

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GNOSIS S.P.A., GNOSIS BIORESEARCH S.A., AND GNOSIS U.S.A., INC.
Petitioners

v.

MERCK & CIE
Patent Owner

Case IPR2013-00117
Patent 6,011,040

Before MICHAEL P. TIERNEY, JACQUELINE WRIGHT BONILLA, and
SCOTT E. KAMHOLZ, *Administrative Patent Judges*.

BONILLA, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

A. Background

Petitioners Gnosis S.p.A., Gnosis Bioresearch S.A., and Gnosis U.S.A., Inc. (collectively “Gnosis”) filed a petition (“Pet.”) to institute an *inter partes* review of claims 1- 3, 5, 6, 8, 9, 11-15, and 19-22 (the “challenged claims”) of U.S. Patent 6,011,040 (Ex. 1004) (the “’040 patent”). 35 U.S.C. § 311. Patent Owner Merck & Cie (“Merck”) timely filed mandatory notices pursuant to 37 C.F.R. § 42.8(a)(2) but did not file a Preliminary Response. Based on the record presented, we conclude that Gnosis has satisfied the burden to show, under 35 U.S.C. § 314(a), that there is a reasonable likelihood that it would prevail with respect to at least one of the challenged claims.

Gnosis petitions on the basis of numerous grounds, asserting that the challenged claims are anticipated under 35 U.S.C. § 102 by European Patent Application EP 0 595 005 A1 (Ex. 1009) (“Serfontein”), and also that the claims are obvious under 35 U.S.C. § 103(a) over Serfontein in view of a number of different references, including: (i) U.S. Patent 5,194,611 (Ex. 1012) (“Marazza”), (ii) Johan B. Ubbink et al., *Vitamin B-12, vitamin B-6 and folate nutritional status in men with hyperhomocysteinemia*, 57 Am. J. Clin. Nutr. 47-53 (1993) (Ex. 1019) (“Ubbink”), and (iii) J.M. Scott et al., *Folic acid to prevent neural tube defects*, 338 The Lancet 505 (1991) (Ex. 1014) (“Scott”). Pet. 7-8. Gnosis raises other obviousness challenges as well. *Id.* Gnosis supports its challenges with a declaration by Joshua W. Miller, Ph.D. (Ex. 1005) (“Miller Decl.”).

For the reasons given below, we institute an *inter partes* review of claims 1- 3, 5, 6, 8, 9, 19, and 20 of the ‘040 patent on two grounds: (1) anticipation by Serfontein, and (2) obviousness over Serfontein and Marazza. We deny the

petition as to anticipation of claims 11-15, 21 and 22 by Serfontein. We institute a review of claims 11, 12, 14, 15, 21 and 22, however, on a third ground: obviousness over Serfontein, Marazza, and Ubbink. Additionally, we institute a review of claim 13 on a fourth ground: obviousness over Serfontein, Marazza, Ubbink, and Scott. Gnosis challenges the claims on additional obviousness grounds in light of other cited prior art. Pet. 7-8. We consider these additional grounds to be redundant to the four listed above, and deny the petition as to them.

B. The Invention

1. Specification

The '040 patent “relates to the use of tetrahydrofolates in natural stereoisomeric form for the production of a pharmaceutical preparation suitable for influencing the homocysteine level, particularly for assisting the remethylation of homocysteine.” Col. 1, ll. 10-14. As explained in the '040 patent, homocysteine is a thiol-containing amino acid that is formed upon demethylation of methionine. *Id.* at ll. 37-38. Hyperhomocysteinemia is a clinical disorder of a permanent or temporary increase of homocysteine in the blood, which can lead to severe cardiovascular, ocular, neurological and skeletal diseases. *Id.* at ll. 42-45, 60-65. Hyperhomocysteinemia results from, for example, a deficiency of certain enzymes in the body, such as : (a) cystathione β -synthase, which is involved in a B₆-dependent transulphuration pathway, where homocysteine is converted to cysteine via cystathionine; or (b) 5,10-methylene tetrahydrofolate reductase, which provides the substrate, 5-methyl-(6S)-tetrahydrofolic acid, for a B₁₂-dependent conversion of homocysteine to methionine. *Id.* at ll. 46-53.

