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Paper 68
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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

SOUTH ALABAMA MEDICAL SCIENCE FOUNDATION
Patent Owner

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Case IPR2013-00116
Patent 5,997,915

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

KAMHOLZ, *Administrative Patent Judge*.

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

# I. INTRODUCTION

## *A. Background*

Petitioner Gnosis S.p.A., Gnosis Bioresearch S.A., and Gnosis U.S.A., Inc. (collectively, "Gnosis") filed a Petition (Paper 3 ("Pet.")) to institute an *inter partes* review of claims 37, 39, 40, 47, 66, 67, 73, 76, 78-81, 83, 84, 86-89, 91, 92, 94-97, 99, 100, 110, and 111 ("the challenged claims") of U.S. Patent No. 5,997,915 (Ex. 1001 ("the '915 patent")).[1] The Board instituted trial for the challenged claims on the following grounds of unpatentability asserted by Gnosis:

| **Reference(s)**[2] | **Basis** | **Claims challenged**[3] |
|---|---|---|
| Serfontein | § 102 | 37, 39, 40, 66, 73, 76, 78, 80, 81, 83, and 84 |
| Serfontein and Marazza | § 103 | 37, 39, 40, 47, 66, 67, 73, 76, 78-81, 83, 84, 86-89, 91, 92, 94-97, 99, 100, 110, and 111 |

Decision to Institute 2-3 (Paper 8 ("Dec.")).

[1] Each of the challenged claims except claims 37, 39, and 40 was added to the patent by issuance of an *ex parte* reexamination certificate on December 13, 2011, upon termination of reexamination proceeding 90/009,680.

[2] The references are: European Patent Application EP 0 595 005 A1 (Ex. 1009 ("Serfontein")) and U.S. Patent No. 5,194,611 (Ex. 1012 ("Marazza")).

[3] Claims 39, 40, 47, 66, 67, 73, 76, 78, and 86 are multiple dependent claims, and claims 79-81, 83, 84, 87-89, 91, and 92 depend from multiple dependent claims. These claims are challenged only to the extent that they trace claim dependency through claim 37. Dec. 7. The other claims from which the multiple dependent claims alternatively depend are not challenged. *Id.*

After institution of trial, South Alabama Medical Science Foundation ("SAMSF") filed a Patent Owner Response in redacted form (Paper 25) and unredacted form (Paper 24). With our authorization (Paper 29), SAMSF filed a replacement Patent Owner Response in redacted form (Paper 31 ("Resp.")) and unredacted form (Paper 30). Gnosis filed a Reply to the Patent Owner Response in redacted (Paper 41 ("Reply")) and unredacted (Paper 43) forms.

SAMSF also filed a Motion to Amend (Paper 26). In it, SAMSF proposed canceling claims 37, 39, 40, 47, 66, 67, 73, 76, 78-81, 83, 84, 86-89, 91 and 92.[4] Motion to Amend 1.

SAMSF also filed a Motion to Exclude certain of Gnosis's evidence (Paper 51 ("PO Motion to Exclude")). Gnosis filed an Opposition (Paper 53), and SAMSF filed a Reply (Paper 59). Gnosis filed a Motion to Exclude certain of SAMSF's evidence (Paper 49 ("Pet. Motion to Exclude")). SAMSF filed an Opposition (Paper 55), and Gnosis filed a Reply (Paper 58).

Gnosis relies upon a declaration of Dr. Joshua W. Miller (Ex. 1005) in support of its Petition. SAMSF relies upon declarations of Dr. Vivian A. Fonseca (Ex. 2013), Dr. Jesse F. Gregory (Ex. 2075), Ivan T. Hofmann (Ex. 2017), Dr. Allen M. Jacobs (Ex. 2008), Dr. Vera A. Katz (Ex. 2016), Dr. Andrew C. Kerr (Ex. 2011), Audy Kent Ladner (Ex. 2022), Dr. Brian C. Reisetter (Ex. 2020), and Dr. Samuel Strada (Ex. 2019) in its Response,

[4] SAMSF proposes to cancel claims 39, 40, 47, 66, 67, 73, 76, 78-81, 83, 84, 86-89, 91 and 92 only to the extent they depend from claim 37. Motion to Amend 1; *see supra* note 3.

along with a deposition of Dr. Miller (Ex. 2064).[5] Gnosis relies upon depositions of Dr. Fonseca (Ex. 1143), Dr. Gregory (Ex. 1142), Mr. Hofmann (Ex. 1146), Dr. Jacobs (Ex. 1144), Dr. Katz (Ex. 1145), and Mr. Ladner (Ex. 1147) in its Reply.

Oral argument was conducted on March 20, 2014. A corrected transcript is entered as Paper 66 ("Tr.").

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

SAMSF's Motion to Amend is granted. As such, only the obviousness challenge to claims 94-97, 99, 100, 110, and 111, to the extent they depend from claim 37, remains at issue in this proceeding.

Gnosis has proved that claims 94-97, 99, 100, 110, and 111, to the extent they depend from claim 37, are unpatentable.

SAMSF's Motion to Exclude Evidence is dismissed as moot.

Gnosis's Motion to Exclude Evidence is denied.

*B. The '915 Patent*

The '915 patent is titled "Compositions for Human and Animal Consumption Containing Reduced Folates and Methods for Making and Using Same," and generally relates to dietary folate supplementation. Ex. 1001, 1:10-12. The patent background explains that folate deficiency has been linked to various birth defects as well as to peripheral vascular disease and other disorders. *Id.* at 1:30-44. The background notes that individuals with peripheral vascular disease often have "abnormal blood

[5] SAMSF also relies on a deposition of Dr. Miller from ITC Investigation No. 337-TA-857 (Ex. 2063), as well as depositions of several other individuals who were not produced by Gnosis in this proceeding.

levels of homocysteine, a precursor to methionine in the folate dependent step of the S-adenosylmeth[i]onine cycle." *Id.* at 1:39-41. The background explains that folate is added to commercial preparations (sometimes in combination with other vitamins, *id.* at 2:10-11) in the form of folic acid (*id.* at 2:31-32), a form which some individuals reportedly do not absorb readily from the intestine upon oral administration. *Id.* at 5:25-26. The background states that "there is reason to believe" that those with poor oral response to folic acid nevertheless will "possess[] adequate oral response to reduced folates." *Id.* at 5:32-34.

The background section of the '915 patent further explains that "the reduced folates found in nature" include compounds such as tetrahydrofolic acid ("THFA" or "THF"), 5-methyl-tetrahydrofolic acid, 5-formyl-tetrahydrofolic, each "having the same L-configuration at carbon-6." *Id.* at 5:52-55 (referring to compounds (II) – (VIII) shown in cols. 3-5). Thus, the '915 patent identifies (6*S*)-THFA, 5-methyl-(6*S*)-THFA, and 5-formyl-(6*S*)-THFA among the "reduced folates found in nature." *Id.*[6] The background notes that recent concerns about adverse effects of the "unnatural isomer component" (i.e., the (6*R*) stereoisomer of 5-formyl-THFA) has led to commercial production of chirally-pure 5-formyl-(6*S*)-THFA for disease therapy. Ex. 1001, 5:57-61. The '915 patent proposes the use of natural isomers of reduced folates in dietary vitamin preparations. *Id.* at 6:18-22.

The detailed description section of the '915 patent specification

[6] The '915 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* Ex. 1012, 1:21-22 ("tetrahydrofolic acid" abbreviated as "THF").

describes the formulation of dietary vitamin preparations that include natural isomers of reduced folate. It discloses the amounts of one or more natural isomers of reduced folate that are to be included in preparations and expresses those amounts as percentages of the recommended dietary allowance ("RDA") or the reference daily intake ("RDI"). *Id.* at cols. 7-8. Inclusion of other nutrients is discussed, along with relative amounts of such other nutrients compared to the natural isomers of reduced folate. *Id.* at cols. 9-10. Various considerations for the manufacture of preparations are addressed. *Id.* at cols. 11-13. The specification of the '915 patent concludes with a listing of several example preparations. *Id.* at cols. 14-17. Among the other nutrients contemplated for inclusion in reduced folate preparations are pyridoxine hydrochloride (vitamin $B_6$) (*id.* at 15:13) and cyanocobalamin (vitamin $B_{12}$) (*id.* at 15:18, 16:15-16).[7] The '915 patent indicates that 25% of the RDI for pyridoxine hydrochloride is 0.5 mg (*id.* at 16:11-12) and 1.5 $\mu$g for vitamin $B_{12}$ (*id.* at 16:15-16).

