No. 18-277
(Related Case No.: 18-1274)

In the
Supreme Court
of the United States

IN RE URVASHI BHAGAT
Petitioner,

v.

ANDREI IANCU, DIRECTOR, U.S. PATENT AND TRADEMARK OFFICE,
Respondent.

On Petition for a Writ of Certiorari to The United States Court of Appeals for the Federal Circuit

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PETITION FOR REHEARING

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MOTION FOR LEAVE TO FILE PETITION FOR REHEARING FILED OUT OF TIME

Court's Precedents Allowing Untimely Petitions:

The Court's precedents show that in exceptional circumstances, as in the present case, the Court has granted untimely petitions for rehearing when accompanied by a motion seeking leave to file out of time. *Gondeck v. Pan Am World Airways*, 382 U.S. 25 (1965); *United States v. Ohio Power Co.*, 353 U.S. 98, 99 (1957).

In *Carlisle v. U.S.,* 517 U.S. 416, 450-451 (1996) Justices Stevens & Kennedy stated, "On rare occasions... we have held that the interest in the evenhanded administration of justice outweighs the interest in finality and granted [petitions for rehearing] even though untimely and even though there is not a word in our Rules that authorized such action."

In *Ohio Power Co.*, this Court stated "We have consistently ruled that the interest in finality of litigation must yield where the interests of justice would make unfair the strict application of our rules. This policy finds expression in the manner in which we have exercised our power over our own judgments, both in civil and criminal cases." "[t]he Court's inherent power over its judgments" include the authority to take action that "would otherwise be out of time under the Rules." Id., at 104.

Procedural history of *Ohio Power Co.* (rehearing granted one year after certiorari and two rehearing denials) and *Gondeck* (rehearing granted three years after certiorari and one rehearing denials) is similar to the present case:

Gondeck	*Bhagat*
Certiorari denied June 11, 1962; Rehearing denied Oct 8, 1962; Rehearing and certiorari granted, decided Oct. 18, 1965	Writ of Certiorari denied October 29, 2018; Rehearing denied October 15, 2019

Exceptional National Intervening Circumstances:

This case is of exceptional national importance exemplified by the public health crisis and economic collapse from COVID-19. In the US as of May 30, 2020, 1.8 million infections, 102,812 deaths, 40 million job losses, and GDP decline of 5% in the 1st quarter of 2020 have been reported from COVID-19[1]. This could have been mitigated had the subject innovations been allowed, as proper, in 2013. The devastation from COVID-19 or similar microbes can still be mitigated with proper government support.

The intervening COVID-19 crisis makes it chillingly clear that the real pandemic is that of deranged metabolic health and impaired immunity, which enables the virus to effect adverse outcomes, death, and destruction, predicted in the US patent application no. 12/426,034.

The Specification and the evidence of record (including eleven expert testimonies) ***forewarned*** that

[1]https://abcnews.go.com/Health/coronavirus-map-tracking-spread-us-world/story?id=69415591; https://www.theguardian.com/business/2020/may/28/us-job-losses-unemployment-coronavirus; and https://www.bea.gov/news/blog/2020-05-28/gross-domestic-product-first-quarter-2020.

the claimed compositions directed to ratios, concentrations, and dosages of omega-6 and omega-3 and other lipids are critical for public health for ***prevention of chronic and infectious diseases***, in light of the overwhelming opposite teachings, poorly understood factors, and miseducation in the lipid art, gravely compromising public health, including ***making them susceptible to infections***.

The crisis hammers in the exceptional national importance of the described innovations, extremely improperly rejected and obstructed by USPTO, and rubber-stamped by the US Court of Appeals for the Federal Circuit on appeal without meaningful review disregarding majority of the Appellant's arguments and ***100% of the evidence cited from record*** including eleven testimonies from esteemed scientists, ***failing to take due account of prejudicial errors.*** 55 Claims were improperly rejected under Title 35 USC §§ 101 and 102(b) by excising limitations from the claims, of which Claims 102, 107, and 119 were *solely* rejected under §101.

The compelling reason for the grant of certiorari in light of COVID-19 are the abuse of discretion and the gross negligence compromising public health! The Federal Circuit "so far departed from the accepted and usual course of judicial proceedings as to call for an exercise of this Court's supervisory power" (Rule 10(a)). Further, the Rehearing will settle important questions of federal law (Rule 10(c)).

The COVID-19 crisis makes it starkly clear that the critical unmet public health need is not met despite the public disclosure of the '034 application in October 2009, and that disclosure alone is not enough,

and patent protected environment is necessary for effectively nurturing the solutions.

This Court must consider that the failure to grant this motion and the rehearing may *permanently foreclose* this innovation for humanity the effects of which may be felt for eternity, as the subject matter will be anticipated or obvious to future applicants from the disclosure, yet the solutions are unlikely to be implemented without patent due to complexity and economic disincentives (discussed infra).

Further Intervening Circumstances:

On May 21, 2019, USPTO issued Patent No. US10,292,958B2 on related application, where granted claim 1 is similar to rejected claim 98 and broader than claims 102, 107, and 119 (solely rejected under §101) in the '034 application. The conflict is prejudicial to the granted patent. The rehearing will resolve the conflict and provide guidance to the courts and USPTO.

There is no prejudice to the Federal Government or the USPTO. There are no circumstances relevant to the equities of this case that make the granting of relief inappropriate.

Therefore, this Motion for Leave to File Petition for Rehearing Filed Out of Time should be granted due to exceptional circumstances of imperative public health and national importance and other intervening circumstances of substantial effect. The Court has discretion and precedent for this compelling grant.

REVISED QUESTIONS PRESENTED UPON REHEARING

1. Is it abuse of discretion under the statutory requirements of the *Administrative Procedure Act, Title 5 U.S.C. §706* for the reviewing Court to disregard 100% of the evidence of record cited in appeal for judicial review?

2. Did the Federal Circuit fail to take due account of the "*rule of prejudicial error"* in failing to consider the Petitioner's substantial loss of rights in USPTO's and its own disregarding of expert testimony of record interpreting claim terms pivotal to the dispute, cited in the appeal for judicial review violating *Administrative Procedure Act, Title 5 U.S.C. §706*?

3. In *Bilski v. Kappos,* 561 U.S. 593, 603, 605 (2010) this Court held that "process" under §101 does not require a "transformation." Do "process" steps recited in claims require "transformation" differentially in "composition" versus "method" claims determined by the preamble?

4. In several §101 decisions, e.g., *Mayo Collaborative Servs. v. Prometheus Labs*, Inc., 132 S. Ct. 1289, 1293 (2012) this Court endorsed case-by-case analysis of §101 issues. Does innovation drawn to critical unmet public health need with potential to benefit every American, mitigate catastrophe like COVID-19, actuate long-term advancement of humanity, and unlikely to take place without patent protection weigh towards eligibility?

PETITION FOR REHEARING

Rehearing is requested pursuant to Rule 44.2.

GROUNDS FOR REHEARING

I. EXCEPTIONAL INTERVENING NATIONAL CIRCUMSTANCES: Public Health Crisis & National Economic Collapse From COVID-19 Could Have Been & Can Be Mitigated by Effective Implementation of the Claimed Innovations Improperly Obstructed by the Federal Circuit by So Far Departing from Accepted Course of Judicial Proceedings Requiring This Court's Intervention—Court Rule 10(a)

A. COVID-19 Rides on the Prevalent Deranged Metabolic Health & Impaired Immunity Which the Claimed Inventions Can Mitigate, Evidenced in the Specification Corroborated by Additional Evidence on Record

Evidence on Severity of COVID-19:

"In the eye of the COVID-19 cytokine storm" N. Vaninov, Nature Reviews Immunology, April 6, 2020[2]

"Not all patients with COVID-19 develop the same symptoms, but the immunological determinants of a poor prognosis are unknown. In this preprint article, Yang, Y et al. followed a cohort of 53 clinically moderate and severe

[2] https://www.nature.com/articles/s41577-020-0305-6

patients; they conducted a multiplex screen for 48 cytokines and correlated these results with lab tests, clinical characteristics and viral loads. They found a marked increase of 14 cytokines in patients with COVID-19 compared with healthy controls. Continuously high levels of three of these cytokines (CXCL10, CCL7 and IL-1 receptor antagonist) were associated with increased viral load, loss of lung function, lung injury and a fatal outcome. These observations offer key insights into the immunopathology of COVID-19 and provide new avenues for prognosis and therapy."

"Coronavirus kills some people and hardly affects others: How is that possible?" LA Times, April 4, 2020[3]

"COVID-19 is… more dangerous for those who have chronic lung disease, diabetes, high blood pressure, weakened immune systems and other underlying health issues."

"People Who Are at Higher Risk for Severe Illness" Centers for Disease Control and Prevention, May 14, 2020[4]

Based on currently available information and

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[3] https://news.yahoo.com/coronavirus-kills-people-hardly-affects-140011768.html

[4] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Funderlying-conditions.html

clinical expertise, **older adults and people of any age who have serious underlying medical conditions** might be at higher risk for severe illness from COVID-19.

"Can Bioactive Lipids Inactivate Coronavirus (COVID-19)?" UN Das, Abstract, Archives of Medical Research, 27 March 2020[5]

"SARS-CoV-2, SARS and MERS are all enveloped viruses that can cause acute respiratory syndrome. Arachidonic acid (AA) and other unsaturated fatty acids (especially eicosapentaenoic acd, EPA and docosahexaenoic acid DHA) are known to inactivate enveloped viruses and inhibit proliferation of various microbial organisms. The pro-inflammatory metabolites of AA and EPA such as prostaglandins, leukotrienes and thromboxanes induce inflammation whereas lipoxins, resolvins, protectins and maresins derived from AA, EPA and DHA not only suppress inflammation but also enhance would healing and augment phagocytosis of macrophages and other immunocytes and decrease microbial load. In view of these actions, it is suggested that AA and other unsaturated fatty acids and their metabolites may serve as endogenous anti-viral compounds and their deficiency may render humans susceptible to SARS-CoV-2, SARS and MERS and other similar viruses' infections. Hence, oral or intravenous administration of AA

[5]https://www.sciencedirect.com/science/article/abs/pii/S0188440920302927?dgcid=rss_sd_all

and other unsaturated fatty acids may aid in enhancing resistance and recovery from SARS-CoV-2, SARS and MERS infections."