The '040 patent discloses that “natural stereoisomeric form of tetrahydrofolates” (“THFA”), which are in a reduced form, refer to “5-formyl-(6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5,10-methylene-

(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid or pharmaceutically compatible salts thereof.” *Id.* at col. 2, ll. 19-27. Thus, the ’040 patent identifies 5-methyl-(6S)-THFA and 5-formyl-(6S)-THFA among the “natural stereoisomeric form of tetrahydrofolates.” *Id.*¹

Example 10 in the ’040 patent describes a “combination preparation comprising 5-methyl-(6S)-tetrahydrofolic acid, vitamin B₆ and vitamin B₁₂” with “pharmaceutically compatible adjuvant substances.” *Id.* at col. 5, ll. 9-19.

2. Claims

Claims 1 and 2, the only independent claims challenged directly, are reproduced below.

1. A method of decreasing homocysteine levels in the human body comprising administering at least one tetrahydrofolate in natural stereoisomeric form to a human subject.

2. A method of preventing or treating disease associated with increased levels of homocy[s]teine levels in the human body comprising administering at least one tetrahydrofolate in natural stereoisomeric form to a human subject.

Dependent claims, such as claims 5 and 6, recite that the tetrahydrofolate in natural stereoisomeric form is:

- [I] 5-formyl-(6S)-tetrahydrofolic acid,
- [II] 5-methyl-(6S)-tetrahydrofolic acid,
- [III] 5,10-methylene-(6R)-tetrahydrofolic acid,

¹ We note that the ’040 patent refers to these compounds in their acid forms but also refers generally to them as “folates,” i.e., in their conjugate base forms. We consider these references synonymous for purposes of this decision. *Accord* Marazza (Ex. 1012), col. 1, ll. 21-22, in which “tetrahydrofolic acid” is abbreviated as “THF.”

- [IV] 5,10-methenyl-(6*R*)-tetrahydrofolic acid,
 - [V] 10-formyl-(6*R*)-tetrahydrofolic acid,
 - [VI] 5-formimino-(6*S*)-tetrahydrofolic acid, or
 - [VII] (6*S*)-tetrahydrofolic acid,
- or salts thereof.

These seven folates [I] – [VII] are termed “reduced” folates because they each have a pteridine ring that is less than fully oxidized, and each is a form of THFA, in which the double bonds between positions 5–6 and 7–8 of the pteridine ring are both reduced. *See, e.g.*, Ex. 1008, pp. 2-3. By comparison, folic acid has a fully oxidized pteridine ring. *Id.*

The seven reduced folates are further termed to be in a “natural stereoisomeric form” because they each have the same L-configuration at carbon 6 on the pteridine ring, as contrasted with the “unnatural isomers,” which have a mirror image configuration, i.e., a D-configuration, at carbon 6. For example, “5-methyl-(6*S*)-tetrahydrofolic acid” is the “*S*” diastereomer of 5-methyl-tetrahydrofolic acid (“5-MTHF”) and has the L-configuration at carbon 6. Likewise, “10-formyl-(6*R*)-tetrahydrofolic acid” is the “*R*” diastereomer of 10-formyl-tetrahydrofolic acid and also has the L-configuration at carbon 6.^{2,3}

Certain challenged dependent claims, such as claims 8 and 9, require use of one specific reduced folate, i.e., [II] 5-methyl-(6*S*)-tetrahydrofolic acid, or a salt

² Each folate recited in claim 5 or 6, for example, has the same L-configuration at carbon 6. The varying “*S*” and “*R*” designations result merely from priority conventions in the IUPAC nomenclature rules. Ex. 1008 at p. 3 (section 2.6, second paragraph).

³ The (6*R*) and (6*S*) forms are most properly termed “diastereoisomers” or “diastereomers” of one another, because they have only partly mirror-image stereospecificity relative to one another. In particular, they both have the “L” configuration at the α -carbon of the glutamate side chain, which is the other stereocenter in 5-methyl-THFA. Marazza (Ex. 1012), col. 1, l. 67 - col. 2, l. 6.

thereof. Other dependent claims, such as claims 11-15, additionally recite that increased levels of homocysteine (as recited in independent claim 2) are associated with “methylene tetrahydrofolate reductase deficiency” or “thermolabile methylene tetrahydrofolate reductase deficiency.”

All challenged dependent claims depend either directly or indirect on independent claim 1 or 2, with the exception of dependent claim 13. Claim 13 depends on independent claim 4, which recites:

4. A method of preventing prenatal neural tube deficiencies associated with increased maternal homocysteine levels comprising administering at least one tetrahydrofolate in natural stereoisomeric form to a female human subject.

Dependent claim 13 recites that the increased homocysteine levels “are associated with methylene tetrahydrofolate reductase deficiency,” and that the tetrahydrofolate “is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.”

