

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

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GNOSIS S.P.A., GNOSIS
BIORESEARCH S.A., and
GNOSIS U.S.A., INC.,

Petitioner,

vs.

SOUTH ALABAMA MEDICAL SCIENCE
FOUNDATION,

Patent Owner.

Case IPR2013-00116
US Patent 5,997,915

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GNOSIS S.P.A., GNOSIS
BIORESEARCH S.A., and
GNOSIS U.S.A., INC.,

Petitioner,

vs.

MERCK & CIE,

Patent Owner.

Case IPR2013-00117
US Patent 6,011,040

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GNOSIS S.P.A., GNOSIS
BIORESEARCH S.A., and
GNOSIS U.S.A., INC.,

Petitioner,

vs.

SOUTH ALABAMA MEDICAL SCIENCE
FOUNDATION,

Patent Owner.

Case IPR2013-00118
US Patent 6,673,381

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GNOSIS S.P.A., GNOSIS
BIORESEARCH S.A., and
GNOSIS U.S.A., INC.,

Petitioner,

vs.

SOUTH ALABAMA MEDICAL SCIENCE
FOUNDATION,

Patent Owner.

Case IPR2013-00119
US Patent 7,172,778

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DEPOSITION OF JOSHUA WILLIAM MILLER, Ph.D.

Wednesday, September 4, 2013

9:31 a.m.

Reported By:

Jennifer Ocampo-Guzman

Job No: 31303

MERCK EXHIBIT
REPLACEMENT 2064
Gnosis v Merck & Cie
IPR2013-00117

<p style="text-align: right;">2</p> <p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p> <p style="text-align: center;">September 4, 2013 9:31 a.m.</p> <p style="text-align: center;">Deposition of JOSHUA WILLIAM MILLER, Ph.D., held at the Hyatt Regency Hotel, Two Albany Street, New Brunswick, New Jersey, pursuant to notice, before Jennifer Ocampo-Guzman, a Certified Real-Time Shorthand Reporter and Notary Public of the State of New Jersey.</p> <p>Reported by: Jennifer Ocampo-Guzman, CRR, CLR JOB NO. 31303</p>	<p style="text-align: right;">4</p> <p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p> <p style="text-align: center;">Miller</p> <p>JOSHUA W. MILLER, called as a witness, having been duly sworn, was examined and testified as follows: EXAMINATION BY MR. PARKER: Q. Good morning, Dr. Miller. As you know, my name is Tom Parker. You and I had met months ago, in relation to a related case before the International Trade Commission. As you know, that you are testifying today and of course, you have just taken the oath. Your testimony will be considered sworn testimony. You understand that, correct? A. Yes. Q. And could you please state your name and address for the record? A. Joshua William Miller, Ph.D., 603 Route 518, Skillman, New Jersey 08558. Q. And by whom are you currently employed? A. Rutgers University. Q. And can you just, what is your title, and just generally, what is the nature</p>
<p style="text-align: right;">3</p> <p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p> <p>APPEARANCES: ATTORNEYS FOR THE PETITIONERS: HUSCH BLACKWELL, LLP 120 South Riverside Plaza, Suite 2200 Chicago, Illinois 60606 BY: JOSEPH E. CWIK, ESQ. joseph.cwik@huschblackwell.com</p> <p>AMIN TALATI 55 West Monroe Street, Suite 3400 Chicago, Illinois 60603 BY: JONATHAN J. KRIT, ESQ. jonathan@amintalati.com</p> <p>ATTORNEYS FOR THE PATENT OWNERS: ALSTON & BIRD, LLP 90 Park Avenue, 15th Floor New York, New York 10016 BY: THOMAS PARKER, ESQ. thomas.parker@alston.com HAIOU QUIN, Ph.D., ESQ. haiou.qin@alston.com ANDREW STERLING, ESQ. andrew.sterling@alston.com</p>	<p style="text-align: right;">5</p> <p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p> <p style="text-align: center;">Miller</p> <p>of your duties? A. I'm professor and chair of the Department of Nutritional Sciences at Rutgers University. My duties include running the department, supervising faculty, other members of the department and doing research. Q. Okay. Now, Dr. Miller, are you being compensated today for your time to appear at the deposition? A. Yes, I am. Q. And what is your compensation? A. \$450 per hour. Q. And is your compensation based in any way on the outcome of this case? A. No, it is not. Q. Now, Dr. Miller, I know you've been deposed before, and so let me just kind of go over, we call them ground rules. As I mentioned before, you are under oath, so you are obligated to answer truthfully. Do you understand that? A. Yes. Q. Okay. With respect to your</p>

<p style="text-align: right;">6</p> <p>1 Miller</p> <p>2 answers, if at all possible, please make them</p> <p>3 verbal so the court reporter can take them</p> <p>4 down.</p> <p>5 Importantly, if you don't</p> <p>6 understand a question, please let me know and</p> <p>7 I will rephrase it for you. Otherwise, if</p> <p>8 you don't ask me to rephrase it, I'll just</p> <p>9 assume that you understood the question; is</p> <p>10 that okay?</p> <p>11 A. Yes.</p> <p>12 Q. Okay. Now, we will attempt to</p> <p>13 accommodate you for, with respect to breaks.</p> <p>14 If you need to take break, just let me know.</p> <p>15 The only caveat there is that we can't take a</p> <p>16 break if there's a question pending.</p> <p>17 Do you understand that?</p> <p>18 A. Yes.</p> <p>19 Q. Now, this morning or today, is</p> <p>20 there any reason why you are not able to</p> <p>21 listen to my question today and provide</p> <p>22 truthful answers?</p> <p>23 A. No reason, no.</p> <p>24 Q. And just a standard question, are</p> <p>25 you on any medication that could impair your</p>	<p style="text-align: right;">8</p> <p>1 Miller</p> <p>2 going to get into what documents they</p> <p>3 reviewed and what was discussed?</p> <p>4 MR. CWIK: Right. I think it's</p> <p>5 work product, that if you asked him</p> <p>6 which documents he was shown in</p> <p>7 preparation, that would be work product,</p> <p>8 and I would assert the work product and</p> <p>9 object on that basis.</p> <p>10 I understand that if you give him a</p> <p>11 document and say, have you ever looked</p> <p>12 at this document sometime before the</p> <p>13 deposition, he can answer that question</p> <p>14 truthfully, but that's really the limit</p> <p>15 and the scope of what should be talked</p> <p>16 about.</p> <p>17 MR. PARKER: No, I agree. In fact,</p> <p>18 I was just going to make it simpler and</p> <p>19 not even bother going into what</p> <p>20 documents were reviewed.</p> <p>21 MR. CWIK: I'm fine with that. The</p> <p>22 simpler, the better.</p> <p>23 Q. Dr. Miller, you understand that --</p> <p>24 you provided I think four declarations in</p> <p>25 connection with these proceedings, correct?</p>
<p style="text-align: right;">7</p> <p>1 Miller</p> <p>2 ability to remember things --</p> <p>3 A. No.</p> <p>4 Q. -- or impair your ability to</p> <p>5 testify truthfully?</p> <p>6 A. No.</p> <p>7 Q. Now, just -- I just want to just</p> <p>8 talk about your preparation for your</p> <p>9 deposition. I don't want to get into your</p> <p>10 conversations with counsel, but did you meet</p> <p>11 with anyone to prepare for your deposition</p> <p>12 today?</p> <p>13 A. Yes, Mr. Krit, on Monday.</p> <p>14 Q. And it was just Mr. Krit?</p> <p>15 A. Yes.</p> <p>16 Q. How long did you meet?</p> <p>17 A. From about 9:15 to -- in the</p> <p>18 morning, to about 4 o'clock in the afternoon.</p> <p>19 Q. And did you review documents?</p> <p>20 A. Yes.</p>	<p style="text-align: right;">9</p> <p>1 Miller</p> <p>2 A. I believe so.</p> <p>3 Q. And you understand that these</p> <p>4 proceedings are before the United States</p> <p>5 Patent and Trademark Office, correct?</p> <p>6 A. Yes.</p> <p>7 Q. And it's -- and I'm just trying to</p> <p>8 lay some groundwork, I'm not trying to quiz</p> <p>9 you on the proceedings. But you understand</p> <p>10 that there is a distinction between the</p> <p>11 matter, the international -- that was before</p> <p>12 the International Trade Commission and the</p> <p>13 one now before the United States Patent and</p> <p>14 Trademark Office?</p> <p>15 A. Yes, I do.</p> <p>16 Q. And with respect to these four</p> <p>17 declarations, did you prepare them?</p> <p>18 A. Yes.</p> <p>19 Q. And they reflect your opinions?</p> <p>20 A. Yes, they do.</p> <p>21 Q. And -- okay. And as you know, in</p> <p>22 your declarations you provide various</p> <p>23 opinions, you talk about prior art, things of</p> <p>24 that nature; is that correct?</p> <p>25 A. Yes.</p>

<p style="text-align: right;">10</p> <p>1 Miller</p> <p>2 Q. And do you recall in these</p> <p>3 declarations you did so through the eyes,</p> <p>4 more or less, of what a person of ordinary</p> <p>5 skill in the art would think about, prior to</p> <p>6 a particular date, correct?</p> <p>7 A. Yes.</p> <p>8 Q. And the reason why I raise that is</p> <p>9 because we're going to be talking a lot about</p> <p>10 what one of ordinary skill in the prior art</p> <p>11 would think/not think, with respect to</p> <p>12 certain issues. So what I want to do is</p> <p>13 if -- I'm going to be asking you these</p> <p>14 questions. If I don't specify a date and</p> <p>15 time period, can we agree, then, can we</p> <p>16 assume what I'm asking you is to refer to, or</p> <p>17 I'm asking you in the context of what a</p> <p>18 person of ordinary skill in the art would</p> <p>19 think prior to 1996. Is that okay?</p> <p>20 A. Yes.</p> <p>21 Q. And the reason why I say that, so I</p> <p>22 don't have to keep repeating it over and over</p> <p>23 again.</p> <p>24 However, if at any time you think</p> <p>25 the date is not clear, you can simply say,</p>	<p style="text-align: right;">12</p> <p>1 Miller</p> <p>2 digits of the patent number?</p> <p>3 A. Yes.</p> <p>4 Q. And there's also the '040 patent?</p> <p>5 A. Yes.</p> <p>6 Q. Okay. And so just let me just kind</p> <p>7 of back up so we have a general</p> <p>8 understanding.</p> <p>9 Bailey patents, you recall those as</p> <p>10 including the '778, '381, '915?</p> <p>11 A. Yes.</p> <p>12 Q. And then the '040 patent is a</p> <p>13 patent that is owned by Merck?</p> <p>14 A. Yes.</p> <p>1</p>
<p style="text-align: right;">11</p> <p>1 Miller</p> <p>2 Mr. Parker, can you clarify what time period</p> <p>3 we're talking about?</p> <p>4 So just to be clear, then, so your</p> <p>5 responses will be directed to a person of</p> <p>6 ordinary skill in the art prior to 1996,</p> <p>7 unless otherwise specified?</p> <p>8 A. Yes.</p> <p>9 Q. Now, you also understand, you</p> <p>10 recall now that the patents that are involved</p> <p>11 in this proceeding before the United States</p> <p>12 Patent and Trademark Office, they're the same</p> <p>13 four patents that were also involved in the</p> <p>14 International Trade Commission?</p> <p>15 A. Yes.</p> <p>16 Q. And you recall that you had</p> <p>17 provided an expert report in that case,</p> <p>18 relating to those same patents, correct?</p> <p>19 A. Yes.</p> <p>20 Q. So I assume you are familiar with</p> <p>21 these patents?</p> <p>22 A. Yes.</p> <p>23 Q. And you probably may not, you may</p> <p>24 or may not remember, they're the four patents</p> <p>25 '778, '381, '915 and those are the last three</p>	

Q. Now, when a mixture of different isomers, rather than a pure isomer, is referenced, it should it be indicated as a mixture by using the symbols D, L or R, S before the chemical name, correct?

MR. CWIK: Objection, form.

A. Correct.

Q. Now, the most recognizable form of folate is folic acid, correct?

A. Yes.

MR. CWIK: Objection, form.

A. I would say, yes.

Q. What about with respect to, is it easier to synthesize folic acid than a substantially chirally pure form of either one of the isomers?

MR. CWIK: Objection, form.

A. I would anticipate that it would be simpler to synthesize folic acid than isolate and synthesize a pure chiral form.

Q. Now, folic acid was the primary folate form used in food fortifications and dietary supplements, correct?

MR. CWIK: Objection, form.

A. Correct, that's correct.

Q. And is that true today?

A. Yes.

Q. Okay. Now, but when reduced, when tetrahydrofolates are synthetically manufactured, they initially take the form of a mixture having both the R and the S form, correct?

MR. CWIK: Objection, form, foundation.

