

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GNOSIS S.p.A., GNOSIS BIORESEARCH S.A.
and GNOSIS U.S.A., INC.,
Petitioners,

v.

SOUTH ALABAMA MEDICAL SCIENCE FOUNDATION and
MERCK & CIE,
Patent Owners.

Case IPR2013-00116 (Patent 5,997,915)
Case IPR2013-00117 (Patent 6,011,040)
Case IPR2013-00118 (Patent 6,673,381)
Case IPR2013-00119 (Patent 7,172,778)

RECORD OF ORAL HEARING

Before: JACQUELINE WRIGHT BONILLA, SCOTT E. KAMHOLZ,
and SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

APPEARANCES:

ON BEHALF OF THE PETITIONER:

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and

Case Nos. IPR2013-00116, IPR2013-00117,
IPR2013-00118, and IPR2013-00119

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March 20, 2014, commencing at 10:02 a.m., at the U.S. Patent and
Trademark Office, 600 Dulany Street, Alexandria, Virginia.

P R O C E E D I N G S

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JUDGE KAMHOLZ: Good morning. We will hear
argument this morning in Case Numbers IPR2013-00116, 118, 119,
Gnosis versus South Alabama Medical Science Foundation. We will
hear argument this afternoon for Case Number IPR2013-00117, Gnosis
versus Merck. Counsels for the parties please introduce yourself,
starting with petitioner?

MR. CWIK: Yes, Your Honor. My name is Joe Cwik, and
I'm here on behalf of petitioners. With me is my co-counsel Jonathan
Krit. Jonathan Krit has been designated lead counsel as of record.

JUDGE KAMHOLZ: Good morning.

1 MR. PARKER: Good morning, Your Honors. My name is
2 Thomas Parker. I'll be speaking on behalf of the University of South
3 Alabama, and with me is my associate colleague, Andrew Sterling, who
4 will be assisting with the presentation.

5 JUDGE KAMHOLZ: Who is here for Merck?

6 MR. PARKER: I'll also be here for Merck as well for the
7 afternoon session, and with that, Your Honor, I just wanted to raise one
8 housekeeping item, and I spoke with counsel as well. Can we have one
9 single transcript and possibly captioned with all four IPRs? Because
10 what that will do is in the afternoon, we may be referring back to
11 statements that were made in the morning session, and we can just
12 simply refer back to the morning session, and if we have it in the same
13 transcript, it may be a bit more clearer to do that as oppose to two
14 certain transcripts, if that's okay with the panel.

15 JUDGE SNEDDEN: Is that acceptable to you?

16 MR. CWIK: Your Honor, that's fine, if we have one
17 transcript. I think that will eliminate some duplication when we're
18 talking in the afternoon. I mean, I think it would not be proper to use
19 the afternoon session to make arguments about the morning patents. I
20 don't think that's the intent of it, but I think a single transcript is
21 acceptable to us.

22 JUDGE KAMHOLZ: Well, to the extent that you've briefed
23 it, any arguments you make at any time in any session are applicable to
24 all cases, but where argument is focused on one case or fewer than all
25 cases, it will perhaps help if you indicate that when making argument.

1 With that in mind, I think that's fine with us to have a single
2 transcript.

3 MR. PARKER: Thank you.

4 MR. CWIK: Thank you, Your Honor.

5 JUDGE KAMHOLZ: Thank you. Per our order dated
6 March 7, 2014, each side will have a total of two hours to argue, one
7 hour in the morning, one hour in the afternoon. The petitioner will go
8 first for each session and should begin by indicating how much time, if
9 any, will be reserved for rebuttal. I'll remind the parties that the
10 petitioner bears the burden of proving any proposition of
11 unpatentability by a preponderance of the evidence.

12 Although motions to seal have been granted and others are
13 pending in these cases, this hearing is public. The final reminder, when
14 referring to demonstratives, please mention the slide number you are
15 referring to so that it's clear in the record.

16 Are there any questions?

17 MR. PARKER: No, Your Honors.

18 MR. CWIK: Your Honor, regarding the slides, I do have
19 hard copies for the judges, if they want them at this time.

20 JUDGE KAMHOLZ: Yes, please.

21 MR. CWIK: May I approach the Bench?

22 JUDGE KAMHOLZ: Of course.

23 MR. PARKER: Your Honors, may I approach the Bench,
24 please? Would you like your copies as well?

25 JUDGE KAMHOLZ: Yes, please.

1 MR. PARKER: Your Honors, we only made one copy to
2 cover all three of the IPRs relating to -- I'll refer to the same set of
3 patents if that's okay.

4 JUDGE KAMHOLZ: Parties, are there any particular set of
5 slides we should we referring to?

6 MR. CWIK: Your Honor, I expect I will primarily be
7 relying on the 116 case, the '915 patent case. The slides are very
8 similar for most of the slides, except for some of the claim charts in the
9 beginning of the slide, and if we get that far -- I'm not sure we will get
10 that far, but if we do, I'll make that indication. I'll even have to change
11 the slides on the computer.

12 So if we can start with the '915 in the 116 case is the one I
13 plan on starting with.

14 JUDGE KAMHOLZ: You may begin when ready.

15 MR. CWIK: Good morning, Your Honors. My name is Joe
16 Cwik, and for the record I'm here on behalf of the petitioners. Your
17 Honors, I would like to give you a brief outline of what petitioners plan
18 on doing with their oral argument today. I am going to start with 20
19 minutes to discuss our prima facie case with respect to the '915, the
20 '381, '778 patents. The parties have collectively called those patents the
21 Bailey patents.

22 Patent owners will then have their one hour of response time,
23 and petitioners will reserve 40 minutes for rebuttal, and the reason we
24 broke out the time that way is, as you can see in the briefing so far,

1 there's been much more briefing and time spent on the issues
2 surrounding the prima facie case than the actual prima facie case itself.

3 When we get to the rebuttal period, Mr. Krit and I will be
4 splitting that time, depending on the issue. We've tried to break up the
5 issues, and we'll be splitting that time.

6 Your Honors, I see my key job today is to explain to you, to
7 the best of my ability, what the petitioner's positions are in this case, so
8 at any time I'm making my presentation you don't understand
9 something and want to interrupt me, please feel free to do so.

10 The first patent I want to talk about is the '915 patent. The
11 '915 patent is generally directed towards the dietary use of a
12 substantially, chirally pure (6S)-5-MTHF, in addition to another
13 vitamin for the purpose of treating folate deficiency.

14 The patent owner has requested to cancel many of the claims
15 that were instituted, and the claims remaining in the '915 patent are
16 claims 94 through 97, 99, 100, 110, 111.

17 JUDGE BONILLA: Explain what "substantial" means when
18 you say substantially chirally pure.

19 MR. CWIK: Substantially chirally pure is the Board in its
20 institute to instigate the case said it was meaning essentially free of the
21 (6R) isomer, so the claims of course are entitled to the broadest
22 reasonable interpretation under the rules here, and we think that -- we
23 agree with the construction that substantially chirally pure would mean
24 an isomer form that would be substantially free of the 6R-5-MTHF
25 form.

1 JUDGE BONILLA: How much can be in there?

2 MR. CWIK: Well, there's no -- I don't think the parties have
3 come up with any hard number. 99 percent, 99 -- it's really just
4 essentially free as a person of ordinary skill in the art would interpret
5 that. I think the word essentially implies that there may be trace
6 amounts of a 6R isomer. The language was not completely free, so
7 there possibly may be 1, 2, maybe up to 5 percent.

8 Does that answer your question, Your Honor?

9 JUDGE BONILLA: Yes, thank you.

10 MR. CWIK: With respect to the '915 patent claims, it's our
11 position that the pending claims are obvious in light of the Serfontein
12 and Marazza reference.

13 The first reference I want to talk about is the Serfontein
14 reference and referring to slide 2 of the 116 case, demonstrative
15 exhibits, for the record this is demonstrative Exhibit 1148. Here we
16 have a cut and paste right out of Serfontein of the first claim of
17 Serfontein, and we think this provides a clear example, a clear teaching
18 of the core teaching of Serfontein, but it's not everything Serfontein
19 teaches, but it's the core teaching which we rely on, and claim 1 claims:
20 "The use in the manufacture of a pharmaceutical preparation for
21 lowering levels of homocysteine or for the prophylaxis or treatment of
22 elevated levels of homocysteine or of clinical conditions associated
23 therewith in a patient of a combination comprising vitamin B6; folate
24 or a suitable active metabolite of folate or a substance which release
25 folate in vivo, and vitamin B12."

1 JUDGE BONILLA: You talk in your brief about how
2 suitable active metabolite refers to basically eight compounds. What
3 about the fact that folate or the substances that release folate in vivo,
4 how many compounds does the word folate and the substance that
5 releases folate -- how many compounds is that?

6 MR. CWIK: Your Honor, we think folate, as it's used in this
7 claim 1 and other examples in the Serfontein refers to folic acid, so that
8 would be one.

9 JUDGE BONILLA: So it doesn't refer to anything else; the
10 term folate only refers to folic acid?

11 MR. CWIK: That's our interpretation of what Serfontein was
12 saying, yes, and as far as a substance which releases folate in vivo,
13 we're not positive what that means. I don't think any of the experts
14 have been able to opine on that. We understand there are two different
15 acids which can be combined to be precursors to folic acid, so if
16 anything, we think that phrase would be limited to additional
17 compounds.

18 JUDGE KAMHOLZ: What about patent owners'
19 contentions about salts, and in effect there's thousands of compounds
20 that fall within this group?

21 MR. CWIK: Right, right, Your Honor. On the issue of the
22 many salts, patent owner I think is misapplying the holdings of In re
23 Petering and In re Schaumann by making that argument.

24 The In re Petering and In re Schaumann argument is this
25 genus species framework, and it's our contention that the genus of

1 active metabolites and folates are eight compounds, and those eight
2 compounds are the same eight compounds that are identified by Dr.
3 Miller. They're identified in figure 21-4 in the Modern Nutrition
4 Handbook that Dr. Miller relied upon, and with respect to those eight
5 compounds, we don't understand patent owners to disagree that those,
6 in fact, are the eight active metabolites that are involved in the folate
7 metabolism process.

8 So what patent owners are doing regarding the salts, Your
9 Honor, is we have the genus, and then we have the eight compounds or
10 the eight species, and what they have done is they've taken one step
11 beyond Petering, one step beyond Schaumann and said, Let's take one
12 individual species and see how many different salts we can connect to
13 it, and that was a step that was not taken In re Petering, In re
14 Schaumann. There's the genus, and then there's the identification of the
15 limited class of eight compounds.

16 For them to try to split hairs and take a single species and
17 say, Well, how many variation of one single species can you imagine,
18 we think that's not the holding of those cases, and even in this case, I
19 think that's an unfair step to take given the scope of the claims we have
20 at issue. The '915 patent claims are not limited to a specific salt. It's
21 not limited to calcium salt or some other type of salt.

22 So I think the problem with their argument is they're saying,
23 Well, Serfontein has to disclose what salts you're talking about, but the
24 claims themselves aren't limited to any such salts, and the same
25 argument concerns the polyglutamation forms, is they're interpreting

1 Serfontein and saying, Hey, look at Serfontein, you have to tell
2 us -- Serfontein has to tell us what polyglutamate forms to disclose the
3 '915 patent claims, but the '915 patent claims aren't limited to any
4 polyglutamate forms, so they're requiring Serfontein to say something
5 that is not actually a limitation of the claims, so I think there's not a
6 commensurate scope analysis that they're doing there.

7 So I think that addresses -- and really the salt question,
8 another point on the salt question is even if Serfontein had said the
9 exact language that's used in one of these challenged claims of the '915
10 patent, here's claim 94, slide 5 in my presentation, this is the first
11 challenged claim that's limited to a substantially chirally pure
12 5-methyl-6S-tetrahydrofolic-acid or a polyglutamate derivative thereof.

13 Their essential argument is, Well, even if Serfontein said that
14 and said that exactly, even though that's what the claim says, Serfontein
15 doesn't teach the invention because Serfontein doesn't tell you what
16 salts. That can't be correct. We have to have a commensurate teaching
17 of the prior art of the actual claims at issue. So to argue that all of the
18 salts are -- can be imagined I think is just an unfair argument. Does
19 that answer your question, Your Honor?

20 JUDGE KAMHOLZ: Yes.

21 JUDGE BONILLA: Just to be clear, Serfontein doesn't talk
22 about any of the eight in particular, the suitable active metabolites. It
23 doesn't talk about anything being chirally pure, distinguishing between
24 a racemic mixture and the different isomers. It doesn't get into that at
25 all?

1 MR. CWIK: Correct. It does not expressly say word to
2 word an identification of those eight compounds, right. We are relying
3 on Dr. Miller's analysis in the Modern Nutrition Handbook as a genus
4 of eight compounds that would be immediately envisaged by a person
5 of ordinary art.

6 JUDGE BONILLA: Well, it would have to be more than
7 eight. It would have to be eight times two, right, for each of the
8 isomers? Is that correct?

9 MR. CWIK: Well, no, Your Honor that's not our position,
10 and Dr. Miller's position, and he continues with his analysis, is he says,
11 Well, in the Modern Nutrition Handbook, figure 21-4 has the eight
12 compounds that are involved in the folate metabolism process, and he
13 notes that figure 21-4 doesn't indicate whether that includes the active
14 isomers or the inactive isomers, but what he does say is in the Modern
15 Nutrition Handbook, it also refers to the IUPAC nomenclature rules,
16 which then, if you look at -- and that was part of our exhibits in our
17 original petition -- does identify the eight isomer active forms, and our
18 contention is the active metabolites of folate as disclosed in Serfontein
19 are not the racemic general metabolites, but the actual active natural
20 reduced folates.

21 JUDGE BONILLA: Is there evidence of record that a
22 racemic mixture wouldn't be active, that it wouldn't work?

23 MR. CWIK: No, I don't think there is evidence that a -- I
24 don't recall evidence I should say that a racemic mixture would not

1 work prior to 1996, and I think there is evidence that a racemic mixture
2 would work, and so...

3 JUDGE BONILLA: So the term active metabolite, it
4 couldn't be a racemic mixture is your position. It would have to be the
5 active isomer.

6 MR. CWIK: Correct. That's how a person of ordinary skill
7 in the art would read it, and again I don't understand patent owners to
8 be disagreeing with that. I don't understand them ever to be saying,
9 Well, the (6R) isomer of the (6S)-5-MTHF. It is the active metabolite
10 of folate. I think that's pretty well established, and I don't remember
11 them contesting that the eight folates are the naturally reduced folates,
12 and another reason that we think the genus is specifically defined as the
13 actual active isomer is that they have a structural similarity.

14 The seven out of the eight active metabolites have an isomer
15 form, which has an L configuration on the six carbon position, so not
16 only would a person of ordinary skill in the art immediately envisage
17 these based on Dr. Miller's testimony and figure 21-4, here, as in
18 Petering, there's actually structural similarity among the reduced
19 natural folates in that they all have this L configuration at the 6 carbon
20 atom position.

21 So continuing just to give you a broad framework of how
22 claims read on Serfontein itself, I first have a claim chart on my slide
23 number 3, which looks at claim 37. Claim 37 is not at issue per se in
24 this case, but it's the independent claim upon which the challenged

1 claims depend on, so just to give us a framework of how
2 Serfontein -- how the claims read on Serfontein, I've put this up here.

3 As far as the first element of claim 37, the core idea here is
4 there's "a method of increasing a human subject's dietary intake of
5 folate in a human," and really the two key concepts here is that the
6 claim is limited to a dietary intake and it's for a human, and Serfontein
7 discloses that it is for a patient defined human, and there's two different
8 places in the record of Serfontein where he indicates that -- it's for
9 dietary preparations are disclosed, and then here he indicates that the
10 invention can also be used in a dietary program. So those elements are
11 meant by Serfontein.

12 Continuing on, the next element is "one or more natural
13 isomers of reduced folate selected from the group consisting of," and
14 then I think there's seven of those natural reduced folates that I was just
15 speaking of. Those are the ones that have the L configuration
16 structurally similar at the 6 carbon position, and we believe that those
17 reduced folates again are taught by the suitable active metabolite of
18 folate language that we just talked about before.

19 The claim continues by requiring an additional vitamin in
20 here. Serfontein discloses the additional item minimum being 5
21 milligrams of vitamin B6, and also has the required greater than 25
22 percent of the daily requirement.

23 And as I said before, claim 94 is the first challenged claim in
24 this case, and this claim, among the other claims that are left in this

1 case, are limited to the substantially chirally pure
2 5-methyl-6S-tetrahydrofolic acid.

3 Regarding the active metabolite of folate, this is a summary
4 of -- this is actually the Board's holding with respect to its conclusions
5 in its decision to institute. We thought that this language was a great
6 summary of what Miller said and Modern Nutrition said, all at the same
7 time, and as you can see at the bottom of this slide, this is slide 6, that
8 we begin to see the eight compounds that are involved in the folate
9 metabolism process. These are the compounds identified in figure 21-4
10 of the Modern Nutrition textbook.

11 And as Your Honor noted, these are really probably the
12 racemic versions that are shown in the figure, but as we move on to
13 Modern Nutrition, we see that there's an identification to the IUPAC
14 nomenclature recommendation, which identifies the natural active
15 folates as having the same six carbon configuration as the
16 (6S)-tetrahydrofolic, and ultimately, Dr. Miller's conclusion is that the
17 active metabolites of folate embrace no more than dihydrofolate and
18 the naturally occurring stereoisomers, i.e. --

19 JUDGE BONILLA: Wouldn't the racemic measure have the
20 same six carbon configuration, one of each?

21 MR. CWIK: It would for the (6S) isomer. I don't know for
22 the (6R) isomer. I don't know. So that is the summary of the
23 Serfontein reference.

24 We also are relying on the Marazza reference as rendering
25 the claims obvious in light of Serfontein as well. What Marazza is

1 doing, Marazza comes along and Marazza recognize that, Hey, there's
2 an increasing interest in this 5-MTHF compound. There's an increasing
3 interest in using it as a vitamin in folate deficiencies. There's also an
4 interest in using it in cancer therapy.

5 So he also recognizes -- we have this interest in it, but we
6 also recognize that there's two isomers in the 5-MTHF. There's the
7 (6S) isomer and the (6R) isomer. He concludes the (6S) isomer is
8 good, and the (6R) isomer is potentially bad, so what he says is, I have
9 to find a way, I have to find a way to separate these, the good (6S)
10 isomers from the bad (6R) isomers, so he comes up with a separation
11 technique for the entire purpose of being able to give a patient the good
12 (6S) isomer, essentially free, pure and not have any of the bad (6R)
13 isomer.

14 So the purpose of Marazza is this is where Marazza teaches
15 that the last limitation in claim 94, that you would want the
16 (6S)-5-MTHF isomer to be essentially free or substantially chirally
17 pure of the (6R) isomer.

18 JUDGE KAMHOLZ: So what other evidence in the record
19 establishes before the invention that (6R) was undesirable for whatever
20 reason?

21 MR. CWIK: I think there's multiple references. I think the
22 Wood reference was a reference that talked about the separation
23 technique. The Ambrosini reference I believe was even in the Board's
24 opinion noting that the (6S) isomer was the preferred one, and those are

1 the two I can remember right now, and also on page 200 of the Cooper
2 and Zittoun reference, and for the record, that's Gnosis's Exhibit 1624.

3 JUDGE BONILLA: What's the date of that reference?

4 MR. CWIK: The Zittoun and Cooper, that's before 1996.
5 That I can tell you for sure.

6 JUDGE BONILLA: Are all the ones you cited pre 19 --

7 MR. CWIK: Yes, Your Honor. Zittoun and Cooper is 1989.

8 JUDGE KAMHOLZ: Mr. Cwik, your time has expired.

9 MR. PARKER: We'll just need one minute to switch the
10 computers.

11 JUDGE BONILLA: Actually I would like to ask some
12 questions before we switch over. I was waiting for you to finish before
13 I ask it.

14 There's a footnote in the patent owner's response talking
15 about how statements that Gnosis made about the Marazza reference.
16 Basically I wanted to ask you if this is some kind of omission that
17 there's a problem with the Marazza reference. It's ineffective. It
18 doesn't work. It's not great. It's too expensive.

19 MR. CWIK: Well, Your Honor, I have two points on that.
20 The first point is that is statements ten years after Marazza, so that's
21 commenting on what is known ten years after Marazza, not what a
22 person of ordinary skill in the art knew as Marazza knew at the time.

23 JUDGE BONILLA: What evidence do you have in the
24 record that that was made ten years later?

1 MR. CWIK: They had submitted the actual paperwork I
2 believe when Gnosis made that statement, so I'm assuming the dates on
3 that. I can't recall exactly though.

4 The second point I want to make about that is that our client,
5 Gnosis, was commenting on the separation technique itself, and we're
6 not citing Marazza for the proposition that it was the best or optimal
7 separation technique. What we're citing from Marazza is the fact that
8 Marazza knew that this racemic compound was something that there
9 was a lot of interest in as a vitamin in folate deficiency states, and he
10 thought so strongly about it, he developed a technique to separate the
11 good (6S) isomers from the (6R) isomers, so it's what he did.

12 Whether the separation technique is the best technique or not
13 is really not relevant to our claims because our claim is just showing
14 that he wanted the (6S) to be pure and essentially free of the (6R)
15 isomer.

16 JUDGE BONILLA: Nobody knew how to separate it, right?
17 If they didn't know how to separate it, they didn't think they could
18 separate it very well, they wouldn't have had motivation to do it, right?

19 MR. CWIK: Right so they did think they could be able to
20 separate it, correct, right.

21 JUDGE KAMHOLZ: Thank you.

22 MR. PARKER: Good morning, Your Honors. For the
23 record, my name is Tom Parker. I'll be speaking on behalf of the patent
24 owner in this particular case, which is South Alabama Medical Science
25 Foundation.

1 Your Honors, if I can, I would like to begin with the '778
2 patent, and I would like to just introduce the two inventors of the '778,
3 which is Dr. June Ayling and Steve Bailey of University of South
4 Alabama Medical School, and I would like to focus on claim 15, which
5 is the only claim now that's being challenged in the '778 patents. Here
6 the Board found that petitioner's demonstrated claim 15 is unpatentable
7 as obvious in view of Serfontein, Ueland, Marazza, and that's ground 2
8 in the Board's decision.

9 So, Your Honors, just for the record for shorthand, with
10 respect to 5-methyl-(6S)-tetrahydrofolic acid, I'll be referring to it
11 either as L-5 or L-5-MTHF, and for the racemic mixture of (6S) and
12 (6R), I'll refer to that as the 5-MTHF.

13 Relying on these three references, the Board concluded that
14 claim 15 may be unpatentable stating that a person of ordinary skill in
15 the art, the POSA, would have had reasonably expected that
16 administering the L-5 would have increased the intercellular pool of
17 L-5, and consequently would have lowered levels of homocysteine for
18 purposes of treating vascular disease resulting from excess levels of
19 homocysteine.

20 Notably, the Board concluded that Serfontein's disclosure did
21 not include a suitable active metabolite of folate, which I'll refer to as a
22 SAMOF, S-A-M-O-F, as being substantially chirally pure, including
23 substantially chirally pure L-5. Now, citing Ueland, the Board noted
24 that Ueland teaches that increasing the intercellular levels of L-5, you
25 will introduce levels of homocysteine in the cells.

1 Now, according to patent owner's expert Dr. Gregory, he
2 opined that claim 15 would not have been obvious because a person of
3 ordinary skill in the art would not have believed that when you
4 combined Serfontein, Ueland and Marazza together, that it would
5 produce an operative formulation; that is, the POSA would not expect
6 that L-5 when administered would be accumulated and retained in the
7 cells and would not effectively increase the intercellular pools of L-5,
8 and that being the case, the POSA would not believe or expect that
9 administering L-5 with lower levels of homocysteine in a human
10 patient.

11 JUDGE KAMHOLZ: Isn't Ueland relied on only for that
12 theory?

13 MR. PARKER: Excuse me?

14 JUDGE KAMHOLZ: Ueland is only relied on for that
15 theory.

16 MR. PARKER: Well, in the Board's opinion --

17 JUDGE KAMHOLZ: In the petitioner's challenge.

18 MR. PARKER: Excuse me?

19 JUDGE KAMHOLZ: In petitioner's challenge, Ueland is
20 relied on for that theory that you've produced on that slide.

21 MR. PARKER: Correct.

22 JUDGE SNEDDEN: Doesn't Serfontein already indicate a
23 link between elevated homocysteine levels and vascular disease?

