SMITH, CHAPMAN & CAMPBELL
1800 North Broadway, Suite 200
Santa Ana, California 92706
Tel: (714) 550-7720
Fax: (714) 550-1251
Attn: William D. Chapman, Esq.
Email: wchapman@smithchapman.com

LITTLETON JOYCE
UGHETTA PARK & KELLY LLP
1 Manhattanville Road, Suite 302
Purchase, New York 10577
Tel: (914) 417-3400
Fax: (914) 417-3401
Attn: Bryon L. Friedman, Esq. (BF-5752)
Email: Bryon.Friedman@LittletonJoyce.com

Attorneys for Defendants

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

MERCK EPROVA AG,	:	Case No. 07 Civ. 5898 (RJS)
Plaintiff,	:	**GNOSIS' RESPONSE TO MERCK'S SUR REPLY TO PLAINTIFF'S OPPOSITION TO MOTION FOR SUMMARY JUDGMENT**
-against-	:	
GNOSIS S.P.A. and GNOSIS BIORESEARCH S.A.,	:	
Defendants.	:	

I. Merck Admits that Gnosis' Nomenclature is "More Closely Aligned" with the World Renowned Cahn, Ingold, Prelog Nomenclature than Merck's is

At the very end of its sur-reply, Merck makes an admission that destroys the foundation upon which its entire case rests. Merck cries foul play by suggesting that Gnosis changed the GRAS report nomenclature from Merck's nomenclature to Gnosis' nomenclature to avoid an inconsistency in this litigation. However, it is clear from Merck's chart at pages 7-9 that Gnosis

did not change the GRAS nomenclature from Merck's nomenclature (L-5-MTHF = pure isomer) to Gnosis' nomenclature (L-5-MTHF = 50/50 mixture), but to the universally accepted Cahn, Ingold, Prelog nomenclature (6S = pure isomer and 6RS = 50/50 mixture). Merck agrees that 6RS unambiguously refers to what it calls the "Mixture Ingredient." In fact, Merck admits that "if Gnosis had correctly labeled its product 6(R,S)-5-MTHF from the start …, there would not have been a lawsuit." Sur-reply, p. 9.

Merck then complains that Gnosis changed the nomenclature from Merck's nomenclature to a nomenclature "**more closely aligned with Gnosis' litigation positions**." Id. (Emphasis added.) This is an admission of major proportions. Merck is admitting that Gnosis' nomenclature in this litigation is "more closely aligned" with the universally accepted Cahn, Ingold, Prelog ("CIP") nomenclature than Merck's is. How can a nomenclature system that is "more closely aligned" with a universally accepted nomenclature like CIP be "literally false"? In an effort to prove Gnosis alleged doctoring of the GRAS report, Merck has admitted that it cannot prove its case on literal falsity.

II. Merck's Nomenclature is Not Unambiguous

Merck claims that Gnosis' own GRAS expert report establishes that Gnosis' usage of the acronym L5 MTHF is literally false. To prove literal falsity, Merck must prove that the acronym L5 MTHF is *unambiguous*. *Time Warner Cable, Inc. v. DIRECTV, Inc*., 497 F.3d 144, I58 (2d Cir. 2007). Not only does Merck fail in its effort, but its sur-reply proves the exact opposite. Dr. Madhusudan Soni - who has a PhD in biochemistry and was the lead author of the report relied upon by Merck - confessed in his deposition and in emails on the subject that the nomenclature regarding the substantially pure isomer (which Merck claims is unambiguous) was "confusing."

While Dr. Soni at times used Merck's nomenclature in his early drafts of the report, he freely confessed he was "confused" by the nomenclature in the literature. For example, he testified as follows:

> Q. And did you find other names that were used for that substantially pure isomer?
>
> A. Because there are several different names, and that was confusing to me also, that -- because in the literature it is referred differently and there were different names.

Chapman Declaration, Exhibit 1 ("Exhibit 1"), Soni at 61:22-62:5.

The fact that Dr. Soni was confused regarding the nomenclature shows that the terminology relied on by Merck is not "unambiguous."

