Trials@uspto.gov
Tel: 571-272-7822

Paper 71
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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 JACQUELINE WRIGHT BONILLA, SCOTT E. KAMHOLZ, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges.*

BONILLA, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. §318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Petitioners Gnosis S.p.A., Gnosis Bioresearch S.A., and Gnosis U.S.A., Inc. (collectively "Gnosis"), filed a Petition to institute an *inter partes* review of claims 1- 3, 5, 6, 8, 9, 11-15, and 19-22 of U.S. Patent No. 6,011,040 (Ex. 1004) ("the '040 patent") pursuant to 35 U.S.C. §§ 311-319. Paper 2 ("Pet."). On June 24, 2013, the Board instituted a trial with regard to each of the challenged claims on at least one ground of unpatentability. Decision to Institute (Paper 12, "Dec.").

After institution of trial, Merck & Cie ("Merck") filed a Patent Owner Response (Papers 36, 37; "Resp.")[1] to the Petition, as well as a Motion to Amend (Paper 28; "Mot. to Amend"). In its Motion to Amend, Merck requested cancellation of claims 1-3, 5, 6, and 13. Mot. to Amend 2. Gnosis filed a Reply to the Patent Owner Response (Papers 44, 45; "Reply").[2]

Gnosis filed a Motion to Exclude (Paper 52; "Pet. Mot. to Exclude") portions of declaration and deposition testimony of certain Merck witnesses, as well as certain exhibits. Merck filed an Opposition to the Motion to Exclude (Paper 58), and Gnosis filed a Reply (Paper 61). In addition, Merck filed a Motion to Exclude (Paper 54) three reference exhibits, as well as copies of two district court complaints. Gnosis filed an Opposition to the Motion to Exclude (Paper 56), and Merck filed a Reply (Paper 62).

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[1] On October 16, 2013, Merck filed a "public" redacted version of its Patent Owner Response (Paper 37), as well as a "confidential" version (Paper 36) and a Renewed Motion to Seal (Paper 33).

[2] On December 31, 2013, Gnosis filed a "public" redacted version of its Reply to the Patent Owner Response (Paper 45), as well as a non-redacted version (Paper 44), designated "Protective Order Material."

An oral hearing was held on March 20, 2014. A corrected transcript of the oral hearing is included in the record as Paper 69 ("Tr.").

The Board has jurisdiction under 35 U.S.C. § 6(c). This Decision is a final written decision under 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

Merck's Motion to Amend, requesting cancellation of claims 1-3, 5, 6, and 13 is granted. Thus, this Decision addresses Gnosis's patentability challenges regarding claims 8, 9, 11, 12, 14, 15, and 19-22 of the '040 patent. For the reasons discussed below, Gnosis has shown by a preponderance of the evidence that claims 8, 9, 19, and 20 are unpatentable under 35 U.S.C. § 102(b), and claims 8, 9, 11, 12, 14, 15, and 19-22 are unpatentable under 35 U.S.C. § 103(a). Both parties' Motions to Exclude are dismissed as moot and/or denied.

A. Related Proceedings

Contemporaneous with its Petition in this proceeding, Gnosis also filed Petitions for *inter partes* review of U.S. Patent Nos. 5,997,915, 6,673,381 B2, and 7,172,778 B2. Pet. 2. The Board has assigned those three Petitions the following case numbers: IPR2013-00116, IPR2013-00118, and IPR2013-00119, respectively. The '040 patent (owned by Merck) is not in the same family as the other three patents, which are related to each other and owned by South Alabama Medical Science Foundation.

Gnosis indicates that Merck asserted the '040 patent and the aforementioned three patents in *Merck & CIE, South Alabama Medical Science Foundation and Pamlab LLC vs. Macoven Pharmaceuticals, Gnosis S.p.A., Gnosis U.S.A., Inc. and Gnosis Bioresearch S.A.*, Case No. 6:12-00027-LED (E.D. Texas), as well as *In the Matter of Reduced Folate Nutraceutical Products and L-Methylfolate Raw Ingredients Used Therein*, Inv. No. 337-TA-857 (International Trade Commission). Pet. 1-2; *see also* Petitions in IPR2013-00116, IPR2013-00118, and

IPR2013-00119. The ’040 patent is also the subject of *ex parte* Reexamination No. 90/011,935, which is currently stayed pending the completion of this proceeding. Paper 10.

B. The ’040 Patent (Ex. 1004)

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.” Ex. 1004, 1:10-14. As explained in the ’040 patent, homocysteine is a thiol-containing amino acid that is formed upon demethylation of methionine. *Id*. at 1:37-38. 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 1:42-45, 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 B_6-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 B_{12}-dependent conversion of homocysteine to methionine. *Id*. at 1:46-53.

The ’040 patent discloses that “natural stereoisomeric form of tetrahydrofolates” (“THFA” or “THF”), 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 2:19-27. Thus, the ’040 patent identifies 5-methyl-(6S)-tetrahydrofolic acid and 5-formyl-

(6S)-tetrahydrofolic acid among the "natural stereoisomeric form of tetrahydrofolates." *Id.*[3]

Example 10 in the '040 patent describes a "combination preparation comprising 5-methyl-(6S)-tetrahydrofolic acid, vitamin B_6 and vitamin B_{12}" with "pharmaceutically compatible adjuvant substances." *Id.* at 5:9-19.

2. Claims

As discussed above, this Decision addresses Gnosis's patentability challenges regarding dependent claims 8, 9, 11, 12, 14, 15, and 19-22 of the '040 patent. All of those claims depend, directly or indirectly, from independent claim 2, which is reproduced below.

> 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.

Ex. 1004, 5:26-29.

Claims 8, 9, 11, 12, 14, 15, 21, and 22 further require a specific tetrahydrofolate, i.e., 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof. Claims 11, 12, 14, 15, 21, and 22 additionally recite that the increased levels of homocysteine (as recited in claim 2) are associated with "methylene tetrahydrofolate reductase deficiency" or "thermolabile methylene tetrahydrofolate reductase deficiency." Claims 9 and 12 further depend from dependent claim 3

[3] 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), 1:21-22, in which "tetrahydrofolic acid" is abbreviated as "THF."

(not at issue here), which requires that "the disease is cardiovascular disease." *Id*. at 5:29-31.

Claims 19 and 21 require administering a tetrahydrofolate in combination with an active substance or adjuvant, and claims 20 and 22 further require that the active substance be at least one B-vitamin.

Challenged claims 19 and 20 depend, directly or indirectly, from claim 5, which recites that the tetrahydrofolate of claim 2 is:

> [I] 5-formyl-(6S)-tetrahydrofolic acid,
> [II] 5-methyl-(6S)-tetrahydrofolic acid,
> [III] 5,10-methylene-(6R)-tetrahydrofolic acid,
> [IV] 5,10-methenyl-(6R)-tetrahydrofolic acid,
> [V] 10-formyl-(6R)-tetrahydrofolic acid,
> [VI] 5-formimino-(6S)-tetrahydrofolic acid, or
> [VII] (6S)-tetrahydrofolic acid,
> or salts thereof.

Those seven folates [I] – [VII], including [II] 5-methyl-(6S)-tetrahydrofolic acid specifically recited in other challenged claims, are "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, 2-3. By comparison, folic acid has a fully oxidized pteridine ring. *Id*.

All seven reduced folates also are 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-(6S)-tetrahydrofolic acid" ("L-5-MTHF") is the "S" diastereoisomer of 5-methyl-tetrahydrofolic acid ("5-MTHF") and has the L-configuration at carbon 6. Likewise, "10-formyl-(6R)-

tetrahydrofolic acid" is the "R" diastereomer of 10-formyl-tetrahydrofolic acid and also has the L-configuration at carbon 6.[4, 5]

C. Prior Art Relied Upon

In relation to the challenged claims at issue, and grounds upon which we instituted *inter partes* review (Dec. 21), Petitioner relies upon the following prior art references:

Reference	**Citation**	**Exhibit No.**
Serfontein	European Patent Appl. EP 0 595 005 A1	Ex. 1009
Marazza	U.S. Patent No. 5,194,611	Ex. 1012
Ubbink	Johan B. Ubbink et al., *Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia*, AM. J. CLIN. NUTR. 57:47-53 (1993)	Ex. 1019

D. Asserted Grounds of Unpatentability

The Board instituted *inter partes* review of the challenged claims of the '040 patent based on the following grounds of unpatentability.

[4] 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, 3 (section 2.6, 2nd ¶).

[5] The (6R) and (6S) 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), 1:67-2:6.

Claims	Basis	Reference(s)
8, 9, 19, and 20	§ 102	Serfontein
8, 9, 19, and 20	§ 103	Serfontein and Marazza
11, 12, 14, 15, 21, and 22	§ 103	Serfontein, Marazza, and Ubbink

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, a claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears. *See* 37 C.F.R. § 42.100(b) (2013). Under the broadest reasonable construction standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). In the absence of such a definition, limitations are not to be read from the specification into the claims. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993).