A. I don't have any firsthand knowledge of synthesizing them, but I believe that's the case.

Q. Now, you recall the Marazza reference?

A. I do.

Q. And when they're initially prepared, they have both the R and the S form, correct?

A. Correct.

<p style="text-align: right;">22</p> <p>4 Q. And then the isomers are separated 5 to produce the chirally pure S form and the 6 chirally pure R form, correct? 7 A. Correct. 8 Q. Now, in the synthesis of these 9 compounds, the isomers in the S form and the 10 R form, it was -- was it generally understood 11 that the synthesis of either of the single 12 isomers was not produced 100 percent pure? 13 MR. CWIK: Objection, form, 14 foundation. 15 A. I don't believe that 100 percent 16 purity is necessarily possible in such 17 chemistry, but it could be substantially 18 pure, yeah, if that makes sense. 19 Q. It does. That's fine. 20 Well, basically, you're right, so 21 the synthesis will produce an isomer that is 22 essentially free of the other isomer, 23 correct? 24 MR. CWIK: Objection, form. 25 Q. I said essentially free, not 26 totally free.</p>	<p style="text-align: right;">24</p> <p>3 5-methyl-(6R)-tetrahydrofolic acid, that 4 refers to the non-naturally-occurring isomer, 5 correct? 6 MR. CWIK: Objection, form. 7 A. Correct. I would say that I 8 wouldn't be 100 percent sure that it's not 9 naturally occurring. I think the more proper 10 would be to say it's in the inactive form; or 11 inert has been used. 12 Q. Well, the term, by itself, is not a 13 reference to the mixture of the R and S 14 stereoisomers, correct? 15 A. That's correct. 16 MR. PARKER: Let me mark the first 17 deposition exhibit as JM-1. 18 (Exhibit 1, Document entitled, 19 "Nomenclature and symbols for folic acid 20 and related compounds," marked for 21 identification, this date.) 22 MR. PARKER: And for the record, 23 let me just note that it has in the 24 lower right-hand corner Gnosis 25 Exhibit 1008. 26 Q. Dr. Miller, do you recognize this</p>
<p style="text-align: right;">23</p> <p>1 Miller 2 MR. CWIK: Objection, form, 3 foundation. 4 A. Yeah. I would stick with the 5 previous answer on that, yeah.</p> <p>17 Q. Now, 5-methyl-(6S)-tetrahydrofolic 18 acid refers to the naturally occurring 19 isomer, correct? 20 A. Correct. 21 Q. And the term 22 5-methyl-(6S)-tetrahydrofolic acid does not, 23 by itself, refer to the mixture of the R and 24 the S stereoisomers, correct? 25 A. That's correct. 26 Q. And with respect to</p>	<p style="text-align: right;">25</p> <p>1 Miller 2 document? 3 A. Yes, I do. 4 Q. And can you identify it, please. 5 A. Yeah, this is the, what's called 6 the International Union of Pure and Applied 7 Chemistry and International Union of 8 Biochemistry and Molecular Biology 9 nomenclature page for naming folic acid and 10 related compounds. 11 Q. And you -- and this document, you 12 relied on in your declaration, correct? 13 A. I did. 14 Q. Now, if you look at page, if you 15 look at page 4, crossing over to page 5? 16 A. Yes. 17 Q. It says there, on the bottom of 5, 18 "The following are some examples of natural 19 stereoisomers," and it has a list. 20 Do you see that? 21 A. That's correct. 22 Q. It goes on to page 6. 23 A. And I would point out that this is 24 now showing us that there are R forms that 25 are listed as being natural stereoisomers, as</p>

1 Miller
 2 well as S forms.
 3 **Q. And with respect to these -- but**
 4 **they are natural stereoisomers, correct?**
 5 A. That's correct, yes.
 6 **Q. Okay. And the nomenclature that's**
 7 **being used is a reference to the single**
 8 **isomer, correct?**
 9 A. Correct.
 10 **Q. It's not a reference to the mixture**
 11 **of the R and the S form, correct?**
 12 A. That's correct.
 13 **Q. And if you follow down, it says,**
 14 **"The following is an example of a mixture of**
 15 **stereoisomers at C-6," and it gives an**
 16 **example, correct?**
 17 A. Correct.
 18 **Q. And are you familiar with the**
 19 **phrase 6 ambo?**
 20 A. Yes.
 21 **Q. And what does that mean?**
 22 A. That means it's a mixture of the S
 23 and R or L and D; or even plus and minus,
 24 sometimes plus and minus is used.
 25 **Q. And so this nomenclature is a**

1 Miller
 2 reference to a mixture of the R isomer and S
 3 isomer, correct?
 4 A. Correct.
 5 **Q. It's not a reference to the single**
 6 **isomer, either the R or the S form, correct?**
 7 A. That's correct.
 8 **Q. And a diastereomeric mixture of**
 9 **6-isomer and the R isomer cannot properly be**
 10 **referred to as the single diastereomer of**
 11 **either isomer, correct?**
 12 MR. CWIK: Objection, form.
 13 A. I didn't quite understand that
 14 question, actually.
 15 **Q. Well, for example, you can't be**
 16 **referring to 5-methyl-(6S)-tetrahydrofolic**
 17 **acid, when you're referring to**
 18 **5-methyl-(6R)-tetrahydrofolic acid, correct?**
 19 MR. CWIK: Objection, form.
 20 A. Yes, if you say (6R), then you mean
 21 (6R). If you say (6S), you mean (6S).

9 **Q. Well, the diastereomeric mixture**
 10 **will have its own distinct name to reference**
 11 **the fact that it is a mixture.**

12 A. It is a mixture, okay.

13 **Q. And the other two compounds will**
 14 **have the distinct names to indicate they are**
 15 **the single isomers?**

16 A. Sure, yes. They have distinct
 17 names, so that people will know what they
 18 are, what they have.

<p style="text-align: right;">30</p> <p>7 Q. If I'm marketing and selling a 8 product that is a 50/50 mixture of the (6S) 9 isomer and the (6R) isomer, I can't be 10 telling people that it's simply the single 11 isomer. 12 A. Yes, I agree with that, yes. If 13 you were selling that product, you need to 14 distinguish that it's a mixture. 15 Q. Why is that, do you believe? 16 MR. CWIK: Objection, form, 17 foundation. 18 A. Yeah, can you ask a more -- 19 Q. Isn't it true that you would do so, 20 because that is the accepted nomenclature? 21 MR. CWIK: Objection, form. 22 A. I'm not sure that that's the reason 23 you would do that. I think the reason you 24 would do that is to indicate to the people 25 who are buying your product what's in it. Q. Now, if you go back to</p>	<p style="text-align: right;">32</p> <p>1 Miller 2 Q. L-5-methyltetrahydrofolic acid? 3 A. Correct. 4 Q. L-5-MTHF? 5 A. Correct. 6 Q. And the reason why I mentioned that 7 is that may be the one I will probably use 8 the rest of the day, because after a while it 9 gets too long. 10 A. Correct. 11 Q. Also with respect to the -- well, 12 let me do the same thing, but with the 13 inactive form, because "unnatural" is not the 14 appropriate phrase; is that correct? 15 A. Correct. 16 Q. So the following chemical names can 17 refer only to the unnatural form of a reduced 18 folate in its R configuration. And that 19 would 5-methyl (6R) tetrahydrofolic acid 20 which we talked about earlier, correct? 21 A. Correct. 22 Q. D-5-methyltetrahydrofolate? 23 A. Correct. 24 Q. 6(R)-5 methyltetrahydrofolate? 25 A. Correct.</p>
<p style="text-align: right;">31</p> <p>1 Miller 2 Exhibit 1008, that lays out the appropriate 3 nomenclature for reduced folates, correct? 4 A. I believe so, yes. 5 Q. Well, with respect to chemical 6 names, I mean, let me just go through the 7 following: These following names can refer 8 only to the single diastereoisomer, and that 9 would include 5-methyl-(6S)-tetrahydrofolic 10 acid, correct? 11 MR. CWIK: Objection, form. 12 Q. Let me just back up. Let me just 13 say the natural isomer, okay. So the 14 following chemical names can refer only to 15 the natural diastereoisomer or single isomer, 16 okay? 17 A. Okay. 18 Q. That would include 19 5-methyl-(6S)-tetrahydrofolic acid, which we 20 talked about before, correct? 21 A. Correct. 22 Q. L-5-methyltetrahydrofolate? 23 A. Correct. 24 Q. (6S)-5-methyltetrahydrofolate? 25 A. Correct.</p>	<p style="text-align: right;">33</p> <p>1 Miller 2 Q. D-5-MTHF? 3 A. Correct. 4 Q. Now -- 5 (Telephone interruption.) 6 MR. PARKER: Sorry about that. So 7 I want to pick up where we left off. 8 Q. Well, let me ask you this: So from 9 a nomenclature standpoint, the presence of 10 both diastereoisomers -- I'm sorry -- the 11 presence of both diastereomers are indicated 12 when describing a diastereomeric mixture of 13 both isomers, correct? 14 MR. CWIK: Objection, form. 15 A. Correct. 16 Q. And as we mentioned before, this 17 could be done using designations R, S or D, 18 L, correct? 19 A. Correct. 20 Q. And, for example, that would be -- 21 MR. PARKER: Hold on. 22 (Telephone interruption.) 23 Q. So examples of nomenclature used to 24 identify diastereomeric mixtures would 25 include 5-methyl-(6R,S)-tetrahydrofolic acid?</p>

<p>34</p> <p>1 Miller</p> <p>2 A. Correct.</p> <p>3 Q. D,L-5-methyltetrahydrofolate?</p> <p>4 A. Correct.</p> <p>5 Q. (6R,S)-5-methyltetrahydrofolate?</p> <p>6 A. Correct.</p> <p>7 Q. And I guess D,L-5-MTHF?</p> <p>8 A. Correct.</p> <p>Q. Okay.</p> <p>23 (Exhibit 2, Copy of U.S. Patent</p> <p>24 No. 5,194,611, marked for</p> <p>25 identification, this date.)</p>	<p>36</p> <p>1 Miller</p> <p>2 A. Correct.</p> <p>3 Q. Now, do you -- can you see anywhere</p> <p>4 in Marazza where he talks about the percent</p> <p>5 yield?</p> <p>6 MR. CWIK: Objection, form.</p> <p>7 A. I would have to look through it.</p> <p>8 Would you like to direct me to a</p> <p>9 location?</p> <p>10 MR. PARKER: Yeah, let me see if I</p> <p>11 have that.</p> <p>12 Q. Look at column 11. Column 11, line</p> <p>13 32. I believe it's 97 percent.</p> <p>14 A. Column 11, line 32. No, that</p> <p>15 doesn't seem -- that's not what I'm seeing.</p> <p>16 Is this example 3 that you are</p> <p>17 looking at.</p> <p>18 Q. Well, if you look at example 7?</p> <p>19 A. Example 7, okay, yes.</p> <p>20 Q. It says, "HPLC analysis shows that</p> <p>21 this product was 96.5 percent pure."</p> <p>22 A. Yes, and there are other examples</p> <p>23 in here which they, at the end they claim</p> <p>24 100 percent purity.</p> <p>25 Q. Right. But at least in some cases</p>
<p>35</p> <p>1 Miller</p> <p>2 Q. Dr. Miller, I've placed in front of</p> <p>3 you what's been marked as JM-2, which also</p> <p>4 has the designation in the bottom right-hand</p> <p>5 corner Gnosis Exhibit 0112, do you see that?</p> <p>6 A. Yes.</p> <p>7 Q. And you recognize this document, do</p> <p>8 you not?</p> <p>9 A. I do.</p> <p>10 Q. Now, this is a patent that is,</p> <p>11 well, purports to be directed to the</p> <p>12 synthesis of 5-methyl-(6S)-tetrahydrofolic</p> <p>13 acid?</p> <p>14 MR. CWIK: Objection, form.</p> <p>15 A. Actually, based on the title,</p> <p>16 separation technique, so I'm not sure</p> <p>17 "synthesis" is the right word.</p> <p>18 Q. I agree, so let me just back up.</p> <p>19 So it's directed to essentially</p> <p>20 resolving the, a diastereomeric mixture of</p> <p>21 the R isomer and S isomer into their</p> <p>22 individual single isomers?</p> <p>23 A. Correct.</p> <p>24 Q. And that includes the</p> <p>25 5-methyl-(6S)-tetrahydrofolic acid?</p>	<p>37</p> <p>1 Miller</p> <p>2 they were less than 100 percent, correct?</p> <p>3 A. That's correct, yes.</p> <p>4 Q. And example 7, that's preparation</p> <p>5 of the mixture, is it not?</p> <p>6 A. Let's see.</p> <p>7 MR. CWIK: Objection, form.</p> <p>8 A. Yes, example 7 is about (6R,S) form</p> <p>9 of MTHF.</p> <p>10 Q. We'll go back to that.</p> <p>11 A. Okay.</p> <p>12 Q. Well, although, well, as far as</p> <p>13 chirally, is chiral purification, is that a</p> <p>14 term you're familiar with?</p> <p>15 A. Sure.</p>