Claims 37 and 110, reproduced below, are illustrative of the claimed subject matter:

> 37. A method of increasing a human subject's dietary intake of folate comprising administering to the human subject a composition for human consumption comprising:
> one or more natural isomers of reduced folate selected from the group consisting

[7] This reference to "vitamin $B_{12}$" was printed in the '915 patent with an obvious typographical error as "vitamin $B_{,2}$." *See* Specification, 19, l. 31, filed July 31, 1998, in underlying patent application serial number 09/117,586.

> of (6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5-formyl-(6S)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid, and poly-glutamyl derivatives thereof; and
>
> a nutritional substance for human consumption being an essential nutrient preparation, the essential nutrient preparation comprising a vitamin other than ascorbic acid, wherein the vitamin is present in an amount equal to or greater than 25% of the daily requirement for the vitamin per customarily consumed quantity of said essential nutrient preparation.
>
> 110. A method according to claim 36 or 37, wherein the one or more natural isomers of reduced folate is substantially chirally pure 5-methyl-(6S)-tetrahydrofolic acid or a polyglutamyl derivative thereof.

All claims that remain under consideration on the merits in this proceeding require that the one or more natural isomers of reduced folate administered be "substantially chirally pure 5-methyl-(6S)-tetrahydrofolic acid or a polyglutamyl derivative thereof."

## II. DISCUSSION

### *A. Claim Construction*

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b);

Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). Claim terms are also 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).

We construed the term "substantially chirally pure" to mean, in the context of the '915 patent, "nearly or entirely free of unnatural isomers of reduced folate." Dec. 16. We determined that no other claim terms required express construction and were to be given their ordinary and customary meanings. *Id.* at 8. Neither party contests those determinations, and we maintain them.

*B. Obviousness of claims 94-97, 99, 100, 110, and 111 over Serfontein and Marazza*

Gnosis argues that the subject matter of the claims under review would have been obvious over the combined teachings of Serfontein and Marazza. Pet. 41-55. SAMSF responds, arguing that Gnosis has not demonstrated the obviousness of the claims (Resp. 1-22), and presenting objective evidence of nonobviousness. *Id.* at 22-59.

We undertake the four factual inquiries of an obviousness analysis: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims at issue; resolving the level of ordinary skill in the pertinent art; and assessing objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

*1. The level of skill in the pertinent art*

"The person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art." *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). This person is of ordinary creativity, not merely an automaton, and is capable of combining teachings of the prior art. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 420-21 (2007).

Neither party directly addresses the level of skill in the pertinent art with evidence, beyond opinions given by their respective experts as to the education and experience of a person of ordinary skill in the art. *See* Ex. 1005 ¶ 9; Ex. 2075 ¶ 11 n.3. The parties do not dispute, however, that one of ordinary skill would have had knowledge of Serfontein and Marazza. We need not resolve the level of skill further, for purposes of this decision.

*2. Scope and content of the prior art*

*a. Overview of prior art references*

*(1) 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." 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 B6, and vitamin B12. *Id.* at 4:40-42. One example preparation contains 5 mg of vitamin $B_6$ ("PL" or "pyridoxal") and 0.5 mg of vitamin $B_{12}$. *Id.* at 8:6, 8:19-49. The preparation may additionally include an antioxidant. *Id.* at Abstr., 6:58–7:2. 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, 2:47-48. 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 discloses that preparations may be suitable for various routes of administration, including injectable, infusible, sub-lingual, and transdermal, as well as oral. *Id.* at 4:19-21, 5:52-56.

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.[8]

*(2) Marazza*

Marazza describes methods for the chiral resolution of 5-methyl-THF into its (6*R*) and (6*S*) diastereomers. Ex. 1012, 1:12-16. Marazza specifically identifies 5-methyl-(6*S*)-THF, i.e., "5-methyl-(6S)-tetrahydrofolic acid" as recited in claim 37, 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, 1:55-67. 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

[8] *See supra* note 6. Like the '915 patent and Marazza, Serfontein uses the terms "folic acid" and "folate" interchangeably. *Compare* Ex. 1009, Title *with id.* at Abstr.

cells. *Id.* at 2:15-32. Marazza thus seeks improved methods for separating the (6*R*) and (6*S*) diastereomers from one another, *id.* at 3:32-36, and describes a method that employs fractional crystallization of ammonium salts of the diastereomers. *Id.* at 3:37-40. 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.

*b. Petitioner's Case-in-Chief*

Gnosis argues that Marazza specifically identifies chirally-pure 5-methyl-(6*S*)-THFA as being a naturally-occurring active metabolite of folate that is suitable for use in vitamin supplements to treat folate deficiency, and that, consequently, one of ordinary skill in the art would have had reason to use 5-methyl-(6*S*)-THFA as the "suitable active metabolite of folate" called for in Serfontein's preparations. Pet. 41-43. Therefore, Gnosis concludes, it would have been obvious to combine Serfontein with Marazza to arrive at the subject matter of claims 94-97, 99, 100, 110, and 111. *Id.* at 41-55.

*c. Patent Owner's Response*

SAMSF presents many arguments in response to Gnosis's challenge. We address them in turn.

*(1) The widespread use of folic acid for folate deficiency*

SAMSF argues that as of the time of invention, around 1996, folic acid was regarded as the gold standard for folate supplementation in food and vitamins, due to its safety, efficacy, bioavailability, and chemical stability. Resp. 2 (citing Ex. 2075 ¶ 13). SAMSF notes that folic acid had been recognized, by then, as a therapeutic or preventative agent for neural tube defects, vascular disease, hyperhomocysteinemia, and megaloblastic

anemia. *Id.* at 2-3 (citing Ex. 2075 ¶¶ 14-15). SAMSF argues that, given the wide acceptance of folic acid for these purposes, one of ordinary skill would not have looked to other forms of folate, including natural isomers of reduced folate. *Id.* at 3 (citing Ex. 2075 ¶ 13).

SAMSF cites paragraphs 13-15 from Dr. Gregory's declaration in support of this argument. *Id.* at 2-3. In these paragraphs, Dr. Gregory cites deposition testimony of Dr. Miller, as well as scholarly publications, supporting SAMSF's contention that folic acid was a primary source of folate for nutrition and treatment of certain diseases. Ex. 2075 ¶ 13 (citing Ex. 2063, 101:1–103:10, 256:13-16; Ex. 2064, 18:9-13; 59-18); ¶ 14 (citing Ex. 1019, 135; Ex. 2026, 765; Ex. 2051, 210, 216; ¶ 15 (citing Ex. 2031; Ex. 2051, 210, 216). But as to whether this general acceptance of folic acid would have discouraged one of ordinary skill from considering other forms of folate, Dr. Gregory states only: "Throughout this declaration, I highlight these and other benefits of folic acid in order to exemplify that the [person of ordinary skill in the art] at the time did not consider natural isomers of reduced folate as a credible source of folate supplementation." Ex. 2075 ¶ 13.

This argument is unpersuasive, because it does not follow that a person of ordinary skill would have avoided alternatives simply because a standard is known to be suitable and to work well. The evidence SAMSF cites here shows that folate has several accepted therapeutic and preventative uses, but none of it credibly shows that other forms of folate were unaccepted or unsuitable. Dr. Gregory does not explain the factual basis for his conclusion that one of ordinary skill did not consider natural isomers of reduced folate as a source of folate supplementation. Consequently, we give

this opinion little weight. *See* 37 C.F.R. § 42.65(a). SAMSF's argument does not persuade us that one with ordinary skill in the art would not have considered reduced and polyglutamylated variants of folic acid for the uses to which folic acid was put.