The Foregoing is Predicted in Specification & Corroborated by Evidence on Record:

"The traditional emphasis on increasing omega-3 and reducing omega-6 consumption often does not result in satisfactory relieves… The current methodologies are confusing for the consumer, hence lead to over consumption or under consumption of critical nutrients with major health consequences." [Specification ¶7]

"Yet another aspect of the present disclosure is the concept of steady delivery of fatty acids, with respect to phytochemicals, antioxidants, and minerals, based on the observation that each time there is a change in dietary lipid delivery/consumption, it upsets the body physiology, sometimes with adverse effects such as headaches, muscle and joint pains, digestive and bowel upset, mental confusion, and anxiety; and at other times it may cause short-lived euphoria and general sense of wellness. **Though the body adapts to the change in 2-3 weeks or longer, long-term effects of the change/consumption outside the optimal range may be harmful.** Furthermore, sudden large fluctuations in fatty acids ingestion can also have acute adverse effects. **Sudden withdrawal of a habitual high long-chain omega-3 fatty acids or immunosuppressive phytochemical/nutrient supply from the host, or**

> **sudden increase in omega-6 fatty acids may result in release of a cytokine storm, with severe consequences** involving systemic inflammatory response (capillary leakage, pyrexia, tachycardia, tachypnoea), multi-organ dysfunction (gastrointestinal, lungs, liver, kidney, heart), and connective tissue damage in the joints. At such instances the host may be most vulnerable to infections, myocardial infarction, stroke, and induction of psoriasis depending upon the rest of the body chemistry and the presence of infectious agents. In less severe manifestations, due to moderate fluctuations in fatty acids and in otherwise salubrious condition, the host may experience sleep disturbance, headaches, muscle cramps, confusion, melancholia, and rage resulting from changes in neurotransmission, excitability of muscle and neural cells, fluctuating eicosanoids, and androgens. **This steady delivery requires a steady dosage within the optimal range lasting approximately 2 to 3 weeks at a minimum**." [Specification ¶39].

Subsequently, Specification provides 17+ examples teaching *dose-effect* and importance of *dosage* (specified administration) of omega-6 and omega-3. E.g., Example 22: A Case Study on Pulmonary Disorders (¶95), and Example 27: Case Studies on Immunity, Autoimmune and Infectious and Inflammatory Diseases (¶103) disclose *susceptibility to infections and compromised immunity* with swings in omega-6 and omega-3 doses. Further, Example 13 (¶74) and Example 24 (¶98) describe *cytokine dysregulation* with improper

omega-6 and omega-3 intake.

Accordingly, Specification provides *seven* tables (no. 3, 10-14, 21) teaching specific ratios, and dosages of omega-6 and omega-3, and all of the claims at issue are drawn to *dosages*[6] of omega-6/omega-3 and *controlled delivery* of the formulation (Cert.Pet.App.68a-90a[7]).

Further, Petitioner cited 46 peer-reviewed scientific papers corroborating the Petitioner's assertions from record upon appeal for judicial review (Pet.App.1a-12a, 43a-53a).

For example,

Harbige and Sharief reported,
"[d]ysregulation of n-6 fatty acid metabolism and cytokines is one mechanism that is important in disease progression, which is modifiable by specific supplementation. Thus, metabolic disturbance of the production of the long chain n-6 fatty acids DGLA and AA affects the physiological integrity of immune cells…" (Pet.App.47a-48a).

Das reported,
"subjects who have lower normal levels and those who are marginally deficient in PUFAs are more likely to develop HCV, HIV, malaria, and bacterial

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[6] Therapeutic use is inherent in the term "dosage"; see https://www.lexico.com/en/definition/dosage; and https://www.sciencestyle.com.au/dose-dosage-dosage-form-dosage-regimen

[7] Certiorari Petition Appendix

> infections. If this hypothesis is true, it indicates that those who fail to produce adequate amounts of lipoxins, resolvins, and protectins **are less likely to recover from these diseases in time**." (Pet.App.48a).
>
> Lu et al. reported,
> "Our results suggested that low concentrations (≤ 200 μ M) of LA promote colorectal cancer cell growth, while high levels (≥ 200 μ M) induce apoptosis of the colorectal cancer cells in vitro." (Pet.App.51a).
>
> Bhagat and Das reported,
> "a sudden withdrawal of or alteration in the proportion of intake of different types of PUFAs may result in a sudden surge in the production or inhibition of certain eicosanoids that may result in unrestrained or significant alterations in production/suppression of cytokines and gene(s) expression that may result in significant alterations in the physiological or pathological processes…" (Pet.App.52a).

Thus, numerous scientific publications corroborated the Specification that health benefit is achieved at specific ratios and *dosages* of omega-6 and omega-3, and improper intake may lead to dysregulation of cytokines and compromised immunity and other pathological conditions. Notably, none of the predating publications described every claimed element or overcame the prejudice against the claimed formulations (Specification ¶6, ¶7).

Further, scientists' testimony repeatedly ratified Petitioner's assertions (Pet.App.14a-38a), including that claimed formulations have anti-viral actions (Pet.App.15a) and great potential to protect and improve public health (Pet.App.22a-23a).

Thus, COVID-19 disaster and infectious diseases generally are rooted in poor underlying metabolic health and the associated weakened immune system, which the claimed innovations can mitigate.

Teaching Is Insufficient & the Innovations Must Take Hold at Public Level:

The critical unmet public health need is not met despite the publication of the Specification in October 2009, evidenced by the incidence of chronic disease and the COVID-19 crisis though the Specification explained plainly that such suffering could be mitigated. This evidences that teaching alone is insufficient, and patent protection is necessary for effective implementation and nurturing of the solutions at public level.

This is partly because of continuing misinformation and disinformation in the art[8], such that even public-health officials misinform. For example, the World Health Organization (WHO) issued the following advice on April 18, 2020[9],

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[8] https://twitter.com/KenDBerryMD/status/1265302016487755776 teaching the opposite of instant claims.

[9] https://twitter.com/WHOEMRO/status/1251413043906478080

"Nutrition advice for adults during #COVID19
Eat unsaturated fats
Don't eat saturated fats"

The problems with WHO advice are:

1. unsaturated fat advice without guidance on which ones (omega 3/6/9) and what dosage; and
2. saturated fat is important (Specification ¶4, ¶72), though it should be restricted.

This contrasts with specific ratios and dosages in instant claims, e.g. Claim 102 solely rejected under §101 (Cert.Pet.App.76a-77a).

Therefore, the innovations must take hold at public level, otherwise public can neither emerge from the suffocating chaos nor obtain dosages of lipids because of variability in nature (Pet.App.17a-18a, 25a-28a, 39a).

Therefore, the innovations at hand are of **exceptional national importance**, with potential to mitigate disasters like COVID-19, saving millions of Americans from suffering and trillions of dollars lost in economic collapse.

B. PTAB Disregarded Critical Parts of the Evidence from Record in Appeal Proceedings Committing a Prejudicial Error

PTAB's dismissal of the limitations, "dosage of omega-6 and omega-3" and "contained in one or more complementing casings providing controlled delivery of the formulation to a subject" as product-by-process (Cert.Pet.App.31a), without a word as to why they

disregarded the testified interpretation of experts (reproduced below), is a ***prejudicial error***.

> "[0012] The use of the word "dosage" in the subject patent application is clearly directed to determination of amount to be administered and/or administration in prescribed amounts (see para 34, 39, 47, 48, 49, 57, 59, 89, 97, 101, and 103). The concentration of nutrients per cup of olives in the reference fails to disclose such predetermined/ prescribed amount to quantify the olives for a person to eat." (Pet.App.18a).
>
> "[005] In light of the specification of the subject patent application, "casing" or "one or more complementing casings providing controlled delivery of the formulation" in amended claims 65, 91, 129 and 130 means one or more casings that are designed to contain one or more dosages of the formulation in order to control the delivery (e.g., substantially avoid inadequate or excess delivery and/or substantially control the release). This is clear from, for example, paragraphs 10, 34, 37, 60, 61, and Tables 16-19 of the specification." (Pet.App.24a-25a, 28a-29a).
>
> "[0021] Further, omega-6/omega-3 are randomly present in many food sources and their preparations. Therefore, some food sources and food preparations may randomly and inconsistently have omega-6/omega-3 within the meets and bounds of the instant claims and some may have omega-6/ omega-3 outside the meets and bounds of instant claims. However, that

> random and inconsistent presence is not motivation for a skilled person to obtain omega-6/omega-3, as directed by instant claims, particularly because there are overwhelming opposite teachings in the art (Lands, Nutrition Reviews 1986:44-6:189-95; Lands, Ann. N.Y. Acad. Sci. 1055: 179–192 (2005); Simopoulos, Ann Nutr Metab 1999;43:127–130; Hamazaki et al. World Rev Nutr Diet. Basel, Karger, 2003:92:109–132) and there are countless products of such teachings on the market. Therefore, random presence of omega-6 and omega-3 cannot be considered to be the "a dosage of omega-6 and omega-3 fatty acids at an omega-6 to omega-3 ratio of 4:1 or greater [or wherein omega-6 fatty acids are greater than 20% by weight of total lipids], contained in one or more complementing casings providing controlled delivery of the formulation to a subject…", wherein dosages are controlled and wherein ratio of omega-6 and omega-3 fatty acids to total lipids is controlled." (Pet.App.38a) (PTAB.App.Br.12-13, Fed.Cir.App.7670-7673).

Specification explained dose-effect of omega-6 and omega-3 is consequential (I.A supra), therefore dosage is a ***critical*** limitation in the claims. There is absolutely no justification for excising the limitation.

Thus, PTAB disregarded critical aspects of the innovation "dosages of omega-6 and omega-3" and "controlled delivery of the formulation to a subject…" without explaining why the scientists' interpretation under oath was disregarded. This was a ***prejudicial***

error, because it resulted in at least the rejection of Claims 102, 107, and 119, solely rejected under section §101, and it made the outcome of the appeal hurtful to the Petitioner, resulting in loss of "substantial rights." *Shinseki v. Sanders*, 129 S. Ct. 1696, 1706, 1708 (2009).

C. The Federal Circuit Disregarded 100% of the Evidence from Record Cited by the Petitioner Upon Appeal for Judicial Review Violating Title 5 U.S.C. §706

> Contrary to 5 U.S.C. §706,
> "In making [its] determinations, the court shall review the whole record or those parts of it cited by a party…" (Pet.App.58a-59a),

the Federal Circuit disregarded *100% of the evidence cited by the Petitioner* in the briefs and submitted to the court in Joint Appendix. The evidence is listed in Appendix A (Pet.App.1a-13a).

The cited references provide evidence of poorly understood factors, opposite teachings, inconsistency of lipids in nature, testimony of scientists on their interpretation of the claims and the prior art, and on USPTO's abuse of discretion and findings unsupported by substantial evidence. See excerpts from cited references in Appendix B-E (Pet.App.14a-57a).

It is a grave violation of §706 by the Federal Circuit to disregard 100% of the cited evidence.

D. The Federal Circuit Failed to Take Due Account of the Rule of Prejudicial Error Violating 5 U.S.C. §706

In *Shinseki v. Sanders*, this Court referred to the error being "prejudicial" when the error results in loss of substantial rights of a party. *Id* at 1706, 1708.

That is clearly the case here, in that at least Claims 102, 107, and 119 are *solely* rejected under §101, and the cited expert testimony on record (I.B supra) as to the interpretation of claim terms is dispositive, and when taken into account overcomes the improper "product-by-process" interpretation imposed by USPTO changing the outcome of the appeal.

Rather, the Federal Circuit excised the claim limitations under §102 analysis also (Cert.Pet.App.5a-6a, bridging paragraph), negating its §102 holdings.