1 MR. PARKER: Serfontein does express that there's a
2 connection between high levels of homocysteine and vascular disease,
3 correct.

4 JUDGE KAMHOLZ: So is the theory of the mechanism
5 particularly relevant here?

6 MR. PARKER: It is, Your Honor, because Ueland says that
7 the only way to increase the cellular levels of L-5 is by administering
8 folic acid because at the time, it was believed that administering L-5
9 would not be retained, would not be polyglutamated and would not be
10 retained in the cells.

11 JUDGE BONILLA: What's the basis for that?

12 MR. PARKER: That is the Wagner reference, and the
13 Wagner reference --

14 JUDGE BONILLA: What Exhibit is that? I'm sorry.

15 MR. PARKER: Excuse me?

16 JUDGE BONILLA: What exhibit is that?

17 MR. PARKER: The Wagner reference is on slide 9, and
18 that's a reference to -- it's referenced -- it's Exhibit 2061 in the Gregory
19 declaration of 2075, paragraph 34. Here Wagner shows that exogenous
20 L-5, even when transported in the cells, remains unpolyglutamated, and
21 therefore it's not being utilized by the cells.

22 Also, we have Dr. Miller's testimony on slide 7 where Dr.
23 Miller testified that L-5 is a poor substrate for polyglutamation, and
24 that being the case, it would not be accumulated in the cells, thus

1 leaving the cells folate deficient, despite the plasma being a wash with
2 L-5.

3 Also there's another reference -- well, there's also the
4 Shane -- we'll refer to it as the Shane reference on slide 8. It's a paper
5 written by Dr. Barry Shane, another leading expert in the folate area,
6 where Dr. Shane indicated that -- which is consistent with Dr. Gregory
7 and Dr. Miller's testimony, that polyglutamation of L-5 is required for
8 retention and accumulation in the cells and for biological activity in the
9 cells.

10 There's also another reference which petitioners rely on,
11 which is the Cichowicz reference, which is slide 10.

12 JUDGE BONILLA: In this Wagner reference, it says it
13 doesn't -- did they compare the L-5 methyl with another 5 methyl with
14 folic acid in that particular paper?

15 MR. PARKER: No, no. What they did was they -- this was
16 done I believe in vitro, and they were showing that in the cells they
17 weren't -- the cells were either not being brought in, or if they were
18 being brought in, they were binding to these particular macro
19 molecules.

20 JUDGE BONILLA: One of the things that the petitioner is
21 saying is that folic acid itself was a poor substrate as well. Is there a
22 way to distinguish this as being a particularly poor substrate, which
23 essentially would teach away, for example?

24 MR. PARKER: The answer is yes. In fact, Dr. Gregory
25 testified on cross examination to that extent pretty extensively. He

1 explained the fact that L-5 and folic acid are poor substrates, that's true.
2 They are relatively speaking, but what happens is the folic acid is
3 readily converted to the tetrahydrofolate, and tetrahydrofolate, as
4 shown in the Cichowicz paper that was shown to Dr. Gregory during
5 his deposition, is an excellent substrate for polyglutamation.

6 L-5, unlike folic acid, is not converted into THF, and so
7 therefore it's not really polyglutamated and retained in the cells, and so
8 only then when it's -- slide 11? Slide 12, so in that particular case that's
9 why the difference is irrelevant because folic acid is converted to THF.
10 L-5 is not.

11 JUDGE BONILLA: If it's such a poor substrate, how does it
12 work then?

13 MR. PARKER: At this point it's unclear. What was
14 believed -- prior to 1996 what was believed was it not be well retained
15 or would not be well accumulated in the cells.

16 So from there, once the THF is polyglutamated, it's
17 converted into the L-5 polyglutamated, and then it's accumulated and
18 drives the remaining reactions forward.

19 So in short, according to Dr. Gregory, if a POSA's goal was
20 to raise the intercellular pool at L-5, that is to cause the cell to retain
21 more L-5 to lower homocysteine levels in the cells, they would believe
22 it could only be done using folic acid. That's suggested in Ueland. The
23 POSA would not believe that administering the exogenous L-5 would
24 achieve that same result because as Drs. Miller and Gregory explained,

1 the L-5 is not well retained and accumulated within the cells; that is,
2 within the intercellular pool.

3 So a reference like -- a reference that's said to teach away,
4 when it suggests explicitly or implicitly that the developments flowing
5 from his disclosure are likely to produce the objective of applicant's
6 invention, and such is the case with Ueland.

7 So whether Marazza in this case discloses an interest, albeit
8 an unexplained interest is of no moment given that, according to Dr.
9 Gregory, Ueland teaches that administering L-5 would be unsuitable
10 for lowering homocysteine levels in human patients, so this goes back
11 now to Serfontein, because Serfontein shows the link between treating
12 vascular disease and with respect to lowering homocysteine, so that
13 would be --

14 JUDGE BONILLA: If that's true, what was
15 Serfontein -- what were they referring to when they said active
16 metabolite?

17 MR. PARKER: Well, it's not defined, suitable active
18 metabolite, and that's the big problem with Serfontein. It's undefined,
19 and so we could --

20 JUDGE BONILLA: It must have meant something. What
21 did it refer to?

22 JUDGE KAMHOLZ: So your position though is that
23 Serfontein says suitable active metabolites, and that L-5 is not a
24 suitable metabolite; is that what you're saying?

1 MR. PARKER: According to Dr. Gregory, who evaluated
2 the reference, his opinion was that the reference is so broad that it does
3 not speak to any specific reduced folate or chirally pure folate, so
4 there's no drawing from Serfontein any specific compound because it's
5 so broad.

6 JUDGE BONILLA: What would it cover?

7 MR. PARKER: It would cover folic acid.

8 JUDGE BONILLA: It's already there, folate --

9 MR. PARKER: That's right.

10 JUDGE BONILLA: So folate and active metabolites, so
11 what would active metabolites refer to?

12 MR. PARKER: That's the whole point, it's undefined. It
13 would refer to -- you know, that is the problem with Serfontein. I
14 mean, our position is that it's not speaking to the person of ordinary
15 skill in the art with respect to any particular compound so as far as its
16 teaching. It's not teaching a specific compound.

17 In fact, Dr. Gregory went one step further. He said, Look,
18 one of ordinary skill in the art looking at Serfontein, given all their
19 examples since they're all focused on folic acid, would in some ways
20 actually lead you away from reduced folates and again continue
21 towards folic acid because at that time, folic acid was the gold standard.
22 It was what everyone was using for folate supplementation.

23 Another case similar this is In re Bell -- I can give you the
24 cites, In re Bell and In re Bart, which is on slide -- I don't know have it
25 on a slide, but I can give you those cites.

1 JUDGE KAMHOLZ: Is L-5 an active metabolite of folate?

2 MR. PARKER: L-5 methyl polyglutamated is biologically
3 active in the system. It's an active metabolite of folate, yes.

4 JUDGE KAMHOLZ: What else is?

5 MR. PARKER: What else is?

6 JUDGE KAMHOLZ: Yes. Can you list them?

7 MR. PARKER: All the various metabolites of folic acid
8 when it's going through the cycle?

9 JUDGE KAMHOLZ: Yes.

10 MR. PARKER: Well, they're the ones that were listed in the
11 reference that petitioners identified. They are part of the cycle.

12 JUDGE KAMHOLZ: If you had a diagram of the cycle in
13 front of you, you could read off to me the active metabolites.

14 MR. PARKER: They would be showing the metabolite, yes.

15 JUDGE KAMHOLZ: About how many?

16 MR. PARKER: There's at least eight or nine.

17 JUDGE BONILLA: Are there any more than what's listed
18 by the petitioner?

19 MR. PARKER: Are there any additional ones? Not that I'm
20 aware of, no. There may be THF maybe one. I'm not sure if that's
21 included. I don't know.

22 JUDGE KAMHOLZ: Why is that too many for one of
23 ordinary skill in the art to at once envisage from Serfontein's
24 disclosure?

1 MR. PARKER: Because In re Petering and all its progeny
2 makes clear when you look at a reference, the POSA has to envisage
3 each member of that genus as if it were written down on paper, okay?
4 So when you look at Serfontein, Serfontein has a number of
5 compositions that talks about topicals, patches, rectal pessaries and
6 various other types of dosage forms, which are going to require certain
7 type of form of folate or metabolite of folate.

8 Which ones, it doesn't say. Which ones we -- which ones
9 work for a rectal pessary, I don't think anyone knows even today, but
10 the point is now you have all these compounds that have to be in a salt
11 form. I think it's all in agreement between the experts that in order to
12 stabilize the drug, it has to be in a particular salt form.

13 JUDGE BONILLA: Well, how do you respond to
14 petitioner's position that you're going too far down the species scales,
15 that you need to match what's in the claims, and it's talking about I
16 guess what I would call subgenus versus genus, which is any kind of
17 folates, and then there's subgenus which is a folate and metabolites, and
18 you're going one step further and going into the species which is
19 dealing with the claim's focus?

20 MR. PARKER: No, I wouldn't think -- I think what we're
21 doing is we're reading what are the members of the species, the
22 member of the genus that is being disclosed by the SAMOF. You have
23 SAMOF. It's undefined, and we have all these examples of all the
24 different types of dosage forms that a SAMOF could be used. I mean,
25 those are Serfontein's compositions.

1 The number of compounds that can be used in that, it's not
2 clear because they don't define it, but if you want to take even the eight
3 or nine compounds that are formed within the folate cycle, realizing
4 that you have to have a certain kind of a salt form for it, that expands
5 the actual species itself.

6 So, no, I would not agree with that we're taking it too far
7 down. We're taking a little reading about --

8 JUDGE BONILLA: How do you respond to petitioner's
9 position that if Serfontein had, in fact, disclosed all eight of those and
10 said a chirally pure form of the particular one, that that wouldn't have
11 been sufficient under your theory because they wouldn't have disclosed
12 all the salts?

13 MR. PARKER: I mean, if I hear your question correctly,
14 that would still have the same problem.

15 JUDGE BONILLA: So even if they had said verbatim
16 what's in the claim in Serfontein, that wouldn't have been sufficient in
17 your mind because they didn't disclose all the salts.

18 MR. PARKER: Right. Are we talking about claims,
19 Serfontein's claims or the claims in the --

20 JUDGE BONILLA: If Serfontein had disclosed exactly
21 what's in your claim creating the substantially free or chirally pure or
22 whatever the language is --

23 MR. PARKER: Right.

1 JUDGE BONILLA: -- that that wouldn't have been
2 sufficient for you because they wouldn't have disclosed all the salts and
3 all the polyglutamated forms and things like that.

4 MR. PARKER: You know, I would say, first of all, I would
5 claim right now, that part of the analysis, what's in our claims in some
6 respects is not relevant. What's relevant first is: What's the disclosure
7 in Serfontein, okay? How broad is it? Is it defined? Is it undefined?
8 Would a POSA immediately envisage all of those members of that
9 class?

10 Then we can go to the claim itself, but first we have to begin
11 with -- remember, we have things that are not written in the document,
12 so we have to -- in In re Petering, of course the POSA can envisage
13 certain compounds as if they were written in that document, and what
14 we're saying is that simply can't be the case. It's an undefined class
15 given the breadth and scope of Serfontein.

16 JUDGE KAMHOLZ: But you're not answering the
17 hypothetical question.

18 MR. PARKER: Okay.

19 JUDGE KAMHOLZ: Which is if your claim, claim 15 as it
20 incorporates claim 1, or claim 94 as it incorporates claim 47, were
21 written down verbatim in a piece of prior art, your argument would still
22 establish or take the position that that disclosure is insufficient to meet
23 the claim; isn't that right?

24 MR. PARKER: No, because then -- I would say then that
25 Serfontein would have a written description problem or an enablement

1 problem because there are no examples enabling one of ordinary skill
2 in the art to practice the invention, so if that claim, our claim was just
3 placed right into Serfontein, you will have other issues as well, and I
4 don't know if that really would help the ability -- would help the ability
5 for the person of ordinary skill in the art to at least envisage all the
6 elements of a class.

7 JUDGE KAMHOLZ: Then what salts does your patent
8 disclose?

9 MR. PARKER: Pentahydrate, calcium salt. I mean, there's a
10 few other salts I can't remember, but there are specific salts that are
11 disclosed. There are a whole series of salts that are disclosed in the
12 specification.

13 JUDGE SNEDDEN: I think I see your position a little
14 differently. I want to -- I see what you're saying to me very simply is
15 Serfontein speaks to suitable active metabolites.

16 MR. PARKER: Right.

17 JUDGE SNEDDEN: And your position is we don't know
18 what that means.

19 MR. PARKER: No.

20 JUDGE SNEDDEN: But we do have evidence to suggest
21 that the L-5 MTHF, it may not be a suitable active metabolite.

22 MR. PARKER: That's correct. Suitable is not defined, and
23 then again I'm going to the Board's grounds now because I want to
24 focus on that because that's where the L-5 was mentioned when

1 they -- or in terms of finding claim 15 unpatentable so, yes, it's
2 undefined, and L-5 would be an unsuitable.

3 JUDGE SNEDDEN: I would like to move on to the
4 evidence that supports that position. Why would a person of ordinary
5 skill in the art not consider this a suitable metabolite?

6 MR. PARKER: Where is the evidence?

7 JUDGE SNEDDEN: Yeah. Yes. Can you just --

8 JUDGE BONILLA: And you're relying on the poor
9 substrate evidence; is that right?

10 MR. PARKER: Yes. We're relying on Dr. Gregory's
11 testimony in his report where he relies on Dr. Miller's testimony in
12 addition to the Wagner reference along with the Shane paper, and now
13 we have the Cichowicz reference, which was just recently added to
14 Gnosis's reply brief.

15 JUDGE KAMHOLZ: Isn't there other evidence that (6S)
16 was thought to be good? There is some evidence that you've put
17 forward that (6S) was considered a poor substrate, so it would not be a
18 good candidate for this kind of therapy, but there's some evidence
19 beyond me that couldn't it be good?

20 MR. PARKER: There is evidence as far as treating -- well,
21 with respect to treating vascular disease?

22 JUDGE KAMHOLZ: Anything.

23 MR. PARKER: Not that -- I can't think of anything
24 jumping -- I can't think of one right now. There might be. I just can't
25 think of one.

1 JUDGE KAMHOLZ: Is there any reference that
2 discusses (6S)'s favor prior to invention?

3 MR. PARKER: The use of (6S), administering (6S) by
4 itself, I mean, we can talk about Marazza, but otherwise I don't
5 believe -- I'm not aware of a reference to that effect, no. And Marazza
6 again is just -- we're focusing on a single sentence of Marazza which
7 says as an interest, but we don't know the basis or really it's not really
8 explained as to what that is.

9 The one case that comes to mind there is the In re Farrell
10 case where perhaps you can name Marazza. It is just a general
11 approach about possibly doing something, but Serfontein and you have
12 Ueland really not giving you sufficient guidance to lead you to the
13 claimed invention.

14 JUDGE KAMHOLZ: Your position is Wagner and perhaps
15 some other references amount to a teaching away?

16 MR. PARKER: Yes, yes. Yes, to a person of ordinary skill
17 in the art, yes.

18 JUDGE KAMHOLZ: So that even if one of ordinary skill
19 once envisaged (6S) tetrahydrofolate as one of the suitable active
20 metabolite in Serfontein, they would nevertheless be discouraged from
21 using it?

22 MR. PARKER: They would be discouraging it for purposes
23 of increasing the intercellular level of L-5 for lowering homocysteine,
24 yes.

1 JUDGE BONILLA: What about the racemic mixture, would
2 they be discouraged from using the racemic mixture of 5-methyl as
3 well? Is there evidence of that?

4 MR. PARKER: For the same reasons, the answer is yes, in
5 addition to those other elements that would discourage the person of
6 ordinary skill in the art, but, yes, that would --

7 JUDGE BONILLA: Because the 5-methyl has poor
8 absorption?

9 MR. PARKER: Excuse me?

10 JUDGE BONILLA: Because the 5-methyl has poor
11 absorption as well for the same reasons you were talking about?

12 MR. PARKER: I would say that that would apply as well,
13 yes.

14 JUDGE BONILLA: Because there's some evidence that the
15 other side has cited that people were using the 5-methyl for different
16 things. If you look at the Godfrey paper, that's to treat depression, but
17 they were using it for different things, so that indicated one skill in the
18 art thought it would be useful. It wasn't such a poor substrate, that it
19 would be useful.

20 MR. PARKER: The answer is yes, in Godfrey -- and again
21 we have testimony from Dr. Stahl, who looked at Godfrey, criticized
22 Godfrey, if you have that one slide, but I want to address your point
23 there, and Le Grazie and Passeri, and what's going on with depression
24 in some respects, nobody knows. It crosses over and enters into the

1 cerebral spinal fluid, and the method of action there, whether or not it's
2 raising or lowering homocysteine, it's just not known.

3 The people are expressing that they're having an improved
4 mood, but why that's happening, even to this day -- even though to this
5 day, it's not clear when you read the papers, they make -- they state
6 unequivocally the method of action is just unknown. So people were
7 using it in the context of depression.

8 There's also a paper they cited Pattini where they're using it
9 with athletes who had lower levels of iron in their blood, and they
10 thought perhaps the 5-MTHF would help them accumulate more iron in
11 the blood. So what that says about the use of the L-5 in terms of
12 treating, for example, vascular disease and increasing or lowering the
13 levels of homocysteine, there's nothing there to be said about it, if you
14 don't know what's going on within the cells.

15 JUDGE BONILLA: So are you suggesting that even though
16 it's a poor substrate, that whatever that problem may be, it's still
17 working. We just don't know why it is. The fact that it's a poor
18 substrate may be irrelevant in this context, is that what you're saying?

19 MR. PARKER: Well, for purposes of depression, we don't
20 know, but I want to go back to the grounds of the patentability which
21 was lowering homocysteine. There we're not going to have that
22 increased level of L-5, and if that's not going to happen according
23 Ueland, you're not going to lower the level of homocysteine.

1 JUDGE BONILLA: So the theory is possibility, possibly
2 that if it's working on depression, it doesn't really have anything to do
3 with homocysteine levels, lowering homocysteine?

4 MR. PARKER: No, there's nothing in the art, nothing in the
5 record that would correlate that definitively. Remember now, Wagner
6 reference has data. Cichowicz has hard data. I believe the Shane paper
7 expresses data, and Ueland also has, to some extent, some data. They
8 have that statement, but there they have the data, and with the
9 depression, again our expert, Dr. Stahl, had gone through those
10 references, and he explained some of the drawbacks of those
11 references, which is on slide 18.

12 So if I may continue, if that's okay? Thank you.

13 JUDGE KAMHOLZ: What is known about the mechanism
14 of action for L-5 methyl in the context of treating or preventing
15 vascular disease in the record?

16 MR. PARKER: Well, right now in the record what we have
17 is that lowering levels of homocysteine, as well as -- there are other
18 components too as explained by Dr. Jacobs, Dr. Fonseca and other that
19 there's also a folate deficiency component which I think interrelates
20 with the homocysteine, but there is that major component of lowering
21 the levels of homocysteine.

22 JUDGE KAMHOLZ: Dr. Fonseca and Dr. Jacobs, do they
23 attribute that effect entirely to the L-5-methyl?

1 MR. PARKER: They attributed the treatment of diabetic
2 peripheral neuropathy as an example -- they attributed that to the L-5,
3 but in combination with the vitamins as well.

4 JUDGE KAMHOLZ: But the combination of L-5-methyl B6
5 and B12.

6 MR. PARKER: Yes.

7 JUDGE KAMHOLZ: Is it the special forms of B6 and B12
8 in Metanx?

9 MR. PARKER: Is it the special forms?

10 JUDGE KAMHOLZ: The methylcobalamin and the
11 pyridoxal-5'-phosphate?

12 MR. PARKER: Right, yes. They look at the actual active
13 ingredients that's expressed on the package inserts, and in their
14 declarations, they analyzed and said, This is why the product is
15 effective, and this is because they're effective is why doctors are
16 prescribing these for the medical ailments -- for the indications that are
17 expressed on the package inserts.

18 Now, I was just talking in regards to the '778 patent, and I
19 think the same would also hold true for the '381 and the '915 patent
20 with respect to the challenged claims, in that although the Board relies
21 upon two references, Serfontein and Marazza, the Board does not rely
22 on Ueland as its grounds, as its basis for unpatentability.

23 However, that's not to say that Ueland or Wagner is
24 irrelevant or the fact that, according to Dr. Gregory, a person of
25 ordinary skill in the art would have understood that administering

1 substantially chirally pure L-5 would not have been sufficiently
2 accumulated and retained in the cells.

3 I'm just bringing to the Courts' attention two cases, which I'm
4 sure the Board is aware of. Whenever you dealing with obviousness
5 issues, you look to the sum of the all the relevant teachings in this
6 regard. So again the prior art we would submit would include Ueland,
7 Wagner, in addition to Serfontein and Marazza.

8 JUDGE KAMHOLZ: Your position is that Marazza stands
9 alone for the proposition that (6S)-5-methyltetrahydrofolate has some
10 special value.

11 MR. PARKER: Well, we stand for the proposition that
12 Marazza, that they would not -- the POSA would not look to the L-5
13 Marazza for utilization in Serfontein's composition, and that Marazza --

14 JUDGE KAMHOLZ: Why not?

15 MR. PARKER: Because of the whole situation with Ueland
16 and Wagner, and also the fact that when you look at Marazza, again
17 we're focusing -- Marazza is all about again synthesizing and separating
18 out the two isomers, and it's also focusing on treatments in conjunction
19 with cancer, okay? We have that one line in Marazza that says there's
20 an interest in using L-5 as a vitamin, for vitamin deficiency.

21 But I would go back to cases like In re O'Farrell. I don't have
22 a specific cite in my head, but anyway, O'Farrell, where there was a
23 situation that was similar, and they characterize that as merely just a
24 general approach to accomplish something, but not really giving you
25 anything further than that, just a general approach to a problem, where

1 Serfontein and Ueland and the others don't give you the necessary
2 guidance to go further.

3 JUDGE KAMHOLZ: Of course Marazza names
4 (6S)-5-methyl with care as a natural active metabolite of folate.

5 MR. PARKER: Yes, that's true.

6 JUDGE BONILLA: And it specifically teaches the natural
7 metabolite as at least one active component in a therapeutic agent
8 required in a vitamin folate deficiency state.

9 MR. PARKER: That's correct. That's exactly what it says.

10 We have that sentence in Marazza that says that, yes, but as Dr.
11 Gregory pointed out, that one -- given what we all know about L-5 and
12 giving it exogenously, that what was understood, they wouldn't
13 necessarily turn to L-5 for Serfontein's composition.

14 Your Honors, if I may, I would like to turn to the secondary
15 considerations, and then if I have time, I would like to go back to the
16 prima facie case, if that's okay with the panel.

17 Your Honors, we submitted evidence, I would submit
18 compelling evidence with respect to the commercial success, industry
19 recognition through licensing, copying of others, satisfaction of the
20 long felt need and industry skepticism and industry praise, among
21 others, as it concerns the inventions that are claimed in all three patents,
22 the '915, '778, and the '381.

23 So let me quickly just try to address going into commercial
24 success. We have to show a nexus. Understood. We have to show the
25 claim -- that the challenged claims cover the product. We have to show

1 that the product, did it acquire some level for success, and we have to
2 show the success is attributable to the patent features of each claim,
3 okay?

4 So I believe we've done that through the declarations of the
5 physicians. In fact, we have here that -- once the patentee demonstrates
6 it, the burden of coming forward with evidence in rebuttal shifts to the
7 challenger. Now, the patent owners retained a marketing expert, Mr.
8 Ivan Hofmann to evaluate PamLab's patented products, Metanx,
9 Cerefolin, Cerefolin NAC, Neevo and NeevoDHA, where he was asked
10 to assess whether these products have, in fact, achieved any
11 commercial success.

12 We'll just introduce Mr. Hofmann. You have his CV. He's
13 an expert in financial forensics and a certified public accountant. Also
14 he has an expertise in analyzing objective indicia about obviousness,
15 among other things.