<p>38</p> <p>5 Q. And we know in many cases and many</p> <p>6 times in these types of syntheses, as I'll</p> <p>7 call them, but in these isolation of isomers</p> <p>8 you are not going to get 100 percent,</p> <p>9 correct?</p> <p>A. That's correct, yes.</p>	<p>40</p> <p>1 Miller</p> <p>2 A. Yes.</p> <p>3 Q. Let me just say this: I will</p> <p>4 represent to you that both Extrafolate-S and</p> <p>5 Metafolin have greater than 95 percent of the</p> <p>6 S isomer, and they both -- and they both</p> <p>7 characterize it as</p> <p>8 5-methyl-(6S)-tetrahydrofolic acid.</p> <p>9 Would you agree that that's an</p> <p>10 accurate way of describing the products?</p> <p>11 MR. CWIK: Objection, form,</p> <p>12 foundation.</p> <p>13 A. I would guess that's probably the</p> <p>14 case, yes.</p> <p>15 Q. So based on that representation,</p> <p>16 that would be appropriate?</p> <p>17 A. Yes.</p> <p>18 MR. CWIK: Same objection.</p> <p>19 Q. And your answer is?</p> <p>20 A. Yes.</p> <p>21 (Exhibit 3, Copy of European</p> <p>22 Patent Application 0,388,827, marked for</p> <p>23 identification, this date.)</p> <p>24 MR. PARKER: Dr. Miller, let me</p> <p>25 place before you what's been marked as</p>
<p>39</p> <p>20 Q. Now, just to be clear, a</p> <p>21 composition or a mixture that is 50/50, let's</p> <p>22 say, with the -- let's just take, for</p> <p>23 example, if you have a diastereomeric</p> <p>24 mixture, and it's 50/50 with respect to the R</p> <p>25 isomer and S isomer, is it also appropriate</p> <p>to say that it's a racemic mixture?</p>	<p>41</p> <p>1 Miller</p> <p>2 JM-3.</p> <p>3 Q. European patent application</p> <p>4 0,388,827, and the corner reason it says</p> <p>5 Gnosis Exhibit 1010.</p> <p>6 MR. PARKER: Sorry.</p> <p>7 Q. Just take a look at Le Grazie.</p> <p>8 Do you recognize this document?</p> <p>9 A. Yes, I do.</p> <p>10 Q. And what is this?</p> <p>11 A. This is a patent for the use of</p> <p>12 5-methyl-tetrahydrofolic acid,</p> <p>13 5-formyltetrahydrofolic acid and their</p> <p>14 pharmaceutically acceptable salts, in the</p> <p>15 preparation of pharmaceutical compositions</p> <p>16 for therapy of organic mineral disturbances.</p> <p>17 Q. And does it also provide a method</p> <p>18 of isolating the individual isomers in the R</p> <p>19 form and the S form?</p> <p>20 MR. CWIK: Objection, form.</p> <p>21 A. I don't remember it doing that. I</p> <p>22 think it's about the use.</p> <p>23 Q. Okay.</p> <p>24 A. When you say -- let's go back.</p> <p>25 Q. No, we can strike that.</p>

<p style="text-align: right;">42</p> <p>1 Miller</p> <p>2 If you would to page 2. I believe</p> <p>3 it's lines 8 through 10, and it says, "In the</p> <p>4 present text, for greater clarity and</p> <p>5 simplicity, the expression</p> <p>6 5-methyltetrahydrofolic acid and the initials</p> <p>7 MTHF refer to compounds having the following</p> <p>8 complete denomination," and then it goes on,</p> <p>9 okay?</p> <p>10 A. Correct.</p> <p>11 Q. So here they're using the acronym</p> <p>12 MTHF to refer to both the diastereomeric</p> <p>13 mixture of the R,S isomer, as well as just</p> <p>14 the single isomer, correct?</p> <p>15 A. That's correct, and they're using</p> <p>16 the plus, minus designations.</p> <p>17 Q. Okay. So the plus refers to the R</p> <p>18 or the S?</p> <p>19 MR. CWIK: Objection, form,</p> <p>20 foundation.</p> <p>21 Q. If you know.</p> <p>22 A. I believe, based on what I'm seeing</p> <p>23 here, that the plus would be the R form, and</p> <p>24 the minus would be the S form.</p> <p>25 Q. So in this particular context, in</p>	<p style="text-align: right;">44</p> <p>1 Miller</p> <p>2 (Exhibit 4, Copy of European</p> <p>3 Patent Application 0,627,435 A1, marked</p> <p>4 for identification, this date.)</p> <p>5 Q. Dr. Miller, let me just place in</p> <p>6 front of you what's been marked as JM-4,</p> <p>7 which also on the bottom right-hand corner</p> <p>8 has Gnosis Exhibit 1011.</p> <p>9 Can you identify what this document</p> <p>10 is?</p> <p>11 A. This is the European patent</p> <p>12 application 0,627,435 A1. The inventor is</p> <p>13 Ambrosini, and it describes a method for</p> <p>14 preparation of (6S) folic acid derivatives by</p> <p>15 chromatographic separation.</p> <p>16 Q. And that includes or is that a</p> <p>17 synonym for 5-methyl-(6S)-tetrahydrofolic</p> <p>18 acid?</p> <p>19 A. Yes. Well, synonym, actually, I</p> <p>20 wouldn't call it a synonym. It says (6S)</p> <p>21 folic acid derivative, so it's forms of folic</p> <p>22 acid, which would --</p> <p>23 Q. Which would include --</p> <p>24 A. Would include, yes, the</p> <p>25 tetrahydrofolates, including MTHF and FTHF.</p>
<p style="text-align: right;">43</p> <p>1 Miller</p> <p>2 Le Grazie, the inventors went out to define</p> <p>3 the term 5-methyl tetrahydrofolic acid,</p> <p>4 correct?</p> <p>5 MR. CWIK: Objection, form.</p> <p>6 A. Yes.</p> <p>7 Q. And they defined it to include the</p> <p>8 mixture as well as the single L isomer,</p> <p>9 correct?</p> <p>10 A. Correct.</p> <p>11 Q. Now, as far as nomenclature goes,</p> <p>12 have you ever seen the term</p> <p>13 5-methyl-(6S)-THFA to refer to the racemic,</p> <p>14 or the mixture --</p> <p>15 MR. CWIK: Objection, form.</p> <p>16 Q. -- of both isomers?</p> <p>17 A. I don't believe so. I don't</p> <p>18 believe I've seen that. I'm not sure.</p> <p>19 Q. Well, if you look -- well, let me</p> <p>20 go on.</p> <p>21 This also refers to the</p> <p>22 5-formyltetrahydrofolic acid, correct?</p> <p>23 A. Correct.</p> <p>24 Q. And the use of the initials FTHF?</p> <p>25 A. Correct.</p>	<p style="text-align: right;">45</p> <p>1 Miller</p> <p>2 Okay. I think I can answer your</p> <p>3 question from before about the nomenclature,</p> <p>4 about, on page 2 it has</p> <p>5 "5-(methyl)-(6S)-tetrahydrofolic acid</p> <p>6 5-(formyl)-(6S)-tetrahydrofolic acid." I</p> <p>7 think that's what you were referring to as</p> <p>8 one of the possible names.</p> <p>9 Q. Yes.</p> <p>10 A. Yes, so, yeah, clearly I actually</p> <p>11 have seen this before.</p> <p>12 Q. I'm sorry. So this basically</p> <p>13 discloses or purports to disclose the method</p> <p>14 for isolating 5-methyl-(6S)-tetrahydrofolic</p> <p>15 acid, correct?</p> <p>16 A. Correct, yes.</p> <p>17 Q. And it also is a, purports to</p> <p>18 disclose a synthesis for 5-formylmethyl --</p> <p>19 A. (6S)-tetrahydrofolic acid. Not</p> <p>20 methyl.</p> <p>21 Q. So 5-formyl-(6S)-tetrahydrofolic</p> <p>22 acid?</p> <p>23 A. Yes.</p> <p>24 Q. And if you look in examples 1, 2, 3</p> <p>25 and 4, you will see the purity there, the, it</p>

<p style="text-align: right;">46</p> <p>1 Miller</p> <p>2 has 98 to 97 -- let me back up.</p> <p>3 Example 1, do you see the purity?</p> <p>4 A. Yes.</p> <p>5 Q. In example 1 --</p> <p>6 (Telephone interruption.)</p> <p>7 MR. PARKER: All right. I've got</p> <p>8 to shut this off.</p> <p>9 Q. Now, with example 1, what reduced</p> <p>10 folate, what isomer is being isolated here?</p> <p>11 A. The calcium salt form of (6S)</p> <p>12 folinate which refers to, I believe, the</p> <p>13 5-formyltetrahydrofolate.</p> <p>14 Q. And for example 2?</p> <p>15 A. Example 2.</p> <p>16 MR. CWIK: Objection, form,</p> <p>17 foundation.</p> <p>18 A. It looks like example 2 doesn't</p> <p>19 work, and so I guess there is no answer to</p> <p>20 that question.</p> <p>21 Q. With respect to example 4?</p> <p>22 MR. CWIK: Same objection.</p> <p>23 A. The purity is greater than</p> <p>24 97 percent. This is the calcium salt of</p> <p>25 methyltetrahydrofolate, the (6S) form.</p>	<p style="text-align: right;">48</p> <p>1 Miller</p> <p>2 still appropriate to refer to the resulting</p> <p>3 compound as 5-methyl-(6S)-tetrahydrofolic</p> <p>4 acid, correct?</p> <p>5 MR. CWIK: Objection, form,</p> <p>6 foundation.</p> <p>7 A. Again, I would say it depends on</p> <p>8 the definition. What it's going to be used</p> <p>9 for would determine whether you would</p> <p>10 consider it pure or not.</p> <p>11 Q. Well, at least according, at least</p> <p>12 with respect to the authors of Ambrosini,</p> <p>13 that they felt that even with the purity of</p> <p>14 greater than 97 percent, they could still</p> <p>15 isolate and characterize what they've</p> <p>16 isolated as 5-methyl-(6S)-tetrahydrofolic</p> <p>17 acid?</p> <p>18 MR. CWIK: Objection, form,</p> <p>19 foundation.</p> <p>20 A. I guess without reading through it</p> <p>21 all again, I don't know what they concluded</p> <p>22 from that, but I presume that they would like</p> <p>23 to be able to say that this is substantially</p> <p>24 pure, for the purposes that it's intended</p> <p>25 for.</p>
<p style="text-align: right;">47</p> <p>1 Miller</p> <p>2 Q. This is on example 4?</p> <p>3 A. That's example 4, yes.</p> <p>4 Q. So in example 4 it's a synthesis</p> <p>5 for 5-methyl-(6S)-tetrahydrofolic acid. When</p> <p>6 I say synthesis, I mean the isolation of</p> <p>7 5-methyl-(6S)-tetrahydrofolic acid from the,</p> <p>8 with respect to the R form, correct?</p> <p>9 MR. CWIK: Same objection.</p> <p>10 A. Yes.</p> <p>11 Q. And the purity reached there,</p> <p>12 according to this, is 97 percent, correct?</p> <p>13 A. Greater than 97 percent.</p> <p>14 Q. Greater than 97 percent, okay.</p> <p>15 And with respect to example 1,</p> <p>16 which was the 5-formyl (6S) tetrahydrofolic</p> <p>17 acid, the purity there was greater than</p> <p>18 98 percent?</p> <p>19 A. By one method. Greater than 97 by</p> <p>20 a different method.</p> <p>21 Q. And with those values, for example,</p> <p>22 like in example 4, even with the purity of</p> <p>23 greater than 97 percent, the isomer 5-methyl</p> <p>24 -- well, it's -- even though the purity is,</p> <p>25 the purity is greater than 97 percent, it's</p>	<p style="text-align: right;">49</p> <p>1 Miller</p> <p>2 Q. Right. And it's certainly, well --</p> <p>3 they're not in here characterizing it as a</p> <p>4 mixture of the R and the S form?</p> <p>5 A. I would agree with that, yes.</p> <p>6</p> <p>MS. QIN: JM-5.</p> <p>19 Q. Do you recognize this document?</p> <p>20 A. Yes, I do.</p> <p>21 Q. And can you identify what this</p> <p>22 document is?</p> <p>23 A. It is a United States patent. The</p> <p>24 lead inventor is Muller. The number is</p> <p>25 6,011,040. We commonly refer to this in this</p>

