard since
4 the language I just read verbatim appears in
5 paragraph 41 of the '414 declaration and 42 of
6 the other declarations, correct?

7 MR. DEMING: Objection, form, asked and
8 answered.

9 THE WITNESS: Paragraph 42 and 43
10 describe what -- my understanding of the
11 determination for the earliest priority and
12 support for a patent claim is, and --

13 BY MR. BEST:

14 Q. That provides your understanding. And
15 that's the standard you applied, correct?

16 MR. DEMING: Objection, form.

17 THE WITNESS: I used that understanding
18 to evaluate the priority dates or -- the
19 priority dates as being described in this
20 application. Again, I rely on counsel for this,
21 and I used my understanding of how a POSA would
22 read the declarations.

23 BY MR. BEST:

24 Q. And when you say the descriptions --

25 A. Or read the descriptions.

1 Q. Sorry.

2 A. I'm sorry, wrong word.

3 Q. When you say "the descriptions" and
4 "this application," are you referring to the
5 '558 provisional?

6 A. Yes.

7 Q. Okay, thank you?

8 MR. BEST: Why don't we take a break.
9 We've been going more than an hour.

10 THE WITNESS: Okay.

11 (Recess taken from 10:10 a.m.
12 to 10:25 a.m.)

13 BY MR. BEST:

14 Q. Welcome back.

15 A. Thanks.

16 Q. Can I ask you to turn in your '414
17 declaration to page 36.

18 A. (Witness complying.)

19 Q. Looks like you're there.

20 A. Yes.

21 Q. Here, you have a discussion concerning
22 a document that you call "EMS."

23 Do you see that?

24 A. Yes. For short of the full title, yes.

25 Q. Right. And that's one of the documents

1 you reviewed in forming your opinions in the
2 case?

3 A. Yes.

4 Q. I think it's Exhibit 1019. Does that
5 look correct from your table?

6 A. Yes.

7 Q. In paragraph 69, in discussing the
8 EMS -- let me try that one again. Withdrawn.

9 In paragraph 69, in discussing the EMS
10 reference, you talk about 5-milligram doses of
11 diazepam that could be administered intranasally
12 in emergencies or seizure patients requiring
13 treatment with benzodiazepines, correct?

14 A. Yes.

15 Q. And why did you include a discussion of
16 this reference here?

17 A. Well, I feel the reference is relevant
18 to the issues at hand because it demonstrates
19 that emergency workers were instructed to and
20 did use the IV commercial form of Valium or
21 diazepam to administer intranasally to
22 individuals in -- that they felt or were told
23 were in need of such an administration.

24 Q. Is it your understanding that this was
25 an effective therapy?

1 A. Yes.

2 Q. And that the dose that is listed there,
3 therefore, is an effective dose in this context?

4 A. That it was effective, and the
5 instructions also indicate that it could be
6 repeated up to a total dose of 20 milligrams if
7 necessary.

8 Q. Okay. Thank you.

9 From your CV, it looks like, unlike
10 most of us, you have been able to spend most of
11 your career at one place in Iowa; is that
12 correct?

13 A. Yes, it is.

14 Q. So have you worked in industry as your
15 primary job at any point?

16 A. Only for short periods. I was an
17 intern in the industry. I did a couple of
18 months' pseudo-sabbatical in the industry.
19 Those were the only times I was essentially
20 employed full time by the pharmaceutical
21 industry.

22 Q. What sort of work did you do in those
23 circumstances?

24 A. So as an intern, I was an early
25 graduate student and I worked in a formulation

1 department under the mentorship of one of their
2 senior formulators and I worked on a couple of
3 different solids development projects.

4 And when I was on my pseudo early
5 sabbatical, I was both learning how the industry
6 worked a little bit more as career development,
7 and I also worked on a -- directly on a project
8 that dealt with intranasal delivery of a peptide
9 compound.

10 Q. Do you happen to recall what compound
11 that was?

12 A. It was vasopressin.

13 Q. Thank you. Have you from your
14 experience, either from the industry or more
15 generally, an understanding of the process of
16 taking a drug from an initial concept to
17 marketed product?

18 A. I have some understanding of that, yes.

19 Q. In general at a high level, how would
20 you describe that process?

21 A. So the process starting with drug
22 discovery and moving forward?

23 Q. Sure.

24 A. Okay, so we'll start with drug
25 discovery. Somehow we discover a potential

1 therapeutic agent for use against a particular
2 pathology, and oftentimes we -- in that
3 discovery, they're going to discover some
4 cousins of that as backup compounds.

5 And a number of pre-clinical studies go
6 on, lots of pharmacology studies, toxicology
7 studies, improvement of the chemical form itself
8 to meet the desired criteria, be it receptor
9 affinity, be it a whole host of things, looking
10 at potential side effects based on other in
11 vitro tests.

12 At some point in time, at least one, if
13 not more than one, of those compounds is
14 selected for further development. Further
15 development begins to involve individuals trying
16 to project a potential human dose and human
17 route of administration and oftentimes at a
18 relatively early point will also involve both
19 pharmacokinetic analyses in animals and will
20 start to involve drug development, formulation
21 development, individuals to be able to prepare
22 both dosage forms appropriate for, first, in
23 human testing, which might not be the final
24 dosage form, and potentially dosage forms that
25 would -- are the preferred final dosage form

1 that were identified for that particular drug.

