

**UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research**

**Citizen's Petition Requesting Evaluation of Ingredients Proposed for Functional Uses
for Inclusion on the Bulk Ingredient Compounding List,**

**Proper Administrative Rulemaking and Revision of FDA Final Rulemaking "List of Bulk
Drug Substances That Can Be Used To Compound Drug Products in Accordance With
Section 503A of the Federal Food, Drug, and Cosmetic Act" issued on February 19, 2019,**

**Revision of the Final Regulatory Impact Analysis Final Regulatory Flexibility Analysis
and Unfunded Mandates Reform Act Analysis, and**

**Revision of the Interim Final Compliance Policy Guidance Regarding Compounded Drugs
Under the Drug Quality and Security Act and the Food and Drug Administration
Modernization and Accountability act of 1997**

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This petition is hereby filed pursuant to 21 C.F.R. § 10.3, 21 C.F.R. § 10.25(a) and 21 C.F.R. § 10.30. Petitioner requests that a docket be opened to allow for the creation of a factual record, public comments and that FDA issue a formal response pursuant to 21 C.F.R. § 10.30(b), (d) and that FDA grant a HEARING on the matters raised. Petitioners primary purpose is to seek reconsideration of FDA's Final Rulemaking "List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act" issued on February 19, 2019 (hereinafter "2019 Final Rule" or "Rule.")

Dockets Affected by this Petition

FDA-2016-N-3464-0029 - Closed

List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

FDA-2016-N-3464-0001 - Closed

List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

FDA-2013-N-1525-0001 - Closed

List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

FDA-2013-D-1444-0037 - Closed

Final Guidance; Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Availability

FDA-2015-N-0030-0001 - Open

Compounding of Human Drug Products Under the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket

FDA-2015-D-3517-0016 - Closed

Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry; Availability

FDA-2013-D-1444-0038 - Open

Final Guidance; Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Federal Regulations Affected by This Petition

21 CFR Part 216

A. Actions Requested

Petitioner respectfully makes the following requests:

Rescind its Position that Nominations of Ingredients for a Functional Use Are Insufficient: FDA rescind its requirement that nominated ingredients that have been historically used or which are nominated for their functional benefits, such as anti-inflammatory or antioxidant effects, must meet the burden of demonstrating effectiveness against specific disease entities. This matter has not been addressed by FDA in any publication and Petitioners ask FDA to reconsider any such proposed or recommended denials of ingredients for the bulk list and offer an additional opportunity where an intent to deny listing remains to nominators to submit a revised statement. Petitioners further ask FDA to refrain from further publication on listing of ingredients for the positive bulk ingredient list and extend the safe harbor for all nominated ingredients that whose nominated or historical uses have functional purposes until such reconsideration has occurred.

Give Proper Notice and Comment of Criteria for Ingredient Nominations and Approvals: FDA develop and issue proper notice and comment rulemaking pursuant to the Administrative Procedures Act (5 U.S.C. § 553 *et seq.*) (APA), as required by the Drug Quality and Security Act (DQSA) (P.L. 113-54) and the Food and Drug Administration Modernization and Accountability Act of 1997 (P.L. 105-115) (FDAMA) in consultation with the Pharmacy Compounding Advisory Committee (PCAC) that gives notice and an opportunity to comment on the actual criteria it has been explicitly using for ingredient nominations and approvals, as are set forth in this Petition, rather than merely listing topic areas and misrepresenting them as if they are the criteria being employed. Petitioners further ask FDA reconsider the criteria it has in fact been employing in making bulk ingredient determinations.

- FDA rescind or revise its Final Rule “List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act” issued on February 19, 2019 as originally noticed in its December 16, 2016 Notice of Proposed Rulemaking (hereinafter “Dec. 16 NPRM”) and its Draft Guidance: Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug and Cosmetic Act issued June 10, 2016 and other guidances in the above-listed dockets and implement the following policies until such time as substantive and procedural means of making scientifically reasonable decisions have been subjected to proper notice and comment rulemaking and nominators have an opportunity to submit comments based upon these actual criteria:

- Revise safe harbor provisions to include all nominated substances, not just those it deemed under its internal review to have sufficient information in the nominating petition(s), until such time as substantive and procedural means of making scientifically reasonable decisions regarding the data required for nomination and criteria for review have been subjected to proper notice and comment rulemaking.

- Place all substances that have been recommended for denial for reconsideration by FDA staff and before the PCAC once proper standards subject to comment have been completed, whether on Bulk Ingredient List 1, or 2 or 3.

- Rescind and correct its inaccurate statements to PCAC that Expanded Use INDs are a viable alternative means of access to ingredients denied placement on the bulk list; potential IND access should have no bearing on the PCAC evaluation process for the 503A Bulk Substance List and denied ingredients should be reconsidered without this false assurance before the Committee.

- As described more specifically in Section VII, FDA modify its criteria in the following manner:
 - An ingredient that is proposed for a functional use shall be evaluated for that use and not required to demonstrate efficacy for a disease indication.

 - An ingredient that has historically been in use to an extent significant in the context of the specialty or community of physicians conducting similar treatment for the indications for use should be approved unless there is reliable evidence that the ingredient presents unacceptable adulteration concerns or potential for adverse reactions significantly greater than approved treatment options.

 - Ingredients that present a significant risk of adulteration will not be listed unless there are reasonable controls that reduce these risks to acceptable levels.

 - The fact that an approved drug already exists for a proposed indication will only lead to the denial of inclusion on the bulk ingredient list if it is found that the available approved medication leads to a complete cure or remission of symptoms or otherwise fully serves the intended purpose unless there is clear evidence of substantial risk that is unreasonable in light of the risks of approved medications for the indication, FDA will not consider any NDA applications for that indication and a review of the proposed reasons why the compounded ingredient should be available shows no reasonable expectation of benefit according to the actual uses and evidence-base of state authorized prescribers with experience in their use as an alternative to or as an additional, adjunctive use with approved treatments.

 - The concern that allowing an ingredient to be compounded might delay treatment from approved medications for the indication should be entirely withdrawn given that these ingredients are provided by prescription by a physician or other authorized health professional based upon his or her sound and state-authorized judgment with regard to the needs of a patient with which FDA has long recognized as outside its jurisdiction.

 - If an ingredient has been determined by any branch of FDA to be GRAS there should be a presumption of safety for placement on the bulk ingredient list at least to the extent that is consistent with the GRAS finding.

These criteria, as more specifically detailed in Section VII, are consistent with Congressional intent and long-standing interpretations of law, will allow physicians a continuing choice of drugs they are trained to use and have historically provided without undue safety concerns, and

patients the benefit of broader treatment options while still having reasonable assurances of safety.

Regulatory Flexibility Act Analysis: - As FDA has now found that it cannot certify that the Rule would not have a significant impact on small businesses under the Final Regulatory Impact Analysis Final Regulatory Flexibility Analysis and Unfunded Mandates Reform Act Analysis (hereinafter "Final RFA Analysis") pursuant to the 5 U.S.C. § 601-612 (RFA), it is incumbent on FDA to explain why it has not used the least restrictive means of meeting reasonable regulatory goals. To meet that requirement, Petitioner's urge FDA to both engage in decision making that is not predicated upon presumptions against the use of ingredients, and where there are legitimate concerns, to determine if special controls or other means could be used to protect public safety without denying physicians or patients access or pharmacies the right to compound these ingredients.

B. Statement of Grounds

The FDA's response to the meningitis outbreak at the New England Compounding Center (NECC) and the resulting Congressional language in the DQSA was not only to reassert jurisdiction over drug compounding, but to take it as an opportunity to completely rewrite the regulatory structure of how physicians access and use compounded drugs as part of their practice. The Agency's overreach has led to a reset of the field that includes a wholesale reconsideration of permitted ingredients and the standards by which they are determined. While the purpose of the DQSA was to create a new type of facility, the 503B outsourcing facility, much of this change has landed upon the traditional compounding pharmacies regulated under Section 503A of the Food, Drug and Cosmetic Act (FDCA), enacted as the FDAMA, even though Congress did not change any language with regard to the regulation of the so-called "503A pharmacy."¹

The selection of ingredients used in compounding has evolved over decades of professional experience in a partnership between communities of physicians and compounding pharmacists and their accrediting and educational bodies and is entirely distinct from the safety concerns that arise when good compounding pharmacy practices are not followed. The therapies developed in this partnership have often been in response to patients that have failed at the treatments FDA believes, on paper, are the only options that should be available. Protocols involving many of the ingredients at issue are taught in US Department of Education recognized university-based programs and continuing medical education programs with CME credit

¹ The DQSA (Public Law 113-54) amended 21 U.S.C. § 301 *et seq.* by creating Section 503B (21 USC 353b), and only amended 503A (21 USC 353a) in the following manner: (a), in the introductory matter, deleted "unsolicited" preceding "receipt"; deleted subsec. (c), which had read: "(c) Advertising and promotion. A drug may be compounded under subsection (a) only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug, class of drug, or type of drug. The pharmacy, licensed pharmacist, or licensed physician may advertise and promote the compounding service provided by the licensed pharmacist or licensed physician." The latter was removed because it was an impingement on free speech as found in *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 122 S. Ct. 1497 (2002). Congress made no substantive changes affecting 503A pharmacies and the legislative history made it clear that it wanted to preserve that practice.

approved as American Commission of Continuing Education (ACCME) programs. The compounding pharmacies are self-governed by accreditation standards by The Pharmacy Compounding Accreditation Board (PCAB),² National Association of Boards of Pharmacy,³ the Organization of International Standards for 9001 Quality Management Systems⁴ and the Joint Commission⁵ which provide standards for ingredient selection and use. Bulk ingredient suppliers, such as Petitioner Medisca, provide libraries of ingredient standards to prescribers. The partnership of physicians, compounding pharmacies and their institutions has been successful.

FDA has discarded these decades of professional experience and imposed an ingredient nomination and decision process in its global review of ingredients that views the field through the narrow lens of single agent studies in often ill-defined categories of disease. Issues of contamination or conduct that steps outside of these professional standards occur in both compounding and pharmaceutical manufacture. This does not call for the elimination of available drugs in one chain of supply any more than the other yet FDA has made the tacit determination that even speculative risks associated with compounding justify restricting available ingredients. As a result, this review process has been slowly and inexorably leading to denials of numerous ingredients that have a long history of safe use.⁶ FDA is substituting its judgment for that of physicians and imposing a view favoring approved drugs based on a risk/benefit analysis that fails to consider the actual benefits or risks of the drugs to which it wants to limit physicians. The Agency claims it is following a “balanced” approach yet one side of the scale is entirely missing.

The Agency is acting without considering how these ingredients are used in practice, which may be for anti-inflammatory, antioxidant or other functional effects FDA acknowledges exist yet intends to deny access by considering disease treatment as the only valid use. This is contrary to law and good health policy. That ingredients rejected may be used as part of treatment protocols, rather than as single agents, including use that is adjunctive to, rather than a replacement for approved medications, is absent from FDA's consideration. This process is leading to decisions at odds with rational decision making and public health. In making radical changes, the Agency frames its regulatory action as insulating consumers from bad choices they might make for ingredients that are only available by prescription, contrary to the very definition of a prescription item as requiring a learned intermediary.

We emphasize that our initiative is solely intended to support the lawful practice of

² <https://www.achc.org/compounding-pharmacy.html> (Last accessed March 17, 2019).

³ <https://nabp.pharmacy> (Last accessed March 17, 2019).

⁴ <https://www.iso.org/home.html> (Last accessed March 17, 2019).

⁵ <https://www.achc.org/compounding-pharmacy.html> (Last accessed March 17, 2019).

⁶ FDA announced it would consider 64 nominations as part of its first review, so far 53 have been reviewed of which 17 were approved, 7 for topical use only and one for oral use only, and 36 denied by any route. The denied list includes well-known and commonly available ingredients such as MSM (methylsulfonylmethane), chondroitin sulfate, curcumin, aloe vera 200:1 freeze dried, D-ribose, and acetyl-L-carnitine, germanium sesquioxide, rubidium chloride, doxy-D-glucose, alanyl-L-glutamine, gluteraldehyde, glycyrrhizin, domperidone, quinacrine hydrochloride and boswellia.

pharmacy compounding, which includes compliance with all state laws and best practice guidances regarding the compounding of sterile and non-sterile products as outlined in the United State Pharmacopeia and elsewhere. The meningitis outbreak Congress sought to address occurred because of a failure to follow proper sterile practices in a facility that was improperly engaged in commercial manufacture, not as a result of lenient permissions to compound any specific ingredient. Other than its separate "Too Difficult to Compound" list, FDA decision making has not been based upon intrinsic risks in compounding any ingredient. The creation of 503B outsourcing facilities subject to Good Manufacturing Practices (GMP's) was a reasonable legislative response supported by Petitioners and we support FDA's response to legitimate concerns about unsafe compounding practices. But the bulk ingredients 503A pharmacies receive are themselves manufactured in GMP-compliant facilities and any valid concerns about 503A handling of bulk ingredients are sufficiently addressed through enforcing the applicable USP sanitary standards, pharmacy accreditation and state pharmacy board oversight.

The public discussion by FDA and some organizations, including those represented on the PCAC, have framed contamination concerns as requiring a presumption against allowing nominated ingredients to be placed on the bulk ingredient list. The argument inaccurately portrays the compounding system as more vulnerable to error and its ingredients less effective than those listed as approved drugs. In the face of public pressure to demonstrate that the drug system is safe, the Agency has looked to whether there are approved drugs it has designated effective for the same indications to assure itself that it is not doing harm by removing these ingredients from the market. Petitioner's organizations represent thousands of physicians who treat hundreds of thousands of patients annually and we write this petition at length to protect our patients' futures and explain why, in our collective experience, this is misguided. Communities of physicians using a range of conventional, integrative, functional and naturopathic approaches in direct care with complex patients see real benefit in patients who have often exhausted conventional routes of diagnosis and treatment. These approaches are practiced by an increasingly broad segment of physicians, in which neither FDA nor PCAC have demonstrated expertise. These are legitimate, recognized activities that provide assistance to many patients including therapeutic interventions based upon a functional understanding of health and disease as well as preventive and wellness services.

Fruits of the FDA Process: Two Striking Examples

FDA, for example, proposes denying approval for compounding a widely sold dietary supplement, Oxitriptan (5-HTP), 2019 Final Rule at 91077, in large part because it presumes a naturally occurring physiologic substance with a history of safe use must demonstrate that it does not have the same side effects as synthetic pharmaceuticals with a different mechanism of action merely because they each treat the same broad diagnostic category. FDA's policy is that physicians should be required to use the synthetic pharmaceutical option known to have these side effects for the ironic justification that the physiologic ingredient might have these same effects. This is illogical on its face, specious as a scientific justification and poor health care policy. Further, FDA ignores the history of safe use in its calculus, the involvement of trained physicians who know and follow the patients for whom they are prescribing, that 5-HTP can be obtained as a dietary supplement and used without the benefit of physician oversight and been used in populations orders of magnitude larger than any Phase 3 clinical trial without any reasonable concern of significant risks.

Based on FDA's actual criteria, the dietary supplement MSM (Methylsulphonylmethane) is pending rejection in large measure because of four cases of bleeding or elevated INR, while the Agency believes that the availability of a COX-2 inhibitor, a drug carrying a black box warning for risk of heart attack and stroke and which is credited for thousands of deaths every year, is not only acceptable but such a clear choice that physicians should be denied MSM as a treatment option in favor of the COX-2 inhibitor. Petitioners seek relief from such determinations as physicians should be able to make informed choices with their patients. The practice of medicine should be free of FDA's view that a drug that has gained its approval must be superior no matter the extent of damage and death that drug has wrought.

While the physician members of Petitioner's organizations might certainly see proper uses of SSRI and COX-2 inhibitors in some cases, their preferred methods based on their education, training, healing orientation, evidence-base and experience are to use functional and nutritional interventions such as 5-HTP and MSM. The FDA position that pharmaceutical drugs should be preferred to such an extent that it proposes curtailing physician access to these long-used natural products is a direct interference in Petitioners' members' practice and, of greater concern, will harm patients. Petitioners submit this Petition detailing our concerns and request that FDA reevaluate how it assesses the field of compounding and its decision-making process on specific ingredients.

FDA's Errors in the Ingredient Review Process

The decisions about MSM, 5-HTP and many other results reached by FDA undermine confidence in the Agency by the professions and the public that the review process is fair, rational or scientifically grounded. The process appears designed to remove ingredients in the name of safety that nonetheless have long histories of safe use in a process which creates a presumption against approval contrary to the extensive experience of the medical and naturopathic communities in partnership with compounding pharmacists.

The Agency is changing fundamental standards of practice, in part by only considering proof of effectiveness based upon incomplete literature reviews. FDA is requiring clinical efficacy and toxicology studies for disease indications at a level inappropriate to the nature of ingredients developed over decades of experience within this partnership. Patients often present with ambiguous conditions such as Chronic Fatigue Syndrome, which do not present with objective evidence of a specific and known condition and thus are not amenable to randomized trials of effectiveness. Cohorts of patients cannot be formed that clearly have the same condition. Relying solely on literature as a measure of effectiveness largely limits review to studies of ingredients as single agents yet the nominated ingredients are often part of clinical protocols that use multiple agents and, a critical use case FDA has entirely overlooked, may be used adjunctively with approved medications. They are used to support patients with chronic conditions that, by definition, are not resolved by pharmaceutical drugs.

FDA's findings that approved drugs should displace compounded medications if it can question the effectiveness of the compounded product for the proposed indication seeks to standardize disease treatment based entirely upon broad diagnostic nomenclature; FDA is not only practicing medicine contrary to long-held jurisdictional principles, it is imposing standards that, if followed by our organizations' members, we would consider substandard practice. No responsible physician treats medication as fungible based on even the most specific ICD-10 diagnostic conditions. Petitioners ask FDA to reconsider the clinical validity of this approach. The assumption underlying the FDA's view that patients may not be allowed access to

treatments until the medical profession has been able to identify consistent markers, form consensus about disease classification and test single ingredients for effectiveness rejects bodies of knowledge ignored by this process which leaves enormous numbers of patients undertreated.

The effect of the FDA's focus on reducing options to approved medications is to standardize medicine even further, though a considerable amount of medical practice is based upon consensus-driven experience. presented. The development of these protocols for compounded drugs is consistent with how much of medicine has been developed. Clinical experience is every bit as critical a guide to good practice as are published studies. In the case of nominated ingredients being routinely rejected, there is both clinical experience and an ample evidence-base to support use.

The meaning of evidence is by necessity filtered through the orientation of the professions and their specialties; Petitioners ask that the Agency recognize its obligation to reflect diverse practice viewpoints rather than limit practice to a single point of view. Petitioners urge the Agency to examine why the listing recommendations it is making are often contrary to those made by the professions with a much deeper knowledge base, history and actual experience in these methods. While Petitioners believe that the evidence submitted on ingredients that have been denied is more than sufficient, the nomination process has filtered out clinical information by asking overworked physicians to crystalize that experience as submissions of literature reviews. That process, combined with the rejection of functional uses and a lack of investigation by the Agency into how these ingredients are in fact used or of representation by diverse schools of thought have skewed the results against approval.

While FDA says it has published criteria that guide a rational decision-making process, general notice about "balancing" findings in four topical areas, physical characterization, safety, effectiveness and history of use is neither legally sufficient to constitute a guide to Agency decision-making, nor are they the criteria in actual use. The Agency has quite plainly been applying a number of specific criteria to its assessments of ingredients for consideration of the 503A bulk ingredient list consistently laid out in FDA's briefing documents. These criteria have not been subjected to notice and comment contrary to the APA and FDCA. Recognition of the "practice of medicine doctrine" has heretofore allowed reasonable individual choices without undue FDA interference. The criteria FDA is applying to ingredient approvals encroach on the right of physicians and other licensed prescribers to practice medicine using long available methods without evidence of unreasonable risk.

One criterion that has not been subjected to notice and comment that is particularly striking is the decision to deny an ingredient for fear that approved drug treatments will not be used. While this may make sense for OTC drugs, it has no application to drugs prescribed by a physician. FDA acknowledges in its Final RFA Analysis that the standards it is imposing are based upon consumer protection in which use of compounded drugs are framed as a matter of consumer choice. Yet they are prescription items, and by definition, neither regulated nor accessed as consumer choices. We ask the Agency to review whether its overt effort to deny compounded medications in favor of approved drugs has been influenced by the large portion of it budget obtained from Prescription Drug User Fee Act (PDUFA) fees.

FDA stilted PCAC decisions by making the highly impractical suggestion that physicians wishing to use rejected ingredients could simply apply for an Expanded Use IND as the route for such use, a nearly insurmountable burden that is only available to patients with life-threatening illness. In order to assure the Committee that a no vote would not deny access, FDA misrepresented Expanded Use INDs as a reasonable alternative to placing an ingredient on the approved bulk list.