C. Claim Construction

We determine the meaning of the claims as a step in our analysis for determining whether to institute a trial. Consistent with the statute and the legislative history of the AIA, the Board will interpret claims of an unexpired patent using the broadest reasonable construction in light of the specification of the patent. *See* Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48766 (Aug. 14, 2012); 37 CFR § 42.100(b).

Gnosis contends that no “special meanings apply to the claim terms in the ’040 patent.” Pet. 8. We agree and determine that, for purposes of this decision, there is no reason to depart from the “heavy presumption” that the claim terms are given their ordinary and customary meanings. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002).

II. DISCUSSION

A. Anticipation of claims 1-3, 5, 6, 8, 9, 11-15, and 19-22 by Serfontein

1. Overview of Serfontein

Serfontein discloses “a pharmaceutical preparation for lowering levels of homocysteine or for the prophylaxis or treatment of elevated levels of homocysteine in a patient.” Serfontein, p. 4, ll. 37-39. This preparation includes “folate or a suitable active metabolite of folate or a substance which releases folate in vivo,” vitamin B₆, and vitamin B₁₂. *Id.* at ll. 40-42. Serfontein identifies “elevated plasma homocysteine” as a “widely accepted” risk factor for “generalised arteriosclerotic disease” (p. 3, ll. 1-3). Serfontein also states that “several hereditary enzyme defects” are known to cause high levels of homocysteine, resulting in various “clinical defects” including “[p]recocious occlusive vascular disease frequently manifested clinically as . . . peripheral vascular occlusion” (p. 2, ll. 34-36 and 47-48). Serfontein discloses administering preparations to “human infants” (p. 4, ll. 25). Serfontein also describes optimizing use of the invention by monitoring homocysteine levels “in human plasma” (p. 12, ll. 32-33). Such teachings indicate that the preparations are to be administered to human patients. Serfontein discloses various dosage regimens, including once-daily dosing (p. 8, ll. 19).

Serfontein neither explains what is meant by “a suitable active metabolite of folate” nor cites any exemplary preparations that specify the source of folate activity as anything other than “folate” or folic acid.

2. Analysis

Gnosis generally argues that “the prior art teaches the administration of 5-methyl-(6S)-tetrahydrofolic acid for decreasing homocysteine levels in a human subject, both alone and in combination with other vitamins.” Pet. 4. Gnosis

contends that Serfontein discloses all elements of every challenged claim. Pet. 10-20. We begin our analysis with independent claims 1 and 2.

a. Claims 1 and 2

As noted by Gnosis (Pet. 8-10), Serfontein discloses the use of a composition comprising “a suitable active metabolite of folate,” as well as vitamin B₆ and vitamin B₁₂. *See, e.g.*, Serfontein, p. 4, ll. 37-42. Serfontein teaches the use of such a composition “for the prophylaxis or treatment of elevated levels of homocysteine” or of clinical conditions associated therewith in a patient. *Id.* For example, Serfontein teaches that elevated homocysteine levels correlate with vascular disease. *Id.* at p. 2, ll. 4-7, 34-48; *see also* Pet. 11; claim 2 (reciting a method of preventing/treating disease associated with increased levels of homocysteine levels).

Serfontein does not refer to a “tetrahydrofolate in natural stereoisomeric form” *per se* as recited in claims 1 and 2. Gnosis argues that “one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid.” Pet. 10-11.

Gnosis cites the declaration testimony of Dr. Miller in support of its arguments. Pet. 10-11 (citing Ex. 1005). Dr. Miller states that he is Professor of Nutritional Sciences at Rutgers University, has held various faculty appointments since 1997, and pursues research focused on “the relationships among B vitamins (folate, B12, B6), homocysteine, and various degenerative disorders.” Miller Decl. (Ex. 1005) ¶¶ 3-4.