2 Lots and lots of work goes on both in
3 the formulation development, early clinical
4 evaluations or still probably pre-clinical in
5 animals potentially, designing first in human
6 trials, doing first in human trials to assess
7 safety primarily, potential bit of dose ranging
8 reevaluation, retuning if necessary, maybe we
9 need to select a whole new drug compound because
10 of an unexpected, something that didn't
11 translate from our animal models or their animal
12 models, whatever.

13 Eventually, you get to final dose and
14 regimen, start testing in individuals with the
15 disease state of interest, do larger scale
16 testing. If everything's looking positive,
17 eventually you get to market.

18 On the formulation development side,
19 there could be potential optimization of
20 formulations, certainly optimization of
21 formulations that are also are impacted by where
22 the manufacturing is intended to happen, what
23 kind of equipment's going -- is going to be
24 used, and a number of other things.

25 Q. I assume you're familiar with the U.S.

1 Food and Drug Administration?

2 A. Yes, I am.

3 Q. Usually, it's called "the FDA."

4 A. Yes.

5 Q. At what point in your experience does
6 FDA start playing a role in the development of a
7 drug?

8 MR. DEMING: Objection to form, scope.

9 THE WITNESS: My understanding is they
10 don't really play a role in the development.
11 They evaluate the activities that were done
12 during development.

13 Certainly any human testing has had to
14 meet FDA requirements before it's -- it can take
15 part. So most of the pre-clinical testing that
16 I talked about early in drug discovery, early
17 formulation development and so forth is usually
18 not subject to significant levels of FDA
19 evaluation. Whether there are discussions with
20 the FDA at that time may have -- there may be --
21 especially, if it's a new drug, first-in-class
22 drug, a drug for a particular indication that
23 has multiple character- -- it doesn't have
24 multicharacteris- -- it fits into one of many
25 categories that the FDA provides additional

1 information to speed regulatory processes at
2 times.

3 So, anyway, certainly before anything
4 is approved for human testing, the FDA evaluates
5 the work that was done to evaluate safety,
6 toxicity to assure that that -- those humans are
7 not being put at undue risk, and there are --
8 and then after human clinical testing starts,
9 the FDA is involved in a high-level oversight
10 capacity, again, to ensure human safety,
11 throughout most of the remaining trials.

12 They're not involved in analysis of
13 data or design of trials until the -- usually
14 until the entity submits their New Drug
15 Application, but there are times where the
16 Agency does have conversations, provides
17 direction, provides priorities to assist in the
18 timely development of the drug product.

19 BY MR. BEST:

20 Q. Does FDA play a role in establishing or
21 enforcing the regulations you discussed
22 yesterday concerning microbial load that a drug
23 might have or sterility?

24 A. Yes, certainly at the time of approval
25 of an NDA, the applicant has to demonstrate that

1 they met the FDA requirements for manufacturing
2 of that product, it meets all of the regulatory
3 standards that are in place.

4 And then there's likely monitoring when
5 there's FDA inspections of a production
6 facility. They will look at batch records to
7 ensure that those standards are still being met
8 based on the manufacturing processes and
9 potentially any followup testing that's being
10 done.

11 Q. Are you aware of any other source of
12 regulations for that microbial load issue or
13 sterility issue?

14 A. In the U.S.?

15 Q. In the U.S.

16 A. I believe the FDA usually relies on the
17 USP as the source to describe the testing,
18 methodologies that they will enforce and
19 determine passing levels or characteristics or
20 whatever.

21 Q. Is it the case that a person of
22 ordinary skill would have been in 2008 or '9 --
23 withdrawn.

24 Is it the case that, in 2008 and 2009,
25 a person of ordinary skill would have been

1 mindful of the requirements that FDA would
2 impose on a new pharmaceutical formulation for
3 nasal administration?

4 MR. DEMING: Objection to form.

5 THE WITNESS: The -- they would be or
6 they could be, and oftentimes there are
7 regulatory consultants who are more expert on
8 understanding specific FDA regulations as
9 written, perhaps, not clearly or the actual
10 meaning of a guidance document, for example.

11 And so -- but those were available.
12 There were additional people that could be
13 brought in to help with expertise, if necessary,
14 in 2008, 2009.

15 BY MR. BEST:

16 Q. Have you an understanding of a concept
17 called "GRAS," G-R-A-S?

18 A. Yes.

19 Q. What's your understanding of that?

20 A. So the acronym is "Generally Recognized
21 as Safe."

22 Currently, the GAS list is kept up more
23 for food products than it is for
24 pharmaceuticals. The pharmaceutical products
25 are -- have a tendency to be listed in the -- in

1 the IIG instead and -- but, you know, there can
2 be both. And so if it's a comm- -- if it's an
3 ingredient that's likely to be ingested, there's
4 a possible -- there's a good reason to check the
5 GRAS list to see if it's listed.