16 Now, petitioners do not dispute that PamLab's patented
17 products and their uses are covered by the challenged claims as set
18 forth in patent owner's response, so as to avoid any questions
19 concerning those particular proofs, I would like to move on just to
20 discuss the evidence showing that PamLab's patented products have
21 achieved commercial success.

22 JUDGE KAMHOLZ: I would like to go into that. First of
23 all, the products on which you're relying for showing commercial
24 success are the five that you just mentioned, the PamLab products; is
25 that correct?

1 MR. PARKER: Yes.

2 JUDGE SNEDDEN: Cerefolin and Cerefolin NAC, Metanx,
3 Neevo, NeevoDHA.

4 MR. PARKER: Yes.

5 JUDGE SNEDDEN: You're not relying on Metafolin,
6 Merck's product?

7 MR. PARKER: No, only with respect to -- when looking at
8 the trend with respect to PamLab purchasing bulk sales of Metafolin,
9 which is in Mr. Hofmann's declaration, he does tie that into -- as
10 another indicator of commercial success in terms of the bulk API that
11 was being purchased by PamLab.

12 JUDGE BONILLA: So just to clarify, that drug is the one
13 that's being sold to the people who are then licensing and
14 manufacturing and selling it? That's the base, if you will, of what
15 they're using?

16 MR. PARKER: Yes, the API Metafolin, which is the
17 substantially chirally pure 5, that's sold to PamLab, for example --

18 JUDGE BONILLA: And is it sold -- it's just that compound
19 by itself and nothing else?

20 MR. PARKER: Right. PamLab then manufactures it into its
21 final dosage form.

22 JUDGE KAMHOLZ: It's not marketed to any consumers?

23 MR. PARKER: Metafolin? No. Merck does no advertising
24 or marketing. They communicate to manufacturers such as PamLab, but
25 just through way of -- just letting them know they have the product.

1 Basically most of the folks contact Merck in terms of whether -- to buy
2 the products, so there's not much advertising going on at that level, no.

3 JUDGE KAMHOLZ: All right. So it would appear, based
4 on the record we have, that these products fall within the scope of the
5 claims that are at issue here.

6 MR. PARKER: Correct.

7 JUDGE KAMHOLZ: To what degree are they coextensive
8 with the claims at issue?

9 MR. PARKER: Coextensive with the issue -- coextensive in
10 the fact that they're covered and that the effectiveness is attributed to
11 the patented features, and I know in the case law it says coextensive,
12 and it has various meanings, but it's coextensive in terms of the scope
13 of the claim.

14 JUDGE BONILLA: It has to be relevant to a patentability
15 feature and something that wasn't already known in the art.

16 MR. PARKER: Yes, that's correct that's correct.

17 JUDGE BONILLA: So here I assume it's the L-5-methyl or
18 is it the use of the L-5-methyl in combination with use of B6 and B12,
19 for example?

20 MR. PARKER: Right. The experts, the physicians make
21 clear that the effectiveness is attributed to the combination of the
22 ingredients, of the other additional vitamins, B6, B12 in addition to the
23 L-5.

24 JUDGE BONILLA: One of the things I don't see relates to
25 market share. Are there other products that have maybe the racemic

1 mixture with those things that are being sold, folic acid if those things
2 are being sold in that capacity?

3 MR. PARKER: No. In fact, the sales are -- there is
4 discussion of the market share because we have to understand
5 that -- PamLab cultivated a new market. Before PamLab actually
6 invested all the money to go forward with these products, people didn't
7 take vitamins seriously. They weren't looking to them as being
8 effective for treating something like diabetic peripheral neuropathy or
9 being effective in treating cognitive impairment, vascular dementia.

10 So they built the market based on these products, so when we
11 say comparison to market share, first of all, I mean, there's the case law
12 that says obviously market share certainly puts things in context.

13 JUDGE BONILLA: Is there evidence of record -- it sounds
14 like you're saying they are the market?

15 MR. PARKER: Right, they are the market.

16 JUDGE BONILLA: And there's nobody else except for the
17 copying that you talked about.

18 MR. PARKER: Right, with respect to the copying, right
19 now they are the only ones that actually have a -- well, right now,
20 except for the copiers, in the medical food market, there are no other
21 products that are out there, medical foods.

22 JUDGE BONILLA: Is there any evidence to support that in
23 the record?

24 MR. PARKER: That what?

1 JUDGE BONILLA: That position, that they were the first,
2 that there was nobody else until they copied? That was one of my
3 questions is whether there was somebody else selling it.

4 MR. PARKER: Well, I know that -- yeah, the evidence in
5 the record would be in the declarations that are cited here on slide 35,
6 and there's also the testimony during the deposition of Dr. Hofmann,
7 who also had those same sentiments, and I can have that citation handy,
8 if you can pull that up.

9 JUDGE KAMHOLZ: Just to go back to the coextensive
10 question, what challenged claims specifically -- let's take Metanx as an
11 example. What claim covers all the features of Metanx or includes all
12 the features of Metanx?

13 MR. PARKER: Well, claim 15 of the '778, which is directed
14 to vascular disease.

15 JUDGE KAMHOLZ: I understand claim 15 covers Metanx.
16 At least we're taking that for the sake of argument.

17 MR. PARKER: Right.

18 JUDGE KAMHOLZ: What claim actually recites all the
19 ingredients that your experts say that what makes that product work --

20 MR. PARKER: That specifically recites B6 and B12?

21 JUDGE KAMHOLZ: Not only just B6 and B12, but B6 in
22 the pyridoxal-5'-phosphate form and the B12 in the methylcobalamin
23 form?

24 MR. PARKER: Right. The claims don't specifically -- for
25 example, the '788 claims don't recite the specific vitamins themselves.

1 JUDGE KAMHOLZ: So where is the nexus?

2 MR. PARKER: The nexus, we have commercial nexus, and
3 we have -- well, we have the claims covering the products, and then we
4 can point to those features, which is the actual essential nutrients,
5 which is the vitamins of ascorbic acid.

6 JUDGE KAMHOLZ: But in the '778 patent. I'm reading
7 from claim 1.

8 MR. PARKER: Right.

9 JUDGE KAMHOLZ: There has to be one or more natural
10 isomers of reduced folates -- that would be the (6S)-methyl specified in
11 claim 15 as being substantially chirally pure.

12 MR. PARKER: Correct.

13 JUDGE KAMHOLZ: And then a nutritional substance. The
14 nutritional substance can be a food preparation and an essential nutrient
15 preparation or a combination thereof. And then when the nutritional
16 substance is an essential nutrient preparation, it will then comprise a
17 vitamin other than ascorbic acid.

18 MR. PARKER: Correct.

19 JUDGE KAMHOLZ: So this claim is a genus of Metanx,
20 correct?

21 MR. PARKER: There's no other claims more narrow than
22 claim 15. I don't know if I can characterize it as a genus. I mean, that's
23 about as narrow as the claims go.

24 JUDGE KAMHOLZ: What I mean is there's no claim that
25 drills down to B6 and B12 --

1 MR. PARKER: There's no claim --

2 JUDGE KAMHOLZ: -- in combination with the
3 L-5-methyl.

4 MR. PARKER: That's correct, there's no claim specifically
5 reciting as a claim element those particular vitamins, that's correct.

6 JUDGE KAMHOLZ: And indeed there's no disclosure in
7 this patent that the B6 might be in the form of pyridoxal-5'-phosphate,
8 is there?

9 MR. PARKER: I believe that there is. I would have to go
10 back and look, but I believe that vitamin B6 and vitamin B12 -- you're
11 referring to the pyridoxine form. I would have to go back and check,
12 but I believe that they have that combination together, maybe not in the
13 same amounts as Metanx, but certainly the combination was there, and
14 I thought even in the Board's decision, I think you mentioned when you
15 were characterizing the specification as including vitamin B6 and
16 vitamin B12.

17 JUDGE KAMHOLZ: There's no doubt that the specification
18 refers to vitamin B6 and vitamin B12.

19 MR. PARKER: Right.

20 JUDGE KAMHOLZ: But my question is whether it refers to
21 the active forms in Metanx.

22 MR. PARKER: Okay. I don't know offhand. I would have
23 to go back and look.

24 JUDGE KAMHOLZ: The standard form of B12 is
25 cyanocobalamin, right?

1 MR. PARKER: Okay, yes.

2 JUDGE KAMHOLZ: The form in Metanx is not
3 cyanocobalamin. It's methylcobalamin.

4 MR. PARKER: Correct.

5 JUDGE KAMHOLZ: Because that is the form that PamLab
6 characterizes as being the active form.

7 MR. PARKER: Correct, okay.

8 JUDGE KAMHOLZ: Methylcobalamin is not disclosed in
9 this specification, is it?

10 MR. PARKER: I would have to check to answer that
11 question. I thought at least with the vitamin B -- terms of the way
12 you're funneling down, I don't know if it's specifically disclosed.

13 JUDGE KAMHOLZ: What we're trying to get at is: To
14 what extent does this claim cover Metanx and Metanx only or the suite
15 of products on which you're relying for the commercial success
16 compared to many other possible combinations for which this
17 commercial success argument may not be relevant?

18 MR. PARKER: Well, all we can do --

19 JUDGE KAMHOLZ: To extent does that amount to a
20 nexus?

21 MR. PARKER: Okay. All we can do is we have multiple
22 products being covered by a single claim. There are other permutations
23 of products that could possibly be put together, made and sold possibly.
24 I don't know. I mean, all we have are the four products. I mean, after

1 all, it takes a long time to develop a product, clinically test it, and get it
2 out there on the market.

3 So I would think at least with the suite of products that we
4 have covered at least by one claim, that that would at least show the
5 coextensive component of the nexus, but what I'm thinking in terms of
6 nexus is just the nexus that there is success. Assume there's
7 commercial success, that it's attributed to the actual combination of
8 ingredients in the products, and that that is itself covered by the claims.

9 JUDGE KAMHOLZ: It's covered by the claims.

10 MR. PARKER: Right.

11 JUDGE KAMHOLZ: It's not recited in the claims however.

12 MR. PARKER: Not at that level, at that level of detail, no,
13 it's not.

14 JUDGE KAMHOLZ: Where in the patent is it appreciated
15 that the combination of -- specific combination of ingredients in
16 Metanx, again as an example, is what gives this product its usefulness
17 or its desirability?

18 MR. PARKER: At this point, all I can say is that at least I
19 know the specification discusses combinations of L-5 together with the
20 B6 and the B12, but not at that specific level of the forms that are in the
21 product itself. I would have to look at that.

22 JUDGE SNEDDEN: Serfontein discloses the use of folates
23 in combination with B6 and B12, only in one dose, right?

24 MR. PARKER: Yes.

1 JUDGE KAMHOLZ: In fact, Serfontein refers to active
2 forms of B6 and B12. It mentions pyridoxine. It doesn't mention
3 methylcobalamin, but it mentions other active forms such as a
4 hydroxycobalamin.

5 MR. PARKER: Okay.

6 JUDGE KAMHOLZ: So is it the notion that the
7 combination of folate with active forms of B6 and B12 is in the prior
8 art?

9 MR. PARKER: No, because Serfontein doesn't disclose
10 substantially chirally pure L-5 so with that --

11 JUDGE KAMHOLZ: But it is the petitioner's contention
12 that one would have envisaged that with the knowledge of Marazza.

13 MR. PARKER: That's their position, but we disagree with
14 that, and again we have our own experts, Dr. Gregory, Dr. Jess
15 Gregory, one of the leading experts in folate in the world, who opined
16 and evaluated the evidence, the references and basically said that this
17 disclosure is just too broad. It doesn't give you exactly -- in other
18 words, it's not speaking and saying anything -- it's not speaking or
19 identifying any particular isomer of reduced folate.

20 JUDGE SNEDDEN: I have a question though. Do you have
21 evidence to suggest that it's because of the chirally pure form of the
22 compound that's being used in the products, that that's the reason why
23 that could be tied to the commercial success?

24 MR. PARKER: Just the L-5 by itself?

1 JUDGE SNEDDEN: Well, I mean, due to the use of the
2 chirally pure form.

3 JUDGE BONILLA: That that's why you can use it to treat a
4 disease.

5 JUDGE SNEDDEN: And not for a combination that may or
6 may not be specifically claimed. You do have it claimed, a chirally
7 pure form.

8 MR. PARKER: Correct.

9 JUDGE SNEDDEN: So do you have evidence to suggest it's
10 due solely to the use of that chirally pure form --

11 JUDGE BONILLA: Versus a racemic mixture or folic acid
12 for instance?

13 MR. PARKER: No. None of those comparisons have ever
14 been done. Those experiments have never been done. I mean, all we
15 have is what we were able to obtain from the physicians, the experts,
16 that we retained in this case and their firsthand use of these products.

17 JUDGE KAMHOLZ: Have you found a citation in your
18 patent about active forms of B6 and B12?

19 MR. PARKER: Not yet. We're still looking. That's
20 something I haven't thought of, but we'll have to just check.

21 JUDGE BONILLA: Just to be clear, it sounds like your
22 position isn't that it was special that they use the L-5-methyl versus, for
23 example, the racemic mixture or folic acid, but the fact that you were
24 using L-5 and B6 and B12, that was the special thing that gave it
25 commercial success?

1 MR. PARKER: Yes, right. As the physicians testified, that
2 the effectiveness -- do you have that slide -- that the effectiveness of the
3 product was a result of the combination of the active ingredient, yes.

4 JUDGE BONILLA: I'm sorry to interrupt. Do you dispute
5 that folate plus B6 plus B12, that that, for example, was a multi vitamin
6 known in the art before?

7 MR. PARKER: It's indicated in Serfontein. What effect that
8 would have on treating vascular disease is just unknown.

9 JUDGE BONILLA: I'm asking because some of your claims
10 aren't specific to the treatment of vascular disease, your composition,
11 for example, and that's just a composition, and then in some of them
12 talk about you treating like you would for a prenatal vitamin --

13 MR. PARKER: That's correct.

14 JUDGE BONILLA: To prevent birth defects and things like
15 that, so some of them weren't that tailored.

16 MR. PARKER: No, they're not, but there they're dealing
17 with obviously nutritional health for women who are pregnant or
18 becoming pregnant, and we have NeevoDHA the supplement, which
19 is --

20 JUDGE BONILLA: But outside of the cardiovascular
21 disease, how do you trigger your compound to commercial success
22 compared to what's known in the art?

23 MR. PARKER: Well, with respect to the -- well, we have
24 the L-5, and we do know the L-5 is very potent, which was an
25 unexpected result.

1 JUDGE BONILLA: So in that case you are relying on the
2 L-5-methyl as being the special thing, that's the claimed feature that's
3 giving it commercial success.

4 MR. PARKER: It's what is giving it commercial success so I
5 can be consistent, but what the commercial success is resting on is the
6 use of this isomerically pure, this pure L-5 in combination with the
7 other vitamins. That was not known in the prior art.

8 JUDGE KAMHOLZ: Would you say that the evidence of
9 commercial success is the most significant evidence of secondary
10 considerations?

11 MR. PARKER: No. Actually I would say the copying is
12 certainly one of them, the extent, the amount of copying that has gone
13 on, which were direct replications of PamLab's patented products.

14 I would also think -- the long felt need as well I think is an
15 important one. Diabetic peripheral neuropathy before Metanx, there
16 really was no treatment that dealt with the underlying symptoms of
17 diabetic peripheral neuropathy, DPN, and that it did, in fact, satisfy the
18 long felt need.

19 In fact, we had -- we have shown evidence in the record that
20 others have tried and failed at least to find something that would
21 alleviate the symptoms. There were things out there for pain, but that
22 was about the extent of it. As far as reversing the damage involved,
23 there was nothing out there.

24 JUDGE KAMHOLZ: How about unexpected results? You
25 mentioned those a moment ago.

1 MR. PARKER: Well, yes. I mean, there are unexpected
2 results in terms of, it was discovered well after '96 that the potency of
3 L-5 was unexpected relative to its racemic counterpart.

4 JUDGE KAMHOLZ: You're referring to the Venn and Fore
5 papers.

6 MR. PARKER: The Venn and Fore papers as analyzed by
7 Dr. Gregory.

8 JUDGE KAMHOLZ: The Venn paper is Exhibit 2058.

9 MR. PARKER: Yes, I can check.

10 JUDGE KAMHOLZ: Yes, it is. Do you have it handy,
11 please?

12 MR. PARKER: Do I have a copy of it?

13 JUDGE KAMHOLZ: Do you have a copy of it.

14 MR. PARKER: The answer is, yes, we can pull that out for
15 you.

16 JUDGE KAMHOLZ: I have a copy as well.

17 MR. PARKER: Do you want me to look at it? What exhibit
18 is it?

19 JUDGE KAMHOLZ: 2058.

20 MR. PARKER: I have it, Your Honor. I have it in front of
21 me.

22 JUDGE KAMHOLZ: Dr. Gregory in his declaration
23 addresses this study starting in paragraph 104 in the '116 case. I think
24 that the paragraph numbers may change in the other declarations.

25 MR. PARKER: Yes.

1 JUDGE KAMHOLZ: But in the '116 records, it starts at
2 paragraph 104.

3 MR. PARKER: Correct.

4 JUDGE KAMHOLZ: He reports that 113 micrograms per
5 day of L-5-methyl for 24 weeks results in a negative 14.6 percent
6 difference in plasma homocysteine levels; is that correct? I believe
7 that's what he says.

8 MR. PARKER: On paragraph 104?

9 JUDGE KAMHOLZ: Yes, in '116.

10 MR. PARKER: He's noting that -- yes, then shows after 24
11 weeks the plasma level -- the plasma homocysteine levels were
12 dropped by 13 percent?

13 JUDGE KAMHOLZ: On a dose of 113 micrograms per day
14 of L-5.

15 MR. PARKER: Correct.

16 JUDGE KAMHOLZ: Thank you.

17 MR. PARKER: Then Fore?

18 JUDGE KAMHOLZ: Then the Fore reference reports that
19 on a dose of 480 micrograms per day of a racemic -- is it racemic or is
20 it just a combination? I believe it's racemic.

21 MR. PARKER: I believe it was racemic, yes.

22 JUDGE KAMHOLZ: Of 5-methyl folate, plasma
23 homocysteine level was reduced only 3 percent after eight weeks.

24 MR. PARKER: Correct.

1 JUDGE KAMHOLZ: On that basis, Dr. Gregory concludes
2 that L-5-methyl was unexpectedly superior to the racemic mixture.

3 MR. PARKER: In terms of potency, yes, that was his
4 observation, yes.

5 JUDGE KAMHOLZ: Were there any other facts on which
6 Dr. Gregory based these opinions, his opinion that L-5 is unexpectedly
7 superior?

8 MR. PARKER: What he has -- I think it's just what you've
9 mentioned, that Venn shows that at 24 weeks, only 13 micrograms per
10 day were used and lowered it 13 percent, and that Fore shows at the
11 higher dose of 480, that that lowered the plasma homocysteine by 3
12 percent, so you have the 240 micrograms per day after eight weeks
13 versus the 11 after 24 weeks, so that's the core of the basis of his
14 conclusion.

15 JUDGE KAMHOLZ: But Venn reports at 24 weeks. Fore
16 reports at eight weeks.

17 MR. PARKER: Yes.

18 JUDGE KAMHOLZ: How are those comparable?

19 MR. PARKER: In one respect, you have such a low amount
20 of the L-5 -- in one respect -- it's not a direct comparison. I mean, it's
21 an indirect comparison, so that -- I mean, I understand that.

22 JUDGE KAMHOLZ: Indirect in that it's two different
23 studies?

24 MR. PARKER: Yes, exactly, two different studies, and I
25 believe in -- his comments were that you had such a low level of 113

1 versus 480 and then if you were to look -- if you take the 480 and
2 divide that by two and do equal parts of the L and the R, the L
3 form -- the R form and the S form that will give you about 240, so you
4 are doubling the amount of what's being actually administered in Venn.

5 JUDGE KAMHOLZ: Doesn't Venn report plasma
6 homocysteine levels at eight weeks, if you look at table 2 on page 660.

7 MR. PARKER: Yes. Yes, he does.

8 JUDGE KAMHOLZ: Why not compare the eight week
9 results in Venn to the eight week results in Fore? Wouldn't that be a
10 fair comparison?

11 MR. PARKER: Would that be a fair comparison? I mean,
12 other than Dr. Gregory's observations in his comments, I wouldn't -- I
13 wouldn't be able to respond to that one way or the other than what he
14 said in his declaration. But there is a difference in time, yes, I agree
15 with that.

16 JUDGE KAMHOLZ: So Dr. Gregory's interpretation has
17 introduced perhaps a degree of incomparability greater than was
18 necessary here for this analysis. He could have compared the eight
19 week data in the two references but did not. He compared eight week
20 in one to 24 week in another.

21 MR. PARKER: Whether he could have done that or not and
22 for the reasons why he didn't do that, I don't know. All I know is he
23 was able to take the references and make this observation about
24 potency.

25 JUDGE KAMHOLZ: The question goes to the weight --

1 MR. PARKER: Yes. Okay. But again I understand it goes
2 to the weight, but also he is a well-regarded expert, and I would think
3 his review of this and his opinions are pretty -- I mean,
4 they tested -- they cross examined him on this particular issue, and his
5 testimony was quite consistent, but the element that you're referring to,
6 I don't know why he didn't make that comparison.

7 JUDGE KAMHOLZ: Okay.

8 JUDGE BONILLA: Can I ask you a question about the
9 copying? You said it was one of your stronger positions.

10 MR. PARKER: Yes.

11 JUDGE BONILLA: Are the products you're talking about,
12 the ones by Macoven and others, are they exactly the same?

13 MR. PARKER: They were exactly the same in terms of the
14 L-5 and the other vitamins in the same form.

15 JUDGE BONILLA: But other things such as inert
16 ingredients applies to the first?

17 MR. PARKER: Excipients to some -- yeah, the excipients
18 may have differed. I'm just not certain about that. They were solid oral
19 dosage forms and how they were manufactured --

20 JUDGE BONILLA: In the exact form of the L-5, the exact
21 form of the B6 and all is exactly the same.

22 MR. PARKER: No, the L-5 for us was a calcium salt. The
23 L-5 for them was a calcium salt -- they were both calcium salts.

24 JUDGE BONILLA: Okay. Then the other vitamins were
25 exactly the same?

1 MR. PARKER: Yes.

2 JUDGE KAMHOLZ: Methylcobalamin.

3 MR. PARKER: Yes, and the reason I'm saying that because
4 we have a package inserts in the record, because in order for them to
5 get linked in those pharmaceutical databases, they have to be identical
6 in terms of their active ingredients.

7 JUDGE BONILLA: So they're sold as equivalent basically.
8 I know there's not equivalence in vitamins.

9 MR. PARKER: Right. They're sold as -- well, they call
10 them generic substitutes.

11 JUDGE BONILLA: Generic substitutes.

12 MR. PARKER: Which one point I want to raise about the
13 copying, that there is a case that was cited by the petitioners, the Purdue
14 case, I'm just drawing a blank on the name of the case. That case
15 doesn't even apply to this situation where it says -- I mean there, under
16 the Hatch-Waxman Act, when you're doing a true generic in the sense
17 where you have a New Drug Application. You've improved a drug,
18 and you want to go to the market with a generic, you have to copy the
19 drug by all accounts. You have to do it. By law you have to do it.

20 That's what Purdue was saying. Copying isn't compelling
21 because you have to do it by law. In this market, that's just not the
22 case, and Dr. Rieser explained that. I will say it's an unregulated
23 market in some respects where you don't have to go to the FDA for
24 approval to market a generic version, and you're not required to copy
25 by any means. It's really done as a marketing strategy, and the only

1 reason why they do that is to get linked because the linking is really a
2 requirement by the database. It's not a government or a regulatory
3 requirement.

4 JUDGE BONILLA: You were talking about the market. Do
5 they sell it as same as PamLab product? Is it actually sold that way?

6 MR. PARKER: Yes, they do. In fact that's exactly --

7 JUDGE BONILLA: That's how it's linked.

8 MR. PARKER: That's how they sell and promote it to the
9 retailers, wholesalers and pharmacy chains, and they make the
10 comparisons, and they refer to it as the generic, and they also go ahead
11 and refer to PamLab as the brand.

12 Also I haven't talked about licensing, and I would like to
13 mention that a bit. And we put a fair amount of evidence of licensing
14 in, and let me just respond to just petitioner's rebuttal.

