

UNITED STATES INTERNATIONAL TRADE COMMISSION

WASHINGTON D.C.

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IN THE MATTER OF:

INV. NO. 337-TA-857

REDUCED FOLATE
NUTRACEUTICAL PRODUCTS
AND L-METHYLFOLATE RAW
INGREDIENTS USED THEREIN.

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CONFIDENTIAL BUSINESS INFORMATION

SUBJECT TO THE PROTECTIVE ORDER

May 6, 2013

9:00 a.m.

Videotaped Deposition of JOSHUA MILLER,
taken by the Complainants, at the Hyatt Regency,
Two Albany Street, New Brunswick, New Jersey,
before David Levy, CSR, RPR, CLR, a Notary Public
of the State of New York.

Job No: 29966

MERCK EXHIBIT
REPLACEMENT 2063
Gnosis v Merck & Cie
IPR2013-00117

<p style="text-align: right;">2</p> <p>1</p> <p>2 A P P E A R A N C E S:</p> <p>3</p> <p>4 O N B E H A L F O F T H E C O M P L A I N A N T S:</p> <p>5</p> <p>6 ALSTON & BIRD, LLP</p> <p>7 90 Park Avenue, 15th Floor</p> <p>8 New York, New York 10016</p> <p>9 BY: THOMAS J. PARKER, ESQ.</p> <p>10 thomas.parker@alston.com</p> <p>11 HAI'OU QIN, Ph.D., ESQ.</p> <p>12 haiou.qin@alston.com</p> <p>13</p> <p>14</p> <p>15 O N B E H A L F O F T H E R E S P O N D E N T S</p> <p>16 MACOVEN PHARMACEUTICALS</p> <p>17 AND PHARMACEUTICALS:</p> <p>18</p> <p>19 JONES WALKER</p> <p>20 8555 United Plaza Boulevard</p> <p>21 Baton Rouge, Louisiana 70809</p> <p>22 BY: MICAH J. FINCHER, ESQ.</p> <p>23 mfincher@joneswalker.com</p> <p>24</p> <p>25</p>	<p style="text-align: right;">4</p> <p>1 Miller - confidential</p> <p>2 VIDEOGRAPHER: Good morning. Here</p> <p>3 begins video recording number one in the deposition</p> <p>4 of Dr. Joshua Miller, taken by the complainants in</p> <p>5 re, Reduced Folate Nutraceutical Products and</p> <p>6 L-methylfolate Raw Ingredients Used Therein,</p> <p>7 investigation number 337 P.A. 857 in the United</p> <p>8 States International Trade Commission, Washington,</p> <p>9 D.C., before the Hon. Theodore R. Essex,</p> <p>10 administrative law judge.</p> <p>11 This deposition is being held at the</p> <p>12 Hyatt Regency, 2 Albany Street, New Brunswick, New</p> <p>13 Jersey, 08901, in conference room J and K, on</p> <p>14 Monday, May 6th, 2013, at approximately 9 o'clock.</p> <p>15 My name is Howard Brodsky, in</p> <p>16 association with the firm of David Feldman</p> <p>17 Worldwide, Inc., and I'm the legal video</p> <p>18 specialist. The court reporter is David Levy, in</p> <p>19 association with David Feldman Worldwide.</p> <p>20 Will counsel please state their</p> <p>21 appearance for the record.</p> <p>22 MR. PARKER: Tom Parker for the law</p> <p>23 firm of Alston & Bird, representing complainants in</p> <p>24 this action.</p> <p>25 MS. QIN: Hai'ou Qin, Alston & Bird,</p>
<p style="text-align: right;">3</p> <p>1</p> <p>2 A P P E A R A N C E S (Cont'd):</p> <p>3</p> <p>4 O N B E H A L F O F T H E G N O S I S P A R T I E S:</p> <p>5 HUSCH BLACKWELL LLP, LLP</p> <p>6 120 South Riverside Plaza, Suite 2200</p> <p>7 Chicago, Illinois 60606</p> <p>8 BY: JOSEPH E. CWIK, ESQ.</p> <p>9 joseph.cwik@huschblackwell.com</p> <p>10</p> <p>11 and</p> <p>12 AMIN TALATI</p> <p>13 55 West Monroe Street, Suite 3400</p> <p>14 Chicago, Illinois 60603</p> <p>15 BY: JONATHAN J. KRIT, ESQ.</p> <p>16 jonathan@amintalati.com</p> <p>17</p> <p>18</p> <p>19</p> <p>20 A L S O P R E S E N T:</p> <p>21 HOWARD BRODSKY, Videographer</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p style="text-align: right;">5</p> <p>1 Miller - confidential</p> <p>2 for the complainants.</p> <p>3 MR. CWIK: My name is Joe Cwik with</p> <p>4 the law firm of Husch Blackwell. I'm here for</p> <p>5 Gnosis USA, Gnosis SpA and Gnosis Bioresearch SA.</p> <p>6 MR. KRIT: Jonathan Krit with the law</p> <p>7 firm of Amin Talati. I'm also with the</p> <p>8 Respondents.</p> <p>9 MR. FINCHER: Micah Fincher with the</p> <p>10 law firm of Jones Walker, representing Macoven</p> <p>11 Pharmaceuticals, LLC and Viva Pharmaceuticals, Inc.</p> <p>12 VIDEOGRAPHER: Will the court reporter</p> <p>13 please swear in the witness.</p> <p>14 J O S H U A M I L L E R , having been duly</p> <p>15 sworn by the Notary Public, was examined</p> <p>16 and testified as follows:</p> <p>17 EXAMINATION BY</p> <p>18 MR. PARKER:</p> <p>19 Q. Good morning, Dr. Miller. If you</p> <p>20 could, state your full name and address for the</p> <p>21 record, please.</p> <p>22 A. Joshua William Miller, 603 Route 518,</p> <p>23 Skillman, New Jersey 08558.</p> <p>24 Q. Now, Dr. Miller, have you ever been</p> <p>25 deposed before?</p>

<p>6</p> <p>1 Miller - confidential</p> <p>2 A. No.</p> <p>3</p> <p>21 So with that, let me just begin. So,</p> <p>22 Dr. Miller, you are an expert that's been retained</p> <p>23 by Gnosis in this case?</p> <p>24 A. Yes.</p> <p>25 Q. Are you also an expert retained by a</p>	<p>8</p> <p>1 Miller - confidential</p> <p>2 A. Um -- I actually have not been</p> <p>3 compensated as of yet.</p> <p>4 Q. Have you submitted any invoices?</p> <p>5 A. No.</p> <p>6 Q. Do you intend to at some point in</p> <p>7 time?</p> <p>8 A. Yes.</p> <p>9 Q. Now, you've submitted an expert report</p> <p>10 in this case, correct?</p> <p>11 A. That's correct.</p> <p>12 Q. And you've also submitted a</p> <p>13 declaration in connection with the proceeding</p> <p>14 before the United States Patent and Trademark</p> <p>15 Office, is that correct?</p> <p>16 A. That's correct.</p> <p>17 Q. And are you aware that the proceeding</p> <p>18 is known by the lawyers as an interparties review?</p> <p>19 A. An interparties review, I'm not</p> <p>20 familiar with that phrase.</p> <p>21 Q. Well, let me ask you this:</p> <p>22 What is your understanding with</p> <p>23 respect to the proceeding in which you've submitted</p> <p>24 a declaration to the Patent Office?</p> <p>25 A. That that will be reviewed by the --</p>
<p>7</p> <p>1 Miller - confidential</p> <p>2 company called Macoven?</p> <p>3 A. That's what I'm told by Mr. Cwik.</p> <p>4 Q. So you are an expert also retained</p> <p>5 on -- I'm sorry, you are an expert retained by</p> <p>6 Macoven as well?</p> <p>7 A. I don't believe I'm being paid by</p> <p>8 Macoven for this. So I'm -- I guess, my testimony</p> <p>9 is mainly for Gnosis.</p> <p>10 Q. Well, you understand that Macoven and</p> <p>11 Viva have retained a Dr. Shane as an expert as</p> <p>12 well.</p> <p>13 A. Yes, I do.</p> <p>14 Q. Is Macoven or is Viva, any of those</p> <p>15 entities, are they compensating you for your time,</p> <p>16 participating in this investigation?</p> <p>17 A. Just Gnosis.</p> <p>18 Q. Now, what is your hourly rate for</p> <p>19 providing services of the type that you're</p> <p>20 providing in this case?</p> <p>21 A. It's \$450 per hour.</p> <p>22 Q. Any idea of how much you've been</p> <p>23 compensated to date?</p> <p>24 A. No, actually.</p> <p>25 Q. Approximately?</p>	<p>9</p> <p>1 Miller - confidential</p> <p>2 by the judge and the lawyers on both sides and that</p> <p>3 my testimony will be used for judgments in this</p> <p>4 case.</p> <p>5 Q. Now, is it your understanding that the</p> <p>6 patent involved in the proceeding before the United</p> <p>7 States Patent and Trademark Office in which you</p> <p>8 submitted a declaration are the same patents that</p> <p>9 are also at issue in this case, this investigation?</p> <p>10 A. Yes.</p> <p>11 Q. Now, with respect to declaration you</p> <p>12 submitted to the United States Patent and Trademark</p> <p>13 Office, that was a sworn statement, was it not?</p> <p>14 A. Yes.</p> <p>15 Q. And you submitted that declaration on</p> <p>16 behalf of -- not on behalf, but you submitted that</p> <p>17 declaration in connection with the petition that</p> <p>18 was filed in the Patent Office by the Gnosis</p> <p>19 entities?</p> <p>20 A. Yes.</p> <p>21 Q. When were you first approached by</p> <p>22 anyone from Gnosis or the Gnosis attorneys seeking</p> <p>23 your participation in those proceedings before the</p> <p>24 Patent Office?</p> <p>25 A. It was in the fall of 2012. October</p>