6 There are things in the IIG that aren't
7 on the GRAS list. And that's all fine and good,
8 but the GRAS list was certainly historically the
9 list that people looked at for determination of
10 previous safety evaluations of specific agents
11 at -- from -- and -- yeah.

12 Q. When you say "IIG," what do you mean by
13 that?

14 A. The Inactive Ingredient Data -- I guess
15 it's, yeah, Inactive Ingredient Database that is
16 provided by the FDA. It's on their website.

17 Q. What is the importance of GRAS in
18 formulation development, if any?

19 MR. DEMING: Objection to form, scope.

20 THE WITNESS: Usually working with
21 agents that are on the GRAS list at the
22 concentrations or exposure levels that are
23 described on the GRAS list, typically the FDA
24 will accept those excipients as being safe
25 included in a product and won't ask for further

1 toxicology evaluations regarding the excipient
2 itself, and so it reduces the amount of testing
3 if one uses a material that's on the GRAS list.

4 BY MR. BEST:

5 Q. Was that the case in 2008 and 2009?

6 A. Sure.

7 Q. Are you familiar with any ingredients,
8 excipient that would be considered GRAS for one
9 form of delivery, oral for example, but not
10 another?

11 MR. DEMING: Objection to form, scope.

12 THE WITNESS: Well, I mean, outside of
13 the acronym GRAS -- so I can't speak to the
14 actual way the GRAS list is currently set up and
15 whether routes of administration are actually
16 part of that or not. I don't remember
17 accurately. It's more part of the Inactive
18 Ingredient Database.

19 But just on a general knowledge
20 standpoint, there are materials that can be
21 viewed as safe, can be used in pharmaceuticals
22 administered via certain administration sites
23 that can't be administered via other sites in
24 view of safety.

25

1 BY MR. BEST:

2 Q. Is that knowledge that you just
3 described about whether some excipients can be
4 used in one site, but not another, a part of the
5 scope of knowledge a person of ordinary skill
6 would have had in 2008 and 2009 in this case?

7 MR. DEMING: Objection to form, scope.

8 THE WITNESS: Yes, a POSA would be
9 aware that there are site -- administration
10 site-dependent toxicities or exposure site
11 toxicities that result from administration site
12 that have a role in evaluating the potential
13 toxicity of a system.

14 BY MR. BEST:

15 Q. And I assume -- I guess it's implicit
16 in your statements before, but let me just ask
17 directly. Withdrawn.

18 There was a GRAS list in 2008 and 2009?

19 A. I'm assuming there was some form of the
20 GRAS list. Whether it was still being provided
21 in hard copy or whether it was online, I --
22 again, I'm not sure, but there was something.

23 Q. Was there an Inactive Ingredient
24 Database in that timeframe as well?

25 A. I don't remember the timeframe of

1 launch of that, at least the version I'm
2 familiar with online.

3 Q. Okay. Was there a pre online version
4 of the Inactive Ingredient Database in your
5 knowledge?

6 A. I don't remember.

7 Q. Okay. When you formulated your
8 opinions in this case, did you consider whether
9 alkyl glycosides generally, or dodecylmaltoside
10 specifically, were on the GRAS list in
11 2008-2009?

12 A. Not directly, no.

13 Q. Did you do so indirectly?

14 A. Well, it had little impact whether they
15 were on the GRAS list or not in my evaluation,
16 and so I -- I knew of them at that time.

17 I have -- didn't have any specific
18 knowledge of their regulatory status at the
19 time.

20 Q. Okay. And so is it fair to say the
21 same -- withdrawn.

22 Have you a sense of whether --
23 withdrawn.

24 Do you know whether dodecylmaltoside or
25 alkyl glycosides were on the Inactive Ingredient

1 Database?

2 MR. DEMING: Objection to form.

3 THE WITNESS: Currently?

4 BY MR. BEST:

5 Q. Currently, first off.

6 A. I don't know specifically. I suspect
7 they would be or could be. I don't know how the
8 FDA determines when it populates the Inactive
9 Ingredient list with a substance.

10 Certainly, the dodecylmaltoside
11 ingredient that are in approved products have
12 been approved for a certain exposure level and
13 route of administration, but whether that has
14 been indicated in the Inactive Ingredient list
15 or whether it's held back because there could be
16 proprietary information since there are only a
17 limited number of products, I don't know. The
18 FDA has -- has interesting ways of determining
19 what -- what and when.

20 But it certainly could be. It
21 doesn't -- I think my understanding is it
22 doesn't have to be immediately, but I would call
23 upon a regulatory expert to help me with that if
24 I needed it.

25 Q. I think it's implicit in your previous

1 answer, but I'll ask directly.

2 Is it the case that you're unaware
3 whether dodecylmaltoside or alkyl glycosides
4 were on the Inactive Ingredient Database in 2008
5 or 2009, assuming it existed at that timeframe?

6 MR. DEMING: Objection, scope.

7 THE WITNESS: I -- yes, I do not know,
8 and it wouldn't have an impact on whether that
9 product containing that agent would be
10 approval-able for use in the U.S.