15 Basically they're contending that the licensing active
16 associated with the challenged patents represents nothing more than a
17 mutually beneficial cross licensing program, and that the licensing
18 activity does not represent a strong belief in the validity of the patents,
19 and I just wanted to point out that there is no such cross licensing
20 program going on between anyone or among anyone, and also to the
21 extent that they're claiming that the challenge -- the licensing, the
22 licensee are going into these licenses simply to get access to Metafolin,
23 that's not true as well, and that I'll refer to the Ladner declaration in
24 paragraph 22 in slide 36 where he basically explains why they took the
25 license, and also how he testified that the products are unique not

1 because of Metafolin but because of the other patented features or the
2 other vitamins that are contained in the products themselves.

3 And also we've submitted declarations for Mr. Ladner, Dr.
4 Katz and Dr. Stratta. They all testified that their company's -- they all
5 testified about their company's belief that the validity of the challenged
6 patents at the time they decided to take a license or in Dr. Strata's case,
7 at the time they were deciding to license the patents to others.

8 JUDGE BONILLA: Well, one of the things that the other
9 side talked about was if there were other patents that were also licensed
10 at the same time, some actually related to the stability of the thing
11 rather than the product itself, and that was what was special about it,
12 was that they figured out something else was stable.

13 MR. PARKER: Right. I mean, Gnosis takes that position,
14 but there's no evidence, none. I mean, doctors prescribing these
15 products because it's -- simply because it's stable or it's crystal, it's just
16 not -- there's no evidence about that. What we have the declaration
17 saying is they prescribe it because it works, and it works because of the
18 ingredients.

19 So I understand their position, but I think at this point,
20 Gnosis would have to do a little bit more than simply raising the
21 potential of speculation that it's the stability or the -- stability of the
22 crystallinity of the product, and it's on slide 34 that is driving the sales,
23 and we would submit that there's no evidence to that effect, and that's
24 cited to the Demarco case which makes clear that we don't have
25 to -- we're not obligated to disprove every negative that's out there.

1 Now, I mentioned on slide 39 we have two experts, Dr.
2 Fonseca, slide 40, Dr. Jacobs. They did put in their declarations, and
3 they were cross examined with respect to long felt need, and I just to go
4 into Gnosis's rebuttal to that, which is saying that methylcobalamin by
5 itself satisfied that need, okay? And they relied on a series of
6 references on slide 41, and each one of these references were shown to
7 both Dr. Fonseca and Dr. Jacobs, and they basically said, No, these
8 references don't show that. In fact, some references don't even show
9 that -- some of these references like Dominguez's reference, 2012,
10 doesn't even show that methylcobalamin alone was enough to
11 effectively treat DPN.

12 And so we cite these. These are the record citations. I can
13 go through each one as to why these were criticized by these experts in
14 the field, and then on redirect, they both testified consistently,
15 independently that prior to 1996, the person of ordinary skill in the art
16 did not consider that methylcobalamin by itself as a viable treatment for
17 DPN. It's on slide 42.

18 JUDGE KAMHOLZ: Why is methylcobalamin by itself
19 relevant as a comparison?

20 MR. PARKER: That's the comparison that they made, and
21 that's the comparison that we were dealing with during their cross
22 examination of our witnesses, so I'm just responding to what's in their
23 reply brief.

24 The other thing I want to mention also is that in their reply
25 brief, what slide is that, there are a lot of references that Gnosis has put

1 forth -- I'm sorry, petitioners put forth in their reply brief, Godfrey, Le
2 Grazie, Passeri. There's a whole -- again not one of them is supported
3 by the expert testimony, and I think in this particular case, I think that's
4 somewhat problematic. I mean, they were shown to our experts. Our
5 experts criticized these references or explained why they were not
6 relevant to the issues, and I think in a situation like this where you have
7 attorneys themselves construing what the reference would mean to the
8 person of ordinary skill in the art is -- should be afforded no weight,
9 particularly now in light -- they put them in front of our own experts,
10 and they basically testified they these did not support the claims, and
11 they now are saying that they support in their reply brief. I just wanted
12 to raise that to the Board's attention.

13 I know in the Board's -- I'm sorry, in the practice guide, they
14 mention that certainly you're going to be expecting that declarations
15 from experts are going to be supporting your position, and the
16 declarations themselves have to be substantiated as well, so in this
17 particular case, we have a whole slew of references that were put in the
18 reply. I can't even address each one of them, but they were addressed
19 by our experts at some point during their cross examination.

20 JUDGE KAMHOLZ: Thank you, Mr. Parker.

21 JUDGE SNEDDEN: I have one last question before you're
22 done.

23 MR. PARKER: Yes.

24 JUDGE SNEDDEN: With regard to the 119 case, '778
25 patent, those claims are directed to the composition.

1 MR. PARKER: They are. They're directed to -- correct.

2 JUDGE SNEDDEN: Slightly different than the methods of
3 use that you have in your patent.

4 MR. PARKER: That's correct.

5 JUDGE SNEDDEN: So when we look at Serfontein and
6 think about their suitable active metabolites, I guess they were
7 suggesting that there is no composition that existed before that
8 contained your molecule.

9 MR. PARKER: That's what we were contending. Just given
10 the scope because in claim 15, you're right, it's a composition
11 depending on effective amount of the reduced folate and the ingredients
12 for treating the conditions that I mentioned in the claim.

13 JUDGE SNEDDEN: I mean, your contention is that there's
14 no rationale that can be used based on the evidence that would combine
15 the molecule with a vitamin to make a folate supplement?

16 MR. PARKER: With respect to a substantially chirally pure
17 form of reduced folate, yes. That's not contained in Serfontein.
18 Hopefully that answered your question.

19 JUDGE SNEDDEN: Yeah, I think so.

20 MR. PARKER: Yes, that's our opinion, that it is not present
21 in Serfontein.

22 JUDGE SNEDDEN: Okay.

23 MR. PARKER: Okay. Thank you.

24 MR. KRIT: Good morning, Your Honors. My name is
25 Jonathan Krit, and I am going to be speaking about the patent owner's

1 teaching away arguments and long felt need arguments, and Mr. Cwik
2 will speak to you again regarding commercial success and licensing for
3 secondary considerations.

4 JUDGE BONILLA: Can I just ask you a quick background
5 question that the patent owner raised in the end here?

6 In your reply you cited a bunch of references, including the
7 one that's up there on the screen, and they make the argument that these
8 were put in the reply along with attorney argument only and not with a
9 declaration of any kind of expert to substantiate what they say. They've
10 asserted in their motions to exclude that we should exclude them as
11 hearsay or at least as argued here, that we shouldn't give them any
12 weight.

13 Do you have a response to that?

14 MR. KRIT: Well, I believe we address this somewhat in our
15 briefing. We've cited a couple of examples where the Board has
16 accepted attorney argument when it's directed to evidence in the record.
17 There is many cases you will find that say mere unsupported attorney
18 argument is given -- isn't given weight, but I believe the cases that
19 they've cited have been in the context of a District Court, where the
20 trier of fact are laymen.

21 Again we think -- our examples I think, they characterized
22 one as one of the two cases -- they may have characterized them both,
23 but one of the two was in the context of anticipation. I don't believe the
24 global case was in context of anticipation. It was in the context of
25 obviousness I believe.

1 There's nothing there that says that that's a distinction, so we
2 believe that it's appropriate. We also think the purpose of inter parte
3 reviews being submitted -- I don't want to overestimate, six to
4 eight -- I'm not sure even the totality of it, because we have the two
5 separate -- these patents and the '040 patent, but if petitioners are
6 required to retain that many experts to comment on every aspect raised
7 by patent owners, it's going to I believe greatly expand the scope of
8 these proceedings beyond what they were envisaged.

9 We present expert testimony with respect to our prima facie
10 case, and we think that these exhibits largely speak for themselves. We
11 don't think we're spinning them to the extent that we are, and when
12 they're not supported in the record, I think that would definitely go to
13 the weight of what we're saying, but we think it is fairly disclosed in
14 the record.

15 So with respect to their teaching away arguments, I think the
16 one I should skip to is the Ueland reference. That was the one that was
17 discussed the most this morning, and I believe that they have
18 mischaracterized Dr. Gregory's testimony on Ueland and on this
19 substrate question, and they've also, at least in their demonstrative
20 slides, and I'm not sure if this was said -- they've misrepresented the
21 Zittoun Cooper reference as we submitted it which directly speaks to
22 this point.

23 So I heard counsel say that Dr. Gregory had testified that
24 folic acid converts to tetrahydrofolate, which everyone agrees is the
25 good substrate for polyglutamization of cells, but that L-5-MTHF does

1 not. I don't think that Dr. Gregory testified that L-5-MTHF is -- does
2 not and folic acid does. I think his testimony was that folic acid would
3 convert to THF, and he didn't speak to L-5-MTHF.

4 If you look at Dr. Gregory's initial declaration, in paragraph
5 72, I believe that's 2075 is the exhibit -- in paragraph 72 he says that
6 POSA would have had questions regarding L-5-MTHF, that
7 administering L-5-MTHF might not necessarily increase the
8 intercellular pool due to its poor substrate qualities. Then when he gets
9 to paragraph 75, he puts forth the belief that only folic acid could
10 increase the intercellular pool.

11 I think with respect to his first opinion, which is that it might
12 not necessarily increase the intercellular pool, patent owner's own
13 authority, the In re Gurley decision, would say that that's not sufficient
14 for a teaching away.

15 The Gurley decision, if I can pull up the Gurley decision.
16 The Gurley stated that: "A known or obvious composition does not
17 become patentable simply because it's been described somewhat
18 inferior to some other product for the same use."

19 So if their argument is that L-5-MTHF may not be as good of
20 a substrate as folic acid, and again I don't think that's in the record,
21 that's not saying that it wouldn't increase intercellular folic or it
22 wouldn't lower homocysteine levels, so I don't think it meets the burden
23 under teaching away.

24 Regardless, we submitted evidence -- they claimed at least in
25 their demonstrative that the Zittoun Cooper reference we submitted

1 didn't address intercellular folic. They also said that it was limited to
2 folinic acid. Even though it's not reflected on slide 10 here, but on page
3 200 at the top, it's continuing a paragraph from page 199, it states: "All
4 polyglutamated folates are transported with the same efficiency and
5 velocity. In some other cells the concentration of folic acid required to
6 generate adequate concentration of intercellular folates is 100 to 200
7 times that of reduced folates, such as 5-methyltetrahydrofoalte, THF,
8 and 5-MTHF, folinic acid. 5-methyl-THF folinic acid are
9 commercially available as racemic mixtures."

10 We presented that in our reply brief at page 14, and we
11 presented it to Dr. Gregory in his deposition testimony, which is
12 Exhibit 1142, and you will find it at page 57.

13 So we have in the record evidence that 5-MTHF and its
14 active component would be -- does not have a problem with
15 polyglutamazation as far as intercellular folate.

16 Now, with respect to some of Dr. Gregory's other teaching
17 away, patent owner's reply brief or response began with the Goodman
18 and Gilman reference, and Dr. Gregory speculated that Goodman and
19 Gilman would teach away from any use of these folates, whether it's
20 folinic acid, racemic acid or 6S --

21 JUDGE BONILLA: I'm sorry, teach away from using any
22 folate at all?

23 MR. KRIT: He testified that, yes, that's at Exhibit 20 -- I'm
24 sorry, yes, he testified that it would teach away from all reduced
25 folates. And so we presented examples of uses -- and teach away from

1 its use for the treatment of folic deficiencies, so we presented examples
2 of its use for reduced folate or folate deficiencies.

3 You see three of the reasons cited here. As I said, their
4 demonstrative slide said the Zittoun Cooper reference was only directed
5 to folinic acid, and at the bottom of page 200, it's not here, there
6 is -- but it is cited in our brief at page 2, and I'm referring to the
7 response brief for the '915 patent, but this is contained in the other
8 briefs as well.

9 There is a recommendation for treating children with folic
10 deficiencies and giving them large doses of folic acid or folinic acid or
11 5-methyl-THF, so there is an example of giving tetrahydrofolate in
12 addition to folic acid in Zittoun and Cooper.

13 Now, Godfrey as was noted, Godfrey was administering
14 methyl tetrahydrofolate for psychiatric uses, but Godfrey was doing
15 this to correct the folate deficiency, so Godfrey, in addition to what it
16 says about the effectiveness as a psychological treatment, it is saying
17 that if you have a folic deficiency, you can treat that folate deficiency
18 successfully with methyl tetrahydrofolate, and table 4, it's not on this
19 slide but cited in our brief at page 2.

20 Table 4 of Exhibit 1019 contains data that clearly is showing
21 the folate deficiency is created by 5-MTHF, and it's doing this through
22 administration over 60 days, and it's not reporting any of the concerns
23 that Dr. Gregory raised.

24 Dr. Stahl, the patent owner notes that Dr. Stahl has been very
25 dismissive -- his testimony was dismissive of all our references. Dr.

1 Stahl admitted that the journal that Godfrey references is called The
2 Lancet, has an extraordinary reputation, and Dr. Stahl cited the Godfrey
3 reference in his own paper as a study supporting the link between folate
4 and depression, and suggesting the efficacy of MTHF in treatment.
5 That's Exhibit 2160 at page 739, reference 33 is the Godfrey reference.

6 And when you look at Dr. Stahl's deposition testimony, you
7 will see that he's dismissing Godfrey based on what he sees as the
8 standards of 2013, not 1996, so if you look at his deposition testimony,
9 which is at Exhibit 2013, page 54, he's characterizing Godfrey as an
10 old-fashioned article and 25 year -- it's 25 years ago, and he's not
11 challenging the physical folate measurements in table 4 relating to the
12 correction of folate deficiency, and I would point out that the
13 Serfontein reference is administering folate and vitamin B6 and B12
14 because on page 3, it identifies that there's been a limit in folate
15 deficiency and increased homocysteine levels.

16 So for somebody looking at Serfontein and looking to see
17 have there been -- what is a suitable active metabolite of folate. We
18 have Marazza saying, Find a suitable active metabolite of folate for
19 folate deficiency, and if there were concerns such as the ones that Dr.
20 Gregory has raised and a person of ordinary skill in the art was
21 surveying the literature, they could see a reference like Godfrey or
22 Pattini, I'll mention Pattini in a moment, and see that MTHF can serve
23 this purpose, and it's undisputed that it was known that the (6S) isomer
24 is the active component because you're administering the racemic, and
25 because the success was after, there were fears that the (6R) might be

1 worse than inert, and in fact it seems that those thoughts or those
2 theories have been borne out.

3 On page 13, we have a slide 13, I'm sorry, we have the
4 Pattini reference, and they've challenged Pattini for saying, Well, this is
5 relating to iron deficiency, but if you look at page 297 of Pattini at the
6 seventh paragraph it states that Pattini is administering the 5-MTHF,
7 the same bioresearch product, to avoid or correct a folate deficiency
8 that was known to be associated with the types of depression.

9 So we feel this is an example of -- a relevant example as
10 treatment of folate deficiency. Moreover, the concerns that Dr.
11 Gregory raised would be applicable to Pattini for this use as well.
12 There was a question of --

13 JUDGE KAMHOLZ: These references refer to the use or
14 the test of 5-methyl tetrahydrofolate for various reasons. Do they show
15 any efficacy?

16 MR. KRIT: They show that in terms of efficacy, you mean
17 for their ultimate purpose?

18 JUDGE KAMHOLZ: Do they show that 5-methyl
19 tetrahydrofolate worked for what they were investigating it for?

20 MR. KRIT: Oh, I believe so. Godfrey reports -- Godfrey is
21 doing it as a conjunctive therapy. Le Grazie and Passeri are doing it
22 straight out. Pattini is doing it for the purpose of hematological factors.
23 I believe all those reports are -- conclude that they were successful.

24 I would also note that Le Grazie is disclosing that it can use
25 either the racemic or the (6S) 5-MTHF, which is indicated by the minus

1 sign. We submitted Exhibit 1134, at page 223 in the second full
2 paragraph to explain the nomenclature that's being used. I don't know
3 if that's been challenged or not.

4 JUDGE BONILLA: So you're saying that you're disclosing
5 the racemic or the L-5-methyl form.

6 MR. KRIT: Correct, that it can use both.

7 Now, Dr. Stahl testified with respect to Le Grazie
8 that -- actually he didn't criticize it. He claimed that he would need
9 more time to analyze it, but he did testify that the Le Grazie discloses
10 that somebody had that idea, obviously wrote it down, and the idea
11 being using the 5-MTHF to treat organic mental illnesses. That is at
12 page 181 through 182 of his testimony, and that's the material
13 disclosure. Somebody had that idea. A person of ordinary skill in the
14 art had conceived of using 5-MTHF.

15 Petitioners also cited -- or the Passeri reference that's not in
16 our slides, and again Dr. Stahl criticized this reference as being
17 unreliable, but he cites it in his own article, Exhibit 2160. He does that
18 again at page 739 and reference number 18.

19 Now, with respect to bioavailability, the petitioner and the
20 patent owner agree, that the reference -- that at the time of the
21 invention, the references on bioavailability of folic acid versus reduced
22 folates was conflicting. On page 7 of their response brief in the '915
23 patent, they characterize Dr. Gregory's paper as "uncertain
24 bioavailability."

1 And we agree, but in the bioavailability -- the relative
2 bioavailability was uncertain, that it wasn't surprising to those of
3 ordinary skill in the art that the study -- that the earlier studies showing
4 greater bioavailability for (6S)-5-MTHF prove to be correct, and in
5 fact -- well, patent owners claimed that Dr. Gregory's paper had a better
6 methodology.

7 Apart from the fact that the earlier paper's methodology
8 turned out to be more accurate by patent owner's contentions, there's
9 nothing that shows that people of ordinary skill in the art simply
10 accepted Dr. Gregory's paper and discounted the earlier studies.

11 They argue that the food folates, the polyglutamate food
12 folates would still be relevant to the question of bioavailability, but Dr.
13 Gregory gave no recommendation for this opinion in his deposition,
14 1142, at 265 to 266, and in contradiction, Dr. Gregory's reference
15 distinguishes the amount of monoglutamate folates from the food
16 folates, and he says that the lower bioavailability of the food folates
17 was known, and there's no disclosure of any implications of -- that the
18 known bioavailability of the food folates would have on the expected
19 bioavailability of the monoglutamate folates. That's on page 1147 in
20 the introduction statement.

21 I want to make sure I use our time efficiently. Let me turn to
22 their contentions on Dr. Fonseca and the Metanx product, and they
23 criticized the studies we submitted on methylcobalamin. First there
24 wasn't a response to the broader question of: Has Metanx satisfied the
25 long felt need?

1 Dr. Fonseca admitted that Metanx is not approved by the
2 FDA in connection to diabetic peripheral neuropathy. It's not
3 recommended by any authority such as the American Diabetic
4 Association. You can find this at page 40 of Exhibit 1143, his
5 deposition testimony, and also page 18 where he discloses the two FDA
6 approved therapies are duloxetine and pregabalin, and Dr. Fonseca
7 admitted that no such recommendations would be made without
8 additional study. In fact, he said his results were "not quite clear"
9 and that "they need to be proven with further studies." Exhibit 1143,
10 and that's at page 48 through 49.

11 If you look at his published study, it states that -- it notes that
12 it doesn't establish whether Metanx is effective as a long-term
13 treatment. That's at page 148, the concluding paragraph, and Dr.
14 Jacobs also from his written literature did not consider the long felt
15 need for DPN therapy satisfied by Metanx.

16 In December 2013, this is Exhibit 1130, on the second page,
17 he wrote -- well, the article he wrote was about the potential of a folinic
18 acid for being a successful treatment of DPN. At the end he lists
19 Metanx as one of a host of nutritional aids, and he said that "proven
20 effective" for either treating the symptoms of DPN or reversing DPN,
21 and that statement is on the second page in the final notes section,
22 second paragraph.

23 Patent owner offered no evidence to evaluate what
24 percentage of individuals who are prescribed medications for DPN use
25 Metanx or how many doctors are prescribing it as opposed to other

1 agents, so we don't think that they've established that Metanx has
2 fulfilled the long felt need for diabetic peripheral neuropathy treatment.

3 Now, if we presume arguendo that it has, then the question
4 is: Is it being satisfied by something that wasn't disclosed in the prior
5 art? We cited at least as far as the studies that were in the prior art the
6 Yaqub study that says that methylcobalamin is effective, but say you
7 disregard our references. You can still look at Dr. Fonseca's own
8 paper, Exhibit 2171, and there he wrote unambiguously that
9 methylcobalamin "has been shown to improve neuropathy symptoms in
10 both humans and animals."

11 And he cited the Yaqub reference and the Yaqub reference
12 and the Watanabe reference in support of this statement. In contrast, he
13 speaks only speculatively about all methyl folates and pyridoxines, the
14 B6 vitamin potential for treatments, and that's at page 147 starting on
15 the right-hand column.

16 And in the same paper or issue of the American Journal of
17 Medicine in which Dr. Fonseca's study was published, there's an
18 editorial by Dr. Vinik, and we cited this in our brief, and it says
19 that -- at the end of it, it calls for additional study to determine which of
20 the three components was responsible for the therapeutic effect, and
21 that's at 96 in the last paragraph. Dr. Fonseca and Dr. Jacobs admitted
22 that they didn't attempt to compare the effectiveness reported for
23 methylcobalamin with the data that they had for Metanx.

24 Now, with respect to the question of whether L-5-MTHF is
25 unexpectedly more potent than racemic, petitioners raised additional

1 argument regarding the Venn study, and there is evidence, which is
2 even if the Venn study had shown a greater than double since the
3 racemic -- if you believe the R isomer is inactive, if you cranked out the
4 data and you saw a greater efficacy, that wouldn't be unexpected. It
5 would be just bearing out what Marazza was talking about with respect
6 to the inference -- that the R isomer may be interfering with folic
7 uptake itself.

8 And as Mr. Cwik mentioned in the morning section, does the
9 Zittoun Cooper reference also have a disclosure regarding the potential
10 inference with the inactive isomer transported into cells. Again that's at
11 page 200 in the top paragraph. So not only is it questioning whether
12 it's -- an unexpected quote, unquote, greater efficacy has been shown,
13 there's also a question of whether it is unexpected.

14 JUDGE KAMHOLZ: Has there been any evidence in the
15 record of what anyone would consider unexpected? Does unexpected
16 mean superior, how much greater efficacy, double, triple?

17 MR. KRIT: I believe implicit in that -- and I'm doing this
18 from recollection, so I need to qualify that. I believe an implicit event,
19 or this may be implicit in the argument that the patent owners provided,
20 was that if you expected the racemic -- if you thought that the racemic
21 was just half inert and half active, then you would expect results sort of
22 commensurate with that in terms of the dosages.

23 Now, I don't know if there's any evidence that the efficacy is
24 straight linear, that you don't get diminishing returns when you take

1 either the racemic or the L-5-MTHF, but I think that was what was
2 underlying their interpretation of that.

3 I should mention also, if I can return to it, that Venn himself
4 postulated that the reason for this difference that you commented on
5 might be because of the blockage or the same transport in the cell issue
6 with the inactive isomer, which is referred to in Marazza, but other than
7 that, no, I'm not aware of anything specifically saying -- relating to
8 what you would expect between the differences, just the broad and I
9 believe uncontested acknowledgment that at worse -- or maybe I should
10 say at best, the racemic, the R isomer is inert and is just not used.

11 So patent owners have argued that, Well, that was
12 theoretical, people weren't convinced at the time of Marazza or at the
13 time of the invention, but I don't think that that's a distinction with a
14 difference. It was disclosed. There were studies. Marazza cites
15 studies, and we introduced them into the record supporting that. That's
16 enough of a reason why people would prefer Marazza's compound.

17 JUDGE BONILLA: Just to clarify, you're talking about the
18 secondary considerations, and then you're switching to go back to the
19 prima facie case. I'm trying to clarify who I should be asking what to.

20 MR. KRIT: Oh, I'm sorry. The question regarding
21 unexpected -- this efficacy is with respect to the secondary
22 considerations.

23 JUDGE BONILLA: Are you covering all the secondary
24 considerations?

25 MR. KRIT: I'm sorry?

1 JUDGE BONILLA: Are you covering all the secondary
2 considerations.

3 MR. KRIT: No, I'm only -- Mr. Cwik is going to cover
4 commercial success and copying.

5 I guess I'll make one last comment, which is they have raised
6 a question about the Scott reference, which was one of the references
7 that we identified as recommending use of 5-MTHF, and Scott
8 identifies a problem or concern with metabolites of folic acid that
9 would expose a fetus to unmetabolized folic acid, a supplement given
10 to expectant mothers for the prevention of neural tube defects, and that
11 Scott was only proposing a low dose trial with 5-MTHF, L-5 -- I'm
12 sorry racemic 5-MTHF, to avoid or to check that for efficacy.