<p>10</p> <p>1 Miller - confidential</p> <p>2 or November. I'm not sure exactly when.</p> <p>3</p>	<p>12</p> <p>1 Miller - confidential</p> <p>2 metabolites that participate in folate metabolism.</p> <p>3 Methyltetrahydrofolate is -- the active form is the</p> <p>4 6(S) isomer and it participates in folate</p> <p>5 metabolism.</p> <p>6</p>
<p>19 Q. Now, just to be clear on nomenclature,</p> <p>20 when you say methylfolate, what are you referring</p> <p>21 to?</p> <p>22 A. I'm referring to an active metabolite</p> <p>23 of folate, folate being the general term for all of</p> <p>24 the forms of folate, including the supplement form,</p> <p>25 which is folic acid, as well as all of the</p>	

<p>26</p> <p>15 Q. Now, are you familiar with any products that are sold in this, in the United States by respondent Macoven?</p> <p>16 A. Um -- only by name on a piece of paper</p> <p>17 or on a website. I have -- I have briefly looked</p> <p>18 at those, that information. But as a product that</p> <p>19 I've seen in a store or have seen people use, I</p> <p>20 have not.</p> <p>21 Q. So are you familiar with a product preferred to as VitaCirc-B?</p> <p>22 A. I think so, yes.</p>	<p>28</p> <p>1 Miller - confidential</p> <p>2 these products to get a sense of what they were.</p> <p>3 Some of that information would be in a package</p> <p>4 insert, but I did not look at the complete package</p> <p>5 inserts of the substances.</p> <p>6 Q. So you're not aware of the uses and indications for these products?</p> <p>7 A. I did briefly review to get a sense of</p> <p>8 what was said on those websites about why they are</p> <p>9 recommended to be -- for use. I do not think I'd</p> <p>10 be able to match up, off the top of my head, which</p> <p>11 use goes with which product except in general</p> <p>12 terms.</p> <p>13 Q. Well then, tell me what uses are you aware of? I understand you're not able to align a particular use with a particular product.</p> <p>14 A. Um-hum. Things like promotion of</p> <p>15 mental function. I think -- now I'm -- I'm not</p> <p>16 sure I want to say specifically something that I'm</p> <p>17 not fully remembering as being the case.</p> <p>18 Q. Would diabetic neuropathy have been included, was that one of them?</p> <p>19 A. I don't recall that.</p> <p>20 Q. What about treating dementia, like vascular dementia?</p>
<p>27</p> <p>1 Miller - confidential</p> <p>2 Q. What is your understanding of that product?</p> <p>3 A. I think the main thing is that it</p> <p>4 contains the methyltetrahydrofolate.</p> <p>5 Q. In the isomerically pure form?</p> <p>6 A. I think so. I don't -- I don't</p> <p>7 necessarily recall the -- match the name up with</p> <p>8 the -- with the ingredients.</p> <p>9 Q. Okay. And are you familiar with the product known as ALZ-NAC?</p> <p>10 A. Again, just seeing it on a page or on</p> <p>11 the website.</p> <p>12 Q. What caused you to inquire about these products? What was it that made you -- well, not made you. Let me back up.</p> <p>13 What was it that caused you to seek information, whether it was background information or specific information, about Macoven's products?</p> <p>14 A. I was provided with the materials by</p> <p>15 the -- by the lawyers.</p> <p>16 Q. Would those materials, would that be what we refer to as a package insert?</p> <p>17 A. Um -- it could be. Mainly, I glanced</p> <p>18 at the -- what was said on the website related to</p>	<p>29</p> <p>1 Miller - confidential</p> <p>2 A. Yes.</p> <p>3 Q. And with respect to the -- I think you -- promoting mental function, would that involve depression?</p> <p>4 A. Yes.</p> <p>5 Q. And schizophrenia?</p> <p>6 A. I would say or, but yes, schizophrenia</p> <p>7 as well.</p> <p>8 Q. And so with respect to the vascular dementia, was your understanding that these Macoven products contained an effective amount of the methyltetrahydrofolate for the treatment, for example, of vascular dementia?</p> <p>9 MR. CWIK: Objection to form.</p> <p>10 Foundation.</p> <p>11 A. Could you repeat the question, just so</p> <p>12 I understand?</p> <p>13 Q. Sure.</p> <p>14 MR. PARKER: Can you repeat the</p> <p>15 question?</p> <p>16 (Record read.)</p> <p>17 MR. CWIK: Same objection.</p> <p>18 A. I can only presume that they contain</p> <p>19 an appropriate amount.</p>

<p style="text-align: right;">30</p> <p>1 Miller - confidential</p> <p>2 Q. What's that based on?</p> <p>3 A. That's based on my understanding of</p> <p>4 the role of folate and methylfolate in folate</p> <p>5 metabolism, and what it would take to optimize</p> <p>6 folate metabolism, what dose would be required. Or</p> <p>7 doses.</p> <p>8 Q. Do you understand that one of the</p> <p>9 issues in this case involves -- well, let me back</p> <p>10 up.</p> <p>11 Are you familiar with the -- one of</p> <p>12 the complainants in this case is referred to as</p> <p>13 PamLab?</p> <p>14 A. Yes.</p> <p>15 Q. And you understand that PamLab also</p> <p>16 sells in the United States products that contain</p> <p>17 methyltetrahydrofolate?</p> <p>18 A. Yes.</p> <p>19 Q. And do you understand that one of the</p> <p>20 issues in this case is that -- well, let me back</p> <p>21 up.</p> <p>22 Do you understand that Macoven sells</p> <p>23 these products, for example, VitaCirc-B, as generic</p> <p>24 alternatives for PamLab products?</p> <p>25 A. I'm aware of that, yes.</p>	<p style="text-align: right;">32</p> <p>1 Miller - confidential</p> <p>2 You can answer.</p> <p>3 A. I believe so.</p> <p>4 Q. So when we're talking about</p> <p>5 therapeutic use, so if a product is</p> <p>6 pharmaceutically equivalent to the brand, then</p> <p>7 essentially, they should have the same effect in</p> <p>8 terms of therapeutic use as the brand; correct?</p> <p>9 MR. CWIK: Objection to form.</p> <p>10 Q. Let me back up. If the generic</p> <p>11 product -- and you can assume hypothetically, if</p> <p>12 the generic product is pharmaceutically equivalent</p> <p>13 to the brand, then you would expect that the</p> <p>14 generic product would have the same therapeutic</p> <p>15 effect as the brand product; correct?</p> <p>16 MR. CWIK: Objection to the form,</p> <p>17 speculation, incomplete hypothetical.</p> <p>18 You can answer.</p> <p>19 A. I would say not being an expert in</p> <p>20 pharmaceuticals or drugs specifically, my</p> <p>21 expectation would be that they would be -- have --</p> <p>22 they would be -- have the same activity.</p> <p>23 Q. Same therapeutic effect?</p> <p>24 A. Same therapeutic effect.</p> <p>25 (A pause in the proceedings.)</p>
<p style="text-align: right;">31</p> <p>1 Miller - confidential</p> <p>2 Q. And in fact, are you aware that the</p> <p>3 products, the Macoven products that are at issue in</p> <p>4 this case, are promoted by Macoven as generic</p> <p>5 alternatives to PamLab products?</p> <p>6 A. Yes.</p> <p>7 Q. Are you familiar with the phrase,</p> <p>8 "Pharmaceutically equivalent"?</p> <p>9 A. Yes.</p> <p>10 Q. What does that mean?</p> <p>11 A. It means a substance that could be</p> <p>12 replaced for another pharmaceutical that will have</p> <p>13 the same active -- activity and therapeutic</p> <p>14 response.</p> <p>15 Q. So if I had a brand product that</p> <p>16 had -- that was -- that had the ability to -- or --</p> <p>17 let me back up.</p> <p>18 So essentially, if I had a brand</p> <p>19 product that had a sufficient amount of MTHF for</p> <p>20 treating, let's say, vascular disease, then a</p> <p>21 product that's pharmaceutically equivalent to that</p> <p>22 branded product would also be, or also should</p> <p>23 contain an effective amount of 5-MTHF 6(S) for</p> <p>24 treating vascular dementia?</p> <p>25 MR. CWIK: Objection to form.</p>	<p style="text-align: right;">33</p> <p>1</p> <p>2</p> <p>3</p> <p>4</p> <p>5</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</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>

8 **Q. All right. Now, Dr. Miller, with**
9 **respect to your background, now, you don't have an**
10 **MD degree, correct?**

11 A. That's correct.

12 **Q. So you don't have a license to treat**
13 **patients, correct?**

14 A. No, I don't.

15 **Q. And so you have no experience in**
16 **treating patients with diabetic neuropathy, do you?**

17 A. I do not.

18 **Q. And do you have any experience in**
19 **treating patients with dementia?**

20 A. I do not.

21 **Q. And do you have any experience in**
22 **treating patients with any psychological disorder?**

23 A. I do not.

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Q. Do you know Steve Bailey?