<p style="text-align: right;">50</p> <p>1 Miller</p> <p>2 proceeding as the '040 patent, and it is</p> <p>3 about the use of the natural stereoisomeric</p> <p>4 form of tetrahydrofolates specifically for</p> <p>5 lowering homocystine levels and the</p> <p>6 pharmaceutical preparation of those</p> <p>7 compounds.</p> <p>8 Q. Okay. And if you look at column 1</p> <p>9 of the '040, it states, "In the present text,</p> <p>10 the expression 'tetrahydrofolate in natural</p> <p>11 stereoisomeric form' refers to the</p> <p>12 5-formyl-(6S)-tetrahydrofolic acid,</p> <p>13 5-methyl-(6S)-tetrahydrofolic acid,</p> <p>14 5,10-methylene-(6R)-tetrahydrofolic acid or</p> <p>15 (6S)-tetrahydrofolic acid or a</p> <p>16 pharmaceutically compatible salt thereof."</p> <p>17 Do you see that?</p> <p>18 A. Yes.</p> <p>19 Q. Now the tetrahydrofolic natural</p> <p>20 stereoisomeric form, including the</p> <p>21 5-methyl-(6S)-tetrahydrofolic acid, that's</p> <p>22 referring to the single isomer, correct?</p> <p>23 A. Correct.</p> <p>24 Q. And not the, not the racemic,</p> <p>25 correct?</p>	<p style="text-align: right;">52</p> <p>6 Q. And claim 1 is, claim 1 is directed</p> <p>7 to decreasing homocystine levels in the human</p> <p>8 body comprising administering at least one</p> <p>9 tetrahydrofolate natural stereoisomeric form</p> <p>10 to a human subject.</p> <p>11 Do you see that?</p> <p>12 A. Yes, I do.</p> <p>13 Q. Okay. And then, if you look at</p> <p>14 claim 8, for example, a method to claim 2</p> <p>15 wherein the tetrahydrofolate is</p> <p>16 5-methyl-(6S)-tetrahydrofolic acid or a salt</p> <p>17 thereof, do you see that?</p> <p>18 A. Yes, I do.</p> <p>19 Q. That's, again, directing to, that's</p> <p>20 referring to the single isomer, correct?</p> <p>21 MR. CWIK: Objection, form.</p> <p>22 A. Yes, it is.</p> <p>23 Q. Not the racemic, right?</p> <p>24 MR. CWIK: Same objection.</p> <p>25 A. Not the mixture, yes.</p> <p>Q. Right, okay.</p>
<p style="text-align: right;">51</p> <p>1 Miller</p> <p>2 A. Not the racemic mixture, yes, that</p> <p>3 is correct.</p> <p>4 Q. And not the diastereomeric mixture</p> <p>5 of the S isomer and R isomer, correct?</p> <p>6 A. Correct.</p> <p>7 Q. Now, in each, if you look at the</p> <p>8 examples. And example 1, for example, in</p> <p>9 example 1, can you identify the</p> <p>10 tetrahydrofolate natural stereoisomeric form?</p> <p>11 A. Yes, it's the formyltetrahydrofolic</p> <p>12 acid (6S) form.</p> <p>13 Q. And in the example 2?</p> <p>14 A. It is the methyltetrahydrofolic</p> <p>15 acid (6S) form.</p> <p>16 Q. And that's a reference to the,</p> <p>17 referring to the single isomer, correct?</p> <p>18 A. Correct.</p> <p>19 Q. Not the racemic, correct?</p> <p>20 A. Not the racemic mixture, yes.</p> <p>21 Q. Or the diastereomeric mixture --</p> <p>22 A. Yes.</p> <p>23 Q. -- of the S isomer and the R</p> <p>24 isomer, correct?</p> <p>25 A. Correct.</p>	<p style="text-align: right;">53</p> <p>1 Miller</p> <p>2 And the same is true for claim 9?</p> <p>3 MR. CWIK: Same objection.</p> <p>4 Q. Your response is?</p> <p>5 A. Yes.</p> <p>6 Q. Let me just put --</p> <p>7 (Discussion off the record.)</p> <p>8 (Exhibit 6, Copy of U.S. Patent</p> <p>9 No. 5,997,915, marked for</p> <p>10 identification, this date.)</p> <p>11 (Exhibit 7, Copy of U.S. Patent</p> <p>12 No. 6,673,381, marked for</p> <p>13 identification, this date.)</p> <p>14 (Exhibit 8, Copy of U.S. Patent</p> <p>15 No. 7,172,778, marked for</p> <p>16 identification, this date.)</p> <p>17 Q. Dr. Miller, let me just place in</p> <p>18 front you the other three patents that are</p> <p>19 involved in these proceedings, which include</p> <p>20 JM-6, which has the Gnosis Exhibit 1001.</p> <p>21 Can you confirm that this is what</p> <p>22 we referred to as the '915 patent?</p> <p>23 A. Yes, I confirm that.</p> <p>24 Q. And with respect to, I'm going to</p> <p>25 hand you what's been marked as JM-7, which</p>

Q. And through chiral resolution, at least there are procedures that you are aware of, chiral resolution procedures, that the resulting isomer, whether it's the R form or

Miller
the S form, is typically greater than 90 percent pure?

MR. CWIK: Objection, form, foundation.

A. The only thing I can really go from is the methods described in these patents and the results that they describe here, which are clearly greater than 90 percent, as it's claimed.

Q. And you have before you the exhibits Marazza and Ambrosini and Le Grazie -- let me go back.

You have Ambrosini and Marazza, correct, which is JM-2 and JM-4?

A. Correct.

Q. Now, these documents discuss isolating the 5-methyl-(6S)-tetrahydrofolic acid by, through chiral separation?

MR. CWIK: Objection, form, foundation.

A. I believe so, yes.

Q. Okay. Now prior to 1996, what other ways were you aware of, or methods that are out there, where one could isolate a, could isolate the natural stereoisomer -- the natural stereoisomeric form of reduced folate, for example, 5-methyl-(6S)-tetrahydrofolic acid?

MR. CWIK: Objection, form.

1 **Miller**

2 **find some way to stabilize them, correct?**

3 MR. CWIK: Objection to form,
4 foundation.

5 A. I believe that would be the case,
6 yes.

7 **Q. And one way of doing that is**
8 **converting the free acid into a salt form,**
9 **for example, calcium salt?**

10 MR. CWIK: Same objection.

11 A. That may protect it. I'm not
12 familiar enough with the chemistry to know if
13 that would be fully protective.

9 **Q. Now, you can put those down for**
10 **just a second.**

11 **With respect to the reduced**
12 **folates, generally, and again staying with**
13 **prior to 1996, are reduced folates in their**
14 **monoglutamate free acid form considered to be**
15 **unstable?**

16 MR. CWIK: Objection to form.

17 A. I would say they're not as stable
18 as folic acid.

19 **Q. They're certainly prone to**
20 **oxidation?**

21 MR. CWIK: Objection to form.

22 A. I believe so, yes.

23 **Q. And the -- and when, if one would**
24 **want to use these compounds, let's say, in a**
25 **pharmaceutical formulation, you would have to**

Q. And do you have any understanding as to why, in the case of Marazza, he would want to isolate them in the salt form?

MR. CWIK: Objection, form, foundation.

A. Potentially, to improve their stability and possibly reduce their reactivity.

Q. Now, if you look at just JM-10 for a second on page 8.

Are you there? I'm going to go 8, 9 and 10.

You have a list of active metabolites, correct?

A. That's correct.

Now, if you can stay with me now on JM-10, I guess paragraph 10. And if I could just direct your attention, you will see the sentence, it says, "One with ordinary skill in the art also would have recognized 5-MTHF to be a racemic mixture that includes the biologically active isomer (6S)-5-MTHF, the S isomer, and the biologically inert isomer, (6R)-5-MTHF, the R isomer."

Do you see that?

A. Yes, I do.

Q. That's a true statement, correct?

Miller

Q. And the nomenclature there refers to the single diastereomer, correct?

A. That's correct.

Q. And you have them presented in the free acid form, correct?

A. Correct.

Q. And also are they in the monoglutamate form?

A. That's not specified here.

Q. And I'm referring to the, I was referring to -- let me back up.

And you understand I was referring to the compounds that are in paragraphs 18 and 19, correct?

A. That's correct.

Q. Now, in your declaration -- (Discussion off the record.)

MR. PARKER: We are going to place before you what's been marked as JM-11.

(Exhibit 11, Copy of European Patent Application 0,595,005 A1, marked for identification, this date.)

Q. Which is Gnosis Exhibit 1009. It's a European patent application bearing numbers

Miller

A. Yes.

Q. And in this particular case here you use the word "inert."

Does that mean having no pharmaceutical action?

A. Yes.

Q. So in this sentence you are indicating that one of ordinary skill in the art would have considered the R isomer as inert, correct?

MR. CWIK: Objection to form.

A. Yes, though I qualify that, that there are suggestions that it might not actually be inert, that it might have off-target effects.

Q. Okay. But you don't say that in this sentence, correct?

A. I don't say that in that sentence, that's true.

Q. Now, they have the words "active isomer," do you see that?

A. Yes.

<p>66</p>	<p>68</p> <p>1 Miller</p> <p>2 A. So I can't tell you how many</p> <p>3 inactive metabolites of folate there are.</p> <p>4 That's more about the degradation of</p> <p>5 products.</p> <p>6 As far as active metabolites of</p> <p>7 folate, as I've written here, I believe that</p> <p>8 there are eight. The one thing that is not</p> <p>9 talked about here is the glutamate chains, so</p> <p>10 each of these eight active forms can have</p> <p>11 different glutamate chains, number of</p> <p>12 glutamates attached to it.</p> <p>13 Q. They can have up to 14.</p> <p>14 MR. CWIK: Objection.</p> <p>15 A. Yeah, whatever the number is,</p> <p>16 greater than 10.</p> <p>17 Q. And all eight metabolites that</p> <p>18 you've listed here are active?</p> <p>19 A. Yes.</p> <p>20 Q. Okay. And I guess, I was going to</p> <p>21 say, aren't all the metabolites in the S</p> <p>22 form, but I guess the answer is no, there's</p> <p>23 one that's not.</p> <p>24 A. There's actually, now that we've</p> <p>25 looked at it, if you look through this list,</p>
<p>67</p> <p>20 Q. So -- well, let me ask you this,</p> <p>21 then: Without the word "active," I mean how</p> <p>22 many metabolites of folate are there --</p> <p>23 MR. CWIK: Objection to form.</p> <p>24 Q. -- inactive and active?</p> <p>25 MR. CWIK: Same objection.</p>	<p>69</p> <p>1 Miller</p> <p>2 you will find there is more than one in the</p> <p>3 (6R) form, looking in paragraphs 18 and 19.</p> <p>4 Q. All right. So basically, now,</p> <p>5 active metabolite folates, you take the</p> <p>6 position that one would immediately envisage</p> <p>7 these eight compounds?</p> <p>8 A. Yes, one of ordinary skill in the</p> <p>9 art I believe would.</p> <p>10 Q. Okay. And then on paragraph --</p> <p>11 well, you say no more than eight compounds.</p> <p>12 Is it possible that it could be</p> <p>13 less than eight compounds that one of</p> <p>14 ordinary skill in the art would envisage?</p> <p>15 A. Yes, and one could -- it depends on</p> <p>16 your definition of "active." Some of these</p> <p>17 compounds might be intermediates between,</p> <p>18 being converted between different forms; but,</p> <p>19 yeah, I would say it's no more than eight.</p> <p>20 Q. And just to be clear, and some of</p> <p>21 ordinary skill in the art, they could</p> <p>22 envisage less than eight?</p> <p>23 A. They might. They might.</p> <p>24 Particularly, I would -- for particularly the</p> <p>25 dihydrofolate, whether they would consider</p>

<p>70</p> <p>1 Miller</p> <p>2 that active.</p> <p>3 And for that matter, they would, if</p> <p>4 they don't consider dihydrofolate active,</p> <p>5 they wouldn't consider folic acid, in and of</p> <p>6 itself, active.</p>	<p>72</p> <p>1 Miller</p> <p>2 suppository which would absorb through the</p> <p>3 rectal mucosa.</p> <p>4 Q. And then you have gels or</p> <p>5 ointments, do you see that?</p> <p>6 A. Yes.</p> <p>7 Q. And you have solution for skin?</p> <p>8 A. Correct.</p> <p>9 Q. So the Serfontein has, discloses in</p> <p>10 addition to oral supplements, didn't it also</p> <p>11 encompasses transdermal patches,</p> <p>12 suppositories, gels, ointments and solutions,</p> <p>13 topical solutions, correct?</p> <p>14 A. Correct.</p> <p>15 MR. CWIK: Objection, form,</p> <p>16 foundation.</p> <p>17 Q. As well as oral supplements?</p> <p>18 A. Correct.</p> <p>19 Q. So basically Serfontein does not</p> <p>20 limit what it regards as suitable to merely</p> <p>21 consumption by humans as oral supplements,</p> <p>22 correct?</p> <p>23 MR. CWIK: Objection, form,</p> <p>24 foundation.</p> <p>25 A. That would appear to be the case,</p>
<p>71</p> <p>4 Q. Now, Serfontein is not limited to</p> <p>5 oral supplements, correct?</p> <p>6 MR. CWIK: Objection to form.</p> <p>7 A. I believe that's the case.</p> <p>8 Q. If you look at page 7, columns --</p> <p>9 I'm sorry, line 37 to 43.</p> <p>10 A. Yes.</p> <p>11 Q. It also lists plasters.</p> <p>12 What are those? Do you know what</p> <p>13 they are?</p> <p>14 MR. CWIK: Objection to form.</p> <p>15 A. I don't know exactly, but from</p> <p>16 what's described here, it's something that</p> <p>17 you would put on the skin that would stick to</p> <p>18 the skin; and then it would contain the</p> <p>19 substance, which would then be absorbed</p> <p>20 through the skin.</p> <p>21 Q. Like a transdermal patch?</p> <p>22 A. Yeah.</p> <p>23 Q. And a rectal series?</p> <p>24 MR. CWIK: Objection, form,</p> <p>25 foundation.</p> <p>A. Yeah, I guess that would be a</p>	<p>73</p> <p>1 Miller</p> <p>2 yes.</p> <p>3 Q. And so suitable active metabolites</p> <p>4 would encompass reduced folates that are</p> <p>5 suitable for use in transdermal patches, oral</p> <p>6 supplements, suppositories, gels, ointments</p> <p>7 and topical solutions, correct?</p> <p>8 MR. CWIK: Objection, form,</p> <p>9 foundation.</p> <p>10 A. Yes, that's correct.</p> <p>11 Q. And suitable, although it's not</p> <p>12 defined in Serfontein, correct, the term</p> <p>13 "suitable"?</p> <p>14 A. That's correct.</p> <p>15 Q. But Serfontein is directed to</p> <p>16 pharmaceutical formulations, right?</p> <p>17 MR. CWIK: Objection, form,</p> <p>18 foundation.</p> <p>19 A. Not solely to pharmaceutical</p> <p>20 formulations.</p> <p>21 Q. What else?</p> <p>22 A. It's also to dietary formulations.</p> <p>23 Q. Anything else?</p> <p>24 A. I don't believe so.</p> <p>25 Q. Okay. And so with respect to</p>

1 **Miller**

2 **pharmaceutical formulations and dietary**
3 **formulations, so suitable would include a**
4 **reduced folate that's in a form that is**
5 **sufficiently stable for use in either a**
6 **pharmaceutical formulation or dietary**
7 **formulation, correct?**