11 BY MR. BEST:

12 Q. Did you investigate whether either the
13 n-Dodecyl-beta-D-maltoside component of some of
14 the claims or the dodecylmaltoside component of
15 the other claims of the challenged patents was
16 considered GRAS in 2008 or 2009?

17 A. Yeah, I --

18 MR. DEMING: Objection, form, scope.

19 THE WITNESS: I don't remember checking
20 the GRAS list for those.

21 BY MR. BEST:

22 Q. Okay. I think its implicit, but I'm
23 going to ask it anyway.

24 Is it also the case you didn't check,
25 assuming there was an Inactive Ingredient

1 Database in 2008-2009, whether those components
2 were on it in that timeframe?

3 MR. DEMING: Same objection.

4 THE WITNESS: Right. And, no, I didn't
5 check. It doesn't limit my ability to evaluate
6 a formulation, nor does it necessarily direct my
7 own research activities about whether materials
8 are on the GRAS list or not. Some materials,
9 yes, others, no, depending on...

10 Q. Have you -- withdrawn.

11 Do you regularly or have you ever
12 checked the GRAS list to determine whether
13 something you're working on is on the list?

14 A. Sometimes --

15 MR. DEMING: Objection, scope.

16 THE WITNESS: Sometimes, yes. I more
17 frequently check the Inactive Ingredient
18 Database now, but, yes, there are times,
19 especially materials where I am interested in
20 knowing what the approved levels and routes of
21 administration for a particular ingredient are.

22 BY MR. BEST:

23 Q. If a person of ordinary skill in 2008
24 and 2009 were going to add a non-GRAS substance
25 to an intranasal pharmaceutical formulation,

1 what kind of testing, if any, would that have
2 required in your view?

3 A. My understanding is it requires
4 additional toxicity and toxicology testing,
5 especially regarding the excipient itself
6 presented at the -- well, both presented at the
7 intended administration site and potentially at
8 other sites, sort of depending on what the
9 product is, and probably evidence where it's
10 unlikely to appear at some site that then
11 doesn't need to be tested.

12 But typically, there's a relatively
13 significant toxicology package that has to be
14 built around that ingredient to demonstrate its
15 safety at the levels that are intended for use
16 in the product.

17 Q. Okay, thank you.

18 I'd like to go back to Exhibit 1010,
19 which is the Meezan document. If you could pull
20 that out. And when you have it, could I direct
21 your attention to paragraph 56.

22 A. (Witness complying.)

23 Q. Are you there?

24 A. I'm there, yes.

25 Q. And my question is: Am I correct --

1 withdrawn.

2 Would you agree with me that
3 paragraph 56 provides no guidance as to whether
4 a particular alkyl glycoside or saccharide alkyl
5 ester is preferred?

6 MR. DEMING: Objection, form, asked and
7 answered.

8 THE WITNESS: (Reviewing document.)

9 The list in the paragraph is simply
10 prefaced by there -- here's a list, can include,
11 but isn't limited to. There's no specific
12 statement about preference.

13 BY MR. BEST:

14 Q. Okay, thank you. And could you page
15 forward to page 15 of the document?

16 A. (Witness complying.)

17 Q. We looked yesterday at paragraph 159,
18 and I'd like you to look there again.

19 A. (Witness complying.)

20 Q. The first sentence states that: "The
21 absorption enhancing effects of the saccharide
22 alkyls were not confined to the alkylmaltosides
23 alone since dodecylsucrose (0.125%, 0.25%,
24 0.375%) also shows a dose-dependent effect in
25 producing ocular absorption of insulin and

1 reduction in blood glucose levels. This effect
2 is observed even at 0.125% saccharide alkyl..."
3 and it goes on.

4 Do you see that?

5 A. Yes.

6 Q. So paragraph 159 is indicating that
7 0.125% of decylsucrose is effective at producing
8 absorption of enhancement of insulin, correct?

9 A. That's what the description states,
10 yes.

11 Q. And the preceding paragraph, 158,
12 states that, in contrast, "0.125% is
13 ineffective" with respect to dodecylmaltoside,
14 correct?

15 MR. DEMING: Objection, form.

16 THE WITNESS: (Reviewing document.)

17 Yes, that's the evaluation comment
18 regarding the data in Table 1.

19 BY MR. BEST:

20 Q. So at 0.125% dodecylsucrose is more
21 effective than dodecylmaltoside, correct?

22 MR. DEMING: Objection, form.

23 THE WITNESS: If everything else was
24 held constant within or between those
25 experiments, it certainly is suggestive that for

1 insulin under these circumstances in this animal
2 model that the 0.125% saccharide alkyl may have
3 been more effective than the 0.125%
4 dodecylmaltoside, but -- one would need to
5 actually look at the data and the variance and
6 things to be assured of that, but that's what it
7 states. So...

8 BY MR. BEST:

9 Q. And you would agree with me that
10 there's no indication in Meezan that there were
11 any differences between the conditions under
12 which those two experiments occurred, correct?

13 A. Meezan is pretty moot on what else
14 about those particular experiments was
15 happening.

16 Q. When you say "moot," do you mean mute?

17 A. Okay, mute is fine, but -- you know,
18 there's some information about how the
19 experiments were conducted, but kind of limited
20 information about formulations.