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A. Yes.

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Q. Do you consider him to be an individual who has expertise in the field of folates?

A. I do.

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81	81

10 **Q. Approximately, do you know how many**
11 **enzymes are involved in folate metabolism?**

12 A. I've never bothered to count them all.
13 Could be -- it could be, certainly, more than ten.

14 **Q. Okay. I'm sorry, let me ask you this:**
15 **Would gamma glutamyl hydrolase be one**
16 **of them?**

17 A. Yes.

18 **Q. Would dihydrofolate reductase be one**
19 **of them?**

20 A. Yep.

21 **Q. Folypoly-glutamate synthase?**

22 A. Yes.

23 **Q. Serine hydroxymethyl transferase?**

24 A. Yes.

25 **Q. Methylenetetrahydrofolate reductase?**

1 **Miller - confidential**

2 A. Yes.

3 **Q. Gamma glutamyl hydrolase?**

4 A. Yes.

5 **Q. Cobalamin-dependent methionine**
6 **synthase?**

7 A. Yes.

8 **Q. Glycine cleavage enzyme?**

9 A. Yes.

10 **Q. Glutamate formiminotransferase?**

11 A. Yes.

12 **Q. Formiminotetrahydrofolate**
13 **cyclodeaminase?**

14 A. Yes.

15 **Q. Methylene tetrahydrofolate**
16 **dihydrogenase?**

17 A. Yes.

18 **Q. Methylene tetrahydrofolate**
19 **cyclohydrogenase?**

20 A. Yes.

21 **Q. Formyl tetrahydrofolate synthase?**

22 A. Yes.

23 **Q. Symethylate synthase?**

24 A. Yes.

25 **Q. Formyl tetrahydrofolate dihydrogenase?**

<p style="text-align: right;">82</p> <p>1 Miller - confidential</p> <p>2 A. Yes.</p> <p>3 Q. Phosphoribosylglycinamide formyl</p> <p>4 transferase -- how about this, GAR formyl</p> <p>5 transferase?</p> <p>6 A. Yes, that's how we know it.</p> <p>7 Q. And then there's phosphoribosylamino</p> <p>8 metazole carboxamide, which is AICAR formyl</p> <p>9 transferase?</p> <p>10 A. Yes. Um-hum.</p> <p>11 Q. 5-formyl tetrahydrofolate cycloligase?</p> <p>12 A. Cycloligase?</p> <p>13 Q. Yes.</p> <p>14 A. Yes.</p> <p>15 Q. Then we have folate/ -- I have</p> <p>16 folate/MTX transport mechanism enzymes associated</p> <p>17 with that?</p> <p>18 A. Yes.</p> <p>19 Q. And glycine methyl transferase?</p> <p>20 A. Yes.</p> <p>21 Q. Now, I mean, each folate, they have</p> <p>22 different chemical properties, correct?</p> <p>23 A. Correct.</p> <p>24 Q. And they have different physical</p> <p>25 properties, correct?</p>	<p style="text-align: right;">84</p> <p>1 Miller - confidential</p> <p>2 stomach --</p> <p>3 A. Stomach is about pH 1.</p> <p>4 Q. Let's go with pH 1.</p> <p>5 A. Um -- I can't say offhand. It's not</p> <p>6 something that I have paid attention enough to, to</p> <p>7 learn it.</p> <p>8 Q. Now, but each folate has its own</p> <p>9 spectral properties.</p> <p>10 A. Yes.</p> <p>11 Q. And some folates are more susceptible</p> <p>12 to oxidation than others at ambient temperature or</p> <p>13 elevated temperatures?</p> <p>14 A. Yes.</p> <p>15 Q. And some folates are more susceptible</p> <p>16 to oxidation than others at different pHs?</p> <p>17 A. Very likely, yes.</p> <p>18 Q. Now, also, folates would have their --</p> <p>19 their bioavailability when taken after</p> <p>20 administration would vary as well.</p> <p>21 A. Correct.</p> <p>22 Q. And just to be clear, bioavailability</p> <p>23 is the degree to which a drug or other substance</p> <p>24 becomes available to the target tissue after</p> <p>25 administration; do you agree with that?</p>
<p style="text-align: right;">83</p> <p>1 Miller - confidential</p> <p>2 A. Correct.</p> <p>3 Q. Different solubility characteristics?</p> <p>4 A. Likely.</p> <p>5 Q. Now, the solubility of folates, is</p> <p>6 that influenced at all by the polar hydrophilic</p> <p>7 character of the X carboxyl group of glutamic acid?</p> <p>8 A. The solubility?</p> <p>9 Q. Yes.</p> <p>10 A. I can't say.</p> <p>11 Q. Well, let me ask you this, though:</p> <p>12 Would the glutamyl conjugates that are</p> <p>13 added on to the folate, would they affect</p> <p>14 solubility, if you had five versus ten versus</p> <p>15 three?</p> <p>16 A. Possibly. I don't know firsthand.</p> <p>17 Q. Well, do you know whether or not</p> <p>18 long-chain polyglutamyl folates are more</p> <p>19 hydrophobic than short-chain polyglutamyl folates</p> <p>20 at low pH levels?</p> <p>21 A. What I do know at low pH levels?</p> <p>22 Q. Yes.</p> <p>23 A. I'm -- I'm -- let me think. Can you</p> <p>24 define low pH for me? What do you mean?</p> <p>25 Q. What's the gastric -- in the</p>	<p style="text-align: right;">85</p> <p>1 Miller - confidential</p> <p>2 A. That is one definition of</p> <p>3 bioavailability, yes.</p> <p>4 Q. What definition do you use?</p> <p>5 A. It depends on the -- what we're</p> <p>6 talking about, the purpose of the question -- the</p> <p>7 subject matter is. In this case, I would agree</p> <p>8 that the appropriate definition would be as you</p> <p>9 stated it.</p> <p>10 Q. Now, as far as factors that influence</p> <p>11 bioavailability of folate after administration,</p> <p>12 viability would be one of them, correct?</p> <p>13 A. Likely, yes.</p> <p>14 Q. How about dispersability?</p> <p>15 A. Yes.</p> <p>16 Q. And also their rate of absorption and</p> <p>17 their transport in metabolism?</p> <p>18 A. Yes.</p> <p>19 Q. They would -- each folate would have a</p> <p>20 different physical interaction with foot</p> <p>21 components, correct?</p> <p>22 A. Uh -- possibly. I don't -- it's not</p> <p>23 necessarily true. Some might have the same.</p> <p>24 Q. And others may have different ones?</p> <p>25 A. Yeah.</p>

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1 Miller - confidential
2 bile acids?

3 A. Possibly.

4 Q. If you look at paragraph 129 --

5 A. Of my report?

6 Q. Yes.

7 (A pause in the proceedings.)

8 A. Okay.

9 Q. And you say here in the middle, "At
10 any one of these steps, inherent differences in the
11 affinities of receptors, transporters and enzymes
12 for different forms of folate could affect the
13 relative bioavailability of folic acid and reduced
14 folates," do you see that?

15 A. Yes.

16 Q. And that's a correct statement, right?

17 A. Yes.

10 Q. And as far as that, what about their
11 interaction with the intestinal microflora, can
12 that differ?

13 A. Yeah, I would think so. In fact, the
14 intestinal microflora may take up different forms
15 of folate differently. Some -- some may prefer one
16 over the other. It's possible. I don't have any
17 data to back up that statement.

18 Q. And I'm sorry, with respect to the
19 folates, the various folates, would they differ
20 with respect to their interaction with pancreatic
21 enzymes? Could they differ?