8 MR. CWIK: Objection, form,
9 foundation.

10 A. I believe that's correct, yes.

11 **Q. Okay. And by itself, reduced**
12 **folates, or at least the free acid form**
13 **reduced folate, is not suitable for a**
14 **pharmaceutical formulation or a dietary**
15 **formulation, correct?**

16 MR. CWIK: Objection, form,
17 foundation.

18 A. Could you repeat that question.

19 **Q. So by itself, a reduced folate in**
20 **its nonsalt form, free acid form, would be**
21 **unstable for use in a pharmaceutical**
22 **formulation or a dietary formulation?**

23 MR. CWIK: Same objection.

24 A. It possibly could be unstable. I
25 don't have direct knowledge.

<p>78</p> <p>(Exhibit 12, Document entitled, "Supplementary material-list of pharmaceutically acceptable acids," marked for identification, this date.)</p> <p>Q. Dr. Miller, I am going to hand you Exhibit, it's a composite exhibit. I'm doing it only -- I think it might be easier, but I could be wrong.</p> <p>(Discussion off the record.)</p> <p>Q. So let me just hand you what's been marked as JM-12. And all this document is, it's a compilation of three documents. The</p>	<p>80</p> <p>1 Miller</p> <p>2 A. I presume so, yeah.</p> <p>3 Q. So, but the point is, there are</p> <p>4 many, many salt forms that are available.</p> <p>5 A. Uh-huh.</p> <p>6 Q. Okay. And reduced folates have</p> <p>7 been converted into salt forms, when being</p> <p>8 used in some, in certain clinical studies,</p> <p>9 correct?</p> <p>10 MR. CWIK: Objection, form,</p> <p>11 foundation.</p> <p>12 A. Salt farms have been used, right.</p> <p>13 Q. And to your knowledge, again, I</p> <p>14 don't if this will refresh your recollection,</p> <p>15 I mean the reduced folate</p> <p>16 5-methyl-(6S)-tetrahydrofolic acid, as sold</p> <p>17 by Merck and Gnosis, are in the calcium salt</p> <p>18 form?</p> <p>19 MR. CWIK: Objection, form,</p> <p>20 foundation.</p> <p>21 A. Again, as I answered before, I</p> <p>22 would have to confirm that by looking at</p> <p>23 package inserts, but I presume that's the</p> <p>24 case.</p> <p>25 Q. Are you familiar with Quatrefolic?</p>
<p>79</p> <p>1 Miller</p> <p>2 first page is just a list of pharmaceutically</p> <p>3 acceptable salts. The next one is a paper, a</p> <p>4 commentary, which, if you look at table 2, I</p> <p>5 believe -- no, I'm sorry, table 5, there's a</p> <p>6 list of additional salts. And then the next</p> <p>7 one is a document that we generated, again,</p> <p>8 with just, it lists various salts,</p> <p>9 pharmaceutically acceptable salts.</p> <p>10 You can peruse the document as you</p> <p>11 see fit, and I'll go over these really</p> <p>12 quickly with you.</p> <p>13 And you can just tell me when you</p> <p>14 are ready.</p> <p>15 A. Okay.</p> <p>16 Q. Just prior to 1996, January 1996,</p> <p>17 there were many available pharmaceutically</p> <p>18 acceptable salts that could be used with</p> <p>19 various compounds, for use in pharmaceutical</p> <p>20 formulations, correct?</p> <p>21 MR. CWIK: Objection to form.</p> <p>22 A. I presume so.</p> <p>23 Q. And they would also include the</p> <p>24 alkaline earth metals, correct?</p> <p>25 MR. CWIK: Objection to form.</p>	<p>81</p> <p>1 Miller</p> <p>2 MR. CWIK: Objection, foundation.</p> <p>3 A. I remember that coming up before, I</p> <p>4 think, yeah.</p> <p>5 Q. So there are many, you don't</p> <p>6 dispute that there are many, there are many</p> <p>7 salt forms that are out there available?</p> <p>8 A. I do not dispute that.</p> <p>9 Q. And these salt forms could be</p> <p>10 potentially used for reduced folates?</p> <p>11 MR. CWIK: Objection, form.</p> <p>12 A. Yes.</p> <p>13 Q. And depending on the salt form, I</p> <p>14 mean it could render -- well, some salt forms</p> <p>15 can be more stable than other salt forms,</p> <p>16 with respect to the -- we're talking about</p> <p>17 the same reduced folate, correct?</p> <p>18 MR. CWIK: Objection, form.</p> <p>19 A. I believe that would be the case,</p> <p>20 but obviously an empirical question.</p> <p>21 Q. Right, but they would not -- well,</p> <p>22 they would have different levels of</p> <p>23 stability.</p> <p>24 A. That would be the expectation,</p> <p>25 but...</p>

1 Miller
 2 MR. CWIK: Objection, form.
 3 **Q. And some may not even be stable at**
 4 **all?**
 5 MR. CWIK: Objection, form.
 6 A. That might be expected, too, yes.
 7 **Q. And some would not necessarily be**
 8 **suitable or appropriate for a reduced folate?**
 9 MR. CWIK: Objection, form.
 10 A. Correct, or as a supplement.
 11 **Q. Or a supplement, that's true.**

10 **Q. But, well, look, I mean you have**
 11 **all these, you have a fair amount of species,**
 12 **if you include the salt forms with respect to**
 13 **reduced folates. So is it fair to say that a**
 14 **person of ordinary skill in the art may**
 15 **envisage some, but they're not going to**
 16 **envisage all of the appropriate salt forms?**
 17 MR. CWIK: Objection to form.
 18 A. Yeah, I mean, I've never seen this
 19 list of potential salts, so I wouldn't have
 20 envisioned this list.
 21 **Q. So they may envision some, but not**
 22 **all of the species?**
 23 MR. CWIK: Same objection.
 24 **Q. Correct?**
 25 A. Possibly, yeah.
Q. For example, if you're -- if a

<p>86</p>	<p>88</p> <p>1 Miller</p> <p>2 small intestine. Some of the folate is</p> <p>3 absorbed by simple diffusion, so.</p> <p>4 Q. Now, would these factors, would</p> <p>5 these factors dictate, in terms of what</p> <p>6 reduced folate you would use or not use?</p> <p>7 MR. CWIK: Objection, form.</p> <p>8 A. Possibly. That might be an</p> <p>9 empirical question. For instance, if you put</p> <p>10 it on the skin, say, in a plaster, you would</p> <p>11 want to figure out whether one is more</p> <p>12 absorbable than the other.</p> <p>13 If it's simple diffusion, some --</p> <p>14 some compounds, even similar compounds like</p> <p>15 5-MTHF and 5-FTHF might have different</p> <p>16 diffusion characteristics. They also might</p> <p>17 have different receptor binding and</p> <p>18 transporter binding characteristics. So for</p> <p>19 each of these situations you might want to do</p> <p>20 experimentation, empirical experimentation.</p> <p>21 It wouldn't change which two that I</p> <p>22 would immediately consider.</p> <p>23 Q. In terms of immediately consider,</p> <p>24 immediately consider in terms of trying them</p> <p>25 out to see if they work?</p>
<p>87</p> <p>13 Q. And so, and your answer would be</p> <p>14 the same with respect to plasters, rectal</p> <p>15 suppositories, gels, ointments and topical</p> <p>16 solutions?</p> <p>17 MR. CWIK: Objection, form.</p> <p>18 A. Yes, it would be, but I would also</p> <p>19 want to consider the mechanism by which the</p> <p>20 substance is absorbed, whether it is done by</p> <p>21 a physiological process, which would be</p> <p>22 receptor-mediated, transporter-mediated, or</p> <p>23 in other cases it could be simple diffusion;</p> <p>24 so when you put it on the skin, that might be</p> <p>25 a possibility. Also we know that there is</p> <p>simple diffusion in the intestinal, in the</p>	<p>89</p> <p>1 Miller</p> <p>2 A. They would be the first things I</p> <p>3 would try.</p> <p>4 Q. And if they didn't work, you would</p> <p>5 turn to the other ones?</p> <p>6 A. Maybe. I might not. I might</p> <p>7 decide that they're just not -- the reasons</p> <p>8 that 5-MTHF and 5-FTHF don't work well, I</p> <p>9 might presume that the others would work even</p> <p>10 less well; so I might abandoned this</p> <p>11 approach.</p>

4 **Q. So then, basically, so if you look**
5 **at suitable active metabolite or folate, if**
6 **you look at this phrase, this genus, if you**
7 **will, when dealing with all these dosage**
8 **forms that we were just discussing, you're**
9 **going to need or require some empirical**
10 **information to make some decisions on which**
11 **one would be suitable?**

12 MR. CWIK: Objection, form.

13 **A. That would be necessary, yes.**

<p>94</p> <p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p> <p>A. Yes, I would agree with that. Q. Now, on that same paragraph, the</p>	<p>96</p> <p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p> <p>Miller isomer and R isomer, so long as it has some amount of S isomer? A. That's correct. Q. Even if the mixture had 10 percent of the S isomer? A. That would depend on what amount was necessary to achieve the biological response that you wish. Yeah. Q. But the board's -- okay, I just want to be clear now. So the board is saying which would include at least some amount of 5-methyl-(6S) THFA. Are you elaborating on that to say "effective amount"? A. Yeah, I mean certainly, you know, "some amount" is a, you know, it's not a very specific statement. So you could argue that you wouldn't want to give somebody a mixture that has, you know, .5 percent methyl-THFA and -- in the (6S) form, and the rest is (6R). So there is some, you know, percentage that you would want at least. Q. Well, on its face you would agree, though, that if you had a mixture that had</p>
<p>95</p> <p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p> <p>Miller board also says, "Among these is 5-methyl THFA," and I'm following the next sentence. MR. PARKER: Start over again? Okay, start over again. Q. Among these is 5-methyl-THFA, which refers generally to 5-methyl-(6S)-THFA, 5-methyl-(6R)-THFA and/or a mixture of the two, although "in," and they have it in quotes, "active form would include at least some amount of 5-methyl-(6S)-THFA," and it says "id." And you understand "id" to be a reference to your Miller declaration, paragraph 10? MR. CWIK: Objection, form. A. Yes, I do. Q. Now, and does that accurately describe your position? MR. CWIK: Objection, form, foundation. Q. Or do you agree with it? A. I agree with that, yes. Q. And so Serfontein, I guess in your opinion, would include any mixture of the S</p>	<p>97</p> <p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p> <p>Miller 10 percent of the S isomer, it did have some amount of the 5-methyl-(6) -- A. Yeah, it would have some amount, yeah. Q. Even if it had one percent of the S isomer, it still had some amount? A. Yes, technically, yes. Q. So -- well, then, at least according to this statement on page 12 that we just read, so Serfontein, I just want to get this straight, so Serfontein would cover not only the racemic, but also any mixture of the two isomers, so long as it had some amount of 5-methyl-(6S)-THFA? MR. CWIK: Objection, form. A. Yeah, I guess I would agree with that, yes. Q. And again, "some amount" could be a range, right, a range anywhere from 1 to 99 percent, for example? MR. CWIK: Objection, form. A. I presume so, but again, it depends on what you're trying to do, right. Q. But a range from 1 percent to</p>

- 1 **Miller**
- 2 **99 percent, that would have some amount.**
- 3 A. Yeah, yes.

<p>102</p> <p>14 Q. Now, Serfontein's emphasis is 15 basically on the use of folic acid, do you 16 agree? 17 MR. CWIK: Objection, form, 18 foundation. 19 A. I would say that the compositions 20 for dosing that are provided as examples are 21 very likely referring to folic acid. As to 22 whether or not Serfontein is specifically 23 saying, "Use folic acid," I don't believe 24 that Serfontein is specifically saying only 25 folic acid. Q. Okay. But at least the folic acid</p>	<p>104</p> <p>1 Miller 2 metabolites" is the reference that is used in 3 Serfontein to those compounds. 4 Q. Let me place in front of you what's 5 been marked as JM-14. 6 (Exhibit 14, Document entitled, 7 "Vitamin B-12, vitamin B-6, and folate 8 nutritional status in men with 9 hyperhomocysteinemia," marked for 10 identification, this date.) 11 Q. It's marked on the right-hand 12 corner as Gnosis Exhibit 1019, entitled, 13 "Vitamin B-12, vitamin B-6 and folate 14 nutritional status in men in 15 hyperhomocystinemia," by Ubbink. 16 Dr. Miller, are you familiar with 17 this publication? 18 A. Yes, I am. 19 Q. Now, you understand your 20 declaration -- well, in your declaration, you 21 don't discuss Ubbink, do you? 22 A. I don't think so, no. 23 Q. So at least at this point you have 24 not expressed any technical opinion on this 25 reference, right?</p>
<p>103</p> <p>1 Miller 2 I would say, well, would you agree is the 3 most prominent compound, because all the 4 examples are folic acid, correct? 5 A. Yeah, most of them say "folic 6 acid," and occasionally they use the term 7 "folate," and so it's not clear which form 8 they're thinking of. So it's possible they 9 could have been thinking just, you know, 10 whatever form of folate; so, yeah, it's just 11 not clear. 12 Q. And folic acid is the only specific 13 compound that's called out by name, correct? 14 A. Yes, I think so, yeah. 15 Q. Now, other than the phrase "As 16 suitable active metabolite folate," is there 17 anything in the 22-page disclosure of 18 Serfontein to support your contention that 19 Serfontein discloses eight reduced folates, 20 which are the ones you've listed on pages 8 21 through 9 of your declaration? 22 MR. CWIK: Objection, form. 23 A. Again, you know, I haven't read it 24 word for word, but I believe that's the case, 25 that this is, that the "suitable active</p>	<p>105</p> <p>1 Miller 2 A. In that declaration, yes, that's 3 correct.</p>