There is no mention of the *cited* expert interpretation of the terms (App.Br.42-45) in the Opinion (Cert.Pet.App.1a-14a).

Thus, the Federal Circuit failed the provision "due account shall be taken of the rule of prejudicial error" violating 5 U.S.C. §706.

E. The Federal Circuit "so far departed from the accepted and usual course of judicial proceedings [] as to call for an exercise of this Court's supervisory power"—Rule 10(a)

In addition to the violations above (I.C-D supra) the Federal Circuit failed to review the issues raised upon appeal, e.g., abuse of discretion by USPTO under "Statement of Issues", discussion of "Errors", and "Abuse of Discretion" in the briefing (App.Br.2, 34-35, 38-39, 77, 80-81). There was *no response* to the issue or the cited evidence, Appendix E (Pet.App.54a-57a) in the Opinion.

Thus, the Opinion is in violation of both §§702 & 706 (Pet.App.58a-59a). It is a grave abuse of discretion, subjecting Petitioner to the very impropriety that was appealed.

Therefore, this Court's supervisory review is warranted.

II. The Rehearing Will Settle Important Questions of Federal Law –Rule 10(c).

A. Do "process" steps recited in claims require "transformation" differentially in "composition" versus "method" claims?

In *Bilski v. Kappos* at 603 this Court held that "process" under §101 does not require a "transformation." Do "process" steps recited in claims require "transformation" differentially in "composition" claims as required by Federal Circuit in '034 application (Cert.Pet.App.14a), versus "method claims" discussed below?

On May 21, 2019, USPTO issued Patent No. US10,292,958B2 [10] on related application where granted claim 1 is similar to rejected claim 98 and broader than claims 102, 107, and 119 solely rejected under §101 in the '034 application.

The preamble of the granted claims recites "A method of preparing a lipid-containing formulation…", versus "A lipid-containing formulation… compris[ing] an intermixture of lipids from different sources…" in the rejected claims.

The conflict is prejudicial to the granted patent. The rehearing will resolve the conflict.

B. Exceptional Circumstances Require Further Clarity on Case-By-Case Adjudication of Eligibility

In *Mayo Collaborative Servs. v. Prometheus Labs*, Inc., 132 S. Ct. 1289, 1293 (2012) this Court endorsed a case-by-case judgment in §101 decisions, stating *"[a]ll inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas," and "too broad an interpretation of this exclusionary principle could eviscerate patent law."*

The '034 application discloses exceptionally important innovations for humanity, solving critical unmet public health need with potential to benefit every American, mitigate catastrophe like COVID-

[10] The patent was issued ten years after the filing, significantly compromising the innovation.

19, and actuate long-term advancement for human health, yet unlikely to take place without proper patent (I.A supra, III. infra).

Are these factors relevant to eligibility?

Is this "useful art" under Article I, Section 8 of the US Constitution that should be promoted?

Does fear of limited exclusivity justify loss of life, prolonged human suffering, compromised advancement in national health and economics, in such a case where chaos of status quo suffocates advancement?

This Court's guidance is ***urgently*** needed on this question.

III. Exceptional Intervening Circumstances Warrant the Court's Exercise of Discretion—Failure to Grant the Rehearing May Permanently Foreclose the Exceptionally Important Innovation for Humanity for Eternity

The subject matter will be anticipated or obvious to future applicants from the disclosure, and without proper patent scope, the solutions may not be implemented or may not take hold, because,

1. Many businesses have economic disincentives to implementing the solutions, e.g. loss of revenue from mass-marketed injudicious foods and drugs and devices, though the nation and humanity as a whole will enormously advance (I.A supra); and

2. The innovations require nurturing at public level (even if disclosure is for skilled persons) without which misinformation and disinformation in the art (I.A supra) will keep public confused and obstruct the innovations from taking hold.

Therefore, the rehearing is of imperative importance for public health and national economics.

CONCLUSION

Exceptional intervening circumstances warrant rehearing.

June 1, 2020

Respectfully submitted,

/s/ Urvashi Bhagat
Urvashi Bhagat
Pro Se Petitioner

CERTIFICATE OF GOOD FAITH

I hereby certify that this Petition for Rehearing from denial of writ of certiorari is presented in good faith and not for delay, and that it is restricted to the grounds specified in Rule 44.2, namely exceptional intervening circumstances of substantial or controlling effect and substantial grounds not previously presented.

June 1, 2020

Respectfully submitted,

/s/ Urvashi Bhagat
Urvashi Bhagat
Pro Se Petitioner

APPENDICES

APPENDIX A

LIST OF EVIDENCE OF RECORD CITED & SUBMITTED TO THE FEDERAL CIRCUIT

EVIDENCING POORLY UNDERSTOOD FACTORS; INCONSISTENCY OF LIPIDS IN NATURE; TESTIMONY OF SCIENTISTS ON INTERPRETATION OF THE CLAIMS AND THE PRIOR ART; AND ON USPTO's ABUSE OF DISCRETION AND FINDINGS UNSUPPORTED BY SUBSTANTIAL EVIDENCE

BUT LEFT UNREVIEWED & UNANSWERED UPON JUDICIAL REVIEW

Fed.Cir.App.

APPENDIX B

EXCERPTS FROM EVIDENCE OF RECORD CITED & SUBMITTED TO THE FEDERAL CIRCUIT BUT LEFT UNANSWERED UPON JUDICIAL REVIEW

TESTIMONIES OF SCIENTISTS

Testimony of Dr. Undurti N. Das (10/3/12, ¶4, Fed.Cir.App.3850)

"In general, **it is believed by many scientists especially, those working in the area of PUFA that a ratio of 1:1 between n-3 and n-6 fatty acids is needed to obtain their beneficial actions despite the fact that there is no material proof of the same**. This belief is based on the empirical calculations of the dietary compositions of pre-agrarian humans and the dietary habits of Eskimos who are relatively free from cardiovascular disease, collagen vascular disease and have a very low incidence of cancer. At the same time it is not realized that Eskimos have relatively short life span in comparison to the modern subjects and are more prone to develop infections such as pneumonias… Since the diet of Eskimos is rich in marine fish whose content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is high, it has been argued that Eskimos are protected from cardiovascular diseases and other modern day diseases due to their high intake of EPA and DHA that are n-3 fatty acids. On the other hand, it is not realized nor believed that this high intake of EPA

and DHA could render them susceptible to develop infections due to the anti-inflammatory actions of these n-3 fatty acids. Thus, there could be two sides to the high intake of n-3 fatty acids as seen in the Eskimos—at one end it may prevent the development of cardiovascular disease and at the other end of the spectrum it may render them prone to develop infections to which they may succumb easily. This argument is supported by the fact that **some n-6 fatty acids have antibiotic like actions (Das UN. "Antibiotic like action of essential fatty acids" Candain Med Assoc J. 1985; 132:1350; Fed.Cir.App.). It is known that linoleic acid, gamma-linolenic acid and arachidonic acid [omega-6 fatty acids] have potent anti-bacterial, anti-fungal, anti-parasitic and anti-viral actions. Though n-3 fatty acids may also have similar antibiotic-like actions they are apparently less potent compared to n-6 fatty acids. Thus, it can be argued that higher intake of n-6 fatty acids have a beneficial action in that their higher intake would prevent or protect against various bacterial, fungal, parasitic, and viral infections**." [Emphasis added].

Testimony of Dr. Kevin L. Fritsche (10/8/12 ¶25-26, Fed.Cir.App.3868-3869)
[Also see Kent L. Erickson (10/7/12 ¶22-23, Fed.Cir.App.3860-3861)]

"[0025] In my opinion as a member of the polyunsaturated fatty acid research community, the position taken in the subject application reflects the current state of the art. The subject application

recognizes that the unpredictable results of early research in this field were incomplete and incorrect due to a failure to account for one or more factors that influence fatty acid metabolism. When the more recent and comprehensive research is taken into account, it is clear that a high ω-6 to ω-3 fatty acid ratio is not detrimental to human or animal health. Instead, as in the subject application, the state of the art now recommends a high ω-6 to ω-3 fatty acid ratio for optimal human and animal health."

"[0026] The subject application contains very important teachings for those skilled in the art that were not understood prior to this disclosure. Most important of those as discussed above is that the prior art failed to fully understand the importance of omega-6 for health. Human and animal tissue contains many times omega-6 as compared to omega-3. Omega-3 is preferentially metabolized. Furthermore, omega-6 has a shorter in-vivo life, possibly due to myriad of critical metabolites that it is a precursor to. Therefore, a lot more omega-6 is required as compared to omega-3. **This disclosure has taught that deficiency of omega-6 is a greater problem.** The disclosure also teaches that certain nutrients including antioxidants and phytochemicals can enhance effective omega-3 in-vivo but inhibit the metabolism of omega-6. The risks of sudden increase of omega-6 or withdrawal of omega-3 have been explained, which was not understood by prior art. **Prior art held that omega-6 causes disease, whereas this disclosure explains that the deficiency of omega-6 may upregulate certain mechanisms, in such a state sudden increase in omega-6**

could have an overflow effect that can lead to myocardial infarction, strokes, infections, and physiological disturbances. Several examples have been given to manage menopause, sleep disorders, neural disease, mental function, musculoskeletal disorders, obesity, diabetes, digestive, reproductive, pulmonary, ophthalmologic, dermatologic, and immune functions. These are multiple significant discoveries. Novel methods of treatment, administration, use, and tailored preparation are also disclosed. Because omega-6 and omega-3 significantly impact the structure and function of basic physiology, the delivery correction has beneficial effect on all diseases. Sufficient direction is provided for the skilled in the art to practice the disclosure." [Emphasis added].

Testimony of Dr. Kent L. Erickson (1/31/14, Fed.Cir.App.5703)

"[003] It is obvious from the instant patent application that composition and formulation claims are directed to man-made product formulations, and not products of nature. For example note "combination" in para 29, 44, 66, 69, 73, "three or more" in para 11, and "incorporation of nuts and nut oils as integral components of formulations" in para 21. Additionally, **the claims of the subject patent are directed to dosage and concentrations of omega-6 and omega-3 in relation to other lipids. However, products of nature do not come with guidance on omega-6 dosage amount or predictable concentrations of any of the lipids**. Lipid content, including omega-6 and

omega-3, of products of nature is extremely variable. This variability depends on the source, background genetics, cultivating conditions, including soils, fertilizer used, and other variable factors, such as hours of sunlight and water composition inherent in the cultivation of plant crops and many other epigenetic factors." [Emphasis added].

Testimonies of Drs. Robert B. Rucker (9/29/14, Fed.Cir.App.6519-6529), Undurti N. Das (9/30/14, Fed.Cir.App.6502-6512), and Pradip K. Rustagi (9/29/14, Fed.Cir.App.6485-6495)

"[0012] The use of the word **"dosage" in the subject patent application is clearly directed to determination of amount to be administered and/or administration in prescribed amounts** (see para 34, 39, 47, 48, 49, 57, 59, 89, 97, 101, and 103). The concentration of nutrients per cup of olives in the reference fails to disclose such predetermined/ prescribed amount to quantify the olives for a person to eat."