13 I think Scott is ambiguous as to what it believes as far as
14 using L-5-MTHF or 5-MTHF as a supplement at the end of the
15 reference. He refers to folic preparations and not folic acid. I think
16 Lucock, the associated reference we submitted, Lucock is clearly
17 concerned with the R isomer. He just says, We don't know the effects
18 of the R isomers, so it could be avoided. He actually missed -- it turns
19 out he's referring unnatural isomer.

20 Regardless, I think it's telling that they didn't refer -- they
21 didn't end with the Barford reference, and the Barford reference stated
22 unambiguously, We have a danger with this unmetabolized folic acid,
23 exposing a fetus to it, let's use or -- I suggest using reduced folate to
24 avoid this.

1 So going all the way back to Barford, the knowledge of
2 administering a reduced folate avoids or will resolve any danger with
3 unmetabolized folic acids which was one of the alleged expected
4 results that patent owners raised.

5 And unless there's any other questions on teaching away or
6 long felt, I'll hand it to Mr. Cwik. Thank you.

7 MR. CWIK: Good afternoon, Your Honors. We've gone
8 passed noon now, so again for the record, my name is Joe Cwik, and
9 I'm here on behalf of the petitioners.

10 I would like to talk about some of the other secondary
11 consideration factors. The first factor I will talk about is the
12 commercial success factor, and the first point I want to raise is the point
13 that Judge Bonilla first raised and that's about market share.

14 We cited the In re Huang case from the Federal Circuit which
15 also cites other cases, the Cable case from the Federal Circuit, the
16 Baxter Travenol case from the Federal Circuit, and what those cases
17 from the Federal Circuit say is it's not enough for commercial success
18 to just tell the Court or whomever what the sales are. You have to put
19 it in a market share context, and here that simply has not been done.

20 We have these alleged treatments for diabetic peripheral
21 neuropathy. How do those treatments, these Pamlab products compare
22 to the other sales of other products that are out there treating diabetic
23 peripheral neuropathy?

24 My co-counsel just recognized there's pregabalin. There's
25 duloxetine, two FDA approved drugs for diabetic peripheral

1 neuropathy. What's the market share? What are the profits of the
2 PamLab patented products compared to the profits of the duloxetine, the
3 pregabalin?

4 That market share data is just not there. They hired an
5 expert. They had Dr. Hofmann who they say was a great expert. He
6 was perfectly capable of making that comparison. He didn't do it. I
7 think the implication is that the comparison was not good. It was not
8 good at all.

9 JUDGE BONILLA: Don't you think it's significant if what
10 they say is that they basically created a market for this product
11 wholesale that didn't exist before.

12 MR. CWIK: Well, they did not create a market for treating
13 diabetic peripheral neuropathy.

14 JUDGE BONILLA: But they created a market for treating it
15 with this particular drug. No one was doing it. They created it and
16 then they were copying it.

17 MR. CWIK: Right, right.

18 JUDGE BONILLA: Doesn't that overcome the problem of
19 the market share problem?

20 MR. CWIK: That's I guess a question of how you're defining
21 the market. If you want to define the market as only their drug in a
22 nutritional non FDA approved type scenario, then I guess they
23 have -- you could define the market that way, but I think from the cases
24 from the Federal Circuit, you look at what's the problem trying to be

1 solved, and the problem trying to be solved is diabetic peripheral
2 neuropathy.

3 Same thing for depression, they've cited the sales of Deplin
4 as success of treating depression, but what about all the other FDA
5 depression drugs out there? How do the sales of Deplin compare to the
6 other FDA depression drugs? That data is not there. It was available to
7 the patent owners. They didn't put it in, and I think the implication is
8 the comparison was not really favorable at all.

9 JUDGE KAMHOLZ: Did you put this question to Dr.
10 Hofmann about whether FDA-approved treatment for diabetic
11 peripheral neuropathy to form part of the relevant market?

12 MR. CWIK: We did ask him if he was aware of other sales
13 of other diabetic peripheral neuropathy products, other depression
14 products. My recollection is we did ask him that, and he said he didn't
15 know, and he didn't do that analysis.

16 The Federal Circuit says if the patent owner fails to do that,
17 that makes the commercial success factor either dispositively gone or
18 makes the commercial success factor very weak on behalf of the patent
19 owner. So that's the first point I want to make on commercial success.

20 The next point on commercial success is another point that
21 the Board has already raised is -- and it deals with the nexus. They of
22 course have to show that the nexus of the commercial success relates to
23 the claimed patents or the claimed challenged patent claims, and I think
24 there's submitted evidence by their experts that they think it's

1 coextensive. I think the Board raised some great questions today of
2 why it could not be coextensive.

3 Here's another factor is, there's all these other patents. This
4 slide, this is slide 22 of our '915 patent, demonstratives, and what this is
5 showing is these are the product inserts for the PamLab patent products.
6 We have the Metanx, the NeevoDHA, the Neevo caplets and the
7 Deplin. This is their own product insert. We didn't make this up. You
8 can see the exhibits in the 2000 range. They filed these exhibits on
9 their own, and as you can see the Metanx shows that some or all of the
10 following patents may apply, and we see some of them that we know,
11 the '915, the '040, but then there's others we haven't spoken about, '904,
12 '168, '490.

13 How much of the commercial success is due to those patents
14 in Metanx? And I can't answer affirmatively how much that is, but I
15 think it goes to the weight of the commercial success factor that there's
16 serious doubts that what they say is the nexus and only the nexus of
17 their challenged claims is really in doubt.

18 JUDGE BONILLA: One of the things the patent owner
19 brought up was this idea of if they make a prima facie case and the
20 burden of persuasion shifts to you to rebut the presumption of nexus, if
21 we assume that's taking place here, then is the burden of persuasion, if
22 you will, on you to show that it's actually due to something else other
23 than what they're saying it is?

24 MR. CWIK: Right, that's what the case says. That's what
25 that case says is if they have met that initial burden, then the burden

1 does shift to us, and we think in the totality of the circumstances, that
2 we have met our burden of showing that there's other factors that are
3 causing the commercial success other than their actually challenged
4 claimed patents.

5 Can I say mathematically how much of the commercial
6 success is due to this or that? I can't, and I don't think they can either,
7 and I don't think their experts ever said 100 percent of the commercial
8 success is due to the challenged claims and the challenged claims only.

9 I think it all goes to the weight of it, and I think this, among
10 other pieces of evidence, much of it from their own documents shows
11 that the nexus issue is really a morass, and we really don't know what
12 the true answer is, and I don't think anyone could ever know for 100
13 percent sure what causes commercial success. I mean, realistically
14 there's many factors, but I want to show the other many factors that
15 likely could have caused the commercial success factor.

16 So to the extent they may read this language and say, Well,
17 this language says some or all of the following patents may apply.
18 We're not saying that these other claims do apply. If they make that
19 argument, then that argument goes away because then all we do is look
20 at the Merck and South Alabama Medical Science Foundation
21 complaint in the Eastern District of Texas. This is the first lawsuit that
22 started the dispute on these patents among the parties.

23 This was filed in Eastern District of Texas in 2012. That
24 case is still pending. It's stayed pending these proceedings, and in their
25 own complaint, they affirmatively say that these PamLab patented

1 products, NeevoDHA, Metanx, Cerefolin NAC and Deplin, all are
2 covered by one or more claims of the '915, '904, '381, '778, '490 and
3 '040 patents.

4 So it's showing that it's just not one patent. It's certainly not
5 just one challenged claim that are covering these products and could be
6 the cause for commercial success.

7 JUDGE BONILLA: Now, you suggested in your reply that
8 it could be that the thing that made it more commercially successful
9 was something that came up covered by one of the other patents.

10 Is there any evidence of record that it was a stability or
11 something else other than what they say it is, which was the three
12 things combined or whatever it is, the individual products? Did you
13 cite anything or do you know of any evidence that says that maybe it
14 was the stability?

15 MR. CWIK: Well, I think -- I'm going to go through these
16 slides. I'm think I'm going to show you the actual circumstantial
17 evidence. I'm not going to say there's direct evidence where an expert
18 actually said that, but I think there's cumulative, circumstantial
19 evidence which we all know is sometimes more persuasive than the
20 actual direct evidence itself.

21 So regarding that issue, that leads right into my next point, is
22 we see the complaint by PamLab when they recently sued someone in
23 the Eastern District of Louisiana, and here they are starting to tell the
24 same story, that it's the Metafolin optimally stabilized form of
25 L-5-MTHF that, in my opinion, is the reason for commercial success to

1 the extent there is such success, and here we see the story starting to be
2 told by PamLab itself.

3 They say in the mid-1990s Merck and Cie, formerly known
4 as Merck Eprova made a key break through and invented a process to
5 synthesize L-methylfolate in stable form. Offered under the name
6 Metafolin, L-methylfolate calcium is the crystalline, stable and
7 diastereoisomerically pure form of folate directly usable by cells in the
8 body.

9 Here's the timeline also supporting the story that that's the
10 optimally stabilized form of Metafolin that's causing the success now.
11 When the '915 patent issued in 1999, did the commercial success
12 happen right away? Why isn't the product going out the door and being
13 sold?

14 Instead what we see is 2002 the Metafolin ingredient is first
15 sold or available for sale in the United States, and that same year they
16 get a patent on their Metafolin compound claiming the stability of the
17 crystalline form of the (6S) 5-MTHF. Two years after the patent is in
18 place, two years after Metafolin is in sales, then we see PamLab
19 patented products in sales, and all of PamLab patented products have the
20 Metafolin ingredient.

21 Here is slide, slide 25, the first reference here is to the
22 declaration of Dr. Vera Katz. Dr. Vera Katz is the Merck witness who
23 offered a declaration. This is from her declaration itself, and here she is
24 highlighting the key component of Metafolin in these products.
25 Paragraph 13 she says: "I consider Metafolin to be a successful

1 product, because Metafolin offers unique, biological benefits as it is a
2 substantially pure, stable, active form of folate. As I noted earlier, it is
3 one of the most important products in Merck and Cie's portfolio
4 because it is a key component of our customers' products."

5 Here she's saying that Metafolin itself is a key component of
6 our customers' products. That to me really applies here. To the extent
7 there's successful sales, it's because of the Metafolin.

8 Now, the next part of this slide is from Frost and Sullivan.

9 Again this is an exhibit they offered themselves. We didn't have to
10 come up with this. They put this in the record themselves, and Frost
11 and Sullivan gives an annual award on a product innovation. The
12 product innovation award didn't go to the PamLab products. It never
13 mentions the word PamLab. The product innovation award goes to
14 Metafolin, and Frost and Sullivan recognizes some of the benefits of
15 this Metafolin product is a product innovation, and what they say is:
16 "Stability issues have deterred the use of natural folates in many
17 applications. However, Merck Eprova AG has made significant
18 advancements in this field with the introduction of Metafolin.

19 Metafolin provides a stable, naturally occurring predominant form of
20 folate." So again more circumstantial evidence to the extent success
21 has occurred, it's being caused by the Metafolin.

22 I mentioned before that the Metafolin compound itself was
23 patented by Merck, and here is some cut and pastes from the actual '168
24 patent that relates to Metafolin itself, and as you can see, the title of the
25 invention is "stable crystalline salts of 5-methyl tetrahydrofolic acid,"

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IPR2013-00118, and IPR2013-00119

1 and this is again in 2002, and once again it's telling a story that prior to
2 2002, the stability had not been optimized for widespread commercial
3 availability.

4 I mean, we obviously have seen examples of Mr. Krit and the
5 other references here that the (6S)-5-MTHF was suitable enough to
6 treat people in various circumstances and scenarios, but not necessarily
7 optimized for wide spread commercial success.

8 JUDGE KAMHOLZ: Thank you, Mr. Cwik.

9 We will adjourn for one and a half hours. We will resume at
10 1:45 to discuss IPR2013-00117.

11 **(Whereupon, at 12:16 p.m., a lunch recess was taken.)**

AFTERNOON SESSION

(1:39 p.m.)

MR. PARKER: Your Honors? Your Honors, if I may just –

JUDGE KAMHOLZ: Mr. Parker, yes.

MR. PARKER: You had asked me just two questions about the SAMSF patents that we talked about, whether they disclose pyridoxine, hydrochloride, and I don't know but other compounds, Vitamin B.

JUDGE SNEDDEN: Pyridoxal --

MR. PARKER: Excuse me?

JUDGE SNEDDEN: Pyridoxal-5'-phosphate.

MR. PARKER: So it doesn't. It discloses pyridoxine hydrochloride and cyanocobalamin, cobalamin but not the methylcobalamin.

JUDGE KAMHOLZ: Thank you.

MR. PARKER: I had two other cites that I mentioned that I would give to you. Can I give that to you now, just two case cites? I mentioned them on the record.

JUDGE KAMHOLZ: Okay.

MR. PARKER: In re Bell, 999 F.2d 781, and In re Bard which is 16 F.3d 380, with a pincite at 382. Thank you.

JUDGE KAMHOLZ: We'll hear argument now in case IPR2013-000117, Gnosis versus Merck and Cie.

The petitioner will begin. Mr. Cwik?

1 MR. CWIK: Yes. Your Honors, again I do have hard copies
2 of the demonstrative exhibits for this case, if you would like them.

3 MR. PARKER: Your Honors, may patent owner as well
4 submit their copies to the panel? May I approach?

5 MR. CWIK: Good afternoon, Your Honors. My name again
6 for the record is Joe Cwik. I'm here on behalf of the petitioners. Today
7 we are talking about the '040 patent in case 2013-00117.

8 Again I would like to give you a brief outline of what we
9 plan on doing with our argument this afternoon. Similar to what we
10 saw this morning, I plan on taking about 20 minutes going through our
11 prime case, anticipation and obviousness for the '040 patent.

12 Patent owner will have their one hour of response argument,
13 and then we will preserve 40 minutes for rebuttal argument, and like
14 this morning, Mr. Krit and I will be splitting the 40 minutes depending
15 on the actual issue being discussed at that time.

16 Again my key job is this afternoon to explain petitioner's
17 arguments to you to the best of my ability. As I go through my
18 presentation, if there's any questions, please feel free to interrupt me.

19 So we're talking about the '040 patent this afternoon, and
20 these claims are generally directed towards the use of the (6S)-5-MTHF
21 with or without a vitamin here for the purpose of lowering
22 homocysteine, and it's our contention that claims 8, 9, 19, 20 are
23 anticipated by Serfontein, and are also obvious in light of Serfontein
24 and Marazza, and those are the same grounds that the Board instituted
25 the trial on.

1 We also contend that the remaining claims of the '040 patent,
2 claims 11, 12, 14, 15, 21 and 22, are obvious in light of Serfontein,
3 Marazza and the Ubbink reference.

4 So the first reference I want to talk about is the Serfontein
5 reference and referring to slide 2, and as we saw this morning, here is
6 claim 1 of the Serfontein reference. It's the core disclosure of
7 Serfontein, and here, like the '040 claims themselves, we have specific
8 language on lowering homocysteine, and it teaches a composition
9 including vitamin B6.

10 JUDGE BONILLA: Can I ask you a quick question before
11 you start getting into the references? It has to do with claim
12 construction. The patent owner is saying they have a claim
13 construction that the 5-methyl form is connected to the single natural
14 isomer that's substantially free from the other isomer.

15 Do you have a contention with that claim construction?

16 MR. CWIK: Yes. We disagree with that claim construction,
17 and to put it in context, if we can look at claim 8. Claim 8 is the first
18 challenged claim in this patent, and so we see the language of claim 8
19 here, and my understanding of their position is that they are reading this
20 sentence to import the limitation that the claim does not just disclose
21 5-methyl-(6S)-tetrahydrofolic acid, but it also includes the limitation
22 that the 5-methyl-(6S)-tetrahydrofolic acid must be essentially free of
23 the inactive, unnatural (6R) isomer, and we believe that that contention
24 is wrong for a couple of reasons.

1 The first reason is that under the Board rules, the Board is to
2 interpret the claims under the broadest reasonable interpretation, and to
3 import express limitations into claim 8 and similar claims we think is
4 not warranted.

5 JUDGE BONILLA: Well, the patent owner does point to the
6 specification, and I think you acknowledge that this is the '040 patent,
7 column 1, starting lines 18, it sets that tetrahydrofolate's in natural
8 stereoisomer form, which is what's in claim 2, which this is limiting it
9 to I guess in claim 8, and says it refers to those what looks like to be the
10 specific stereoisomers.

11 Is that a clear definition of what that claim means?

12 MR. CWIK: I don't think that the -- the (6S) isomer means
13 of course the (6S) isomer. I would not contend that the (6S) isomer by
14 definition includes the (6R) isomer.

15 I think the relevant point we're making here is that claim 8,
16 which depends on claim 2, is a comprising claim, so it is possible that
17 the (6R) isomer is anticipated here. I mean, it doesn't exclude the (6R)
18 isomer by using the comprising language.

19 JUDGE BONILLA: So it's not so much that their
20 interpretation is wrong. It's just that they don't look at the fact that the
21 claim uses comprising meaning it would have this isomer and could
22 also have the other one as well?

23 MR. CWIK: I don't know if I heard you correctly, but our
24 contention is that it does not include the limitation of essentially free of
25 the (6R) isomer in claims 8 and the other dependent claims.

1 JUDGE BONILLA: Because of the comprising language.

2 MR. CWIK: That's part of it, and in addition to the fact that I
3 think the broadest reasonable interpretation would be not to import that
4 limitation into this claim.

5 JUDGE KAMHOLZ: If the (6S) is commingled with (6R),
6 how can you say that it's in its naturally stereoisomeric form?

7 MR. CWIK: Because the claim 8 is claiming some (6S)
8 isomer form. It's not limited to -- so if there was a racemic mixture that
9 had (6R) and (6S), it would have some (6S)-5-MTHF in it.

10 So moving on, we have a slide here, this is slide 3, showing
11 how claim 2, which is the dependent claim -- which is the independent
12 claim on which the dependent claims rely on, and it shows how claim 2
13 reads on the Serfontein reference with respect to the other elements,
14 and the first elements of course are "a method of preventing or treating
15 disease associated with increased levels of homocysteine levels in the
16 human body."

17 And here we have some additional language where we see
18 that Serfontein discloses that the elevated homocysteine levels are
19 associated with vascular diseases such as myocardial and cerebral
20 infarction, pernicious occlusive vascular disease and things of that
21 nature.

22 Here's the rest of claim 2. This is slide 4 comprising at least
23 one tetrahydrofolate in natural stereoisomeric form to a human subject,
24 so here of course at least in claim 2, we're not limited to the
25 (6S)-5-MTHF, but as I said before, as we get to claim 8, we are limited

1 to the 5-methyl-(6S)-tetrahydrofolic acid, and as we discussed this
2 morning, it's our contention that the Serfontein phrase of active
3 metabolites and folates includes eight compounds, one of those
4 compounds being the exact 5-methyl-(6S)-tetrahydrofolic acid.

5 The next slide, slide 6, is --

6 JUDGE BONILLA: Before we go on on that, can we talk a
7 little bit about the patent owner was citing the Ueland reference and the
8 Wagner reference as suggesting that the 5-methyl wouldn't be
9 considered an active metabolite, a suitable active metabolite.

10 Can you address some of the things they talked about in
11 regards to those references, particularly in their -- they talked about
12 Wagner and the fact that it talked about how the 5-methyl, unlike the
13 folate itself, wasn't metabolized?

14 MR. CWIK: Yes, Your Honor. That's dealing with the
15 substrate activity, and that's really a surrounding issue that Mr. Krit is
16 prepared to speak on, if it's okay that he address that because he
17 addressed that this morning as well.

18 MR. KRIT: As I understand the demonstrative slides that
19 were submitted for the '040 case, what they said -- first they said
20 Ueland only describes folic acid, and you can presume from that and
21 this discussion about the substrate activity that Ueland would teach
22 away from using 5-MTHF.

23 I don't believe there's anything in the record that has said that
24 L-5-MTHF would -- that they've said would not have the -- support any
25 polyglutamization, would not lower homocysteine. They have claimed

1 that folic acid -- I think, if I understand their argument, and I'm
2 referring to page 15 of their brief, that, Well, we know from Ueland
3 that folic acid works. We know somehow it's working, but you
4 wouldn't necessarily think that L-5-MTHF would work because of this
5 poor substrate activity.

6 And also they say that -- from their slides that Ueland doesn't
7 describe anything but folic acid, and that's not true. Ueland actually
8 describes a successful use of folinic acid, and folinic acid, if you look at
9 the Cichowicz reference is also listed as a similar substrate. If you look
10 at the abstract of the Cichowicz reference, they're all bad or poor
11 substrates except for tetrahydrofolic.

12 So their first argument is teaching -- it's a complete teaching
13 away, and then as I was saying earlier, if you look at Dr. Gregory's
14 declaration, it's inconsistent. He says you wouldn't necessarily
15 believe -because folic acid works, you wouldn't necessarily believe that
16 L-5-MTHF would work, and then they also make this separate, you
17 would be sure that it wouldn't work.

18 We noted that in Zittoun Cooper on page 200, it talks about
19 transport of folic into cells in the context of folic deficiency, and it talks
20 about, for example, the inactive isomer of 5-MTHF and 5-MTHF not
21 being transported into this -- or blocking transport into the cells.

22 JUDGE BONILLA: Can you explain a little bit about
23 Wagner?

24 MR. KRIT: Wagner, as I've understand, they said earlier
25 Wagner doesn't make a comparison from folic acid and

1 methyltetrahydrofolate. Wagner, like Cichowicz, discloses that
2 5-MTHF is a poor substrate for polyglutamization in cells, and we
3 don't dispute that. As they're -- Dr. Gregory testified, they're both poor
4 substrates. He said that L-methylfolate is, quote, a little better, end
5 quote.

6 JUDGE BONILLA: There's something in Wagner, and this
7 is something I try to figure out. It says PT glut, which I assume is folic
8 acid, but not 5-methyl as the same thing, was metabolized significantly.
9 Is that suggesting that folic acid is metabolized but the 5-methyl is not?
10 Is that what --

11 MR. KRIT: This is in the Wagner reference?

12 JUDGE BONILLA: This is in the Wagner reference.

13 MR. KRIT: If you give me one moment? Do you have the
14 exhibit, anybody, for Wagner?

15 JUDGE BONILLA: It's in the '116 case, 2061. I guess it's
16 the same in all. 2060.

17 MR. KRIT: Could you -- forgive me, Your Honor, can you
18 again point where in the Wagner reference that is?

19 JUDGE BONILLA: Where it says the part about
20 metabolizing?

21 MR. KRIT: What page were you reading from?

22 JUDGE BONILLA: Well, it says it in the abstract. The title
23 talks about transport of 5-methyl and folic acid in these cells, and then
24 it says around the middle of the abstract that the PT glut, which I
25 interpret that that's folic acid bound to glutamate, but not the 5-methyl

1 which metabolized significantly. I'm trying to understand the
2 significance of that teaching, if any.

3 MR. KRIT: Sure. And I can only say this from my
4 immediate take on this, is that as patent owner said, this was I guess a
5 test -- this was sort of an experimental model, and they maybe in terms
6 of just describing in their timeframe how much metabolization had
7 happened on the folic acid compared to the 5-MTHF.

8 I recall patent owner saying that there was no comparison
9 that could be drawn from this as far as folic acid and 5-MTHF. I know
10 I can't -- I don't have the ability to draw a comparison so I'll take patent
11 owners at their word for that. I can't speak to -- that's speculation on
12 my part as to what that exchange may be saying. I don't see it as the
13 ultimate conclusion from my laymen's perspective.

14 I know later we're going to be talking about -- I guess we
15 could talk about it now but the Harpey study that was cited in Ueland,
16 and also the Reglan study that spoke of 5-MTHF as being the ideal or
17 the envisaged, the preferred substance for lowering homocysteine.