FDA consistently overstated risks and undervalued benefit of compounded ingredients, going so far as to unfairly screen or misrepresent the evidence provided by nominators to the PCAC. FDA's actions do not adequately consider the health risks of reducing available therapeutic measures across the spectrum of conventional, integrative and naturopathic therapies. These approaches may include delivery of other routes of administration or prescribed custom formulations of nutrients. Many of these are naturally occurring physiologic compounds whose use is based on knowledge of metabolic or other pathways. As they are not subject to patent protections, there is no viable incentive for investment in targeted clinical trials yet there is nonetheless a substantial amount of data appropriate to the clinical decisions that have heretofore been made by physicians with their compounding pharmacist partners with comparatively little safety concern.

Petitioners appreciate that FDA now acknowledges it cannot certify that the Final Rule will not have an adverse economic impact on small businesses. As a result, the Agency is required to show that it gave proper consideration to means of accomplishing its proper objectives that would have less economic impact. The Agency not only understates this impact but did not make this required statement under the RFA beyond mentioning a single ingredient. In explaining its rationale, the Agency cites the need to ensure that consumers choices are limited to those that have been chosen by FDA because of an alleged information asymmetry with consumers, a goal inappropriate to professionally prescribed medications. Less economically adverse means to communicate concerns could be used to provide reasonable assurances of safety.

These Errors Make Reconsideration of Individual Ingredients an Insufficient Remedy

In its 2019 Final Rule, FDA repeatedly states that the process is an open one in which concerned parties can provide feedback, propose additional indications, offer supporting materials with regard to particular nominated ingredients, address the interpretation of submitted studies, the side effects of FDA-approved products to which the Agency would limit physicians in any particular case or other particular responses. FDA also notes "that its application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and also is the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it is not applying the criteria correctly in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List." 84 FR at 4699 (Response 13).

The difficulty, however, is that the presumption against the listing of nominated ingredients and the application of FDA's purported criteria to that end is pervasive. While Petitioners may submit re-nominations or petitions in support of some nominated ingredients, this is an insufficient remedy because the barriers imposed by the FDA's structural approach to these decisions, as detailed in this Petition, are fundamental and Petitioner's therefore seek reconsideration of its overall approach by the Agency.

Background of Petitioners

American Association of Naturopathic Physicians

The American Association of Naturopathic Physicians (AANP) is a national professional association (<https://www.naturopathic.org>) representing 4,500 licensed naturopathic physicians⁷ in the United States. Its members are physicians trained as experts in natural medicine. They are trained to find the underlying functional causes of a patient's condition rather than focusing on symptomatic treatment. Naturopathic doctors (NDs) perform physical examinations, take comprehensive health histories, treat illnesses and order lab tests, imaging procedures and other diagnostic tests. NDs work collaboratively with all branches of medicine, referring patients to other practitioners for diagnosis or treatment when appropriate. NDs attend four-year, residential graduate level programs at institutions recognized through the US Department of Education. There are currently seven such schools in North America.

Naturopathic medical schools provide equivalent foundational coursework as MD and DO schools. Such coursework includes cardiology, neurology, radiology, obstetrics, gynecology, immunology, dermatology, and pediatrics. Degrees are awarded after extensive classroom study and clinical training. In order to be licensed to practice, an ND must also pass an extensive postdoctoral exam and fulfill annual continuing education requirements. In addition, ND programs provide extensive education unique to the naturopathic approach, emphasizing disease prevention and whole person wellness. This includes the prescription of clinical doses of vitamins and herbs and safe administration via oral, topical, intramuscular (IM) and intravenous (IV) routes.

Currently, 20 states and territories license NDs to practice. In 9 of those states, NDs function as primary care physicians with prescribing rights. Where NDs are state licensed, they enjoy the same latitude to enjoy the practice of medicine without undue federal regulation as their medical doctor counterparts. Naturopathic physicians have an excellent safety record with licensing boards, a low incidence of malpractice, and provide treatments that are effective and safe. As they are extensively trained in pharmacology, NDs are able to integrate naturopathic treatments with prescription medications, often working with conventional medical doctors and osteopathic doctors as well as compounding pharmacists to ensure safe and comprehensive care. Compounded medications are an important part of treatment provided by NDs.

The Integrative Medicine Consortium

The Integrative Medicine Consortium (IMC) (<http://integrativemedicineconsortium.org>) began in 2006 when a group of Integrative Medicine leaders joined together to give a common voice, physician education and support on legal and policy issues. The IMC has been involved in the assessment of risk as applied to the integrative field generally, including participation in the

⁷ In many states, naturopathic doctors are licensed practitioners authorized to order and administer compounded medications, though, while recognized in 21 states, the District of Columbia and Puerto Rico, some state laws disallow their use of the term "physician." In this Petition the term "licensed health care practitioner" is used in some instances to cover all practitioners whose licensed scope of practice includes such ordering and use, but for simplicity the term "physician" is often used and intended to cover all practitioners with prescribing authority.

design of malpractice policies suited to the practice of integrative care along with quality assurance efforts for the field such as initiating the move toward developing a professional board certification process. IMC and its member organizations have collectively held over a hundred conferences, attended by tens of thousands of physicians, in which clinical methods that involve the proper use of compounded drugs are a not infrequent topic and taught with approved Category I CME credits. Petitioner IMC's effort is based on the collective experience of over 6,000 doctors; in addition to the AANP, the IMC represents the following organizations:

American Academy of Environmental Medicine

The American Academy of Environmental Medicine (AAEM) was founded in 1965 (<https://www.aaemonline.org>) and is an international association of physicians and other professionals interested in the clinical aspects of humans and their environment. The Academy is interested in expanding the knowledge of interactions between individuals and their environment, as these may be demonstrated to be reflected in their total health. The AAEM provides research and education in the recognition, treatment and prevention of illnesses induced by exposures to biological and chemical agents encountered in air, food and water.

American College for Advancement in Medicine

The American College for Advancement in Medicine (ACAM) (www.acam.org) is a not-for-profit organization dedicated to educating physicians and other health care professionals on the safe and effective application of integrative medicine. ACAM's healthcare model focuses on prevention of illness and striving for total wellness. ACAM is the voice of integrative medicine; its goals are to improve physician skills, knowledge and diagnostic procedures as they relate to integrative medicine; support integrative medicine research; and provide education on current standard of care as well as additional approaches to patient care. Celebrating 40 years of service, ACAM represents nearly 800 physicians in 30 countries. ACAM is dedicated exclusively to serving the needs of the integrative medicine industry.

International College of Integrative Medicine

The International College of Integrative Medicine (ICIM) (www.icimed.com) is a community of dedicated physicians who advance innovative therapies in integrative medicine by conducting educational conferences, supporting research, and cooperating with other scientific organizations, while always promoting the highest standards of practice.

Academy of Integrative Health & Medicine

The Academy of Integrative Health & Medicine (AIHM) (<https://www.aihm.org>) is dedicated to engaging a global community of health professionals and health seekers in innovative education, leadership, inter-professional collaboration, research and advocacy that embraces all global healing traditions, to promote the creation of health and the delivery of evidence-informed comprehensive, affordable, sustainable person-centered care. It offers educational programs, including a fellowship program recognized by the American Board of Integrative Medicine, recognized by the American Board of Physician Specialties.

Medisca

Medisca (www.medisca.com) is a leading FDA-registered supplier of quality pharmacy compounding products and offers excellent service to the North American, Australian and international markets. It provides the compounding industry with the highest quality active pharmaceutical ingredients (APIs), including controlled substances; excipients in the form of bases, oils, colors and flavors; and equipment and devices. Medisca also offers a library of studies for the safe and effective delivery of compounded medications.

McGuff Compounding Pharmacy Services, Inc.

McGuff Compounding Pharmacy Services, Inc. (<http://www.mcguffpharmacy.com>) (MCPS) is a veteran owned, family operated, small business licensed as a compounding pharmacy in 48 states and all US territories and protectorates. MCPS operates as a 503A compounding pharmacy and provides sterile and non-sterile compounded drugs to a variety of customers including but not limited to independent physician practices and patients, hospitals, contract research organizations, state and federal institutions. MCPS currently serves over 12,000 patients.

Dedicated to compounding drugs that meet quality standards, MCPS is independently certified or accredited by the National Association of Boards of Pharmacy, Pharmacy Compounding Accreditation Board and Organization of International Standards for 9001 Quality Management Systems. MCPS is inspected annually by multiple state and federal regulatory agencies to assure all compounded drugs meet applicable requirements.

Standing of Petitioners

While any interested person may file a citizen's petition with FDA, Petitioners' note that as professional associations whose member medical and naturopathic physicians, their patients and pharmaceutical partners all have a direct interest in prescribing, compounding, providing bulk ingredients or benefitting from compounded medications generally and specifically those affected by FDA's actions affecting inclusion on the bulk ingredient list specifically as defined in 21 USC § 353a(b)(1)(A)(III). Petitioners would have standing to assert their own claims and those of their members in a civil action in the event of a final agency action or enforcement contrary to the requests for relief raised in this petition or other triggering event. *See Tummino v. Torti*, 603 F. Supp. 2d 519, 522 (E.D.N.Y. 2009) (Organizations and individuals had standing to litigate the denial of an FDA citizen petition seeking greater access to contraception); *United States v. Comprehensive Drug Testing Inc.*, 513 F.3d 1085 (9th Cir. 2008) (Physician associations granted standing as identified with their members; an association has standing to sue on behalf of its members when they would otherwise have independent standing to sue, the interests sought to be protected are germane to the organization's purpose, and the claim asserted does not require the participation of individual members in the lawsuit); *Professionals and Patients for Customized Care v. Shalala*, 56 F.3d 592 (5th Cir. 1995) (Pharmacy organization granted standing for review of CPG 7132.6, compounding guidance alleged as in violation of APA).

See also NRDC Inc. v. United States FDA, 710 F.3d 71 (2^d Cir. 2013) (Environmental organization provisionally granted standing to seek court mandate for FDA to complete regulation regarding antimicrobial soaps); *Nat'l Mining Ass'n v. Jackson*, 768 F. Supp. 2d 34 (D.D.C. 2011) (Standing granted organization because additional burdens on members); *Farm-*

To-Consumer Legal Def. Fund v. Sebelius, 734 F. Supp. 2d 668 (N.D. Iowa 2010) (Standing provisionally granted group to oppose FDA raw milk labeling, noting that a plaintiff has standing if his or her conduct is clearly proscribed by the government regulation); *N.Y. State Ophthalmological Soc'y v. Bowen*, 272 U.S. App. D.C. 170, 854 F.2d 1379 (1988) (Association granted standing to contest payment rule even though no instances of denial); *Pharmaceutical Mfrs. Asso. v. Finch*, 307 F. Supp. 858 (D. Del. 1970) (Industry trade group granted standing for preliminary injunction on new standards for effectiveness of drugs).

C. Argument

I. The Requirement That Ingredients Used for Functional Purposes must Establish Efficacy for Disease Indications Is Directly Contrary to the Food, Drug, and Cosmetic Act and Bad Public Health Policy.

A. An Ingredient Solely Intended to Affect the Function of the Body Is a Drug; Nothing in the Food, Drug, and Cosmetic Act Allows FDA to Restrict the Bulk List of Compounded Ingredients to Those it Finds Have Demonstrated to Be Effective for Treatment of Disease.

FDA has required that a nominated ingredient be demonstrated effective for a disease indication and has precluded legitimate uses of ingredients FDA acknowledges have anti-inflammatory, antioxidant effects or other functional uses. Such a requirement is without basis, neither lawful nor clinically required as certain ingredients are used solely for their functional effects or nutraceutical value and may not be intended to treat, cure or even prevent specific disease states.⁸ Ingredients may be used for anti-inflammatory, antioxidant or alkalinity effects, to correct micronutrient deficiencies, enhance nutritional absorption and gut health or enhance the microbiome among many other purposes. They may be used to support the body's capacity to recover from disease, a valid purpose known from an understanding of metabolic pathways and clinical experience but which is not as amenable to demonstration by controlled trials as the paradigm of single agents acting on specific disease that is the Agency's primary method of review. Individual ingredients or combinations might be compounded for oral use to create synergistic formulas to enhance a patient's healing capacity that can support recovery from a wide range of diseases.⁹ FDA was completely silent on this point in response to comments in the

⁸ This is not a specific disease prevention claim under a disease rubric based upon long-term trials testing individual ingredients against specific diseases, but is based upon the view that enhancing the inherent healing capacity of the body is an appropriate supportive measure to take to prevent, mitigate or treat a wide range of illnesses and is often done to offer supportive care as an adjunctive treatment that might target underlying process, such as inflammation, even where there are treatments that have shown some effectiveness available. The scope of practice of physicians is not limited to treating specific diseases, chief complaints may include generalized complaints of fatigue or pain of unclear origins that are often presented by patients that have exhausted conventional means of care including pharmaceuticals.

⁹ Nutritional, integrative and functional medicine are fields in their own right. See for e.g. Gaby A. *Nutritional Medicine*, Fritz Perlberg Publishing (2011) (1326 pages); Werbach M., Moss J., *Textbook of Nutritional Medicine*, Third Line (1999) (740 pages); Katz D. *Nutrition in*

2019 Final Rule though it has been repeatedly raised by Petitioners.¹⁰

Imposing a disease model on compounding practice and requiring documentation of effectiveness against a disease when the ingredient has an appropriate role to play in improving function is expressly contrary to the FDCA, which defines a drug as including products whose sole claim is that it affects the function of the body. 21 U.S.C. § 321(g)(C). Such intended use is sufficient to be defined as a drug; nothing in that definition limits either the definition or the proper intended use of a drug to the disease claim listed separately at 21 U.S.C. § 321(g)(B).¹¹ If one markets an ingredient with the sole claim that it affects physiologic function without first obtaining NDA approval, FDA can and routinely does issue warning letters or take enforcement actions to remove such products from the market absent any disease claim.¹² The converse is also

Clinical Practice: A Comprehensive, Evidence-Based Manual for the Practitioner (2nd Ed.) LMW (2008) (592 pages) to give but a few examples. Nutritional medicine is an integral part of integrative and functional medicine, fields that also have numerous textbooks providing a understanding of this approach as well as its evidence-base. *See for e.g.*, Kligler B, Lee RA, *Integrative Medicine: Principles for Practice*, McGraw-Hill (2004) (700 pages); Rakel, D. *Integrative Medicine* (4th Ed.) (2017) (1152 pages). Naturopathic medicine also has a strong evidence base exhibited in text books for that field, including Pizzorno J. *et al. The Clinician's Handbook of Natural Medicine*, Churchill Livingstone (3rd Ed. 2015) (1008 pages). Petitioner raises these sources not as an effort to supplant FDA's proper consideration of research specific to the nominated ingredients, but to note that there are well-grounded, professionally recognized approaches to care that are based in a different paradigm than single agent performance against specific disease that was FDA's sole consideration, based on known metabolic or other functional effects that supports patients' innate ability to respond to the stresses of dysfunction and disease.

¹⁰ Petitioners have repeatedly made this argument in comments, *see* Comments of the American Association of Naturopathic Physicians (AANP) and the Integrative Medicine Consortium (IMC) filed March 16, 2017 at 7-8, 16, in responses to requests for information as nominators, *see for e.g.*, letter of January 26, 2018, in face-to-face meetings with Agency personnel on April 20, 2018 among others and in a September 12, 2018 presentation before the PCAC committee. No response in any form, including in the 2019 Final Rule, or change in any requirements, has occurred.

¹¹ "The term "drug" means . . . (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals..." 21 U.S.C. § 321(g). Nothing in the language of the DQSA or FDAMA limits this definition of a "drug" and provides any basis for restricting compounded drugs to Section (B) disease indications. The guidance documents define an active pharmaceutical ingredient (API), or bulk drug substance, as "any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, *or to affect the structure or any function of the body...*" (*emphasis added*). FDA is not following its own guidance.

¹² FDA has in fact criminally prosecuted an animal compounding pharmacy under this same statutory scheme for improperly compounding a drug whose intended purpose was to enhance the functioning of race horses, rather than to treat disease. *United States v. Kohll's Pharm. &*

true; where a product provides functional support it is properly a drug that should be considered on the merits of that claim without imposing a requirement that there be a disease indication. FDA cannot have it both ways in its interpretation of its enabling legislation.

Nothing in the language of the DQSA or FDAMA limits this definition of a “drug” and provides any basis for restricting compounded drugs to disease indications and ignoring functional uses. Where a pharmacist compounds on lawful scripts for the prescriber’s purpose of affecting physiologic function, no claim is made about disease treatment. FDA’s criteria impose a burden of proof for a claim not undertaken by the physician or pharmacist and improperly restricts an entire basis for clinically proper and lawful use. Assessing claims has always been based upon manufacturer’s intent, *see for e.g. Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 203 (ED NY 2015) which is not applicable to physician prescribing or compounding.¹³

Even if FDA were to have made findings that nominations for functional uses are insufficient, which it has not, this would not be lawful given the clear language of the FDCA. Even if FDA interpreted prescribing practice by licensed prescribers within the confines of the treatment room as only allowed to target a disease rather than give functional support, which it also has not, this would be an unprecedented invasion of medical practice. While FDA is focused on the disease model and, at first reading, its exclusion of functional uses of ingredients might have been an oversight, FDA’s briefing documents have expressly excluded consideration of functional uses. FDA has told nominators AANP and IMC that functional causes are not sufficient, specifically stating, for example, with regard to quercetin that “the uses ‘antioxidant’ . . . are insufficiently precise to guide FDA’s review,” saying for quercetin for example that the:

nomination also includes ‘anti-inflammatory effects.’ FDA considers anti-inflammatory effects to be a mechanism of action, rather than a treatment option for a disease condition. In this review, anti-inflammatory effects are considered to the extent it was found to be relevant as a mechanism of action for asthma, allergy, hypertension, and cancer prevention and treatment. FDA letter to Petitioner/nominators dated February 7, 2018.

FDA’s position is so extreme that on choline chloride, for example, which those Petitioners who were nominators proposed for “neuropathic disorder,” FDA requested we be more specific as to the “disease state(s) or health condition(s)” we are proposing and informed us that “neuropathic disorder” is insufficiently precise. This suggests not only that a disease state is required but that it must be presented with the highest level of ICD-10 specificity. Neuropathy can be sufficiently documented and billed as ICD-10 G90. A claim of treating “neuropathic disorders” would certainly qualify as an improper drug claim on an unapproved product and basing approval upon whether a physician chooses to use choline chloride for peripheral, autonomic, diabetic or other form of neuropathy, which may share common underpinnings, within the scope of their training

Homecare Inc. (WDLA) July 6, 2017, Filed 2017 U.S. Dist. LEXIS 105265, Op. at 3.

¹³ Compounding pharmacies are not even permitted to market their ingredients with therapeutic claims. Compounded medications are not labeled for use and are expressly exempt from the “new drug” provisions at 21 USC § 321(p) that a new drug must be “safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof,” *Med. Ctr. Pharm. v. Mukasey*, 536 F.3d 383 (5th Cir. 2008) (*rev’d on other grounds, Med. Ctr. Pharm. v. Holder*, 634 F.3d 830 (5th Cir. 2011); *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 at 364, 122 S. Ct. 1497 (2002) (unaffected by the DQSA.)

seeks to apply an improperly high threshold to matters that fall within the purview of state authorized medical and compounding practice. While Petitioners appreciate the effort to focus the review of the clinical evidence, to the extent that a disease indication were in fact the basis for use, as long as choline chloride were shown to have a valid role in any form of neuropathy that should be sufficient to allow a physician the ability to access it for their patients guided by his or her knowledge and experience. The request for specificity, which is not a requirement necessary to evaluate the claim and which goes beyond that needed to obtain a label claim for a pharmaceutical under an NDA, seems to have been erected to create an intentional obstacle to the approval of long-used ingredients. It is also inconsistent with the lack of FDA authority to limit the use of a compounded ingredient to certain indications. Petitioners have posed our objection to this position¹⁴ but FDA maintains this view, failing to address it in the 2019 Final Rule.

When the issue of barring an ingredient readily available as a dietary supplement comes up at the PCAC meetings, FDA staff simply cite the legislative distinction between drugs and dietary supplements as written by Congress with the statement that the statutory requirements are different and FDA must make drug determinations about what qualifies to be a drug. *See for e.g.*, Transcript November 20, 2017 p.m. at 163-164; 84 FR at 4702-03 (Response 16). While FDA's reasoning appears straightforward it misses key aspects of law and practice. While it's true that Dietary Supplement Health Education Act (DSHEA) sets out a different schema, the difference is that it carves out an allowance for OTC claims limited to structure and function.¹⁵ The DSHEA does not remove the right of prescribers to use drugs for functional purposes. The Agency response is that ingredients have to be evaluated by drug and not food standards, but in so doing has conflated drug standards with disease indications. As a result, FDA has deviated from its own statutory definitions, pressed ahead and refused to consider such uses without any administrative findings on the matter or recognition of the issue. Petitioners maintain that this is an action which is clearly arbitrary, capricious and an abuse of discretion and asks the Agency to reconsider.