"[0014] The subject patent application has disclosed important factors that were neither conventional nor understood by the prior art regarding omega-6 and omega-3 fatty acids. Prior to April 2008, the state of the polyunsaturated fatty acid (PUFA) art had held that high amounts of omega-6 PUFAs were unhealthy for humans and animals. Numerous publications taught to keep omega-6 less than 4% of calories, (*Lands, Nutrition Reviews 1986:44-6:189-95; Simopoulos, Ann Nutr Metab 1999;43:127–130; Hamazaki et al. World Rev Nutr Diet. Basel, Karger, 2003:92:109–132*), which equals less than 11.4% of

dietary fat (proxy for lipids) based on ~35% dietary calories from fat generally recommended *(USDA & USDHHS "Dietary Guidelines for Americans 2010"*). This teaching applied to omega-6 from all foods, including omega-6 from nuts and seeds. Therefore, prior art teaches omega-6 less than 11.4% of total dietary fat, including from combination of walnuts, soybeans and sunflower seeds. Furthermore, *Lands, Ann. N.Y. Acad. Sci. 1055: 179–192 (2005),* teaches, less than 0.5% of calories from omega-6, i.e. less than 1.42% of dietary fat based on 35% of dietary calories from fat (page 183, 4th paragraph). The teaching is specific to "a [average] day's menu," i.e. including walnuts, soybeans, and sunflower seeds. Lands discloses distance-learning sites hosted by US National Institutes of Health (http://web.archive.org/web/20051212173212/http://efaeducation.nih.gov/ sig/kim.html), which "use the USDA data base of 6,000 different foods, more than 12,000 servings of food, to create an interactive, computerized, personalized, daily menu-planning program..." (page 188). It is well known that walnuts, soybeans, and sunflower seeds are part of the USDA database of foods (see http://www.nal.usda.gov/fnic/foodcomp). Thus, *Lands* teaches omega-6 less than 1.42% of total dietary fat, and "distance-learning sites" were developed to help users implement this teaching. Thus, the prior art overwhelmingly teaches omega-6 less than 11.4% of total fat including from walnuts, soybeans and sunflower seeds, which is outside the scope of instant claim 91. Thus, the limitation "omega-6 fatty acids are greater than 20% by weight of the total lipids," in claim 91 is neither well understood, nor conventional or routine in prior art,

rather there is overwhelming opposite teaching in prior art."

"[0019] The quest to find lipid formulations that lead to good health is a long-felt unmet need. *Holman, J. Nutr. 128: 427S–433S, 1998* explains, "The discovery of the essentiality of the long-chain fatty acids was made by Burr and Burr (1929) at the University of Minnesota Medical School. … At that time, essentiality meant growth and prevention of the dermatitis observed when a fat-free diet was fed to rats. Both linoleic and linolenic acids provided these functions." In 1960, Holman proposed an index of EFA deficiency status. In 1974, a misconception about omega-6 fatty acids began, which in part was based on inappropriate extrapolation about the effects of ingested omega-6 from data based on injected omega-6. For example, *Silver et al., Science (1974) 183:1085-1087,* injected sodium arachidonate into the marginal ear veins of rabbits, which caused death by platelet aggregate occlusion of the pulmonary microcirculation. Silver concluded that arachidonic acid (AA) was harmful to health because such aggregation could lead to thrombotic diseases such as pulmonary embolism, myocardial infarction, and stroke. However, contrary to the misunderstanding of the prior art, a given agent can have very different effects depending on its route of administration, and results from administration by one route—such as injection—cannot be equated to results from administration by another route—such as ingestion. Other researchers also concluded that omega-6 PUFAs were linked to the pathogenesis of diseases such as pulmonary embolism, myocardial infarction, and stroke. In contrast to the negative effects caused by omega-6 PUFAs, early research

had suggested that ω-3 PUFAs provided health benefits, including suppressing the pathogenesis of the same diseases that high omega-6 fatty acid levels were believed to promote.

[0020] Accordingly, prior art overwhelmingly teaches to keep omega-6 consumption less than 11.4% of dietary fat as discussed in paragraph [0014], and prior art overwhelmingly teaches omega-6 to omega-3 ratios less than 4:1. For example, European Patent Application 1510133A1 teaches omega-6 to omega-3 ratio of 1:1; *Hulbert. Biol. Rev. (2005), 80, pp. 155–169* teaches omega-6 to omega-3 ratios closer to 1:1 and teaches against omega-6 to omega-3 ratios 16.67:1*;* Mustad et al., US Patent 7,759,507 B2 teaches omega-6 to omega-3 ratio 0.25:1-3:1 (abstract); DeMichele et al., US5780451 teaches omega-6 to omega-3 ratio: 0.25-4.0 (Table 10); and www.whfoods.com teaches omega-6 to omega-3 ratio around 2:1 (see paragraph [0010]). This is a very small sample of such teachings.

[0021] Further, consistent with the widely-held belief that omega-6 is inflammatory and omega-3 is anti-inflammatory, in the prior art, when in-vitro and/or in-vivo omega-6 levels or the metabolites of omega-6 are found to be suppressed by certain nutrient(s) or omega-3 uptake or metabolism is enhanced by a certain nutrient(s), the nutrient(s) is(are) recommended as anti-inflammatory and its use is encouraged. For example, prior art has recommended use of vitamin E, curcumin, flavonoids, and other phytochemicals for suppression of PGE2 an arachidonic acid (omega-6) metabolite, assumed to be inflammatory, or inhibition of cycloxygenases (COX-1 and -2), enzymes responsible

for formation of PGE2 (*Wu D. et al. Am J Physiol. 1998 Sep;275(3 Pt 1):C661-8*; *Shah et al., Biochemical Pharmacology, Vol. 58, pp. 1167–1172, 1999; O'Leary et al. Mutat Res. 2004 Jul 13;551(1-2):245-54*). Prior to the filing of the subject application, one of ordinary skill in the art would have thought that it was beneficial to suppress omega-6 activity (and the activity of cyclooxygenases). However, the current patent application teaches that long-term deficiency or suppression of omega-6 activity is harmful (see para 39, 71, 85, 95, 98). These findings have been validated by recent publications (e.g. *Calder Biochimie 91 (2009) 791–795* and *Andreasson K. Prostaglandins & other Lipid Mediators 91 (2010) 104–112*.

[0022] Furthermore, the prior art places emphasis on low omega-6 to omega-3 ratios without teaching amounts, and not on high ratios with upper limit on omega-6 amounts, as taught by subject patent application. As noted previously, Mark et al. neither teach a consistent ratio nor total omega-6 amounts. Without knowledge of the absolute values, the ratio has little meaning. To be of value, the ratio must be taught with amounts. Further, to be of value amounts of total omega-6 fatty acids have to be taught not just LA. This is a shortcoming in the art at large and there are significant gaps in the teaching.

[0023] Thus, the art recognized in 1929 that the problem existed as noted in paragraph [0019]. However, the art has failed to solve the long-felt, critical and unmet need until the April 2008 priority date of the subject patent

application, i.e. for ~80 years. There have been many persistent attempts as evidenced by the references cited above (e.g. *Mark et al., whfoods.com*, *Lands 1986 and 2005; Simopoulos 1999; Hamazaki et al., 2003 supra*), but the problem has not been solved. Lipid art has been struggling to find what are the right combinations of omega-6 and omega-3 and other lipids for consumption, how to keep the fatty acids stable on shelf (without formation of toxic compounds) but bio-available in-vivo (*Chen and Chaiyasit supra*). Inventions of instant claims 65, 91, 98, 122, 129, and 130 have devised the solutions. Thus, the invention of the subject patent application solves a long-felt critical persistent unmet need, and has great potential to protect and improve public health."

"[0025] In my opinion as a member of the polyunsaturated fatty acids research community, the position taken in the subject application reflects the current state of the art. The subject application recognizes that the unpredictable results of early research in this field were incomplete and incorrect due to a failure to study long-term effects of higher omega-6 administration and to account for one or more factors that influence fatty acid metabolism. When the more recent and comprehensive research is taken into account as disclosed by the subject patent application, it is clear that omega-6 PUFAs above 20% by weight of total lipids are desirable, and omega-6 to omega-3 ratios of 4:1 or greater, wherein omega-6 are less than 40g, are desirable since human and animal tissue contains ~10x more long-chain omega-6 as compared to long-chain omega-3,

and utilization of omega-6 is higher (*Morse. Prostaglandins, Leukotrienes and Essential Fatty Acids 2009:81:373–389*). Furthermore, as disclosed by subject patent application in general phytochemicals and antioxidants increase requirement of omega-6 and reduce requirement/tolerance of omega-3 (also see *Thiebaut et al, Int. J. Cancer: 124, 924–931 (2009)*).

[0026] Thus, the limitations recited in independent claims 65, 91, 129 and 130 of the subject patent application are meaningful limitations. The limitations are not arbitrary. They are well-reasoned and directed at much needed lipid solutions, particularly in light of mass erroneous teachings and confusion in the lipid art. The subject patent application has disclosed upper limits of omega-6 throughout the disclosure, and a detailed example is disclosed in Table 20 along with calories administered. Using the information disclosed in various examples and rest of the disclosure, someone skilled in the art can formulate an omega-6 and/or omega-3 supplement or an entire nutritional formulation."

[Emphasis added].

Testimonies of Drs. Robert B. Rucker (4/30/15; Fed.Cir.App.7230-7231) and Undurti N. Das (4/30/15; Fed.Cir.App.7239-7240)

"[005] In light of the specification of the subject patent application, **"casing" or "one or more complementing casings providing controlled delivery of the formulation" in amended claims 65, 91, 129 and 130 means one or more casings**

that are designed to contain one or more dosages of the formulation in order to control the delivery (e.g., substantially avoid inadequate or excess delivery and/or substantially control the release). This is clear from, for example, paragraphs 10, 34, 37, 60, 61, and Tables 16-19 of the specification.

[006] In light of the specification of the subject patent application, "intermixture of lipids [fatty acids] from different sources" means a mixture, wherein at least fatty acids and/or other lipids are integrated from at least two "different sources" to enhance the usefulness of the formulation over a "single" source. "Different sources" means different oils, butters, nuts, seeds, herbs, sweeteners, and/or other foods and/or their different varieties (containing different lipid profiles). This is clear from, for example, paragraphs 8, 9, 11, 21, 22-27, 30, 62 and 64 and Table 2 of the specification.

[007] On September 29, 2014 [Rucker] [September 30, 2014 Das], I declared (see paragraph [0024]) that the physical and chemical properties of "A lipid-containing formulation comprising a man-made mixture of different products" including omega-6 and/or omega-3 fatty acids is necessarily different from what occurs in nature because of at least the reasons recited below. The same reasons hold true for "intermixture of lipids [fatty acids] from different sources" as opposed to a "single" source.

a. In nature, omega-6 and omega-3 occur in plant and animal tissue and organs primarily as part of triacylglycerols (TAG) (e.g. TAG constitute 89.6% of tallow and 97.9% of soybean oil) and in very small amounts as part of free fatty acids (e.g.