Dr. Miller states that the phrase “active metabolite of folate” as used in Serfontein is “a phrase one of ordinary skill in the art would recognize to constitute a genus of no more than eight compounds.” Miller Decl. ¶ 10. To support his statement, Dr. Miller refers to the textbook *Modern Nutrition in Health and*

Disease, 7th Ed. (1988), which, according to Dr. Miller, describes “the biochemistry and metabolism of the active metabolites of folic acid . . . within the text and in Figure 21-4.” *Id.* at ¶ 18. Chapter 21 of *Modern Nutrition* is reproduced as Exhibit 1007. The paragraph bridging the columns on p. 391 of Ex. 1007 identifies eight compounds, not including variants resulting from glutamylation, as those that are “normally found . . . in foods or in the human body in significant concentrations”:

- (1) 7,8-dihydrofolate (“DHF”);
- (2) 5,6,7,8-tetrahydrofolate (“THF”);

and six “one carbon adduct[.]” forms of THF, listed in Figure 21-3 (Ex. 2007, p. 392):

- (3) N⁵formyl tetrahydrofolic acid (“THFA”);
- (4) N¹⁰formyl THFA,
- (5) N⁵formimino THFA,
- (6) N^{5,10}methenyl THFA,
- (7) N^{5,10}methylene THFA, and
- (8) N⁵methyl THFA.

Fig. 21-4 in *Modern Nutrition* illustrates how each of these eight compounds participates in a human folate metabolism pathway. Ex. 1007, p. 399. *Modern Nutrition* does not address the stereo-specificity of the tetrahydrofolates, but Dr. Miller notes that it does refer (p. 391) to an IUPAC nomenclature recommendation (submitted as Exhibit 1008), which identifies the “natural” folates as those having the same 6-carbon configuration as (6*S*)-tetrahydrofolate. Miller Decl. ¶ 18. From this disclosure, Dr. Miller concludes that one of ordinary skill in the art would have recognized “active metabolites of folate” as embracing “no more than” DHF and the naturally-occurring stereoisomers (i.e., those having the

L-configuration at carbon 6) of the other seven compounds listed above.

Miller Decl. ¶¶ 19-20.

Dr. Miller then explains that, of those eight compounds, only 5-methyl-(6S)-THF and 5-formyl-(6S)-THF would have been recognized by one having ordinary skill in the art as being “the active metabolites of folate *suitable* for consumption by humans as oral supplements.” Miller Decl. ¶ 21 (emphasis in original). Dr. Miller bases this statement on disclosure in European Patent Application EP 0 627 435 A1 (Ex. 1011) (“Ambrosini”) identifying these two compounds as being the more stable “‘in vivo active forms of folic acid’” and that “‘it is well known that the active forms are the (6S) ones.’” *Id.* (quoting Ambrosini, p. 2, ll. 5-6 and 31-32).

Upon review of Gnosis’s analysis and supporting evidence, we determine that Gnosis has demonstrated that there is a reasonable likelihood that it would prevail with respect to both claims 1 and 2 on the ground that these claims are anticipated by Serfontein. As discussed above, Serfontein discloses expressly all limitations of claims 1 and 2 except that the reference does not expressly refer to “tetrahydrofolate in natural stereoisomeric form” as recited in the claims. Serfontein *passim*. Serfontein at best makes a nonspecific reference to “a suitable active metabolite of folate.” *See id.* at, e.g., p. 4, l. 41. Gnosis addresses this gap with testimony of Dr. Miller, a professor of nutritional sciences whose relevant training and experience satisfy us that he is qualified to testify as to the understanding of a person of ordinary skill in the art at the time of the invention. *See* Miller Decl. ¶¶ 3-4.

We accept, for purposes of this decision, Dr. Miller’s testimony that one of ordinary skill in the art would have understood the phrase “a suitable active metabolite of folate” in Serfontein as referring to one of at most eight different

compounds. *See* Miller Decl. ¶ 10. Among these is 5-methyl-THFA, which refers generally to 5-methyl-(6*S*)-THFA, 5-methyl-(6*R*)-THFA, and/or a mixture of the two, although an “active” form would include at least some amount of 5-methyl-(6*S*)-THFA. *Id.* 5-methyl-(6*S*)-THFA is a tetrahydrofolate in “natural stereoisomeric form” (*i.e.*, [II]). Miller Decl. ¶ 18. Dr. Miller’s opinion has factual basis in the *Modern Nutrition* textbook, IUPAC nomenclature recommendations, and passages from Ambrosini that Dr. Miller cites.