III. Dr. Soni is not an Expert in Stereochemistry Nomenclature

Furthermore, Dr. Soni is not an expert in stereochemical nomenclature such that he could qualify to establish a worldwide standard for naming the subject product. The GRAS report was not intended to set a worldwide standard for nomenclature. Dr. Soni explained the purpose of a GRAS report and the fact that he was not attempting to establish nomenclature, as follows:

> Q. Okay. What is the purpose of a GRAS report?
>
> A. The purpose of GRAS report is to make sure that, as per the FDA regulations, there is a safety information, and that safety information support that particular substance to be used in food.

Exhibit 1, Soni at 21:15-19.

Q. Were you attempting to, in this -- in your work, were you attempting to establish nomenclature for these products?

A. No, I was not. I was just making sure that the product Gnosis is interested is identical to the ones which have the safety-related information.

Exhibit 1, Soni at 62:6-11

IV. Merck's Fingerprints are all over the Alleged "Independent, Scientific Literature" Merck Claims Establishes its Nomenclature as Universally Accepted

Furthermore, a careful review of the early GRAS reports using Merck's nomenclature clearly show the source of that nomenclature is not a reputable, independent scientific organization, but Merck itself. Merck now would have the Court believe that Merck can establish its nomenclature as unambiguous by reference to documents it created and put in the public domain. Dr. Daniel W. Armstrong, one of Merck's experts on organic chemistry, admits that Merck's "fingerprint" may be found on the articles on which he – and Merck – rely to establish that L-5-MTHF unambiguously refers to the 6S Product. Dr. Armstrong put it this way:

Q. Isn't it true that the ones that use the D,L nomenclature that we've looked at all have some fingerprint of Merck on them?

MR. MUKERJEE: Objection.

A. I'd have to go back and check, I know certainly some of them were

associated with Merck or had some

fingerprint, as you put it.

Exhibit 2, Deposition of Daniel W. Armstrong, at 300:19-301:3. (Emphasis added.)

Although Dr. Armstrong said he would have to "go back and check" to know whether the articles he was relying on to establish a universal, unambiguous nomenclature were authored by Merck, he knew that at least "some" of those articles had Merck's "fingerprint" on them. It was not too difficult to "go back and check" to see whether the articles Merck relies on to establish an unambiguous nomenclature had Merck as their source.

Below is a list of the references Merck relies on in its sur-reply and the sources where that information came from. As can be seen from the chart, Merck's "fingerprint" is all over the "scientific" and "industry" information Merck claims prove that its nomenclature is universal and unambiguous. The left column is Merck's reference to the GRAS report; the right column is the source of where the information came from.

Merck's Nomenclature in the GRAS Report	**Merck's "Fingerprint" on the Sources of that Nomenclature**
"Enzymatic reduction of folic acid leads to formation of the L-diastereoisomer tetrahydrofolate at the carbon number 6, also designated as L-tetrahydrofolate." See, Spataro Dec., Ex. 1 (GNO08852).	The terms used here are in a general section of the GRAS report and were likely influenced by any one of the articles with Merck's "fingerprints." See specific references to Merck's authorship or influence on the sources below. Exhibits attached to Declaration of William D. Chapman ("Chapman Decl."), as follows: **-Exhibit 3**, "Compendium of food additive specifications Addendum 13, 65th Meeting," Joint FAO/WHO Expert Committee on Food Additives ["JECFA"]; **-Exhibit 4**, "Final Assessment Report, Application A566, L-5-METHYLTETRAHYDROFOLATE, CALCIUM AS A PERMITTED VITAMIN FORM OF FOLATE," The Food Standards