0.04% in rapeseed oil and 2.37% in sesame oil). The unsaturated fatty acids on triacylglycerols and phospholipids have low volatility. Free fatty acids are highly unstable causing odors, foaming, and reduced smoke points. Lipid sources that have been improperly stored can have high free fatty acid content.

b. In nature omega-6 and omega-3 occur along with several prooxidants (<3ppm), such as iron and copper, and antioxidants (<2%), such as phytosterols, tocopherols, and hydrocarbons. Prooxidants can accelerate lipid oxidation by directly interacting with unsaturated fatty acids to form lipid hydroperoxides (e.g. lipoxygenases and singlet oxygen) or by promoting formation of free radicals (e.g. transition metals or ultraviolet light promoted hydroperoxide decomposition). Antioxidants can retard lipid oxidation under certain conditions but promote lipid oxidation under other conditions.
c. Oxidation of omega-6 and omega-3 is one of the major causes of quality deterioration in lipid mixtures. The oxidation affects many physical and chemical characteristics such as flavor (rancidity), color, texture, and the nutritive value of mixtures. In addition, lipid oxidation produces and adds byproducts (e.g. aldehydes and ketones) to the mixture.
d. The only way to obtain "a man-made mixture of different products" comprising omega-6 and/or omega-3 fatty acids is to either mix plant/animal tissue itself or extract omega-6 and/or omega-3 fatty acids in free fatty acid form and then mix them. Either way the physical and chemical properties of the resulting mixture will be significantly and markedly different from what

occurs in nature because composition of triacylgycerols versus free fatty acids will change, and composition of prooxidants versus antioxidants will change. Additionally, triglyceride composition will change with respect to the type of fatty acids and the positional distribution of fatty acids (sn- position) on the glycerol backbone, affecting the physical and chemical properties.

e. Further, the physical properties of the mixture have a dramatic effect on lipid oxidation chemistry. For example dependent on whether the mixture is an oil-in-water emulsion, a bulk oil, or a mixture of another kind. Such mixtures contain polar lipids such as monoacylglycerols, diacylglycerols, free fatty acids, phospholipids, sterols, cholesterols, phenolic compounds, and oxidation by-products, many of which are amphiphlic. These amphiphilic molecules can self-assemble due to hydrophobic interaction from small amounts of water to form a variety of different types of association colloids, including lamellar structures and reverse micelles. These nano- or micro-environments can alter the physical location of prooxidants, antioxidants, and oxidation substrates (e.g. hydroperoxides).

(Chen et al., and Chaiyasit et al., supra)

It should also be kept in perspective that in nature there is extreme variability in lipid, antioxidant, and pro-oxidant content from species to species and even within species. Thus, hand of man in a "man-made mixture" will necessarily introduce variations to lipid configurations found in nature with major effect on physical and chemical properties of the lipid

formulation. Thus, man-made lipid mixtures are necessarily different in physical and chemical properties from what occurs in nature.

[008] **Lipid sources, such as oils, butters, nuts, seeds, and herbs have 100s of compounds. Therefore, when lipids from different sources are intermixed, the resulting mixture will necessarily have different physical and chemical properties, as discussed above. A hypothetical mixture of lipids from Source A and lipids from Source B, where the resulting mixture has exactly the same properties as Source A or B is first practically impossible, and second, if possible, it would be an extremely complex scientific endeavor. There would be no motivation for a skilled artisan to intermix lipids from Source A and Source B to achieve exactly the same properties as Source A or Source B in the resulting formulation."**

[Emphasis added].

Testimony of Dr. Kent L. Erickson (5/31/15, Fed.Cir.App.7320-7327)

"[005] In light of the specification of the subject patent application, **"casing" or "one or more complementing casings providing controlled delivery of the formulation to a subject" in amended claims 65, 91, 129 and 130 refer to formulations packed in casings such that controlled amounts/ dosages of the formulations are provided for consumption by the subject so that inadequate and excess**

intake/ingestion of the formulation is substantially avoided. This is clear from, for example, paragraphs 10, 34, 37, 60, 61, and Tables 16-19 of the specification.

[006] In light of the specification of the subject patent application, "intermixture of lipids [fatty acids] from different sources" refers to a mixture, wherein at least fatty acids and/or other lipids are integrated from at least two "different sources" to enhance the usefulness of the formulation over a "single" source. "Different sources" refers to different oils, butters, nuts, seeds, herbs, sweeteners, and/or other foods and/or their different varieties (containing different lipid profiles). This is clear from, for example, paragraphs 8, 9, 11, 21, 22-27, 30, 62 and 64 and Table 2 of the specification. For example, paragraph 30 clearly establishes that the purpose of the intermixtures is to incorporate "synergy among complementing nutrients from different sources" and "using different sources avoids concentrated delivery of specific [lipid] phytochemicals that may be harmful in excess."

"[009] On January 31, 2014, in reference to US Patent No. 5,549,905 by Mark et al., I had declared that one-liter composition of Mark et al. is not the representative quantity of the total amount provided to the pediatric patient. The dosage of Mark et al. compositions to be provided to the patient has not been stated specifically but could be a few milliliters to several liters. Mark et al., do not disclose the upper or safe limit of omega-6 dosage. The declaration was written keeping in perspective that the outstanding rejections from the Office then pertained to instant Claim 65(2). In light of the

currently pending rejections from the Office, I further declare as follows.

[0010] It is not possible to ascertain what Mark et al. is teaching with regard to omega-6 to omega-3 ratios. In SUMMARY OF INVENTION, column 2, lines 24-26 and 37-39, Mark et al. teach a composition having an "omega-3 to omega-6 fatty acid ratio of approximately 4:1 to 6:1" or omega-6 to omega-3 of 1:4 to 1:6. In DETAILED DESCRIPTION, column 4 lines 21-23, Mark et al. teach "The lipid profile containing such long chain triglycerides is designed to have a polyunsaturated fatty acid omega-6 (n-6) to omega-3 (n-3) ratio of approximately 4:1 to 6:1." It is not possible to ascertain omega-6 to omega-3 ratio from the table in column 4 because *only* 86% of the fatty acids are disclosed, 14% of the fatty acids are missing. Even though the table recites "TOTAL SAT/ TOTAL MONO/ TOTAL POLY" but that is clearly incorrect because the table also recites "TOTAL 86" underneath the column heading "% of Total Fatty Acids." Furthermore, based on the kind of compositions Mark et al. disclose (e.g., in column 5 and 6), it is not possible for non-fatty acid containing lipids to add up to 5.4g lipids missing from the table in column 4, because non-fatty acids containing lipids in such sources are present in extremely small amounts in 38.5g of lipids (see http://ndb.nal.usda.gov/ndb/search/list). Therefore, based on the disclosure right above the table in column 4 lines 21-23, the table in column 4 appears to disclose fatty acids of triglycerides only. Further, the ratio in column 6 line 15 of Mark et al. also appears to be based on 86% of the fatty acids in table in column 4 (C18:2 n6 12.2 ÷ C18:3 n3 = 5.08). Therefore, my expert opinion is that the omega-6 to

omega-3 ratio 4:1 to 6:1 taught by Mark et al. in column 4 and N6:N3 ratio 5:1 in column 6 is in triglycerides.

[0011] Mark et al consistently discloses and claims omega-6 to omega-3 ratios in triglycerides, not in total lipids. A composition of triglycerides is the focus of entire Mark et al disclosure, for example see abstract, column 2 lines 9-11, 21-23, and 48-51, and column 4 lines 1-23, and all of the independent claims 1, 9, and 15. Mark et al. claim 6 is a dependent claim on claim 1. The claim 1 and claim 6 in combination read as follows:

> An enteral composition designed for pediatric patients comprising:
>
> - a hydrolyzed protein source comprising approximately
> - 12% of the total calories;
> - a carbohydrate source; and
> - a lipid source comprising a mixture of medium and long chain triglycerides, wherein at least 55% of the lipid source are medium chain triglycerides [. The composition of claim 1] <u>further comprising</u> an omega-6 to omega-3 fatty acid ratio of approximately 4:1 to 6:1.

Therefore, the Mark et al. omega-6 to omega-3 ratio claimed in claim 6 (and claim 17) is also in fatty acids of triglycerides."

[0012] Triglycerides are a subset of total lipids. Total lipids are well known by persons of ordinary skill in the art to include free fatty acids, mono-glycerides, di-glycerides, glycolipids, and phospholipids, which contribute fatty acids to total

lipids. The lipid sources that Mark et al discloses (in column 2, 4, 5, and 6) safflower oil, canola oil, soy oil, coconut oil (MCT), residual milk fat, and soy lecithin are known to contain free fatty acids, mono-glycerides, di-glycerides, glycolipids, and phospholipids, which contain omega-6 and omega-3 fatty acids (*Chen et al., Critical Reviews in Food Science and Nutrition, 51:901–916 (2011); Chaiyasit et al., Critical Reviews in Food Science and Nutrition, 47:299–317 (2007)*). Soy lecithin, for example, can contain ~90% glycolipids and phospholipids, and the soy lecithin phospholipids can be rich in omega-6 and omega-3 fatty acids (*Scholfield CR, Journal of the American Oil Chemists' Society, vol. 58, no. 10 (October 1981), p. 889-892; ALC, American Lecithin Company, Downloaded from Internet on December 28, 2014*). Thus, Mark et al entire disclosure discloses omega-6 to omega-3 fatty acid ratios in triglycerides only, and fails to count fatty acids from free fatty acids, mono-glycerides, di-glycerides, glycolipids, and phospholipids in its compositions and omega-6 to omega-3 ratios. When omega-6 to omega-3 ratio is 4:1 to 6:1 in triglycerides, it can be 1:4 to 1:6 in total lipids, as recited in column 2 lines 24-26 and 37-38 of Mark et al. Thus, in my expert opinion, Mark et al has not disclosed omega-6 to omega-3 ratio of 4:1 or greater in total lipids as in instant claims 65, 129, and 130.

[0013] Further, column 4, lines 40-60 of Mark et al. disclose 12.2% C18:2 n6, which is linoleic acid (LA), and 2.4% C18:3 n3, which is alpha-linolenic acid (ALA), which is <u>not</u> the disclosure of 12.2% omega-6 fatty acids and 2.4% omega-3 fatty acids. Likewise, the amount of linoleic acid 4.7g, and alpha-linolenic

acid 0.9g is disclosed, not that of total omega-6 and total omega-3 fatty acids. The percentage or amount (dosage) of total omega-6 or omega-3 cannot be calculated because the table in column 4 *only* discloses 86% of the fatty acids; 14% of fatty acids are missing from the table.