<p style="text-align: right;">106</p> <p>13 Q. So where is the data that's 14 directed to the use of a reduced folate? 15 MR. CWIK: Objection to form. 16 A. That's not what I'm referring to. 17 What I'm referring to is, in this paper 18 they're looking at folate status. 19 Q. Right. 20 A. And so if you look at table 4 on 21 page 51 -- 22 Q. Right. 23 A. -- they talk about the nanomoles 24 per liter of folate in the placebo group and 25 the vitamin-supplemented group; and that measurement is not a measurement of folic</p>	<p style="text-align: right;">108</p> <p>1 Miller 2 racemic 5-MTHF as (6S)-5-MTHF, okay. Now in 3 this litigation, Gnosis took the position 4 that 1 gram of the (6S)-MTHF would 5 essentially have a similar potency or same 6 potency as 2 grams of 5-MTHF. 7 Do you agree with this statement, 8 and if so, why? 9 MR. CWIK: Objection, form, 10 foundation, hypothetical. 11 A. So let me just be clear. So what 12 we have here is 1 milligram, is what you 13 used? 14 Q. One -- 15 A. 1 gram? 16 Q. 1 gram. 17 And by the way, I don't want to get 18 into overdosing, so if a milligram is better, 19 we will do milligrams. 20 A. I understand that. 21 So the -- if it's by itself, the 22 presumption is that the racemic mixture of 23 the two is what you're referring to, versus 24 the active form by itself; and the 25 presumption is that, say, a 2-milligram</p>
<p style="text-align: right;">107</p> <p>1 Miller 2 acid. It's a measurement of the circulating 3 folate; and primarily that would be 4 methyltetrahydrofolate, and there probably 5 will be some formyltetrahydrofolate, both in 6 the monoglutamate form. Very little, if any, 7 would be actual folic acid. 8 Q. Now, what was administered to the 9 subjects in this study was folic acid, 10 correct? 11 MR. CWIK: Objection, form, 12 foundation. 13 A. Let me just verify that. Very 14 likely it is folic acid. 15 Yes, the supplement contained 16 1 milligram folic acid. 17 Q. And in Ubbink, he makes no 18 conclusion directed to administering reduced 19 folate to patients, right? 20 A. I don't believe so. 21 MR. CWIK: Objection, form. 22 Q. Now, Dr. Miller, in a prior 23 litigation that you were not involved with, 24 Gnosis was -- and they will disagree, but 25 they can object -- Gnosis was promoting its</p>	<p style="text-align: right;">109</p> <p>1 Miller 2 racemic mixture would contain 1 milligram of 3 the active form. And the question is whether 4 or not you would have the same potency. 5 And my answer would be that it's 6 possibly, possible that you would not have 7 the same potency, for a couple of reasons. 8 One is there was literature at the time 9 showing that the -- what we call the inactive 10 or inert form actually might inhibit the 11 absorption, via competitive inhibitor, of the 12 absorption of the active form. So you could 13 envision a situation that by giving the 14 inactive form, you block some of the active 15 form from getting absorbed; and therefore 16 less would get in, and it would be less 17 potent. That's one thing that could be 18 envisioned. 19 The other objections that were 20 raised or, you know, possible negative 21 effects of the inactive form is that there 22 was some suggestion in the literature that it 23 might actually get into cells and inhibit 24 important reactions. So these publications 25 that pointed this out suggested that, you</p>

<p style="text-align: right;">110</p> <p>1 Miller</p> <p>2 know, maybe the pure active form would be,</p> <p>3 would be best, would be more prudent.</p> <p>4 Q. So, then, by simply just doubling</p> <p>5 up on the racemic, then you would -- you</p> <p>6 would not expect the same level of efficacy?</p> <p>7 A. I think I would --</p> <p>8 MR. CWIK: Same objection.</p> <p>9 A. I think I would couch it by saying,</p> <p>10 I would not be surprised if it did; but it's</p> <p>11 also possible that the effect of the -- the</p> <p>12 potential negative effect of the inactive</p> <p>13 form would be, you know, minor and not of</p> <p>14 concern; so, again, an empirical question.</p> <p>15 Q. And is this something that one of</p> <p>16 ordinary skill would have understood prior to</p> <p>17 1996?</p> <p>18 MR. CWIK: Objection, form,</p> <p>19 foundation, hypothetical.</p> <p>20 A. I believe so.</p> <p>21 Q. And just so I get your answer</p> <p>22 clear, your response is, your position is</p> <p>23 that, that you would couch it by saying that</p> <p>24 I would not be surprised if it had the same</p> <p>25 level of efficacy, that is, by doubling up</p>	<p style="text-align: right;">112</p> <p>1 Miller</p> <p>2 health of the individual.</p> <p>3 Q. And you're, just to be clear,</p> <p>4 you're saying that the, biologically, it</p> <p>5 would not, they would not be biologically</p> <p>6 significant to the point where it would</p> <p>7 affect the health of the individual?</p> <p>8 MR. CWIK: Objection, form.</p> <p>9 A. Well, I wouldn't be surprised if</p> <p>10 they weren't --</p> <p>11 Q. Okay.</p> <p>12 A. -- okay? But I also would want to</p> <p>13 know if, you know, there were actual</p> <p>14 biologically significant effects. And I</p> <p>15 wouldn't be surprised if there were, because</p> <p>16 there's a theoretical basis for it.</p> <p>17 Q. Okay. On the one hand, I just want</p> <p>18 to understand, you're saying that you</p> <p>19 wouldn't be surprised if they had the same</p> <p>20 efficacy, but on the other hand, you're</p> <p>21 saying you wouldn't be surprised if they</p> <p>22 don't have the same efficacy?</p> <p>23 A. That's correct. That's correct,</p> <p>24 because I'm a scientist. You know, there's a</p> <p>25 theoretical concern --</p>
<p style="text-align: right;">111</p> <p>1 Miller</p> <p>2 the racemic versus the single isomer; but</p> <p>3 it's also possible that the effect of, the</p> <p>4 potential negative effect of the inactive</p> <p>5 form would present minor, minor concern --</p> <p>6 MR. PARKER: Well, let me back up</p> <p>7 again.</p> <p>8 Q. Okay. So what you're saying is</p> <p>9 that, that you would be surprised if it had</p> <p>10 the same efficacy, but it's possible that the</p> <p>11 effects of the, the potential negative effect</p> <p>12 of the inactive form could present a minor</p> <p>13 concern or not of concern, is that fair? And</p> <p>14 you may want to have to repeat that, because</p> <p>15 there's a lot of negatives in there.</p> <p>16 MR. CWIK: Objection to form.</p> <p>17 A. I agreed essentially, except at the</p> <p>18 end about the minor. I wouldn't -- there</p> <p>19 could be, you know -- you know, more</p> <p>20 significant effects than just minor.</p> <p>21 If we're talking just about minor</p> <p>22 or no effects, then there would be no</p> <p>23 concern. The issue is whether or not, at</p> <p>24 those doses, those negative effects become</p> <p>25 biologically significant and might affect the</p>	<p style="text-align: right;">113</p> <p>1 Miller</p> <p>2 Q. Right?</p> <p>3 A. -- which may or may not be</p> <p>4 biologically important. So if we did the</p> <p>5 studies, I wouldn't be surprised if the study</p> <p>6 went one way, which might be that there is no</p> <p>7 concern, biological, it's not significant.</p> <p>8 And I wouldn't be surprised if we found that</p> <p>9 it was biologically significant. That's how</p> <p>10 we think.</p> <p>11 Q. And is that basically how, was that</p> <p>12 the view amongst those of ordinary skill in</p> <p>13 the art prior to 1996?</p> <p>14 MR. CWIK: Objection to form,</p> <p>15 foundation .</p> <p>16 A. Well, in this case I could envision</p> <p>17 some people saying, you know, using their</p> <p>18 understanding of the area and saying, oh,</p> <p>19 this isn't a problem and not being concerned</p> <p>20 with it. And I can see others who might say,</p> <p>21 no, no, wait a minute. We should be</p> <p>22 concerned with this. And the reason I can</p> <p>23 say the latter is that there were actual</p> <p>24 published statements along those lines at the</p> <p>25 time.</p>

<p style="text-align: right;">114</p> <p>1 Miller</p> <p>2 Q. So, again, just to break it down,</p> <p>3 so that those that would say it isn't a</p> <p>4 problem, not being concerned, those are the</p> <p>5 folks that would, in your mind, say that it</p> <p>6 would have the same efficacy --</p> <p>7 MR. CWIK: Objection, form,</p> <p>8 foundation.</p> <p>9 Q. -- versus those that would say, no,</p> <p>10 it won't have the same efficacy, because it's</p> <p>11 going to cause these other problems?</p> <p>12 MR. CWIK: Objection, form,</p> <p>13 foundation.</p> <p>14 Q. If you could help me distinguish</p> <p>15 between the two.</p> <p>16 A. There could be sort of -- there are</p> <p>17 different aspects of this. It's fairly</p> <p>18 complex, as you're obviously intimating here.</p> <p>19 The -- let's break it down a little</p> <p>20 bit further.</p> <p>21 Somebody might not be concerned, if</p> <p>22 it's simply about competitive inhibition,</p> <p>23 because they may say, well, yeah, there is</p> <p>24 some competitive inhibition between the</p> <p>25 active and inactive form for absorption, but</p>	<p style="text-align: right;">116</p> <p>1 Miller</p> <p>2 Let me back up. Let me back up.</p> <p>3 Q. So essentially, if you double the</p> <p>4 content of the 5-MTHF, relative to the</p> <p>5 6-MTHF, there are those who are skilled in</p> <p>6 the art that would accept, that would expect</p> <p>7 similar potency, efficacy, and there are</p> <p>8 those that would not expect similar potency</p> <p>9 or efficacy, right?</p> <p>10 MR. CWIK: Objection to form.</p> <p>11 A. I think we can say that, because</p> <p>12 the latter group, there were published</p> <p>13 concerns suggesting that it might be better</p> <p>14 to give the pure active form.</p> <p>15 Q. And you, as an experienced expert,</p> <p>16 do you see any issues with, say, for example,</p> <p>17 physicians administering 5-MTHF double the</p> <p>18 amount relative to what they would have</p> <p>19 normally given a patient with (6S)-MTHF, if</p> <p>20 they wanted to save money?</p> <p>21 MR. CWIK: Objection to form,</p> <p>22 foundation.</p> <p>23 A. I can't say one way or the other,</p> <p>24 because I don't know the answer to the, to</p> <p>25 the question of whether or not the negative</p>
<p style="text-align: right;">115</p> <p>1 Miller</p> <p>2 at the doses we are giving plenty of the</p> <p>3 active form gets in, it's not a problem, you</p> <p>4 have the effect. That would be one concern</p> <p>5 that some might say, that's important, and</p> <p>6 some might say it's not important.</p> <p>7 The second would be, if the</p> <p>8 inactive, the so-called inactive inert form</p> <p>9 actually gets into the body, into cells and</p> <p>10 then might actually be inhibiting reactions.</p> <p>11 That, again, that would be a different</p> <p>12 question. That would be more concerning, if</p> <p>13 it was occurring.</p> <p>14 But, again, you might have people</p> <p>15 saying, oh, no, we don't think that's</p> <p>16 important and others suggesting that it is.</p> <p>17 Q. So, then, if one of ordinary skill,</p> <p>18 so assume for a second the 5-MTHF, the</p> <p>19 racemic, was less expensive, and the</p> <p>20 (6S)-MTHF is obviously more money. So, and</p> <p>21 when you're administering to a patient, you</p> <p>22 want to give them a certain dose of the</p> <p>23 active form, so on the one hand, you could</p> <p>24 have, if they were --</p> <p>25 MR. PARKER: Strike that.</p>	<p style="text-align: right;">117</p> <p>1 Miller</p> <p>2 effects are important.</p> <p>3 Q. Okay.</p> <p>4 A. But -- but I -- I would say that I</p> <p>5 could see a physician giving the racemic</p> <p>6 mixture.</p> <p>7 Q. Okay.</p> <p>8 MR. PARKER: So with that, why</p> <p>9 don't we -- it's 12:30, we should break</p> <p>10 for lunch. I probably have couple</p> <p>11 hours, at most.</p> <p>12 (Discussion off the record.)</p> <p>13 (Lunch recess taken at 12:31 p.m.)</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>

foundation.

8 A. You are -- yes, I believe this is
9 correct, that they were claiming that there
10 were genetic differences among individuals in
11 the metabolism of folic acid that they were
12 claiming supported the use of the methyl
13 folate instead.