Gnosis asserts that no "special meanings apply to the claim terms in the '040 patent." Pet. 8. Merck contends that the recited phrase "5-methyl-(6S)-tetrahydrofolic acid" (which Merck also calls "L-5-MTHF") refers only to the "single natural isomer substantially free of its enantiomer," i.e., L-5-MTHF substantially free of D-5-MTHF, a non-natural isomer. Resp. 2-5. Merck also states that our Decision to Institute "implicitly [took] the position that a teaching in the prior art of administering a diastereoisomeric mixture of L-5-MTHF and D-5-

MTHF having any % proportion of the natural and unnatural isomer would meet" this claim element, because "all that is required is 'at least some amount' L-5-MTHF." *Id*. at 2-3 (citing Dec. 11).

As noted above, the challenged claims recite a method "comprising administering at least one tetrahydrofolate in natural stereoisomeric form to a human subject," where the tetrahydrofolate is, for example, "5-methyl-(6S)-tetrahydrofolic acid" or a salt thereof. Ex. 1004, challenged claims. Nothing in the challenged claims themselves, nor the specification of the '040 patent, indicates that the phrase "5-methyl-(6S)-tetrahydrofolic acid" refers to the natural isomer only when it is substantially free of its non-natural enantiomer, i.e., excludes the non-natural isomer present in a mixture of isomers. In fact, the claims and specification do not mention or define "substantially free" (a term proffered by Merck) in any context, and Merck does not suggest otherwise. Resp. 2-5.

Even assuming, as Merck points out, that "examples of the '040 patent describe compositions containing only the natural isomer," such examples do not correspond to the entire disclosure in the specification, or otherwise dictate that we import a limitation into the claim that is not recited. *Id*. at 4; *see Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1354 (Fed. Cir. 2012) ("While claim terms are understood in light of the specification, a claim construction must not import limitations from the specification into the claims"); *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc*., 381 F.3d 1111, 1117 (Fed. Cir. 2004) ("[E]ven where a patent describes only a single embodiment, claims will not be 'read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction'" (quoting *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004)).

The claims and specification of the ’040 patent, as a whole, do not indicate that the recited methods comprising administering L-5-MTHF exclude administering a mixture comprising both L-5-MTHF (natural form) and D-5-MTHF (non-natural form). A broadest reasonable reading of the challenged claims as a whole, in the context of the entire disclosure in the ’040 patent, indicates that one may meet the challenged claims if, *inter alia*, one administers “5-methyl-(6S)-tetrahydrofolic acid” (L-5-MTHF), regardless of whether one administers it as part of a mixture with other things, such as the corresponding non-natural isomer. There is no requirement in any challenged claim that one must administer L-5-MTHF or its salt by itself, substantially free of its enantiomer, or otherwise separate from a mixture comprising both L-5-MTHF and D-5-MTHF.

B. Anticipation of claims 8, 9, 19, and 20 by Serfontein

1. Overview of Serfontein (Ex. 1009)

Serfontein discloses “a pharmaceutical preparation for lowering levels of homocysteine or for the prophylaxis or treatment of elevated levels of homocysteine in a patient.” Ex. 1009, 4:37-39. This preparation includes “folate or a suitable active metabolite of folate or a substance which releases folate in vivo,” vitamin B_6, and vitamin B_{12}. *Id.* at 4:40-42. Serfontein identifies “elevated plasma homocysteine” as a “widely accepted” risk factor for “generalised arteriosclerotic disease.” *Id*. at 3:1-3. 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.” *Id*. at 2:34-36, 47-48. Serfontein further describes that elevated homocysteine levels correlate with myocardial infarction. *Id*. at 2:4-7, 34-48. Serfontein discloses administering preparations to “human infants.” *Id*. at 4:25. Serfontein also

describes optimizing use of the invention by monitoring homocysteine levels "in human plasma." *Id*. at 12:32-33. Such teachings indicate that the preparations are to be administered to human patients. Serfontein discloses various dosage regimens, including once-daily dosing. *Id*. at 8:19.

Serfontein does not explain what is meant by "a suitable active metabolite of folate," nor describe any exemplary preparations including a folate source as anything other than "folate" or folic acid.

2. Analysis

In its Petition, Gnosis provides a claim chart and relies on a Declaration by Dr. Joshua Miller (Ex. 1005) in support of its contention that Serfontein describes each and every element of claims 8, 9, 19, and 20. Pet. 8-20. In its Patent Owner Response, Merck contends that the reference does not disclose "administering at least one tetrahydrofolate in natural stereoisomeric form," such as "5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof," as required by the claims. Resp. 5-10 (citing Ex. 2001 ¶¶ 65-80).

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 B_6 and vitamin B_{12}. *See, e.g.*, Ex. 1009, 4:37-42. Serfontein describes 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 describes that elevated homocysteine levels correlate with myocardial infarction and vascular disease. *Id*. at 2:4-7, 34-48; *see* Pet. 11.

Serfontein does not refer to a "tetrahydrofolate in natural stereoisomeric form" *per se*, or 5-methyl-(6S)-tetrahydrofolic acid (L-5-MTHF). Gnosis contends, however, 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.

In support, Gnosis cites the declaration testimony of Dr. Miller. Pet. 10-11 (citing Ex. 1005 ¶ 21). 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." Ex. 1005 ¶ 10. To support his statement, Dr. Miller refers to the textbook *Modern Nutrition in Health and Disease*, 7th ed. (1988) ("*Modern Nutrition*"), 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.* ¶ 18.

Gnosis provides a copy of Chapter 21 of *Modern Nutrition* as Exhibit 1007. In this chapter, *Modern Nutrition* describes that folate and folic acid are "the preferred synonyms" for pteroylglutamate and pteroylglutamic acid, and that pteroylglutamic acid (folic acid) is "an oxidized compound [that] is not normally found as such in food or in the human body in significant concentrations." Ex. 1007, 391. Instead, "[t]he forms that are found in such sources are the reduced forms indicated in Figure 21-3." *Id*. (citing Fig. 21-3, *id*. at 392). The chapter further describes that "all [forms found in food and in the body] are reduced folates and, except for 7,8-dihydrofolate, all are 5,6,7,8-tetrahydrofolates (THF)." *Id*. In addition, the chapter states that "the number of glutamate residues may vary from one to seven, and sometimes up to 11, each linked by peptide bonds." *Id.*

In Figure 21-3 and in the descriptions discussed above, *Modern Nutrition* identifies eight relevant compounds, including six "1-carbon adduct[]" forms of THF, but not including variants resulting from glutamylation, 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"),

(3) N^5formyl tetrahydrofolic acid ("N^5formyl THFA") ("5-FTHF"),

(4) N^{10}formyl THFA,

(5) N^5formimino THFA,

(6) $N^{5,10}$methenyl THFA,

(7) $N^{5,10}$methylene THFA, and

(8) N^5methyl THFA (i.e., 5-MTHF).

Id. at 391-92. Fig. 21-4 in *Modern Nutrition* also illustrates how each of these eight compounds participates in a human folate metabolism pathway. *Id*. at 399.

Modern Nutrition does not address the stereospecificity of the tetrahydrofolates, but Dr. Miller states that it refers on page 391 to an IUPAC nomenclature recommendation (submitted as Ex. 1008), which identifies the "natural" folates as those having the same configuration at the 6-carbon as (6S)-tetrahydrofolate. Ex. 1005 ¶ 18; Ex. 1007, 391, 1st col.; Ex. 1008, 3 (stating that "[r]educed compounds are indicated by the prefixes 'dihydro-', 'tetrahydro-', etc.," and "[a]ll of the known natural stereoisomers have the same configuration as (6*S*)-tetrahydrofolate"). 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. *Id*. ¶¶ 19-20.

Dr. Miller then states that, of those eight compounds, only the 6S diastereoisomers of 5-MTHF (i.e., L-5-MTHF) and 5-FTHF (i.e., L-5-FTHF) 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." *Id*. ¶ 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 disclosing that "it is well known that the active forms are the 6(S) ones." Ex. 1005 ¶ 21 (quoting Ex. 1011, 2:5-6 and 30-33).

In response, Merck contends that Gnosis necessarily relies on the phrase "suitable active metabolite of folate" in Serfontein, which Merck abbreviates "SAMOF." Resp. 5 (citing Ex. 2001 ¶ 65). Contrary to Gnosis's position that this phrase refers to a limited number of compounds, Merck contends that "the scope of SAMOF is extraordinarily broad." *Id*. at 7. Citing a Declaration by Dr. Jesse Gregory (Ex. 2001), who refers to portions of Dr. Miller's deposition testimony (Exs. 2063, 2064), Merck states that "compounds falling within the scope of SAMOF potentially encompass thousands of reduced folates in any form," including salt forms, and "polyglutamate forms and crystalline forms." *Id*. at 7, 8 (citing Ex. 2001 ¶¶ 73, 74). In addition, Merck contends that Serfontein describes different preparations for dose forms comprising "SAMOF, such as (1) sub-lingual tablets; (2) plasters designed for skin absorption; (3) rectal pesaries; (4) formulated gels or ointments; or (5) topical solutions." *Id*. at 7.