[0014] Furthermore, Mark et al. define "lipids" as "safflower oil, canola oil, soy oil, coconut oil, residual milk fat, and soy lecithin" (see column 5 last paragraph), however, these recited substances are not 100% lipids as per conventional definition of lipids (*Fahy et al. J. Lipid Res. 2005. 46:839–861; The Nomenclature of Lipids, J Lipid Res. 1978 Jan;19(1):114-28*). The "lipid" recited by Mark et al. are known to contain non-lipids (see *Chen and Chaiyasit Supra*), even if in small amounts. It is evident from Mark et al. column 5 and 6 that Mark et al, simply add weight of sources of lipids (CANOLA OIL 13%, SOY OIL 16%, COCONUT OIL MCT 60%, RESIDUAL MILK FAT 6%, SOY LECITHIN 5%) to arrive at 38.5g/L "lipids". My assessment is that small part of missing 5.4g of "lipids" in table in column 4 may not be lipids as conventionally defined, but majority of the 5.4g missing lipids are fatty acids which contain omega-6 and omega-3 fatty acids. Additionally, Mark et al. has a separate category where lipid vitamins are listed in column 6. Therefore, Mark et al "total lipids" cannot be compared to "total lipids" in instant claims, which refer to conventional definition of lipids.

[0015] Furthermore**, I do not believe that the amounts of LA and ALA disclosed in table in column 4 of Mark et al. are "dosages" because**

there is no disclosure anywhere in Mark et al. regarding what might be suitable daily dosages of <u>omega-6 or omega-3</u> for children between the ages of 1-10 years. It should be noted that one-year-old child can have a body weight that is 100 lbs. less than a 10-year old child, with dramatically different omega-6 and omega-3 daily dosage requirements. In column 5 Mark et al. state "the composition of the present invention meets NAS-NRC RDAs for children ages 1-10 years in 1000 calories. The high vitamin and mineral concentration of the present invention is of practical benefit because typical feeding regimens (e.g. 50mL/hour for 20 hours/day) will meet all needs. …none of the vitamin or mineral concentrations are so high that there is any risk of approaching toxic levels, even at 2000-2500 kcal per day." As evident, the statement "typical feeding regimens (e.g. 50mL/hour for 20 hours/day) will meet all needs" is in context of vitamin and mineral concentration, not omega-6 and omega-3 dosage. Also caloric requirement for a 1-10-year old child varies from 800-2600 per day. Therefore, feeding regimen of Mark et al. compositions may be few milliliters for a 1-year old child and few liters for a 10-year old child. In fact, Mark et al. state feeding regimen may be 2 or 2.5 liters per day (2000-2500 kcal per day) without specifying any age group or upper limit in liters. Therefore, as declared previously (see paragraph [009] above) dosage of Mark et al. compositions to be provided to the patient has not been stated specifically but could be a few milliliters to several liters. Therefore, Mark et al., simply disclose a concentration of LA and ALA in the composition, but not the upper or safe limit of omega-6 dosage. In contrast instant specification consistently teaches

daily dosages with specific directions on how to practice the daily dosages throughout the disclosure. In light of the specification, the reference to "dosage" in instant claims is to achieving correct daily dosage via supplements and/or full diet (for example, see paragraphs 34-38).

[0016] **Mark et al is not a credible reference. The reference uses terms such as "Total" and "lipids" negligently as in the table in column 4 and in column 5 last paragraph, and the reference fails to teach compositions with total omega-6 and omega-3 in total lipids, even though minor omega-6 and omega-3 constituents of free fatty acids, mono-glycerides, di-glycerides, glycolipids, and phospholipids can have major impact on the properties of the formulation and health of subject consuming such formulations. A practitioner using Mark et al. will not know what omega-6 to omega-3 ratios to use in total lipids and how much omega-6 and omega-3 to put into Mark et al formulations, and how to practice omega-6 and omega-3 dosages because of negligent use of terms, and gaps and inconsistencies in the disclosure.**

[0017] **Therefore, due to the preponderance of evidence in paragraphs [009]-[0015] above, in my expert opinion Mark et al. is not an operable reference.**

[0018] "Olives" is one of the ~130 foods listed on the site www.whfoods.com. The archived version of "Olives" (published March 14, 2006) is http://web.archive.org/web/20060314112112/http://w

ww.whfoods.com/genpage.php?pfriendly=1&tname=foodspice&dbid=46. Olives In-depth Nutrient Analysis "ONA" (published March 14, 2006) is the associated page http://web.archive.org/web/20060314112106/http://www.whfoods.com/genpage.php?tname=nutrientprofile&dbid=111 disclosing nutrients in Olives. There is no suggestion in either Olives or ONA for "intermixture of lipids [fatty acids] from different sources," as recited in instant claims in paragraph [004]. As a skilled artisan, I consider one or more servings of olives to be a single source and I do not consider each olive to be a different source of lipids [fatty acids] from one another. Unless there is a specific, different type of olive added to the olives to enhance usefulness of the olives (as discussed above). There is no such suggestion of such a combination in either Olives or ONA.

[0019] "Walnuts" is one of the ~130 foods listed on the site www.whfoods.com. The archived version of "Walnuts" (published November 9, 2006) is http://web.archive.org/web/20061109221131/http://www.whfoods.com/genpage.php?pfriendly=1&tname=foodspice&dbid=99. Walnuts In-depth Nutrient Analysis "WNA" (published November 9, 2006) is associated page http://web.archive.org/web/20061109221127/http://www.whfoods.com/genpage.php?tname=nutrientprofile&dbid=132 disclosing nutrients in Walnuts. There is no suggestion in either Walnuts or WNA for "intermixture of lipids [fatty acids] from different sources" as recited in the instant claims and in paragraph [004]. As a skilled artisan, I consider one or more servings of walnuts to be a single source and I do not consider each walnut to be a different source

of lipids from one another. Unless there is a specific, different type of walnut added to the walnuts to enhance usefulness of the walnuts (as discussed above). There is no such suggestion of such a combination in either Walnuts or WNA.

[0020] It is important to note that the significance of "total lipids" as a category is not well understood in the art, even though the definition/classification of lipids is very well known (see *The Nomenclature of Lipids, J Lipid Res. 1978 Jan;19(1):114-28*). The effect of important lipid components, such as various phytochemicals in health and physical and chemical properties of formulations is not well understood. Food labeling practices routinely ignore important lipid components, as evidenced by Mark et al, ONA, WNA, and whfoods.com in general. Further, various authoritative nutrient databases (such as USDA databases) similarly disperse lipids over various categories and miss to report several important lipids and significance of "total lipids" as a category. Even authoritative guidelines do not recognize the significance of "total lipids" as a category as evidenced by FDA Nutrition Facts Labeling requirements (http://www.fda.gov/Food/ IngredientsPackagingLabeling/ LabelingNutrition/ucm274593. htm#see3) and Dietary Guidelines for Americans http://www.cnpp.usda.gov/sites/default/files/dietary_ guidelines_ for_ americans/ PolicyDoc.pdf. Typical disclosure is of total fat and omega-6/omega-3 as percent of fat, percent of fatty acids or percent of calories. For these reasons, unless a reference expressly teaches the effect of various lipid components on omega-6/omega-3 requirements and/or specifically teaches to obtain omega-6/omega-

3 as a ratio of total lipids, one cannot presume that skilled artisans will be motivated to obtain omega-6/omega-3 as a ratio of total lipids. For at least these reasons, I do not believe that references such as Mark et al, ONA, or WNA will motivate a skilled artisan to obtain omega-6/omega-3 as a percent of or ratio of total lipids.

[0021] Further, omega-6/omega-3 are randomly present in many food sources and their preparations. Therefore, some food sources and food preparations may randomly and inconsistently have omega-6/omega-3 within the meets and bounds of the instant claims and some may have omega-6/ omega-3 outside the meets and bounds of instant claims. However, that random and inconsistent presence is not motivation for a skilled person to obtain omega-6/omega-3, as directed by instant claims, particularly because there are overwhelming opposite teachings in the art (*Lands, Nutrition Reviews 1986:44-6:189-95; Lands, Ann. N.Y. Acad. Sci. 1055: 179–192 (2005); Simopoulos, Ann Nutr Metab 1999;43:127–130; Hamazaki et al. World Rev Nutr Diet. Basel, Karger, 2003:92:109–132*) and there are countless products of such teachings on the market.
Therefore, random presence of omega-6 and omega-3 cannot be considered to be the "a dosage of omega-6 and omega-3 fatty acids at an omega-6 to omega-3 ratio of 4:1 or greater, contained in one or more complementing casings providing controlled delivery of the formulation to a subject…", wherein dosages are controlled and wherein ratio of omega-6 and omega-3 fatty acids to total lipids is controlled."
[Emphasis added].

APPENDIX C

EXCERPTS FROM EVIDENCE OF RECORD CITED & SUBMITTED TO THE FEDERAL CIRCUIT BUT LEFT UNANSWERED UPON JUDICIAL REVIEW

ON UNPREDICABILITY OF OMEGA-6 (or n-6) AND OMEGA-3 (or n-3) IN NATURE & THE TRANSFORMATION OF NATURAL PRODUCTS UPON EXTRACTION OF OILS

Variability in Oleic and Linoleic Acid Content of Safflower Oil. **Knowles PF. Economic Botany, 1965, Volume 19, Issue 1, pp 53-62 (Fed.Cir.App.5472-5474)**

"Levels of oleic acid varied from 8.9 to 86.8% and linoleic acid from 8.7-84.6% [in safflower oil from seeds from different geographies closely positively correlated with iodine levels]." (Fed.Cir.App.5472-5474)

Role of Physical Structures in Bulk Oils on Lipid Oxidation. **Chaiyasit et al., Critical Reviews in Food Science and Nutrition, 47:299–317 (2007) (Fed.Cir.App.6650-6668)**

"During oil extraction, plant cells are destroyed by crushing operations and cell membranes are solubilized into the released oil" (page 306 col. 1-2, ¶3, Fed.Cir.App.6657).

"Heat and pressure also accelerate fatty acid hydrolysis. Fatty acid hydrolysis, and thus mono- or diacylglycerol formation are especially prevalent in olive" (page 304 col. 2 ¶3, Fed.Cir.App.6655).