18 So I guess I would say apart from us not -- apart from there
19 not being anything in Ueland that speaks to this as being a disadvantage
20 of using a reduced folate that had low polyglutamization, whether it
21 was folic acid or -- I'm sorry, MTHF or folinic acid as shown in
22 Cichowicz to be poor substrates, that was not a teaching away to people
23 in the art or at least to across the art. We have these direct suggestions
24 which overcome it.

25 JUDGE BONILLA: Thank you for going out of order.

1 MR. KRIT: Thank you.

2 MR. CWIK: Just continuing, Your Honor, again the analysis
3 with respect to what the acting metabolite folates in Serfontein means
4 would be essentially the same analysis in the '040 patent as it would be
5 in the Bailey patents. We put up slide 6 that contains the Board's
6 summary of the evidence on that topic, and it's the same.

7 Text that was used in the Bailey patents that we discussed
8 this morning, and of course it does list in this slide 8 active metabolites
9 or folates, and then of course the figure 21-4, Modern Nutrition, shows
10 those eight acting metabolites in graphic pictorial form.

11 And we've discussed the fact that the Modern Nutrition then
12 points a POSA to the IUPAC nomenclature recommendation teaching
13 that as far as the active isomer forms of the metabolites involved in the
14 metabolite process, those are the reduced natural folates that all have
15 the same 6-carbon configuration of an L at the 6 carbon position, and
16 those are the eight active metabolites of folates.

17 Again the Board has found the claims, some of the claims
18 anticipated by Serfontein but also obvious in light of Marazza, and
19 again Marazza has the same teaching here that it did at the '915 patent,
20 that there was an express interest in the use of the 5-MTHF compound,
21 and based on that interest, coupled with the fact that there was a
22 concern that the (6R) isomer was potentially bad or interfering with the
23 uptake of folates themselves, that there was a desire to separate the
24 good (6S) isomers from the (6R) isomers into pure separate forms.

1 So Marazza does that. He proposes a process for doing that.
2 That process is patented, and that we think teaches at a minimum that
3 the (6S) isomer in pure form was preferred.

4 So even if the Board were to accept the patent owner's claim
5 interpretation that the (6S)-5-MTHF is essentially free of the (6R)
6 isomer in the claim language, even though it expressly does not say
7 that, then Marazza would take care of the essentially free (6R) isomer
8 issue just as it did in the Bailey patents.

9 Here's the actual text of the Marazza patent itself, and again
10 here's the language that we focused on this morning. The key language
11 is at the first paragraph where it says "there exists an increasing interest
12 for the application of this natural metabolite as at least one active
13 compound therapeutical agent, for example, as vitamin in folate
14 deficiency states."

15 Here we're seeing those same types of words that Serfontein
16 himself used, active, compound, metabolite. It's almost word for word.
17 It's pretty remarkable on how similar that language is to Serfontein
18 itself.

19 Then the rest of the paragraph of Marazza is shown on this
20 slide number 9 whereas Marazza is discussing his reasons why he
21 wants to separate the good (6S) isomer from the potentially bad (6R)
22 isomer, and it's not just himself that believes that there are concerns to
23 be had about the (6R) isomer, but he notes that there is the Weir study.

24 He indicated that the (6R) isomer is inert and excreted as
25 such in an unchanged form, and then he also cites to the Chello

1 reference where it's "been postulated, that the unnatural (6R)-
2 diastereoisomer could interfere to the folate transport system through
3 the cell membranes of mammals, including humans."

4 Claims 11, 12, 14, 15, 21, and 22, these add another
5 limitation concerning the methylene tetrahydrofolate reduction enzyme
6 being the cause of the higher levels of homocysteine, and we see that
7 the Ubbink reference itself can be accepted as the limitations to
8 someone well known, to a POSA that higher homocysteines could be
9 caused by a defect in this enzyme or even the thermolabile variant of
10 this enzyme, and Ubbink itself is a study assessing vitamin B12, B6
11 and folate nutritional status in men with hyperhomocystinemia.

12 JUDGE KAMHOLZ: Do you want to take more time?

13 MR. CWIK: No, that's fine. I'll cut it there again.

14 MR. PARKER: Good afternoon, Your Honors. For the
15 record, my name is Thomas Parker, and I'll be speaking on behalf of
16 patent owners, Merck and Cie.

17 Your Honors, if I may, I would like to just begin with the
18 panel's discussion with Wagner in the abstract. It does indicate that the
19 folic acid, not the L-5-MTHF was metabolized significantly after 60
20 and 90 minutes of information, so there is a --

21 JUDGE BONILLA: Can you explain what metabolite means
22 there?

23 MR. PARKER: In the assay, metabolized in terms of
24 actually being taken into the cells and being converted into a
25 metabolite, and what they see in the studies --

1 JUDGE BONILLA: So if it's metabolized, that means it
2 goes through the biochemical pathway that's involved, the folic acid
3 pathway?

4 MR. PARKER: Right, exactly.

5 JUDGE BONILLA: So it's doing what it's supposed to be
6 doing.

7 MR. PARKER: Well, exactly right. Because it's being
8 found bound to the micromolecules, it is not doing what it's supposed
9 to do.

10 JUDGE BONILLA: Is there any explanation or is there
11 evidence that explains that?

12 MR. PARKER: No. All we have is at page 3531 in Wagner,
13 which is Exhibit 2061 where they just speak about it in terms of under
14 the conditions of the present study, and it goes on, and I'm looking at
15 the column on the right-hand side. It talks about how they look at
16 isolated -- hepatocytes did not significantly metabolize the L-5, and
17 then it goes on.

18 JUDGE BONILLA: I was reading the paper in isolation, and
19 I was trying to understand what metabolized meant, and I was hoping
20 that there was something, a declarant evidence or something to explain
21 what that meant.

22 MR. PARKER: Well, according to Dr. Gregory's
23 interpretation was it was, in fact, showing that L-5 was not being
24 utilized.

1 JUDGE BONILLA: He said something about it not being
2 taken up by the cell; is that correct, or am I miss understanding what he
3 said?

4 MR. PARKER: In paragraph 29 he discusses Wagner, and I
5 think he references that.

6 JUDGE BONILLA: What does he say exactly on that?

7 MR. PARKER: He says that it talks about it. It is not well
8 retained in the cells. He talks about the Wagner indicating that it's not
9 significantly metabolized.

10 JUDGE BONILLA: Does he use the word metabolized?

11 MR. PARKER: Yes, quoting Wagner.

12 JUDGE BONILLA: This is paragraph 29 of --

13 MR. PARKER: 29.

14 JUDGE BONILLA: -- which Exhibit?

15 MR. PARKER: Yes, Exhibit 2001.

16 JUDGE BONILLA: All right.

17 JUDGE KAMHOLZ: Does he not say that the problem was
18 it would not accumulate the tissues?

19 MR. PARKER: Yes.

20 JUDGE KAMHOLZ: As opposed to being metabolized?

21 MR. PARKER: In other words, since it's not being
22 accumulated and retained in the cells, it's not being -- it's this mass
23 effect, that it's sufficient amounts being accumulated and not just
24 pushing the reactions forward within the folate cycle.

1 JUDGE KAMHOLZ: Does Wagner clearly say that
2 5-methyl does accumulate?

3 MR. PARKER: I guess like I said 20 percent, but it's being
4 bound by these macromolecules which indicates it's not being
5 metabolized and utilized. It's just sitting in the cells being bound by
6 these molecules.

7 JUDGE KAMHOLZ: I'll ask you again: Do you conclude
8 that metabolized here means utilized as opposed to destroyed?

9 MR. PARKER: All I have is -- the basis I have is what Dr.
10 Gregory says in his declaration.

11 JUDGE KAMHOLZ: He doesn't explain what metabolize
12 means.

13 JUDGE BONILLA: He just says, if I'm reading it
14 correctly -- and point me to something else, he says instead the
15 L-5-methyl is not well retained in the cells.

16 MR. PARKER: Right.

17 JUDGE BONILLA: But Wagner seems to suggest that it is
18 taken up by the cells. Then it just talks about how it's not metabolized.

19 MR. PARKER: Right.

20 JUDGE BONILLA: I was trying to understand that
21 distinction and where the declaration might explain it.

22 MR. PARKER: Well, the distinction as I understand is that
23 it was that they're bond to intercellular macromolecules.

24 JUDGE BONILLA: They're taken up -- it says like 20
25 percent of it was bound.

1 MR. PARKER: Right. It may be that --

2 JUDGE BONILLA: Is that what happens, 20 percent of it is
3 bound, and therefore it's not metabolized because it's bound?

4 MR. PARKER: Right, and if it's bound, it's not being
5 utilized.

6 JUDGE BONILLA: What about the other 80 percent?

7 MR. PARKER: That may be -- the 80 percent
8 could -- reading this it's possible that it's still floating the plasma.

9 JUDGE BONILLA: But it isn't taken up by the cell, you
10 mean?

11 MR. PARKER: Yes.

12 JUDGE BONILLA: But the whole point of the paper is how
13 it's being transported inside the cell, right?

14 MR. PARKER: Well, the point of the paper is that there's
15 not enough or at least there's a small amount being transported in the
16 cells, and of that, it's bound to intercellular macromolecules.

17 JUDGE BONILLA: Just to be clear, there's no evidence to
18 declarant or anybody else talking about Wagner is saying? This is what
19 we -- paragraph 29 is the only one that we have.

20 MR. PARKER: Dr. Gregory is the only declarant discussing
21 the Wagner paper, and the only testimony we have is with Dr. Miller.

22 Yes, Dr. Gregory is the only declarant, and he also refers to it
23 again in paragraph 97, footnote 13. He talks about Wagner, but
24 essentially that might be similar to what he said previously. But, no,
25 there's in other declarant talking about Wagner, Your Honor.

1 If I may proceed, I know time runs quick. I would like to get
2 to Harpey, and then I would like to move on to the anticipation.
3 Counsel mentioned that Harpey -- well, counsel mentioned Harpey, the
4 Harpey reference, and then there are two of them. And this is on -- I'm
5 going to refer to the reply brief at page 3, which refers to the Harpey as
6 a success in controlling homocysteine with respect to utilizing oral
7 5-MTHF, okay?

8 Now, that's their interpretation. There are two exhibits.
9 Exhibit 1026, Harpey I, and then there's also Harpey II, which is 1027.
10 Now, when Dr. Gregory was shown both Harpey references, he
11 testified, this is slide 9 -- he testified that Harpey I and Harpey II
12 collectively show that 5-MTHF was ineffective. Specifically he
13 testified that collectively Harpey I and Harpey II teach away from using
14 5-MTHF to lower homocysteine levels. Collectively Harpey I and
15 Harpey II show that 5-MTHF cannot lower homocysteine, but in fact it
16 actually went up, so that in Dr. Gregory's opinion, Harpey II showed
17 that 5-MTHF was completely ineffective.

18 Now, their own expert, Dr. Miller, in a prior litigation,
19 testified that Harpey I would "very well could have" discouraged the
20 POSA from using 5-MTHF to lower homocysteine. So we have
21 petitioner's own expert supports -- is consistent with Dr. Gregory's
22 interpretation of these references.

23 Now, on rebuttal, you will hear counsel mention the fact,
24 Well, Dr. Gregory said that it lowered homocysteine, but he clarified
25 his testimony later on during his deposition. Since I don't have a

1 chance to respond, I know they're going to come back to show that to
2 you, so I did want to mention he did clarify that.

3 Now, they also mention that Harpey is also referenced in
4 Ueland. That is true, but Ueland does not identify any reduced folate as
5 a viable method of treating high levels of homocysteine or identify any
6 other reduced folates for that matter. Instead it promotes folic acid, and
7 then if you look at pages 492 to 493, there's a list of potential
8 modulated plasma homocysteine. First on the list is folic acid, neither
9 folinic acid or 5-MTHFs -- 5-MTHF is on the list.

10 There are other references that -- I'm sorry. Petitioner relies
11 on slides 10, 11, 12, these are all shown and put forth in front of our
12 experts. They said -- they gave their views on these particular
13 references, their comments, but the one thing that I wanted to just raise
14 is this is where an attorney's interpretation of the prior art becomes
15 problematic.

16 I mean, the references say what they say. Harpey I and
17 Harpey II in fact ended up teaching away from the claimed invention,
18 so you have the technical data in Harpey. You have it in Ueland. You
19 have it in Wagner. You have testimony from Dr. Gregory and others
20 with respect to the references relied upon by petitioner, but the question
21 becomes what the petitioner's references mean to the person of ordinary
22 skill in the art in light of the prior art as a whole.

23 So petitioners have not adequately answered the question,
24 despite the fact that they retained an expert, Dr. Miller, and they did
25 not bring him forth in rebuttal. Perhaps they were afraid of what he

1 was going to say. So we have the testimony of experts on the record
2 about the prior art and also the caution when lawyers are trying to
3 characterize the prior art, they tend to make mistakes or they are not
4 able to characterize them correctly.

5 JUDGE KAMHOLZ: A question about Harpey I and II.
6 Testing 5-methyltetrahydrofolate, was it tested by itself or was it tested
7 in combination with vitamins such as B6 and B12?

8 MR. PARKER: Vitamin B12 may have been one of them. I
9 know there was an in vitro study, an in vitro assay that was done. I
10 would have to look at my reference and my colleagues can look that up
11 so I can respond to your question properly.

12 JUDGE KAMHOLZ: Thank you.

13 MR. PARKER: With respect to claim construction that was
14 addressed earlier, I know that they had a position that they stated here,
15 but in their reply brief, I didn't see any challenge to our claim
16 construction, so I was assuming that they were not going to challenge it
17 and it was being adopted, but that being said, we do lay out -- we do
18 present a claim construction, which basically we construe in the
19 terms -- go to slide 3, please? The 5-methyl-(6S)-tetrahydrofolic acid
20 was directed to a single natural isomer, which is the 5-methyl-THF or
21 salt thereof, free or substantially free of chirally pure isomer.

22 JUDGE BONILLA: Even assuming that we agree with you
23 and the tetrahydrofolate in the natural chirally pure form refers to a
24 particular isomer, how do you address the fact that the claim actually

1 recites a method comprising an unnatural isomer, meaning it would
2 cover, for example, a racemic measure?

3 MR. PARKER: Right. Even with that comprising, this goes
4 back to the invention itself. The invention is using the natural isomeric
5 form of the compound for various uses, so it almost -- it's almost by
6 definition means specifically directed to use a natural isomer. It's
7 almost by definition excluding the unnatural isomer.

8 JUDGE BONILLA: The claim would be -- In the claim I see
9 the word comprising. It could have said consisting essentially of, or it
10 could have said chirally pure such as some of the other claims, but it's
11 not here, so are we sort of stuck on what the claim says? It says
12 comprising. It seems to me you have to have it here, but you could
13 have somewhere in there -- you could be administering racemic
14 measure.

15 MR. PARKER: I understand comprising is in there. It's an
16 open ended phrase, and my only response or my response to that would
17 be at least with that particular frame, by definition, it's almost by
18 definition a self exclusion, if you will, of the unnatural isomer, but
19 everything else applies in terms of it being open-ended and other things
20 could be within the scope of the claim.

21 Your Honor, in response to your question, they were using
22 the 5-MTHF together with is it pyridoxine and vitamin B12 and
23 methionine.

24 JUDGE KAMHOLZ: Pyridoxine, vitamin B12.

25 MR. PARKER: Pyridoxine, vitamin B12.

1 JUDGE KAMHOLZ: Pyridoxine and vitamin B12.

2 MR. PARKER: I was mispronouncing it, correct. In fact,
3 it's in the title of Gnosis Exhibit 1026.

4 JUDGE KAMHOLZ: Thank you.

5 MR. PARKER: Now, with respect to the '778 case this
6 morning, in that decision, the Board recognized that Serfontein did not
7 disclose substantially chirally pure reduced folates.

8 We would submit that that interpretation would equally apply
9 here, and that being the case, if the Board were to adopt our claim
10 construction, then we would submit that there would be no anticipation.

11 Now, Gnosis takes the position that the person of ordinary
12 skill in the art would immediately envisage every species within the
13 scope of Serfontein. I know we discussed that this morning, and I
14 understand -- we talked about In re Petering, so I don't know -- unless
15 the Board has any questions, I'll just move on to the obviousness, but in
16 terms of anticipation, we have our claim construction, and we believe
17 that if the Board were to follow how to interpret the Serfontein in the
18 '778 case, then there would be no anticipation.

19 JUDGE BONILLA: If we interpret the claim differently
20 than you do in that comprising means they can have a racemic measure,
21 do we have a problem with Serfontein again?

22 MR. PARKER: Well, again Serfontein does not -- for
23 anticipation purposes? No, and the reason being is because we have to
24 step back and we have to ask the question: Does one of ordinary skill
25 in the art read in Serfontein -- would they envisage every element in the

1 class that falls within the scope of the suitable active metabolite of
2 folate, so if the answer to that question is, no, they would not, then
3 there would be no anticipation because it doesn't disclose any particular
4 reduced folate.

5 So just to put in another way, if the POSA reads Serfontein,
6 they must envisage each member of that genus, leaving no ambiguity in
7 their mind just as surely as if it was identified in the reference.

8 JUDGE KAMHOLZ: If we adopt petitioner's argument that
9 suitable active metabolite of folate is that set of eight compounds that
10 one of ordinary skill in the art would have immediately envisaged, and
11 if we construe the claim as not excluding the racemic mixture, do you
12 concede that the claim is anticipated?

13 MR. PARKER: No, we do not, Your Honor.

14 JUDGE KAMHOLZ: Why not?

15 MR. PARKER: If I'm hearing your question properly,
16 because those eight compounds on that list are not enough. I mean, do
17 those -- are they suitable for use of any of the formulations, any of the
18 examples of the formulations in Serfontein? And the answer is, We
19 don't know. We don't know what form they have to be in. We don't
20 know what's suitable for a topical lotion versus what's suitable for
21 a -- as a rectal pessary, as well as the other dosage forms that are listed
22 in Serfontein.

23 So it's really about the disclosure itself. It's so broad. It
24 makes -- it has zero preference for reduced folate of any kind. It only
25 emphasizes folic acid, and that's it, so from that, that's still I think-- that

1 would establish or at least show that clearly that what the inventor there
2 was thinking was maybe not necessarily any particular reduced folate
3 in mind, and if he didn't have a particular reduced folate in mind, then
4 you can't read that reference and draw from it any particular reduced
5 folate for any particular purpose, so there would be no anticipation.

6 JUDGE KAMHOLZ: You have to give some meaning to
7 "metabolite of folate" because Serfontein uses those words.

8 MR. PARKER: Correct.

9 JUDGE KAMHOLZ: Is your position that they are
10 meaningless or they are so ambiguous that no meaning can be attached
11 to that?

12 MR. PARKER: I'm almost ready to say that, yes. They
13 reference in Serfontein, what was the phrase, releasing folate or
14 whatever it is, that portion in the claim, folate releases. No one knows
15 what that means. None of the experts were even able to figure out what
16 that means, so we questioned can we even discern what suitable active
17 metabolite is, suitable in terms of what and for what purpose?

18 JUDGE KAMHOLZ: Let's say active metabolite for folate.
19 Suitable is an additional qualifier, so you have the universe of active
20 metabolites. Suitable active metabolites would be a subset of that, so is
21 there difficulty understanding what active folate of folate means?

22 MR. PARKER: They're biological active compounds within
23 the cycle that get converted in the metabolites, so from a biological
24 perspective, I know what it means outside the scope of Serfontein, but

1 in Serfontein, the word suitable has to have a meaning, okay, and the
2 word --

3 JUDGE KAMHOLZ: It's a limiting meaning.

4 MR. PARKER: A limited meaning.

5 JUDGE KAMHOLZ: Limiting meaning.

6 MR. PARKER: Right, limiting meaning, correct.

7 JUDGE KAMHOLZ: So if there's eight or ten compounds in
8 the folate cycle and those are the active metabolites, some are suitable
9 and some of them are not.

10 MR. PARKER: But those compounds in and of themselves
11 are not suitable, and that was even admitted by Dr. Miller. He said
12 they have to be placed in some sort of salt form in order for them to be
13 utilized in the compositions, and that was his testimony directly, so
14 that's where we're at with respect to Serfontein in terms of its
15 suggestive power, if you will, or teaching.

16 JUDGE KAMHOLZ: The problem is that Serfontein does
17 not say that they must be in salt form.

18 MR. PARKER: Yes, that's -- well, wait a minute. What it
19 says is that -- Dr. Miller testified and conceded that in order for any of
20 these compounds to work, they have to be in salt form. What salt form,
21 he didn't know, and we know there's a whole list of potential salt forms
22 that would have to be -- that will have to be utilized, and Dr. Gregory
23 testified selecting a salt form was not easy, and it was not one of -- that
24 one of person in ordinary skill in the art could do, my words, without
25 carrying experimentation.

1 JUDGE BONILLA: Is there any evidence that the usual
2 course of salts in calcium, sodium, that those wouldn't work?

3 MR. PARKER: The only evidence -- what we have is the
4 evidence of -- we have Dr. Gregory's testimony saying that one of
5 ordinary skill in the art would not be able to grasp the pros and cons of
6 which salt would be appropriate than another salt.

7 JUDGE BONILLA: Would they have a reason to believe
8 that any of the salts wouldn't work?

9 MR. PARKER: Dr. Gregory testified that he had reason to
10 believe that not all salts would work.

11 JUDGE BONILLA: What was his evidence or basis for that
12 statement?

13 MR. PARKER: That was his testimony.

14 JUDGE KAMHOLZ: Don't your claims make the salt
15 optional?

16 MR. PARKER: Our claims, the claims in the '040 say any
17 salt thereof, you're correct.

18 JUDGE KAMHOLZ: Wherein the tetrahydrofolate, claim 8,
19 5-methyl-(6S)-tetrahydrofolic acid or a salt thereof.

20 MR. PARKER: Correct.

21 JUDGE KAMHOLZ: So where is Serfontein inadequate for
22 failing to disclose salt compounds?

23 MR. PARKER: It's inadequate because are we
24 comparing -- if I could put the claim aside because that's talking about
25 a written description situation, but here we're talking --

1 JUDGE KAMHOLZ: I'm talking about scope.

2 MR. PARKER: Okay, scope. Serfontein, by the fact -- we're
3 talking about Serfontein's compositions. The Board's grounds is
4 basically saying you can take the L-5 from Marazza and put it in
5 Serfontein's compositions, and Serfontein's compositions, there's at
6 least six of them, different ones, which form of the salt would work.
7 That is the class. In fact, it's an undefined class because within that
8 class of salt forms, if we look at them all from one spectrum to the
9 other, not all of them are going to work.

10 JUDGE BONILLA: Serfontein says it point blank. It says
11 suitable active metabolite folate, and Marazza says this active natural
12 metabolite, at least one active compound, and then it refers specifically
13 to the 5-methyl and talks about the two different isomers.

14 Why wouldn't one in the ordinary skill in the art immediately
15 envisage the 5-methyl as a racemic or as the L confirmation in light of
16 the suitable active metabolite?

17 MR. PARKER: Why would not -- so in other words why
18 wouldn't a person of ordinary skill in the art envision the L-5?

19 JUDGE BONILLA: We talked about a metabolite of folate
20 is one of the eight, and one of those eight is the 5-methyl, and then
21 Marazza specifically says that it's a natural metabolite. It's an active
22 compound. Reading that, why wouldn't that anticipate?

23 MR. PARKER: Because his -- again where we are -- we
24 have to go back. How big is the class in Serfontein? How big is it?
25 Would the person of ordinary skill in the art immediately envisage that

1 entire class? If the answer is no, then Serfontein cannot, as a matter of
2 law, be an anticipatory reference. That's In re Petering and all its
3 progeny. If that class is so large and undefined, it can cannot be an
4 anticipatory reference, period. That's where it ends.

5 JUDGE KAMHOLZ: What's the evidence that the class is
6 larger than eight compounds that Dr. Miller testified to? What's your
7 best evidence on that?

8 MR. PARKER: Dr. Gregory's interpretation of Serfontein in
9 light of the prior art, his testimony, his declaration.

10 JUDGE KAMHOLZ: Is there a particular cite you can give
11 us?

12 MR. PARKER: With Dr. Gregory? Sure, absolutely.

13 JUDGE KAMHOLZ: You can give it later.

14 MR. PARKER: Sure. My best evidence would be our
15 expert, Dr. Jess Gregory.

16 JUDGE KAMHOLZ: I know you have many things you
17 want to cover.

18 MR. PARKER: I do. They didn't put forth an expert to rebut
19 this. They did not put forth any evidence at all to rebut it. They could
20 have but they didn't. They chose not to.