B. The FDA Rejection of Functional Uses for Ingredients Is an Arbitrary and Capricious Rejection of an Approach to Health Care Absent Any Review or Determination of the Value of These Approaches.

The Agency's restriction to disease indications is not only inverted on the law, but poor public health policy. While Petitioners' and others' nominations are based on evidence and experience that these ingredients indeed have a role to play in preventing, mitigating or treating disease, the presumption that an item may be refused placement on the bulk list even if there may be proper and legitimate functional or nutritional uses as their sole basis is not clinically

¹⁴ Correspondence on Dec 16 NPRM Docket FDA-2015-N-3534 dated February 21, 2018; *also* FDA Quercetin Briefing document, August 9, 2018 at 2 n. 1.

¹⁵ Petitioners are concerned that FDA appears to be exercising its long-standing antipathy toward dietary supplements in this manner, and that it may be preparing an argument to present to Congress that ingredients that could not even be approved as compounded drugs under the DQSA should not be available to the public under DSHEA. This was even raised as a possibility several times, *see for e.g.* the November 20, 2017 PCAC meeting by Ned S. Braunstein, M.D., who suggested that FDA go to Congress for this purpose. The problems with such a tactic aside, the proper approvals of needed medications should not be skewed by any such agenda.

well-grounded. The Agency has asserted that it has followed APA requirements, 84 FR at 4708 (Response 38), but it has never addressed the issue of functional uses for ingredients.

A peculiarity in the process outlined by FDA is that a significant number of the ingredients that have been or are likely to be denied are available as a dietary supplement, which means patients can access similar products with less quality assurance and without physician or pharmacist supervision even though it is barred from the bulk ingredient list. If a product is available under the DSHEA and has a history of safe use there should be a strong presumption favoring approval that should only be overcome by evidence, not speculation, of safety risks.

This oddity has caused considerable discussion at PCAC meetings.¹⁶ Resveratrol, for example, was nominated by the National Community Pharmacists Association because of its strong antioxidant properties. The health effects of antioxidants are well-recognized and as an ingredient in a compounded formulation could have obvious value. FDA's position, however, is that physicians should not be able to offer such support to their patients unless the evidence reaches the additional, and different, threshold of evidence that it can treat disease. Such a requirement is not clinically required nor sensible. FDA recommended the denial of resveratrol, which it considered both for the treatment of pain and impaired glucose tolerance. In its briefing paper FDA noted that "Resveratrol appears to have anti-inflammatory, antioxidant, anticancer, and other effects in many in vitro, ex vivo and in vivo models." November 20, 2017 PCAC meeting Briefing Paper on Resveratrol at 29. Yet use of this tool is to be denied.

While FDA was concerned about bioavailability and bimodal dosing responses, *id* at 147, 155, this not only discounts the knowledge of physicians about dosing but was within the context of managing disease and not an assessment of the role it can play as an antioxidant as an agent for wellness, prevention of ill-health, functional support for a healthy immune system and for the body's capacity to recover from disease. Other examples of ingredients that that have been nominated for functional uses but recommended for denial at least in part because of the disease indication requirement include 5-HTP (oxitriptan), alanyl-L-glutamine, acetyl-L-carnitine, and N-acetyl-D-glucosamine (recommended for topical use only).¹⁷

Support for optimal function or therapeutic support are legitimate purposes undertaken especially by medical practitioners whose approaches are considered integrative, functional, nutritional or naturopathic medicine, approaches which are completely missing from FDA consideration.¹⁸ Clinical modeling and evidence of the role of antioxidants, for example, in

¹⁶ See, for e.g., June 17, 2015 at 132-134, 171-179, 183-188, October 27, 2015 at 54-80, 102-104.

¹⁷ Many of the products nominated and recommended for rejection are naturally occurring physiologic compounds produced by the body, such as 5-HTP, N-acetyl-D-glucosamine and acetyl-L-carnitine. Functional, nutritional and integrative medicine are based in part on an understanding of metabolic pathways whose ideal function can be supported with such substances. This material is rarely taught in medical school and thus not part of most physician's treatment considerations. Without suggesting that safety concerns are absent in such products, Petitioners ask FDA to consider whether such physiologic compounds present the same requirements for demonstrations of safety and efficacy given that these compounds are endogenous rather than synthetic and which are often used in doses near physiologic levels.

¹⁸ FDA wisely contracted with the Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) to assess how ingredients proposed for inclusion on the 503B ingredient list were actually used by physicians. The lack of effort to understand actual use of

optimal functioning are less susceptible to controlled study but the evidence for many of these ingredients for such use is nonetheless ample. Quercetin, recommended for denial at the September 12, 2018 PCAC meeting, is a well-studied anti-inflammatory and antioxidant and is thus a valuable support for healthy functioning of the immune system. The health effects of antioxidants are well-recognized, and as an ingredient in a compounded formulation could have obvious value. The perhaps unintended consequence of FDA's view is apparently that ingredients that provide the benefit of prevention generally should not be available to physicians for patient support but rather that patients must first develop disease, whereupon there is an FDA-approved drug awaiting them that is "effective" to manage their symptoms. Petitioner asks FDA to reconsider the merits of this position.¹⁹

A consequence of FDA's approach is pressure toward the medicalization of all health care, reducing supportive measures and interventions to only those that target specific diseases. There are many underlying functional issues that physicians should remain free to address, including not only inflammatory disease and its many downstream consequences but others such as a functional intestinal disorder known as leaky gut²⁰ or metabolic syndromes.

These uses are of particular concern for naturopathic physicians and physicians that practice integrative, functional or nutritional medicine, whose education, training and practice focus make use of ingredients in a fashion that has had little if any attention from FDA but a valid role to play, nonetheless. The omission of functional care considerations has been pervasive in the ingredient review process as many of the ingredients reviewed are physiologic ingredients compounded for functional purposes. Nutrients may be used by physicians practicing functional medicine²¹ pursuant to schools of medical or naturopathic thought, taught in properly

ingredients proposed for the 503A list appears to have undercut FDA's appreciation of the uses of many of the nominated ingredients.

¹⁹ FDA did not address the disease indication issue as part of its request of nominators in its original request, nor has not subjected the wisdom of this health policy to notice and comment. This is but one of many major health policy decisions that are completely absent from its Dec 16 NPRM, failing both in its legal duties and obligations to understand the arena it is regulating. See nominators comments on "Proposed Rule: List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act," Docket No. FDA-2016-N-3464 dated March 16, 2018.

²⁰ See for e.g., Mu Q, Kirby J *et al.* Leaky Gut As a Danger Signal for Autoimmune Diseases, *Front Immunol.* 2017; 8: 598.

²¹ A helpful definition of functional medicine is offered by the Institute for Functional Medicine: "Functional Medicine is a systems biology-based approach that focuses on identifying and addressing the root cause of disease. Each symptom or differential diagnosis may be one of many contributing to an individual's illness.... a diagnosis can be the result of more than one cause. For example, depression can be caused by many different factors, including inflammation. Likewise, a cause such as inflammation may lead to a number of different diagnoses, including depression. The precise manifestation of each cause depends on the individual's genes, environment, and lifestyle, and only treatments that address the right cause will have lasting benefit beyond symptom suppression."

<https://www.ifm.org/functional-medicine/what-is-functional-medicine/> (last accessed December 10, 2018).

recognized universities or credentialed educational programs that receive ACCME Category I CME certification. Certain interventions are already recognized by patients and payors alike as valuable, as evidenced by coverage by both public and private insurers. This field of practice has been unrecognized and entirely overlooked in FDA's regulatory scheme; it has taken no evidence, consulted no experts in the field of nutritional, functional or naturopathic medicine, its response to Petitioner's concern is unresponsive, 84 FR at 4702-03 (Response 26) and made no relevant findings.

II. The Proposed Criteria Noticed for Comment are Not in Fact the Criteria FDA is Using; the Actual Criteria are Bad Policy and Bad Science.

A. The Criteria Published for Evaluation of Nominated Ingredients Is Not an Accurate Statement of the Criteria Actually Used by FDA to Evaluate Nominated Ingredients for the Bulk List.

While FDA has previously published guidance about the generic criteria by which it will review nominated ingredients, over the past three years FDA has been overtly applying a number of highly restrictive criteria in its briefing documents, recommendations to the PCAC and in its first published decisions in the 2019 Final Rule. None of these are stated in the proposed criteria published in the federal register notice. As a result, FDA has not subjected its actual criteria to notice and comment as required.

In actual practice FDA is employing the following specific criteria in the recommendations it has made in its briefing documents throughout the ingredient approval process it began in 2014, in the Dec. 16 NPRM and now the 2019 Final Rule. Under the general rubric of a "balancing test," actual FDA practice has been to:

- presume that if an ingredient is nominated for a specific indication for which an approved drug exists the nominated ingredient will be denied for even minimal safety risks.
- impose a standard that an ingredient can be rejected in part from a concern that its use by a physician could unnecessarily delay treatment with an approved medication.
- allow unproven concerns for safety or lack of effectiveness to override a history of safe use of an ingredient.
- impose a substantial burden of evidence while failing to include all available evidence of effectiveness.
- impose a standard that an ingredient can be rejected in part upon the finding that a condition the ingredient is proposed to treat is "serious."

These are the criteria that in fact have been overtly and explicitly driving FDA's consideration of nominated ingredients. The published standards in the 2019 Final Rule and before that the NPRM, that an ingredient can be characterized, that safety and efficacy should be weighed and historical use considered are simply general topics and set forth none of the standards actually employed.²² Petitioners ask FDA to examine and determine the actual criteria

²² For an example of what legally appropriate criteria looks like, *see* 21 CFR § 312.305(b), reproduced *infra* at 58, fn. 96.

it is using for an assessment of ingredient listings given the defects noted in this Petition and our suggested criteria and properly publish its criteria for comment before proceeding further with any additional ingredient determinations or additional notices of proposed rulemaking.

B. The Four “Criteria” FDA Has Used Are Merely Topic Areas, Are Not Legally Sufficient to Serve as Criteria and Leave the Agency with Impermissibly Subjective Decision-making.

Rather than publish for comment the criteria the FDA has quite explicitly been using, the Agency has published four generic categories – physical characteristics, safety, efficacy, and historical use – and alleges it is making determinations based on some “balance” the Agency will find within these categories.²³ A criterion is a “standard on which a judgment or decision may be based.”²⁴ Nothing in the broad categories set forth in the 2019 Final Rule come close to providing a standard by which an ingredient may be judged. Rather, they provide broad opportunities for the Agency to exercise highly subjective judgment.

That the published topic areas do not sufficiently describe FDA’s decision-making can be clearly seen by reviewing Petitioners’ proposed criteria, which also could be described by referring to these same four topical areas but which would lead to very different results. The numerous standards used in ingredient review noted in this Petition are ambiguous, arbitrary and have not been subjected to notice and comment. FDA takes the position that it may exclude an ingredient from the list where it is able to articulate some “safety concerns associated with the use of the [proposed] substance in compounded drug products.” 81 Fed. Reg. 91075. As demonstrated in this Petition, this standard is ambiguous and not grounded in a reasonably specified consideration. As an additional legal matter, FDA fails to define what constitutes “significant safety concerns.” Given the Agency’s application of those standards to the examples addressed in this Petition, MSM and 5-HTP among many other ingredients, that vague standard has been applied in a prejudicial and irrational manner against ingredient approvals. This standard is inadequate as it leaves the Agency with unfettered discretion to determine whether there “are other safety concerns” associated with the substances. *See John D. Copanos and Sons, Inc. v. Food and Drug Admin.*, 854 F.2d 510, 522 (D.C. Cir. 1988) (FDA should issue regulations that are “precise and do not call for the exercise of discretion or subjective judgment”) (citations omitted). The gap between FDA’s stated and actual criteria have skewed the process from the outset, as the information requested for nominated ingredients did not alert physicians or pharmacists about the scope of the material or the nature of FDA’s consideration.

While the Agency has asserted that it has followed APA requirements, 84 FR at 4708 (Response 38), the reliance on unarticulated standards apparently adopted by FDA are inconsistent with the *Pearson* line of cases. *See for e.g. Pearson v. Shalala*, 130 F. Supp. 2d 105 (D.D.C. 2001). The *Pearson* cases curtailed FDA restrictions on health claims where less restrictive means were available. While the *Pearson* cases are not directly apposite as they involved a First Amendment matter of commercial speech in contrast to DQSA and FDAMA

²³ For example, Interim Policy on Compounding Using Bulk Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry, January 2017 at 8; Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act, Guidance. October 2015.

²⁴ <https://www.merriam-webster.com/dictionary/criterion> (Last accessed December 14, 2018.)

grants of Congressional authority to regulate compounded drugs presented here, the *Pearson* cases note that such a grant is constrained by the requirements of the APA which prohibits the Agency from creating standards that are ill-defined, arbitrary and capricious. The *Pearson* court found that FDA violated 5 U.S.C. § 706(2)(A) of the APA for “a government agency to declare—without explanation—that a proposed course of private action is not approved.” *Pearson v. Shalala*, 164 F.3d 650, 660 (D.C. 1999). This was further seen as a deprivation of a liberty interest under the Fifth Amendment, which also applies to professional and commercial activities. *Brown v. S.C. State Bd. of Educ.*, 301 S.C. 326, 329, 391 S.E.2d 866, 867 (1990) (citing *Greene v. McElroy*, 360 U.S. 474, 79 S. Ct. 1400, 3 L. Ed. 2d 1377 (1959)). See also *Byrne's Adm'rs. v. Stewart's Adm'rs.*, 3 S.C. Eq. (3 Des. Eq.) 466, 479 (1812); *Schwartz v. Board of Bar Examiners*, 353 U.S. 232, 77 S. Ct. 752, 1 L. Ed. 2d 796 (1957).

The *Pearson* cases considered the issue of whether FDA had properly promulgated a standard of “significant scientific agreement” as applied to the threshold for making health claims on dietary supplements. In the compounding arena, FDA has not promulgated a reviewable and proper standard by which ingredient nominations can be reviewed and which were the subject of proper feedback from the professional community.

A similar issue was raised during the Drug Efficacy Study Implementation (DESI) process, for which FDA had to draft, publish and implement regulations defining “substantial evidence” leading to a showing of effectiveness under the 1962 Amendments. From the Agency’s own description of its history, “FDA was challenged to devise a method by which those drugs ruled ineffective could be legally removed from the market . . . FDA’s initial legal efforts to remove bioflavonoid drugs and an UpJohn fixed combination drug called Panalba were enjoined by the courts. Faced with the prospect of conducting formal administrative hearings on every drug it proposed to have removed from the market, the agency changed its approach, led by FDA’s Director of the Bureau of Medicine (and later Commissioner) Dr. Herbert Ley. Ley supported the drafting, publication and implementation of regulations defining ‘substantial evidence’ leading to a showing of effectiveness under the 1962 Amendments.”²⁵ (Citations omitted). Once proper criteria were in place, “the courts upheld the Agency's new approach and according to Peter Barton Hutt, FDA’s Chief Counsel from 1971-1975, no hearings were deemed necessary.”²⁶ See for e.g. *Upjohn Co. V. Finch*, 422 F.2d 944 (6th Cir. 1970).

FDA claims in its telling of its history to have learned from the legal challenges to DESI that it must ensure that it has clear standards in place but it has not followed that lesson with compounded ingredients. The need for clear standards is heightened because FDA is proposing to remove ingredients that have long been on the market in which there are vested interests both economically and clinically, which may not be done in an arbitrary fashion.

C. FDA Is Obligated to Subject its Actual Criteria, and Not Simply Announce Topic Areas, for Notice and Comment.

The initiative that FDA has undertaken is a considerable rewrite of how physicians may avail their patients of the benefits of compounded drugs. Despite its brief effort in 1998-99, the Agency has never previously conducted a comprehensive review of what drugs may be compounded and rarely limited ingredients. Particularly given the reasonable expectations for

²⁵ http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm#_edn63 (last accessed November 3, 2017).

²⁶ *Id.*

continuing clinically viable conduct since the FDMA was passed 20 years ago, and the long history of use before that, such dramatic changes should only occur with the input of the professional community about the actual criteria by which it is making such decisions. While FDA has sought input from industry the actual criteria employed have never been presented in any form with a request for comment. The method and standards for review of long-used ingredients will shape the use of over 425 drugs that have heretofore been available. FDA's obligations for such a change in established practice require it to involve the public through rulemaking about its actual standards rather than merely generic calls to look at characteristics, safety, efficacy and a cursory nod toward history of use.

While Petitioners appreciate that FDA has issued Compliance Policy Guidance documents for comment and held listening sessions, feedback from these activities from the medical community as a whole has not been reflected in FDA policy. Comments have not been sought on the actual criteria employed in FDA briefing documents and the proposed rule is inadequate under APA. FDA appears to be avoiding publication of its actual criteria as they are not defensible from a legal, scientific or policy perspective. The Agency is obligated to define a standard that provides guidance to the public, professions, and a reviewing court; however, there are no standards contained with the published criteria upon which a reviewing court could tell if a given decision was consistent with the alleged criteria, which make them arbitrary and capricious on their face.

This is not only a legal concern; the absence of full participation by the scientific, professional and patient community in decisions about the standards for consideration that would have afforded FDA an understanding of the importance, nature and manner of use of compounded drugs across a broad spectrum of medical specialties, the management of respective risks and benefits would have led to consideration of proper criteria upon which ingredient nominations should be made.

D. The Actual Criteria Employed are Bad Public Health Policy.

Petitioners ask FDA to reconsider and revise the actual criteria in use as they are not grounded in sensible policy. Taking each of the actual criteria used in FDA PCAC briefing documents in turn:

- 1) *presuming that if an ingredient is nominated for a specific indication for which an approved drug exists the nominated ingredient will be denied for even minimal safety risks.*

FDA recommendations have been based upon the position that an approved treatment for the proposed indication creates a strong presumption against approving the ingredient. The requirement that an ingredient nominator has a burden to demonstrate that there is a "treatment void" before allowing use is poor science, poor policy, poorly defined and inconsistent with any other drug review process. It is a standard that has not been subjected to much needed notice and comment.

FDA claims that this is not in fact a criterion it is using because it is not one of the four listed "criteria." 84 FR at 4699 (Response 5). Yet FDA expressly relied on this criterion in the 2019 Final Rule for oxitriptan (5-HTP) and silver protein mild as well as many ingredients pending publication such as MSM. Saying that it is merely "relevant," *ibid.*, while disavowing that it is a clearly a stated criterion that has been part of the discussion of virtually every

nominated ingredient, failing to declare it and subject it to notice and comment is especially concerning to Petitioners given FDA's decision to favor approved drugs without accountability for that approach. Contrary to FDA's suggestion, Petitioners have never suggested that FDA "exclude consideration of the existence of FDA-approved or OTC monograph drug products where relevant." *Ibid*. The drug landscape should of course be considered. But FDA is overtly and repeatedly finding that where an approved drug exists for the nominated indication, and has been found by the Agency to be safe, it creates a strong presumption against the nomination.

There are a number of unfounded and unconsidered premises in FDA's reasoning. It assumes that the choice between an approved pharmaceutical and a compounded medication is an "either/or," an "A/B" choice. There is no basis for this presumption. Many patients come to the physician members of Petitioners' organizations because they have tried and failed pharmaceutical options. Further, these therapies may be used in combination,²⁷ including use that is adjunctive to the use of approved medications. The FDA has also presumed that these choices will be made by consumers, rather than by the trained professionals who prescribe and follow them, which is not the clinical nor legal reality. Yet all of the discussion and decision-making about ingredients have been based on the false, unexplored premise that these ingredients would supplant approved medications and lead consumers into uninformed options.²⁸

That there is an approved product for an indication by no means suggests that patients have available a complete resolution of their illness. The proposition that no other solutions are needed or that nominated ingredients do not have a demonstrable role to play is clearly not an assumption that can be drawn. Such a demonstration is not a requirement for an IND/NDA application, research for new drugs in virtually all areas continue despite available products, and there is no rationale for imposing this unusual threshold on compounded products.

Not surprisingly, contrary to the FDA's assertion, 84 FR at 4701 (Response 10), the PCAC findings have been inconsistent, in some cases the existence of an approved treatment for an indication has been a basis for denial, in other cases the Committee has voted to allow a drug to be available as an alternative treatment. FDA claims the criteria are being applied consistently, *ibid*, but this is not the case. PCAC voted, for example, for approval for topical tea tree oil to allow it to be available as an alternative treatment²⁹ while declining other nominations, such as domperidone³⁰ because an approved drug allegedly was already available. Petitioner takes no issue with the general idea that there should be flexibility in weighing one criteria more heavily for one bulk drug substance than another given the risks and benefits that may be presented by a particular substance. *Ibid*. But there is no discernable basis for these distinctions between cases where having other options available was made, revealing them to be

²⁷ An important use case for compounding is to be able to mix multiple ingredients together to achieve synergistic effects or at least provide multiple agents. Where serotonin conversion from 5-HTP is a legitimate, desired and properly followed clinical purpose, for example, the co-factors zinc, vitamin B6, vitamin B3 and vitamin C support this conversion. Pain creams may use ingredients in which cofactors and coenzymes are used to enhance absorption and impact.