22 A. They could. I don't have any direct
23 knowledge that they do.

24 Q. And what about with respect to, could
25 they differ with respect to their interaction with

<p>90</p> <p>23 Q. Now, in paragraph 15, you state, "In</p> <p>24 general, a limitation is inherent and in the public</p> <p>25 domain if it is the "natural result flowing from" a</p>	<p>92</p> <p>1 Miller - confidential</p> <p>2 If you can answer.</p> <p>3 A. I would suspect that not every person</p> <p>4 of ordinary skill in the art would come to that</p> <p>5 conclusion, but that I and a significant percentage</p> <p>6 of those of ordinary skill in the art would come to</p> <p>7 that conclusion.</p> <p>8 Q. Not a hundred percent, but</p> <p>9 significantly.</p> <p>10 A. Yeah.</p> <p>11 Q. A significant amount of individuals.</p> <p>12 So just to be clear, it's not -- it</p> <p>13 doesn't necessarily have to happen each and every</p> <p>14 time with respect to each person of skill in the</p> <p>15 art, right?</p> <p>16 A. Yes.</p>
<p>91</p> <p>1 Miller - confidential</p> <p>2 disclosure of the prior art reference.</p> <p>3 Do you see that?</p> <p>4 A. Yes.</p> <p>5 Q. What did you mean by "natural result</p> <p>6 flowing from"?</p> <p>7 A. That one of -- I always forget the</p> <p>8 phrase -- a person who has the ordinary skill in</p> <p>9 the art would recognize from what is said that it's</p> <p>10 referring to specific things, whether or not they</p> <p>11 are explicitly said.</p> <p>12 Q. Okay. So basically, so -- so if</p> <p>13 information is not explicitly said, a person of</p> <p>14 ordinary skill in the art would understand it to be</p> <p>15 implicitly included within the reference; is that</p> <p>16 what your understanding is of "natural result</p> <p>17 flowing from"?</p> <p>18 A. Yes, um-hum.</p> <p>19 Q. And is that something that -- your</p> <p>20 understanding, I know you're not a lawyer, is that</p> <p>21 something that happens each and every time a person</p> <p>22 of ordinary skill in the art would review that</p> <p>23 reference, they would see that implicit disclosure?</p> <p>24 MR. CWIK: Objection. Calls for legal</p> <p>25 conclusion.</p>	<p>24 (Pages 90 to 93)</p>

<p style="text-align: right;">98</p> <p>5 Q. Okay. So let me just hand you the --</p> <p>6 why don't we go with the '778 patent, which is the</p> <p>7 formulation patent. Are you familiar with that</p> <p>8 one?</p> <p>9 A. Yes.</p> <p>10 Q. All right. What was, when you read</p> <p>11 that patent, what was the problem that the</p> <p>12 inventors were trying to solve?</p> <p>13 A. Could I look at the patent itself?</p> <p>14 Q. Yes.</p> <p>15 A. Do we need a sticker?</p> <p>16 Q. No, because this has been previously</p> <p>17 marked as Complainant's Exhibit number 76.</p> <p>18 MR. CWIK: I'm going to object to</p> <p>19 form, foundation, speculation.</p> <p>20 Q. You don't have to answer 'till I give</p> <p>21 counsel a copy.</p> <p>22 (A pause in the proceedings.)</p> <p>23 Q. Okay, if you'd just let me know,</p> <p>24 Dr. Miller, when you're ready?</p> <p>25 A. I'm ready.</p>	<p style="text-align: right;">100</p> <p>1 Miller - confidential</p> <p>2 A. That's correct.</p> <p>3 Q. Okay.</p> <p>4 A. Yes. And specifically, the conditions</p> <p>5 that are stated here are "treatment and/or</p> <p>6 prevention of vascular disease and/or a female's</p> <p>7 risk of having a miscarriage and/or having a fetus</p> <p>8 with a neural tube defect, or other birth defects</p> <p>9 as listed here."</p> <p>10 Q. Now, would you also agree that one of</p> <p>11 the problems that the inventors were trying to</p> <p>12 solve was develop formulations or means in which to</p> <p>13 treat individuals who were folate deficiency with</p> <p>14 something other than folic acid?</p> <p>15 MR. CWIK: Objection, form,</p> <p>16 foundation.</p> <p>17 A. I believe so.</p> <p>18 Q. This is Dr. Shane's report, which is</p> <p>19 JM-9.</p> <p>20 EXH (Deposition Exhibit 9, report of</p> <p>21 Dr. Barry Shane, marked for identification, as of</p> <p>22 this date.)</p> <p>23 Q. Did you read Dr. Shane's report,</p> <p>24 Dr. Miller?</p> <p>25 A. Yes, I did.</p>
<p style="text-align: right;">99</p> <p>1 Miller - confidential</p> <p>2 Q. So when you read the '778 patent which</p> <p>3 is in front of you now, when you read this patent,</p> <p>4 what was the problem that the inventors were trying</p> <p>5 to solve?</p> <p>6 MR. CWIK: Objection, form,</p> <p>7 foundation, speculation.</p> <p>8 If you can answer.</p> <p>9 Q. Well, if you didn't consider it,</p> <p>10 that's fine, too.</p> <p>11 A. No, I can -- I can refer to my report.</p> <p>12 Q. Sure.</p> <p>13 A. Where I have made a statement about</p> <p>14 this.</p> <p>15 I wrote, "Like the '915 patent, the</p> <p>16 asserted claims of the '778 patent generally relate</p> <p>17 to compositions comprising one or more natural</p> <p>18 isomers of folate and a vitamin or other food</p> <p>19 substance."</p> <p>20 And then there is a picture --</p> <p>21 Q. A claim.</p> <p>22 A. -- a snapshot of one of the claims</p> <p>23 directly as written, and --</p> <p>24 Q. And just to be clear, you're reading</p> <p>25 from paragraph 64?</p>	<p style="text-align: right;">101</p> <p>1 Miller - confidential</p> <p>2 Q. Okay. Now, prior to the '95-'96 time</p> <p>3 frame, folic acid was generally considered to be</p> <p>4 relatively safe, inexpensive, bioavailable and he</p> <p>5 efficacious, correct?</p> <p>6 A. Yes, except there were expressed</p> <p>7 concerns that were published that suggested that</p> <p>8 excess non-metabolized folic acid might have some</p> <p>9 harmful effects.</p> <p>10 Q. And if you look at paragraph 27, page</p> <p>11 9 of your report, you state that it was -- yes, you</p> <p>12 say that "the non-naturally occurring compound,</p> <p>13 folic acid, is often used to provide folate to</p> <p>14 human subjects," do you see that?</p> <p>15 A. Yes.</p> <p>16 Q. That's a true statement, right?</p> <p>17 A. Yes.</p> <p>18 Q. And one of the reasons why it was</p> <p>19 often used was because it was safe, correct?</p> <p>20 A. Generally considered safe.</p> <p>21 Q. Right. It was inexpensive, correct?</p> <p>22 A. Yes.</p> <p>23 Q. It was also considered stable,</p> <p>24 correct?</p> <p>25 A. Yes.</p>

<p style="text-align: right;">102</p> <p>1 Miller - confidential</p> <p>2 Q. And it was considered to be</p> <p>3 bioavailable, correct?</p> <p>4 A. Yes.</p> <p>5 Q. And it had shown some efficacy.</p> <p>6 A. Yes.</p> <p>7 Q. Okay. Now, if you look at Dr. Shane's</p> <p>8 report at page 13, which is JM-9, if you look at</p> <p>9 the third -- well, actually, the second full</p> <p>10 paragraph, page 13 of Dr. Shane's report, he says,</p> <p>11 "Folic acid" -- hold on, strike that.</p> <p>12 Okay, second sentence, he's referring</p> <p>13 to folic acid, but tell me if I'm wrong, he states,</p> <p>14 "Folic acid is the most common form of folate used</p> <p>15 in supplements and in fortified food products</p> <p>16 because it is highly bioavailable and chemically</p> <p>17 stable and it is converted to tetrahydrofolate, the</p> <p>18 active co-enzyme form of folate."</p> <p>19 Do you see that?</p> <p>20 A. Yes.</p> <p>21 Q. And you agree with that statement,</p> <p>22 right?</p> <p>23 A. Yes.</p> <p>24 Q. And then on page 25 of Dr. Shane's</p> <p>25 report -- if I can find it -- okay. Then he goes</p>	<p style="text-align: right;">104</p> <p>1 Miller - confidential</p> <p>2 have been available for over 50 years, they are</p> <p>3 less stable than folic acid, particularly in</p> <p>4 solution, and are more expensive to produce," do</p> <p>5 you see that?</p> <p>6 A. Yes.</p> <p>7 Q. Do you agree with that statement?</p> <p>8 A. Yes, we talked about the solution</p> <p>9 issue. I have to take Dr. Shane's word for that.</p>
<p style="text-align: right;">103</p> <p>1 Miller - confidential</p> <p>2 on, if you look at the second full paragraph,</p> <p>3 second sentence, he says, "As folic acid is</p> <p>4 normally metabolized to all tetrahydrofolates, it</p> <p>5 continues to be the primary folate form added to</p> <p>6 fortified foods and supplements to improve folate</p> <p>7 status."</p> <p>8 And Dr. Miller, do you agree with that</p> <p>9 statement?</p> <p>10 A. Yes.</p> <p>11 Q. And then on page 19, the second full</p> <p>12 paragraph, but the very last sentence, he states,</p> <p>13 "As 5-methyltetrahydrofolate is a poor substrate</p> <p>14 for the synthesis of polyglutamates, the ability of</p> <p>15 tissues to accumulate folate is reduced and the</p> <p>16 functional folate deficiency is compounded by a</p> <p>17 reduction in cellular folate levels," and then he</p> <p>18 goes on, "Paradoxically, this can lead to an</p> <p>19 increase in plasma folate because tissues fail to</p> <p>20 retain folate."</p> <p>21 Do you agree with that statement?</p> <p>22 A. Yes.</p> <p>23 Q. And then, one more, if you'll just go</p> <p>24 back to page 25, and the first, second full</p> <p>25 paragraph, he states, "Although tetrahydrofolates</p>	