Merck further contends that SAMOF, as described in Serfontein, refers to a compound that is sufficiently stable for use in the formulations identified in Serfontein. *Id*. According to Merck, however, each of the eight compounds described in Dr. Miller's Declaration (Ex. 1005 ¶¶ 18-20) is in the free acid form, which is unstable, and therefore, "unsuitable." Resp. 7-8 (citing Ex. 2001 ¶ 67). Merck contends that when one considers suitable potential acid salts of these compounds, one would consider "over 100, resulting in thousands of potential species of compounds within the class SAMOF," when multiplied by many possible glutamation states. *Id*. at 8. Merck also contends that, other than referring

to SAMOF, Serfontein emphasizes folic acid and fails to attach "significance to using a particular reduced folate, let alone L-5-MTHF." *Id*. Thus, according to Merck, an ordinary artisan would not have envisaged immediately each member of the entire class of compounds within SAMOF. *Id*. at 8-9; *see also* Dec. 11 (*citing In re Petering*, 301 F.2d 676, 681 (CCPA 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")).

Lastly, Merck relies on its proposed claim construction of "5-methyl-(6S)-tetrahydrofolic acid" as referring to the natural isomer free or essentially free of the unnatural isomer. Resp. 9. According to Merck, Serfontein cannot anticipate any of the challenged claims because this reference indiscriminately covers "the entire continuum of compositions containing relative proportions of the natural and unnatural isomer of reduced folate (1% to 99%), making no express mention as to the exclusion of any particular amount of the unnatural isomer." *Id*.

In relation to this last point, as we explain above, the challenged claims do not require administering L-5-MTHF or its salt by itself, substantially free of its D 5 diastereoisomer, or otherwise separate from a mixture comprising both L-5-MTHF and D-5-MTHF. Thus, we are not persuaded by Merck's contentions based on its unreasonably narrow reading of the claims.

The issue then becomes whether an ordinary artisan would have envisaged, at once, each member of a limited class of compounds encompassed by the phrase "suitable active metabolite of folate" in Serfontein. *See Petering*, 301 F.2d at 681. Merck does not dispute Gnosis's position that one would have envisioned the eight reduced folate compounds, including 5-methyl-tetrahydrofolic acid (N^5-methyl THFA or 5-MTHF), disclosed in *Modern Nutrition* (Ex. 1007, 391-392) in some

form when reading the phrase "suitable active metabolite of folate" in Serfontein (Ex. 1009, 4). *Accord* Tr. 25:1 21. Rather, Merck essentially argues that one would have envisaged "thousands" of sub-species of compounds or preparations falling with the eight species of compounds falling within the genus of "suitable active metabolites of folate" disclosed in Serfontein. Resp. 7. The challenged claims at issue, however, recite compounds in terms of a "tetrahydrofolate in natural stereoisomeric form," and more specifically, in terms of seven THF compounds, such as 5-methyl-(6S)-tetrahydrofolic acid (i.e., L-5-MTHF), or their salts generally. Thus, the claims do not recite, and are not limited to, any specific salt, polyglutamate and/or crystalline form or preparation type.

Thus, even assuming one would have envisaged "thousands" of unclaimed salt, polyglutamate and/or crystalline forms or preparations, as Merck contends, such a fact does not undermine Gnosis's contention, and evidence in support, indicating that one would have envisaged a small number of compounds, including 5-methyl-(6S)-tetrahydrofolic acid or its salt, i.e., the "natural" form of 5-MTHF, when reading the phrase "suitable active metabolite of folate" in Serfontein.

On this record, we are persuaded by Dr. Miller's testimony that an ordinary artisan reading the phrase "suitable active metabolite of folate" in Serfontein would have at once envisaged each of the compounds in the small number of compounds that Dr. Miller identifies, including 5-methyl-(6S)-tetrahydrofolic acid, as recited in challenged claims.[6] Testimony by Dr. Gregory (Ex. 2001 ¶¶ 66-82), cited by

[6] We determine, however, that Dr. Miller's assertion that one having ordinary skill in the art would regard only L-5-MTHF and L-5-FTHF 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."

Merck, does not persuade us otherwise in view of what the challenged claims themselves recite, i.e., a "tetrahydrofolate in natural stereoisomeric form," such as "5-methyl-(6S)-tetrahydrofolic acid, or salt thereof," without reciting any specific salt, polyglutamate, crystalline or dose form of any kind.

We are persuaded that Serfontein describes a limited number of relevant compounds by virtue of its express teaching of administering a "suitable active metabolite of folate" in a relevant method, and "it is of no moment that each compound is not specifically named or shown by structural formula in that publication." *See* Ex. 1009, 4:37-42; *In re Petering*, 301 F.2d at 681; *In re Schaumann*, 572 F.2d 312, 316-17 (CCPA 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 were identified in the reference by name."); *Eli Lilly and Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1376-77 (Fed. Cir. 2006).

The evidence also demonstrates by a preponderance of evidence that Serfontein describes the use of "at least one tetrahydrofolate in natural stereoisomeric form," such as 5-methyl-(6S)-tetrahydrofolic acid, in combination with vitamin B_6 and B_{12}, to treat or prevent disease, such as cardiovascular disease, associated with increased levels of homocysteine levels in a human, as recited in the challenged claims. Ex. 1009, 4:37-42; 2:4-7, 34-48; 18:50-56

Upon review of Gnosis's Petition and supporting evidence, as well as Merck's Patent Owner Response and supporting evidence, we conclude that Gnosis has demonstrated, by a preponderance of the evidence, that Serfontein anticipates claims 8, 9, 19, and 20 of the '040 patent.

C. Obviousness of claims 8, 9, 19, and 20 over Serfontein and Marazza

1. Overview of Marazza (Ex. 1012)

Marazza describes methods for the chiral resolution of 5-methyl-THF into its (6R) and (6S) diastereoisomers. Ex. 1012, 1:12-16. Marazza specifically identifies 5-methyl-(6S)-THF (or L-5-MTHF), i.e., 5-methyl-(6S)-tetrahydrofolic acid as recited in claims 8, 9, and 5 (upon which claims 19 and 20 depend), 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 1:21-28, 55-67. Marazza cites a number of earlier studies expressing concern that the unnatural (6R) diastereoisomer of 5-methyl-THF interferes with folate uptake in mammalian cells. *Id*. at 2:15-32. Marazza therefore seeks improved methods for separating the (6R) and (6S) diastereoisomers from one another, and describes a method that employs fractional crystallization of ammonium salts of the diastereoisomers. *Id.* at 3:32-40. In this regard, Marazza states that it provides "a simple, cheap and efficient process, by which a mixture of (6RS)-diastereoisomers of a N^5-methyl-THF-derivative may be separated into the pure, single (6R) and (6S)-di[]astereoisomers." *Id*. at 3:32-36.

2. Analysis

In its Petition, Gnosis quotes Marazza as stating that "N^5-methyl-THF," i.e., 5-methyl-(6S)-tetrahydrofolic acid (L-5-MTHF), "is the predominant circulating form of reduced folates in mammals." Pet. 21 (citing Ex. 1012, 1:20-28). Gnosis contends that Marazza also identifies "natural" 5-methyl-(6S)-THFA (i.e., L-5-MTHF), as separated from "unnatural" 5-methyl-(6R)-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 L-5-MTHF. Pet. 21-25 (citing Ex. 1012, 1:27-28, 3:31-35).

Thus, Gnosis concludes, it would have been obvious to an ordinary artisan to use L-5-MTHF, as disclosed in Marazza, as an "active metabolite of folate" in Serfontein's method, and one would have had a reasonable expectation of success in doing so. Pet. 21-22.

The parties do not dispute that one of ordinary skill would have had knowledge of Serfontein and Marazza. Marazza expressly discloses salts of 5-MTHF and describes processes for separating the natural "6S" form of 5-MTHF from the "unnatural (6R)-diastereoisomer." Ex. 1012, 1:10-19, 1:55-2:20. Because Marazza taught that "[t]here exists an increasing interest for the application of this natural metabolite [(L-5-MTHF)] as at least one active compound in a therapeutic agent, for example as vitamin in folate deficient states," an ordinary artisan would have had reason to use L-5-MTHF as the "suitable active metabolite of folate" in Serfontein's method. *Id*. at 1:25-28; Ex. 1009, 4:37-42.

In relation to such teachings, Merck responds that generally, prior to 1997, an ordinary artisan would not have considered "natural isomers of reduced folate as a credible source for folate supplementation," citing Dr. Gregory's Declaration in support. Resp. 11 (citing Ex. 2001 ¶ 12). Specifically, Merck first contends that folate metabolism, via the methionine cycle, is complex and not well understood. *Id*. at 11-13. Merck contends that because of its complexity and "the potential to disrupt these folate cycles (among others) thereby causing undesired side effects," one would not have considered reduced folates to be a credible alternative to folic acid. *Id*. at 12-13. Merck's underlying reasoning here, based on the "complexity" of the methionine cycle, however, suggests that one would never consider using *any* compound involving complicated biochemical pathways as a therapeutic agent, a contention Merck neither makes nor supports with evidence. Moreover, the record does not establish adequately that one would have thought folic acid

acted differently from natural reduced folates in relation to the asserted "undesired side effects" in relation to the methionine cycle. *Id*. at 11-13. On that note, Merck does not suggest that one would not have considered folic acid as a credible source for folate supplementation at the time of invention. *See, e.g., id*. at 15.