21 JUDGE KAMHOLZ: Rebut what?

22 MR. PARKER: Rebut Dr. Gregory's interpretation about
23 how a person of ordinary skill in the art would interpret Serfontein with
24 respect to scope and that particular issue. We had Dr. Miller's
25 testimony which actually supports our position. Now, Dr. Miller did

1 not put a rebuttal in. That was their choice for whatever reasons.
2 They're entitled not to put it in. So let them just move on, if I may.

3 JUDGE KAMHOLZ: Yes.

4 MR. PARKER: Obviousness, let me take a look at
5 obviousness with respect to claims. Well, let me -- again, how am I
6 doing on time?

7 JUDGE KAMHOLZ: You have 36 minutes.

8 MR. PARKER: Let me go to Ubbink now. The Board
9 basically found the patents, this is slide -- we have to find the slide.
10 The Board found claims 11, 12, 14, 15, 21 and 22 over Serfontein were
11 obvious in view of Serfontein, Marazza and Ubbink, and the Board's
12 analysis is set forth -- I don't need to repeat it.

13 Now, we've already discussed the state of the art in the
14 morning session with respect to Ueland, Wagner which would -- which
15 is our position it would teach away from using L-5 to reduce
16 homocysteine levels in patients.

17 Now, at the outset their own expert, Dr. Miller, offered no
18 opinion on Ubbink in his declaration, and during cross, Dr. Miller
19 confirmed he was offering no opinion on Ubbink, and petitioner's reply
20 includes no response to Dr. Gregory's opinions or testimony as to how
21 a POSA would view Ubbink in light of the prior art so Dr. Gregory's
22 opinions and testimony in this regard remain un rebutted.

23 So unless the Board has any questions, we will rest on our
24 papers with respect to the issue concerning obviousness regarding

1 claims 11, 12, 14, 15, 21 and 22 with respect to Serfontein, Marazza
2 and Ubbink.

3 Your Honor, with respect to the citation to the record with
4 respect to Gregory, Dr. Gregory, it's paragraph 74? Paragraph 74.

5 JUDGE KAMHOLZ: Is that in his declaration in case 117?

6 MR. PARKER: Yes. Yes, it is.

7 JUDGE KAMHOLZ: Thank you.

8 MR. PARKER: Now, let me -- so I don't lose too much time,
9 I would like to talk a little bit about commercial -- not a little. I would
10 like to talk about commercial success. Just as with the other patents,
11 we've submitted the commercial success with respect to the challenged
12 claims of the '040 patent dealing with -- I'm sorry secular
13 considerations which included commercial success, recognition,
14 copying, satisfaction and the long felt needs and industry skepticism
15 and praise, and we've submitted evidence of commercial success, again
16 submitting the declaration of Mr. Hofmann.

17 Let me just get to Gnosis' contention with respect to our
18 evidence of commercial success which really boils down to four
19 particular arguments. The first one is we discussed earlier they talked
20 about stability, and they talked about the crystallinity of Metafolin, and
21 I thought -- what I was saying is they gave the impression that it wasn't
22 until Merck was able to come out with a commercialized stable form of
23 L-5, that a market developed.

24 I think that's what they were trying to present to the panel,
25 which I found odd because in the same brief, they state, and they recite

1 to Reggev, back in 1997, before then, any stability issues with respect
2 to reduced folates or L-5 were sufficiently overcome.

3 So I don't quite understand the contradiction there, but as I
4 mentioned before, it's the doctors and physicians who prescribe these
5 drugs. It's the doctors and physicians who actually observe the
6 efficacy, and they prescribe the drugs because they're efficacious, and
7 as we talked about earlier, in this case as well, they do mention the fact
8 that it's the ingredients, the combination of L-5 plus the vitamins, and
9 I'll get to Deplin in a second, that actually are the basis for the reasons
10 why doctors are prescribing the drugs.

11 JUDGE KAMHOLZ: There is no claim in '040 that
12 combines the folate with vitamins.

13 MR. PARKER: No, there is. With respect to --

14 JUDGE BONILLA: Claim 22 does.

15 JUDGE KAMHOLZ: Yes, 20 and 22.

16 MR. PARKER: 20 -- well, yeah 19 has a vitamin
17 requirement. 20, 21 and 22.

18 JUDGE KAMHOLZ: The other claims, however, do not.

19 MR. PARKER: Claim 8 and 9 does not.

20 JUDGE KAMHOLZ: They're broader in scope.

21 MR. PARKER: Yes. Now, Gnosis also makes -- Gnosis
22 takes the position that these products are covered by multiple patents,
23 and they showed you the package inserts which listed many patents,
24 and by the way, the language there that was there used was "may," and

1 I want to respond to that, I didn't get a chance to respond to it in the
2 morning, but it is applicable here.

3 They identify all these patents. They don't speak in terms of
4 claims, okay? They don't tell -- they don't do any claim by claim
5 analysis, and again they don't put any expert to even describe how is it
6 that one claimed feature in this patent could have an impact of the
7 commercial sales with respect to these products? So all they're doing
8 now is just listing patents without going further because some of those
9 patents don't even cover the products. I mean, it's on the package
10 inserts, and they didn't go through the exercise to even identify exactly
11 which ones cover what.

12 So it's -- I don't know how it's helpful. It's not helpful to me.
13 I don't know how it's helpful to the Board. They could have done a lot
14 more. In fact, the case law requires that they do more. It's not
15 about -- we're not obligated to prove every negative. We have to meet
16 our burden. I understand that, and we have to show the nexus. I
17 understand that as well, but it's not enough to simply flash on the screen
18 a package insert with a list of patents and say nothing more, no claim
19 analysis, no discussion about the patents, no experts saying how it
20 could impact, if at all. Nothing.

21 Why didn't they bring forth at least an expert to enlighten us
22 to it? It was their choice. Perhaps they didn't like what their expert
23 would have to say.

24 JUDGE KAMHOLZ: But isn't their point that in a multiple
25 patent situation where a product lists a number of patents -- I

1 understand that you're not necessarily saying that each of these
2 products is covered by each of the patents listed, but isn't the point that
3 in a multiple patent situation, the patent owner has to be or ought to be
4 a little more precise in attributing which of the patented features is the
5 basis of the commercial success?

6 MR. PARKER: In the situation -- what we have in a
7 multiple patent case, the answer is no, so long as we meet the burden of
8 showing the other three factors, claim, covers the product, the product
9 is successful and the success is attributable to the features. I'm sorry,
10 the claim --

11 JUDGE KAMHOLZ: The product is claimed.

12 MR. PARKER: The claims cover the product. The product
13 is claimed, and the product is successful, and that success is attributable
14 to the features of the claims.

15 JUDGE KAMHOLZ: Part of the issue here is the difference
16 between "the claim covers the product" and "the product is claimed. "

17 MR. PARKER: I don't understand the distinction. I
18 apologize.

19 JUDGE KAMHOLZ: Where, for example, is it
20 claimed -- we're talking about the '040 case.

21 MR. PARKER: Yes, of course.

22 JUDGE KAMHOLZ: So these claims, the broadest claims at
23 issue here, require only the (6S)-methylnetetrahydrofolate or a salt
24 thereof.

1 MR. PARKER: For use of treating a disease such as
2 homocysteine, correct.

3 JUDGE KAMHOLZ: Correct, but Metanx has other
4 additional ingredients.

5 MR. PARKER: Two additional active ingredients, yes.

6 JUDGE KAMHOLZ: So there's no claim here that is
7 specifying all the active ingredients of that product.

8 MR. PARKER: There's no claim specifying the L-5 with the
9 vitamin B6 and vitamin B12, correct.

10 JUDGE KAMHOLZ: Right. So does that mean the product
11 is covered by the claims but the product is not claimed?

12 MR. PARKER: In the --

13 JUDGE KAMHOLZ: Enlighten us because that's the
14 concern we have.

15 MR. PARKER: I will. So the product is patented in my
16 view so long as it's covered by the claim because if we wanted to
17 pursue a patent infringement, which we have, we asserted those claims
18 against the potential infringer, and in that case we would have a claim
19 for actual patent infringement so the product in that connection is
20 covered.

21 JUDGE KAMHOLZ: But the claims at issue here cover
22 embodiments that would not necessarily possess all of the active
23 ingredients in a combination to which you attribute their benefit.

24 MR. PARKER: The claims are broader than the products
25 being sold, claim scope, yes.

1 JUDGE KAMHOLZ: So how does the evidence that relates
2 only to a portion of the claim scope save the entire claim?

3 MR. PARKER: Now, I think -- just my interpretation of
4 what's required by us, by patent owner, is the claim as it stands, I mean,
5 it's going to be broader than the product, but that doesn't mean that you
6 can't -- that attributing commercial success to the invention within that
7 scope wouldn't -- is not possible.

8 I guess what I'm trying to get at, I'm trying to address your
9 question, yes, the claims -- there are certain claims that are broader in a
10 product, yes, they are, and does -- is it required that we need a claim
11 that says every specific element in order to prove -- in other words,
12 does Metanx have to have -- we have to have a claim that has B6, B12
13 and those very specific types of formations and -- I'm sorry, forms in
14 order to obtain an appropriate nexus for commercial success?

15 I would say, no, that's not the case.

16 JUDGE KAMHOLZ: Why not?

17 MR. PARKER: Because I don't know of any case law that
18 requires that. Demarco, it says so long as the -- if the product is
19 covered by the claim, you've at least met it. Now, whether you've met
20 it fully whether or not you're commensurate in scope, we have to
21 discuss that. That's an issue we can discuss that, but then we go
22 further --

23 JUDGE KAMHOLZ: I'm sorry, in your briefing, you do no
24 more than drop a footnote as to the scope; is that right?

1 MR. PARKER: Well, we believe that the claims that -- we
2 have multiple products that are being sold. For example, claim 8
3 covers every single one of these products including Deplin. As I
4 mentioned before, these are medical products. I don't know how many
5 more products we would need in order to convince a Court, tribunal, as
6 to whether or not that we were commensurate in scope.

7 JUDGE BONILLA: Let me ask you a related question. So
8 my understanding is you need to show commercial success has some
9 nexus to a patentable feature, something that wasn't already known in
10 the art.

11 MR. PARKER: Correct.

12 JUDGE BONILLA: Presumably the idea of decreasing
13 homocysteine using, for example, folic acid was already known in the
14 art; is that correct?

15 MR. PARKER: Yes.

16 JUDGE BONILLA: That was known, so it seems to me that
17 you would need to show that the commercial success was somehow
18 related to the fact that you were using natural a stereoisomeric form or
19 perhaps using 5-methyl or something instead of folic acid.

20 MR. PARKER: Yes, right.

21 JUDGE BONILLA: What evidence do you have of that?

22 MR. PARKER: I have evidence that the actual L-5 is being
23 effective?

24 JUDGE BONILLA: If that's the thing that's giving it
25 commercial success.

1 MR. PARKER: What we have is basically -- we don't have
2 anything isolated that says that L-5 by itself would be effective in
3 treating diabetic peripheral neuropathy.

4 JUDGE BONILLA: You can see where I'm going. Just
5 because it was a folate could have been the reason why it was
6 commercially successful as a multi vitamin.

7 MR. PARKER: Right, but to your point I don't know of any
8 approved -- of any folate such as folic acid that was actually -- could
9 be -- was actually used and commercialized and effectively treated
10 vascular disease for example.

11 JUDGE BONILLA: The claim is not related to vascular
12 disease here. Here they're just disease associated with high levels of
13 homocysteine so it could be anything, right?

14 MR. PARKER: With respect to claim 8. Claim 9 is vascular
15 disease, but you're right about the scope of claim 8.

16 JUDGE BONILLA: I don't see vascular disease in this case.
17 Am I wrong?

18 MR. PARKER: If it goes back and you follow the
19 dependency --

20 JUDGE BONILLA: Oh, I see it.

21 MR. PARKER: -- of claim 3.

22 JUDGE BONILLA: I see it. All right. But with regard to
23 the others where it doesn't specify cardiovascular disease, you would
24 need to have commercial success in relation to using either folic acid
25 for a disease or the L isomer in particular, right? We're trying to find

1 the nexus between commercial success. It can't be just because you
2 have folic acid as a multi vitamin because that was known in the art.

3 MR. PARKER: That's right. Well, folic acid was known in
4 the art, but folic acid wasn't -- I mean, again I'm just focusing on the
5 purpose for these products. I mean, Metanx has a specific use as does
6 Cerefolin and NeevoDHA and Deplin, so I don't know to what extent
7 folic acid -- in other words, to say that anyone even thought of the prior
8 art to use this combination for treating let's say -- again vascular
9 disease, but I understand that the scope of claim 8 is not limited to that.

10 There's also -- we also mention in our brief that there are a
11 number of factors that Dr. Gregory identified, there is a few of them. I
12 think that's -- I believe that's on slide 21, disadvantages that were
13 known in the prior art that would dissuade a person from using reduced
14 folates, particularly L-5 MTHF.

15 I don't have time to go through each and every one of them,
16 but I do want to mention the bioavailability, and I want to mention the
17 fact that Dr. Gregory in his declaration indicates that it was believed
18 and it was understood by the POSA that reduced folates were less
19 bioavailable than folic acid, and now Gnosis showed data, and they
20 showed -- from Dr. Gregory's paper. I don't know if you recall that.
21 Was his paper is -- what exhibit was it?

22 Can you show slide 23? I believe it was 1032, Exhibit 1032.
23 That body of data and Dr. Gregory's paper, the whole point of his paper
24 was to show that the data that petitioner's relied on were that it was
25 unreliable, and that it was -- the methodology that was used was

1 unreliable, and that it did not change the POSA's view that reduced
2 folates were less bioavailable than folic acid, so they're
3 mischaracterizing Dr. Gregory's paper.

4 He says it in his conclusion. It's clear what he meant and
5 what he said, and they examined him extensively on this paper, and he
6 told them exactly what I've just described to you, that this data was
7 not -- the data is not about showing one way or the other whether the
8 reduced folates are more bioavailable than folic acid.

9 My problem was with the data itself, and he cites to a series
10 of other papers in his declaration to support his proposition that prior to
11 1997, that the person of ordinary skill in the art did consider reduced
12 folates less bioavailable than folic acid, and that would be a factor in
13 terms of discouraging a POSA from using reduced folates because folic
14 acid seemed to be the gold standard, so I wanted to just address that.

15 JUDGE KAMHOLZ: Were there any advantages to
16 methylfolate appreciated at the time?

17 MR. PARKER: At that time, I'm trying to think. Were there
18 any -- were there any advantages to reduced folate? I can't think of one
19 right now. Folinic acid was used.

20 JUDGE BONILLA: The Godfrey paper talks about using
21 the methylfolate to treat depression.

22 MR. PARKER: Right, that's a good example. I want to talk
23 about Godfrey. So Godfrey -- and we have to get into the distinction
24 here because Godfrey again is depression. It says nothing about what's
25 going on inside the cells. Same thing with Zittoun Cooper and all the

1 other references that they mentioned, they were all put forth in front of
2 Dr. Gregory and Dr. Stahl, and Dr. Gregory would indicate they don't
3 tell you what's inside the cell.

4 Depression, there is a component to depression where there's
5 a correlation of high levels of homocysteine in people who are
6 depressed, but whether or not the actual reduced folate is lowering the
7 levels of homocysteine, it's never been shown. They don't know --

8 JUDGE BONILLA: Well, in Godfrey they talk about a
9 folate deficiency.

10 MR. PARKER: Right, what they're showing is they're
11 showing the level of folate in the plasma, and Dr. Gregory in his
12 declaration mentions a big distinction. The issue is not what's in the
13 plasma. The issue is what's being retained in the cell in terms of being
14 effective, especially when you're dealing with lowering homocysteine.

15 So with Godfrey, yes. Godfrey shows improvement, but I
16 also want to make a note about Godfrey. Can you show the STAR-D
17 slide, please? And there's one thing -- go back. Go back. There's one
18 thing about the references that petitioner relies on. Godfrey, Passeri
19 and Guaraldi. This is from Dr. Stahl's testimony. There's a STAR-D
20 project, which was a comprehensive study to determine the effective
21 treatment for MDD.

22 This study began right around the time of the invention, and
23 then it was published obviously thereafter, but there was something
24 significant about the study that Dr. Stahl pointed out. He testified that

1 the omission of methylfolate, racemic methylfolate, folic acid, and it
2 goes on, there was no oversight. They were purposely left out.

3 At the time of STAR-D, these compounds were not
4 considered as viable treatment options based on the data from Godfrey,
5 Passeri and Guaraldi, and he indicated these studies were reviewed,
6 evaluated and then rejected as inferior.

7 I know they're going to say that Dr. Stahl cites to some of
8 these references in his papers, but when you look at his testimony too,
9 he also explains what was going on in his mind when he was writing
10 these papers and making these citations. I think his testimony will
11 speak for itself.

12 JUDGE KAMHOLZ: How is Dr. Stahl connected to the
13 STAR-D project?

14 MR. PARKER: He was familiar with that project, and he
15 was testifying based on what he knew from firsthand knowledge.

16 I also want to talk about, there's two other references that
17 petitioner cites dealing with the notion that Dr. Gregory's position that
18 skilled artisans were concerned about administering L-5 in human
19 plasma -- I mean in humans that can have unhealthy consequences, and
20 they mentioned Barford and Scott.

21 In the Scott reference, if you read it, Scott was not about
22 replacing folic acid with 5-MTHF. It was not. The question in Scott
23 was: How does folic acid work in terms of preventing or reducing the
24 incidents of DPN, and he came up with the study, high doses of folic

1 acid, low doses of folic acid, and also he thought about an additional
2 arm to that study which would be giving doses of 5-MTHF.

3 Even in that study, in that paper itself -- by the way, the
4 study was never carried out, but even in that particular paper, he
5 mentions that L-5 -- 5-MTHF may not be effective, so with respect to
6 Scott, it wasn't about replacing one with the other. It was just basically
7 carrying out the study. I want to make that clear.

8 Then you talk about Barford, and Barford does mention
9 using reduced folates, folinic acid, and that was in 1980, the use of
10 folinic acid as a way of avoiding the problems with metabolites, folic
11 acid. That was mentioned in Barford. Then ten years later came Scott,
12 but my only point is this: I would view that as a potential conflict in
13 the references in terms of what they're saying to a person of ordinary
14 skill in the art, but who am I how to say the POSA would interpret or
15 construe that back in 1996?

16 I can't without an expert, and I feel as though the attorney
17 argument in that respect should not -- are unable to do that as well
18 because how do they reconcile the references? That's the whole point
19 of having these experts, to explain to us and enlighten us about how
20 they would fit in with the relative issues at hand.

21 Now, stability, slide 24. Slide 24. Stability. Again in
22 petitioner's paper they take the position unequivocally that stability of
23 5-MTHF was sufficiently overcome by 1996 using the Reggev
24 reference. Now, our expert looked at all these references, Reggev,
25 Godfrey Pattini and others, and basically said, When you read these

1 references, it has nothing to do with stability. There's no stability data.
2 There's no discussion about humidity, discussion about stability or
3 discussion about temperature. There's nothing -- there's no indication
4 whether the batches were made on a daily basis, a bi-daily basis, a
5 monthly basis. That's just not there.

6 You can't draw any inferences from those references about
7 stability. Now, that's coming from our Dr. Gregory, but the opposite is
8 coming from Gnosis' counsel and their interpretation of what the
9 references meant.

10 JUDGE KAMHOLZ: What slide is this?

11 JUDGE BONILLA: It must be from the other cases?

12 MR. PARKER: It was omitted from the -- inadvertently
13 omitted from the prior case so we called it up. It was supposed to be in
14 this presentation, but it was -- it's in the morning session slides.

15 JUDGE KAMHOLZ: This is slide 24 from the '116.

16 MR. PARKER: Yes that was inadvertently omitted from the
17 other one. I apologize for that.

18 Now, with respect to Metanx, we had two experts, Dr. Jacobs
19 and we had Dr. Fonseca, and Gnosis takes the position that there's
20 no -- I don't know how they put it, that there was no -- no one accepted
21 it as some -- I forget the phrase they used, but they did explain
22 that -- let me go back and find it a second. Hold on. That they did not
23 testify that Metanx is an accepted standard of care in treating DPN, and
24 the answer is that's not true.

1 I mean, Dr. Fonseca is a leading authority in this area, and he
2 recommends Metanx to all his patients, and Dr. Jacobs testified that it,
3 in fact, is considered to be an accepted standard of care for treating
4 DPN, so their statement is not reflective at least of cross examination
5 testimony they obtained from either of these two gentlemen, which
6 combined have over 60 years of experience in terms of telling us what
7 was available for treating DPN, what was not, and then what is now
8 effective and what is now useful.

9 And another thing too is about the timing. We're talking
10 about satisfying the need as of the date of the invention. They're
11 talking about situations that occurred in 2012 and 2010. I notice that in
12 some of their references. They mention lactoprotein. That was
13 something that came back from Dr. Jacobs in 2010 or more even more
14 recent, so I don't know how it's relevant to the issues here.

15 JUDGE KAMHOLZ: How do you respond to the question
16 of the market? You can get to that later if you need to.

17 MR. PARKER: No, no, no. That's a good point. I would
18 like to get to that because they asked Mr. Hofmann did the
19 market -- and you heard Mr. Cwik say, Well, he just didn't make a
20 comparison because perhaps he was afraid, he didn't want to see -- he
21 may get bad information that wasn't helpful. That's not what he said,
22 and let me cite for the record Deposition Exhibit 1146, 95, 8 through
23 25; 96, 15 -- 96, line 15 to 97 line 3; 97, line 20 to page 98, line 14.

24 He said that any comparison was unnecessary. He made two
25 points. You can't compare medical foods to other drugs that are

1 approved under New Drug Applications. They're two different
2 markets. They're apples and oranges. That's what he said. So any
3 comparison in that regard he said was unnecessary, and he also
4 testified, which is also reflected in his declaration, that these -- that a
5 market comparison wasn't necessary as well because they cultivated the
6 market for medical foods.

7 No one took medical foods seriously up until PamLab finally
8 invested millions of dollars to do actual clinical studies. No one was
9 ever doing clinical studies with vitamins. It was unheard of at that
10 time, and so Mr. Hofmann testified that, Are there competitors in the
11 medical foods market to PamLab? At this point? No. Instead what
12 they're doing is they're copying them. That's their solution, not
13 developing, not commercializing -- I'm sorry, not doing any clinical
14 studies but copying.

15 There could be competition. There could be other ways
16 of -- other different forms and combinations, and they can do clinical
17 studies but no one seems to want to do it. They would rather just copy
18 wholesale PamLab's products and capitalize on their market.

19 JUDGE BONILLA: So is it your position the relevant
20 market we should be talking about is medical foods?

21 MR. PARKER: The relevant market is medical foods.

22 JUDGE BONILLA: Would that include multi vitamins and
23 that type of thing?

24 MR. PARKER: Prescription medical foods.

25 JUDGE BONILLA: Prescription?

1 MR. PARKER: Yes.

2 JUDGE BONILLA: Limited to prescription?

3 MR. PARKER: Yes, prescription medical foods, and that's a
4 very important distinction.

5 JUDGE BONILLA: Why does the prescription part matter?

6 MR. PARKER: Because you have over the counter. My
7 understanding is with Mr. Hofmann, that that comparison wouldn't be
8 important. Why would it matter? I don't have a direct answer because
9 not all medical foods -- I mean, medical foods, the prescription is a
10 special market on to itself.

11 JUDGE KAMHOLZ: Why wouldn't the market for each of
12 these drugs be the people who are in need of treatment for which these
13 drugs are given? For example, for Metanx, why isn't the market
14 diabetic peripheral neuropathy?

15 MR. PARKER: In this particular case because they're
16 prescription drugs, and you're absolutely correct. I mean, certainly they
17 are -- they have to be the market.

18 JUDGE KAMHOLZ: If a patient has this condition --

19 MR. PARKER: Correct.

20 JUDGE KAMHOLZ: -- and I'm the physician, I'm aware of
21 the various options for treating that condition. Is this drug -- there's
22 that drug, there's this medical food. I'm choosing among those. Why is
23 that not the market?

24 MR. PARKER: The patients themselves?

1 JUDGE KAMHOLZ: The physicians. They're all by
2 prescription.

3 MR. PARKER: The physicians? Okay. They would be the
4 market. They're the ones who are actually prescribing and giving it to
5 the patients.