*(2) The prior art would have discouraged use of 5-methyl-(6S)-THFA to treat deficiency*

SAMSF argues that the state of the art, as of 1996, would have discouraged one of ordinary skill from using natural isomers of reduced folate for treating folate deficiency. Resp. 5. SAMSF relies principally on a statement in the Goodman & Gilman pharmacology textbook that folinic acid,[9] while indicated for use in cancer treatment, is "not indicated for use in the treatment of folic acid deficiency." *Id.* (quoting Ex. 2036, 1304) (emphasis and internal quotation marks omitted).[10] According to SAMSF, this statement indicates that folinic acid is "not suitable" for treating folate deficiency. *Id.* (citing Ex. 2075 ¶ 29). SAMSF argues that Dr. Miller conceded that this statement would have "dissuaded" a person of ordinary skill from using folinic acid to treat folate deficiency. *Id.* (citing Ex. 2063, 157:3-6); Ex. 2327, 15. SAMSF argues that the caution directed to folinic acid would have dissuaded one of ordinary skill from using any reduced folate. *Id.* at 5-6 (citing Ex. 2075 ¶ 29).

This argument is not persuasive, because the evidence does not bear out SAMSF's contentions. Goodman & Gilman states simply that folinic acid is not *indicated* for treating folate deficiency. *See* Ex. 2036, 1304. It

[9] Folinic acid is a synonym for 5-formyl-THFA. *E.g.* Ex. 1001, 5:35-36.

[10] Exhibit 2036 is an excerpt from GOODMAN AND GILMAN, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (8th ed. 1990).

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, 152:8–153:3 (Dr. Miller opining that the basis for the "not indicated" statement may be the higher cost or lower availability of folinic acid compared to folic acid).

Moreover, SAMSF provides no credible explanation for why Goodman & Gilman's statement concerning folinic acid (5-formyl-THFA) is relevant to the issue of whether one of ordinary skill would have considered the use of other reduced folates, particularly 5-methyl-THFA, for treating folate deficiency. SAMSF cites paragraph 29 of Dr. Gregory's declaration, but Dr. Gregory's testimony merely echoes the argument, without providing underlying facts or data to support his opinion. We give his opinion on this point little weight as a result.

SAMSF argues further that one of ordinary skill, in 1996, would have been dissuaded from using reduced folates for treating folate deficiency, because the prior art indicated that reduced folates were inferior to folic acid in several properties, including, bioavailability, substrate activity, disruption of folate metabolism, stability, and commercial availability. Resp. 6 (citing Ex. 2075 ¶ 30).

*(a) Bioavailability*

SAMSF argues that data concerning bioavailability of 5-methyl-(6*S*)-THFA, in 1996, was inconsistent but suggested that 5-methyl-(6S)-THFA

was less bioavailable than folic acid.[11] Resp. 6-7 (citing Ex. 1032; Ex. 2075 ¶¶ 31-32 (citing Ex. 2035, 777S; Ex. 2048, 474)). SAMSF argues that persons of ordinary skill "overlooked" using reduced folates because they were less bioavailable than folic acid. *Id.* at 7.

This argument is unpersuasive, because SAMSF does not explain credibly why the bioavailability of reduced folates was considered to be so low as to discourage one of ordinary skill from using it for dietary purposes. The evidence SAMSF puts forward indicates, at most, that the bioavailability of reduced folates was less than that of folic acid. The evidence does not indicate that the bioavailability of reduced folates was too low to be useful, or otherwise of such a character as to render reduced folates unsatisfactory for the purpose of folate supplementation. Mere inferiority of a modification does not make that modification unobvious. *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.").

*(b) Substrate activity*

SAMSF argues that one of ordinary skill would not have considered using 5-methyl-(6*S*)-THFA instead of folic acid for dietary folate supplementation because 5-methyl-(6S)-THFA is a poor substrate for polyglutamation. Resp. 7-10. According to SAMSF, 5-methyl-(6S)-THFA inhibits the ability of human tissue to store folate, because it is a poor

[11] Bioavailability, in the context of dietary intake (i.e., oral administration), is usually expressed as a percentage and reflects the portion of the administered dose that reaches the systemic circulation.

substrate for polyglutamation. *Id.* at 7 (citing Ex. 2075 ¶¶ 33-34).[12] SAMSF argues that a person to whom 5-methyl-(6*S*)-THFA is administered would experience a "folate-deficient" state, even though the person's system is "awash" with nonglutamylated 5-methyl-(6*S*)-THFA, because cells cannot retain it. *Id.*; Ex. 2075 ¶¶ 33-34.

To support this argument, SAMSF relies on cross-examination testimony of Dr. Miller. Ex. 2075 ¶ 33 (citing Ex. 2063, 103:11-22). Dr. Miller's testimony is as follows:

> Q. And then on page 19, the second full paragraph, but the very last sentence, he states, "As 5-methyltetrahydrofolate is a poor substrate for the synthesis of polyglutamates, the ability of tissues to accumulate folate is reduced and the functional folate deficiency is compounded by a reduction in cellular folate levels," and then he goes on, "Paradoxically, this can lead to an increase in plasma folate because tissues fail to retain folate."
>
> Do you agree with that statement?
>
> A. Yes.

Ex. 2063, 103:11-22 (emphasis omitted). This testimony forms part of an exchange in which Dr. Miller was quoted statements from a "Report of Dr. Barry Shane" and asked whether he agreed with each statement. *Id.* at 100:20-22; 102:7–104:9; 272:7. The "Report of Dr. Barry Shane" is not identified further, and SAMSF does not identify whether a copy of this report is of record in this proceeding.

[12] Polyglutamation may be a mechanism by which folate is sequestered within cells. *E.g.*, Ex. 2061, 3534 ("[F]ormation of polyglutamates may be one mechanism for keeping folate compounds in the cells.").

SAMSF also relies on the following statement from a scientific paper (Horne et al., Exhibit 2061) concerning 5-methyl-(6*S*)-THFA transport: "Thus, under the conditions of the present study, isolated hepatocytes did not significantly metabolize 5-$CH_3$-$H_4$-PteGlu." Ex. 2061, 3531.[13] Dr. Gregory cites this statement, as well as the testimony of Dr. Miller, reproduced above, as evidence that one of ordinary skill in the art would have been discouraged from using 5-methyl-(6*S*)-THFA. Ex. 2075 ¶¶ 33-34; Resp. 7-8.

This argument is not persuasive, because the evidence SAMSF cites (through Dr. Gregory) does not support it credibly. Dr. Miller was asked: "Do you agree with that statement?" after being quoted the statement from the "Report of Dr. Barry Shane." Ex. 2063, 103:21. The question was presented in the present tense. Nothing in the relied-upon testimony indicates that Dr. Miller was told to consider the statement in any context other than the present day. We take Dr. Miller's affirmative answer, therefore, as an indication that he agrees with the statement as of the date of the deposition: May 6, 2013. Dr. Miller's answer is not fairly read as an indication that Dr. Miller would have agreed with the statement as of the earliest filing date of which the '915 patent is accorded benefit (January 31, 1996). Dr. Miller's testimony, consequently, is not evidence of the content of the prior art, or of the level of ordinary skill in the pertinent art, at the time the invention was made. For this reason, we accord Dr. Miller's testimony in this regard little weight.

[13] The term "5-$CH_3$-$H_4$-PteGlu" is synonymous with 5-methyl-THFA. Ex. 2061, 3529 n.1.

The single sentence SAMSF relies upon from Horne et al. does not support SAMSF's argument, because SAMSF 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-methyl-THFA is processed in vivo. In addition, this single sentence is taken out of context. SAMSF (through Dr. Gregory) cites this sentence as evidence that 5-methyl-(6*S*)-THFA would not accumulate in tissues. Ex. 2075 ¶ 34. But the cited sentence does not indicate what SAMSF proposes; rather, the sentence indicates that 5-methyl-THFA is not significantly metabolized by isolated hepatocytes under the particular experimental conditions. *See* Ex. 2061, 3531. It does not say that 5-methyl-(6*S*)-THFA, or 5-methyl-THFA, for that matter, fails to accumulate. Other experiments reported in this paper demonstrate that 5-methyl-THFA *does*, in fact, accumulate in the cells studied. *See, e.g.*, Ex. 2061, 3534 ("In the present study we have shown that 5-$CH_3$-$H_4$-PteGlu . . . is concentrated by hepatocytes."). Moreover, SAMSF cites no credible evidence that other forms of folate, such as folic acid, reasonably would have been expected to be polyglutamated, or otherwise metabolized, within the timeframe and experimental conditions reported in Exhibit 2061.