21 Q. Got it. With respect to paragraph --
22 withdrawn.

23 Could I direct your attention to
24 paragraph 164?

25 A. Okay.

1 Q. Here, there's a discussion of the use
2 of tetradecylmaltoside, or TDM, in
3 insulin-containing eye drops administered to
4 rats, correct?

5 A. Well, they also include nose drops in
6 the description, but, yes, eye drops also.

7 Q. Sure. Absolutely. And just focusing
8 first on the eye drops, those eye drops of
9 tetradecylmaltoside employed 0.125%
10 tetradecylmaltoside, correct?

11 A. That's what the table -- data table
12 indicates.

13 Q. And a by "the data table," you're
14 referring to Table 2, correct?

15 A. Yes.

16 Q. And according to Meezan, 0.125%
17 tetradecylmaltoside produced "a prompt and
18 prominent drop in blood glucose levels."

19 Do you see that?

20 A. Yes.

21 Q. Meaning that tetradecylmaltoside
22 produced an absorption enhancement effect on the
23 insulin in the eye drops that were administered,
24 correct?

25 A. Yes.

1 Q. And, again, in contrast,
2 dodecylmaltoside at that same dose, let's say,
3 also was ineffective?

4 MR. DEMING: Objection.

5 MR. BEST: Withdrawn.

6 BY MR. BEST:

7 Q. In contrast, dodecylmaltoside at that
8 same dose, 0.125%, was ineffective, correct?

9 MR. DEMING: Objection to form.

10 THE WITNESS: Well, based on a
11 comparison of the data between Table 1 and
12 Table 2, it's suggestive that the 0.125%
13 dodecylmaltoside had limited effect on that
14 experimental group.

15 The effect seems more significant in
16 the -- in the group described in Table 2. And
17 Table 2 doesn't include any indication of
18 standard deviation or variation that Table 1
19 has, so it's really pretty difficult to actually
20 evaluate those numbers.

21 Statements -- Meezan's interpretation,
22 you know, would lead you to that 0.125%
23 tetradecylmaltoside was effective, and the data
24 they provide in Table 1 does not look like, at
25 least for the group of animals, that group wise

1 there was any statistical change in the blood
2 glucose concentrations.

3 BY MR. BEST:

4 Q. Which is consistent with Meezan's
5 statement that 0.125% was ineffective, correct?

6 A. With Meezan's statement, yes.

7 Q. And the reduction that is shown in
8 blood glucose levels in Table 2 is consistent
9 with Meezan's statement that there is a prompt
10 and prominent drop in blood glucose levels,
11 correct?

12 MR. DEMING: Objection to form.

13 THE WITNESS: Yes, potentially for the
14 one rat that was tested.

15 BY MR. BEST:

16 Q. Could I ask you to -- it's probably on
17 separate pages -- withdrawn.

18 Would you please look at Table 3.

19 A. (Witness complying.)

20 Q. Table 3 presents data for
21 insulin-containing eye drops that included three
22 different surfactants, dodecylsucrose,
23 decylmaltoside and tridecylmaltoside, correct?

24 A. That's what the table states, yes.

25 Q. And over the time course from 0 to

1 120 minutes over which the insulin eye drops
2 were added at 0.5% concentration, all of those
3 three agents showed reduction in blood glucose
4 levels, correct?

5 A. That's what the data suggests, yes.

6 Q. And the levels at 120 minutes for those
7 three surfactants are, for dodecylsucrose 112,
8 for decylmaltoside 87, and for tridecylmaltoside
9 75, correct?

10 A. As shown in the table, yes. I'm not
11 sure whether those represent a mean or an
12 individual value, but that's what the numbers
13 state.

14 Q. If you turn back a page to page 15,
15 Table 1 -- there's a column of information in
16 Table 1 pertaining to eye drops containing
17 dodecylmaltoside at 0.5%, the right-hand column,
18 correct?

19 A. Yes.

20 Q. And that's the same concentration of
21 alcohol glycoside that was present in the eye
22 drops in Table 3, correct?

23 A. Yes.

24 Q. The data for the 0.5% dodecylmaltoside
25 show a drop from T zero of 379 to 120 minutes of

1 123, correct?

2 A. With the error variance included in
3 those numbers, yes.

4 Q. That's right. And the error variance
5 on the 120-minute number is plus or minus 5,
6 correct?

7 A. Yes.

8 Q. So the lowest value that would fall
9 within those error bars for the 0.5%
10 dodecylmaltoside would be 118, correct?

11 A. Within two standard deviations,
12 essentially, yes.

13 Q. Okay. And 118 --

14 A. Or within, I guess, 1 standard
15 deviation. Sorry.

16 Q. That's okay.

17 What that demonstrates is that the
18 dodecylmaltoside effectiveness at 0.5% is not as
19 good as any one of the three surfactants stated
20 in Table 3, correct?

21 MR. DEMING: Object to form.

22 THE WITNESS: I don't have any good way
23 of actually evaluating that. The data may be
24 suggestive, but, again, the data in Table 3 may
25 have been for only one animal.