Merck also contends that an ordinary artisan would have understood that reduced folates, such as L-5-MTHF:

(1) were not as bioavailable as folic acid;
(2) had poor substrate activity for synthesis of polyglutamates in the body;
(3) disrupted the "exquisite control" involved in a body's folate regulation;
(4) had poor stability; and
(5) had limited commercial availability and were more difficult to synthesize than folic acid.

Resp. 13 (citing Ex. 2001 ¶ 27).

In relation to (1) the bioavailability of naturally occurring reduced folates, evidence cited by Merck, and specifically, Dr. Gregory's Declaration and cited references therein, suggest that folic acid is more bioavailable than natural folates. *Id*.; Ex. 2001 ¶ 28. Such evidence does not suggest, however, that prior to 1997, an ordinary artisan would have had reason to think that naturally occurring reduced folates were not bioavailable at all, or otherwise had no use, i.e., were unacceptable or unsuitable, as therapeutic agents. *See*, *e.g.*, Ex. 2001 ¶ 28 (citing Gaull et al., (1996) at 777S (Ex. 2035) (stating that "folic acid is approximately twice as bioavailable as the naturally occurring folate conjugates present in food")); *see also In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) ("just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes."). Moreover, in its Reply, Gnosis points us to evidence indicating the contrary. Reply 13 (citing Ex. 1029, 200 (stating that "[i]n some other cells, the concentration of folic acid required to generate adequate

concentrations of intracellular folates is 100-200 times that of reduced folates such as 5-methyl tetrahydrofolate (THF)")). In view of the totality of evidence on this record, we are persuaded that ordinary artisans would have considered chemically related natural variants of folic acid for the uses to which folic acid was put. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

In relation to (2) substrate activity for the synthesis of polyglutamates, Merck's Dr. Gregory refers to deposition testimony of Gnosis's Dr. Miller, which Merck interprets as stating that "as L-5-MTHF is a poor substrate for polyglutamation, it inhibits the ability of the cellular tissues to store this folate," and "L-5-MTHF is not well retained in cells." Ex. 2001 ¶ 29 (citing Ex. 2063, 103:11-22 (deposition testimony by Dr. Miller discussing a "report of Dr. Barry Shane")).[7] Dr. Gregory further refers to "Wagner (1978) at 3531 ('Thus, under the conditions of the present study, isolated hepatocytes did not significantly metabolize 5-CH3-H4PteGlu [i.e., L-5-MTHF].')," as well as a paragraph in Shane (Ex. 2052). *Id*. (citing Ex. 2052, 539-40).

When reviewing the evidence as a whole before us, we are not persuaded that an ordinary artisan, especially one reading Serfontein and Marazza, would have had reason to think that natural reduced folates had no use as therapeutic agents, particularly considering the "complex" nature of relevant biochemical

[7] Dr. Miller's deposition testimony in this regard forms part of an exchange in which he was quoted statements from a "report of Dr. Barry Shane" and asked whether he agreed with each statement. Ex. 2063, 100:20-22; 102:7-104:9; 272:7. The relied-upon testimony does not identify the "report" further, and Merck does not identify where a copy of this report is of record in this proceeding. In addition, nothing in the relied-upon testimony indicates that Dr. Miller was told to consider statements in the report in any context other than present day, rather than in the context of what an ordinary artisan would have understood in 1997 or earlier.

pathways. *See* Resp. 12; Ex. 2001 ¶ 19. For example, Merck does not explain how an experimental result, obtained under particular conditions in vitro from cells isolated from their normal environment, is probative of how 5-MTHF is processed in vivo. In addition, Dr. Miller states in his deposition that in some cases, "[t]here would be certain metabolic blocks in folate metabolism that would warrant use of a specific reduced form over the folic acid." Ex. 2063, 105:6-9; *see also id*. at 103:11-105:23. In addition, other evidence of record suggests that L-5-MTHF *does*, in fact, accumulate in isolated hepatocytes. *See* Ex. 2061, 3534 ("In the present study we have shown that 5-CH_3-H_4-PteGlu . . . is concentrated by hepatocytes").

Moreover, we are not persuaded by Merck's discussion of Ueland (Ex. 1013) in this context. Resp. 14-16. Our review of Ueland indicates that it adds nothing to the discussion about what one would have known about L-5-MTHF as a substrate for polyglutamation, or whether L-5-MTHF would accumulate in tissues. *See, e.g.*, Ex. 1013, 486, 2nd col., 488, 1st col, 489 (discussing "Folic acid"), 495 (stating that "[p]lasma homocysteine level is decreased by high doses of folic acid").

In relation to (3) Merck's contention that reduced folates would disrupt the body's "exquisite control" of folate regulation, Merck states that one would have thought that L-5-MTHF, but not folic acid, would produce "detrimental health impacts in humans," and "potentially caus[e] undesirable health issues." Resp. 17 (citing Ex. 2001 ¶¶ 38, 39). Under Merck's reasoning regarding the body's "exquisite control" of folate regulation, however, one would never consider using any compound involved in complicated, i.e., "controlled," biochemical pathways as a therapeutic agent, a contention Merck does not make or support with evidence.

Moreover, Merck does not explain adequately why or how one would have thought folic acid would act differently from L-5-MTHF in relation to asserted "detrimental" or "undesirable" effects. *Id*. Merck does not explain sufficiently why an ordinary artisan would have thought that L-5-MTHF would "bypass [] internal feedback loops," but folic acid "would still be subject to the body's internal regulation." *Id*. Dr. Gregory's testimony, as cited by Merck, likewise does not provide sufficient explanation. *See* Ex. 2001 ¶¶ 38, 39. For example, Dr. Miller's agreement that "5-methyltetrahydrofolate bypasses the enzyme methylenetetrahydrofolate reductase" does not establish sufficiently that L-5-MTHF would "bypass [] internal feedback loops" in a detrimental way. *Id*. ¶ 38 (citing Ex. 2064, 153:18-154:23, 163:5-9).

Merck's contentions that reduced folates (4) were considered unstable and (5) difficult to synthesize, and therefore had limited commercial availability, likewise do not persuade us that one would have had reason to think that natural reduced folates had no use as therapeutic agents, especially upon reading Serfontein and Marazza. *See* Resp. 17-19. One of ordinary skill in the art is presumed to have been aware of both Serfontein and Marazza. *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Serfontein calls for a "suitable active metabolite of folate" in preparations used to correct folate deficiency and treat diseases associated with elevated levels of homocysteine. Ex. 1009, 3:30-35, 4:37-42. Marazza specifically identifies chirally-pure L-5-MTHF as an active metabolite of folate suitable for use as a therapeutic agent in folate deficient states. Ex. 1012, 1:21-28. The close similarity of purpose and disclosure between these references would have provided sufficient rationale for one of ordinary skill in the art to have combined the teachings therein. *See KSR*, 550 U.S. at 418.

Even assuming it was understood that reduced folates were less stable and harder to synthesize, such considerations would not have taught away from using Marazza's 5-methyl-(6S)-tetrahydrofolic acid salt as a "suitable active metabolite of folate" in Serfontein's method in view of express teachings in both references. *See, e.g.*, *Fulton*, 391 F.3d at 1201; *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (stating that "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes"). Likewise, any "focus" by references, such as Ueland or Serfontein, on folic acid, likewise did not teach away from using a "suitable active metabolite of folate" as disclosed expressly in Serfontein. Resp. 14-16, 20-21; Ex. 1009, 4:37-42.

In relation to Marazza, Merck contends that this reference's teaching of "an increasing interest" in using 5-methyl-(6S)-tetrahydrofolic acid as a "vitamin in folate deficient states" was incorrect, citing Goodman and Gilman, a pharmacology textbook. Resp. 21-22 (referring to Ex. 2036, and quoting Ex. 1012, 1:25-28). Specifically, Merck quotes Goodman and Gilman as stating that "[t]he principal indication for the use of folinic acid [5-FTHF] is to circumvent the action of inhibitors of dihydrofolate reductase, such as methotrexate . . . . *It is not indicated for use in the treatment of folic acid deficiency*." *Id*. at 21-22 (emphasis in Resp.) (quoting Ex. 2036, 1304). Goodman and Gilman states simply, however, that folinic acid is not *indicated* for treating folate deficiency. Ex. 2036, 1304. It does not follow from this statement that folinic acid is not *suitable* for treating deficiency because there may be reasons other than suitability to explain why folinic acid is not indicated for that purpose. *See, e.g.*, Ex. 2063, 151:24-154:18 (Dr. Miller opining that the basis for the "not indicated" statement may be the higher cost or shorter shelf life of folinic acid compared to folic acid). Moreover, as Merck notes, Goodman and Gilman refers to "reduced folate 5-formyl

tetrahydrofolic acid (5-FTHF)," but does not mention other reduced folates, such as L-5-MTHF, which is expressly discussed in Marazza. Resp. 21. Merck does not explain adequately why Goodman and Gilman's statement concerning folinic acid (5-FTHF) is relevant to the issue of whether one of ordinary skill would have considered the use of other reduced folates, particularly 5-MTHF, for treating a disease associated with increased levels of homocysteine. Thus, we remain persuaded that one reading Serfontein would have considered 5-methyl-(6S)-tetrahydrofolic acid (L-5-MTHF) a viable choice, as expressly taught in Marazza, for a suitable active metabolite of folate in Serfontein's method.