Thus, we find the cited evidence to be sufficient to demonstrate a reasonable likelihood that claims 1 and 2 are anticipated by Serfontein. In particular, on this record, we find Dr. Miller’s testimony sufficient to establish that an ordinary artisan reading “suitable active metabolite of folate” in Serfontein would have at once envisaged each of the compounds in the small genus Dr. Miller identifies, including 5-methyl-(6*S*)-tetrahydrofolic acid.⁴ *See In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962) (affirming anticipation where, although the prior-art patent “did not expressly spell out the limited class” of about twenty compounds, “one skilled in this art would, on reading the [prior-art] patent, at once envisage each member of this limited class”); *In re Schaumann*, 572 F.2d 312, 316-17 (C.C.P.A. 1978) (affirming anticipation by concluding that where the reference “embraces a very limited number of compounds closely related to one another in structure, . . . the reference provides a description of those compounds just as surely as if they

⁴ We determine, however, that Dr. Miller’s assertion that one having ordinary skill in the art would regard only 5-methyl-(6*S*)-THF and 5-formyl-(6*S*)-THF as the “active metabolites of folate *suitable* for consumption by humans as oral supplements” (Ex. 1005, ¶ 21) is irrelevant to how one of ordinary skill in the art would have understood Serfontein. Serfontein does not limit what it regards as “suitable” to merely “consumption by humans as oral supplements.”

were identified in the reference by name.”). The evidence also demonstrates, for the purposes of instituting *inter partes* review, that Serfontein disclosed to an ordinary artisan the use of “at least one tetrahydrofolate in natural stereoisomeric form,” such as 5-methyl-(6*S*)-tetrahydrofolic acid, to decrease homocysteine levels or to treat/prevent disease associated with increased levels of homocysteine levels in a human.

For these reasons, we conclude that there is a reasonable likelihood that Gnosis will prevail in proving anticipation of claims 1 and 2 by Serfontein by a preponderance of the evidence.

b. Claims 3, 5, 6, 8, 9, 19, and 20

Claims 3, 5, 6, 8, 9, 19, and 20 each depend, either direct or indirectly, from independent claim 1 or 2. Claim 3 depends on claim 2, but specifies that the disease associated with increased levels of homocysteine levels is cardiovascular disease. Claims 5 and 6, which depend on claim 2 and 3 respectively, recite that the tetrahydrofolate is one of the seven specific folates [I] – [VII] mentioned above. *Supra* pp. 4-5. Claims 8 and 9, which also depend on claim 2 and 3 respectively, recite that the tetrahydrofolate is [II] 5-methyl-(6*S*)-tetrahydrofolic acid, or a salt thereof. Claim 19, which depends on claim 5, specifies that “the tetrahydrofolate is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.” Claim 20 depends on claim 19, and requires that “the pharmaceutically compatible active substance comprises at least one B-vitamin.”

Gnosis argues that Serfontein anticipates claim 3, 5, 6, 8, 9, 19, and 20 for the same reasons that it anticipates claims 1 and 2: that Serfontein discloses features meeting all limitations of the claim, among them 5-methyl-(6*S*)-THFA, a tetrahydrofolate in natural stereoisomeric form, which an ordinary artisan would

“at once envisage” as one of the eight compounds satisfying the “active metabolite of folate” disclosed in Serfontein. Pet. 12-15, 19-20. Regarding claim 3, Gnosis also argues that Serfontein teaches that elevated homocysteine levels correlate with vascular disease. Pet. 12-13 (citing Serfontein, p. 2, ll. 4-7, 34-54). For claims 19 and 20, Gnosis further points out that Serfontein discloses the use of a composition comprising “a suitable active metabolite of folate,” and well as vitamin B₆ and vitamin B₁₂, where vitamin B₆ and vitamin B₁₂ correspond to a “pharmaceutically compatible active substance” as recited in claims 19 and 20. Pet. 19-20; *see also* Serfontein, p. 4, ll. 37-42.

We have reviewed Gnosis’s arguments and evidence for each of these claims and find that Gnosis has demonstrated a reasonable likelihood that it will prevail in proving anticipation of claims 3, 5, 6, 8, 9, 19, and 20 by Serfontein by a preponderance of the evidence.

c. Claims 11-15, 21, and 22

Claims 11, 12, 14, 15, 21, and 22 each depend, either direct or indirectly, from claim 2 or 3. Claim 13 depends from independent claim 4. Claims 11-15, 21, and 22 all specify that the tetrahydrofolate is 5-methyl-(6*S*)-THFA, or a salt thereof, and that the increased levels of homocysteine are associated with either “methylene tetrahydrofolate reductase deficiency” or “thermolabile methylene tetrahydrofolate reductase deficiency.”

Regarding claims 11-15, 21, and 22, Gnosis reiterates arguments as discussed above regarding claims 1-3, 5, 6, 8, 9, 19, and 20. In addition, in relation to the “methylene tetrahydrofolate reductase deficiency” or “thermolabile methylene tetrahydrofolate reductase deficiency” also recited in claims 11-15, 21, and 22, Gnosis points to a disclosure in Serfontein that states: “The clinical condition of homocysteinuria, is an inborn error of metabolism which is either

caused by an enzyme defect in the transsulfuration pathway or a similar defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine.” Pet. 15-19, 20 (citing Serfontein, p. 3, ll. 20-23).