1 Typically when we look at insulin
2 effect when we're measuring blood glucose, we're
3 looking at decrease in blood glucose level, not
4 absolute blood glucose concentration in the
5 subjects. So again, suggestive, but wouldn't
6 draw a hard and fast conclusion based on the
7 data provided.

8 BY MR. BEST:

9 Q. Suggestive that the three surfactants
10 that are evaluated in Table 3 provide a better
11 absorption enhancement effect on insulin than
12 does dodecylmaltoside, correct?

13 MR. DEMING: Objection to form, asked
14 and answered.

15 THE WITNESS: Maybe.

16 BY MR. BEST:

17 Q. Well, it has to be suggestive of
18 something. What does it suggest?

19 MR. DEMING: Objection to form, asked
20 and answered.

21 THE WITNESS: It suggests I would like
22 to be sure that this -- the data in Table 3 is
23 representative of more than one subject and it's
24 capable of being reproduced.

25

1 BY MR. BEST:

2 Q. Okay, lacking data that are
3 reproducible from a bunch of animals, you cannot
4 conclude from what Meezan tells you whether or
5 not one of these alkyl glycosides that are
6 evaluated is effective, correct?

7 MR. DEMING: Objection to form.

8 THE WITNESS: Is effective regarding
9 decreasing blood glucose levels or is -- is
10 effective for what?

11 BY MR. BEST:

12 Q. Is effective as an absorption enhancer.

13 MR. DEMING: Object to the form.

14 THE WITNESS: I mean, these data
15 describe the inclusion of various alkyl
16 glycosides with insulin at... I'm not sure I
17 know the insulin concentration here. I think we
18 talked about that yesterday and dose and so
19 forth.

20 But, you know, the data indicate that
21 the dodecyl -- or the alkyl glycosides showed a
22 decrease in blood glucose concentrations
23 following administration. There is also not an
24 administration of control, but again, they're
25 suggestive that there was an effect.

1 BY MR. BEST:

2 Q. Thank you for that, but my question was
3 a bit different, so I'll re-ask it or a version
4 of it. Withdrawn.

5 Absent having reproducible data showing
6 administration to more than one animal, you, at
7 least, cannot conclude from Meezan whether one
8 of the alkyl glycosides that are tested would be
9 effective as absorption enhancers, correct?

10 MR. DEMING: Objection to form, asked
11 and answered.

12 THE WITNESS: No, again, the data in
13 Table 3 indicate that they had -- they had the
14 effect that insulin is known to have to decrease
15 blood glucose and that, again, sort of filling
16 in some of blanks among the experiments, it's
17 certainly suggestive that the inclusion of the
18 alkyl glycosides caused a change in blood
19 glucose level.

20 Some of the comparisons between these
21 and so forth, I'm a little less convinced, but,
22 you know, there is a decrease, it is
23 suggestive -- it's consistent between the alkyl
24 glycosides, and having faith that there were
25 enough controls between the formulations,

1 certainly suggested that the alkyl glycosides
2 did result in a decrease in the blood glucose
3 level.

4 BY MR. BEST:

5 Q. Through enhancement of absorption of
6 insulin?

7 A. Most likely, yes.

8 Q. Okay, thank you.

9 MR. BEST: I would like to take a
10 break. It can be a fairly short one, but I
11 would like to confer with my colleagues.

12 THE WITNESS: Okay.

13 (Recess taken from 11:07 a.m.
14 to 11:16 a.m.)

15 BY MR. BEST:

16 Q. Welcome back.

17 A. Thanks.

18 Q. So yesterday I think the very first
19 document we looked at was the USP entry for
20 Vitamin E. Do you recall looking at that?

21 A. Yes.

22 Q. You can pull it out if you like, but I
23 have a question concerning the packaging and
24 storage discussion in it.

25 I think you suggested or hypothesized

1 that one of the reasons for the cautions that
2 are stated here, to preserve in tight
3 containers, to protect from light, to cover with
4 a blanket of inert gas, was a concern that
5 Vitamin E might oxidize; is that right?

6 A. Oftentimes, those same instructions are
7 provided for materials that oxidize.

8 Q. And is that a form of degradation?

9 A. I -- yeah, I believe that would be a
10 generally-accepted definition. It's a chemical
11 change in the substance and -- and, yeah, we --
12 in pharmaceuticals, we usually refer to those as
13 "degradants."

14 Q. Are you aware, one way or the other, of
15 whether Vitamin E can discolor as it degrades
16 over time?

17 A. (Reviewing document.)

18 I have an estimate, but I don't have an
19 absolute answer. I mean, I know what I think,
20 but I would need further information.

21 I would go look at a couple of other
22 things before I would declare that, yes, I know
23 that it changes -- I know that it can
24 potentially change color, I know that it's kind
25 of available in a spectrum of colors, but -- I

1 think I'm aware that there can be a color change
2 on degradation, but, again, I'd need -- I would
3 look at further support to be sure of that.