Merck also contends that Marazza "does not relate to lowering serum homocysteine levels," and focuses on "cancer therapy, not addressing any issue regarding homocysteine." *Id*. at 22. Marazza states, however, that ordinary artisans understood that one could use 5-methyl-(6S)-tetrahydrofolic acid "in a therapeutic agent, for example as vitamin in folate deficiency states." Ex. 1012, 1:21-28. Immediately thereafter, Marazza further states that such therapeutic agents "may *also* be used" in relation to reducing toxicity of cancer treating compounds. *Id*. at 1:28-33 (emphasis added). Thus, any "focus" by Marazza on cancer therapy would not have detracted from the express teaching in the same reference that L-5-MTHF was a known suitable active metabolite of folate.

Lastly, Merck contends that Marazza "clearly leaves [an ordinary artisan] uncertain regarding the biological function of the unnatural isomer," i.e., the 6R form of 5-MTHF. Resp. 24. Our reading of Marazza, however, indicates that this reference suggests that the unnatural 6R form "is inert and is excreted," or possibly "could interfere to the folate transport system." Ex. 1012, 2:8-20. In view of Marazza's teaching about beneficial uses of the natural 6S form, and its disclosed methods for separating the 6S and 6R diastereoisomer forms, we are persuaded that

an ordinary artisan would have had reason to use the 6S form of 5-MTHF by itself, separated from the 6R form, when using the natural reduced folate as a suitable active metabolite of folate in Serfontein's method.

In addition to the contentions above, Merck argues that objective indicia (secondary considerations) further establish non-obviousness of the claimed subject matter. Resp. 28. We analyze Merck's proffered evidence in this regard in section E. below.

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

1. Overview of Ubbink (Ex. 1019)

Ubbink presents a study assessing vitamin B_{12}, vitamin B_6 and "folate nutritional status" in men with hyperhomocysteinemia. Ex. 1019, 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 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*. (nomenclature and citation omitted).

2. Analysis

Gnosis argues that claims 11, 12, 14, 15, 21, and 22 would have been 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." Pet. 22, 28-33 (citing Ex. 1019, 50, 2nd col.). 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 L-5-MTHF 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.

Merck responds that Ubbink does not make up for the previously mentioned "deficiencies" in Serfontein and Marazza, discussed above. Resp. 25. In relation to Ubbink itself, Merck contends that this reference "is a study involving only folic acid," and "provides no data using L-5-MTHF, and makes no conclusions about using L-5-MTHF." *Id*. at 25-26. Thus, according to Merck, "there is no suggestion in Ubbink that [L-5-MTHF] would be effective in dealing with methylene tetrahydrofolate reductase deficiency or thermolabile methylene tetrahydrofolate reductase deficiency." *Id*. at 26. Merck further contends that "Ubbink independently reinforces the state of the art teaching at the time, including Ueland, that the correct course of action would be to use folic acid." *Id*. at 27.

As noted above, Ubbink teaches that it was known that "elevated plasma homocysteine concentrations are associated with increased risk for premature occlusive vascular disease," consistent with teachings in Serfontein. Ex. 1019, 50, 2nd col.; Ex 1009, 2:34-48. Ubbink further teaches that hyperhomocysteinemia may be due to deficient enzymes, such as "a thermolabile variant of

methylene[]tetrahydrofolate reductase, an enzyme required in the remethylation of homocysteine to methionine." Ex. 1019, 50, 2nd col.

For reasons discussed already, we are persuaded that an ordinary artisan would have had reason to use 5-methyl-(6S)-tetrahydrofolic acid as a suitable active metabolite of folate in Serfontein's method as a means to prevent or treat a disease associated with increased levels of homocysteine levels. We also are persuaded that one would have had reason to believe, upon reading Ubbink, that increased levels of homocysteine were associated with enzymes deficiencies, such as "methylene tetrahydrofolate reductase deficiency," or "thermolabile methylene tetrahydrofolate reductase deficiency," as recited in claims 11, 12, 14, 15, 21, and 22. Merck's contentions that Ubbink provides data regarding folic acid, but not L-5-MTHF in particular, is inadequate to persuade us otherwise, especially in view of what an ordinary artisan would have known in relation to methylene tetrahydrofolate reductase, "an enzyme required in the remethylation of homocysteine to methionine" using 5-MTHF. *Id.*; Ex. 1007, 399, Fig. 24-1.

E. Objective Indicia of Non-Obviousness

In addition to the contentions above, Merck argues that objective indicia, including commercial success (Resp. 28-40), licensing (*id*. at 41-43), copying (*id*. at 43-47), long-felt but unmet need (*id*. at 47-52), unexpected results (*id*. at 52-54), previous skepticism (*id*. at 54-56), and later industry praise (*id*. at 56-60), "is the most probative evidence showing that the inventions of the claims at issue are non-obvious." *Id*. at 28. In support, Merck relies on, *inter alia*, Declarations of multiple witnesses. *See, e.g.*, Exs. 2001 (Gregory), 2003 (Gardner), 2005 (Stahl), 2007 (Jacobs), 2010 (Kerr), 2015 (Katz), 2017 (Hoffman), 2020 (Reisetter), 2022 (Ladner).

In relation to the asserted objective indicia, Merck cites evidence stemming from several products. Resp. 28-29. Those products are:

1. Metafolin®, a trade name for substantially chirally-pure 5-methyl-(6S)-tetrahydrofolic acid (L-5-MTHF), as a calcium salt, manufactured and sold by Merck, for use in nutritional supplements and medicinal foods (Resp. 28-29 (citing Ex.2015 ¶¶ 9, 11));[8]
2. Cerefolin®, which contains Metafolin® (L-5-MTHF), riboflavin (vitamin B_2), cyanocobalamin (a form of vitamin B_{12}), and pyridoxine hydrochloride (a form of vitamin B_6), for the clinical dietary management of hyperhomocysteinemia (Resp. 29 (citing Ex. 2022 ¶ 30; Ex. 2001 ¶¶ 123-46); Ex. 2251 (package insert));
3. Metanx®, which contains Metafolin® (L-5-MTHF), methylcobalamin (another form of vitamin B_{12}), and pyridoxal 5'-phosphate (another form of vitamin B_6), for the clinical dietary management of endothelial dysfunction in patients with diabetic peripheral neuropathy ("DPN") (Resp. 29 (citing Ex. 2022 ¶ 30; Ex. 2001 ¶¶ 123-46); Ex. 2001 ¶¶ 125-128; Ex. 2007 ¶ 10; Ex. 2078 (package insert));
4. Deplin®, which contains Metafolin® (L-5-MTHF), for the clinical dietary management of the metabolic imbalances associated with depression and schizophrenia, including adjunctive use for treatment of major depressive disorder ("MDD") (Resp. 29 (citing Ex. 2022 ¶ 30; Ex. 2001 ¶¶ 123-46); Ex. 2001 ¶¶ 135-137; Ex. 2003 ¶¶ 36-37; Ex. 2005 ¶¶ 34-35; Ex. 2162 (package insert));

[8] During the oral hearing, counsel for Merck clarified that it does not rely on Metafolin® *per se* in relation to commercial success, but rather on products containing Metafolin®. Tr. 38:22-40:2.

5. CerefolinNAC®, which contains Metafolin® (L-5-MTHF), methylcobalamin, and N-acetylcystine, for the clinical dietary management of metabolic imbalances associated with mild or moderate cognitive impairment ("MCI") and vascular dementia (Resp. 29 (citing Ex. 2022 ¶ 30; Ex. 2001 ¶¶ 123-46); Ex. 2001 ¶¶ 129-132; Ex. 2010 ¶¶ 29-30; Ex. 2085 (package insert));
6. Néevo® prescription prenatal vitamins, which contains Metafolin® (L-5-MTHF) and a range of vitamins and minerals, including the cyanocobalamin form of vitamin B_{12} and the pyridoxine hydrochloride form of vitamin B_6, for nutritional supplementation during pregnancy and pre- and post-natal periods (Resp. 29 (citing Ex. 2022 ¶ 30; Ex. 2001 ¶¶ 123-46); Ex. 2001 ¶¶ 139-143; Ex. 2079 (package insert)); and
7. NeevoDHA® prescription prenatal vitamins, which contains Metafolin® (L-5-MTHF), methylcobalamin, pyridoxine hydrochloride, algal oil (a source of docosahexaenoic acid ("DHA")), and a range of other vitamins and minerals, for nutritional supplementation during pregnancy and pre- and post-natal periods (Resp. 29 (citing Ex. 2022 ¶ 30; Ex. 2001 ¶¶ 123-46); Ex. 2001 ¶¶ 139-143; Ex. 2080 (package insert)).