"Figure 2 Refining stages of edible oils and the major impurities removed []

Degumming: Phospholipids, trace metals, pigments, carbohydrates, and proteins
↓
Neutralization: Free fatty acids, phospholipids, pigments, trace metals, sulfur, and insoluble matter
↓
Washing : Soap (form by free fatty acids or glycerols with sodium hydroxide)
↓
Drying: Water
↓
Bleaching: Pigments, oxidation products, trace metals, and traces of soap
↓
Filtration: Spent bleaching earth
↓
Deodorization: Free fatty acids, mono- and diacylglycerols, oxidation products, pigments, decomposition products, pesticides, sterols, sterol ester, tocopherols, and other antioxidants
↓
Physical refining: Free fatty acids, mono- and diacylglycerols, oxidation products, pigments, decomposition products, and pesticides
↓
Polishing: Any residual traces of oil insoluble"
(Page 305, Fed.Cir.App.6656)

Minor Components in Food Oils: A Critical Review of their Roles on Lipid Oxidation Chemistry in Bulk Oils and Emulsions **Chen et al., Critical Reviews in Food Science and Nutrition, 51:901–916 (2011) (Fed.Cir.App.6670-6685)**

"Oil seed extraction will produce a crude oil that contains lipids such as phospholipids and sterols in addition to triacylglycerols. However, the extraction process will also produce conditions where triacylglycerols can react with enzymes such as lipase and lipoxygenase to form hydrolytic products of triacylglycerols (e.g., monoacylglycerols, diacylglycerols, and free fatty acids) and lipid oxidation products such as hydroperoxides. Oil refining is performed to reduce the concentration of these minor components as they can negatively impact the quality of the oil. For instance, caustic alkali is used to remove free fatty acids in neutralization step since free fatty acids cause foaming and decreases the smoke point of oils." (Page 902, col. 2 ¶2, Fed.Cir.App.6671)

"The amount of DAG [diacylglycerols] and MAG [monoacylglycerols] reported in the crude oil are therefore composed of two parts, inherent concentrations in the seeds and those formed after crushing the seeds and during refining." (Page 904, col. 1 ¶2, Fed.Cir.App.6673)

Walnut (Juglans regia L.): genetic resources, chemistry, by-products. **Martinez *et al.* J Sci Food Agric 2010; 90: 1959–1967, (Fed.Cir.App.6614-6622)**

"When kernels are whole-ground and the oil is extracted, most phenolics remain in the flour…" (Page 1964, col. 1 ¶2, Fed.Cir.App.6619)

"Although walnut kernels contain a diverse array of phenolic and polyphenolic compounds with strong antioxidant and radical-scavenging properties, only minor amounts could be present in the extracted oils" (Page 1965, col. 1, ¶2, Fed.Cir.App.6620).

APPENDIX D

EXCERPTS FROM EVIDENCE OF RECORD CITED & SUBMITTED TO THE FEDERAL CIRCUIT BUT LEFT UNANSWERED UPON JUDICIAL REVIEW

ON TEACHINGS OF OMEGA-6 (or n-6) AND OMEGA-3 (or n-3) IN THE ART VERSUS THE SUBJECT PATENT APPLICATION

(Chronologically listed)

Renewed Questions about Polyunsaturated Fatty Acids. **Lands WEM. Nutrition Reviews Vol. 44. No. 6 June 1986 (Fed.Cir.App.4263-4266)**

"The period from 1930 to 1960 provided many nutritional studies on the nature of essential fatty acids (EFAs) that led to the conclusion that 'Properly, the term essential fatty acids should include only those substances which are active both for growth and for maintenance of dermal [skin] integrity, limiting the term to linoleic and arachidonic acids [omega-6 fatty acids] and to such other acids as may be derived metabolically from them." Id. page 189, col. 1 ¶3 (Fed.Cir.App.4263).

"Between 1964 and 1974 we developed an awareness of the oxidative conversion of the EFA arachidonate (20:4 n-6) into prostaglandin, and of the pharmacologic inhibition of that conversion by nonsteroidal anti-inflammatory agents like aspirin

and indomethacin. Pharmacologic and physiologic studies demonstrated important roles for prostaglandins in a wide range of endocrine and autacoid-mediated events. The use of pharmacologic agents to alter the course of those events permitted rapid discovery of many relationships between prostaglandins and physiologic and pathophysiologic processes. Between 1974 and 1979, revolutionary reports on thromboxane, prostacyclin, and leukotrienes were published. These discoveries provided major new insights into disease processes associated with arthritis, asthma, atherosclerosis, thrombosis, tumor proliferation, and a variety of immune-inflammatory disorders."
Id. page 190, col. 2 ¶2-3 (Fed.Cir.App.4264).

"**Ingestion of about 1 percent of daily calories as linoleate (18:2 n-6) is widely acknowledged as the approximate amount required to meet the need for EFAs in rats or humans**. The frequent use of linoleate to conduct most assessments of EFA requirements has not defined the amount of arachidonate that may meet minimal needs. Since dietary linoleate is only partially converted to arachidonate, much less dietary arachidonate can apparently meet minimal needs. Again, the question of normal physiology vs pathophysiology needs to be addressed in detail by carefully controlled nutrition studies. Certainly, increased frequency of thrombosis or asthma is not a desired condition. Can the ingestion of supra-optimal amounts of n-6 EFAs promote pathophysiology? Can our diet promote unwanted overresponses in our eicosanoid defense reactions? We currently invest massive resources into the pharmacologic inhibition

of excessive eicosanoid mobilization. Id. page 192, col. 1-2 ¶3 (Fed.Cir.App.4266). [Emphasis added].

"An example of excessive EFA availability was provided by Silver et a1, who showed that injected arachidonate, 20:4 n-6, (but not 18:2 n-6, 20:3 n-6, 20:3 n-3, 20:5 n-3, or 22.6 n-3,) killed rabbits in 3 minutes. Similarly, when Seyberth et al fed 6 g of arachidonate daily to healthy volunteers, they found it necessary to remove half the subjects from the study in progress because of indications of an increased tendency for thrombosis… Increased experimental tumors associated with increased dietary linoleate may also reflect excessive mobilization of eicosanoids that could enhance metastatic events and the establishment of secondary tumors." Id. page 192, col. 2 ¶2-3 (Fed.Cir.App.4266).

***The Slow Discovery of the Importance of ω3 Essential Fatty Acids in Human Health*, Holman RT. J. Nutr. 128:427S-433S (1998) (Fed.Cir.App.231)**

"The ω6 and ω3 acids compete for the same enzyme sites involved in these reactions. As intake of 18:3ω3 increases, metabolic products of linoleic acid are suppressed, and linoleic acid itself is increased in the liver lipids. Conversely, with constant dietary 18:3ω3 and increasing dietary 18:2ω6, ω3 products are suppressed, but 18:3ω3 itself increased in liver lipids. Strong suppression of ω6 metabolism was accomplished by <2% of calories of 18:3ω3, whereas an equal suppression of ω3 metabolism required nearly 10 times as much dietary linoleate. Omega 3

PUFA are more strongly conserved than are the ω6 PUFA. Suppression of 20:4ω6 by dietary 18:3ω3 of 20:4ω6 to 50% of its maximum value occurred at ~0.5% of calories of 18:3ω3, whereas suppression of 22:6ω3 to 50% of its maximum level by dietary 18:2ω6 occurred at 7% of calories of 18:2ω6. To be equally competitive, these precursors, 18:2ω6 and 18:3ω3, should be in the ratio of 14:1. **Equality of competition, however, may not be the criterion for optimal function. Yehuda and Carasso (1993), in studies of cognition in rats, found the optimum functional ratio of ω6/ω3 to be 4:1." 428 S. col. 2**. [Emphasis added].

Essentiality of and Recommended Dietary Intakes for Omega-6 and Omega-3 Fatty Acids
Simopoulos et al., Ann Nutr Metab 1999;43:127–130 (Fed.Cir.App.4446-4449)

"The Workshop on the Essentiality of and Recommended Dietary Intakes (RDIs) for Omega-6 and Omega-3 Fatty Acids was held at The Cloisters, National Institutes of Health (NIH) in Bethesda, Md., USA, April 7–9, 1999. The workshop was sponsored by the National Institute on Alcohol Abuse and Alcoholism-NIH, the Office of Dietary Supplements-
NIH, The Center for Genetics, Nutrition and Health, and the International Society for the Study of Fatty Acids and Lipids, and cosponsored by several industry groups." (Page 127, col. 1 ¶1, Fed.Cir.App.4446)

"One recommendation deserves explanation here. After much discussion consensus was reached on the

importance of reducing the omega-6 polyunsaturated fatty acids (PUFAs) even as the omega-3 PUFAs are increased in the diet of adults and newborns for optimal brain and cardiovascular health and function. This is necessary to reduce adverse effects of excesses of arachidonic acid and its eicosanoid products. Such excesses can occur when too much LA and AA are present in the diet and an adequate supply of dietary omega-3 fatty acids is not available." (Page 128, col. 1 ¶2, Fed.Cir.App.4447)

"The working group recognized that there are not enough data to determine Dietary Reference Intakes (DRI), but there are good data to make recommendations for Adequate Intakes (AI) for adults as shown in table **1 [wherein upper limit of omega-6 (LA) taught is 4.44-6.67 g/day and 2-3% of energy, and omega-3 (LNA+DHA+EPA) taught is 2.87, therefore omega-6 to omega-3 ratio taught is 1.55-2.32]." [30 scientists ratify the recommendation at page 130.]** (Page 128-130, col. 2 ¶3, Table 1, Fed.Cir.App.4447-4449) [Emphasis added].

Polyunsaturated fatty acids in the pathogenesis and treatment of multiple sclerosis. Harbige and Sharief. British Journal of Nutrition (2007), 98, Suppl. 1, S46–S53 ((Fed.Cir.App.200)

"[d]ysregulation of n-6 fatty acid metabolism and cytokines is one mechanism that is important in disease progression, which is modifiable by specific supplementation. Thus, metabolic disturbance of the production of the long chain n-6 fatty acids DGLA and AA affects

the physiological integrity of immune cells, in that they have a limited ability to produce TGF-b, under relapse conditions, which is important for the regulation of pro-inflammatory cytokine production e.g. TNF-a, IL-1b, IFN-g as well as other cellular biological functions." [Emphasis added].

Can essential fatty acids reduce the burden of disease(s)? **Das UN. Lipids in Health and Disease 2008, 7:9 (Fed.Cir.App.879)**

"It is envisaged in this hypothesis that the plasma and tissue concentrations of various PUFAs and their beneficial metabolites such as PGI2, PGE1, lipoxins, resolvins, and protectins will be lower in various low-grade systemic inflammatory conditions compared to normal. This hypothesis implies that in **subjects who have lower normal levels and those who are marginally deficient in PUFAs are more likely to develop HCV, HIV, malaria, and bacterial infections. If this hypothesis is true, it indicates that those who fail to produce adequate amounts of lipoxins, resolvins, and protectins <u>are less likely to recover from these diseases in time</u>**. Since, various PUFAs can be obtained from diet or supplemented from external sources; it will be interesting to study the therapeutic benefits of various ω-3 and ω-6 fatty acids in the diseases that have been enumerated above. It is important to study which type (ω-3, ω-6 or both) of fatty acids and in what combination or ratio and which form (oral or parenteral) are most suited to suppress or give relief from various diseases." (Fed.Cir.App.879) [Emphasis added].

Omega-6 Fatty Acids and Risk for Cardiovascular Disease
A Science Advisory From the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. **Harris et al. Circulation 2009;119;902-907 (Fed.Cir.App.205-207)**

"[**s]ome individuals and groups have recommended substantial reductions in omega-6 PUFA intake**. The purpose of this advisory is to review evidence on the relationship between omega-6 PUFAs and the risk of CHD and cardiovascular disease." (Page 902, col 1 ¶1, Fed.Cir.App.205)

"Conclusion: This advisory was undertaken to summarize the current evidence on the consumption of omega-6 PUFAs, particularly LA, and CHD risk. Aggregate data from randomized trials, case-control and cohort studies, and long-term animal feeding experiments indicate that the **consumption of at least 5% to 10% of energy from omega-6 PUFAs reduces the risk of CHD relative to lower intakes**. The data also suggest that higher intakes appear to be safe and may be even more beneficial (as part of a low–saturated-fat, low-cholesterol diet). In summary, the AHA supports an omega-6 PUFA intake of at least 5% to 10% of energy in the context of other AHA lifestyle and dietary recommendations. To reduce omega-6 PUFA intakes from their current levels would be more likely to increase than to decrease risk for CHD." (Page 904 col. 2 ¶4, Fed.Cir.App.207).