<p style="text-align: right;">122</p> <p>1 Miller - confidential</p> <p>2 I mean, is the use of the term</p> <p>3 "folate" in Serfontein any different from the way</p> <p>4 in which you understand that term to be used?</p> <p>5 A. Um -- when Serfontein uses the phrase</p> <p>6 "folate or a suitable active metabolite of folate"</p> <p>7 suggests to me that the first word, "Folate" in</p> <p>8 that phrase, is reference to the folic acid.</p> <p>9 Often this occurs that, even with</p> <p>10 scientists who should know better, that they will</p> <p>11 use folate when they really intend to mean folic</p> <p>12 acid and vice-versa, and it's dependent on the</p> <p>13 context.</p> <p>14 Q. So in Serfontein, it's your position</p> <p>15 that the term "folate" is equated with folic acid?</p> <p>16 A. I believe so. That would be my</p> <p>17 reading of that -- that phrase.</p> <p>18 Q. And the substance which releases</p> <p>19 folate in vivo, would that also include folic acid</p> <p>20 as well?</p> <p>21 A. Well -- well, if there was a substance</p> <p>22 that releases folate, it could -- that folate that</p> <p>23 is released could very well be folic acid. I will</p> <p>24 say that I don't really understand, or I don't know</p> <p>25 of anything that that phrase, part of the phrase is</p>	<p style="text-align: right;">124</p> <p>1 Miller - confidential</p> <p>2 AFTERNOON SESSION</p> <p>3 (12:59 p.m.)</p> <p>4 JOSHUA MILLER, having been</p> <p>5 previously sworn, resumed the stand and</p> <p>6 testified further as follows:</p> <p>7 VIDEOGRAPHER: Here begins video</p> <p>8 recording number 2. The time is 12:59. We are on</p> <p>9 the record.</p> <p>10 EXAMINATION (Cont'd.)</p> <p>11 BY MR. PARKER:</p> <p>12 Q. Okay. Dr. Miller, before we broke for</p> <p>13 lunch, we were talking about the Serfontein</p> <p>14 reference. Is that reference still in front of</p> <p>15 you?</p> <p>16 A. Yes.</p> <p>17 Q. Now, and I believe you testified</p> <p>18 previously that you're familiar with this</p> <p>19 reference, correct?</p> <p>20 A. Yes.</p> <p>21 Q. Okay. Now, Serfontein is directed to</p> <p>22 pharmaceutical preparations, is that correct?</p> <p>23 A. Yes.</p> <p>24 Q. And if you look on the first page, the</p> <p>25 title -- well, it says here, "Pharmaceutical</p>
<p style="text-align: right;">123</p> <p>1 Miller - confidential</p> <p>2 referring to. I don't know of any substance that</p> <p>3 releases folic acid. I don't quite understand what</p> <p>4 is meant by that.</p> <p>5 Q. Is that because Serfontein doesn't</p> <p>6 define what it meant by that?</p> <p>7 A. Yeah, I don't believe that's the case.</p> <p>8 Q. All right.</p> <p>9 MR. PARKER: This would be a good time</p> <p>10 to take a break for lunch.</p> <p>11 VIDEOGRAPHER: Here ends video</p> <p>12 recording number 1. The time is 12:11. We are off</p> <p>13 the record.</p> <p>14 (Luncheon recess: 12:11 p.m.)</p>	<p style="text-align: right;">125</p> <p>1 Miller - confidential</p> <p>2 preparations for lowering homocysteine levels</p> <p>3 containing vitamin B-6, folic acid and vitamin</p> <p>4 B-12;" do you see that?</p> <p>5 A. Yes.</p> <p>6 Q. And then it goes on and it has another</p> <p>7 description. Do you see that below that, another</p> <p>8 pharmaceutical preparation?</p> <p>9 A. Yes.</p> <p>10 Q. Now, with respect to Serfontein and</p> <p>11 the pharmaceutical preparations that it purports to</p> <p>12 disclose, they essentially cover all forms of</p> <p>13 folate, correct?</p> <p>14 A. Um -- not necessarily.</p> <p>15 Q. Well, it covers the salt forms,</p> <p>16 correct?</p> <p>17 A. Yes.</p> <p>18 Q. Free acid form?</p> <p>19 A. Yes.</p> <p>20 Q. And the various reduced folates that</p> <p>21 have various glutamate linkages?</p> <p>22 A. Yes.</p> <p>23 Q. Now, you'll agree that Serfontein does</p> <p>24 not indicate any preference with respect to any</p> <p>25 particular reduced folate, correct?</p>

<p style="text-align: right;">126</p> <p>1 Miller - confidential</p> <p>2 A. That's correct.</p> <p>3 Q. In fact, Serfontein provides no</p> <p>4 definition as to what the meant by "suitable active</p> <p>5 metabolite of folate," correct?</p> <p>6 A. I don't believe so.</p> <p>7 Q. And in Serfontein, there are no</p> <p>8 working examples of any pharmaceutical preparation</p> <p>9 consisting of a specific reduced folate; correct?</p> <p>10 A. I believe that's the case, yes.</p> <p>11 Q. Now, in fact, example 2 in Serfontein,</p> <p>12 you may refer to it if you have to, that example</p> <p>13 specifically is directed to folic acid, correct?</p> <p>14 A. That's what is specifically said in</p> <p>15 the box describing the contents of that.</p> <p>16 Q. Right. And in example 3, the contents</p> <p>17 of the pharmaceutical preparation that's revealed</p> <p>18 there contains folic acid, correct?</p> <p>19 A. That's correct.</p> <p>20 Q. The same is true for example 4?</p> <p>21 A. Yes.</p> <p>22 Q. And is the same true for example 5?</p> <p>23 A. Yes.</p> <p>24 Q. The same is true for example 6?</p> <p>25 A. Yes.</p>	<p style="text-align: right;">128</p>
<p style="text-align: right;">127</p> <p>1 Miller - confidential</p> <p>2 Q. And the same is true for example 7,</p> <p>3 correct?</p> <p>4 A. Yes.</p> <p>5 Q. Now, example 8 refers to folate,</p> <p>6 correct?</p> <p>7 A. Correct.</p> <p>8 Q. But folate's not defined in this</p> <p>9 document as being, or corresponding to folic acid,</p> <p>10 correct?</p> <p>11 A. It hasn't explicitly stated by using</p> <p>12 the term "folate," it's unclear just looking at</p> <p>13 that table.</p> <p>14 Q. So it's unclear looking at this table</p> <p>15 what compound is being included?</p> <p>16 A. Yes.</p>	<p>17 Q. Okay. But there's no embodiment --</p> <p>18 well, let me back up.</p> <p>19 With respect to the -- as you refer to</p> <p>20 it as embodiment on page 11 of your report, doesn't</p> <p>21 give you the amounts of vitamin B-6 or folate or</p> <p>22 B-12 or any other ingredient, right?</p> <p>23 A. That's correct, yeah.</p> <p>24 Q. And you'll agree, right, that there's</p> <p>25 no specific mention of either 6(S)-5-MTHF, or</p>

130	132
<p>1 Miller - confidential</p> <p>2 6(S)-5-FTHF, specific mention.</p> <p>3 A. That's correct.</p> <p>4 Q. And there's no mention of using any</p> <p>5 particular, any specific reduced folate in a</p> <p>6 substantially chirally pure form.</p> <p>7 A. That's correct.</p> <p>8 Q. And you'll agree that there are no</p> <p>9 working examples of "suitable active metabolites of</p> <p>10 folate."</p> <p>11 A. That's correct.</p>	<p>4 Q. Now, with respect to the glutamyl</p> <p>5 polymers, they can range anywhere from one to 11,</p> <p>6 is that fair?</p> <p>7 A. Yes.</p> <p>8 Q. And they go as high as 14?</p> <p>9 A. Perhaps. I don't have any direct</p> <p>10 knowledge of somebody measuring a 14-glutamate</p> <p>11 folate. But theoretically, yes.</p> <p>12 Q. And salt forms, they could include the</p> <p>13 alkaline earth metals?</p> <p>14 A. Yes.</p> <p>15 Q. As well as the alkaline metals?</p> <p>16 A. Yes.</p> <p>17 Q. And ammonium?</p> <p>18 A. Yes.</p> <p>19 Q. And glucuronate salt, which I don't</p> <p>20 know if you know, that's Gnosis' salt form.</p> <p>21 A. Yes.</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p>