6 JUDGE KAMHOLZ: But the physician is making the
7 choice of which of these prescription materials to give.

8 MR. PARKER: Right, and that's assuming there are choices,
9 and there aren't any choices because even with the testimony -- with
10 respect to even with Dr. Jacobs and Dr. Fonseca, there is no other
11 treatment that actually can reverse the damage that's done on DPN. Up
12 until this point, all you had was medication that can deal with the pain.
13 That was it.

14 JUDGE KAMHOLZ: Do you have any data comparing sales
15 of Metanx to the other prescription drugs?

16 MR. PARKER: No data. No data, not in this situation, no.
17 And for the reasons that we just -- for the reasons that I just described,
18 but that question was posed to Mr. Hofmann, and he did give that
19 response.

20 Now, on the industry praise, we've submitted declarations
21 about that, and Gnosis' response to that was they focused on the
22 Merck's receipt of the Frost and Sullivan award, and they characterize it
23 as being simply limited to just L-5, but again, I mean, if you look at Dr.
24 Katz's testimony, in her declaration at paragraph 69, I'm talking about
25 Exhibit 2016, they explained because she was part of this process

1 firsthand when they actually gave the award, that it was given for the
2 adoption of a new technology of a product, not simply for an innovative
3 component of a product.

4 And then when she was asked a lot of questions about this,
5 she testified that on cross examination that the award was given based
6 on the success of Merck's licensee's product which shows the award
7 was not simply on Merck's Metafolin, but on the normal use of the
8 component of products covered by the challenged claims, such as the
9 ones we mentioned with respect to PamLab.

10 JUDGE BONILLA: Petitioner had pointed earlier to
11 evidence indicating that the thing that was special there was because it
12 was a stable -- it was a stable natural metabolite.

13 MR. PARKER: He showed you an excerpt from that entire
14 document. Honestly I would have to look at the rest of it but, yeah, he
15 showed an excerpt, but I can't see now what the context is. I don't
16 know if we have the full picture. We might, but at the same time
17 though, I do want to recognize that we do have testimony of the
18 individual who actually received the award on behalf of Merck.

19 Now, with respect to copying, in this particular case,
20 Gnosis' -- petitioner's response is essentially the same. It relies on the
21 Purdue case, and I talked about that this morning so I'll rely on my
22 comments about, that if that's okay with the panel.

23 Again with respect to going back now to the multiple patents
24 that petitioner will raise, that they raise in their reply, there are cases I
25 would like to cite, but basically hold that patent owners is not required

1 to attribute any particular amount of success to any particular
2 challenged claim. All it has to do is once it meets its burden -- you can
3 have commercial success, even though that we'll call it bucket of
4 success is due to other factors, that does not -- that does not prohibit the
5 Court or the panel attributing weight to that commercial success.

6 And the cases I have for that are EI DuPont, 903 F.Supp.
7 680, pincite 768 to 68; Al-Site 841 F.Sup 1318, 1327, and Continental
8 Can on 948 F.2d 1264 with a pincite at 1273.

9 Here again when it comes to all of these patents, it's not -- as
10 the Demarco case said, it's not our burden to show all the negative of
11 all imaginable contributing factors. I'm checking my notes.

12 Now, licensing, again petitioner's response to the licensing
13 evidence is the same as put forth this morning. At least their reply brief
14 is the same, so I'll rely on my comments from the morning session.

15 Also let me just talk about the long felt need with respect to
16 the overall patent, and that's dealing with Deplin, and we've submitted
17 the declaration of Dr. Stahl. That's slide 16, and also Dr. Gardner.

18 JUDGE BONILLA: Those experts talk about the fact that it
19 was supposedly unexpected to use the L-5-methyl as inject treatment
20 for the particular depression issue, right?

21 MR. PARKER: Right. They talked about the -- the success
22 in terms of using the vitamin L-5, as an augmentative therapy to
23 existing antidepressant treatments.

1 JUDGE BONILLA: But this goes back to the Godfrey
2 reference, right? It suggested using the 5-methyl for exactly that
3 particular disease, the major depression, the MDD?

4 MR. PARKER: Right. Now, the one thing about Godfrey is
5 Godfrey included individuals who were already on antidepressants, but
6 Godfrey doesn't come -- at least establish start -- we're talking about
7 augmentative therapy, which is a whole different population of folks
8 who can't respond well to antidepressants or who can't respond at all to
9 antidepressants or they can take high doses of existing antidepressants,
10 so with Godfrey you have that situation, but with Godfrey, again
11 notwithstanding Dr. Stahl's criticism of Godfrey, but the fact of the
12 matter is it doesn't really go out there and suggest that as far as an
13 augmentative therapy for depression that is using it for someone who is
14 already on antidepressants or who is having problems with
15 antidepressants.

16 It's a long winded answer, but I apologize. If you want to ask
17 me again, I'll try to respond.

18 JUDGE BONILLA: The title it says
19 "enhancement of the recovery from psychiatric illness by
20 methylfolate."

21 MR. PARKER: Right. There's a major distinction in all
22 these references. These are not studies specifically aimed at whether or
23 not a particular product is an effective augmentative therapy for MDD,
24 major depressive disorder.

1 JUDGE KAMHOLZ: Any other questions for Mr. Parker?

2 Thank you.

3 MR. PARKER: Thank you, Your Honors.

4 MR. KRIT: Hello again, Your Honors. So as I mentioned
5 when I briefly came up during the prima facie case, in addition to the
6 reduced folate references that we submitted in connection to the Bailey
7 patents, we submitted two or three, if you count the Harpey references
8 as individual, references regarding the specific use of 5-MTHF to
9 reduce homocysteine, and the patent owner talked about Harpey and I'll
10 get to that in a moment, but I would like to talk about Reglan which
11 wasn't discussed because I heard the Board ask patent owner, Were
12 there any advantage known to using methylfolate.

13 And Reglan states some of those advantages, so Reglan is a
14 reference which is proposing a trial to lower homocysteine in
15 schizophrenic patients. It states in its summary theoretically -- this is
16 Exhibit 1141 in the summary. In the summary it states theoretically
17 MTHF should be the optimal treatment here, but more importantly is
18 the disclosure on page 150, and it says from a theoretical point of view,
19 our patients should be supplemented with MTHF as the drug of choice.
20 MTHF is the form of folate that is taken up by cell. Supplementation
21 of folate without a methylene would only enhance the accumulation of
22 methylene THF, which might be harmful. As previously has been
23 postulated that accumulated methylene THF is associating the
24 formaldehyde which condenses biogenic means in psychotogenic
25 compounds.

1 It cites the Godfrey study, and then at the end of the page, it
2 says efforts are underway to find a supply of MTHF.

3 So here -- this reference is dated 1994, so here in 1994, we
4 have someone or someone proposing the direct use of MTHF to
5 administer for lowering homocysteine values, levels, and we cited in
6 our petition -- it's not in our reply brief, but in our petition we noted the
7 Federal Circuit has appeared to hold that when you have a citation on
8 the use of a racemic drug and it's known which isomer is the active
9 stereoisomer, that doing that separation is obvious, and I don't think it's
10 disputed that the isomer has been disputed -- that it was known that the
11 S isomer was the active isomer in 5-MTHF.

12 I think it's -- and in terms of -- I know on their slides they
13 raise Dr. Stahl's characterization of Reglan. I think it's Dr. Stahl, but in
14 their demonstrative slide, what they said about Reglan was it's
15 theoretical, but the '040 patent is theoretical. Nowhere in the '040
16 patent is there a disclosure that Merck made these compounds and
17 tested them on homocysteine.

18 They were going from the same prior art disclosures
19 regarding folate and homocysteine and postulating and constructively
20 reducing the practice that the -- that the administration of the (6S)
21 isomers.

22 Now, with respect to Harpey, which is Exhibit 1026 and
23 1027, the Harpey reference and as was noted is teaching the use of
24 either folinic acid or MTHF in conjunction with three other agents, and

1 Harpey II in 1027, it's clear from reading Harpey II that the authors are
2 discontinuing the studies because of stability concerns with MTHF.

3 This is 1983, so this predates the Reggev reference. It
4 predates the bioresearch reference, and most importantly, it predates the
5 1991 Merck that we submitted which they never mentioned which
6 called their reduced these -- their success isomers, naturally folate
7 isomers "sufficiently stable."

8 So Harpey predates all of that, and as we have not disputed,
9 there were stability concerns back then, but even then when they use
10 Harpey, it's clear that they are reporting it as lowering homocysteine.
11 They report that they changed the formulation. They lowered the
12 amount of folate from the previous formulation which had been 15
13 milligrams a day.

14 JUDGE BONILLA: Can you remind us again, I'm sorry,
15 which evidence said it was sufficiently stable?

16 MR. KRIT: Oh, that is the '655 -- the Muller 655 patent, and
17 one moment. It's in my stability section. That is Exhibit 1025 at
18 column 1, line 16. There it is. And the term sufficiently stable is in the
19 second paragraph.

20 JUDGE KAMHOLZ: What about Dr. Miller's testimony that
21 Harpey really --

22 MR. KRIT: Dr. Miller was referring to Harpey I and in
23 Harpey I they speculate, and I'm trying to pull it out to quote it directly
24 but in Harpey I, they say 5-MTHF would be a good agent to use here,
25 but it's probably too unstable. Notwithstanding their concerns about

1 the stability of 5-MTHF, then we proceed to Harpey II to disclose, and
2 they went ahead and tried it.

3 As I was saying in Harpey II, they lowered -- they don't say
4 why, they lowered the total amount of folic. They had been giving 15
5 milligrams of folinic acid in Harpey I, and they changed that to 5
6 milligrams of MTHF twice a day in this treatment, and they also
7 used -- they had differing dosage of the vitamin B12 in Harpey I. They
8 went with the lower dosage of that, and then they
9 report "homocystinemia did not rise above 13 micromoles per liter (233
10 micromoles per liter before treatment)."

11 Then they follow that by saying that the 5-MTHF was
12 discontinued because of stability. So they're not reporting
13 dissatisfaction with the lowering of homocysteine by this treatment that
14 included 5-MTHF. It does disclose problems with stability, and if the
15 patents were dated 1983, that would be a more powerful argument, but
16 as we -- as some of our evidence has shown, the stability issues had
17 been resolved. I think patent owner mischaracterizes why we presented
18 a number of our references including, for example, Godfrey.

19 Their expert, Dr. Gregory, testified that because of these
20 various concerns including stability, he alleged that a person of
21 ordinary skill in the art would not use reduced folate. They would just
22 use folic acid. It was proven. It was stable. That's all they would use,
23 so we kept presenting it. All these examples that state on their face that
24 they're using reduced folates, whether it's the 5-MTHF or the 5-MTHF
25 or in the Le Grazie case the specific (6S)-5-MTHF.

1 When we asked about this in terms of the stability, How do
2 you explain these uses, his testimony was only that he would continue
3 to have, the term he used, was "concern" in his deposition testimony.
4 We still have these concerns, and he believes the POSA would have
5 these concerns. Concerns isn't I think conceptually different than
6 stating affirmatively I wouldn't use them, and that takes me back to
7 comments I would like to make, if we can return to Ueland.

8 I don't believe that it's disputed that 5-MTHF is taken up in
9 cells to some degree. Marazza talks about the uptake into cells issue.
10 The Zittoun Cooper reference speaks of the uptake into cells of both
11 5-MTHF and 5-FTHF. We also have Harpey showing efficaciousness.
12 So we have patent owners citing the Wagner and the statement in
13 Ueland saying that a person of ordinary skill in the art would make
14 these connections with Ueland and Wagner and the reports of
15 Cichowicz and decides that it's not as well taken up in the cells. It's not
16 as well contained in the cells as folic acid.

17 I can't speak to what Wagner shows. I can quote again
18 Zittoun Cooper stating that in terms of interest of folate in some other
19 cells, the concentration of folic acid required to generate adequate
20 concentration of intercellular folates is 100 to 200 times that of reduced
21 folates such as 5-methyltetrahydrofolate and folinic acid.

22 However, even if we assume arguendo that the records show
23 that 5-MTHF is not taken up in the cells as well as if you use folic acid,
24 by their own -- as I mentioned this morning, by their own authority,
25 that's not a teaching away. That doesn't import even in the In re Gurley

1 case, showing something -- and we will admit that it shows this, we
2 disagree with that, but showing that something -- that the claim -- the
3 reference that says the claimed invention would not work as well in the
4 prior art does not import patentability.

5 JUDGE KAMHOLZ: What's the most unfavorable
6 construction you can put to your case?

7 MR. KRIT: The most unfavorable or unfavorable
8 construction that I could put? So attack my own case?

9 JUDGE KAMHOLZ: Yes.

10 MR. KRIT: Give me a moment. I would have an easier time
11 if we were in District Court and I had the burden. I could take the
12 evidentiary burden.

13 Notwithstanding -- I'm trying to do my honest best here.
14 Notwithstanding these uses, somebody of ordinary skill in the art
15 would follow the maximum, that no one gets fired for buying IBM, that
16 folic acid -- it was ruled that the Ueland article, even though it's 1989
17 reports far more cases with folic acid than the one -- it reports the one,
18 though it states it outright. You're right, it uses the word folinic acid in
19 discussing -- in its description of the heartbeat reference, but there are
20 more uses with that, so go with the tried and true. I don't think that's
21 the standard here.

22 The standard is, Was this obvious to somebody of ordinary
23 skill in the art, and I think we're seeing in these references that people
24 of ordinary skill in the art conceived of this issue. Reglan in 1994 is
25 directly conceiving of this use, but for he's going by the knowledge that

1 racemic is available. It would be -- and isn't thinking in terms of the
2 (6S) isomer is available.

3 JUDGE KAMHOLZ: Study after study after study looking
4 at 5-methyltetrahydrofolates, it's not clear to me that the consensus
5 emerges from all of these references, it's good for anything or
6 especially better or especially worse for anything, so many studies over
7 so long, why is it not until Pamlab that there's a product on the market?

8 MR. KRIT: Oh, I think that goes to the question of, Are you
9 capable of producing (6S)-5-MTHF for these trials and you can order it
10 from Sigma-Aldrich or from Bioresearch or what have you, and can
11 you make this as a production process, and if we go the Merck process,
12 there's a comment in there where they say, If we're going to use these
13 basically in vitamins, we're going to need a method for making one and
14 at least have a patent for it.

15 So I think it's a question of availability. I think it's a
16 question -- it's a question of the folic acid was -- with the exception of
17 the concern about unmetabolized folic acid, was working.

18 JUDGE KAMHOLZ: It's not that 5-meythl was maybe so
19 borderline? What's the point of investing huge amounts of resource in
20 a drug that doesn't seem to --

21 MR. KRIT: Well, at the time it was more expensive and that
22 could be a concern, but going back to something the Board said,
23 Serfontein is -- those words, patent owners wishes to erase them, are
24 there. He's conceived of using folic acid or an active metabolite of
25 folate to prevent -- to then prevent the world from using these, to tell

1 Reglan, for example, you can't use the pure isomer, once we've made
2 our prima facie case, I think takes clear evidence to the contrary, not
3 that there was an advantage to using 5-MTHF but there was a reason
4 why these people were wrong, the ones who did disclose it.

5 Again these are the only people that disclosed it and made it
6 into published studies. I'm not a statistical expert, but I think it's fair to
7 assume that if you had these people even advertising the use of the
8 reduced folate, you had more people who had conceived it.

9 I'm not sure. Did that answer your question?

10 Quickly with respect to the Barford reference.

11 JUDGE BONILLA: I'm sorry, which reference?

12 MR. KRIT: The Barford reference. I don't know if the
13 numbers match up, so let me check. This would be I think Exhibit
14 1016. And the patent owners said that Barford describes folinic
15 acid -- it says folinic acid, and here you have the lawyers interpreting
16 Barford to say something else, and Barford suggests this folinic acid. I
17 think calcium gluconate is the term the expert uses. As an example, she
18 has a broad disclosure example she says -- she says it will be prudent to
19 avoid this by using a reduced folate, such as, and from memory calcium
20 gluconate. We're not spinning the specific example she gave. She said
21 reduced folates in general as a way of getting over a metabolite of folic
22 acid.

23 The point they're making, again it's a speculative concern of
24 Dr. Gregory, that people of ordinary skill in the art would have feared
25 that they would mess up the folate metabolism if they were

1 administering the reduced folates. There is no reflection in the record
2 of anyone expressing that fear in any other references that we've
3 presented, and there is this concern with unregulated amounts of
4 unmetabolized folic acid, and yet that didn't stop people from
5 continuing on with folic acid.

6 So we think this is another red herring. This is a case where
7 we don't -- we don't have to speculate as to whether Dr. Gregory's
8 suspicions about this broad teaching away from the use of reduced
9 folate was correct. We see that people of ordinary skill in the art
10 concede to their use.

11 With respect to diabetic peripheral neuropathy, once again to
12 return to this, we cited their own experts for their statement about what
13 was efficacious in the prior art, and we cited their own deposition
14 testimony as far as whether the Metanx product, this is Dr. Fonseca,
15 was -- had established itself as a satisfactory -- satisfaction of a long
16 felt need.

17 They admitted it's not been approved by the FDA. They
18 admitted it hasn't been recommended by any authority, and they
19 admitted that it won't be recommended until there's more study, and
20 their own study said that Dr. Fonseca's clinical study said we don't
21 know from this if it works as a long-term treatment for diabetic
22 peripheral neuropathy.

23 As far as the Deplin product for long felt need, we submitted
24 a number of -- as the Board recalled, we had the Godfrey reference.
25 We have the -- we cited this reference, which also showed it is an open

1 label study, but it did administered depressed patients with 50
2 milligrams a day. We had another reference to 1054, DiPalma, which
3 clinical results are reported in our study appear to support our
4 hypothesis that methylfolate at 30 mg TID has a positive effect on
5 depressive signs on symptoms in alcoholics, but I don't think Deplin
6 excludes alcoholics, and you see the Deplin product itself cite these
7 studies.

8 So I think it's difficult for a patent owner to argue that the
9 success of the Deplin product is a result of something that wasn't
10 disclosed in the prior art, and I think that would -- unless the Board has
11 additional questions, that would make a good segue to Mr. Cwik for
12 secondary considerations.

13 MR. CWIK: For the record, this is Joe Cwik on behalf of
14 petitioners again.

15 Your Honors, I would like to address a few more of the
16 secondary considerations that we didn't have a chance to get to in the
17 morning. First of all, I want to talk about the secondary consideration
18 of industry praise. We've talked about this briefly, but they have
19 submitted this award from Frost and Sullivan where the Metafolin
20 product was given the award as being the innovative award.

21 We've heard opposing counsel talk about the testimony of
22 Dr. Katz, and Dr. Katz says, Well, my interpretation was Frost and
23 Sullivan gave the award, they weren't really just giving it to Metafolin
24 alone, they were giving it to our competitors' product, but I ask that you
25 actually read the actual award itself. It's Exhibit 2182. It's clearly

1 talking about Metafolin, and Dr. Katz simply doesn't have the
2 foundation to testify what Frost and Sullivan meant to say or what they
3 meant to award. It's clear on its face what they meant to award it for.
4 It was for the Metafolin product only.

5 The licensing secondary consideration, this is slide 32, this is
6 the stipulation among the parties, Exhibit 2311. I'm sorry, 2311, and
7 paragraph 12, and here again this is just more evidence going to the
8 nexus or shall we say the lack thereof, and they have submitted
9 licensing saying that the licensing is indicative of the strength of the
10 actual patent invention, but the licensing is much more than covering
11 the patented inventions that we're talking about today.

12 The parties have stipulated that the licensing agreement that
13 we're talking about does cover the '040 patent, but it also covers the
14 '168 patent, which is the stability optimized patent of Merck that we've
15 talked about. It covers the challenged Bailey patents, which the parties
16 have defined as the '985, '381 and similar patents. It covers other
17 Bailey patents including '904, '360, '725, '490, '981, the Canadian
18 patent.

19 Also importantly it gives Pamlab the ability to buy Metafolin
20 itself and not have to get a (6S)-5-MTHF isomer from other people in
21 the world such as my own client, and lastly it -- the agreement
22 also -- Pamlab licensed the use of Merck's Metafolin trademarks, and in
23 some of the product inserts you will see they use the Metafolin
24 trademark. They are clearly happy to have the use of using that

1 Metafolin trademark because there's been what we think is a lot of
2 success regarding the ingredient itself.

3 They licensed Merck's analytical support, application
4 know-how, so to the extent they say there's a license and licensing
5 generating fees, I think there's a lot of evidence, circumstantial
6 evidence that not all of the weight should go to the patented invention
7 itself, if much at all.

8 I want to talk a little bit about the copying issue, and as
9 counsel noted that the copying issue is not exactly the same between an
10 FDA drug approved type product and this medical food type product,
11 but I think the analogy is very clear.

12 I cited the Purdue Pharma case, and the Purdue Pharma case
13 said, Well, if the generic company has to copy the branded product in
14 order to get FDA approval and in order to get it into the hands of the
15 consumers, then that's really not copying itself, because there's no other
16 way to possibly make this product, what they're going is they're
17 following the regulatory framework to get it into the hands of the
18 consumers, but here, this is essentially the same framework.

19 Here we have these database companies. These database
20 companies, they have databases that a pharmacist can look at, so when
21 a doctor writes a prescription, he writes a prescription for Deplin, for
22 example, and he says, Okay, well, I can go into my pharmacy database
23 and they have this insurance or they're under this healthcare plan, I
24 have to dispense a generic or I want to dispense a generic, they look at
25 the database.

1 And they say, Okay, here it is, here's a generic to Deplin, I
2 will prescribe this, it's cheaper for the consumer, so the pharmacy
3 databases, and it's called Medispan, and there's Redbook, and there's
4 some others, it's all explained in Mr. Reisetter's declaration, and his
5 declaration is here in 2020 in this case, and paragraphs 22 to 32, he
6 talks about his pharmacy database company essentially being the
7 gatekeepers. If you want to get these generic products into the hands of
8 consumers, you have to go through these pharmacy databases and list it
9 as a generic, or its' really not going to happen.

10 So the analysis is the same from the Purdue Pharma case
11 from this case, because what we have is the same situation, that if
12 you're the generic company, you have to copy the product, in order to
13 get to the gatekeeper, whether it's the FDA or the pharmacy database
14 companies in order to get it into the hands of the consumer, so I think
15 the reasoning is right on on almost the same as the Purdue Pharma case.

16 Briefly, another thing that we have not talked about today but
17 that was in their briefs is that this -- their briefs regarding prior
18 litigations, and they try to disparage Gnosis and some of the problems
19 they had in discovery and the false advertising case in the Southern
20 District of New York a few years ago, but if they're going to talk about
21 prior litigation, I mean, I think the important fact to remember about
22 prior litigation is one year ago, we're involved in an ITC case
23 proceeding here in Washington, D.C., and it was going full speed.

24 We had a trial date around June, and three or four weeks
25 right before the trial when we were ready to go, they settled with

1 Macoven, and then they told Gnosis that we're going to withdrew the
2 claims, we're not going to go through the trial, and at that point, we had
3 no choice to oppose that one way or the other.

4 So I think if you're going to look at what does the prior
5 litigation tell you, I think the prior litigation tells you that they were
6 barreling down a decision at the ITC as to whether these patents were
7 going to be invalid. They withdrew. They picked up their stakes, took
8 their tent home, and we've proceeded in this case as well. So that's that
9 on that secondary consideration.

10 At various times they have criticized us for not addressing
11 every single point in one of their response briefs or not every single
12 paragraph of one of their expert declarations, but we have to look at the
13 reality here is that we had 15 pages to prepare a reply brief, and with
14 the oversized font, there was no possible way we could absolutely
15 address every one of their expert declarations, every one of their 60
16 pages of text, and you have to remember, as well as the context is we
17 had our 60 page initial petition, but the Board found many of our
18 grounds redundant as to Serfontein and Marazza, so we've had maybe a
19 total of 20 pages of briefing where they've had 50 I think to the extent
20 we had page limitations in this case.

21 And I think that's all we wanted to say at this point in time,
22 so on the basis of that, we would rest our case, and thank you for your
23 time and effort.

24 JUDGE KAMHOLZ: Thank you. The hearing is adjourned.

25 (Whereupon, at 3:44 p.m. the hearing was concluded.)

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