We find this disclosure in Serfontein to be insufficient to establish that the reference discloses, expressly or inherently, the specific enzyme deficiencies recited in the claims.

As noted above, claims 11-15, 21, and 22 recite a method of preventing or treating a disease associated with “methylene tetrahydrofolate reductase deficiency” or “thermolabile methylene tetrahydrofolate reductase deficiency.” As stated by Gnosis, Serfontein mentions “an enzyme defect in the transsulfuration pathway or a similar defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine.” Serfontein, p. 3, ll. 20-23. Gnosis does not establish in its petition, however, that the enzyme defects mentioned in Serfontein actually refer to a methylene tetrahydrofolate reductase deficiency in particular. *See* Pet. 15-20.⁵ Along these lines, we note that Fig. 21-4 in *Modern Nutrition* (Ex. 1007, p. 399) indicates that remethylation of homocysteine to methionine occurs via an enzyme called “homocysteine-methyl transferase,” not methylene tetrahydrofolate reductase. In addition, Gnosis points to nothing in Serfontein describing a deficiency of a “thermolabile” enzyme, as recited in claims

⁵ In relation to the recited enzyme deficiencies, Gnosis cites no evidence in support of its position except the Serfontein reference. Pet. 15-20. We note that Dr. Miller addresses these limitations in paragraphs 25 and 26 of his declaration (Ex. 1005). Dr. Miller’s declaration does not adequately explain, nor cite evidence in paragraphs 25 and 26 explaining, why one of ordinary skill would have understood the teaching of “an enzyme defect in the transsulfuration pathway or a similar defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine” in Serfontein to refer to the methylene tetrahydrofolate reductase deficiencies recited in claims 11-15, 21, and 22.

14 and 15. For these reasons, we conclude that Gnosis has not demonstrated a reasonable likelihood that claims 11-15, 21, and 22 are anticipated by Serfontein by a preponderance of the evidence.

B. Obviousness of claims 1- 3, 5, 6, 8, 9, 19, and 20 over Serfontein and Marazza

1. Overview of Marazza

Marazza (Ex. 1012) describes methods for the chiral resolution of 5-methyl-THF into its (6*R*) and (6*S*) diastereomers. Marazza, col. 1, ll. 12-16. Marazza specifically identifies 5-methyl-(6*S*)-THF, i.e., [II] 5-methyl-(6*S*)-tetrahydrofolic acid recited in claims 5, 6, 8, 9, and 11-15, as a “natural metabolite” of folate that may be used “as at least one active compound” in a vitamin therapy for folate deficiency. *Id.* at ll. 21-28, 55-67. Marazza cites a number of earlier studies expressing concern that the unnatural (6*R*) diastereomer of 5-methyl-THF interferes with folate uptake in mammalian cells. Col. 2, ll. 15-32. Marazza therefore seeks improved methods for separating the (6*R*) and (6*S*) diastereomers from one another, and describes a method that employs fractional crystallization of ammonium salts of the diastereomers. *Id.* at col. 3, ll. 32-40. In this regard, Marazza states that it provides “a simple, cheap and efficient process, by which a mixture of (6*RS*)-diastereoisomers of a N⁵-methyl-THF-derivative may be separated into the pure, single (6*R*) and (6*S*)-diastereoisomers.” *Id.* at ll. 32-36.

2. Analysis

Gnosis quotes Marazza as stating that “N⁵-methyl-THF,” i.e., [II] 5-methyl-(6*S*)-tetrahydrofolic acid (“5-methyl-(6*S*)-THFA”), “is the predominant circulating form of reduced folates in mammals.” Pet. 21 (citing Marazza, col. 1, ll. 20-28). Gnosis argues that Marazza also identifies “natural” 5-methyl-(6*S*)-THFA, as separated from “unnatural” 5-methyl-(6*R*)-THFA, as suitable for use in oral

vitamin supplements, and that one of ordinary skill in the art would, therefore, have had reason to use 5-methyl-(6*S*)-THFA as the “suitable active metabolite of folate” described in Serfontein’s preparations. Pet. 21-25 (citing Marazza, col. 1, ll. 27-28, col. 3, ll. 31-35). Thus, Gnosis concludes, it would have been obvious to combine Serfontein with Marazza to arrive at the subject matter of claims 1-3, 5, 6, 8, 9, 19, and 20. *Id.*