<p>150</p> <p>15 Q. Now, you've heard of the textbook, 16 Goodman & Gilman? 17 A. Yes. 18 Q. Do you actually have a copy of that in 19 your office? 20 A. I do not.</p> <p>24 Q. Do you understand that it's a leading 25 authoritative source for pharmacology?</p>	<p>152</p> <p>1 Miller - confidential 2 not indicated for treating folate deficiency, is 3 that correct? 4 A. That's correct. 5 Q. And you say "with no accompanying 6 explanation or statement." 7 A. That's correct. 8 Q. Then you go on and you state "this 9 statement may have simply been a recognition of 10 high cost at the time of using 5-FTHF for folate 11 supplementation compared to folic acid," do you see 12 that? 13 A. That's correct. 14 Q. What's your basis for that statement? 15 A. My belief that indeed, folic acid was 16 the more readily available and cheaper alternative 17 for this purpose. 18 Q. And because, and for that reason, 19 then, no one would want to consider or turn to 20 5-FTHF for folate supplementation? 21 A. I would not say that no one would want 22 to consider that. I would say that you would 23 typically think to use the folic acid under those 24 circumstances knowing about folic acid as you can 25 obtain it over-the-counter, it's cheap, inexpensive</p>
<p>151</p> <p>1 Miller - confidential 2 A. I do.</p> <p>24 Q. And you acknowledge that Goodman & 25 Gilman state that the 5-formyltetrahydrofolate is</p>	<p>153</p> <p>1 Miller - confidential 2 supplement, it's more difficult to find 5-FTHF, and 3 it may require a prescription if it's leucovorin. 4 Q. Now, let me just place in front of you 5 the excerpt, I believe, which is the eighth edition 6 of Goodman & Gilman. I believe this is 1990, or 7 actually, it is 1990. 8 I just want to, you could confirm that 9 for yourself, and I just want to -- this is the one 10 that you're referring to in your report. You can 11 confirm that, too. 12 (Handing document to witness.) 13 MR. CWIK: Did you say what exhibit 14 that was? 15 MR. PARKER: JM- -- 16 THE WITNESS: Twelve. 17 MR. PARKER: -- 12. 18 EXH (Deposition Exhibit 12, excerpt 19 from Goodman & Gilman textbook, marked for 20 identification, as of this date.) 21 Q. Is that the reference to Goodman & 22 Gilman you're referring to in your report? 23 A. Yes, it is. 24</p>

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**Q. But it's certainly not encouraging to
a person of ordinary skill in the art to use 5-FTHF
for folate supplementation, correct?**

A. I would agree with that, yeah.

<p style="text-align: right;">162</p> <p>1 Miller - confidential</p> <p>2 A. I don't know. And that's exactly the</p> <p>3 point, is that because the language was -- was not</p> <p>4 specific, and they didn't give examples, wasn't</p> <p>5 clear why they had said this.</p> <p>6 Q. Okay. Now, there are other two</p> <p>7 references that you rely on in your opinions in</p> <p>8 connection with this case, and I refer to them as</p> <p>9 Harpey I and Harpey II references, and I'm going to</p> <p>10 give you a copy of those. And weight mark those,</p> <p>11 Harpey I as JM- --</p> <p>12 MS. QIN: 17.</p> <p>13 EXH (Deposition Exhibit 17, Harpey I</p> <p>14 reference, marked for identification, as of this</p> <p>15 date.)</p> <p>16 MR. PARKER: And Harpey II as JM-18.</p> <p>17 EXH (Deposition Exhibit 18, Harpey II</p> <p>18 reference, marked for identification, as of this</p> <p>19 date.)</p> <p>20 Q. Can you confirm, Dr. Miller, that</p> <p>21 you're familiar with these two references and these</p> <p>22 are the same two references that you were relying</p> <p>23 on in this case?</p> <p>24 A. Yes. They are the ones, I recognize</p> <p>25 them.</p>	<p style="text-align: right;">164</p> <p>1 Miller - confidential</p> <p>2 even when supplied with exogenous 5-methyl THF," do</p> <p>3 you see that?</p> <p>4 A. I do.</p> <p>5 Q. So in this situation, even putting --</p> <p>6 this is -- I understand this is now in vitro, that</p> <p>7 growing these tissues, this tissue culture,</p> <p>8 fibroblasts, is that correct?</p> <p>9 A. Yes.</p> <p>10 Q. Even adding exogenous 5-MTHF didn't</p> <p>11 provide any effect, correct?</p> <p>12 A. That's what they report, yes.</p> <p>13 Q. Okay. And then they go on and they</p> <p>14 mention that vitamin B-12 supplementation may</p> <p>15 enhance methionine -- well, let me stop there, I</p> <p>16 apologize.</p> <p>17 It says, "This finding might explain</p> <p>18 the requirement for exogenous methionine in our</p> <p>19 patient," do you see that?</p> <p>20 A. Yeah. Well, actually, I don't, I'm</p> <p>21 not seeing it right now, so point me to the exact</p> <p>22 line.</p> <p>23 Q. On page 277, where it says, it says,</p> <p>24 "Although 5-methyl THF would be desirable for use</p> <p>25 in therapy, it is probably too unstable," do you</p>
<p style="text-align: right;">163</p> <p>1 Miller - confidential</p> <p>2 Q. And Harpey I is JM-18?</p> <p>3 A. Seventeen.</p> <p>4 Q. Seventeen. Now, you acknowledge --</p> <p>5 let me back up.</p> <p>6 With respect to Harpey I, you do</p> <p>7 acknowledge that, in this reference, it does state</p> <p>8 that, although 5-methyl THF would be desirable for</p> <p>9 use in therapy, it is probably too unstable,</p> <p>10 correct?</p> <p>11 A. I do.</p> <p>12 Q. And the 5-methyl THF, that's a</p> <p>13 reference to the racemic mixture of the 6(S) isomer</p> <p>14 and the 6(R) isomer, correct?</p> <p>15 A. Correct.</p> <p>16 Q. Now, saying that the compound is too</p> <p>17 unstable for therapeutic use would in some respects</p> <p>18 discourage some of those persons of ordinary skill</p> <p>19 in the art from using this particular compound for</p> <p>20 the purpose mentioned in Harpey I, correct?</p> <p>21 A. It very well could have, yes.</p> <p>22 Q. And it goes on, it says, "Furthermore,</p> <p>23 fibroblasts from patients with a deficiency of</p> <p>24 5,10-MTHF reductase cannot grow in tissue culture</p> <p>25 medium in which homocysteine replaces methionine,</p>	<p style="text-align: right;">165</p> <p>1 Miller - confidential</p> <p>2 see that phrase? Okay. And then we go on, we read</p> <p>3 the passage dealing with the tissue culture.</p> <p>4 A. Um-hum.</p> <p>5 Q. And then following, it talks about,</p> <p>6 where it is, "This finding might explain the</p> <p>7 requirement for exogenous methionine in our</p> <p>8 patient."</p> <p>9 Do you see that?</p> <p>10 A. Yes.</p> <p>11 Q. Essentially, because -- well, it goes</p> <p>12 on and then we can put this all together. "Vitamin</p> <p>13 B-12 supplementation may enhance methionine</p> <p>14 formation but only in the presence of 5-methyl THF.</p> <p>15 In our case, every attempt to lower the dose of</p> <p>16 vitamin B-12 resulted in reappearance of lethargy,"</p> <p>17 okay?</p> <p>18 A. Um-hum.</p> <p>19 Q. So in this situation, the authors were</p> <p>20 reluctant to give 5-methyl THF for purposes of</p> <p>21 enhancing methionine formation and instead, gave</p> <p>22 the patient methionine directly.</p> <p>23 MR. CWIK: Objection, foundation.</p> <p>24 Q. Is that a fair reading of this</p> <p>25 reference?</p>