²⁸ See discussion *infra* at 69-71.

²⁹ For example, transcript, PCAC Meeting, June 23, 2016 afternoon session at 138 (member explaining basis for recommendation to approve tea tree oil).

³⁰ October 27-28, 2015 PCAC meeting minutes at 9.

inconsistent, arbitrary and capricious.³¹

Regulating compounded drugs by whether there are already available drugs by indication is troubling as proper treatment cannot be simplistically determined by broad diagnostic categories. In the pending case of MSM, for example, an ingredient FDA has recommended with PCAC support be denied, a search of arthritis in DSM-10 yields not only osteoarthritis, and rheumatic conditions but a variety of related inflammatory and other disorders. Diagnosis is a matter of taxonomy with limited predictive power as to what medications will work, even within the same precise diagnosis let alone the broad categories FDA is applying. To use the existence of such approved therapies as a bar to the listing of an ingredient as an additional part of the armamentarium is irrational and demonstrates the arbitrary and capricious nature of this standard, which the Agency has avoided subjecting to notice and comment.

The assessment that an “effective” drug is available fulfills the need for a given condition is also a misuse of the term “effectiveness.” Chronic disease, by definition, cannot be cured but merely managed. That a medication may “effective” only means that it has demonstrated an ability to show some improvement. The case of MSM offers an important example of the difficulties with this view that the availability of approved medications for arthritis should suffice.³² Millions of arthritis sufferers do not have adequate relief, and the fact that certain medications have demonstrated their effectiveness to FDA’s satisfaction sufficient to go to market by no means demonstrates that adequate treatment is available. This is due to individual differences in disease and response to medication, contraindications for use, medication conflicts, adverse reactions or merely incomplete results. Many diseases are chronic and approved drugs only ameliorate symptoms with partial success that varies wildly between patients. A drug may offer partial relief and be “effective” yet leave patients still suffering. Some drugs may only be offered to ameliorate symptoms while other to effect a cure, yet not even this

³¹ Another concern is that FDA has interpreted the admittedly “ambiguous” clinical need language of Section 503B, 21 U.S.C. § 353b(a)(2)(A)(I) for outsourcing facilities as including a requirement that nominators explain why an available approved drug product is not suitable for a particular patient population, 79 FR 37750 at 37752 (July 2, 2014). 79 Fed. Reg. 37751. This is yet another version of the criterion that an approved drug fully displaces the need for a compounded ingredient and alters the meaning of “clinical need” in the Act which contains no such requirement. FDA’s request in many cases is unreasonable, especially given the breadth of FDA’s interpretation of an available drug for the “same” indication. In addition to numerous defects in the requirement that a treatment void exists, a correct reading of the FADMA and the DQSA’s legislative history is that ingredients should be allowed that have historically been used where there is a reasonable safety profile or history of safe use. Physicians should themselves be able to determine clinical need for compounded medications. Finally, while FDA is using this language to create both lists, 503B does not apply to 503A traditional compounders.

³² FDA Briefing Document for MSM states that “[t]here appears to be, at best, a suggestion of possible efficacy in reducing pain based on differences in pain-related outcomes, in support of the use of MSM in patients with joint pain associated with OA. . . . Pain is a serious condition for which there are a number of approved alternative therapies. These alternatives have been shown to effectively treat OA pain.” Review of Methylsulfonylmethane (MSM) for Inclusion on the 503A Bulk, September 25, 2015 letter at 13, appended to Drug Substances List, FDA Briefing Document, PCAC Meeting October 27 and 28, 2015. To conflate a showing in clinical trials that some drugs have shown effectiveness for pain with a showing that other solutions are not needed is an error Petitioners hope FDA will reconsider and engage in a course correction.

distinction has made its way into FDA's briefing discussions. To say that one or more effective drugs is available is by no means the same as saying that the disease is effectively treated. The latter proposition would startle the large population of arthritis sufferers. The use of this criterion deviates so markedly from acceptable public health considerations that it appears to be a tactical means of denying access rather than a valid determination.

The need for a broad spectrum of anti-inflammatory medications, as one example, is clear and there are numerous classes of such medications including steroids, traditional non-steroidal anti-inflammatory drugs (NSAIDs), drugs that block TNF alpha, and COX-2 inhibitors. The FDA analysis of whether there already exists an approved drug to treat an indication has been so devoid of depth that it hasn't even considered the range and relative risks of different anti-inflammatory drugs available for a condition such as arthritis or that such drugs are only one possible vector for treatment.³³

Addressing these concerns, the FDA said in its final rule:

Even if a compounded drug product has fewer side effects than an FDA approved or OTC monograph drug product, if it does not treat the condition at issue, it may be of no or limited benefit to the patient. Regarding the comment that approved alternatives should only be considered when there is evidence that the FDA-approved drug product or OTC monograph product fully addresses patients' needs, we disagree. While not one of the four criteria, as described in the 2016 proposed rule and reflected in reviews completed and presented to the PCAC, under certain circumstances, the existence of an approved drug product or OTC monograph product to treat the condition, even where the product may not fully address patients' needs, is relevant to FDA's evaluation of one or more of the four criteria. For example, in considering the effectiveness criterion, the existence of an approved drug product or OTC monograph product may weigh against placing a substance on the 503A Bulks List when the condition to be treated is very serious or life threatening because of the serious consequences that could result from use of an ineffective or less effective treatment alternative (2016 proposed rule, 81 FR 91071 at 91075.)

84 FR at 4699-4700 (Response 5).

There are numerous difficulties with FDA's position. FDA acknowledges that is it "unlikely that candidates for the 503A Bulks List will have been thoroughly investigated in in vitro or in animal toxicology studies, or that there will be well-controlled clinical trials to substantiate their safe use in humans." 84 FR at 4701 (Response 11). It is thus difficult to evaluate with certainty the value of these therapies, particularly given individual differences in patient conditions and responses to drugs. In practice, physicians follow the effect of treatment, so to deny access due to concern that patients are not being properly treated is less supportable and superimposes the results of a literature review over the knowledge of physicians with clinical experience following results in actual patients. It presumes that nominated ingredients are used as single agents when they are often employed as part of protocols in which there are

³³ There is little consideration given in the FDA analysis to Type 2 errors of omission; the loss of a clinical tool is never really considered as a serious omission. The concept that there must be a demonstration of a "treatment void" is used to end the need for any real analysis of the role an ingredient plays.

synergistic effects; reliance on single agent studies are certainly an important window on understanding, it is not true to actual medical or naturopathic practice and provides a stilted result. The basis for use of ingredients may be because of demonstrated metabolic effects that are important in supporting recovery from disease, which provide a sufficient basis for use according to medical principles of practice that have great value to patients irrespective of whether statistical results are available when reduced to single agents for identified diseases. Many of these ingredients are used adjunctively with approved medications to enhance overall treatment effects. The FDA analysis ignores all of these clinical realities.

Many pharmaceuticals with approved NDAs could not have survived the evident standard FDA adopts in its final conclusion about MSM, continuing this example of Petitioners' difficulties with FDA's approach:

The safety of MSM as described in the literature consists mostly of non-serious adverse events, with the most common side effects consisting of gastrointestinal upset, fatigue, insomnia, and headache. However, there have been adverse events of concern reported in the literature that include increased blood pressure, increased effectiveness of anticoagulants, and elevated liver function tests. A search of the FAERS database showed **four**³⁴ reports of either bleeding or increased INR. Limitations of the literature reports as well as the FAERS database severely limit the ability to determine causality of the adverse events, but reports of a possible interaction with anticoagulants such as warfarin both in the literature and in FAERS cases provide corroboration for the finding. Notably, there are a number of approved alternative treatments for osteoarthritis that have been demonstrated to be safe and effective. (Emphasis added).
FDA Briefing Document, Pharmacy Compounding Advisory Committee (PCAC) Meeting, October 27 and 28, 2015 at 15.

FDA is applying a threshold in which even a *de minimis* basis for concern about safety is sufficient to reject a nomination if there is an approved drug, which is not a standard applied to NDA approvals nor rational here. This bias against compounded medications presumes that compounded drugs that have been safely used, in many cases widely so for decades, have a higher burden than do new drugs which have no track record at all other than limited numbers in clinical trials, and whose post-marketing track record is ignored. This presumption is unfounded, as discussed *infra* at 30-34. For good reason, there is no such standard even for drugs seeking to be mass marketed under an NDA/IND application. No such requirement that a drug fulfill a treatment void is part of the requirements found at 21 CFR § 314.50 (Contents and form of an NDA.) A pharmaceutical does not even necessarily have to demonstrate that it has a risk-benefit advantage. To impose such a standard on approved pharmaceuticals would remove many approved drugs from the market and there is no rational basis for applying a stricter standard to compounded drugs. This is particularly obvious given that this is not even a standard required for OTC drug approval which, unlike compounded drugs, may not have a physician involved in treatment decisions. If nominated substances, such as MSM, can offer patients relief alongside other available treatments, then FDA's standards barring its use cannot amount to fair,

³⁴ Compare this with the conservative estimate of 3,200 deaths annually from NSAIDs, discussed *infra* at 27, fn.36. Four cases of bleeding over the previous history, *cf.* 3,200 deaths annually.

reasonable or compassionate health policy.

In denying 5-HTP in part because “there are multiple FDA- approved drug products available for the treatment of insomnia” (Dec 16 NPRM at 91077) FDA fails to consider that benzodiazepines, hypnotics, sedatives and OTC options like antihistamines all have well-known side effects that can include dependence, amnesia, dangerous hangover and other adverse effects and which may be contraindicated because of conditions such as asthma, urinary retention or concomitant use of opiates or other medications. The balancing of the approved therapies that are displacing the compounded ingredient does not even include the adverse effect profiles of the approved ingredients, an oversight that belies any claim of “balance” FDA claims it is applying to this process. There is in fact, no balance at all in the application of this actual criteria.

FDA states that it has “considered the side effects of alternative therapies as part of the safety criterion where information is available and relevant.” 84 FR at 4699 (Response 5). Petitioner finds this to be entirely inaccurate. In the examples we have given, there is no discussion whatsoever of the side effects of COX-2 inhibitors and antidepressants, which it finds are the safe alternatives, in the Agency’s briefing documents. None of the side effects presented by this substance are noted. Indeed, on no ingredient reviewed to date is there evidence in the record that the side effects of approved pharmaceuticals raised as precluding use were considered. This has been a pervasive omission in the Agency’s consideration.

In what appears to be an effort to create a misleading lack of data, the Agency notes an absence of “data comparing the safety profiles of compounded drug products with approved drug products...” 84 FR at 4699 (Response 5). This implies the need for head-to-head comparative data, a standard that only arises because of the false equivalence raised by FDA’s model. The need for head-to-head comparisons would be an unreasonable standard. Properly assessed, including the wide use of many the nominated ingredients as dietary supplements, safety has been well-established and the safety record of approved drugs is certainly well-known though ignored in FDA’s review.

Finally, physicians may have informed reasons to approach an indication differently, such as attempting to resolve a functional cause found in that patient or according to a different school of medicine rather than merely to achieve on-going symptom management as is often the scope of approved pharmaceuticals. This and other clinically significant differences are absent from FDA and PCAC’s narrow reasoning. Petitioners ask FDA to reconsider the merits of this approach.

- 2) *imposing a standard that an ingredient can be rejected in part from a concern that its prescription by a physician could unnecessarily delay treatment with an approved medication.*

A corollary of this first criterion, FDA has imposed a standard that an ingredient can be rejected in part from a concern that its use could unnecessarily delay treatment with an approved medication, again favoring approved medications as treatment choices without consideration of other professional points of view. It has left insufficient treatment results and adverse effects of approved medications out of the equation. FDA is imposing one professional lens upon which treatment can be assessed and ignoring how these ingredients are used in practice, such as adjunctively along with an approved treatment. Petitioner asks FDA to reconsider whether it has engaged in a broad understanding of use and a fair comparison of the clinical need, safety and effectiveness of nominated ingredients.

FDA uses this criterion for 5-HTP, Dec 16 NPRM at 91077 and in many of the FDA briefing paper recommendations. *See for e.g.*, FDA Briefing Document October 2015 at 108, 170 (curcumin); FDA Briefing Document October 2015 at 153, 191 (germanium); FDA Briefing Document June 2016 at 111 (dichloroacetate). This standard is improperly borrowed from the review of OTC medications where a patient may self-treat without guidance and contains a number of baseless assumptions when applied to prescription medication.

This standard assumes, devoid of basis or any finding on the matter, that physicians are unable to assess the respective benefits and risks of compounded drugs versus approved medications. It misstates the issue as one of consumer rather than medical choice. The FDA position is that the use of a medication that gained approval is so obviously the better option no matter the actual clinical circumstances that neither a treating physician nor an informed patient should be in a position to make a determination about appropriate care contrary to FDA based upon its literature review. The fact that a drug has been subjected to the resource intensive process available for patented medications may say more about the financial opportunity surrounding the drug than the effectiveness of the drug compared to those that have arisen over decades of experience with compounding options. Further, as noted above, reducing all patients with the same general indication as having the same needs in response to treatment is a gross misunderstanding of clinical realities. Patients diagnosed with a broad and generic diagnosis such as "depression," for which there is no known marker or etiology, and which refers to numerous conditions with different etiology and symptomatology, cannot be presumed to have better responses to approved medications than the compounded medication selected by their physician who knows that patient's specific medical issues, contraindications, and medication responses.

Illnesses like depression that are merely categorized by symptoms can be seen through different lenses by different schools of medical thought and is clearly not a consistent clinical entity. For some it's a brain disease, for others it is a functional deficit in the endocrine or immune systems, certain cellular dysfunctions such as mitochondrial or inflammatory disease, the result of undiagnosed medical ailments or situational stressors or dysfunctions in life management, among an extensive list. Certainly, patients with a myriad of dysfunctions present as depressed. The FDA presumption that depression is a single entity or at least all subject to the same treatment such that serotonin reuptake inhibitors (SSRIs) and similar medications should preempt additional tools to treat this highly diverse patient population is unsupportable, inexcusably bad science and poor policy.

Whether termed a criterion or not, FDA is presuming that extremely broad diagnostic categories are better predictors of success than the professional judgment of the physician actually treating the patient. For FDA to presume that it can substitute its judgment via the drug approval process for that of a physician is a major regulatory misadventure. It is certainly not what Congress intended and passing the DQSA or the FDAMA nor scientifically sensible.

The idea that listing an ingredient might delay the use of an approved drug completely overlooks that some ingredients are used adjunctively, not as a sole treatment. An ingredient with likely but unproven anticancer effects might be added to an IV along with conventional chemotherapeutic or other agents, immune enhancing drugs might be given to bolster treatments for a range of diseases or otherwise ameliorate side effects from treatment. This consideration is entirely absent from any of FDA's considerations which presume without basis that the ingredient would replace approved drugs. It will thus ban useful ingredients under this criterion without any comment that this action will prevent physicians from using ingredients adjunctively along with approved drugs. Petitioner asks FDA to reevaluate its approach.

- 3) *imposing highly restrictive thresholds for absence of side effects and allowing unproven concerns for safety or effectiveness to override a history of safe use of an ingredient.*

FDA has not properly considered that the statutory requirement to consider historical use as a factor, as well as reasonable policy considerations, creates a presumption of safety for those ingredients that have been in use unless there is evidence that the ingredient presents a risk. FDA has instead taken a contrary position and creates a barely rebuttable presumption against listing nominated ingredients, noting for example that “in many cases, there are minimal data available concerning the safety, including side effects, of compounded drugs. The absence of information does not mean that safety risks do not exist.” 84 FR at 4702 (Response 13). While that is of course accurate as a logical matter, most of the nominated ingredients have long histories of compounded use and also use as a dietary supplement which provide a significant track record. FDA argues against the inclusion of the record of use as dietary supplements by saying that “[t]he availability of a substance as a dietary supplement is not a criterion considered when evaluating a substance for inclusion on the 503A Bulks List. 84 FR at 4702 (Response 16).³⁵ This response documents that the Agency is ignoring the safety data presented by the voluminous use of most nominated ingredients and the lack of reported safety concerns from even self-initiated and unsupervised use. Whether it is a criterion is not the issue, particularly given the manner in which FDA is using its broad interpretation of “criteria” in every other case to allow in any consideration it wishes to consider, such as claiming that considering whether there are approved drugs available is not a criterion while a frequently dispositive consideration. The relevant “criteria” here would be safety.

The Agency also deflects consideration of this body of information by saying that “[d]ietary supplements are intended for oral ingestion only, are not intended to be used to treat diseases, and therefore, are subject to a different legal and regulatory scheme than drug products.” 84 FR at 4702 (Response 16). The difference in legal and regulatory scheme is irrelevant on the question of safety on ingredients that a track record from wide use.³⁶ Whether there are adverse reports to FDA or in the literature for use as a dietary supplement is such strong evidence about the safety of these ingredients for oral use that to assign little if any weight to consideration appears to Petitioners to be arbitrary and capricious.

The FDA does note historical use in compounding in its briefing materials, but are merely noted in a seeming effort to satisfy the statute rather than considered as support for acceptance on the bulks list. The Agency has assigned historical use as a criterion but Petitioners understand DQSA’s direct requirement to be a presumption that historical use should carry some weight given that Congress did not wish to disturb traditional compounding. Most, if not all, of the nominated ingredients FDA and the PCAC have recommended not be listed have extensive histories of use, which while noted in the briefing papers as a factual finding has not been given reasonable or appropriate weight in decisions.

Petitioners do not disagree with FDA that “historical use may weigh more heavily in some cases than others.” 84 FR at 4699. But the evidence is often not actually part of the

³⁵ The Agency goes on to say “[i]n contrast, approved drug products have been demonstrated to be safe under the conditions of use set forth in the approved labeling, and the benefits of the drug product for the approved conditions of use have been found to outweigh the risks.” *See* discussion of this issue at 38-41.

³⁶ See discussion of other routes of administration at 41-42.

consideration. For example, while rejecting 5-HTP FDA notes that “[t]he length of time oxitriptan has been used in compounding is uncertain, although it has been discussed in scientific journals dating back approximately 40 years.” FDA does not then note the lack of adverse reporting nor does it note that 5-HTP has also had the considerable exposure of use as a dietary supplement, yielding a track record of safety the Agency has not properly considered. Yet this listing fell to the Agency’s speculative side effects which are known to occur with approved medications even though their mechanism of action is quite different. Congress noted its intent to protect traditional compounding when it passed the DQSA³⁷. Petitioners ask the Agency to consider that the nominations are supported by physicians who are seeking to have access to needed ingredients for their patients, not drug companies seeking to mass market and advertise medications in which profit motives are far more likely to skew conduct.

FDA has created reasonable barriers for entry for mass market drugs with the NDA process, but applying those mechanisms, even with the reduced level of scrutiny in place, where physicians are seeking to treat their patients with small quantities of drugs requires different standards that recognize the difference in financial rewards and incentives. New drugs do not have the data set of historical use shown in the laboratory of actual use that is available for compounded drugs. FDA, contrary to that experience, has created presumptions that place a burden on nominators to show clinical data on effectiveness as well as valid safety studies even where historical use reveals no basis for concern and where there is not a basis for a high degree of caution.

FDA reviews have consistently given undue weight to any side effects, giving disqualifying weight even when side effects are comparatively mild difficulties or when they are merely speculative. In the 2019 Final Rule the potential for gastric stress for the dietary supplement 5-HTP is given as a primary reason for refusing access to compounding this commonly used dietary supplement. In denying 5-HTP for depression, FDA also notes that “[a]dditionally, medications used to treat depression have been linked to an increase in suicidal thinking and behavior. There are no data to suggest that oxitriptan would be free of similar risks . . .” Dec 16 NPRM at 91077; 2019 Final Rule at 4702 (Response 16). The lack of significant reports of adverse effects resulting from widespread use carried no weight with FDA, which instead employed a false equivalence with SSRI products and, without legal basis or any reasonable justification, attempts to shift the burden of proof onto nominators to overcome FDA speculation about clinical safety:

Additionally, medications used to treat depression have been linked to an increase in suicidal thinking and behavior. There are no data to suggest that oxitriptan would be free of similar risks, and compounded drugs do not include labeling that

³⁷ See, for e.g., Congressional Record 9/28/2013 H5960, Mr. Upton. Noting basis, and stating:

“Mr. Speaker, this bill upholds the current section 503(a) of the law, and provides it with the clarity that FDA needs by eliminating the unconstitutional provisions. The bill also requires FDA to engage in meaningful communication with State boards of pharmacy. Further, under this bill, entities engaged in sterile drug compounding can voluntarily register with FDA and operate under FDA regulation. *Finally and importantly, this bill protects traditional pharmacy compounding that occurs in community pharmacies across the country.*” (Emphasis added).

would adequately warn physicians and patients of such risks.^{38]}

In the 2019 Final Rule, the Agency states that “[r]egarding the argument that the mechanism of action of oxitriptan is demonstrably different from that of approved therapies, as previously stated in FDA’s review, the psychoactive action of oxitriptan is related to increased production of serotonin in central nervous system tissue.” 84 FR at 4702 (Response 16).