SAMSF also argues that the evidence that 5-methyl-(6*S*)-THFA is not retained in cells (Dr. Miller's testimony and Horne et al.) in turn suggests that administering 5-methyl-(6*S*)-THFA would not have been expected to increase the intracellular pool of folate. Resp. 8-10. According to SAMSF, folic acid has its beneficial effects by increasing the intracellular pool of folate. *Id.* (citing Ueland et al., Ex. 1025, in IPR2013-00119; Ex. 2075 ¶¶ 70-77). SAMSF reasons that because Dr. Miller's testimony and Horne et

al. suggest that administration of 5-methyl-(6*S*)-THFA would not have the effect of increasing the intracellular pool of folate, one of ordinary skill would not have considered using 5-methyl-(6*S*)-THFA for this purpose. *Id.* This argument is not persuasive, because its premise is not credible. Dr. Miller's testimony and Horne et al. do not show that 5-methyl-(6*S*)-THFA fails to accumulate in cells, as discussed above.

*(c) Disruption to folate metabolism*

SAMSF argues that one of ordinary skill would not have considered it obvious to administer 5-methyl-(6*S*)-THFA for folate supplementation, due to concerns that direct administration of a particular metabolite of folate could disrupt the normal folate metabolism, such as by deranging internal feedback loops. Resp. 10-11 (citing Ex. 2075 ¶¶ 35-36 (citing Ex. 2052, 540-41; Ex. 2063, 240:2-11, 241:20–242:6;[14] Ex. 2064, 153:18–154:23, 157:2-22, 163:5-9; Ex. 2065, 73:5-9; Ex. 2081, 23-42)); *see also* Resp. 3-5 (describing complexity of folate metabolism). SAMSF argues that folic acid, in contrast, would be subject to normal metabolic regulation and would have been, therefore, the preferred choice to one of ordinary skill in the art. *Id.* at 11.

This argument is not persuasive, because SAMSF does not identify credibly any portion of the cited evidence that shows that such a concern about 5-methyl-(6*S*)-THFA existed at the time the invention was made.

SAMSF (through Dr. Gregory) cites deposition testimony of Dr. Miller as evidence that there were "concerns" that administration of

[14] Lines 3-11 on page 240 and lines 1-6 on page 242 are redacted in Exhibit 2063 as filed by SAMSF.

5-methyl-(6*S*)-THFA would bypass normal enzymatic feedback loops. Ex. 2075 ¶ 35 (citing Ex. 2064, 153:18–154:23, 163:5-9). We disagree with SAMSF's characterization of Dr. Miller's testimony. Dr. Miller states that the levels of S-adenosyl methionine and S-adenosyl homocysteine (two compounds involved with folate in methyl group transfers), as well as their ratio, are under biochemical control (Ex. 2064, 154:7-16), and that 5-methyl-THF bypasses the enzyme methylene tetrahydrofolate reductase, which produces 5-methyl-THF (*id.* at 163:5-9). Dr. Miller expresses no "concern" that anything untoward would result from administration of 5-methyl-(6*S*)-THFA.

Other testimony of Dr. Miller that SAMSF cites similarly does not evidence "concern" about administering 5-methyl-(6*S*)-THFA. SAMSF points to a statement by Dr. Miller that administering 5-methyl-(6*S*)-THFA would be "bypassing [one] aspect of the control mechanisms" as evidence of concern that "all" of the "exquisite control" of folate metabolism would be extinguished. Ex. 2075 ¶ 112 (citing Ex. 2064, 157:2-22). This is a mischaracterization of Dr. Miller's testimony. Dr. Miller specifically denies that direct administration of 5-methyl-(6*S*)-THFA would effectively bypass the exquisite control of folate metabolism. Ex. 2064, 157:2-6.[15] Instead, he states only that administration of 5-methyl-(6*S*)-THFA would bypass the inhibition of methylene tetrahydrofolate reductase (the enzyme that forms 5-methyl-(6*S*)-THFA in vivo). *Id.* at 157:13-16. Moreover, Dr. Miller does not express any concern, in the cited testimony, that such bypassing would

[15] "Q. And so when you provide large amounts of 5-methyl-THF directly, are you effectively bypassing this exquisite control? A. No, I wouldn't say that."

have any deranging effect on folate metabolism. And although Dr. Miller does agree that folate metabolism is complex (*see* Ex. 2063, 240:2), and does not deny that disruption of folate metabolism could have serious adverse effects (*see* Ex. 2064, 154:7-16), Dr. Miller does not state, in the cited testimony, that administration of 5-methyl-(6*S*)-THFA would cause disruption.

SAMSF also cites deposition testimony of Dr. Ralph Green. Ex. 2075 ¶ 113 (citing Ex. 2065, 73:5-9). According to SAMSF, Dr. Green testifies that administration of a "large or otherwise" bolus of 5-methyl-(6*S*)-THFA would "have the propensity, the capacity to disrupt those exquisite controls." *Id.* This evidence is not persuasive because the facts or data underlying it are not disclosed adequately. Dr. Green's opinion that a bolus of 5-methyl-(6*S*)-THFA would have the propensity to disrupt folate metabolism is premised on his assertion that 5-methyl-(6*S*)-THFA, itself, exerts "considerable influence" and "exquisite control" over the "entire pathways" of folate metabolism. *See* Ex. 2065, 72:8-14, 22-24. Dr. Green does not explain the basis for this opinion, such as by reference to some scientific treatise, peer-reviewed paper, or other authority. Dr. Green refers to similar views having been expressed by Dr. Barry Shane in a "report of Dr. Shane," *id.* at 72:17, but SAMSF has not identified whether this report is of record in this proceeding. For these reasons, we accord Dr. Greene's testimony on this point little weight.

SAMSF also cites pages 540-51 of Exhibit 2052 as expressing "concern." This exhibit is a review article by Pietrzik et al. discussing the pharmacokinetics and pharmacodynamics of folic acid compared to 5-methyl-(6*S*)-THFA. Ex. 2052, 535. The portion of this article that

SAMSF cites describes how 5-methyl-(6*S*)-THFA is synthesized in vivo and indicates that an inadequate level of 5-methyl-(6*S*)-THFA results in an elevated plasma homocysteine level. *Id.* at 540-41. The cited portion of the article neither refers to administration of 5-methyl-(6*S*)-THFA nor expresses concern that excess 5-methyl-(6*S*)-THFA would derange feedback loops.

*(d) Stability*

SAMSF argues that folic acid was known, at the time of invention, to be "highly stable" and therefore "considered superior" to reduced folates, and that reduced folates were known to be less resistant to oxidation than folic acid. Resp. 11 (citing Ex. 2075 ¶ 37). SAMSF, through Dr. Gregory, cites testimony of Dr. Miller in support of this argument. Ex. 2075 ¶ 37 (citing Ex. 2063, 100:10–104:9, 256:13-16; Ex. 2064, 59:9-18, 130:3-16).[16] Dr. Miller testifies that (*a*) folic acid was considered stable (Ex. 2063, 101:23-25), (*b*) reduced folates are less stable than folic acid (Ex. 2064, 59:9-18), (*c*) reduced folates were considered by some to be unstable (Ex. 2063, 256:13-16), and (*d*) the limited stability of reduced and methylated folates requires cold storage conditions (Ex. 2064, 130:3-18).[17]

[16] Dr. Gregory also cites the '915 patent itself in support of this argument. The patent is admissible, however, only as evidence of what it describes. 37 C.F.R. § 42.61(c). To the extent the '915 patent includes data upon which SAMSF relies to prove the truth of the data, Dr. Gregory's declaration is insufficient to authenticate the data, because Dr. Gregory does not state that he has first-hand knowledge of how the data was generated. *See id.*

[17] SAMSF also cites a scientific paper dated 2002 as evidence that 5-methyl-tetrahydrofolate is regarded as less stable than folic acid, even today. Ex. 2075 ¶ 37 (citing Ex. 2075 ¶ 42 (citing Ex. 2023, 734, 740)). We do not consider this evidence further, because the relevant time period for obviousness considerations is the time the invention was made.