<p style="text-align: right;">166</p> <p>1 Miller - confidential</p> <p>2 A. Could you state your question again?</p> <p>3 Q. Sure.</p> <p>4 A. Because I want to get it right.</p> <p>5 Q. Right. In this reference, the authors</p> <p>6 state, "This finding might explain the requirement</p> <p>7 of exogenous methionine in our patient." They are</p> <p>8 referring to the experiment where the exogenous</p> <p>9 5-MTHF was not effective for growth. Then they go</p> <p>10 on and they state, "Vitamin B-12 supplementation</p> <p>11 may enhance methionine formation but only in the</p> <p>12 presence of 5-methyl THF. In our case, every</p> <p>13 attempt to lower the dose of vitamin B-12 resulted</p> <p>14 in reappearance of lethargy."</p> <p>15 A. Yes.</p> <p>16 Q. So here, the authors were reluctant to</p> <p>17 administer the 5-MTHF for purposes of supplementing</p> <p>18 the methionine formation along with the vitamin</p> <p>19 B-12 and instead they gave their patient exogenous</p> <p>20 methionine.</p> <p>21 A. Correct.</p>	<p style="text-align: right;">168</p> <p>1 Miller - confidential</p> <p>2 Q. And then they are looking --</p> <p>3 considering ways to treat this individual who has,</p> <p>4 I would imagine, incredibly high levels of</p> <p>5 homocysteine, is that correct?</p> <p>6 A. Yes, that's correct.</p> <p>7 Q. And they administered to the child</p> <p>8 5-MTHF, five milligrams, along with OH B-12, .5</p> <p>9 milligrams per day orally, and they report that</p> <p>10 homocysteinemia did not rise above 13 micromoles</p> <p>11 per liter. And I guess prior to that, she was at</p> <p>12 233 micromoles per liter.</p> <p>13 A. Correct.</p> <p>14 Q. Okay but they go on and they indicate</p> <p>15 that 5-methyltetrahydrofolate has to be withdrawn</p> <p>16 because of its instability.</p> <p>17 A. That's correct.</p> <p>18 Q. And then they went back to the</p> <p>19 previous treatment, correct?</p> <p>20 A. Correct.</p>
<p>22 Q. Now, in Harpey II, JM-18, they talk</p> <p>23 about a child suffering from 5,10-MTHF reductase</p> <p>24 deficiency, correct?</p> <p>25 A. Yes.</p>	<p style="text-align: right;">169</p> <p>1 Miller - confidential</p> <p>2 Q. So basically, in Harpey II, the</p> <p>3 5-tetramethylhydrofolate had to be withdrawn</p> <p>4 because of instability, correct, according to the</p> <p>5 office?</p> <p>6 A. Correct.</p>

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1 Miller - confidential

2 A. Yes.

3 Q. And basically, Marazza is really
4 directed to a separation technique for mixtures
5 that contain the two diastereoisomers?

6 A. That's correct.

7 Q. And the diastereoisomers of 5 -- is it
8 5-MTHF, right? It's basically directed to a
9 separation technique, correct?

10 A. Correct.

11 Q. And then on the first page, first
12 column, column 1, "Background of the invention," do
13 you see that, it says, "There exists an increasing
14 interest in the application of this natural
15 metabolite as at least one active compound in a
16 therapeutic agent, for example, as vitamin and
17 folate deficiencies," it states. Correct?

18 A. Correct.

19 Q. Now, it uses the phrase, "There exists
20 and increasing interest," okay?

21 A. Um-hum.

1
20 reference, JM-24 --
21 EXH (Deposition Exhibit 24, copy
22 of '611 patent, Marazza, et al, marked for
23 identification, as of this date.)
24 Q. -- which is Marazza. Now, you've made
25 this reference, correct?

25 Q. So when you say "reasonable

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Miller - confidential

A. I don't believe that's the case.

Q. And Marazza does not mention or relate to lowering serum homocysteine levels, correct?

A. No, no, it doesn't.

Q. And Marazza doesn't mention anything with respect to increased levels of homocysteine associated with any MTHFR deficiency, correct?

A. No.

Q. Now, a couple of things. First of all, it says in column 2, there exist no agreements about the function of the 6(R) diastereoisomer of the N-methyl THF, correct?

A. That's correct.

Q. And also there's no working examples, there's nothing about, in terms of amounts to be used, or administered to patients, correct?

A. That is correct.

Q. And that the primary teaching of this reference is essentially separation technique, getting a mixture of the two diastereoisomers, correct?

A. Yes.

Q. Now, Marazza does not talk about combining any reduced folate with any vitamin other than ascorbic acid?

A. I don't believe so.

Q. Or so I'm clear, Marazza doesn't disclose or reveal combining the reduced folate with any vitamin.

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1 **Miller - confidential**

2 **Now, the Ueland reference is also**
3 **directed to the use of folic acid, right?**

4 A. No, there is a -- a statement in
5 there, statement or paragraph, talking about the
6 intracellular pool of 5-methyl 6(S) --

7 **Q. Right, so the intracellular pool is**
8 **what's happening in vivo after administration of**
9 **folic acid, correct?**

10 A. Exactly, yes.

11 **Q. It's not talking about administering**
12 **the 6(S)-5-MTHF exogenously, correct?**

13 A. Yes.

14 **Q. Let me just identify, that is JM-28.**
15 **And can you just identify what that document is for**
16 **the record?**

17 **EXH (Deposition Exhibit 28, review**
18 **article by Ueland and Refsum, "Plasma**
19 **homocysteine, a risk factor for vascular disease;**
20 **Plasma levels in health, disease, and drug**
21 **therapy" marked for identification, as of this**
22 **date.)**

23 A. That's the Ueland reference.

24 (A pause in the proceedings.)

25 **Q. Okay, now, Ueland knew, I guess, as**

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1 **Miller - confidential**

2 **you pointed out, that it talks about increasing the**
3 **pool of 6(S)-5-MTHF after administration of folic**
4 **acid, is that correct?**

5 A. That's correct.

6 **Q. Now, you understand that the Bailey**
7 **patent, as well as the '040 patent, they are not**
8 **directed to use of folic acid, correct?**

9 A. Correct.

10 **Q. In fact, is it fair to say that what**
11 **they were trying to do was develop supplements**
12 **other than folic acid?**

13 A. Correct.

218

220

16 **Q. Now, looking at Ueland now, a little**
 17 **bit more. Now, does Ueland mention anything about**
 18 **using vitamins B-6 or B-12 in correction with**
 19 **folate derivatives?**

20 A. I don't remember offhand, but I will
 21 presume that the answer is yes because this is a
 22 review article about homocysteine and they very --
 23 they definitely would discuss in here using folate
 24 as well as B-12 and B-6 to lower homocysteine
 25 levels, and would very likely have talked about

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1 Miller - confidential
 2 combining all three.
 3 But without reading through it
 4 carefully, to -- taking the time to do that, it
 5 would be difficult for me to find it because it's a

13 **Q. So, right. So basically at the end**
 14 **it's suggesting that you'd only administer B-6 or**
 15 **B-12, or combine it with 5-MTHF if the person is**
 16 **deficient in B-6 or B-12. Otherwise it would have**
 17 **no effect, correct?**

18 A. Correct. In -- I would say that in
 19 intervention studies that have been carried out,
 20 placebo versus vitamin, they typically include all
 21 three vitamins because they want to have maximal
 22 reduction of homocysteine in the population that
 23 they are studying; and so, while folate will have
 24 the greatest effect, there are other studies that
 25 are not being cited here where B-12 had its own

56 (Pages 218 to 221)

1 Miller - confidential
2 smaller but significant effect, and B-6 typically
3 in those studies didn't have an effect. And
4 there's -- there's reasons for that. But we don't
5 need to go into it at this point in time.

6 **Q. Again, I understand all of that. Just**
7 **so it will be clear, so basically at the end, this**
8 **reference is suggesting that you would only**
9 **administer B-6, B-12, with 5-MTHF if that**
10 **individual was deficient in those particular**
11 **vitamins, correct?**

12 A. That's what I would do, yes.

13 **Q. That's what the reference says.**

14 A. Yes.

15 **Q. Thank you.**

5 **Q.** Okay. Now, if I could just direct
6 your attention to paragraph 127 of your opening
7 report, okay, and in this paragraph, you state, "I
8 agree that Dr. Ayling, and a co-inventor of the
9 Bailey patents, Mr. Steven Bailey, discovered a
10 subpopulation of individuals for whom DHFR activity
11 varied more than was known or would have been
12 expected by one of ordinary skill in the art, and
13 that 5-MTHF and/or 6(S)-5-MTHF should be more
14 uniformly bioavailable to such individuals."

15 **Do you see that?**

16 **A.** I do. I would say that, since I wrote
17 this report, I've seen Dr. Shane's report with a
18 reference to the Whitehead reference, and I have
19 changed my opinion on that.

18 **Q.** Okay. But now, just sticking with
19 what's in your report, okay, so again, I understand
20 what you just said with respect to the Whitehead
21 reference and Dr. Shane's report and you've now
22 changed your opinion. But at the time you wrote
23 your report, you considered Dr. Ayling and
24 Dr. Bailey to have discovered that subpopulation,
25 correct?

1 **Miller - confidential**

2 A. Yes, because that was the only

3 reference I was aware of that had shown this.