There is no evidence or clinical reasoning that supports risk of suicidal ideation. The mechanisms of action are demonstrably different. 5-HTP is a naturally occurring precursor to the neurotransmitter serotonin while the antidepressant drugs at issue are reuptake inhibitors. A precursor is a naturally occurring biochemical mechanism that exists within the body and subject to physiologic feedback, while SSRIs operate on a synthetic targeted binding mechanism not known to occur naturally. Yet FDA has taken the simplistic approach that because the mechanisms involve serotonin, and the same general class of illness, depression, the adverse reactions presented by each could be similar even though the mechanisms of action are substantially different.

FDA also expresses the legitimate concern that “oxitriptan, particularly with concomitant use of antidepressant drug products, could result in serotonin syndrome, a life-threatening drug interaction, and cases that are likely to be serotonin syndrome have been reported with the use of oxitriptan as a dietary supplement (Ref. 10). In fact, one source cited by a commenter warns against taking oxitriptan with certain approved antidepressants because both increase the brain chemical serotonin and taking both ‘might increase serotonin too much and cause serious side effects including heart problems, shivering, and anxiety’ (Ref. 7).” *Ibid.* This ignores that the ingredient would be used under medical supervision and that concomitant use of antidepressant drugs specifically, and polypharmacy generally, are well within the purview and expertise of physicians and the consistent application of this view would confound approval for a great many drugs.³⁹ That the Agency questions the effectiveness of 5-HTP while at the same time is concerned about serotonin when used in excess or in combination with SSRIs seems contradictory to Petitioners.

This is another instance in which the Agency is clearly operating under a presumption against the approval of compounded ingredients. Arguing that absence of safety data satisfactory to the Agency is a basis to reject oxitriptan, FDA argues this is reasonable because of the alleged safety of approved drugs. *Ibid.* Yet despite its general assurance that it did consider the safety profiles and risks and benefits of the approved drugs it contrasted with nominated ingredients, a proper analysis would have included in the balance being sought a consideration of the fact that SSRI medications have a number of significant side effects⁴⁰ including the very same suicidal ideation and behavior FDA affixes without basis to 5-HTP and an effectiveness profile only

³⁸ Letter dated May 18, 2015, Review of Oxitriptan for Inclusion on the 503A Bulk Drug Substances List at 10, appended to FDA Briefing Document to PCAC for Meetings dated June 17 and 18, 2015.

³⁹ This interaction is well-known and information about it is readily available. WebMD, for example, notes it as a major interaction, <https://www.webmd.com/vitamins/ai/ingredientmono-794/5-htp> (Last accessed March 18, 2019).

⁴⁰ See for e.g., <https://www.drugs.com/sfx/prozac-side-effects.html> (last accessed December 15, 2018).

slightly better than placebo.⁴¹ Yet this is approved for the mass prescription market. FDA, based on speculation unsupported by evidence and without consideration of differing mechanisms of action, are instructing physicians that SSRIs must be the preferred proper means of treatment and are attempting to shunt physicians into prescribing the medication that indeed is known to have this very safety concern.⁴² There is no justifiable basis for this position.

Of course, how safety is measured is one of the difficulties with the manner in which FDA is exercising judgment. A case in point is curcumin, which FDA recommended and the PCAC agreed should not be placed on the bulk list on October 27, 2015 for reasons that included lack of safety. This decision may have appeared to have been justified when a patient died in March 2017 after receiving an infusion containing curcumin. Imprimis Pharmaceuticals, the firm that dispensed the curcumin IV, noted in an August 7, 2017 press release that it appears the death was due to an allergic or hypersensitivity reaction. FDA confirmed this, also determining there may have been issues with the emulsion prepared by ImprimisRX.⁴³ The pharmacy states it has dispensed the same curcumin emulsion over 30,000 times without other incident. Hypersensitivity reactions are a wide-spread risk that plague most drugs.⁴⁴ The safety record of curcumin is greater than many approved drugs and the use of one death to justify a safety concern would be inconsistent with FDA's policies in any other arena of regulation and an effort at justification, not reasonable policy.

In the example of the pending rejection of MSM, the level of proof required implies a higher standard than reasonable for physician prescribed and monitored substances, particularly where widely available as dietary substances. The Briefing Document itself notes that MSM is widespread and the “[u]se of MSM has been reported in North and South America, Australia, and European and Asian countries” and lists over 100 proprietary names used world-wide for MSM. Yet the Agency found it unsafe principally because of four reported cases of bleeding or increased INRs. Decrying the “limited safety data” and lack of “long-term assessment or dose-response studies,” FDA concludes that the “safety of short-term MSM administered orally is

⁴¹ See for e.g., Jakoben JC et al. Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. *BMC Psychiatry*, 17(1):58 (Feb 8, 2017) (“The effect estimate, however, was below our predefined threshold for clinical significance...”).

⁴² As well as insomnia, drowsiness, nausea, dry mouth, diarrhea, nervousness, agitation or restlessness, dizziness, sexual problems, such as reduced sexual desire or difficulty reaching orgasm or inability to maintain an erection (erectile dysfunction), headache and blurred vision. Source: <https://www.mayoclinic.org/diseases-conditions/depression/in-depth/ssris/art-20044825> (last accessed March 8, 2019).

⁴³ <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm570192.htm> (last accessed December 15, 2018).

⁴⁴ Adverse drug reactions account for 3 to 6% of all hospital admissions and occur in 10 to 15% of hospitalized patients, result in morbidity, prolonged hospitalization and risk of mortality. Y-H Thong B and Tan T, Epidemiology and risk factors for drug allergy, *Br J Clin Pharmacol*. 2011 May; 71(5): 684–700; Adverse drug reactions affect 10-20% of hospitalized patients and more than 7% of the general population. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Allergy Clin Immunol*. 2005 Aug;5(4):309-16.

poorly characterized based on available literature,⁴⁵ but then concedes that the “safety of MSM as described in the literature consists *mostly of non-serious adverse events*, with the most common side effects consisting of gastrointestinal upset, fatigue, insomnia, and headache.” (Emphasis added).⁴⁶ The Agency concluded that:

Based on the minimal evidence of efficacy, the possibility of a potentially serious interaction with anticoagulants and risk of bleeding, and the availability of approved alternatives, MSM should not be included on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

FDA Briefing Document, Pharmacy Compounding Advisory Committee (PCAC) Meeting, October 27 and 28, 2015 at 15.

Yet the very history FDA documented that adverse events are generally not serious should be given priority under the FADMA/DQSA but is ignored because FDA is erecting unreasonable thresholds of adverse events Petitioners believe that few, if any, approved drugs would meet.

One rationale for this excessive caution about side effects is the untested presumption that physicians will be unaware of the risks,⁴⁷ and that the risks are greater because compounded drugs are not labeled by FDA. FDA notes with regard to MSM that there is “a possible risk for an interaction with warfarin leading to an increased risk of bleeding” of which physicians would be unaware. In the 2019 Final Rule, FDA suggests that the absence of FDA labeling on compounded medications prevents FDA from communicating concerns to physicians who otherwise would not obtain needed information about the use of an ingredient; this is so concerning to the Agency that it finds in this a basis to simply not allow the ingredient to be used. While the Agency is right to recognize the importance of the drug approval and labeling process, physicians making the effort to include compounded medications are independently educated about their use. FDA has discounted the role of the physician while making no finding that physicians would erroneously use compounded medications if labeling was not in place, or that physicians lack the skill and training to understand the use of these compounds even in serious conditions. Moreover, this position ignores the fact that the compounding pharmacist is trained, certified and accountable for verifying each prescription, performing drug interaction checking and preparing the prescription per established standards before dispensing to the

⁴⁵ A discussion that seems to belie FDA’s comment that “it recognizes that it is unlikely that candidates for the 503A Bulks List will have been thoroughly investigated in in vitro or in animal toxicology studies, or that there will be well-controlled clinical trials to substantiate their safe use in humans.” 84 FR at 4701 (Response 11).

⁴⁶ FDA Letter dated September 25, 2015. Review of Methysulfonylmethane (MSM) for Inclusion on the 503A Bulk Drug Substances List, *ibid* at 15.

⁴⁷ To the contrary, as another example of the expertise of compounding pharmacists that has not been taken into consideration, where patients are sensitive to sulfa, molybdenum might be added to MSM as a cofactor for sulfite oxidase needed to convert sulfa containing ingredients. This allows the compounding pharmacist to reduce the likelihood of adverse reactions, in partnership with physicians, by knowing and customizing medications in a manner that are part of physician considerations in prescribing but which have not been considered by FDA.

patient who is offered a clinical consult to assure compliance with prescribed use.

There is no reasonable clinical or legal basis upon which the absence of labeling, which Congress did not see fit to require of compounded drugs and is inconsistent with the nature of this practice, can be used as basis to deny listing to an ingredient. Were the professions most familiar with prescribing MSM truly represented on the PCAC, Agency staff or consultants, it would have been noted that awareness of drug interactions is precisely the role of the health care professional and that this particular interaction is well-known. These risks are well-understood to be present in most of the anti-arthritic medications on the market and which are routinely managed by prescribing physicians.⁴⁸ The Agency's basis for rejecting MSM as a compounded ingredient, while allowing other medications with the same or worse effects, does not have a rational basis.

There does not appear to be a rational basis for FDA's recommendation on MSM or on 5-HTP, offered as examples of pervasive problems with FDA's process. Indeed, by FDA's own discussion, both of these drugs appear to have a better safety profile than their approved alternatives. If MSM can't be marketed for the rare side-effects reported, Petitioners ask the Agency, if it does not reconsider this actual criteria, to offer an explanation about why COX-2 inhibitors are allowed to remain on the market.⁴⁹

⁴⁸ Comparing this concern for bleeding due to MSM with prophylactic use of aspirin in heart disease—a different indication but one that highlights how differently FDA judges risk-benefit ratios even for OTC medications in which there is likely no physician involvement—is the concern for bleeding, which is treated very differently even with limited benefit. The NNT for the daily use of an 81 mg aspirin tablet for patients without a previous MI shows a very poor return since as it is estimated that only 1 in 1667 had a cardiovascular problem prevented, 1 in 2000 had a non-fatal heart attack prevented, and 1 in 3000 had a non-fatal stroke prevented. No deaths were prevented. Against these weak numbers, patients on a similar order of magnitude had a major bleeding event (1 in 3333). Yet daily 81 mg dosing has been found to be acceptable. It is unclear by what standards a daily aspirin taken over the counter is a wise choice whereas MSM administered by a physician is not. While the American Heart Association and American College of Cardiology have recently revised its recommendation, <https://www.heart.org/en/news/2019/03/18/avoid-daily-aspirin-unless-your-doctor-prescribes-it-new-guidelines-advise> (Last accessed March 19, 2018), this nonetheless demonstrates the application of very different standards to the risk of compounded medications without good cause.

⁴⁹ FDA concluded in 2005 that the health benefits of celecoxib outweigh the potential risk in certain informed patient populations. Yet FDA does not believe that the most informed population, physicians, can handle decision-making about MSM even though it has far less risk. Compare the four reported cases to a conservative estimate of the number of all NSAID-related deaths of about 3,200 annually. Sources: Public Health Advisory. FDA announces important changes and additional warnings for COX-2 selective and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). April 7, 2005; Ask the Expert: Do NSAIDs Cause More Deaths Than Opioids? Practical Pain Management 13:10 Nov/Dec 2013. <https://www.practicalpainmanagement.com/treatments/pharmacological/opioids/ask-expert-do-nsaids-cause-more-deaths-opioids> (last accessed December 15, 2018).

- 4) *imposing a substantial burden of evidence while failing to include or misrepresenting available evidence of effectiveness.*

Of the numerous difficulties with the scientific review FDA has conducted of nominated ingredients, its subjective effort to “balance” its review is shown in instances where the quantitative aspects of side effects have been clearly stilted. For example, the mere potential of carcinogenic risk presented without any quantification are accepted as fatal to a nomination, but when nominators show benefits, FDA then faults lack of details or significance of quantification⁵⁰. FDA has made a number of inaccurate and inappropriate statements minimizing benefits, such as a statement by an FDA staff member to the PCAC Committee on acetyl-L-carnitine that a 40% reduction in pain may not be significant,⁵¹ minimizing a significant result in a characterization that is quite alarming from a public health official. Such a reduction would clearly be considered highly significant by a pain patient or were it for an NDA application. Such a reduction would be significant in a study even of opioids. Such statements demonstrate, if not substantial and direct bias, a lack of proper professional consideration of the merits of compounded drugs.

Another window into the FDA view of its ingredient review is that a drug recommended by FDA and PCAC for denial, quinacrine, had previously been an approved drug, fell off the list because it has been off the market, and received a denial recommendation even though FDA had previously accepted a monograph on the drug. Even though FDA had once formally approved it, the compounding approval process is so skewed against approval that it was denied.

In conducting its reviews, FDA has cited studies that attempt to place a nominated ingredient in a head-to-head competition with a marketed product. In the case of tea tree oil for topical use, for e.g., FDA cited a study finding that tea tree oil was inferior to benzoyl peroxide for acne.⁵² That such a comparison has a valid role in a recommendation for denial misperceives both the role that compounded drugs play within the physicians' toolkit and FDA's role under the DQSA and FDAMA. There is no clinical basis or statutory obligation upon a nominated ingredient to show that is superior to currently available drugs for there to be a valid basis for its use. Nor is it good science to presume that single studies like this fairly account for all uses, all cases, or even certain findings on the matter at issue. There may be valid reasons a physician would prefer a compounded ingredient such as patient sensitivity to the approved medication, the other healing properties of tea tree oil, its longer time remaining in place, its use in combination products, its greater effectiveness for a specific condition among many others. FDA has recommended against allowing the compounding of an ingredient as innocuous and well-accepted as Aloe Vera because of available wound products,⁵³ which is not sensible on its face.

In Petitioners' example of MSM, FDA sets forth an unreasonable standard for clinical evidence:

From the clinical perspective, there is limited evidence from controlled clinical

⁵⁰ See for e.g., Transcript, PCAC Meeting, March 8, 2016 afternoon session at 107, 126-129 discussion about acetyl-L-carnitine.

⁵¹ Transcript, FDA PCAC Meeting, March 8, 2015, afternoon session at 124.

⁵² Transcript, PCAC Meeting, June 23, 2016, afternoon session at 132.

⁵³ Transcript, FDA PCAC Meeting, March 8, 2016 at 20.

trials, based on pain-related outcomes, that orally administered MSM may be minimally effective for the reduction of joint pain associated with osteoarthritis. The optimal dose of MSM is unknown, and there have been no dose-finding studies reported in the literature.

Id.

While the limitations of published controlled studies of natural products may seemingly create a basis for denial, it places an undue burden and improperly high threshold upon products, which unlike new drugs, have histories of safe use. FDA appears to be requiring the existence of clinical studies for products that have survived the “laboratory” of clinical use and close physician supervision that under a reasonable schema would have less need to rely upon literature to demonstrate safety and effectiveness. It also ignores that physicians’ decisions about dosing such benign ingredients is based on what is often extensive clinical experience shared at medical conferences in seminars that receive approved Category 1 CME credit. Doses can be titrated to determine therapeutic levels. Physicians do not need to rely entirely upon such studies or the FDA’s determinations about dosing to be able to safely use such medications.

FDA says that it “finds no reason to reduce the amount of evidence FDA has considered necessary to support a recommendation to include a bulk drug substance on the 503A Bulks List and believe that doing so would not be in the interest of public health.” 84 FR at 4701 (Response 11). This misses the concern, as the issue is not the amount of evidence but the nature of and interpretation of that evidence.

One aspect of the difficulty Petitioners have with FDA’s position is that in conducting its reviews, FDA has been filtering the studies provided by nominators, in some cases selecting studies that show more limited support for effectiveness. A.J. Day, PharmD, RPh, Director of Pharmacy Consulting at the Professional Compounding Centers of America (PCCA), which nominated a number of ingredients, told the PCAC Committee that FDA appears to be cherry-picking studies submitted to only show negative data. Similarly, the adverse event reporting doesn’t appear to be assessed from the “balanced” perspective FDA claims, as admittedly trivial effects are being cited as reasons to reject nominations.

When evidence is reviewed, FDA frequently misrepresents the evidence. Taking just one example of many, in this case from the FDA review of Quercetin, FDA represented a study provided by nominators in support of its use in treating hypertension as showing a lack of evidence for management of blood pressure, citing Egert S at al. *Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype*. J Nutr. 2010 Feb;140(2):278-84. FDA dismissed the author’s conclusions of a positive effect, stating that “[o]nly one [genetic] subgroup, apoE3, had a significant change in systolic blood pressure. Other subgroups showed no difference. This data does not support the use of quercetin for the treatment of hypertension.” Review of Quercetin Dihydrate for Inclusion on the 503A Bulk Drug Substances List, August 9, 2018 at 30.

Baseline Data	(insufficient data)	Effect Arm	Null Arm
Genotype	ApoE2	ApoE3	ApoE4
N	3	60	26
SBP, mm Hg	NA	129.7±13.2	133.70±17.8

Intervention			
Post quercetin Δ	NA	<3.4 \pm 9.8	Author states no sig
Egert S et al. Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype. J Nutr. 2010 Feb;140(2):278-84.			

The study tested 3 genotypes. There was insufficient data for one, and of the remaining two, the data showed it significantly lowered systolic blood pressure (SBP) in the cohort that composed 70% of randomly selected study subjects.⁵⁴ Minimizing the result by stating that only one of multiple genotypes were affected is misleading. Further, both groups included normotensive individuals as hypertension was not an inclusion criterion, resulting in a large variable baseline blood pressure.⁵⁵ This is significant because the effect of quercetin on lowering SBP is dependent upon whether it is elevated. The quercetin claim is that it reduces BP in hypertensive patients, not all patients.⁵⁶

This critical aspect of the mechanism of quercetin goes to the heart of FDA’s misperception of natural ingredients as their targeted effect is to assist restoration of normal physiology rather impose mechanistic effects such as BP medications that cause blood vessel dilation irrespective of blood pressure. This is a an instructive example of the advantages of functional, physiologic interventions nutritional interventions that can often be offered by nutritional ingredients. Petitioner requests that FDA more accurately reflect and consider the data regarding the evidence on behalf of ingredients in its briefing documents.

- 5) *imposing a standard that an ingredient can be rejected in part upon the finding that a condition the ingredient is proposed to treat is “serious.”*

FDA also cites the seriousness of a proposed indication as a basis to reject listing an ingredient, particularly where there is an approved drug claimed to treat similar conditions. Certainly, the general proposition that “when a bulk drug substance is proposed to treat a more serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy,” 84 FR at 4700, is not controversial. But FDA has been consistently recommending denial of therapies on this basis.

⁵⁴ This sample is representative of the number of apoE genotypes found in most studies. See for e.g., Lahoz, C et al. Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study, *Atherosclerosis*. 154:3, 15 February 2001 (529-537) (64%). It is thus not an insignificant finding.

⁵⁵ The effect arm (ApoE3) varied from 113.70/73 to 145.70/90.6. The null arm (ApoE4) varied from 115.9/73.9 to 151.5/93.5.

⁵⁶ See for e.g. Randi L. et al. Quercetin Reduces Blood Pressure in Hypertensive Subjects. *The Journal of Nutrition*, Volume 137, Issue 11, 1 November 2007, Pages 2405–2411. “Previous studies have shown no reduction in BP of normotensive individuals. See for e.g., Conquer JA, et al. Supplementation with quercetin markedly increases plasma quercetin concentration without effect on selected risk factors for heart disease in healthy subjects. *J Nutr*. 1998;128:593–7. See also Egert S at al. Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype. *J Nutr*. 2010 Feb;140(2):278-84.

There's no rational basis for such a standard. FDA uses this standard in the 2019 Final Rule in its rejection of 5-HTP, in part, because depression is a "serious condition." The fact that an indication may be serious provides no basis for prohibiting knowledgeable physicians from using an ingredient as part of an overall treatment plan. There is no basis to relegate compounded medications to use in only minor conditions. Yet this major presumption underlies the rejection many of the Agency's other decisions, including the 2019 Final Rule finding with regard to piracetam:

In particular, the Agency's proposal regarding this substance is based on the limited evidence of benefit associated with piracetam, the seriousness of the conditions for which piracetam was nominated to be used, and the availability of safe and effective FDA-approved medications for many of these uses. NPRM at 91077.