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<p style="text-align: right;">130</p> <p>Q. Now, let me ask you this. Would you agree with the following statement: "An important limiting aspect of reduced and methylated folates is that their stability is limited and cold storage conditions are required to avoid the formation of related impurities, since they are highly active molecules"?</p> <p>MR. CWIK: Objection, form, foundation.</p> <p>A. I would agree that's the general view of those comments by the experts in the area.</p> <p>Q. And that was -- and this was prior to 1996?</p>	<p style="text-align: right;">132</p> <p>Q. Dr. Miller, I'm going to place before you what's been marked as JM-17, although it has another exhibit sticker with JM-2 that was referring back to the, your prior deposition, so just ignore that.</p> <p>This is JM-17. This is your rebuttal expert report in the action involving the ITC. I just want to ask you a few questions here. Your understanding.</p> <p>You need a minute to peruse the report?</p> <p>A. Yeah.</p> <p>Q. Just let me know when you are ready.</p> <p>A. Okay.</p> <p>Q. Okay. Now, if you recall, and correct me if I'm wrong, that the gist of this report was to basically, it was your</p>
	<p style="text-align: right;">133</p> <p>Miller</p> <p>explanation as to, as to whether certain things were not covered, for example, by the '040 patent, certain activities, and also certain things and activities that were not covered by, let's say, the Bailey patents, correct?</p> <p>A. That's correct.</p> <p>MR. CWIK: Objection, objection, form.</p> <p>Q. Okay. And let me just go with the -- let's stay with the '040 patent, where the caption is, "There Are Substantial Uses For (6S)-5-MTHF Not Described By the Claims of the '040 Patent," correct?</p> <p>A. Yes.</p> <p>Q. And your reference to the '040 patent should be in your pile. I just want to let you know, for your ready reference, it's there.</p> <p>A. Yep.</p> <p>Q. Now, in your report on page, I guess it's paragraph 10 in your report, you basically just -- I know you were summarizing, you summarized -- well, you</p>

<p style="text-align: right;">134</p> <p>1 Miller</p> <p>2 noted that the claim elements of the '040</p> <p>3 patent include a decrease in homocystine</p> <p>4 levels in the human body.</p> <p>5 Do you see that?</p> <p>6 A. Uh-huh.</p> <p>7 Q. Then you go on to talk about</p> <p>8 preventing and treating diseases associated</p> <p>9 with decreased levels, homocystine levels.</p> <p>10 And then you go into preventing neural tube</p> <p>11 deficiencies associated with increased</p> <p>12 homocystine levels, right?</p> <p>13 A. Yes.</p> <p>14 Q. And that was your interpretation of</p> <p>15 some of the elements of the claim?</p> <p>16 A. Yes.</p> <p>17 Q. Now, you go on, and you mentioned</p> <p>18 that, on paragraph 11, (6S)-5-MTHF may be</p> <p>19 used to provide folate to a human subject in</p> <p>20 need of folate, and then you say, "See</p> <p>21 example in my initial report."</p> <p>22 Then you go on and you say,</p> <p>23 "Accordingly, (6S)-5-MTHF is useful for,</p> <p>24 among other uses, ameliorating folate</p> <p>25 deficiencies known to be associated with poor</p>	<p style="text-align: right;">136</p> <p>1 Miller</p> <p>2 essentially explaining that that use of</p> <p>3 (6S)-5-MTHF was not described by the claims</p> <p>4 of the '040 patent, correct?</p> <p>5 MR. CWIK: Objection, form.</p> <p>6 A. That's correct.</p> <p>7 Q. And then on the next page, on the</p> <p>8 next page, where the heading there is, "There</p> <p>9 Are Substantial Uses For (6S)-5-MTHF Not</p> <p>10 Described By the Claims of the Bailey</p> <p>11 Patent," correct?</p> <p>12 I'm sorry, do you see that? Do you</p> <p>13 see that section? That's on page 7.</p> <p>14 A. Page 7.</p> <p>15 Yes.</p> <p>16 Q. And then on page 7 you go on to</p> <p>17 describe uses that are not covered by the</p> <p>18 claims of the Bailey patents, correct?</p> <p>19 MR. CWIK: Objection, form.</p> <p>20 A. I'm not sure on page 7 --</p> <p>21 Q. Paragraph 19 --</p> <p>22 A. 19, okay.</p> <p>23 Q. -- 20 and 21.</p> <p>24 A. Yes, okay.</p> <p>25 Q. Okay. So is that a fair statement,</p>
<p style="text-align: right;">135</p> <p>1 Miller</p> <p>2 diet, alcoholism, malabsorptive disorders,</p> <p>3 megaloblastic anemia, soreness and</p> <p>4 ulcerations of the tongue and oral mucosa and</p> <p>5 depression."</p> <p>6 Do you see that?</p> <p>7 A. Yes, I do.</p> <p>8 Q. So in this report you were</p> <p>9 explaining that these uses of (6S)-5-MTHF</p> <p>10 were not described by the claims of the '040</p> <p>11 patent, correct?</p> <p>12 MR. CWIK: Objection to form.</p> <p>13 A. Correct.</p> <p>14 Q. And also, if you go to page 13, I'm</p> <p>15 sorry, I'm sorry, paragraph 13, you're also</p> <p>16 mentioning, you also talk about the Avery</p> <p>17 Sports & Nutrition Almanac, which, according</p> <p>18 to your paragraph 13, "Which recommends</p> <p>19 folate supplementation as a way to ensure</p> <p>20 adequate folate intake, if one's diet does</p> <p>21 not include sufficient natural sources of</p> <p>22 folate," and you go on to give examples.</p> <p>23 Do you see that?</p> <p>24 A. Yes, I do.</p> <p>25 Q. And on paragraph 13 you were</p>	<p style="text-align: right;">137</p> <p>1 Miller</p> <p>2 then, with respect to paragraphs 19, 20, 21,</p> <p>3 that you were basically describing uses of</p> <p>4 (6S)-5-MTHF not described by the claims of</p> <p>5 the Bailey patent?</p> <p>6 MR. CWIK: Objection, form.</p> <p>7 A. I believe so, yes.</p> <p>8 Q. Now, if you can take a look at the</p> <p>9 '915 patent?</p> <p>10 A. Okay.</p> <p>11 Q. Now, if you look at claim 37. You</p> <p>12 see that's a method of increasing a human's</p> <p>13 dietary intake of folate?</p> <p>14 A. Yes.</p> <p>15 Q. And you are familiar with this</p> <p>16 patent, correct?</p> <p>17 A. Yes.</p> <p>18 Q. So this claim is essentially</p> <p>19 directed to folate supplementation, correct?</p> <p>20 MR. CWIK: Objection to form,</p> <p>21 foundation.</p> <p>22 A. Yes.</p> <p>23 Q. Or, let me rephrase it this way:</p> <p>24 It's directed to folate supplementation as a</p> <p>25 way to ensure adequate folate intake,</p>

<p style="text-align: right;">138</p> <p>1 Miller</p> <p>2 correct?</p> <p>3 MR. CWIK: Same objection.</p> <p>4 A. Sure, yes.</p> <p>5 Q. And that would include if one's</p> <p>6 diet does not include sufficient sources of</p> <p>7 folate, right?</p> <p>8 MR. CWIK: Same objection.</p> <p>9 A. Yes.</p> <p>10 Q. Okay. And as far as the -- and</p> <p>11 that particular use that I just described is</p> <p>12 the same use that you opined and indicated</p> <p>13 that it was not covered by the '040 patent,</p> <p>14 correct?</p> <p>15 MR. CWIK: Same objection, form.</p> <p>16 A. I think what was being talked about</p> <p>17 here was the difference between supplying the</p> <p>18 (6S)-5-MTHF alone versus in combination with</p> <p>19 other vitamins. So if you look at section,</p> <p>20 or claim 37, I think the reading here is it's</p> <p>21 the preparation comprising of vitamin other</p> <p>22 than ascorbic acid, meaning that it would</p> <p>23 include the reduced folate form that they're</p> <p>24 using as well as another vitamin or more or</p> <p>25 several vitamins, but none of which being</p>	<p style="text-align: right;">140</p>
<p style="text-align: right;">139</p> <p>1 Miller</p> <p>2 ascorbic acids.</p> <p>3 Q. And they refer to them as essential</p> <p>4 nutrients, right, in the claim?</p> <p>5 MR. CWIK: Objection, form.</p> <p>6 A. Yes.</p> <p>7 Q. So with respect to the '040 patent,</p> <p>8 you indicated that ameliorating --</p> <p>9 MR. PARKER: Well, let me back up.</p> <p>10 A. With respect to the '040 patent,</p> <p>11 you opine that folic supplementation, as a</p> <p>12 way to ensure adequate folate intake, was not</p> <p>13 included in the '040 patent, because it was</p> <p>14 directed to lowering homocystine, correct?</p> <p>15 MR. CWIK: Objection, form.</p> <p>16 A. Yes, correct.</p> <p>17 Q. And the '915 patent is not</p> <p>18 necessarily directed to lowering homocystine,</p> <p>19 correct?</p> <p>20 MR. CWIK: Objection, form.</p> <p>21 A. That patent is more generally about</p> <p>22 improving folate status.</p> <p>23 Q. And if you look at, I believe I may</p>	<p style="text-align: right;">141</p> <p>1 Miller</p> <p>2 A. Certainly, yeah.</p> <p>3 Q. Now, just going back to Serfontein</p> <p>4 now. Serfontein, in your opinion, basically</p> <p>5 discloses, to a person of ordinary skill in</p> <p>6 the art, eight reduced folates, eight active</p> <p>7 folates?</p> <p>8 A. Yes, I believe so. That's</p> <p>9 affirmative.</p> <p>10 Q. Now, of those eight, now, the</p> <p>11 reading of Serfontein would suggest that all</p> <p>12 eight of these reduced folates that you</p> <p>13 envisaged, that you say one of ordinary skill</p> <p>14 in the art, one of ordinary skill in the art</p> <p>15 would envisage would be effective in treating</p> <p>16 or lowering homocystine, correct?</p> <p>17 A. Can you restate that for me,</p> <p>18 please?</p> <p>19 Q. All right. Let me back up.</p> <p>20 The Serfontein -- you can put</p> <p>21 Serfontein in front of you, if you have to.</p> <p>22 The Serfontein reference discloses</p> <p>23 compositions for lowering homocystine, right?</p> <p>24 A. Correct.</p> <p>25 Q. And so it's essentially, it's</p>

<p style="text-align: right;">142</p> <p>1 Miller</p> <p>2 directed to lowering levels of homocystine,</p> <p>3 we agreed, right?</p> <p>4 A. Yes.</p> <p>5 Q. Okay. So then, if you look at page</p> <p>6 2, I think at lines 1 through 3, and I'll</p> <p>7 quote, "The present invention relates to</p> <p>8 pharmaceutical preparations for lowering</p> <p>9 levels of homocystine or for the prophylaxis</p> <p>10 or treatment of elevated levels of</p> <p>11 homocystine in patients and for counteracting</p> <p>12 the harmful effects associated with</p> <p>13 homocystine."</p> <p>14 So does that reflect your</p> <p>15 understanding as to the nature of</p> <p>16 Serfontein's disclosure?</p> <p>17 A. Yes.</p> <p>18 (Discussion off the record.)</p> <p>19 MR. PARKER: So you can read back</p> <p>20 my last question to the witness, and his</p> <p>21 answer.</p> <p>22 (A portion of the record was read.)</p> <p>23 Q. So Serfontein is not directed to</p> <p>24 ameliorating folate deficiencies known to be</p> <p>25 associated with poor diet, correct?</p>	<p style="text-align: right;">144</p> <p>1 Miller</p> <p>2 be surprised if they would -- that they</p> <p>3 worked. We might predict that they might not</p> <p>4 work as well, based on the biochemistry, but</p> <p>5 they could be envisioned to work to lower</p> <p>6 homocystine.</p> <p>7 Q. Would the outcomes be, would it be</p> <p>8 fair to say more or less similar, but they</p> <p>9 wouldn't be, you couldn't expect --</p> <p>10 MR. PARKER: Well, let me back up.</p> <p>11 Q. Would they, would the outcomes, so</p> <p>12 you wouldn't be surprised if the outcomes</p> <p>13 were more or less similar?</p> <p>14 MR. CWIK: Objection, form.</p> <p>15 Q. And I'm talking outcome.</p> <p>16 A. Yeah, I wouldn't be surprised. I</p> <p>17 probably would predict that they wouldn't be</p> <p>18 as effective, but I wouldn't be surprised if</p> <p>19 they were.</p> <p>20 Q. As effective, but the outcome would</p> <p>21 be roughly the same?</p> <p>22 MR. CWIK: Same objection.</p> <p>23 A. The outcome might not be as robust.</p> <p>24 Q. As robust, okay.</p> <p>25 A. Yeah.</p>
<p style="text-align: right;">143</p> <p>1 Miller</p> <p>2 A. That's correct.</p> <p>3 Q. And Serfontein is not directed to</p> <p>4 folate supplementation as a way to ensure</p> <p>5 adequate folate intake, correct?</p> <p>6 A. That's correct.</p> <p>7 Q. So it's basically, essentially</p> <p>8 directed to lowering homocystine, right?</p> <p>9 A. Correct.</p> <p>10 Q. So now, so now, with respect to,</p> <p>11 let's go back to now these eight reduced</p> <p>12 folates.</p> <p>13 If -- I mean hypothetically, of</p> <p>14 those eight reduced folates that are listed</p> <p>15 in your declaration, if you were to show, if</p> <p>16 you were to have shown that the</p> <p>17 5-methyl-(6S)-tetrahydrofolic acid was</p> <p>18 effective to reduce levels of homocystine,</p> <p>19 could one of ordinary skill in the art expect</p> <p>20 that the other reduced folates would provide</p> <p>21 a similar outcome?</p> <p>22 MR. CWIK: Objection, form,</p> <p>23 foundation.</p> <p>24 A. I guess the way I would put it is I</p> <p>25 think that the experts in the area would not</p>	<p style="text-align: right;">145</p> <p>1 Miller</p> <p>2 Q. But let's -- if they were to be, if</p> <p>3 they were to have similar outcomes, would you</p> <p>4 be surprised?</p> <p>5 MR. CWIK: Same objection.</p> <p>6 Q. I'm using the word "similar." I'm</p> <p>7 not using the word "exact."</p> <p>8 A. I get it, I get it.</p> <p>9 Q. As robust.</p> <p>10 A. No, I wouldn't be surprised.</p> <p>11 Q. And so that would be true for</p> <p>12 lowering homocystine as well?</p> <p>13 I'm saying outcome, so the outcome</p> <p>14 I'm talking about is lowering homocystine.</p> <p>15 A. Yeah, that's the outcome I thought</p> <p>16 you were referring to, yes.</p> <p>17 MR. CWIK: Objection, form.</p> <p>18 Q. Okay, so we're clear.</p> <p>19 Would the same be true for</p> <p>20 improving folate status?</p> <p>21 MR. CWIK: Objection, form.</p> <p>22 A. Yes, the same answer.</p> <p>23 Q. Or prevent or treat vascular</p> <p>24 disease?</p> <p>25 MR. CWIK: Objection, form.</p>

1 Miller
2 A. The same, yeah.
3 **Q. Okay.**

1 Miller

2 (A brief recess was taken.)