SAMSF argues that the lower stability of reduced folates was one reason why they were not considered suitable for therapeutic use prior to 1996. Resp. 11-12 (citing Ex. 2075 ¶¶ 38-39). SAMSF cites further testimony of Dr. Miller in support of this argument. Ex. 2075 ¶ 38 (citing Ex. 2063, 102:12–103:10, 103:23–104:9). Dr. Miller's testimony, however, is given in the context of his consideration of the "Report of Dr. Barry Shane." Ex. 2063, 102:12–103:10, 103:23–104:9. We accord that testimony little weight, for the reasons given above in section II.B.2.c(2)(b).

SAMSF also cites five scientific papers, Buehring (Ex. 2030), Harpey I (Ex. 1030), Harpey II (Ex. 1031), Etienne (Ex. 2032), and Stout (Ex. 2054), as evidence that reduced folates are less stable than folic acid. Ex. 2075 ¶¶ 38-39. In particular, SAMSF highlights Harpey I (published in 1981) for expressing doubts about the therapeutic usefulness of 5-methyl-THF due to its instability, and Harpey II (published in 1983) for indicating that 5-methyl-THF therapy was attempted but withdrawn due to instability. *Id.* ¶ 38; Tr. 102:16-18.

Gnosis acknowledges that there were "early concerns expressed in the prior art regarding the stability" of reduced folates, but argues a preparation of 5-methyl-THF of adequate stability for therapeutic use had become available (from Bio-Research, Milan, Italy) after the Harpey papers and before the time the invention was made. Reply 6; Tr. 136:1-3. In particular, Gnosis cites three scientific papers as evidence, Reggev (Ex. 1028), Godfrey (Ex. 1019), and Pattini (Ex. 1077), all published prior to 1996. SAMSF argues, in reply, that the Reggev, Godfrey, and Pattini papers do not discuss stability of reduced folates. Tr. 125:21–126:9; Ex. 2327, 24 (citing Ex. 1142, 149:4–153:6, 158:25–159:21, 159:25–160:23).

The evidence on this issue supports Gnosis's position. Although Dr. Miller acknowledges that reduced folate stability is less than that of folic acid, such that even special handling is required to avoid degradation, and other evidence SAMSF cites supports its argument that reduced folates are relatively unstable compared to folic acid, SAMSF cites no credible evidence that 5-methyl-(6*S*)-THFA was regarded as unsuitable for therapeutic use, aside from Harpey I and Harpey II. But even Harpey I and Harpey II do not support SAMSF's position convincingly when considered in the context of other evidence of record. The doubt Harpey I expresses about 5-methyl-THFA was insufficient to discourage an attempt to use it in Harpey II, and the failure reported in Harpey II was insufficient to discourage the development of the Bio-Research preparation. The evidence shows that interest in the use of 5-methyl-THFA for various therapeutic purposes persisted until the time the invention was made, despite setbacks. Harpey I and II may reflect the state of the art many years before the invention was made, but they do not necessarily reflect the state of the art at the time of invention.

SAMSF's argument that the Reggev, Godfrey, and Pattini papers include essentially no express discussion of stability is also unpersuasive. These papers show, implicitly, that the Bio-Research preparation of 5-methyl-THFA had sufficient stability to conduct human testing.

*(e) Commercial availability*

SAMSF argues that reduced folates had limited commercial availability at the time the invention was made, because they were difficult to synthesize. Resp. 12-13. SAMSF cites testimony of Dr. Miller to the effect that folic acid was cheaper and more readily available than reduced

folates, for the purpose of folate supplementation, because it was easier to synthesize folic acid than it was to synthesize and isolate a chirally pure reduced folate. *Id.* (citing Ex. 2063, 152:8-17, 104:2-9; Ex. 2064, 19:9-16; Ex. 2075 ¶¶ 40-41 (citing same from Exs. 2063-64)). SAMSF argues that the "impracticability" of synthesizing or obtaining reduced folates would have discouraged one of ordinary skill from using them and would have, instead, continued to use folic acid as the "only credible alternative." *Id.*; Ex. 2075 ¶¶ 40-41.

This argument is not persuasive, because the evidence SAMSF cites does not show that making or acquiring reduced folates was "impracticable" or so problematic as to discourage their use. At best, Dr. Miller's testimony shows that folic acid was regarded as easier to make or buy than reduced folates. It does not follow that one of ordinary skill in the art would have been dissuaded from using reduced folates. *See In re Mouttet*, 686 F.3d at 1334.

*3. Differences between the claimed subject matter and the prior art*

*a. Petitioner's arguments*

Gnosis argues that Serfontein discloses all limitations of each challenged claim except the use of substantially chirally pure 5-methyl-(6*S*)-THFA. Pet. 10-11, 41-45, 53-55. Gnosis argues that Marazza discloses substantially chirally pure 5-methyl-(6*S*)-THFA. *Id.* at 41-45, 53-55.

*b. Patent Owner's arguments*

*(1) Serfontein*

SAMSF argues that a person of ordinary skill in the art would disregard Serfontein's reference to "a suitable active metabolite of folate"

because that phrase is so vague, and encompasses so large a class of compounds, as to be meaningless. Resp. 13-17. SAMSF argues that Serfontein's broad and non-specific reference to "a suitable active metabolite of folate" instead would have driven one of ordinary skill to use tried-and-true folic acid. *Id.* at 14 (citing Ex. 2075 ¶ 55). SAMSF points out that all of Serfontein's examples use folic acid, not active metabolites of folate, and that Serfontein suggests no advantages of active metabolites over folic acid. *Id.* SAMSF also cites testimony of Dr. Miller, again through Dr. Gregory. *Id.* at 15 (citing Ex. 2063, 125:10-22; Ex. 2064, 73:25–74:10, 78:23–81:12; Ex. 2075 ¶¶ 60-61). According to SAMSF, Dr. Miller acknowledges that the phrase "a suitable active metabolite of folate" potentially encompasses thousands of permutations of folates in various salt forms and having various glutamate linkages. *Id.* SAMSF argues that the class of "suitable active metabolites of folate" was effectively undefined, due to the large number of possible salt forms, as well as the range of possible crystalline forms, and also due to uncertainty as to which compounds would be "suitable" for the uses specified in Serfontein. *Id.* at 16-17 (citing Ex. 2075 ¶¶ 62-63, 66). SAMSF concludes that the uncertainty surrounding Serfontein's disclosure of "a suitable active metabolite of folate" would simply have led one of ordinary skill away from reduced folates and toward the conventional folic acid. *Id.* at 17 (citing Ex. 2075 ¶¶ 67-68).

This argument is unpersuasive because it addresses only what the Serfontein disclosure, alone, would have conveyed to one of ordinary skill in the art, not what the *combination* of the Serfontein and Marazza disclosures would have conveyed. In the obviousness challenge on which this review

was instituted, Gnosis relies on Serfontein for a general, nonspecific reference to "a suitable active metabolite of folate" and on Marazza for a specific identification of 5-methyl-(6*S*)-THFA as a "natural metabolite" of folate that may be used "as at least one active compound" in a vitamin therapy for folate deficiency. *See* Pet. 42 (citing Ex. 1012, 1:21-28). Whether Serfontein's reference to "a suitable active metabolite of folate" was so undefined as to have been meaningless to one of ordinary skill in the art does not address whether Marazza's disclosure, of which one of ordinary skill is presumed to have been aware,[18] would have led one of ordinary skill to the claimed subject matter when combined with Serfontein.

To the extent SAMSF argues that Serfontein teaches away from the use of "a suitable active metabolite of folate," we are unpersuaded. First, SAMSF cites no legal precedent for the notion that an approving disclosure of a feature could ever amount to a teaching away of that feature. The case law concerning teaching away makes clear that "a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Implicit in this rule is that there must be some "teaching" in the reference, other than the disclosure relied upon to assert obviousness, that would have led the person of ordinary skill away from using that disclosure.

[18] "The person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art." *In re GPAC Inc.*, 57 F.3d at 1579.