Petitioners agree that where a proper balancing of factors is being performed, a drug for which it has been shown to lack benefit nominated for a life-threatening condition deserves close scrutiny. But FDA is skewing its considerations to such an extent that it is rejecting ingredients for uses for conditions like depression just because the condition may be serious. The Agency's distrust of physicians is quite remarkable and not based on an administrative record that can support it. Petitioners are aware of no previous agency action grounded in a view that physicians cannot be trusted to make proper decisions. There is no basis for such a finding or intervention into long-standing practice in which all reasonable options should be available for use.

E. The Criteria in Actual Use Are Based upon the Unsustainable Presumptions That Approved Drugs Are Intrinsically Safer than Compounded Drugs, That the Risks and Benefits of Compounded Medications Can Be Presumed to Be Inferior to Approved Drugs Without Actual Comparison and that Quality Control Issues Cannot Be Better Managed by Assurance Methods Rather than Limiting Available Ingredients.

The presumption favoring approved drugs that pervades FDA's consideration of nominated ingredients are intrinsically safer than compounded drugs does not stand up to scrutiny. The presumption that the drug approval process results in drugs so much safer or more effective than compounded Drugs that the bulk list should be limited to instances where approved drugs are absent for consideration is not supportable. The presumption that quality control issues are best addressed by limiting available ingredients rather than quality assurance methods is not reasonable nor accurate. While FDA offers as a rationale for restricting available ingredients that there are approved drugs in place, Petitioners member physicians extensive experience is that this is not the case and we urge FDA to reconsider the basic premises of its approach to compounding.

The Agency strenuously makes the case about the need to reign in prescribing of compounding drugs by frequent references to the NECC tragedy and findings of unsanitary conditions at some compounding pharmacies. FDA has apparently determined that part of the solution is to reduce the opportunity to make such errors by limiting available options. Yet the Agency has directly addressed this issue by diligently working to oversee regulatory guidelines that enhance safety. State and federal oversight of compliance with USP 797, USP 800 and other applicable requirements are the direct and appropriate response to this concern, including the

Agency's the draft guidance "Insanitary Conditions at Compounding Facilities: Guidance of Industry" (August 2016).

Justifying a reduction in available ingredients, FDA cites 130 warning letters and 100 recalls of compounded drugs⁵⁷ involving a fraction of the nearly 8,000 compounding pharmacies in the US.⁵⁸ In contrast, FDA lists 185 warning letters to registered drug establishments just since 2015 including only those for cGMP violations⁵⁹ and nearly 800 drug recalls of approved drugs in just 2018 alone.⁶⁰ There is no nexus between the inappropriately high clinical standards FDA is applying to its review of compounded medications and the actual landscape when considering all drug sources. If FDA's logic was sound, it would reduce the number of approved medications because of violations of cGMPs and drug recalls, but of course that is not the case.⁶¹

Underpinning FDA's reasoning is the apparent view that products that have passed monograph review or clinical trials have demonstrated that they are safe, and therefore, are presumably safer than compounded medications. But this cannot be reasonably presumed, particularly in light of any fair comparison with the safety record of approved drugs, a critical step FDA fails to include in its "balanced" view of ingredients. The FDA Adverse Event Reporting System (FAERS) shows that in 2017 alone there were 164,252 deaths and 906,941 serious incidents that were life-threatening or resulted in hospitalization or disability, congenital anomaly and/or other serious outcome⁶² some due either to medication errors but many to the intrinsic risks of the medication. There were an estimated 78,414 emergency department visits

⁵⁷ FDA's Human Drug Compounding Progress Report: Three Years After Enactment of the Drug Quality Security Act (January 2017) at 10.

⁵⁸ American Pharmacy Association FAQs about Pharmaceutical Compounding, <https://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding> (last accessed December 18, 2018).

⁵⁹ <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm594437.htm> (last accessed December 10, 2018).

⁶⁰ <https://www.fda.gov/Drugs/DrugSafety/DrugRecalls/default.htm> (last accessed December 10, 2018).

⁶¹ Petitioners are not suggesting that the size of these two markets are equivalent, the number of approved drug prescriptions is certainly 100s of times the number of compounded medications. But the record of approved drugs shows substantial difficulties orders of magnitude larger than for compounded medications, of which warning letters are just one indication as noted by the large number of adverse reactions noted in this Petition. Sources: <https://www.statista.com/statistics/238702/us-total-medical-prescriptions-issued/> (last accessed December 10, 2018); Utilization and Costs of Compounded Medications for Commercially Insured Patients, 2012-2013, McPherson T. <https://www.jmcp.org/doi/pdf/10.18553/jmcp.2016.22.2.172> (last accessed December 10, 2018).

⁶² FDA FAERS Report, <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070461.htm> (last accessed December 1, 2018).

annually for non-abuse-related overdoses just of acetaminophen-containing products.⁶³ The GAO has estimated that the FAERS system captures only 1% to 10% of all adverse reactions.⁶⁴ In 2010, there were 4.9 million visits to emergency rooms for drug-related emergencies, of which approximately 2.3 million visits were not due to abuse but from patients taking medications as prescribed.⁶⁵

The under-reporting to FAERS is not only a lack of comprehensive reporting, but reported deaths generally cite the underlying disease even if a drug reaction was responsible for death. The drug approval process itself is not highly predictive of outcomes, as nearly one in three drugs approved in the past decade have had major safety issues after market approval.⁶⁶ Particularly given the track record of approved drugs, there is little basis upon which to ground the notion that review and approval implies such a higher safety than the long-used compounded ingredients Congress recognized as having important historical uses that they should be given an untested presumption of superior safety.

In its responses to comments in the 2019 Final Rule, the Agency constructs an artificial void in the data by saying that it is unable to find “comparative” information about the rates or adverse effects between approved and compounding drugs. 84 FR at 4702 (Response 17). Yet there is ample data on the adverse event profiles of proposed approved drug alternatives which was not considered.

Many approved pharmaceuticals have black box warnings or a record of significant adverse events yet remain on the market. The safety record of pharmaceutical products is arguably of greater concern than can be demonstrated for compounded drugs. In the case of MSM, for example, the difficult safety profile of the approved COX-2 inhibitor, celecoxib (marketed as “Celebrex®”) has a black box warning⁶⁷ based on potential damage that far exceeds the four bleeding or INR events referenced as possibly linked to MSM even when taking data limitations into account. To the extent that such comparisons are useful, a proper

⁶³ Budnitz DS1, Lovegrove MC, Crosby AE. *Am J Prev Med.* 2011 Jun;40(6):585-92. Emergency department visits for overdoses of acetaminophen-containing products.

⁶⁴ FDA Adverse Events Database: Time to Worry? Fivefold increase in little more than a decade by John Fauber, Reporter, *Milwaukee Journal Sentinel/MedPage Today*; Kristina Fiore, March 17, 2017 <https://www.medpagetoday.com/publichealthpolicy/fdageneral/63903> (last accessed December 1, 2018).

⁶⁵ Highlights of the 2010 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits, Substance Abuse and Mental Health Services Administration, <https://www.samhsa.gov/data/sites/default/files/DAWN096/DAWN096/SR096EDHighlights2010.pdf> (last accessed December 15, 2017)

⁶⁶ Nearly 1 In 3 Recent FDA Drug Approvals Followed by Major Safety Actions; The withdrawal of these drugs poses concerns about a push for less regulation, Lupkin S, *Kaiser Health News* on May 9, 2017 <https://www.scientificamerican.com/article/nearly-1-in-3-recent-fda-drug-approvals-followed-by-major-safety-actions/> (last accessed December 12, 2018).

⁶⁷ **Celebrex® Black-Box Warning:** Cardiovascular Risk: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (See WARNINGS).

consideration would include a head-to-head risks and benefits. But FDA has not put the adverse effects of approved drugs on the scale; while claiming to conduct a “balanced” assessment, FDA gives the adverse effects of approved drugs a complete pass and their consideration is entirely absent.

The benefit of a presumption of superior effectiveness on the part of approved drugs is also highly questionable. Many approved drugs demonstrate post-market borderline effectiveness at best. Creating a head-to-head competition by condition is not only baseless as a standard, but certainly cannot be grounded in a presumption mere approval for the mass-marketed drug. Returning to NNT statistics, practice experience shows that approval does not mean a treatment void has been filled. Many of the largest-selling pharmaceuticals on the market show benefits that are modest at best and arguably outweighed by their risks. Studies of statin drugs, for example, show that even in patients with no heart disease, 83 patients prescribed have to be on statins to prevent one heart attack and 125 must be on statins to prevent one stroke; the evidence of effectiveness is not overwhelming. Yet 1 in 50 patients developed diabetes and 1 in 10 suffered muscle damage.⁶⁸ Based on this considerable evidence, patients on statin drugs are at least arguably more likely to be harmed than helped.

The drug approval process itself does not have a predictive track record clearly superior to the decades of safe use found in the compounding industry either globally or on the specific ingredients that have been reviewed. It certainly belies the idea that the literature review being conducted can correctly identify the appropriate cost-benefit analysis relevant to the compounded medications being reviewed or justify the presumption that approved drugs are safer. By telling doctors they should prescribe a drug with a black box warning over a commonly and safely used dietary supplement, FDA has made quite plain that the decision-making process it brings to this arena is not resulting in a fair evaluation. Petitioners urge FDA to reconsider its approach.

F. The Availability of Differing Routes of Administration Is a Vital Part of Compounding Practice.

In its 2019 Final Rule, FDA suggests that its removal of ingredients will have little impact because these ingredients will remain available as dietary supplements. 84 FR at 4702 (Response 16); 84 FR at 4704 (Response 20). Yet a critical loss in patient care include uses via routes that include intravenous, injections into joints or other sites, transdermal, intrarectal, intravaginal, sublingual, nebulized or transmucosal including nasal applications. Carefully controlled intravenous therapy allows for nutrient absorption not affected by gastrointestinal disorders and mobilization of nutrients into cells by means of high concentration gradient and higher doses of nutrients possible by mouth without intestinal irritation. Sublingual routes of administration may also be of help with ingredients which present absorption issues in certain patients. While such uses must be done with knowledge and care and Petitioners respect FDA's expertise in such matters, such use does not present a problem requiring a solution.

The translation from oral applications to other routes of administration is routinely determined by compounding pharmacists who have the training and expertise in the pharmacokinetics of oral versus other routes and are able to calculate appropriate dosing and

⁶⁸ <http://www.thennt.com/nnt/statins-for-heart-disease-prevention-with-known-heart-disease/> (last accessed December 17, 2018).

vehicles for delivery.⁶⁹ Compounding pharmacists have information about half-life to determine dosing frequency. They have extensive resources available to draw upon in making such determinations from standards determined by the Joint Commission and The Pharmacy Compounding Accreditation Board,⁷⁰ ingredient resources such as PubChem,⁷¹ Toxnet,⁷² USP dietary ingredient and NF monographs and USP 797 standards among many others. Compounding pharmacists have hardcopy texts on hand as required by state pharmacy boards, including works that provide information needed to calculate solubility, stability, bioavailability and other aspects of an ingredient's kinetics as required by each pharmacy board to safely translate into other routes of administration. Ingredient wholesalers, such as Petitioner Medisca, have product methods and formulas they provide pharmacies based upon their research and experience. Compounding pharmacists consider specifics such as whether the processing leaves residual solvents or other toxic residues, whether or not the material crosses the blood/brain barrier. They review prescriptions with an understanding of the patient's history such as whether or not a female patient is of child-bearing age and the patient's other drug histories including any allergies. The pharmacist, upon careful review, assists the physician in choosing only those ingredients whose proven specifications render the ingredient appropriate for intended use.

Many of the nominated ingredients, such as MSM, are single molecules of high purity and are soluble, stable and can be compounded as sterile solutions. There is sufficient published research that allows compounding pharmacists to make such determinations as they have been doing successfully for decades. Petitioners recognize that some ingredients, such as extracts from botanical products, require special care and may not be suitable for some routes. This learning has been based in part on shared experience as is true in all of medical practice. These uses have historically been developed, experience gained and shared at medical conferences. Adopting ingredients to other routes of administration falls within the expertise of compounding pharmacists and there has been no failure in that system that was addressed by Congress or that FDA has cited in this rulemaking process. Proceeding without any fact-finding or evidence in the record that this vital role for compounding products creates undue risk will leave many patients underserved. There is a rich body of knowledge gained within the medical community that is of vital interest to Petitioners; FDA's action deeply undercuts this important experience and approach to care and we hope FDA will acknowledge this by changing its regulatory course.

G. Ingredients That Have Been Found by the Agency to Be GRAS Should Be Presumed for Placement on the Bulk Ingredient List Barring Significant Evidence of Harm.

In contrast, some ingredients recommended for denial, such as MSM, have been recognized by the Agency as Generally Recognized as Safe (GRAS). Other GRAS dietary supplements nominated as ingredients that face removal from the market include glutathione,

⁶⁹ See for e.g.,

<https://www.pharmacist.com/frequently-asked-questions-about-pharmaceutical-compounding> (Last accessed March 18, 2019).

⁷⁰ <https://www.achc.org/compounding-pharmacy.html> (Last accessed March 12, 2019).

⁷¹ <https://pubchem.ncbi.nlm.nih.gov/compound> (Last accessed March 11, 2019).

⁷² <https://toxnet.nlm.nih.gov> (Last Accessed March 12, 2019).

methione, glycerrhizin, choline chloride and alanyl-L-glutamine. This designation is recognized but not accepted in FDA's review because, even though it was the Agency's own determination, FDA reviewers were unable to confirm the basis upon which the Center for Food Safety and Applied Nutrition (CFSAN) made the determination.⁷³ This demonstrates the extent of the presumption against compounded ingredients by the Agency and its rejection of evidence of safety; even its own work cannot stand up to scrutiny. FDA's recommendation has no rational basis.

In the case of MSM, CDER minimized its sister branch's determination by noting that this was only for food use, and that the original studies were not available to review. FDA Briefing Document, October 27 and 28, 2015. CFSAN had accepted the submitter's conclusion that MSM is GRAS for use in foods under the conditions of use stated in the notice (for use as an ingredient in meal supplement and meal replacement foods, fruit smoothie-type drinks, and fruit-flavored thirst quencher-type beverages at levels up to 4,000 mg/kg and in food bars such as granola bars and energy-type bars at levels up to 30,000 mg/kg).

The oral doses nominated for MSM as a compounded ingredient were for oral capsules of strengths ranging from 20 - 500 mg, which is at least an order of magnitude below the level CFSAN found GRAS for ingestion. For FDA to now say that this presents a safety risk is not scientifically valid, particularly when the Agency gives an exhaustive list of studies showing no finding of toxicity, an extremely high LD, and limited reported adverse reactions consistent with or less than widely marketed drugs. Against global and long historical use, the Agency falls back on an absence of studies by inappropriately applying near IND/NDA standards of proof. The Agency further claims approval cannot be made because MSM crosses the brain-blood barrier, which has not been subjected to sufficient study. This is specious because that physiologic property was in fact part of all the studies that found no or limited toxicity and the studies that convinced CFSAN that MSM was GRAS at much higher doses.

In its 2019 Final Rule, the Agency says that GRAS determinations may not apply to other routes of administration. 84 FR at 4700. While Petitioners believe that the Agency is unduly cautious in its interpretation of data, given the Agency's authority to restrict route of administration it is difficult to see the basis for this argument. As noted above, we believe such a restriction would be harmful but in any event this certainly provides no basis to restrict oral uses especially when dose and frequency data comparable to the GRAS determination can be taken into account. In the example of MSM, the Agency's refusal to accept an assessment that an order of magnitude higher doses than nominated demonstrates the extent to which the thresholds it is applying to approval of compounded ingredients is without basis. On its face, an item that is listed as GRAS should not be rejected for concerns about safety. At the very least, Petitioners request that FDA subject this issue to notice and comment rulemaking.

H. There Are Significant Patient Populations Who Are Not Responsive to Available Diagnoses and Treatments Which Require Different Approaches to Care; Restrictions to Standardized Treatment Will Be Especially Harmful to These Patients.

A consideration entirely absent from FDA's consideration that merits more specific

⁷³ FDA Letter dated September 25, 2015. Review of Methsulfonylemethane (MSM) for Inclusion on the 503A Bulk Drug Substances List at 4, appended to FDA Briefing Document for PCAC Meeting dated October 27 and 28, 2015.

mention is that compounded medications for disease treatments are often done because approved diagnostic methods or medications have been treatment failures. Patients often seek care of an integrative or naturopathic physician after conventional means have been exhausted. Certainly all categories of approved drugs have significant number of patients who fail at treatment, and these approaches provide alternative options. While FDA may have concerns about some compounded medications being first-line treatments, not only should greater latitude be given to physicians but patients who have failed at approved drugs should not be denied the opportunity for assistance because of global presumptions about approved drugs.

Many standard, nationally accepted guidelines and recommendations work well for many medical conditions. Petitioners represent or compound for physicians whose practices include a significant portion of patients that do not respond to these mainstream approaches or experience adverse effects that preclude them from being good candidates. This includes patients for whom the diagnosis is wrong, unclear, or perhaps as yet unknown. And when a seemingly accurate diagnosis does exist for them, they either don't respond to traditional treatment, they experience adverse effects, or the treatments FDA prefers are contraindicated. The support offered by integrative and naturopathic physicians may include functional approaches that support the body's intrinsic healing mechanisms, an important approach for any patient but which is especially important for patients with complex conditions or who are treatment failures.

The Agency's reliance on disease categories does not address the great many patients who present without a clearly defined clinical entity. Patients who present with Chronic Fatigue Syndrome, for example, do not present with objective evidence of a specific and known condition but rather diffuse symptoms that could be forms of a wide range of difficult to diagnose or proposed illnesses such as myalgic encephalomyelitis, mitochondrial disease, mold sensitivities, occult viral or bacterial infections, immune dysfunctions, complex hormonal imbalances, physiologic stress reactions and numerous others. Where there is not a discrete and objective disease entity, conducting randomized trials of the effectiveness of an ingredient is simply not possible as cohorts of patients that clearly have the same condition cannot be formed. The assumption underlying the FDA's approach that patients may not have access to treatments until the medical profession has been able to identify objective markers, form consensus about disease classification, and test single ingredients for effectiveness leaves enormous numbers of patients untreated. While FDA has simply rejected the poor public policy in its methods out-of-hand, 84 FR at 4707-08 (Response 35) it has not addressed this issue. While the FDA's methods may be limited to only being able to weigh single agent impacts on known disease entities, that limitation does not exist in the reality of clinical practice or in the scope of practice or training of physicians treating actual patient complaints. Petitioners ask FDA to seriously consider the matter in which the lens through which it view patient care by definition excludes important means of patient support.

III. The FDA Stance Violates the Law and Long-Held FDA Policies.

A. FDA's Approach Improperly Interferes with the Practice of Medicine and Ignores the Role of Physician Judgment in its Standards of Ingredient Review.

FDA's regulatory authority and jurisdiction is limited by the right of physicians to practice medicine. FDA has a limited ability to interfere in the practice of medicine, *see Chaney*

v. Heckler, 718 F.2d 1174, 1179 (D.C. Cir. 1983) (“FDCA’s legislative history expresses a specific intent to prohibit FDA from regulating physicians’ practice of medicine.”) *rev’d on other grounds*, 470 U.S. 821 (1985). What is commonly referred to as FDA’s “practice of medicine exception” developed directly out of Congress “not want[ing] to interfere with physicians’ treatment of their patients.” *U.S. v. Algon*, 879 F.2d 1154 (3d Cir. 1989). As described in the Agency’s own interpretation of legislative history, “[t]hroughout the debate leading to enactment [of the FDCA], there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to Congressional understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient.” Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16503 (Aug. 15, 1972); *see also* Proposed New Drug, Antibiotic, and Biologic Drug Regulations, 48 Fed. Reg. 26720 (June 9, 1983) (“In FDA’s Drug Bulletin of April 1982, the agency sought to clarify and reiterate the position that the [FDCA] does not regulate the ‘practice of medicine.’”); Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco to Protect Children and Adolescents, 61 Fed. Reg. 44396, 45182 (Aug. 28, 1996) (“FDA’s practice-of-medicine policy is based on FDA’s long-standing policy of not interfering with the practice of medicine.”).

Physicians exercising treatment choices within the confines of their state medical practice acts and pharmacy laws are practicing medicine. Such drugs are supplied to support medical practice and are prescribed, compounded and used within that context, not manufactured nor placed on the market as are drugs subject to NDA requirements. Petitioners urge FDA to therefore only remove ingredients from use for which there is clear evidence they are dangerous and for which there is no reasonable use when the entire spectrum of functional medical and naturopathic care is considered, not simply individual, selected indications.

FDA’s response to this concern is simply to say that “[t]he FD&C Act establishes the framework for regulating the drugs that physicians may prescribe. Within this framework, once a drug becomes legally available, with certain limited exceptions, FDA does not interfere with physicians’ decisions to use it when they determine that in their judgment it is medically appropriate for their patients. The Agency believes that this rulemaking is consistent with this framework and does not overregulate.” 84 FR at 4707 (Response 34). Petitioners’ discussion demonstrates, at the very least, that FDA has not adequately considered these issues.