	Australia New Zealand ("FSANZ"); -**Exhibit 5**, Venn et al., 2003, "Comparison of the effect of low-dose supplementation with L-5-methyltetrahydrofolate or folic acid on plasma homocysteine: randomized placebo-controlled study"; -**Exhibit 6**, Venn, et al, 2002, "Increase in Blood Folate Indices Are Similar in Women of Childbearing Age Supplemented with [6S]-5-Methyltetrahydrofolate and Folic Acid"; -**Exhibit 7**, Bostom, et al., "Controlled Comparison of L-5-Methyltetrahydrofolate Versus Folic Acid for the Treatment of Hyperhomocysteinemia in Hemodialysis Patients."
"These studies include data on racemic mixture of 5-MTHF (6R,S-isomer) as well as pure isomers particularly 6S-also called L-isomer)." See id. (GNO08859).	The study that addresses the pure isomer is a JECFA study in which Merck supplied the reference material, and presumably the nomenclature, as well. **Merck's "Fingerprint"** "Reference standard solution Accurately weigh 50 mg of L-5-methyltetrahydrofolic acid, calcium salt (**Merck Eprova AG**, CH-8200 Schaffhausen, Switzerland)..." (MERCK0001934, also MERCK0001936). Chapman Decl., Exhibit 3, (Emphasis added.)
When describing assessments of the substantially pure isomer ingredient by such organizations as the Joint FAO/WHO Expert Committee on Food Additives and the Food Standards Australia New Zealand, the ingredient is named "L-MTHF-Ca" or "L-MTHF." See id. (GNO08861-62).	As stated above, Merck provided JECFA, or Joint FAO/WHO Expert Committee on Food Additives, material for their report and presumably provided their nomenclature as well. The Food Standards Australia New Zealand (FSANZ) application was submitted by Merck and therefore presumably used their nomenclature, as well. **Merck's "Fingerprint"** "The FSANZ safety assessment of L-MTHF-Ca was based on chemistry metabolism and toxicity data published in scientific literature and provided to the agency by **Merck Eprova AG**." Chapman Decl., Exhibit 4. (Emphasis added.)

(When detailing a clinical trial, the substantially pure isomer ingredient used in the trial is described): "Although L- or 6S-isomer of 5-MTHF was used in this study.. . ." See id. (GNO08874).	The clinical trial referenced (Venn, et al., 2003), was co-authored by Rudolf Moser, an employee of Merck and therefore used Merck's nomenclature. Merck also provided the supplements. **Merck's "Fingerprint"** *"Bernard J Venn, Timothy J Green,* ***Rudolf Moser****, and Jim I Mann* 1 From the Department of Human Nutrition, University of Otago, Dunedin, New Zealand (BJV, TJG, and JIM), and **Eprova AG, Schaffhausen, Switzerland (RM)**. 2 Supported by The Otago Medical Research Foundation (Laurenson Foundation) and the Bristol Meyers Squibb Mead Johnson Award. **Eprova AG (Switzerland) provided the supplements**." Chapman Decl., Exhibit 5, (Emphasis added)
"[E]ffects of 6S-isomer of 5-MTHF (L-MTHF) supplementation on certain health endpoints have been extensively investigated in a number of studies.. . ." See id. (GNO08875).	They reference Venn et al., 2002 which was also authored by Rudolf Moser, an employee of Merck. Another reference is Bostom et al., 2000, which again Merck provided the reference solution. **Merck's "Fingerprint":** **"**Bernard J. Venn,* Timothy J. Green,*2 **Rudolf Moser,**** Joanne E. Mckenzie,† C. Murray Skeaff* and Jim Mann* **Department of Human Nutrition and †Preventive and Social Medicine University of Otago, Dunedin, New Zealand and* *****Eprova."*** Chapman Decl., Exhibit 6, (Emphasis added). **Merck's "Fingerprint"** "L-5-methyltetrahydrofolate (**Eprova**)…" Chapman Decl., Exhibit 7, (Emphasis added.)

It is clear from the above that the sources for the information relied on by the GRAS panel when it used the Merck nomenclature was not some independent, scientific body but Merck itself. One thing that should be clear from all that has been filed in this case is that Merck's nomenclature is anything but unambiguous.

V. Gnosis Changed the Draft GRAS Report to Align With the Universally Accepted Cahn, Ingold, Prelog Nomenclature

Below is a chart documenting the changes/non changes from the October 3, 2009 Draft GRAS report to the November 5, 2009 Draft of GRAS Report. This chart shows two things: First, Gnosis did not change the language to be consistent with its own position in this litigation, but to be consistent with the CIP nomenclature which is undisputedly accepted worldwide. Second, the nomenclature in the October 3, 2009 Draft GRAS report was inconsistent and Gnosis changed it in an effort to be more consistent. There is nothing sinister about the changes.