More importantly, we are unpersuaded because SAMSF does not cite credible evidence in support of its "teaching away" argument. SAMSF argues, in effect, that Serfontein teaches away from using "a suitable active metabolite folate," despite Serfontein favorably disclosing exactly that, because the disclosure is discouragingly vague. *See* Resp. 13-17. Dr. Gregory echoes this argument, *see* Ex. 2075 ¶ 67. SAMSF, through Dr. Gregory, cites numerous portions of Dr. Miller's testimony but no other evidence. *Id.* ¶¶ 54-67 (citing Ex. 2063, 82:24–84:21, 85:10-25, 87:10–88:17, 122:2-13, 122:21–123:4, 125:10–126:10, 129:24–130:11; Ex. 2064, 59:11–60:6, 62:23–63:7, 71:3–73:20, 73:25–74:10, 74:19-25, 78:15–82:11, 87:12–88:22, 90:4-13, 95:24–98:3, 102:13–103:14, 139:7-22). Dr. Miller's relevant testimony can be summarized as follows:

1. Serfontein's class of "suitable active metabolites of folate" includes many variations of eight fundamental compounds (Ex. 2064, 62:23–63:7, 78:23-80:12, 81:5-12);[19]
2. The variations stem from choice of salt form and glutamylation state, among other considerations (Ex. 2063, 125:10-22);
3. The variations can affect a given folate's chemical, physical, and biological properties, including stability, absorbability, bioavailability, and in vivo function (Ex. 2063, 82:24–84:21,

[19] The fundamental compounds are those identified in Dr. Miller's declaration: (1) 7,8 dihydrofolic acid; (2) (6*S*)-tetrahydrofolic acid; (3) 5-methyl-(6*S*)-tetrahydrofolic acid; (4) 5-formyl-(6*S*)-tetrahydrofolic acid; (5) 10-formyl-(6*R*)-tetrahydrofolic acid; (6) 5,10-methylene-(6*R*)-tetrahydrofolic acid; (7) 5,10-methenyl-(6*R*)-tetrahydrofolic acid; and (8) 5-formimino-(6*S*)-tetrahydrofolic acid. Ex. 1005 ¶¶ 18-20; Dec. 10-11; Ex. 2075 ¶ 53; Tr. 25:1-21.

85:10-25, 87:10–88:17; Ex. 2064, 59:11–60:6, 74:19-25, 78:15–82:11, 87:12–88:22); and

4. Serfontein itself provides little guidance for one of ordinary skill to select a particular folate from this class (Ex. 2063, 125:23–126:10, 129:24–130:11; Ex. 2064, 71:3–73:20, 73:25–74:10, 90:4-13, 95:24–98:3, 102:13–103:14).

SAMSF argues that Serfontein's class of "suitable active metabolite[s] of folate" includes potentially thousands of variations, given that there are over one hundred suitable salt forms of the reduced folates, as well as numerous polyglutamate forms. Resp. 15-16 (citing Ex. 2075 ¶ 61). SAMSF argues further that Serfontein provides essentially no guidance on determining which particular variations would have been "suitable." *Id.* at 16 (citing Ex. 2075 ¶ 63). SAMSF argues, through Dr. Gregory, that the many considerations that figure in determining what compounds fall within the class require "a considerable amount of experimentation" to sort out. Ex. 2075 ¶65. The need for experimentation, says Dr. Gregory, would have made it "impossible" for a person of ordinary skill in the art to know all of the compounds that make up Serfontein's class. *Id.*

SAMSF concludes that a person of ordinary skill, confronted by Serfontein's vague and directionless disclosure about "suitable active metabolite[s] of folate," compared to its specific reference to, and numerous examples including, folic acid, would have selected folic acid and avoided the reduced folates. Resp. 17 (citing Ex. 2075 ¶¶ 67-68).

SAMSF's evidence does not credibly support this conclusion. Dr. Miller does not express an opinion, in the cited testimony, that a person of ordinary skill would have been discouraged by Serfontein from using

reduced folates. It is Dr. Gregory who concludes this, but he cites only Dr. Miller's testimony as support for it. Dr. Gregory does not explain how Dr. Miller's testimony leads Dr. Gregory to his conclusion. For example, Dr. Gregory does not address why the level of skill in the art is such that one of ordinary skill would be so utterly unable to navigate a class of closely-related compounds.[20]

Moreover, Dr. Gregory's deposition evidence casts some doubt on his conclusion. Dr. Gregory testified that one of ordinary skill in the art would not have considered seriously salt forms that were not in "common understanding or consideration." *See* Reply 8 (citing Ex. 1135, 191:17–193:5) (quotation at 192:3-4).[21] Dr. Gregory did not specify how many of the hundred-or-more salts one of ordinary skill would have been considered, though he named only four—calcium, barium, sodium, and potassium—as ones commercially available at the time. *See* Ex. 1135, 192:20–193:2. It is not clear, then, on the evidence of record, whether the class of "suitable active metabolite[s] of folate" would encompass thousands of compounds, based on many possible salts, or some significantly smaller number, based on salts one of ordinary skill in the art would have seriously considered. For these reasons, we determine that Dr. Gregory's opinion is not supported by credible facts or underlying data, and we give it little weight.

[20] According to Dr. Gregory, persons of ordinary skill in the art may be "researchers and/or medical practitioners that conduct research on, or possess sufficient knowledge about, folate metabolism." Ex. 2075 ¶ 11 n.3.

[21] Exhibit 1135 presents excerpts of Dr. Gregory's deposition transcript. A complete transcript was filed as Exhibit 1142.

SAMSF cites *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) and *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994), in support of its teaching away argument. Tr. 24:23-24, 85:20-21. These cases stand for the uncontroversial proposition that disclosure of a large genus does not, by itself, render obvious individual species within that genus. *In re Bell*, 991 F.2d at 784 (amino acid sequence does not render obvious one particular nucleic acid sequence among the undecillion-odd ($10^{36}$) sequences that could encode the amino acid); *In re Baird*, 16 F.3d at 382 (generic chemical formula does not, by itself, render obvious one particular compound out of about one hundred million compounds). SAMSF does not explain the relevance of these cases to the selection of a species from a far smaller set, nor how these cases support its argument that Serfontein's generic disclosure teaches away.

*(2) Marazza*

SAMSF argues that Marazza does not (*a*) suggest that a reduced folate is better than folic acid; (*b*) disclose using folates for lowering serum homocysteine levels; nor (*c*) explain the role of the unnatural isomer. Resp. 17-21 (citing Ex. 2075 ¶¶ 81-88). These arguments are unpersuasive, because Gnosis does not rely on Marazza for any of these disclosures. Gnosis relies on Marazza simply for the precise identification of chirally-pure 5-methyl-(6*S*)-THFA as an active metabolite of folate suitable for oral administration to increase folate levels. *See* Pet. 41-43.

SAMSF argues also that it would not have been obvious to combine chirally-pure 5-methyl-(6*S*)-THFA with vitamin $B_{12}$ because 5-methyl-(6*S*)-THFA, unlike folic acid, does not mask vitamin $B_{12}$ deficiency. Resp. 21-22 (citing Ex. 2075 ¶¶ 89-92). SAMSF offers no

evidence, other than a bare assertion by Dr. Gregory, that 5-methyl-(6*S*)-THFA does not mask vitamin $B_{12}$ deficiency. *See* Ex. 2075 ¶ 90. Dr. Gregory does not identify facts or data that lead him to this conclusion. We give it, therefore, little weight.

*4. Objective indicia of non-obviousness*

SAMSF argues that several lines of objective evidence (or "secondary considerations") demonstrate the non-obviousness of the claims under review. Resp. 22-59. In particular, SAMSF argues commercial success (*id.* at 23-34), licensing (*id.* at 34-38), copying (*id.* at 38-43), long-felt but unmet need (*id.* at 43-48), discovering and solving an unrecognized problem (*id.* at 49-51), unexpected results (*id.* at 52-54), skepticism (*id.* at 54-56), and praise (*id.* at 56-59).