FDA’s actions are inconsistent with its historical and important recognition of the reasonable latitude that should be allowed physicians to determine clinical need in practice. Physicians have direct relationships with patients and their involvement in compounding is not only prescribing but often administering or overseeing use. That physicians’ directly administer many compounded drugs places them in a unique position. Unlike many NDA approved drugs which generally are merely prescribed, compounded medications are often subject to more, not less, professional control over selection and use.

One of the bases for the rejection of physician’s role is an unfounded but overt distrust of physicians’ knowledge. At the November 20, 2017 PCAC meeting, p.m. session at 156, 163, FDA staff stated with regard to several ingredients that physicians would have no understanding of the proper dosing, potential adverse reactions, or special considerations such as the bimodal dosing concern for Resveratrol. This view pervades the ingredient determination process but is without basis. FDA has conducted no fact-finding on the knowledge of physicians who use compounded ingredients and based on Petitioners’ experience the FDA view reflects a lack of understanding of integrative medical and naturopathic education and training. Further, given that

there is little representation among either FDA staff or the PCAC committee of practicing physicians outside of academic or hospital settings who use compounded medications, there is little basis upon which an understanding or experience to inform this process.

There are legitimate professional differences of opinion arising from differences in paradigm and experience. Addressing one specific practice area of interest to all Petitioners, where states have chosen to authorize naturopathic physicians⁷⁴ the right to practice, Petitioners believe that FDA should not undercut that professions accepted body of knowledge and scope of ingredient interventions, particularly as FDA does not have the participation of any naturopathic physicians and no expertise in this body of knowledge or the proper use of such ingredients according to that school of thought.⁷⁵ FDA may believe that drug choices are matters of science and thus neutral regardless of professional background, but treatments are inevitably tied to the philosophy of medicine underpinning any profession or specialty⁷⁶ which guide where in the biological system it targets an intervention. Solutions are inextricably tied to the question that is asked. There are other useful questions than what specific symptom set can be affected by what

⁷⁴ FDA's description of its thorough process in seating PCAC members notwithstanding. 84 FDR at 4706 (Response 26), FDA did not actually respond to this concern. FDA's reference to this profession as "naturopaths," *ibid*, is a term or art that refers to practitioners that did not attend an accredited, Department of Education recognized four-year residential program to achieve eligibility for a state license. Petitioners represent naturopathic physicians which is a licensed profession. The use of the term "naturopaths" suggests that FDA may not have an adequate understanding of the profession. As many states have authorized the use of natural approaches, including natural compounded ingredients, even if FDA has a bias against such approaches Petitioners ask FDA to consider whether it should preempt such state decisions, especially without any apparent understanding or consideration of them.

⁷⁵ For its review of 503B ingredients, FDA recently contracted with the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) to conduct research and outreach to solicit input from the public, including medical specialists, to better understand the use of certain bulk drug substances for that list. One of the members of the advisory committee to M-CERSI is a naturopathic physician. Petitioners applaud the inclusion of a naturopathic physician for the 503B process, though even there, the scope of the contract is simply to determine usage and not to provide input on the evidence-base or clinical understanding behind such use. Further, the 503B review is more limited and FDA's understanding would be enhanced by inclusion of other schools of thought in all aspects of ingredient review.

⁷⁶ Naturopathic medicine, for example, is based on principals that include recognition of the healing power of nature and a focus on identifying and treating causes. <https://www.naturopathic.org/content.asp?contentid=59> (last accessed December 1, 2018). Regulations that impose a preference for pharmaceutical options is in many cases a direct violation of the therapeutic order, an approach naturopathic doctors use that first removes obstacles and creates conditions in which the body can heal itself before attempting pharmaceutical means. The preference for functional uses of natural products is a core tenant of naturopathic principles, held by a professions that 21 states have authorized as appropriate practice. FDA is undercutting the profession without cause, basis or evident awareness. *See* <https://www.gaia.com/article/therapeutic-order-7-tenets-naturopathy> (last accessed December 1, 2018.)

single, ideally patentable, agent. With the exception of physicians practicing integrative and nutritional medicine, medical physicians generally do not have the training, experience, or orientation in nutritional and related therapies to attend to the clinical use of many of the proposed ingredients.⁷⁷ Many compounded ingredients across the spectrum of medical specialties are appropriately in use as part of protocols or to accomplish purposes that are not considered by FDA. FDA is not taking into account professional viewpoints and context of clinical use for the spectrum of professional orientations or training that are outside the expertise of the FDA and PCAC panel, including that of integrative or naturopathic medicine.⁷⁸

The PCAC discussion of DMPS is an example of flaws in the review process. A decision pending federal register publication, DMPS was ultimately recommended by the PCAC for the bulk list because it is the only effective treatment for arsenic poisoning. FDA and the Committee were concerned about its use by some physicians as a means of detoxifying mercury, in part because of exposure to amalgam fillings as well as fish consumption and other exposures. Without any factual basis and with no findings or consideration of the matter at all, and without any evident expertise on the issue or reflection on the subpopulation recognized as having a mercury allergy, FDA staff and PCAC members quickly jumped to the conclusion that such use would be improper.⁷⁹ The only reason the recommendation did not include a restriction to the treatment of arsenic poisoning is because the Act does not allow approval only for specific indications. But that FDA and the Committee accepted that such use was inappropriate as matter of opinion without the presentation of any expert discussion or evidence about the nature of this practice and the importance of DMPS for use in mercury detoxification reflects a bias and deep flaw in the decision-making process. It is one example that demonstrates that the process FDA has established does not have the evidentiary power needed to reach the decisions FDA has undertaken.

⁷⁷ This might explain why FDA has engaged in the oversimplified analysis that reduces ingredient use to disease indications, as it does not have a sufficient experience with of functional practice and is more familiar with a disease model.

⁷⁸ Integrative medicine is a recognized medical specialty by the American Board of Integrative Medicine, a board certification under the auspice of the American Board of Physician Specialties, <http://www.abpsus.org/integrative-medicine> (Last accessed September 1, 2018). The recognition by appropriate credentialing body establishes this approach to medicine in a fashion recognized under some state laws, and FDA should not undercut such practices merely because of any skepticism or limited familiarity with them.

That naturopathic medicine is recognized by 21 states, the District of Columbia and Puerto Rico, <http://www.naturopathic.org/content.asp?contentid=57>. (last accessed September 1, 2018) establishes this as a profession with legitimate practice rights and its own body of professional literature and methodology for understanding health interventions which should be accommodated by FDA. There are no integrative physicians, naturopathic physicians or physicians with skills in nutritional medicine involved in FDA's process and no evident expertise on these methods.

⁷⁹ Transcript, FDA PCAC Meeting, June 23, 2016, p.m. session at 154, 169-70, 189-91.

B. FDA's Approach Improperly Interferes with the Practice of Pharmacy and Ignores the Role of the Physician / Pharmacist Partnership as State Authorized Practice.

The practice of pharmacy is subject to regulation and oversight long recognized as the province of the States. As with the practice of medicine, this is long-standing FDA policy under which pharmacies have practiced, in part because practicing pharmacy is not considered drug manufacturing. The partnership between physician and pharmacist allows for a collegial consideration of the physiology, dosing and adverse effects. The work of physicians and pharmacists in partnership for patient care has long been respected by FDA, even after the passage of the FDAMA which remains unchanged since 1997. A federal court recognized, for e.g., in *United States v. Franck's Lab, Inc.*, 816 F. Supp. 2d 1209, 1247 (M.D. Fla. 2011) that compounding from bulk substances is allowed under and governed by Florida law:

The Florida Drug and Cosmetic Act, Fla. Stat. §§ 499.001 et seq., defines "manufacture" as the preparation, deriving, compounding, propagation, producing, or fabrication of any drug, device, or cosmetic, Fla. Stat. § 499.003(30), and "manufacturer" as a person who prepares, derives, manufactures, or produces a drug, device or cosmetic, Fla. Stat. § 499.003(31). However, the term manufacturer does not include a pharmacy that is operating in compliance with pharmacy practice standards as defined in the Florida Pharmacy Act and rules adopted thereunder. Fla. Stat. § 499.003(31). Those standards and rules expressly provide for compounding from bulk substances

The court in *Franck Lab* granted summary judgment to the laboratory in an FDA action because Congress did not intend to give FDA *per se* authority to enjoin long-standing, widespread, state-regulated practice of pharmacists, in this case filling a veterinarian's prescription for a non-food-producing animal by compounding from bulk substances. This case was decided long after the FDAMA was enacted, which to this day regulates 503A pharmacy practice and was not altered by the passage of the DQSA and thus remains good law.

The motive for small, traditional pharmacy compounding is treatment, rather than mass marketing.⁸⁰ For a pharmacy to cross the line and step outside a state regulated pharmacy into manufacturing, there "must be evidence of large-scale compounding activity." *Schaerrer v. Stewart's Plaza Pharmacy, Inc.*, 2003 UT 43, ¶ 2, 79 P.3d 922, 925 (Sup.Ct.). While FDA arguably has the authority under the FDAMA, Petitioner maintains that imposing regulations intended for restricting manufacture on compounding where that is not in fact occurring is an overreach by FDA. Like *Franck Lab*, *Schaerrer* was decided after the FDAMA was law, which remains the law. While FDA decisions appear to implement its view that traditional compounding pharmacies are routinely crossing the line into inappropriate manufacture as did NECC, that is a separate and distinct issue from that of ingredient review and is not a basis for removing ingredients from the market and interfering with state practice.

⁸⁰ Industry representative William Mixon, RPh, MS, FIACP noted during a PCAC meeting that compounding pharmacies do not advertise or market the availability of specific drugs. Transcript, FDA PCAC Meeting, February 24, 2015 morning session at 87.

C. FDA's Actions are as a Matter of Law Arbitrary and Capricious as FDA has not Properly Articulated Standards for Approving Compounded Ingredients, Particularly Ingredients That Have Historically Been on the Market.

The many difficulties with the standards described in this comment constitute arbitrary and capricious agency actions. Petitioners therefore ask the Agency to reconsider. This affects both nominations that were rejected as deficient on List 3, those listed for rejection in the 2019 Final Rule and those that have been proposed for rejection based on unvetted criteria.

Congress typically recognizes that the pre-existing marketing of a product vests certain rights to continue and have expressly included grandfathering provisions, such as the 1938 grandfather clause at 21 U.S.C. § 321(p) and the 1962 clause which was contained in the transitional provisions of the amendments to the FDCA. As the FDA correctly notes, 503A of the FD&C Act does not provide a grandfather provision. 84 FR at 4708 (Response 36). While Congress did not expressly provide a "grandfather" provision in the 503A traditional compounding section of the FDCA, there was no basis for it to have anticipated the need for such language in this twenty year old statute because the DQSA did not make any substantive amendments to section 503A and nothing in the DQSA instructed FDA to reevaluate items that have been used for decades. The statutory language in fact states that historical use was a primary criterion upon which any judgments should be made. 21 USC § 353a(c)(2). Where companies have had ingredients on the market for a considerable time, and practitioners have as a community developed protocols for their use upon which they rely, there is a vested economic and clinical interest such that, before wholesale changes are contemplated, grandfathering is generally addressed by Congress.

Though Congress did not include an express grandfathering provision in DQSA. Congress expressed the view that in passing the DQSA they were not disturbing traditional compounding practice, and had no basis to anticipate that the Agency would rewrite the field requiring an express grandfathering provision.

Virtually all of the ingredients at issue for compounding pharmacies have been on the market for lengthy periods. FDA is effectively removing a number of drugs from the market now, both unilaterally for nominations it considered insufficient on List 3, and through the NPRM process by failing to properly notice its actual criteria in violation of the APA. Compounded drugs are carved out of the definition of new drugs, 21 USC § 353a(a), and where they have been used historically nothing in the FDCA generally, or the creation of 503B outsourcing facilities specifically, places compounded medications under a schema that substitutes a requirement for a high threshold of clinical studies for clinical experience. While FDA has created a separate process for review, the lesson of the DESI experience is that for such a review to be acceptable for the removal of drugs already on the market it must be grounded in clear scientifically sound standards and subject to a proper process. Petitioners believe that the lessons of the DESI process were not followed and request that FDA consider whether a hearing would assist in better understanding of Petitioners' concerns about the scientific and public policy standards being employed.

D. The Probity of FDA's Decisions on Compounding Would be Served if the Agency Accounted for the Conflicts of Interest Given its Financial Incentives to Favor Approved Drugs Over Compounded Drugs.

FDA appears to be restructuring the field of compounded medications to protect the pharmaceutical industry from which it receives substantial fees. This certainly gives the appearance, if not an actual, conflict of interest for these determinations. This provides an apparent explanation for the Agency elevating approved medications over compounded medications without offering an opportunity for notice and comment about the actual criteria which weigh heavily against the inclusion of compounded ingredients. In its Final Regulatory Impact Analysis, the Agency acknowledges that its rule will shift financial compensation from compounding pharmacies to drug manufacturers. Final Regulatory Analysis at 14.

The financial conflicts of interest presented by the fees pharmaceutical companies pay FDA has been a subject of frequent concern.⁸¹ The fees paid under the Prescription Drug User Fee Act (PDUFA), constituting forty-five percent of the Agencies fiscal 2016 budget, have been estimated to have contributed over \$7.6 Bn to the Agency since PDUFA was passed in 1992. Use fees for a single application can be over \$2 million.⁸²

As set forth in this Petition, the criteria FDA has been reluctant to subject to notice and comment overtly favor the use of approved drug products for which PDUFA fees have been paid to the exclusion of compounded products. The standard that a compounded drug cannot be listed if there is an approved drug that might be able to treat the proposed condition is anti-competitive rather than a scientifically sound determination. It certainly raises the conflict of interest concerns about PDUFA in a more direct manner than has heretofore been litigated.⁸³ While the impact of PDUFA on drug approvals can be debated statistically, the nature of the scientifically strained decisions FDA is making is consistent with an overall skew toward approved drugs whose review generates these fees. A number of the criteria FDA is applying without notice and

⁸¹ See for e.g. The Damaging Impact of PDUFA and Why It Should be Repealed <http://ahrp.org/the-damaging-impact-of-pdufa-and-why-it-should-be-repealed/> (last accessed December 1, 2018); Perspective: a Legal Challenge of the Prescription Drug User Fee Act, 29 *J.L. & Health* 85.

⁸² Business Insider: The government agency in charge of approving drugs gets a surprising amount of money from the companies that make them, L. Ramsey and L. Friedman Aug. 17, 2016) <http://www.businessinsider.com/fda-user-fees-from-pharmaceutical-companies-2016-8> (last accessed December 17, 2018).

⁸³ Few PUDFA cases have been reported, and none of them challenge the legality or discretion of FDA to charge user fees or even question the possible conflicts of interest PDUFA may pose. *Pharmaceutical Research and Manufacturers of America v. HHS*, 2014 WL 2171089 (D.D.C. 2014) was litigated over a question of discounting the user fee for orphan drugs, *State-Trade Inc. v. FDA*, 869 F.Supp.2d 95 (D.D.C. 2012) was litigated over a question of whether a manufacturer seeking approval of two strengths of same drug should be assessed one user fee, and *Winston Labs v. Sebelius*, 2009 WL 8631071 (N.D. Ill. 2009) was litigated over a question of waiving the user fee for small businesses. See Perspective: a Legal Challenge of the Prescription Drug User Fee Act, 29 *J.L. & Health* 85 (2015). The barriers FDA is raising against compounded drugs squarely raises this question of conflict of interest in a posture that has not yet been presented to a court.

opportunity for comment to the ingredient listings expressly favor removing compounded products that compete with approved pharmaceuticals. The public health would be best served if FDA considered the conflicts of interest it may have given the considerable user fees it receives for pharmaceutical approvals, which present the conflict of interest favoring approved drugs in stark terms.

FDA responded to our concerns by asking what we were suggesting the Agency could do to address this perceived conflict of interest. 84 FR at 4705 (Response 24). This Petition details the steps we ask the Agency to take to correct the definitive conflict in the actual criteria FDA is employing to favor approved drugs over nominated ingredients. The clearest step it could take is to ensure that the actual effectiveness and known side-effects of the alternative approved drug is part of its calculus in its briefing materials and discussion with the PCAC committee rather than sequestering those drugs for which it has been paid fees from an actual comparative consideration. FDA is implementing a schema that may seem to give reassurance that that it is not interfering with treatment yet does by entirely avoiding inclusion of the risks and benefits of approved drugs as part of its calculus. This highly skewed methodology appears to protect those from whom it has received PDUFA payments from competitive use of compounded drugs.

E. FDA's Criteria Restricting Ingredients in Favor of Approved Drugs is an Improper Restraint of Competition.

The fact that the Agency is limiting products in the marketplace based on what already is on the market to treat ostensibly the same condition essentially limits competition and enforces monopoly conditions. This runs counter to the intent behind the Food, Drug, and Cosmetic Act "to protect the financial interests of consumers as well as their health." *United States v. Lane Labs-USA, Inc.*, 427 F.3d 219, 227 (3d Cir. 2005). Placing restrictions that limit physician choices to approved drugs over continued use of historically available compounded drugs will increase the costs to consumers where the compounded products cost less or provide less risky alternatives and will create conditions for increases the prices of pharmaceutical drugs.

This is especially onerous where the rejection of ingredients is based on a rejection without fair consideration of the varied schools of medicine that use these medications and the professional physician/pharmacist team decision-making and involvement in use of the medication; there is no rational basis for FDA to create monopoly conditions by substituting its judgment for that of licensed professionals.

F. FDA's Actions are Arbitrary and Capricious Because They Are Disconnected from the Basis for the DQSA and FDAMA, Congressional Intent or any Previous Standards Employed in Drug Regulation.

FDA appears to have interpreted the Congressional response to the NECC matter by purposely attempting to reduce patient access to compounding in the alleged interest of safety. In announcing restrictive standards FDA cites at every turn the dangers presented by contamination of the sort that occurred at NECC as the underlying basis for its actions, yet there is no evidence that its actual criteria address any nexus between potential contamination and its finding on specific ingredients. In none of the listing denials or limitations to topical use has the Agency cited an unusual risk of contamination as a basis. Even though the references to the NECC failure to maintain sterile conditions has been repeatedly offered in FDA's guidances and the 2019 Final Rule as justification for the Agency's actions, nothing in FDA's stated or actual

criteria, other than its too difficult to compound list, bears any nexus to this concern.

The actions taken by FDA are not rationally related to the safety issues raised by the NECC event or inspection concerns. Given that the DQSA arose from 503A pharmacy sterility concerns, which have been addressed in a Guidance entitled "Insanitary Conditions at Compounding Facilities," 81 FR 5144 (August 4, 2016) rather than a concern for any specific drug ingredient, the requirement that ingredients not subject to a USP monograph or a component of an approved drug be subjected to the stilted criteria in use by FDA has no legislative basis or rationale. FDA addressed this concern by saying that it also has a legitimate interest in effectiveness, 84 FR at 4708 (Response 38); while that is certainly legitimate, the validity of these determinations are the subject of the Petition. Along with a presumption against findings of effectiveness, the NECC matter has been used in public discussion to drive the acceptance of a curtailed formulary even though there is no nexus between that event and the ingredient decisions being made.

It is also significant that NECC was found to be engaged in manufacturing rather than handling small quantities in individual scripts,⁸⁴ which exacerbated the contamination issues. Yet FDA is now attempting to regulate even appropriate compounding done in a manner consistent with the history of traditional pharmacies under an elevated review standard contrary to its well-established historical position. As detailed in the 2011 *Franck Lab* decision, FDA prior to the creation of 503B outsourcing facilities had been operating under FDA Compliance Policy Guide Sec. 460.200, Pharmacy Compounding (May 2002) (2002 Guide) which makes no mention of any public health concerns associated with these drugs, nor does it make sweeping assertions of FDA's authority to regulate the practice. Rather, its "Discussion" section begins with the statement that "FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance." 2002 Guide at 2. Even though FDA asserted that "all of [FDAMA] is now invalid" in light of the Ninth Circuit's severability holding in *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 122 S. Ct. 1497 (2002), the 2002 Guide nonetheless "appears to embrace FDAMA's effusive attitude towards traditional pharmacy compounding." *Franck*, 816 F.Supp at 1226. The focus of the guidance is FDA's desire to eradicate improper manufacturing, which, with regard to bulk drugs, is framed as an issue of scale:

FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing and distributing unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice and that violates the Act. Such establishments and their activities are the focus of this guidance. Some "pharmacies" that have sought to find shelter under and expand the scope of the exemptions applicable to traditional retail pharmacies have claimed that their manufacturing and distribution practices are only the regular course of the practice of pharmacy. Yet, the practices of many of these entities seem far more consistent with those of drug manufacturers and wholesalers than with those of retail pharmacies. For example, some firms receive and use large quantities of bulk drug substances to manufacture large quantities of

⁸⁴ See for e.g. Compounding Pharmacy Owner Not Guilty of Murder After 60 Meningitis Deaths, J. Bidgood, March 22, 2017 quoting Acting United States attorney for Massachusetts, William D. Weinreb, <https://www.nytimes.com/2017/03/22/us/meningitis-new-england-compounding-center-barry-cadden.html> (last accessed December 3, 2018).

unapproved drug products in advance of receiving a valid prescription for them. Moreover, some firms sell to physicians and patients with whom they have only a remote professional relationship. Pharmacies engaged in activities analogous to manufacturing and distributing drugs for human use may be held to the same provisions of the Act as manufacturers. 2002 Guide at 3. *Franck Lab* at 1226.