4 Q. What would you look at to satisfy
5 yourself of the answer to that question?

6 A. It would potential- -- you know, I
7 might -- if Vitamin E were in the Handbook of
8 Pharmaceutical Excipients, I would look there.
9 And otherwise, I would look -- I could look
10 at -- I could potentially look at other products
11 that were Vitamin E products to see whether
12 there's an indication that they change color
13 when stored inappropriately, or I could go to
14 the primary literature, likely, and find
15 research articles about Vitamin E degradation
16 pathways and mechanisms, and those would likely
17 contain information about changes in color.

18 Q. Is a color change in Vitamin E likely
19 to indicate a form of degradation?

20 A. It indicates some change. It depends
21 on the system, whether it's Vitamin E degrading,
22 whether it's something else.

23 Q. Would a person of ordinary skill have
24 to create the composition in which that person
25 is interested that contains Vitamin E in order

1 to test whether Vitamin E is stable in that
2 system?

3 MR. DEMING: Objection to the form.

4 THE WITNESS: That's probably the most
5 straightforward way to do that.

6 Yeah, I'm unaware of ways to assure
7 chemical stability in a multicomponent system
8 without actually preparing the system. You can
9 make estimates, but...

10 BY MR. BEST:

11 Q. As part of your work in industry on the
12 projects you described earlier, was one of the
13 questions you sought to assess at various times
14 the stability of the components of the
15 formulation system you were investigating?

16 A. At the -- the work I was doing, no.
17 The work I was doing was preparing new batches
18 each time immediately before we were testing
19 them to do whatever we were evaluating. So we
20 were not ready to look at stability of the
21 composition, so we just did immediate
22 preparation.

23 Q. Okay. Before this matter -- by "this
24 matter," I mean your work for Padagis against
25 Neurelis or in cases involving Neurelis -- have

1 you ever testified before on behalf of Padagis,
2 to your knowledge?

3 A. Not to my knowledge.

4 Q. Have you any other relationships with
5 Padagis aside from your position as consultant
6 and expert?

7 A. No.

8 Q. How many cases, roughly, would you say
9 you've been retained as an expert witness in
10 through the years?

11 A. Okay, probably over about 25 years of
12 expert activities, oh, maybe... maybe 50 times.

13 Q. Have you been deposed in most of those
14 50 occasions or in a substantial --
15 substantially less than those occasions?

16 A. I don't think it's 50 percent. I think
17 that's too high an estimate.

18 Q. So you would estimate in fewer than
19 50 percent of the retentions you've discussed
20 you've been deposed previously?

21 A. I think so.

22 Q. Have you testified at trial previously?

23 A. I have.

24 Q. Have you testified at a jury trial?

25 A. I have.

1 Q. And at a bench trial?

2 A. Yes.

3 Q. How many times have you testified at
4 trial, to your recollection?

5 A. It's, I think, four, five.

6 Q. I understand you recently were deposed
7 in a case called "Janssen Pharmaceuticals
8 against Alchem Labs" that's cited in New Jersey,
9 let's say, in October. Does that ring a bell?

10 A. Yes.

11 Q. Without revealing anything confidential
12 about the subject matter, what at a high level
13 was the purpose of your testimony in that case?

14 A. I provided expert testimony regarding
15 obviousness of formulations and -- and -- yeah,
16 I think that -- I know that there were probably
17 a couple of other aspects.

18 Q. In addition to obviousness, have you
19 previously testified concerning the question of
20 whether claims are enabled?

21 A. Yes.

22 Q. Have you testified previously
23 concerning the question of whether claims have
24 written description?

25 A. Yes.

1 Q. Have you testified previously
2 concerning whether claims are anticipated?

3 A. Yes.

4 Q. In the various circumstances that
5 you've offered opinions as an expert, have you
6 ever offered the opinion that claims are
7 non-obvious?

8 A. Yes.

9 Q. Roughly how many times would you guess
10 you've done so?

11 A. I mean, there -- I -- the majority of
12 the claims in one of my engagements I -- my
13 opinion was they were non-obvious.

14 There probably have been others where
15 I -- the claims were non-obvious. I'm not sure
16 those claims were asserted in the particular
17 cases.

18 Q. Have you previously -- withdrawn.

19 In the Janssen against Alchem case,
20 were you offering the opinion that the claims
21 involved were obvious?

22 A. Yes.

23 Q. About how many times before this case,
24 meaning ours, have you offered the opinion that
25 claims are obvious?

1 A. I guess the majority of my engagements
2 have led to my reaching the opinion that the
3 claims at hand were obvious.

4 Q. Have you worked -- withdrawn.

5 Do you understand the distinction that
6 is often drawn between brand pharmaceutical
7 companies, on the one hand, and generics, on the
8 other?

9 A. Yeah, what kind of distinction?

10 Q. Just --

11 A. Business plans or locations? I mean,
12 size of company? What distinction?

13 Q. The categorization, the fact that there
14 are, on the one hand, brand companies and, the
15 other hand, generic companies.

16 A. On a very high level
17 compare-and-contrast based in their API
18 situations, yes.

19 Q. About how much percentage-wise, let's
20 say, of the work you have done where you've
21 offered expert opinions in patent matters has
22 been for brand companies as you understand that?