In this case, SAMSF cites evidence stemming from five products. Resp. 23-24. The five products are:

1. Metanx® medical food, which contains 5-methyl-(6*S*)-THFA, methylcobalamin (a form of vitamin $B_{12}$), and pyridoxal 5´-phosphate (a form of vitamin $B_6$), for treating diabetic peripheral neuropathy (Resp. 27-28 (citing Ex. 2008 ¶ 32; Ex. 2013 ¶ 32; Ex. 2022 ¶ 37; Ex. 2075 ¶ 128); Ex. 2078);
2. Cerefolin® medical food, which contains 5-methyl-(6*S*)-THFA, riboflavin (vitamin $B_2$), cyanocobalamin (another form of vitamin $B_{12}$), and pyridoxine hydrochloride (another form of vitamin $B_6$), for mild cognitive impairment and vascular dementia (Resp. 28 (citing Ex. 2011 ¶¶ 29-30, 42-43; Ex. 2022 ¶¶ 46-47; Ex. 2075 ¶ 141); Ex. 2251);

3. CerefolinNAC® medical food, which contains 5-methyl-(6*S*)-THFA, methylcobalamin, and N-acetylcystine, for mild cognitive impairment and vascular dementia (Resp. 28 (citing Ex. 2011 ¶¶ 29-30, 42-43; Ex. 2022 ¶¶ 46-47; Ex. 2075 ¶ 141); Ex. 2085);
4. Néevo® prescription prenatal vitamins, which contains 5-methyl-(6*S*)-THFA 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. 28-29 (citing Ex. 2022 ¶¶ 60-63; Ex. 2075 ¶ 150); Ex. 2079); and
5. NeevoDHA® prescription prenatal vitamins, which contains 5-methyl-(6*S*)-THFA, methylcobalamin, pyridoxine hydrochloride, algal oil (a source of docosahexaenoic acid ("DHA")), and a range of vitamins and minerals, for nutritional supplementation during pregnancy and pre- and post-natal periods (Resp. 28-29 (citing Ex. 2022 ¶¶ 60-63; Ex. 2075 ¶ 150); Ex. 2080).

Each of the products is manufactured and sold by Pamlab, under sublicense from Merck & Cie, a licensee of the '915 patent. Resp. 23-24. Each of the five products includes substantially chirally-pure Metafolin® 5-methyl-(6*S*)-THFA as an active ingredient,[22] in combination with other active and inactive ingredients. *Id.* at 24, 29-30.

[22] I.e., the products contain the (6*S*) diastereoisomer nearly or entirely free of the unnatural (6*R*) diastereoisomer. *See* Resp. 24.

*a. Commercial success*

SAMSF offers evidence that the Pamlab products have had annual sales over the past several years measured in the millions of dollars, with revenue and profit growth year-to-year. Resp. 24-26. SAMSF argues that the commercial success of the products is attributable to the claimed features of the claims under review. *Id.* at 27-31. In particular, SAMSF argues that the indicated uses for the products (noted above) "align" with the claimed use of "increasing a human subject's dietary intake of folate," and that the products are prescribed by clinicians because their specific combinations of active ingredients (also noted above) are effective for treating those particular uses. *Id.* at 28-31. SAMSF also argues that Pamlab's sales figures understate the commercial success, because some sales are lost to copycat products by other companies. *Id.* at 31-34.

*b. Licensing*

SAMSF offers evidence that Merck first licensed the '915 patent in 2000, after prevailing over competitors for the license, and has since sought to expand both the term and scope of its license. *Id.* at 34-36, 38. Merck, in turn, sub-licensed the patent to Pamlab in 2002, as well as to other companies, and Pamlab itself has sub-licensed the patent further. *Id.* at 36-37. SAMSF argues that the royalty stream from the licenses is "substantial," measured in millions of dollars. *Id.* at 37. SAMSF argues that Merck still receives weekly requests to sublicense the patent. *Id.* at 38.

*c. Copying*

SAMSF offers evidence that six companies have made and sold copies of one or more of the Pamlab products listed above and that those

copies contain the same active ingredients, in the same dosages and for the same purposes, as the Pamlab products. *Id.* at 39-43.

*d. Long-felt need*

SAMSF offers evidence that the '915 patent satisfied a long-felt, but unsatisfied, need to treat diabetic peripheral neuropathy. *Id.* at 43-48.

*e. Unrecognized problem*

SAMSF offers evidence that the inventors of the '915 patent recognized that there exists a sub-population of individuals for whom folic acid has poor bioavailability due to variations in the activity of the enzyme dihydrofolate reductase. *Id.* at 49. According to SAMSF, the inventors realized that administration of 5-methyl-(6*S*)-THFA would alleviate this problem by providing a more uniformly bioavailable form of folate than folic acid. *Id.* at 49-51.

*f. Unexpected results*

SAMSF offers evidence purporting to show that 5-methyl-(6*S*)-THFA has unexpectedly greater potency than racemic 5-methyl-THFA. *Id.* at 52-53. SAMSF cites a paper by Venn et al. (Ex. 2058), which reports that administration of 5-methyl-(6*S*)-THFA at a dose of 113 $\mu$g/day for 24 weeks lowered plasma homocysteine by 14.6%. Resp. 53. SAMSF cites a second paper, by Fohr et al. (Ex. 2034), which reports that administration of racemic 5-methyl-THFA at a dose of 480 $\mu$g/day for 8 weeks lowered plasma homocysteine by 3%. Resp. 53. Venn et al. cite the Fohr paper, and note that the Venn dose of 5-methyl-(6*S*)-THFA was less than half of the half of Fohr's racemic dose of 5-methyl-THFA that was the (6*S*) diastereoisomer. *Id.* (citing Ex. 2058, 660-61). SAMSF argues that this result was unexpected, because chirally-pure 5-methyl-(6*S*)-THFA was more effective

at lowering plasma homocysteine than more than double the dose of 5-methyl-(6*S*)-THFA mixed with its (6*R*) partner. *Id.* Dr. Gregory characterizes the potency of 5-methyl-(6*S*)-THFA as "much greater" than 5-methyl-THFA on this basis and opines that the magnitude of the increased potency was unexpected. Ex. 2075 ¶¶ 104-107. Dr. Gregory also cites a study by Akoglu et al. (Ex. 2027), which reports that administration of 5-methyl-(6*S*)-THFA at a dose of 1 mg/day for 8 weeks lowered plasma homocysteine by 37%, whereas administration of 1 mg/day of folic acid lowered plasma homocysteine by 24% at 8 weeks. Ex. 2075 ¶ 108.

SAMSF also argues that a paper by Willems et al. (Ex. 2062), published in 2004, shows that reduced folates, particularly 5-methyl-(6*S*)-THFA, are significantly more bioavailable that folic acid. Resp. 54 (citing Ex. 2075 ¶ 109). SAMSF argues that, taken together, the evidence from the papers summarized above demonstrates unexpectedly superior properties of 5-methyl-(6*S*)-THFA. *Id.* (citing Ex. 2075 ¶ 110).

*g. Skepticism*

SAMSF argues that one of ordinary skill in the art would have been skeptical of using 5-methyl-(6*S*)-THFA therapeutically, due to concerns about disrupting folate metabolism, stability, and bioavailability. Resp. 54-56 (citing Ex. 2075 ¶¶ 111-118). SAMSF also relies on the portions of Dr. Miller's testimony addressed above in section II.B.2.c(2)(c). Finally, SAMSF refers to recommendations by the Food and Drug Administration and by the Centers for Disease Control regarding folate fortification of the U.S. food supply. Resp. 55-56 (citing Ex. 2075 ¶ 118). SAMSF represents these recommendations as having not considered 5-methyl-(6*S*)-THFA a sound option. *Id.* at 56 (citing Ex. 2075 ¶ 118).

SAMSF does not further identify the recommendations, nor does it indicate that the recommendations have been made of record in this proceeding.

*h. Praise*

SAMSF argues that several of its witnesses praise various Pamlab products and also testify to praise by others in the medical community. *Id.* at 56-57. SAMSF offers evidence that Merck was given the "Product Differentiation Innovation Award" by Frost & Sullivan for Metafolin brand 5-methyl-(6*S*)-THF. *Id.* at 57-58. Finally, SAMSF offers evidence that Gnosis intentionally mislabeled racemic 5-methyl-THF as substantially chirally pure 5-methyl-(6*S*)-THF. *Id.* at 58-59.

*5. Analysis*

One of ordinary skill in the art is presumed to have been aware of both Serfontein and Marazza. *See In re GPAC Inc.*, 57 F.3d at 1579. Serfontein calls for a "suitable active metabolite of folate" in oral preparations to correct folate deficiency (Ex. 1009, 3:31-32, 4:41, 5:4-5), and Marazza specifically identifies chirally-pure 5-methyl-(6*S*)-THFA as an active metabolite of folate suitable for oral use to increase folate levels. Ex. 1012, 1:21-28, 1:36-37. The close similarity of purpose and disclosure between these references provides sufficient rationale for one of ordinary skill in the art to have combined them. *See* Pet. 43; *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. at 418. SAMSF's many arguments against the combination of Serfontein and Marazza, and against the use of reduced folates before the date of invention, all fail to persuade us, for the reasons discussed above in sections II.B.2.c and II.B.3.b.