Except Metafolin®, which is manufactured and sold by Merck, each of the products above is manufactured and sold by Pamlab under sublicense from Merck. *Id*. at 28-29, 32-38. As noted above, each of the Pamlab products includes Metafolin® (L-5-MTHF) as an active ingredient, either alone (in the case of Deplin®) or in combination with other active and inactive ingredients.

Merck argues, and Gnosis does not dispute, that administration of each of the above Pamlab products to a patient falls within the scope of the claims under review. Resp. 28.

It is not sufficient, however, that a product or its use merely falls within the scope of a claim in order for objective evidence of nonobviousness tied to that product to be given substantial weight. There must also be a causal relationship, termed a "nexus," between the evidence and the claimed invention. *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). A showing of sufficient nexus is required in order to establish that the evidence relied upon traces its basis to a novel element in the claim, not to something in the prior art. *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013). Objective evidence that results from something that is not "both claimed and novel in the claim" lacks a nexus to the merits of the invention. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Nexus must exist in relation to all types of objective evidence of nonobviousness. *GPAC*, 57 F.3d at 1580 (generally); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success); *In re Antor Media Corp.*, 689 F.3d 1282, 1293 (Fed. Cir. 2012) (licensing); *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012) (copying); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1313 (Fed. Cir. 2006) (failure of others); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need); *Kao*, 639 F.3d at 1069 (unexpected results); *Stamps.com Inc. v. Endicia, Inc.*, 437 F. App'x 897, 905 (Fed. Cir. 2011) (skepticism); *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008) (praise).

Thus, for objective evidence to be accorded substantial weight, the record "must establish a nexus between the evidence and the merits of the claimed invention." *GPAC*, 57 F.3d at 1580. Moreover, establishing nexus involves a showing that novel elements in the claim, not prior-art elements, account for the objective evidence of nonobviousness. *See Kao*, 639 F.3d at 1068. As the Federal

Circuit explains, "[t]o the extent that the patentee demonstrates the required nexus, his objective evidence of nonobviousness will be accorded more or less weight." *GPAC*, 57 F.3d at 1580. Thus, the stronger the showing of nexus, the greater the weight accorded the objective evidence of nonobviousness. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985).

1. Commercial Success

Merck points us to evidence of commercial success of the Pamlab products, citing dollar figures for net sales, growth in sales over the years, licensing arrangements between Pamlab and Merck, as well as sales of unauthorized copies of the Pamlab products. Resp. 29-40. Merck contends that such commercial success is "directly attributable to claimed features" of the challenged claims. *Id.* at 32-38.

Notably, however, with the exception of Deplin®, all Pamlab products contain a number of specific active ingredients combined with L-5-MTHF (Metafolin®). In relation to commercial success, the evidence must show "both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent." *GPAC*, 57 F.3d at 1580 (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988); *Crocs, Inc. v. International Trade Com'n*, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010). Our review of the '040 patent indicates that, while it discloses using vitamins B_6 and B_{12} in combination with L-5-MTHF generally, it does not mention specific forms of any vitamins, minerals, or other active ingredients, in relation to combination products. Ex. 1004, 3:11-22, 5:9-21. Nor does the '040 patent mention such specific combinations for use in particular indications, such as those presented in package inserts for the different Pamlab products. *Id.*; *see also* Exs. 2078-80, 2085, 2162, 2251 (package inserts).

Consistently, the challenged claims themselves do not recite the various active ingredient combinations found in Pamlab products (except Deplin®), nor recite any specific uses other than to "prevent[] or treat[] disease associated with increased levels of homocyteine levels" generally, as recited in independent claim 2. At most, the challenged claims recite certain tetrahydrofolates, such as L-5-MTHF, and in the case of claim 22, also recite "at least one B-vitamin." Thus, we are not persuaded that the '040 patent presents adequately that "the thing (product or method) that is commercially successful is the invention *disclosed and claimed* in the patent." *GPAC*, 57 F.3d at 1580 (emphasis added).

Moreover, regarding products other than Deplin®, the record before us does not establish that commercial success of such products, in relation to the indicated uses, is due to the use of L-5-MTHF in particular, rather than the use of a bioavailable folate of any kind generally, in combination with specific other ingredients, such as certain B vitamins.

In addition, to the extent Merck contends that special advantages exist in relation to Pamlab's unique combination products, Merck implies that other formulations (having different components or forms) would not offer necessarily the same benefits for the same therapeutic goals. Consequently, the challenged claims encompass numerous species for which Merck offers not only no objective evidence of nonobviousness, but also suggests implicitly would not work as the Pamlab products work. We are left, then, with no adequate basis on which to conclude that the other embodiments falling within the claim will behave in the same manner as the embodiments for which evidence is offered. *See Kao*, 639 F.3d at 1068.

We note that Merck describes Deplin®, which comprises Metafolin® (L-5-MTHF) as its only active ingredient, for use in adjunctive treatment of major

depressive disorder ("MDD"). Resp. 33-34. The challenged claims do not recite this particular use. To the extent that Merck contends that the objective evidence has nexus with the challenged claims through administration of L-5-MTHF, without regard to what other specific active ingredients accompany it, we are not persuaded. Marazza discloses the use of L-5-MTHF as an oral vitamin agent for treatment of folate deficiency. Ex. 1012, 1:21-28, 1:36-37.

Furthermore, evidence of record indicates that the use of methylfolate (5-MTHF) generally for the treatment of depression, such as MDD, or schizophrenia due to folate deficiency, was known previously in the art. Ex. 1024, 392. As disclosed in Godfrey et al. in 1990, researchers already knew to "use[] the methyl derivative of folate for treatment as it is this form which is actively transported across the blood brain barrier and which is detectable in the cerebrospinal fluid in concentrations three times greater than in serum." Ex. 1024, 392, 1st col.; *see also* Reply 2.[9] Consistently, in 1990, Le Grazie taught the use 5-MTHF "in the therapy of organic mental disturbances." Ex. 1010, Abstract; *see also id*. at 2-3, 7

[9] During the oral hearing, Merck argued that, during a deposition, Dr. Stahl questioned what an ordinary artisan would have understood or found credible in Godfrey (Ex. 1024) and/or Le Grazie (Ex. 1010), citing Ex. 2313, 53:16-55:12, 84:15-85-6 (regarding Godfrey), 181:9-183:20 (regarding Le Grazie). *See, e.g.,* Tr. 32:20-33:7 (referring to Merck's slides citing Ex. 2313). Our reading of that deposition testimony by Dr. Stahl (Ex. 2313, 53:16-55:12, 84:15-85-6), which provides conclusory opinions at best, does not persuade us that an ordinary artisan reading Godfrey and/or Le Grazie (which cites Godfrey) would have failed to understand or find credible Godfrey's teachings regarding the use of 5-MTHF for the treatment of major depression or schizophrenia. For example, when questioned about a statement in Godfrey that a "close association between depression and folate deficiency has been reported and there is also much interest in methylation and schizophrenia" (Ex. 1024, 392, 1st col.), Dr. Stahl opined that "I think most people thought this was baloney," without providing a basis for that opinion. Ex. 2313, 53:16-55:12.

(describing (±) and (-) 5-MTHF, and clinical trials verifying therapeutic effects of 5-MTHF in "organic mental disturbances with depression of mood," and use of MTHF calcium salt); *see also* Reply 3.

Accordingly, before 1997, an ordinary artisan had reason to use 5-MTHF, rather than synthetic folic acid for example, for the treatment of diseases, such as MDD and schizophrenic, requiring that folate cross the blood brain barrier to be effective. We are persuaded by Gnosis's position that Merck "attribute[s] the effectiveness of Deplin® to the ability of 6(S)-5-MTHF to cross the blood-brain barrier, yet this is the same reason prior art researchers administered 5-MTHF." Reply 10 (citing Resp. 51). Further, as discussed above, as early as 1993, an ordinary artisan had reason to use the 6S form of 5-MTHF in particular, as it was known to be "the predominant circulating form of reduced folates in mammals," and useful in treating folate deficient states. Ex. 1012, 1:21-29; *see also* Ex. 1010, 2:22-33.

Based on evidence before us, we are not persuaded that "the objective indicia of non-obviousness [is] tied to the novel elements of the claim at issue" in this case. *Institut Pasteur*, 738 F.3d at 1347; *Kao*, 639 F.3d at 1068. As such, insufficient nexus exists.

Accordingly, based on the record before us, we find evidence of nexus in relation to commercial success to be tenuous. We therefore accord Merck's cited evidence of commercial success little weight.