23 A. Yeah, probably less than 10 percent.

24 Q. And has the remainder then been for
25 generics?

1 A. In a general sense, yes.

2 Q. Have you, in your recollection, ever
3 had any of your opinions excluded by a court?

4 A. Not to my knowledge.

5 Q. Without revealing the content of any
6 conversations you may or may not have had with
7 counsel, did you do anything to prepare for your
8 depositions yesterday and today?

9 A. Yes.

10 Q. Again, without revealing any
11 conversations, what did you do?

12 A. I read my dec- -- read or glanced
13 through in the case of -- the declarations had
14 some overlap, so I read one version and glanced
15 at the changes in the other versions. I read
16 some of the -- re-read some of the documents
17 that I used initially to come to my opinions. I
18 spoke with counsel. Um... that's most of what
19 I've done.

20 Q. How much time would you say you spent
21 preparing for your depositions yesterday and
22 today?

23 A. So prior to yesterday how much time did
24 I spend?

25 Q. Let's start with that.

1 A. Okay.

2 Q. Fair enough. Withdrawn.

3 Prior to yesterday, how much time do
4 you think you spent preparing for this
5 deposition?

6 A. Probably on the order of fifteen to
7 twenty hours.

8 Q. Did you meet with counsel --

9 A. Yes.

10 Q. -- to prepare for the deposition?

11 A. Yes, I did.

12 Q. For how long did you do so?

13 A. About seven or eight hours in person,
14 and I had a phone conversation for a couple of
15 hours prior to that.

16 Q. With whom did you meet on those two
17 occasions?

18 A. The phone conversation was with Corey
19 Casey, and then I met in person -- Corey was
20 virtual, but I met in person with Mark.

21 Q. When did the in-person meeting with
22 Mark occur?

23 A. Monday of this week.

24 Q. And do you recall when, roughly, the
25 phone conversation or Zoom conversation occurred

1 with Corey Casey?

2 A. I think it was Friday the week before.

3 Q. Have you had any discussions with
4 anyone other than your lawyers concerning the
5 subject matter of your testimony?

6 A. No.

7 Q. Did you review all of the materials
8 listed in your Materials Considered tables in
9 your declarations?

10 A. At some point in time while preparing
11 my declarations, yes.

12 Q. Aside from those materials, did you --
13 do you recall reviewing any materials
14 specifically for the purpose of preparing those
15 declarations?

16 A. I may have checked a chemical structure
17 in other resources, but that's probably it.

18 Q. Aside from the materials on your
19 Materials Considered list, did you consult any
20 other sources in preparing for -- withdrawn.

21 Did you consult anything other than the
22 materials on your Materials Considered list that
23 provided you a basis for your testimony in this
24 deposition?

25 A. So prior to submitting my declarations,

1 likely -- or let me just -- I'll expand on that,
2 that, you know, I may have looked at other
3 resources when I was preparing my declaration,
4 when I was forming an opinion on the claims, and
5 some of those resources didn't contain the
6 specific information that I was -- I was -- I
7 thought was in those. Sometimes it was
8 repetitive, whatever, there were -- I'm sure
9 there were other things that I looked to that
10 and then determined that they weren't -- they
11 didn't contain the information I needed to form
12 my opinions.

13 Q. And my question may have been unclear,
14 so I'll do it again. Although, thank you for
15 that. Withdrawn.

16 Did you consult any materials other
17 than those listed on your Materials Considered
18 list for the purpose of providing support for
19 your testimony in the deposition today?

20 A. Not to my recollection, no.

21 Q. Or yesterday?

22 A. No. Yeah, inclusive.

23 Q. Okay, thank you.

24 MR. BEST: I have no more questions at
25 this time. I pass the witness.

1 MR. DEMING: No questions.

2 MR. BEST: Then we're all done.

3 THE WITNESS: All right.

4 (Deposition concluded at 11:33 a.m. CST.)

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

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

PADAGIS US LLC,
Petitioner, Case Nos. IPR2025-00464
vs. IPR2025-00465
NEURELIS, INC., IPR2025-00466
Patent Owner.

_____/

VOLUME II

I hereby certify that I have read the
foregoing transcript of my deposition given at
the time and place aforesaid, consisting of
pages 203 to 294, inclusive, and I do again
subscribe and make oath that the same is a true,
correct, and complete transcript of my
deposition so given as aforesaid and includes
changes, if any, so made by me.

MAUREEN DONOVAN, PH.D.

SUBSCRIBED AND SWORN TO
before me this ____ day
of _____, A.D. ____.

1 REPORTER CERTIFICATE

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

5 That previous to the commencement of
6 the examination of the witness, the witness was
7 by me duly sworn in person to testify the whole
8 truth concerning the matters herein;

9 That the foregoing deposition was
10 reported stenographically by me in person and was
11 thereafter reduced to printed transcript by me,
12 and constitutes a true record of the testimony
13 given and the proceedings had;

14 That the said deposition was taken in
15 person by me at the time and place specified;

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

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

24 IN WITNESS WHEREOF, I do hereunto set
25 my hand this 17th day December, 2025.

DEBORAH HABIAN, CSR, RMR, CRR, CRC
IL CSR NO. 084-02432 (exp. 5/31/27)