Set against Gnosis's evidence is the array of objective evidence SAMSF puts forward in support of the nonobviousness of the claims. This

evidence is based on the five products made and sold by Pamlab under sublicense from Merck. SAMSF argues, and Gnosis does not dispute, that administration of each of the five Pamlab products to a patient falls within the scope of the claims under review. Resp. 24 (citing Ex. 2075 ¶¶ 133, 147, 160).

It is not sufficient, however, that a product or its use merely be 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 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 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).

All types of objective evidence of nonobviousness must be shown to have nexus. *In re GPAC Inc.*, 57 F.3d at 1580 (nexus 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); *In re 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). 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), *cert. denied*, 475 U.S. 1017 (1986).

Objective evidence of nonobviousness must also be reasonably commensurate in scope with the claim. *In re Kao*, 639 F.3d at 1068. This does not mean that the proffered evidence must reach every embodiment within the scope of the claims, so long as an "adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner." *Id.*

SAMSF argues that nexus is established when the thing (product or method) on which the evidence is based is "covered by the patent." Resp. 23-24 (citing *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010)). As discussed above, however, a showing of nexus also involves establishing that novel elements in the claim, not prior-art elements, account for the objective evidence put forward to show nonobviousness. *In re Kao*, 639 F.3d at 1068.

SAMSF does not identify what novel elements in the claims under review anchor its objective evidence. Instead, it argues that the combinations of active ingredients in the five products account for the products' effectiveness in treating their respective disease targets and, therefore, success. Resp. 29-30 (regarding CerefolinNAC, Néevo and NeevoDHA), 47-48 (regarding Metanx); *see also* Ex. 2022 ¶ 94 (Ladner declaration) ("[W]e sell a unique blend of ingredients to treat certain

conditions."). SAMSF emphasizes that the "unique" aspects of the products' formulations account for their success. *E.g.*, Resp. 29-30.

The difficulty with this argument is that the claims under review do not recite the various active ingredient combinations found in the products. The claims require administering a composition containing at least chirally-pure 5-methyl-(6*S*)-THFA (or a polyglutamyl derivative) and a nutritional substance comprising a vitamin other than ascorbic acid. The nutritional substance may include any number or combination of vitamins, in any chemical form, so long as at least one of them is not ascorbic acid and is provided in the recited amount. The particular combination of active ingredients in any of the products is not recited as an element (or combination of elements) of any claim under review. As such, the objective evidence for each product lacks a clear nexus with the claims.[23]

The degree to which SAMSF touts the products' targeting of particular therapeutic goals with unique formulations underscores its failure to show that the objective evidence is commensurate with the scope of the claims. SAMSF ascribes the therapeutic value of each product to its unique formulation. *See* Resp. 29-30, 47-48; *see also* Ex. 2022 ¶ 94 (quoted *supra*). By arguing the special advantages of the unique formulations, SAMSF implies that other formulations would not necessarily offer the same benefits for the same therapeutic goals. Consequently, the claims under review

[23] To the extent that SAMSF argues that the objective evidence has nexus with the claims through administration of 5-methyl-(6*S*)-THFA, without regard to what other active ingredients accompany it, this is not persuasive, because Marazza discloses the use of 5-methyl-(6*S*)-THFA as an oral vitamin agent for treatment of folate deficiency. *See* Ex. 1012, 1:21-28, 1:36-37.

encompass numerous species for which SAMSF offers not only no objective evidence of nonobviousness, but also implicitly suggests would not work as the 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 In re Kao*, 639 F.3d at 1068.[24]

Gnosis makes a strong argument for obviousness of the challenged claims. We agree with Gnosis that the language Marazza uses to describe 5-methyl-(6*S*)-THFA—"this natural *metabolite* as at least one *active* compound in a therapeutical agent, for example as vitamin in *folate deficiency states*" (Ex. 2012, 1:26-28 (emphasis added))—would have commended 5-methyl-(6*S*)-THFA to one of ordinary skill in the art as being one of Serfontein's "suitable active metabolite[s] of folate."

SAMSF's objective evidence is not sufficient to overcome this strong argument. As noted above, all types of objective evidence cited by SAMSF require a nexus with the claimed subject matter. But SAMSF's evidence, based on the unique formulations of the Pamlab products, is tied to combinations of elements not found in the claims under review. 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

[24] SAMSF argues that its "long-felt need" evidence concerning Metanx is reasonably commensurate in scope with the claims, because Dr. Miller testifies that other reduced folates would be expected to work if 5-methyl-(6*S*)-THFA works. Resp. 48 n.10 (citing Ex. 2064, 144-146). We disagree for the reasons given above.

commercial success, licensing, copying, and long-felt need, because this evidence is tied especially intimately to specific Pamlab products.

The evidence of unrecognized problem, unexpected results, skepticism, and praise also lack nexus because they are tied in particular to 5-methyl-(6*S*)-THFA. Although use of 5-methyl-(6*S*)-THFA for dietary folate supplementation is recited in the claim, it is a prior art element. *Supra* note 23. Consequently, it cannot be used to tie the objective evidence to the claimed subject matter. *See Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011) ("If commercial success is due to an element in the prior art, no nexus exists.").

Because SAMSF has not shown nexus persuasively, and because SAMSF has not explained how the objective evidence specific to "unique[ly]" formulated products supports the conclusion that other embodiments would perform similarly, the objective evidence does not persuade us that the apparent success of the Pamlab products can be traced to the claimed invention. At best, SAMSF's objective evidence relates to unclaimed species embodiments. When we balance Gnosis's strong evidence of obviousness against the objective evidence of nonobviousness, we determine that a preponderance of the evidence supports Gnosis's argument that it would have been obvious to combine Serfontein and Marazza to reach the subject matter of claims 94-97, 99, 100, 110, and 111, to the extent they depend from claim 37.

Accordingly, we conclude that Gnosis has demonstrated the unpatentability of claims 94-97, 99, 100, 110, and 111, to the extent they depend from claim 37, by a preponderance of the evidence.

## III. MOTION TO AMEND

SAMSF moves the cancellation of claim 37 and, to the extent they depend from that claim, claims 39, 40, 47, 66, 67, 73, 76, 78-81, 83, 84, 86-89, 91, and 92.[25] Paper 26, 1. Gnosis does not oppose. The motion is granted.

## IV. MOTIONS TO EXCLUDE EVIDENCE

### *A. SAMSF's Motion*

SAMSF moves to exclude Gnosis Exhibits 1092, 1093, 1095, 1097, and 1098 as inadmissible hearsay. PO Motion to Exclude 1-2.

We dismiss SAMSF'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 2008, 2011, 2013, 2016, 2017, 2020, 2022, 2024, 2039, 2048, 2049, 2050, 2052, 2055, 2063, 2064, 2065, 2073, 2074, 2075, 2082, 2090, 2099, 2134, 2148, 2149, 2180, 2183, 2184, 2185, 2188, 2213, 2214, 2229-2241, 2281, 2296, 2283, and 2284, in whole or in part, citing various provisions of the Federal Rules of Evidence. Pet. Motion to Exclude 1-15.

We deny Gnosis's motion. 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

[25] *See supra* notes 3-4.

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.

## V. CONCLUSION

Gnosis has proved, by a preponderance of the evidence, that the subject matter of claims 94-97, 99, 100, 110, and 111 would have been obvious over the combined teachings of Serfontein and Marazza.

## VI. ORDER

For the reasons given, it is

ORDERED that claims 94-97, 99, 100, 110, and 111 of U.S. Patent No. 5,997,915 are determined to be UNPATENTABLE;

FURTHER ORDERED that SAMSF's Motion to Amend claims is *granted*, and, accordingly, that claim 37 be CANCELED, and that claims 39, 40, 47, 66, 67, 73, 76, 78-81, 83, 84, 86-89, 91, and 92 be CANCELED to the extent they depend from claim 37;

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

FURTHER ORDERED that Gnosis's Motion to Exclude Evidence is *denied*; 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.

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