[Emphasis added].

Polyunsaturated fatty acids and inflammatory processes: New twists in an old tale. **Calder PC. Biochimie 91 (2009) 791–795 (Fed.Cir.App.2774)**

"The n-6 fatty acid AA gives rise to eicosanoid mediators that have established roles in inflammation and AA metabolism is a long recognised target for commonly used anti-inflammatory therapies. **It has generally been assumed that all AA-derived eicosanoids are pro-inflammatory. However, this is an over-simplification since some actions of eicosanoids are anti-inflammatory (e.g. PGE2 inhibits production of some inflammatory cytokines**) and it has been discovered quite recently that PGE2 inhibits production of inflammatory leukotrienes and induces production of inflammation resolving lipoxin A4… assumptions that: (a) all mediators formed from AA
are pro-inflammatory; (b) eicosanoids produced from EPA are always less potent than those formed from AA; (c) EPA is the main, perhaps the only, anti-inflammatory n-3 PUFA; and (d) anti-inflammatory actions of n-3 PUFAs always relate to changes in synthesis of lipid mediators, have all been shown to be incorrect. It is clear that the actions of n-6 and n-3 PUFAs and their derivatives on inflammatory processes involve more mechanisms and are more complex than previously recognised." (Page 794, col.2 ¶1, Fed.Cir.App.2774). [Emphasis added].

Linoleic acid suppresses colorectal cancer cell growth by inducing oxidant stress and mitochondrial dysfunction. **Lu et al., Lipids in Health and Disease 2010, 9:106 (Fed.Cir.App.4291)**

"Our results suggested that **low concentrations (≤ 200 μ M) of LA promote colorectal cancer cell growth, while high levels (≥ 200 μ M) induce apoptosis of the colorectal cancer cells in vitro**. On the other hand, low concentrations of LA (≤ 200 μ M) did not promote normal (HUVEC) cell proliferation while high concentrations (≥ 200 μ M), which were cytotoxic to tumor cells, induced only 10~20% decrease in the number of HUVEC. These results suggest that LA is toxic to tumor cells with little or no cytotoxic action on normal cells." (Page 7, col. 1-2, Fed.Cir.App.4291). [Emphasis added].

Potential role of dietary lipids in the prophylaxis of some clinical conditions. **Bhagat and Das. Arch Med Sci 2015; 11, 4: 807–818 (Fed.Cir.App.7366-7372)**

"[s]tudies have shown that adult human brain consumes AA and DHA at rates of 17.8 and 4.6 mg/day, respectively (ratio–3.87:1), respectively [35]. Further, it was shown that most adult human tissue contains approximately 10 times AA as compared to DHA [36]. This demonstrates that AA requirement is 4 to 10 times that of DHA. Furthermore, it has been shown to be equally competitive, LA and ALA should be in the ratio of 14:1 [32]. Based on this logic the ratio between w-6-to-w-3 of 15–17:1 in diets is not the problem, the problem is the other factors that

influence the metabolism of w-6 and w-3." (Pages 808-809, col. 2 ¶3, Fed.Cir.App.7366-7367)

"[i]t is likely that cellular stores of PUFAs and phytochemicals and other co-factors that alter fatty acid and eicosanoid metabolism play a significant role in several disease processes. **It is possible that a sudden withdrawal of or alteration in the proportion of intake of different types of PUFAs may result in a sudden surge in the production or inhibition of certain eicosanoids that may result in unrestrained or significant alterations in production/suppression of cytokines and gene(s) expression that may result in significant alterations in the physiological or pathological processes** including changes in LDL, HDL and cholesterol [135–137]. Such sudden and, sometimes, even gradual and unanticipated changes in the concentrations of various PUFAs, eicosanoids, cytokines, oxidative stress, HDL (may make HDL dysfunctional), LDL, cholesterol, triglycerides and other bioactive molecules may render the host vulnerable to infections, myocardial infarction, stroke, and other diseases and their complications [138–157].

In view of this, it is essential to determine the individual necessity of various monounsaturated, w-6, w-3 and other fatty acids, antioxidants, and phytochemicals and administer them accordingly. Such an individualized approach may be more fruitful in tackling several diseases in which PUFAs are believed to play a significant role. Development of such personalized dietary lipid programs for different types of subjects depending on

their age, gender, dietary practices, environmental factors (such as temperature, season, etc.), hormonal status, stress and strain of life and other life style factors (such as exercise, etc.) and genetic background is probably necessary and important to derive the best out of PUFAs, phytochemicals, vitamins and other co-factors for optimum health and to ward off diseases."

(Page 814, col. 1 ¶2-3, Fed.Cir.App.7372) [Emphasis added].

APPENDIX E

EXCERPTS FROM EVIDENCE OF RECORD CITED & SUBMITTED TO THE FEDERAL CIRCUIT BUT LEFT UNANSWERED UPON JUDICIAL REVIEW

ON ABUSE OF DISCRETION BY USPTO

Rehearing Request Submitted to PTAB on June 14, 2016 (Fed.Cir.App.7920-8040)

[t]he Board overlooked and misapprehended numerous facts, arguments, and evidence of record and misapplied the law… [Fed.Cir.App.7921]

The Board has abused its discretion. The Decision (1) is clearly unreasonable, and arbitrary; (2) is based on an erroneous conclusion of law; (3) rests on clearly erroneous fact-findings; and (4) involves a record that contains no evidence on which Board could rationally base its decision…
[Fed.Cir.App.7922]

Misapprehended FF 1: The Board overlooked that the Specification (¶ 34) teaches the feature "the lipid formulation disclosed herein may be administered to an individual in any orally accepted form," after the qualifier, "In some embodiments…" (emphasis added). The Board overlooked that the Specification (¶ 34) also teaches "The lipid formulations may be packaged in … contained in any one or more of… capsule, soft-gel capsule… hard capsule… single dosage packet or a resealable packaging… may be delivered using a gelatinous case, a vial, a pouch or a

foil," which is limiting over "any orally accepted form." The Board also overlooked that regarding "casing" Das and Rucker Declarations 4/30/15 state,

> "*In light of the specification of the subject patent application, "casing" or "one or more complementing casings providing controlled delivery of the formulation" in amended claims 65, 91, 129 and 130 means one or more casings that are designed to contain one or more dosages of the formulation in order to control the delivery (e.g., substantially avoid inadequate or excess delivery and/or substantially control the release). This is clear from, for example, paragraphs 10, 34, 37, 60, 61, and Tables 16-19 of the specification.*" (Das and Rucker Decl. 4/30/15 ¶ 5; Erickson Decl. 5/31/15 ¶ 5) (Also see response submitted on May 1, 2015, page 27).

Overlooked FF 1A: Board has overlooked that the term "dosage" is commonly used in the art as,

> "*controlled/specified amount to ingest at one time or regularly during a period of time*," evidenced by five commonly used dictionaries. (App. Br. 15; Rep. Br. 4; response submitted May 1, 2015, 28-29).

[Fed.Cir.App.7928-7929]

Applicant's Petition to Chief Administrative Patent Judge at PTAB, July 5, 2016
(Fed.Cir.App.8043-8063)

1. Procedural Violations by the Board

A. Rehearing Request was denied without specific answers to why particular facts and points of law were overlooked and without addressing the points misapprehended and why the law was misapplied, and why Appellant's arguments directed to undesignated new grounds of rejection were not to be heard. The Decision on Request for Rehearing did not point with particularity the part of the Decision where the points raised by Appellant had been considered by the Board.

B. The Board overlooked to consider the record as a whole in the Decision dated April 15, 2016. "Determination of patentability is made on the entire record." In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).
…

C. The denial of the Rehearing Request violated Applicant/Appellant's right to be heard on the points that were new points raised (undesignated new ground of rejection) by the Board in the Decision, which were never raised by the Examiner (37 CFR 41.52(a)(2)(4))…

[Fed.Cir.App.8045-8046].

3. Overlooked and Misapprehended Arguments, Errors in Board's Analysis, and Misapplication of Law Pertaining to 35 USC §101 Issues
…
G. The Board failed to apprehend that nature cannot provide claimed "dosage" commonly defined as, "controlled/specified amount to ingest at one time or regularly during a period of

time," at least because nature is unpredictable in lipid content and cannot provide "controlled/specified amount" or "controlled delivery of the formulation to a subject." (Dec. 4/15/16 FF6, Reh. Req. Overl. FF 1A, 6A, 28-29).

…

[Fed.Cir.App.8051]

6. Abuse of Discretion

A. Appellant has expressly and repeatedly disclaimed "multiple walnuts (or olives) or multiple cups of walnuts (or olives) of a type; or a fruit, a nut, or a vegetable by process."…

B. …IF BOARD CAN ARBITRARILY OVERLOOK SUPPORT FROM THE SPECIFICATION THEN ARGUE THAT SUPPORT IS NOT PRESENT THEN THE PROVISION IN 37 CFR 41.37(c)(1)(iii), "pro se Appellant is not required to submit 'Summary of claimed subject matter' with concise explanation of the subject matter defined in each of the rejected independent claims, with reference to the specification in the Record by page and line number" IS A DECEPTION AND A PENALTY TO PRO SE APPELLANTS. Clearly, there is no such intention in 37 CFR 41.37(c)(1)(iii), and the Board has abused the discretion…

[Fed.Cir.App.8060-8061].

APPENDIX F

STATUTORY PROVISIONS

Title 5 U.S.C. § 702:

> "A person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute, is entitled to judicial review thereof. An action in a court of the United States seeking relief other than money damages and stating a claim that an agency or an officer or employee thereof acted or failed to act in an official capacity or under color of legal authority shall not be dismissed nor relief therein be denied on the ground that it is against the United States..."

Title 5 U.S.C. § 706:

> To the extent necessary to decision and when presented, the reviewing court shall decide all relevant questions of law, interpret constitutional and statutory provisions, and determine the meaning or applicability of the terms of an agency action. The reviewing court shall—
>
> (1) compel agency action unlawfully withheld or unreasonably delayed; and
>
> (2) hold unlawful and set aside agency action, findings, and conclusions found to be—
>
> (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;

(B) contrary to constitutional right, power, privilege, or immunity;

(C) in excess of statutory jurisdiction, authority, or limitations, or short of statutory right;

(D) without observance of procedure required by law;

(E) unsupported by substantial evidence in a case subject to sections 556 and 557 of this title or otherwise reviewed on the record of an agency hearing provided by statute; or

(F) unwarranted by the facts to the extent that the facts are subject to trial de novo by the reviewing court.

In making the foregoing determinations, **the court shall review the whole record or those parts of it cited by a party, and due account shall be taken of the rule of prejudicial error**.

[Emphasis added].