Upon review of Gnosis’s analysis and supporting evidence, we determine that Gnosis has demonstrated that there is a reasonable likelihood that it would prevail with respect to claims 1 and 2 on the ground that these independent claims would have been obvious over Serfontein and Marazza. On the present record, we agree with Gnosis that Marazza identifies 5-methyl-(6*S*)-THFA as an “active metabolite of folate” by referring to “the application of this natural metabolite as at least one active compound.” *See* Marazza, col. 1, ll. 25-27. We agree, again on the present record, that one of ordinary skill in the art would have found it obvious in view of this disclosure to use 5-methyl-(6*S*)-THFA as the “suitable active metabolite of folate” in Serfontein’s preparations.

Gnosis’s arguments concerning obviousness of dependent claims 3, 5, 6, 8, 9, 19, and 20 over Serfontein and Marazza parallel those given for anticipation by Serfontein, as well as those discussed above: Marazza’s preparation of the “pure, single” diastereomer 5-methyl-(6*S*)-THFA (col. 3, ll. 32-36) meets the limitations of these dependent claims, and that various passages in Serfontein meet the respective limitations of the other claims. Pet. 23-28, 31-32. We conclude that Gnosis has demonstrated a reasonable likelihood that these challenged claims are unpatentable.

For these reasons, we conclude that there is a reasonable likelihood that Gnosis will prevail in proving obviousness of claims 1- 3, 5, 6, 8, 9, 19, and 20 over Serfontein and Marazza.

C. Obviousness of claims 11, 12, 14, 15, 21, and 22 over Serfontein, Marazza, and Ubbink

1. Overview of Ubbink

Ubbink (Ex. 1019) presents a study assessing vitamin B₁₂, vitamin B₆ and “folate nutritional status” in men with hyperhomocysteinemia. Ubbink, p. 47, Title and Abstract. Ubbink states that “[n]umerous studies have indicated that elevated plasma homocysteine concentrations are associated with increased risk for premature occlusive vascular disease.” *Id.* at p. 50, 2nd col. Ubbink further teaches that the “reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, [i.e.,] cystathionine-β-synthase deficiency or possession of a thermolabile variant of methylenetetrahydrofolate reductase [], an enzyme required in the remethylation of homocysteine to methionine.” *Id.* (citation omitted).

2. Analysis

Gnosis argues that claims 11, 12, 14, 15, 21, and 22 are obvious for the same reasons that other challenged claims are anticipated by Serfontein, and obvious over Serfontein in view of Marazza, as discussed above. Additionally, Gnosis refers to the above-quoted portions in Ubbink, and particularly the passage describing “a thermolabile variant of methylene [] tetrahydrofolate reductase” (Ubbink p. 50, 2nd col.). Pet. 22, 28-33. Gnosis relies on this passage to support the argument that Ubbink describes an association between increased levels of homocysteine in the body and “methylene tetrahydrofolate reductase deficiency” or “thermolabile methylene tetrahydrofolate reductase deficiency,” as recited in

claims 11, 12, 14, 15, 21, and 22. According to Gnosis, one of ordinary skill in the art would have had reason to use 5-methyl-(6S)-THFA as the “active metabolite of folate” described in Serfontein for the purpose of preventing or treating a cardiovascular disease associated with the particular enzyme deficiencies recited in these claims, as taught in Ubbink. Pet. 22-23.

We have reviewed Gnosis’s arguments and evidence for each of these claims and conclude that Gnosis has demonstrated a reasonable likelihood that it will prevail in proving obviousness of claims 11, 12, 14, 15, 21, and 22 by Serfontein, in view of Marazza and Ubbink, by a preponderance of the evidence. The cited evidence is sufficient to demonstrate a reasonable likelihood that an ordinary artisan reading Serfontein, Marazza, and Ubbink would have understood that natural folates, such as 5-methyl-(6S)-tetrahydrofolic acid in particular, could be used to treat/prevent a cardiovascular disease associated with elevated levels of homocysteine caused by methylene tetrahydrofolate reductase deficiency, such as thermolabile methylene tetrahydrofolate reductase deficiency.