2. Licensing

Merck refers to licensing by Pamlab and other companies of the '040 patent as additional objective evidence of nonobviousness. Merck does not indicate, however, whether these companies licensed other additional patents from Merck and/or others in order to manufacture and sell its products. *See* Resp. 41-43

(arguing that companies thought the ’040 patent was valid and licensed it to “avoid infringement,” citing testimony by Dr. Katz (Ex. 2015) and Mr. Ladner (Ex. 2022)). We note that package inserts for the Pamlab products, for example, indicate that other patents “may apply,” including U.S. Patent No. 6,441,168 (“the ’168 patent”), as pointed out by Gnosis. Ex. 2162 (Deplin® insert); Exs. 2078-80, 2085, 2251 (other package inserts); Reply 11. Evidence of companies licensing the ’040 patent, among other relevant patents, provides inadequately nexus, by itself, in relation to objective evidence of nonobviousness based on such licenses.

As noted by Gnosis, the ’168 patent, which issued in 2002, and also assigned to Merck, relates to “highly crystalline salts” of 5-MTHF having “excellent stability,” after indicating “it has not been possible hitherto to identify a commercially feasible method which is suitable for the production of salts of 5-methyltetrahydrofolic acid” that are “satisfactorily stable” and “of high purity.” Ex. 1044, 1:44-61; Reply. 10-11. Gnosis provides evidence indicating that “no sales of Pamlab’s products occurred until 2004, predictably after the 2002 release of Metafolin®.” *Id*. at 11 (citing Ex. 2311, “Parties’ Joint Stipulation of Undisputed Facts,” ¶¶ 65-72).

Thus, evidence indicates that companies, such as Pamlab, licensed other patents relating to different forms of specific components in its products, and not merely the ’040 patent reciting broader subject matter. In relation to what is more broadly claimed in the challenged claims, as discussed above, the evidence indicates that subject matter encompassed by the challenged claims of the ’040 patents was known in the art prior to 1997. *See also Institut Pasteur*, 738 F.3d at 1347; *Kao*, 639 F.3d at 1068.

Consequently, based on the record before us, we find evidence of nexus in the context of licensing to be tenuous. We therefore accord Merck's cited evidence of licensing little weight.

3. Copying by Others

Merck contends that a number of Pamlab competitors, such as Macoven, Viva Pharmaceuticals, and others, replicated Pamlab's formulations for sale for the same indicated uses. Resp. 43-47. For the same reasons discussed above in relation to commercial success and licensing, however, we are not persuaded that this "objective indicia of non-obviousness [is] tied to the novel elements of the claim at issue" in this case, which do not recite specific formulations for specific uses. *Institut Pasteur*, 738 F.3d at 1347; *Kao*, 639 F.3d at 1068.

Consequently, based on the record before us, we find evidence of nexus in the context of copying to be tenuous. We therefore accord Merck's cited evidence of copying little weight.

4. Long-Felt but Unmet Need

Merck contends that claims 8 and 11 of the '040 patent, reciting L-5-MTHF in particular, "fulfilled a long-felt but unmet need for an adjunctive therapy for treating Major Depressive Disorder ("MDD")." Resp. 48, *see also id*. at 47-52. Merck states that "[p]rior to June 1997, others tried, but failed, to create effective adjunctive treatments for MDD." *Id*. at 49 (citing Ex. 2005 ¶¶ 29-33, 46; Ex. 2003 ¶¶ 30-35, 48).

As discussed above, however, the use of methylfolate, i.e., 5-MTHF, for the treatment of MDD due to folate deficiency was known in the art. Ex. 1024, 392; Ex. 1010, Abstract, 2-3, 7 (describing (±) and (-) 5-MTHF, clinical trials verifying therapeutic effects of 5-MTHF in "organic mental disturbances with depression of mood," and use of MTHF calcium salt). As discussed above, we are persuaded

that Merck "attribute[s] the effectiveness of Deplin® to the ability of 6(S)-5-MTHF to cross the blood-brain barrier, yet this is the same reason prior art researchers administered 5-MTHF." Reply 10 (citing Resp. 51). Testimony by Dr. Stahl (*see, e.g.*, Ex. 2005 ¶¶ 29-33) and Dr. Gardner (*see, e.g.*, Ex. 2003 ¶¶ 30-35, 48), cited as evidence by Merck (Resp. 47-52), do not address relevant teachings in the prior art in this regard. Further, as discussed above, L-5-MTHF itself was known in the art as early as 1993, as "the predominant circulating form of reduced folates in mammals," and for use in treating folate deficient states. Ex. 1012, 1:21-29; *see also* Ex. 1010, 2:22-33.

Consequently, we are not persuaded by Merck's contentions in relation to long-felt but unmet need.

5. Unexpected Results

Merck contends that substantially chirally-pure L-5-MTHF is unexpectedly more potent than racemic 5-MTHF and more bioavailable than folic acid. Resp. 52-54. For example, Merck contends that "at the time of the invention, [an ordinary artisan] would not have known (or even predicted) that L-5-MTHF was significantly more potent than racemic 5-MTHF." Resp. 53 (citing Ex. 2001 ¶¶ 106-108).

As an initial matter, as explained above, the challenged claims encompass the use of racemic 5-MTHF, and are not limited to the use of L-5-MTHF substantially free of its enantiomer. As recently explained by the Federal Circuit, "[i]t is the established rule that 'objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.'" *Allergan, Inc. v. Apotex, Inc.*, Appeal No. 2013-1245, slip op. 22-23 (Fed. Cir. June 10, 2014) (quoting *Application of Tiffin*, 448 F.2d 791, 792 (CCPA 1971); citing *Kao*, 639 F.3d at 1068). Here, Merck's contentions regarding unexpected

results in relation to L-5-MTHF versus racemic 5-MTHF are not commensurate in scope with the claims at issue.

Moreover, as discussed above, in 1993, Marazza identified specifically chirally-pure L-5-MTHF as an active metabolite of folate suitable for use as a therapeutic agent in folate deficient states. Ex. 1012, 1:21-28. In addition, Marazza stated that "[i]t has been assumed, that the unnatural (6R)-diastereoisomer of N^5-methyl-THF is inert," but cites earlier studies expressing concern that the unnatural (6R) diastereoisomer of 5-MTHF interferes with folate uptake in mammalian cells. *Id*. at 2:15-32. Thus, Marazza sought improved methods for separating the (6R) and (6S) diastereoisomers from one another. *Id.* at 3:8-40. We are persuaded that such teachings would have suggested to an ordinary artisan that L-5-MTHF would have been more potent than racemic 5-MTHF comprising both active L-5-MTHF (active) and D-5-MTHF (inert and/or interfering).

In relation to bioavailability, Merck contends that "it was unexpectedly shown that the bioavailability of L-5-MTHF is significantly greater than folic acid." Resp. 54 (citing Ex. 2001 ¶ 111). In support, Merck cites testimony by Dr. Gregory (Ex. 2001 ¶ 111), who in turn cites Willems et al. (Ex. 2062, 827), without pointing adequately to evidence indicating that such bioavailability was, in fact, "significantly greater" or that the ascertained bioavailability was unexpected. In view of teachings in Marazza, and other references, that L-5-MTHF was "the predominant circulating form of reduced folates in mammals," we are not persuaded that it was unexpected that L-5-MTHF was more bioavailable than folic acid. Ex. 1012, 1:20-28; Ex. 1010, 2:22-33; *see also* Reply 13 (citing Ex. 1029, 200 (stating that "[i]n some other cells, the concentration of folic acid required to generate adequate concentrations of intracellular folates is 100-200 times that of reduced folates such as 5-methyl tetrahydrofolate (THF)")).

We note that Merck also refers to a reference by Gregory et al. (Ex. 1028) when discussing bioavailability of L-5-MTFH versus folic acid, as understood before 1997. Resp. 13 (citing Ex. 1031, but referring to Ex. 1028). In this reference, Dr. Gregory states that study results "indicate that differences exist in the bioavailability of monoglutamyl folates under these experimental conditions." Ex. 1028, abstract. Merck does not point us to where this reference or other evidence indicated to one of ordinary skill in the art before 1997 that folic acid would be more bioavailable than L-5-MTHF in all relevant conditions. Rather, the evidence before us as a whole indicates that one would have understood that assessed "bioavailability" would depend on testing conditions, and therefore variability under different conditions would exist.

Consequently, we are not persuaded by Merck's contentions in relation to unexpected results.

6. Industry Skepticism/Skepticism of Experts

Merck contends that "[a]t the time of the invention, the industry was skeptical about even using L-5-MTHF as a means to lower homocysteine levels," referring to "possible adverse health effects" and "its disruptive effects over the folate regulation within the human body." Resp. 54 (citing Ex. 2001 ¶¶ 113-120).