3 **Q. Dr. Miller, are you familiar with**
4 **the acronym SAM?**

5 A. Yes.

6 **Q. What does that stand for?**

7 A. S-adenosylmethionine.

8 **Q. And are you familiar with the**
9 **acronym SAH?**

10 A. Yes, I am.

11 **Q. And what does that stand for?**

12 A. S-adenosylhomocysteine.

13 MR. CWIK: Objection, form.

14 **Q. And do these compounds play --**
15 **well, what role, if any, do these compounds**
16 **play in the metabolism of reduced folate?**

17 MR. CWIK: Objection.

18 **Q. Just generally, if you could say it**
19 **generally, if you could describe it**
20 **generally.**

21 MR. CWIK: Objection, form.

22 A. They are intermediates in the
23 conversion of methhionine to homocystine.
24 Particularly SAM, we call it SAM, S-A-M, is
25 an inhibitor of the enzyme

<p style="text-align: right;">154</p> <p>1 Miller</p> <p>2 methylenetetrahydrofolate reductase.</p> <p>3 So, in short, in biochemical terms,</p> <p>4 they are substrates and products in one</p> <p>5 carbon metabolism as well as allosteric</p> <p>6 effectors.</p> <p>7 Q. And are the levels of SAM and SAH</p> <p>8 and the SAM/SAH ratio, are they under, under</p> <p>9 what I would call tight control in tissues,</p> <p>10 because their increases and decreases can</p> <p>11 have serious adverse effects on reactions</p> <p>12 that use SAM as a substrate?</p> <p>13 MR. CWIK: Objection, form.</p> <p>14 A. The word "tight" is a little</p> <p>15 subjective, but, yes, their levels are under</p> <p>16 biochemical controls.</p> <p>17 Q. Your colleague used exquisite</p> <p>18 control.</p> <p>19 Is that a term?</p> <p>20 A. Yeah, exquisite is more of a</p> <p>21 qualitative rather than a quantitative term.</p> <p>22 Some of us look at these pathways as being</p> <p>23 exquisite.</p> <p>24 Q. So just so I understand, so then</p> <p>25 when methionine levels increase, let's say</p>	<p style="text-align: right;">156</p> <p>1 Miller</p> <p>2 A. Sarcosine.</p> <p>3 Q. What role does that compound play?</p> <p>4 MR. CWIK: Same objection.</p> <p>5 Q. Generally.</p> <p>6 A. I'm afraid that I'm not remembering</p> <p>7 exactly at the moment. It would be clear to</p> <p>8 me, if I saw the pathways, but...</p> <p>9 Q. So then, when methionine levels are</p> <p>10 low, the SAM levels drop, and this relieves</p> <p>11 the inhibition of MTHFR?</p> <p>12 MR. CWIK: Same objection.</p> <p>13 A. Yes.</p> <p>14 Q. And then, therefore, more</p> <p>15 5-methyl-THF is produced, which allows the</p> <p>16 synthesis of methionine and the restoration</p> <p>17 of SAM; is that accurate?</p> <p>18 MR. CWIK: Same objection.</p> <p>19 A. Yes.</p> <p>20 Q. And at the same time the</p> <p>21 5-methyl-THF is an inhibitor of the GNMT and</p> <p>22 prevents the removal of SAM via the GNMT</p> <p>23 reaction?</p> <p>24 MR. CWIK: Same objection.</p> <p>25 A. That's correct.</p>
<p style="text-align: right;">155</p> <p>1 Miller</p> <p>2 after eating a protein-containing meal,</p> <p>3 liver, SAM or AdoMet increases; is that true?</p> <p>4 MR. CWIK: Objection to form.</p> <p>5 A. Yes.</p> <p>6 MR. CWIK: Foundation.</p> <p>7 Q. And the extra SAM is removed by</p> <p>8 methylating glycine to sarcosine via the GNMT</p> <p>9 enzyme?</p> <p>10 MR. CWIK: Same objection.</p> <p>11 A. Some of the SAM is removed in that</p> <p>12 manner, yes.</p> <p>13 Q. Is sarcosine -- how do you</p> <p>14 pronounce it?</p> <p>15 A. Sarcosine.</p> <p>16 Q. Sarcosine, is it needed?</p> <p>17 MR. CWIK: Same objection.</p> <p>18 A. Is it needed?</p> <p>19 Q. Or is it needed to remove, is it</p> <p>20 needed with respect to removing the SAM by</p> <p>21 methylating the glycine to sarcosine?</p> <p>22 MR. CWIK: Same objection.</p> <p>23 Q. Well, let me ask you this, then:</p> <p>24 So what role does the sarcosine -- I'm sorry,</p> <p>25 am I pronouncing it right?</p>	<p style="text-align: right;">157</p> <p>1 Miller</p> <p>2 Q. And so when you provide large</p> <p>3 amounts of 5-methyl-THF directly, are you</p> <p>4 effectively bypassing this exquisite control?</p> <p>5 MR. CWIK: Same objection.</p> <p>6 A. No, I wouldn't say that.</p> <p>7 Q. How would you --</p> <p>8 A. Well, the exquisite control is,</p> <p>9 there is several aspects to it. So what you</p> <p>10 are bypassing is, if there is an inhibition</p> <p>11 of methylenetetrahydrofolate reductase, for</p> <p>12 whatever reason, it could be a genetic</p> <p>13 defect, it could be some inhibitor, that if</p> <p>14 you give 5-methyl-THF, yes, you would be</p> <p>15 bypassing that aspect of the control</p> <p>16 mechanisms.</p> <p>17 Q. Well, would the net effect in this</p> <p>18 regard would be an increase in methionine in</p> <p>19 SAM?</p> <p>20 MR. CWIK: Same objection.</p> <p>21 A. Yes, as well as a reduction in</p> <p>22 homocystine.</p>

Q. What about the -- well, if you use

159

1 **Miller**
2 **a very, a megadose, a high dose of**
3 **5-methyl-THF, what are the potential adverse**
4 **effects, if any, of that?**

5 MR. CWIK: Same objection.

6 A. I'm not envisioning any theoretical
7 effects at the moment.

8 I would suggest that, if you ask me
9 which would I be more concerned with, it
10 would be the excess folic acid versus excess
11 methyltetrahydrofolate.

12 **Q. Right, but having all of this, this**
13 **high dose of 5-methyl-THF will essentially**
14 **bypass all of this exquisite control, right?**

15 A. No, it doesn't bypass all the
16 exquisite control. It will increase SAM
17 levels, SAM will still have other effects.
18 There will be SAH levels that have, also have
19 allosteric control effects. So it really
20 depends on what aspect of one carbon
21 metabolism you're actually talking about.

?

- 6 **Q. Okay, so basically, so the premise**
7 **is that 5-methyltetrahydrofolate bypasses the**
8 **enzyme methylenetetrahydrofolate reductase,**
9 **which is the step that produces 5-MTHF?**
 A. Correct.

13 **Q. Dr. Miller, just going back, I just**
14 **want to clarify, with respect to the**
15 **Serfontein, Serfontein does not mention or**
16 **identify any particular reduced folate,**
17 **correct?**

1 A. That's correct.

4 **Q. And with respect to the dosage**
5 **forms that he identifies, he does not**
6 **explicitly identify a preference for a**
7 **particular reduced folate?**

A. That's correct.

13 **Q. And just to be clear, when I said,**
14 **he identifies, I meant Serfontein identifies.**

MR. PARKER: No further questions.

<p style="text-align: right;">174</p> <p>1</p> <p>2</p> <p>3 C E R T I F I C A T E</p> <p>4 STATE OF NEW JERSEY)</p> <p>5 : ss.</p> <p>6 COUNTY OF MIDDLESEX)</p> <p>7</p> <p>8 I, Jennifer Ocampo-Guzman, a Notary</p> <p>9 Public within and for the State of New</p> <p>10 Jersey, do hereby certify:</p> <p>11 That JOSHUA WILLIAM MILLER,</p> <p>12 Ph.D., the witness whose deposition is</p> <p>13 hereinbefore set forth, was duly sworn and</p> <p>14 that such deposition is a true record of the</p> <p>15 testimony given by the witness.</p> <p>16 I further certify that I am not</p> <p>17 related to any of the parties to this action</p> <p>18 by blood or marriage, and that I am in no</p> <p>19 way interested in the outcome of this</p> <p>20 matter.</p> <p>21 IN WITNESS WHEREOF, I have</p> <p>22 hereunto set my hand this 10th day of</p> <p>23 September 2013.</p> <p>24</p> <p>25 JENNIFER OCAMPO-GUZMAN, CRR, CLR</p>	<p style="text-align: right;">176</p> <p>1</p> <p>2 (Continued):</p> <p>3 ----- EXHIBITS -----</p> <p>4 JM FOR I.D.</p> <p>5</p> <p>6 Exhibit 12, Document entitled,</p> <p>7 "Supplementary material-list of</p> <p>8 pharmaceutically acceptable acids"78</p> <p>9</p> <p>10 Exhibit 13, Decision,</p> <p>11 Case IPR2013-00119.....91</p> <p>12 Exhibit 14, Document entitled,</p> <p>13 "Vitamin B-12, vitamin B-6, and folate</p> <p>14 nutritional status in men with</p> <p>15 hyperhomocysteinemia".....104</p> <p>16</p> <p>17 Exhibit 15, Document entitled,</p> <p>18 "Enhancement of recovery from</p> <p>19 psychiatric illness by methylfolate"...118</p> <p>20</p> <p>21 Exhibit 16, Errata sheet.....123</p> <p>22</p> <p>23 Exhibit 17, Rebuttal Expert</p> <p>24 Report of Joshua W. Miller, Ph.D.....132</p> <p>25</p>
<p style="text-align: right;">175</p> <p>1</p> <p>2 ----- I N D E X -----</p> <p>3 WITNESS EXAMINATION BY PAGE</p> <p>4 JOSHUA W. MILLER MR. PARKER 4</p> <p>5 MR. CWIK 170</p> <p>6 ----- EXHIBITS -----</p> <p>7 JM FOR I.D.</p> <p>8 Exhibit 1, Document entitled,</p> <p>9 "Nomenclature and symbols for</p> <p>10 folic acid and related compounds".....24</p> <p>11 Exhibit 2, Copy of U.S. Patent No.</p> <p>12 5,194,611.....34</p> <p>13 Exhibit 3, Copy of European Patent</p> <p>14 Application 0,388,827.....40</p> <p>15 Exhibit 4, Copy of European Patent</p> <p>16 Application 0,627,435 A1.....44</p> <p>17 Exhibit 5, Copy of U.S. Patent No.</p> <p>18 6,011,040.....49</p> <p>19 Exhibit 6, Copy of U.S. Patent No.</p> <p>20 5,997,915.....53</p> <p>21 Exhibit 7, Copy of U.S. Patent No.</p> <p>22 6,673,381.....53</p> <p>23 Exhibit 8, Copy of U.S. Patent No.</p> <p>24 7,172,778.....53</p> <p>25 Exhibit 9, Declaration of Joshua W.</p> <p>Miller, Ph.D., ['040 patent].....57</p> <p>Exhibit 10, Declaration of Joshua W.</p> <p>Miller, Ph.D., ['778 patent].....57</p> <p>Exhibit 11, Copy of European Patent</p> <p>Application 0,595,005 A1.....63</p>	<p style="text-align: right;">177</p> <p>1</p> <p>2</p> <p>3 I N S T R U C T I O N S T O W I T N E S S</p> <p>4</p> <p>5 Please read your deposition over</p> <p>6 carefully and make any necessary</p> <p>7 corrections. You should state the reason</p> <p>8 in the appropriate space on the errata</p> <p>9 sheet for any corrections that are made.</p> <p>10 After doing so, please sign the</p> <p>11 errata sheet and date it.</p> <p>12 You are signing same subject to the</p> <p>13 changes you have noted on the errata</p> <p>14 sheet, which will be attached to your</p> <p>15 deposition.</p> <p>16 It is imperative that you return</p> <p>17 the original errata sheet to the</p> <p>18 deposing attorney within thirty (30)</p> <p>19 days of receipt of the deposition</p> <p>20 transcript by you. If you fail to do so,</p> <p>21 the deposition transcript may be deemed</p> <p>22 to be accurate and may be used in court.</p> <p>23</p> <p>24</p> <p>25</p>

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