D. Obviousness of claim 13 over Serfontein, Marazza, Ubbink, and Scott

1. Overview of Scott

Scott (Ex. 1014) is entitled “Folic acid to prevent neural tube defects.” Scott discloses that various forms of dietary folates, such as folic acid, are converted in the body to “the single circulating form of 5-methyltetrahydrofolate (5-MTHF).” Scott, p. 505, 1st col. Scott further teaches that folic acid is a neurotoxin and convulsant in laboratory animals. *Id.* Scott advises pregnant women “to protect themselves by taking a lower dose of folic acid or more food that is rich in or fortified with folate.” *Id.* Scott also suggests conducting studies to assess whether administering certain levels of folic acid or 5-MTHF (i.e., 5-methyl-THFA) prevents neural tube defects. *Id.* at 1st col., 2nd col.

2. Analysis

Gnosis argues that claim 13 is obvious for the same reasons that other challenged claims are anticipated by Serfontein, and obvious over Serfontein in view of Marazza and Ubbink, as discussed above. Pet. 47-54. Additionally, Gnosis states that the Scott reference “is particularly relevant to Claim 13, which is directed to ‘preventing prenatal neural tube deficiencies associated with increased maternal homocysteine levels,’” as recited in independent claim 4. Pet. 45. Gnosis argues that “Scott discloses the use of 5-MTHF instead of folic acid when administering folate for the prevention of neural tube defects in order to avoid exposing the mother and fetus to unmetabolized folic acid, considered to be a neurotoxin.” *Id.*; *see also id.* at p. 54 (noting that Scott is “specifically directed to the prevention of neural tube defects”).

We have reviewed Gnosis’s arguments and evidence for claim 13 and conclude that Gnosis has demonstrated a reasonable likelihood that it would prevail in proving obviousness this claim over Serfontein, in view of Marazza, Ubbink, and Scott, by a preponderance of the evidence. The record before us supports the assertion by Gnosis that “one of ordinary skill in the art would have been motivated to use 5-methyl-(6S)-tetrahydrofolic acid as the active metabolite of folate in the preparations disclosed by Serfontein when treating an expectant mother to lower homocysteine levels so as to avoid the neurotoxicity dangers identified by Scott.” Pet. 47. All four references discuss the impact of folates on the body. An ordinary artisan reading references discussing folic acid and its natural counterparts, such Serfontein, Marazza, and Ubbink, would have understood that other relevant references, such as Scott, suggested that folates, including 5-methyl-(6S)-THFA, were useful to prevent prenatal neural tube deficiencies.

E. Remaining Grounds of Unpatentability

In addition to the four grounds of unpatentability that have been discussed above involving Serfontein alone and Serfontein in view of Marazza, Ubbink, and Scott, Gnosis also alleges multiple alternative grounds with respect to the challenged claims. Upon review of those alternative grounds, we conclude that they are redundant in light of the grounds on the basis of which we institute review.

III. CONCLUSION

For the foregoing reasons, we determine that Gnosis has demonstrated that there is a reasonable likelihood of its proving unpatentability of claims 1- 3, 5, 6, 8, 9, 11-15, and 19-22 of the '040 patent by a preponderance of the evidence.

IV. ORDER

For the reasons given, it is

ORDERED that the Petition is *granted* as to claims 1- 3, 5, 6, 8, 9, 11-15, and 19-22 with respect to the following grounds:

1. Unpatentability of claims 1- 3, 5, 6, 8, 9, 19, and 20 under 35 U.S.C. § 102 for anticipation by Serfontein;
2. Unpatentability of claims 1- 3, 5, 6, 8, 9, 19, and 20 under 35 U.S.C. § 103(a) for obviousness over Serfontein in view of Marazza;
3. Unpatentability of claims 11, 12, 14, 15, 21 and 22 under 35 U.S.C. § 103(a) for obviousness over Serfontein in view of Marazza and Ubbink; and
4. Unpatentability of claim 13 under 35 U.S.C. § 103(a) for obviousness over Serfontein in view of Marazza, Ubbink, and Scott;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '040 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial;

FURTHER ORDERED that all other grounds presented in Gnosis's petition are *denied*, and no ground other than those specifically granted above is authorized for the *inter partes* review as to claims 1- 3, 5, 6, 8, 9, 11-15, and 19-22; and

FURTHER ORDERED that an initial conference call with the Board is scheduled for 3 PM Eastern Time on July 24, 2013. The parties are directed to

the Office Trial Practice Guide, 77 Fed. Reg. 48756, 48765-66 (Aug. 14, 2012) for guidance in preparing for the initial conference call, and should come prepared to discuss any proposed changes to the Scheduling Order entered herewith and any motions the parties anticipate filing during the trial.

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