Merck does not explain adequately, however, why one would have thought L-5-MTHF would act differently from folic acid (also in the prior art) in relation to asserted "health" or "disrupted" effects. *Id*. at 54-56. Merck does not explain sufficiently why an ordinary artisan would have thought that L-5-MTHF would bypass controls, while folic acid would not. *Id*. Dr. Gregory's testimony, as cited by Merck, likewise does not provide sufficient explanation. Ex. 2001 ¶¶ 113-120.

7. Industry Praise

Merck contends that the "patented features of the '040 patent have garnered significant praise," as seen in articles describing the "superior safety and efficacy of L-5-methylfolate as an adjunctive treatment for MDD." Resp. 56-57. Merck also refers to praise by its experts regarding Metanx® and CerefolinNAC® in relation to the treatment of specific diseases. *Id*. at 58. In addition, Merck notes an award it received for Metafolin®, i.e., L-5-MTHF used in Pamlab's products. *Id*. at 58-59. Merck also points out that Gnosis "intentionally misrepresented its bulk racemic product, 5-MTHF calcium salt as the substantially pure active isomer L-5-MTHF calcium salt." *Id*. at 59-60.

Once again, however, for the same reasons discussed above, we are not persuaded that Merck establishes sufficient nexus in relation to the products being praised versus what is "both claimed and novel in the claim." *Kao*, 639 F.3d at 1068.

8. Analysis of Objective Indicia of Non-Obviousness as a Whole

The bulk of Merck's evidence regarding objective indicia of non-obviousness relies on products made and sold by Pamlab under sublicense from Merck. One difficulty with Merck's position, however, is that the challenged claims do not recite, and the '040 patent does not disclose, the specific active ingredient combinations found in the Pamlab products (except Deplin®), and do not recite or disclose the specific indicated uses of such products (including Deplin®). In addition, as discussed above, to the extent that Merck argues that the objective evidence has nexus with the claims through administration of L-5-MTHF, without regard to other active ingredients accompanying it, we are not persuaded. Marazza expressly discloses the use of L-5-MTHF as an oral vitamin agent for treatment of folate deficiency. Ex. 1012, 1:21-28, 1:36-37. As such, the

objective evidence for each product lacks a sufficient nexus in relation to the challenged claims.

Gnosis makes a strong argument for obviousness of the challenged claims. We agree that the language Marazza uses to describe L-5-MTHF—"this natural *metabolite* as at least one *active* compound in a therapeutical agent, for example as vitamin in *folate deficiency states*" (emphasis added)—would have commended L-5-MTHF to one of ordinary skill in the art as being one of Serfontein's "suitable active metabolite[s] of folate." Ex. 1012, 1:25-29; Ex. 1009, 4:37-42.

Merck's objective evidence is not sufficient to overcome the strong showing of obviousness in this case. As noted above, all types of objective evidence cited by Merck require a nexus with the claimed subject matter. Merck's evidence relies, however, on combinations of certain components and/or specific therapeutic uses not recited in the challenged claims. As a result, the causal relationship between the claimed subject matter and the objective evidence is tenuous, at best.

This is particularly true for the evidence of commercial success, licensing, copying, and industry praise, because that evidence is tied intimately to certain Pamlab products indicated and sold for specific uses. *See Allergan*, slip op. 22-23 ("It is the established rule that 'objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.'") (quoting *Tiffin*, 448 F.2d at 792); *Kao*, 639 F.3d at 1068. By contrast, the challenged claims relate to the use of a natural tetrohydrofolate, e.g., L-5-MTHF, to prevent or treat any disease associated with increased levels of homocysteine. The claims do not require any particular use, nor any specific combination with other components, except in claim 22, which recites generally "at least one B-vitamin."

Merck's evidence of long-felt need, unexpected results, and skepticism also lack sufficient nexus because they are tied in particular to L-5-MTHF. The use of "natural" 5-MTHF (i.e., L-5-MTHF) was known in the art, as discussed above. Consequently, it cannot be used to tie the objective evidence to the claimed subject matter. *See Tokai*, 632 F.3d at 1369 ("If commercial success is due to an element in the prior art, no nexus exists").

Because Merck has not shown adequate nexus persuasively in relation to any asserted objective indicia, and/or because evidence before us does not support sufficiently Merck's contentions, e.g., in relation to long-felt need, unexpected results, and skepticism, Merck's cited objective evidence does not persuade us that the challenged claims would not have been obvious to an ordinary artisan in 1997. When we balance Gnosis's strong evidence of obviousness against Merck's asserted objective evidence of nonobviousness, we determine that a preponderance of the evidence supports Gnosis's position that it would have been obvious to combine the teachings of Serfontein and Marazza to reach the subject matter of claims 8, 9, 19, and 20, and to combine the teachings of Serfontein, Marazza, and Ubbink to reach the subject matter of claims 11, 12, 14, 15, 21, and 22.

Accordingly, we conclude that Gnosis has demonstrated the unpatentability of claims 8, 9, 11, 12, 14, 15, and 19-22 of the '040 patent by a preponderance of the evidence.

III. MOTION TO AMEND

Merck moves to cancel claims 1-3, 5, 6, and 13. Mot. to Amend 2. Gnosis does not oppose. The motion is granted.

IV. MOTIONS TO EXCLUDE EVIDENCE

A. Merck's Motion

Merck moves to exclude Gnosis Exhibits 1054 (DiPalma et al.), 1060 (Bottiglieri et al.), and 1141 (Regland et al.) as inadmissible hearsay, as well as Exhibits 1102 and 1103 (district court complaints) for lack of authentication. PO Mot. to Exclude 1-2.

We dismiss Merck's motion as moot, because we do not rely on any of the objected-to evidence in our final Decision.

B. Gnosis's Motion

Gnosis moves to exclude Exhibits 2001, 2007, 2010, 2015, 2017, 2020, 2022, 2063, 2064, 2065, 2073, and 2074 (witness/expert declaration or deposition testimony, expert reports, or lists), in whole or in part, citing various provisions of the Federal Rules of Evidence. Pet. Mot. to Exclude 1-11.

We deny Gnosis's motion regarding these exhibits relating to witness testimony, reports, or lists. Similar to a district court in a bench trial, the Board, sitting as a non-jury tribunal with administrative expertise, is well-positioned to determine and assign appropriate weight to evidence presented. *See, e.g.*, *Donnelly Garment Co. v. NLRB*, 123 F.2d 215, 224 (8th Cir. 1941) ("One who is capable of ruling accurately upon the admissibility of evidence is equally capable of sifting it accurately after it has been received . . . ."). Thus, in this *inter partes* review, the better course is to have a complete record of the evidence to facilitate public access as well as appellate review. *See id.* ("If the record on review contains not only all evidence which was clearly admissible, but also all evidence of doubtful admissibility, the court which is called upon to review the case can usually make an end of it, whereas if evidence was excluded which that court regards as having been admissible, a new trial or rehearing cannot be avoided."). We have

considered Gnosis's arguments for excluding the above-mentioned evidence, but either do not rely on the specific portions of evidence cited by Gnosis in our Decision, or assign weight to the evidence as appropriate in view of the entire record before us.

Gnosis also moves to exclude Exhibits 2039, 2048, 2049, 2052, 2055 (scientific references cited by Dr. Gregory) and Exhibits 2082, 2090, 2099, 2134, 2148, 2149 (print-outs from third parties), 2180, 2183, 2184, 2185, 2229, 2188, 2213, 2214, 2188, 2213, 2214, 2281, 2296, 2283, 2284 (relating to Macoven and Viva products or district court documents), 2230-2241 (third-party survey documents), again citing various provisions of the Federal Rules of Evidence. Pet. Mot. to Exclude 8, 11-14. We dismiss Gnosis's motion as moot in relation to those exhibits because we do not rely on any of those objected-to evidence in our final Decision.

V. CONCLUSION

Gnosis has proved, by a preponderance of the evidence, that: (1) Serfontein anticipates claims 8, 9, 19, and 20; (2) claims 8, 9, 19, and 20 would have been obvious over the combined teachings of Serfontein and Marazza; and (3) claims 11, 12, 14, 15, 21, and 22 would have been obvious over the combined teachings of Serfontein, Marazza, and Ubbink.

VI. ORDER

For the reasons given, it is

ORDERED that claims 8, 9, 11, 12, 14, 15, and 19-22 of U.S. Patent No. 6,011,040 are determined to be UNPATENTABLE;

FURTHER ORDERED that Merck's Motion to Amend claims is *granted*, and, accordingly, that claims 1-3, 5, 6, and 13 be CANCELED;

FURTHER ORDERED that Merck's Motion to Exclude is *dismissed as moot*;

FURTHER ORDERED that Gnosis's Motion to Exclude is *denied-in-part and dismissed as moot-in-part*; and

FURTHER ORDERED that because this is a final Decision, parties to the proceeding seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

For PETITIONER:

Jonathan J. Krit
Janine A. Moderson
Amin Talati, LLC

Joseph E. Cwik
Erik B. Flom
Husch Blackwell LLP

For PATENT OWNER:

Thomas Parker
Jitendra Malik
Alston & Bird, LLP

Brion P. Heaney
Anthony J. Zelano
Millen, White, Zelano & Branigan, P.C.