Nomenclature used in Expert Panel's October 3, 2009 Draft of GRAS Report for Mixture Ingredient	**Nomenclature used in Expert Panel's November 5, 2009 Draft of GRAS Report for Mixture Ingredient**
Referring to the pure	**Referring to the pure**
L-5-MTHF	6(S)-5-MTHF
L-5-MTHF-Ca	6(S)-5-MTHF calcium salt
6S-form	6S-form
6(S) isomer	6(S)-isomer
L-isomer	L-isomer, 6(S)-5-MTHF
L-MTHF	6(S)-5-MTHF
6(S) 5-MTHF	6(S)-5-MTHF
L(6S)-MTHF	6(S)-5-MTHF
L-diastereoisomer	L-diastereoisomer
S-diastereoisomer	S-diastereoisomer
5-MTHF (L-isomer)	6(S)-5-MTHF isomer
L-MTHF-Ca	6(S)-5-MTHF calcium salt
6(S)	6(S)
Referring to the mixture	**Refering to the mixture**
6R,S-5-METHYLTETRAHYDROFOLATE	6(R,S)-5-METHYLTERTAHYDROFOLATE
5-MTHF	5-MTHF, 6(R,S)-5-MTHF
6R,S-isomer	6(R,S)-5-MTHF
6(R)-isomer	6(R)-isomer
6(R) 5-MTHF	6(R)-5-MTHF
D-5-MTHF-Ca	6(R)-5-MTHF calcium salt
6R,S-5-MTHF-Ca	6(R,S)-5-MTHF calcium salt
6R-form	6R-form
D-diastereoisomer	D-diastereoisomer

R-diastereoisomer	R-diastereoisomer
6R,S-5-MTHF	6(R,S)-5-MTHF, 6(R,S)-5-MTHF calcium salt
6(R)	6(R)

VI. Mr. Berna Did Not Know About the Filing of the NDI

Mr. Berna testified that Gnosis was "in the process of " filing an NDI and "we will do it." Sur-reply, p. 2, 3. He testified that "up until now (February 8, 2010)," Gnosis had not filed an NDI with the FDA. Although he signed the papers before his deposition, there is no indication that he knew that the lawyers had filed the papers with the FDA. Furthermore, Merck has been allowed to review the documents and submit its sur-reply and therefore, has suffered no prejudice.

VII. Conclusion

Merck admits that Gnosis' nomenclature is "more closely aligned" with the world renowned Cahn, Ingold, Prelog standard than Merck's nomenclature is. Based on that admission, and solid evidence that support it, Merck cannot prove that Gnosis' nomenclature is unambiguously false. Merck cannot even prove that any of the nomenclature for this product is unambiguous. The nomenclature is all over the board.

Merck cites to Dr. Soni, one of the GRAS experts, to attempt to establish that its nomenclature is unambiguous. Dr. Soni testified clearly that he was confused with the nomenclature, which proves just the opposite. Furthermore, Dr. Soni is not a stereochemistry expert, he is an expert in toxicology.

Merck's claim that the scientific community universally support its position is belied by a close reading of the sources it relies on. Merck's own expert admits that Merck's fingerprint is on the very articles it claims establish universal support for its position.

The changes made by Gnosis to the Draft GRAS report were not sinister at all. The early draft demonstrates Dr. Soni's confusion over terminology also exhibited in the "scientific" literature. Finally, Mr. Berna was unaware of the actual filing of the NDI because that was handled by his US lawyers. In any event, Merck has shown no prejudice even if he had been.

Based on all the papers filed, Gnosis' Motion for Summary Judgment must be granted and Merck's Motion for Summary Judgment must be denied.

Dated: November 17, 2010

SMITH, CHAPMAN & CAMPBELL

By: /s/
William D. Chapman, Esq.
Attorney for Defendants

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of GNOSIS' REPLY TO PLAINTIFF'S OPPOSITION TO GNOSIS STATEMENT OF MATERIAL FACTS

was served on 11/17/2010 on counsel as follows:

ALSTON & BIRD LLP
90 Park Avenue
New York, NY 10016-1387

Robert E. Hanlon, Esq.
Thomas J. Parker
Natalie C. Clayton
Vicotoria E. (Ford) Spataro
Attorneys for Plaintiff Merck Eprova AG

Dated: November 17, 2010

/s/
William D. Chapman