<p>238</p> <p>1</p> <p>2</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p>240</p> <p>1 Miller - confidential</p> <p>2 A. Sure, yes.</p>
<p>239</p> <p>1 Miller - confidential</p> <p>2 Q. So if you had a population, people may</p> <p>3 have defects in various steps, but not the same</p> <p>4 steps.</p> <p>5 A. Um-hum.</p> <p>6 Q. And so because of that, if I</p> <p>7 understand it correctly, the inference or the --</p> <p>8 extending the logic further is that, well,</p> <p>9 obviously, you're not going to have a balanced and</p> <p>10 uniform level of bioavailability among the</p> <p>11 population because people could have varying</p> <p>12 defects in the genes responsible for the enzymes,</p> <p>13 whether they were severe, slight, moderate, but</p> <p>14 that can contribute to having various levels of</p> <p>15 bioavailability.</p> <p>16 A. Not just the enzymes but the</p> <p>17 transporters and receptors and -- that are also</p> <p>18 involved in getting the folates to where they are</p> <p>19 supposed to go.</p> <p>20 Q. And that, too, is somewhat of a</p> <p>21 complicated process, correct?</p> <p>22 A. Sure, yes.</p> <p>23 Q. And all the various substrates or the</p> <p>24 compounds involved in that process, they all have</p> <p>25 different physiological properties.</p>	<p>20 Q. So when you mentioned that, in your</p> <p>21 response, because I do want to just kind of just</p> <p>22 focus on one thing, just to, for my sake get it</p> <p>23 shorter, you said, I would -- I mean, that you</p> <p>24 acknowledged that Dr. Green and Dr. Gregory have</p> <p>25 talked about the complexity of folate metabolism,</p>

1 Miller - confidential

2 **Q. And that is considered a highly**
3 **regarded publication.**

4 A. Yes.

5 **Q. And as far as bioavailability of**
6 **folates, do you consider Dr. Gregory to be one of**
7 **the leaders in that field?**

8 A. I do.

17 **Q. Now, they published their work in**
18 **PNAS?**

19 A. That was Bailey and Ayling you're
20 referring to?

21 **Q. Yes.**

22 A. Yes.

23 **Q. And what does PNAS stand for?**

24 A. Proceedings of the National Academy of
25 Sciences.

24 A. It could, yes.

25 (A pause in the proceedings.)

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**Q. Well, prior to 1995-'96 time frame,
the 5-MTHF was, I mean, you've seen some references
where individuals considered it to be unstable.**

A. Correct, yes.

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1 MR. PARKER: Okay, Dr. Miller, I have
20 no further questions at this time.
21 MR. CWIK: Okay, we have no further
22 questions, so we will reserve signature and we're
23 done.
24 VIDEOGRAPHER: Here ends video
25 recording number 3. This concludes the video

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1 Miller - confidential
2 recorded deposition of Dr. Joshua Miller, taken by
3 the complainants on Monday, May 6th, 2013. The
4 time is 17:22, and we are going off the record.
5 (Time noted: 5:22 p.m.)
6
7

8 JOSHUA MILLER
9

10 Subscribed and sworn to before me
11 this ____ day of _____, 20____.
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13

14 NOTARY PUBLIC
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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	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 style="text-align: center;">C E R T I F I C A T E</p> <p>I, DAVID LEVY, a Certified Shorthand Reporter and Notary Public within and for the State of New Jersey, do hereby certify:</p> <p>That JOSHUA MILLER, the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true record of the testimony given by the witness.</p> <p>I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.</p> <p>IN WITNESS WHEREOF, I have hereunto set my hand this 7th day of May, 2013.</p> <p style="text-align: center;">_____ DAVID LEVY, CSR, RPR, CLR</p>	<p style="text-align: center;">----- I N D E X (Cont'd.)-----</p> <p>DEPOSITION EXHIBITS (JM) FOR IDENT.</p> <p>Exhibit 7 Excerpt from Green expert report 75</p> <p>Exhibit 8 List of folate compounds 79</p> <p>Exhibit 9 Report of Dr. Barry Shane 100</p> <p>Exhibit 10 European patent application, Serfontein, et al 106</p> <p>Exhibit 11 Declaration of Joshua S. Miller, Ph.D. 109</p> <p>Exhibit 12 Excerpt from Goodman & Gilman textbook 153</p> <p>Exhibit 13 Excerpt from Goodman & Gilman, 1986 155</p> <p>Exhibit 14 Excerpt from Goodman & Gilman, 1985 155</p> <p>Exhibit 15 Various definitions from New American Medical Dictionary 157</p> <p>Exhibit 16 Excerpt from Goodman & Gilman, 2001 159</p> <p>Exhibit 17 Harpey I reference 162</p> <p>Exhibit 18 Harpey II reference 162</p> <p>Exhibit 19 Article, "Folic Acid and L-5-Methyltetrahydrofolate," Shane, et al 174</p>
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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	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 style="text-align: center;">----- I N D E X -----</p> <p>WITNESS EXAMINATION BY PAGE</p> <p>JOSHUA MILLER MR. PARKER 5</p> <p>REQUESTS (RQ) PAGE</p> <p>RQ 21</p> <p>DIRECTIONS (DI) PAGE</p> <p>DI 17</p> <p>DI 22</p> <p>DI 23</p> <p>DI 24</p> <p>DEPOSITION EXHIBITS (JM) FOR IDENT.</p> <p>Exhibit 1 Expert report of Joshua W. Miller, Ph.D. 33</p> <p>Exhibit 2 Rebuttal expert report of Joshua Miller, Ph.D. 33</p> <p>Exhibit 3 Printout from Office of Dietary Supplements, NIH, re folate 51</p> <p>Exhibit 4 Sports Nutritional Almanac 59</p> <p>Exhibit 5 Document re Thorne Research 61</p> <p>Exhibit 6 U.S. patent application, Bailey, et al 65</p>	<p style="text-align: center;">----- I N D E X (Cont'd.)-----</p> <p>DEPOSITION EXHIBITS (JM) FOR IDENT.</p> <p>Exhibit 20 Reference, Lucock, et al 180</p> <p>Exhibit 21 Reference, Scott, et al 180</p> <p>Exhibit 22 European patent application, Ambrosini, et al 188</p> <p>Exhibit 23 Zittoun/Cooper reference 195</p> <p>Exhibit 24 Copy of '611 patent, Marazza, et al 199</p> <p>Exhibit 25 Article, "Enhancement of recovery form psychiatric illness by methylfolate," Godfrey, et al 204</p> <p>Exhibit 26 Excerpt from Clinical Trials Journal 205</p> <p>Exhibit 27 Article, "Homocysteine and Marginal Vitamin Deficiency," Stampfer, et al 212</p> <p>Exhibit 28 Review article by Ueland and Refsum, "Plasma homocysteine, a risk factor for vascular disease; Plasma levels in health, disease, and drug therapy" 214</p> <p>Exhibit 29 Copy of '472 patent 222</p> <p>Exhibit 30 Article, Regland, et al, "Homocysteine and schizophrenia as a case of methylation deficiency" 246</p>

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<p>1 2 ----- I N D E X (Cont'd.)----- 3 DEPOSITION EXHIBITS (JM) FOR IDENT. 4 Exhibit 31 Article from New England 251 Journal of Medicine, Czeizel, et al 5 Exhibit 32 Article, "Folic acid - an 265 innocuous means to reduce 6 plasma homocysteine," Brattstrom, et al 7 8 Exhibit 33 Article, "Moderate 265 homocysteine - a possible 9 risk factor for 10 arteriosclerotic 11 cerebrovascular disease," Brattstrom, et al 12 13 14 15 16 17 18 19 20 21 22 23 24 25</p>	<p>1 2 E R R A T A 3 4 I wish to make the following changes, for 5 the following reasons: 6 7 PAGE LINE 8 ____ CHANGE_____ 9 REASON:_____ 10 ____ CHANGE_____ 11 REASON:_____ 12 ____ CHANGE_____ 13 REASON:_____ 14 ____ CHANGE_____ 15 REASON:_____ 16 ____ CHANGE_____ 17 REASON:_____ 18 ____ CHANGE_____ 19 REASON:_____ 20 ____ CHANGE_____ 21 REASON:_____ 22 23 24 WITNESS' SIGNATURE DATE 25</p>
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<p>1 2 3 INSTRUCTIONS TO WITNESS 4 5 Please read your deposition over carefully and 6 make any necessary corrections. You should state 7 the reason in the appropriate space on the errata 8 sheet for any corrections that are made. 9 After doing so, please sign the errata sheet and 10 date it. 11 You are signing same subject to the changes you 12 have noted on the errata sheet, which will be 13 attached to your deposition. 14 It is imperative that you return the original 15 errata sheet to the deposing attorney within thirty 16 (30) days of receipt of the deposition transcript 17 by you. If you fail to do so, the deposition 18 transcript may be deemed to be accurate and may be 19 used in court. 20 21 22 23 24 25</p>	