The passage of the DQSA provides a solution to this issue by creating 503B outsourcing facilities subject to cGMPs as an intermediate step for larger scale compounding. Congress did not alter the FDAMA or traditional compounding. Compounding has historically allowed physicians to make judgments within their expertise. In the name of a general concern about safety and under the banner of the specific contamination issues that occurred at the NECC, the Agency is changing fundamental standards of practice and propounding unreasonably high standards of evidence for physicians and pharmacies that have not violated these boundaries and not presented a risk to public safety. The Agency has created high hurdles for approval of ingredients unrelated to the event that triggered the DQSA and with little assessment of the impacts such a reset of the field will cause in lost opportunities for treatment and innovation.

IV. FDA Should Address the Significant Flaws in the Process by Which the Ingredient Nomination and Review Has Been Conducted.

A. The Ingredient Nomination Process Is Flawed; The Rejection of over 300 Applications, as well as the Manner in Which the Review Process is Being Undertaken on the Remaining Nominations, Should be Revised.

The difficulties with the criteria for listing began with the nomination process itself, which has undermined the validity of the process. Nominators were not provided adequate information about FDA standards, which has been a moving target, a problem that still has not been resolved with the issuance of the 2019 Final Rule. Given the lack of notice about the actual criteria as shown in its decisions, nominators have not been given a fair opportunity to support their requests. FDA responded to this concern by stating that: "FDA is applying the four criteria set forth in rulemaking when evaluating bulk drug substances for inclusion on the list. FDA considers the information requested in the July 2014 Request for Nominations and bases its decision on the physical and chemical characterization, safety, effectiveness, and historical use of the bulk drug substance in compounded drug products." 84 FR at 4706-07 (Response 29). This Petition has set forth the actual criteria in use by the Agency under which it is judging nominations. Petitioners' proposed criteria, listed at the end of this Petition, fit within these same four topic areas as well but would lead to very different results, conclusively demonstrating that FDA did not give notice as to its actual criteria.

FDA's response that nominators had adequate notice by virtue of these broad topic areas simply confirms that nominators had insufficient notice and why it was critical that FDA provide proper notice and comment. Nominators had no reason, for example, to expect that ingredients would be rejected because of a presumption against listing if there was an approved drug for the indication or because the use proposed was for a serious disease. Nor is it accurate that nominators were provided information about FDA's actual considerations. *See* Response 30, 84 FR at 4607. Petitioner appreciates that the Agency recognized the need to clarify the

renomination process. Response 31, *Ibid.* Reconsideration should be given to determinations made thus far as a result.

The nomination process has been undermined because the actual criteria were never published so meeting FDA's informational needs has been unnecessarily difficult. The Agency's actions have created a moving target; the requests for nominations did not request that nominators submit long-term studies as a specific request,⁸⁵ for example, however at the November 20, 2017 meeting of the PCAC FDA began using the absence of long-term safety data as a basis for denial, which it had not even requested from nominators. Transcript, p.m. session at 23, 45, 49, 96, 98, 113, 120. This moves what had been a review of long-used compounded ingredients closer to new drug review. This requirement was not only absent from the nomination requests, thus making it difficult to gain proper consideration for nominated ingredients but is not a standard that complies with Congressional intent.

These same problems pervade the FDA position with the regard to the over 300 nominations it placed on List 3 simply deemed inadequate in one fell swoop and without detailed comment. This was one of the reasons that courts initially rejected the DESI process. Nominators have noted to FDA that the absence of deficiency letters has left them unable to respond to an action made without any notice of basis,⁸⁶ leaving these items without a safe harbor and with no reasonable opportunity to resolve FDA concerns. Petitioners ask the Agency to establish a reasonable means to address the items it has placed on List 3.

The management of PCAC meetings has also left Petitioners with a number of outstanding concerns. In its vote on alpha-lipoic acid, FDA proposed that it be accepted for oral use but questioned intravenous use for concern about its aqueous stability. Not only was this issue addressed by presenter Arthur Berkson, M.D. but Doug Tran, PharmD from McGuff Compounding Pharmacy flew in from California with results of extensive bench testing that addressed the question of aqueous stability. Many of the members of the PCAC were clearly swayed by the evidence and would have voted to allow IV use, but FDA would not allow that vote to occur. This does not appear consistent with the requirements of use of an Advisory Committee under the Federal Advisory Committee Act (FACA) (Pub.L. 92-463, 86 Stat. 770, enacted October 6, 1972), as the Committee is supposed to be able to make its determinations without being "inappropriately influenced by the appointing authority," 5 U.S.C. § 5(b)(3). Petitioners are concerned that the Committee should have been allowed to offer its determination on the issue without restriction by the Agency. The lack of opposing viewpoints and willingness of the PCAC committee to take different positions from FDA has been an ongoing concern.

B. FDA Has Skewed the Decision Process by Improperly Stating That an Expanded Use IND Is a Reasonable Alternative to Approval.

FDA also skewed the PCAC decision process, in a manner questionable under FACA, by inaccurately advising the Committee that if they recommend denying listing to an ingredient they are not denying use because a physician can readily access an "Expanded Access IND" by

⁸⁵ See for e.g., Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations Action: Notice; revised request for nominations. 79 FR 37747 (July 2, 2014).

⁸⁶ See for e.g., McGuff Pharmacy letter to FDA dated September 30, 2014, reproduced in FDA PCAC Briefing Materials dated October 27-28, 2015 at 28.

applying with FDA for use.⁸⁷ Shifting the burden to individual physicians to go through the arduous IND process, which is available under extremely limited circumstances, rather than providing reasonable allowance for access to nominated ingredients via the process designed to consider their use is inefficient and extremely burdensome.

The Agency denies that the alternative route of an IND was a part of the Agency's considerations, 84 FR at 4700, which may be true but is beside the point; Petitioners' concern is the Agency overtly and intentionally gave presentations to the PCAC Committee and informed them that physicians would still have access to these ingredients via the IND process. The Agency's carefully worded denial about its internal considerations does not claim that it did not affect the outcome of PCAC votes. FDA's discussion of IND's was for the clearly stated purpose of influencing PCAC to accept FDA's denial recommendations by assuring them they could deny listing ingredients and they would still be reasonably available. Petitioner asks the Agency to recognize it is disingenuous given its repeated statements to the PCAC that they could vote to refuse a listing without denying patients given the availability of Expanded use IND's to then argue that "it cannot control the content of the PCAC's discussions or its advice." *Ibid.* The impact of this misinformation clearly derailed the approval process given that the alleged option was noted by Committee members as forming the basis for their "no" vote on a number of ingredients.⁸⁸ Despite FDA's disclaimer of effecting the outcome, on the Notice of Proposed Rulemaking, FDA again stated that an ingredient denied for listing may be available by filing an IND (NPRM at 91077). The economic report entitled Preliminary Regulatory Impact Analysis Initial Regulatory Flexibility Analysis Unfunded Mandates Reform Act Analysis provided as Exhibit 14 on the NPRM docket, as does the Final RFA Analysis, reiterate FDA presumption that physicians seeking to use a medication that has been denied listing as a bulk ingredient could readily obtain an Expanded Use IND. The legal criteria for obtaining an IND, as well as experience, shows this to be highly unlikely and extremely burdensome. Petitioner sees as an effort at inappropriate influence by the appointing authority in violation of 5 U.S.C. § 5(b)(3).

As a threshold matter, the ingredient review process is intended to make a determination, not shunt responsibility onto physicians across the country who may wish to use a rejected ingredient to undertake an arduous and difficult effort to obtain an IND. If FDA is going to impose restrictions on use, it is the Agency's responsibility to make a fair assessment now while it is focusing its and nominators' resources on the review. If there is a basis to approve a drug for use for an IND then the drug should be given proper consideration for approval in this review.

Contrary to the FDA's statement to the PCAC, obtaining an IND is an extremely difficult and costly process. Particularly if more than one or two patients are involved, this route is only reasonably available to institutionally-based physicians with a need for use sufficient to justify the considerable time and expense of submitting an intermediate-sized IND. The barriers are complex, costly and prohibitive. FDA even suggests that this is the solution that should be used to justify the single use of a medication in an emergency.⁸⁹

That Expanded Use INDs are not a viable option due to these difficulties was pointed out to the Committee in a presentation entitled "Committee IND Applications in the Community Setting" on June 23, 2016 by A.J. Day, PharmD, RPh. of PCCA. Dr. Day attempted to navigate

⁸⁷ See for e.g., discussion, FDA PCAC meeting dated June 17, 2015 at 28-57.

⁸⁸ See for e.g., piracetam, FDA PCAC meeting dated February 23, 2015 at 162.

⁸⁹ See for e.g., chloramphenicol, Transcript, FDA PCAC meeting dated February 23, 2015 at 87.

the IND pathway and advised the Committee of the practical difficulties and demonstrated to the Committee that FDA representations were not accurate. That these misrepresentations skewed the Committee's decision is clear, in part, because after this presentation PCAC issued its first approvals. The comments of some of the PCAC members made it clear that they had agreed with FDA's recommended denial because of this representation. This is true of Piracetam, whose denial is proposed in the NPRM, which was denied in significant part because of this inaccurate FDA guidance to the PCAC.⁹⁰ Not a single ingredient was listed over FDA guidance until the presentation by Dr. A.J. Day.

An Expanded Use IND submission requires over 25 completed pages of documents, and FDA has stated that incomplete submissions will not be reviewed. Approval is granted only for one year and will then need to be renewed. The application process is fraught with administrative confusions and difficulties. Some applications require Form FDA 1571 and 1572, others Form FDA 3926, which is only valid for individual patient IND's, submitted by licensed physicians.⁹¹

Approval by an Institutional Review Board (IRB) is another major obstacle as it is required in any use of an experimental therapy, 21 C.F.R. Parts 50 and 51. Dr. Day and his staff contacted the IRB panels of 32 hospitals and research institutions from around the country, four commercial IRB and physician and patient groups for assistance with access to an IRB and navigation of the IND process to see if it would be possible to submit an application for domperidone, whose denial was predicated in significant part on the alleged availability of an Expanded Use IND. The answer was "no" in all cases.

This stands in stark contrast with FDA representations to the Committee:

If he or she [the physician or healthcare provider in a small community] does not have a local IRB, they can use a central IRB, and many of those provide their services for free for expanded access or compassionate use." They had no experience with compounded medications and their experience was mostly limited to IND's sponsored by drug manufacturers. After several days of discussion, one commercial IRB said they would consider being the IRB of record. Their fee would be a minimum of \$3,000 per individual patient IRB review. Before submitting an application, however, it required that the "investigator" must complete a 16-module training course that takes four or more hours to complete. Depending on work load, turnaround for IRB review could be

⁹⁰ In the discussion and vote on Piracetam, IND's were discussed as a mechanism for patient access instead of adding items to the Bulk Substances List. Even though there were no safety concerns voiced by FDA, the ingredient was denied and PCAC members explaining their vote made comments such as "if there's an alternative so they won't be denied medication or the drug," "it also sounds like it may be made available for the specific cases through the expanded use IND." PCAC Meeting, February 24, 2015 at 179.

⁹¹ Intermediate-size patient population INDs, and treatment INDs, must use Form FDA 1571 "FDA is concerned that physicians requesting expanded access for an individual patient may have encountered difficulty in completing Form FDA 1571 and providing the associated documents because Form FDA 1571 is not tailored to requests for individual patient expanded access." At the very least, FDA should clarify the parameters for use of individual patient INDs via Form 3296.

as short as 10-12 business days, after the submission is verified complete.⁹²

Dr. Day also contacted FDA Help Line for assistance in assembling a domperidone application and found no help other than a referral to an IRB database. His effort to gain assistance from the FDA CDER Office was not only not useful but displays how little the FDA itself understands the process and issues involved. Despite these enormous obstacles, FDA has repeatedly represented to the Committee that an Expanded Use IND is a simple means to provide ingredients they deny and they need not be concerned about unavailability.⁹³

The process is highly complex and unclear even as to what forms to use. There is confusion about Expanded Access IND vs. Expanded Access Protocol, and patient waiting periods, extreme difficulty finding an IRB panel to work with, insurmountable IRB fees shouldered by physicians, a need to hire consultant to navigate the IND process, hours of paperwork requirement for both the IRB and FDA, and no clarity about medication access assuming IND is submitted and approved.

Even after the high administrative burden, difficulty of applying for an Expanded Use IND and the need for emergency administration was raised, FDA continued to represent that this was a reasonable option and should be considered as a basis to believe that a denial of an ingredient listing on the bulk list would not deny access to the medication.⁹⁴ Staff comments to

⁹² Transcript, PCAC meeting, June 23, 2016 at 68-69.

⁹³ FDA's Dr. Jarow: "The simplest, if I was on the other side, if I was a rheumatologist who wanted the easiest, least burdensome approach, would be if someone opened up a treatment expanded access IND. That would be the least burdensome." FDA Dr. Jenkins: "There seems to be an assumption that no one is going to develop this drug for commercial use, and I don't think we should assume that to be the case...if it's not on the list, that may prove to be the incentive that someone needs to bring an application to bear." March 8, 2016, Quinacrine Discussion.

⁹⁴ Regarding Domperidone, a physician testified as to the difficulty accessing an IRB when trying to submit IND for domperidone:

FDA Dr. Rajpal: "[our form] says if IRB review cannot be accomplished, it directs them to contact the FDA Human Subject Protection Branch."

FDA Dr. Korvick: "So again, we can try to help facilitate that issue if they're working with us. We also have individual patient INDs under this program, or there are physicians who apply to enroll multiple patients if they have a clinic that has more than one patient.

PCAC Dr. DiGiovanna: "To use in the equation that the expanded IND is an acceptable alternative really suggests to me that that's coming from someone who hasn't tried to get an expanded IND."

PCAC Dr. Davidson: "Would this drug be eligible for an emergency IND?"

FDA Dr. Griebel: "An emergency IND is just another expanded access version...a single-patient IND in which the patient's in an emergency situation. You still have to have a 1572...Really the only difference is that you can submit to the IRB after the fact...The division has to scrutinize the situation to see if this is truly an emergency situation for the patient..."

PCAC Mr. Humphrey: "I do recognize that there is a clinical need for this drug, but you can get it through the IND process. I may be somewhat a little biased because of where I work, but we deal with expanded access drugs nearly every week. And while the process is cumbersome and onerous when you first do it, after a few times it gets a lot easier."

PCAC Dr. Pharm: "I feel like I'm getting confused by our own advisory committee

PCAC, Exhibit 14 in the 2016 NPRM, and the Final RFA Analysis vastly under-represent the cost and difficulty in gaining such approvals and the amount of time this would take from patient care.

A valid assessment would take into account that not all physicians practice within large, well-funded institutional settings that have administrative staff and resources to make such an application; for compounding pharmacies, it ignores that these are not patent medicines and therefore there is insufficient return to make such investments practical.⁹⁵ Even where they are possible what it would primarily accomplish is to increase the costs of such medications.

The denial by PCAC also increases the risk of denial for an application because the ingredient will have been reviewed by FDA and PCAC and have been denied, thus creating a higher threshold to overcome according to FDA's rules⁹⁶ to gain approval. In addition, FDA's own Guidance Document "Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers: Guidance for Industry (June 2016) is clear that Expanded Use IND's are not intended for unapproved drugs:

...expanded access uses are not primarily intended to obtain information about the safety or effectiveness of a drug. *Expanded access to an investigational drug can only be provided under a treatment IND or protocol ... if the sponsor is actively pursuing, with due diligence, marketing approval of the drug for the expanded access use.* Expanded access, access, and treatment use may also refer to (1) use

because I swear in previous meetings we've had votes where we voted no based on the fact that there was an IND process. I remember that being people's justification." "the conversation in the past has always been if there's a way to get it through an IND, go that route and hope for the FDA approved process to -- especially if there is such a compelling need that there are going to be providers that will be looking to create a product that's going for FDA approval."

Reference: February 23, 2015 morning session transcript, Dr. Kashoki.

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444499.pdf>

⁹⁵ This raises another economic impact on small businesses that should be addressed by FDA as part of its initial analysis required under the RFA. *See* discussion at 49-56.

⁹⁶ (b) Criteria. The criteria in § 312.305(a) must be met; and FDA must determine that:

- (1) There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and
- (2) There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

21 CFR § 312.315 (Intermediate-size patient populations.) *See* discussion at 74 FR 40900, 40944 (August 13, 2009). If the ingredient has been reviewed and rejected by FDA and PCAC, an IND would have a very difficult burden surmounting these two criteria as FDA would have already made an adverse finding about them, a detail never discussed by FDA. These criteria are also useful to note as they provide an example of how an actual criterion is crafted, unlike the four topical areas FDA is claiming are its criteria in the case of compounding approvals.

in situations when a drug has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of a similar, but unapproved drug (e.g., foreign-approved drug product) to provide treatment during a drug shortage of the approved drug; (3) use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS) for diagnostic, monitoring, or treatment purposes, by patients who cannot obtain the drug under the REMS; or (4) use for other reasons.

Expanded Use Guidance at 3. (Emphasis added).

As an unapproved drug for which the listed exceptions would rarely apply, nominated ingredients by the FDA's own description, even were the extreme hurdles toward application overcome, would likely not be approved. Further, this guidance states that the single patient IND via Form 3296 requires that the patient have a life-threatening condition,⁹⁷ greatly restricting the applicability of this provision. Many patients with debilitating acute or chronic conditions will not meet this criterion, making the broad alternative avenue suggested by FDA simply unavailable.

The IND discussion at PCAC also ignores an array of regulatory and liability issues and raises difficult questions or limitations on how a substance may be marketed to the extent that is allowed, the specific mechanism by which a medication would reach patients, how protocol for different medicines would be established, what inclusion and exclusion criteria a physician would have to develop in order to complete any type of IND, what pharmacies could participate, and who would provide the Letter of Authorization for compounding or determinations about importing rather than compounding. Product availability cannot be assumed if a drug is not listed on the bulk ingredient list. Domperidone, as an example, had been imported as a manufactured product dispensed from single pharmacy in Texas. Further, physicians and institutions face increased liability for using products under an IND rather than from an approved list. In addition, FDA has 30 days to review IND submissions, and while FDA has represented to the Committee that it may do so sooner, it can also take substantially longer.

Historically, availability of compounded drugs has been the vehicle to allow access to a wide array of medications that have valid uses but which cannot for economic or other reasons complete the prohibitively expensive formal review process, including PDUFA fees. By skewing the presumption against approval and attempting to shunt many of these drugs into IND's, FDA is creating a deep change in the historical role of compounding, closing the exception that has allowed for use that is not available in any other means, including the Expanded Use IND process that FDA has been grossly misrepresenting to the Committee.

While this issue was not noted for response in the 2019 Final Rule, the supporting Regulatory Flexibility Analysis report in this docket asked for comment about whether or not physicians would use the Expanded Use IND process. For the reasons set forth here, the answer in most circumstances is a resounding "no."

In addition to presenting its own issue, the misrepresentation of Expanded Use IND's is an example of the errors that occur when the process is not properly guided by the participation

⁹⁷ Individual Patient Expanded Access Applications: Form 3296. Guidance for Industry, June 2016 at 3. The FDA finally concedes in its Final RDA Analysis that "[f]or expanded access INDs, sponsor-investigators must show that the drug product will treat a serious or immediately life-threatening disease or condition when no satisfactory alternative therapy exists." Final RFA Analysis at 13. This was not explained in the FDA presentations to the PCAC.

of the professions that occurs through timely and accurate notice and comment rulemaking, and a proper stance of openness to the wisdom and experience⁹⁸ of the professionals actually involved in the field. At the very least, Petitioner asks FDA to correct its misrepresentations to the Committee and submit those ingredients for reconsideration that were denied based upon this misinformation.

V. Compounding Nutrients are Clinically Appropriate and Legally Proper Activities That FDA is Overturning or Ignoring Without Addressing the Impacts of its Actions.

A. FDA is Outlawing the Clinically Valuable Practice of Nutritional Compounding Without Assessing the Impacts of its Actions or Providing a Rational Basis for its Actions.

A nutrient compounding practice unrecognized and entirely overlooked in FDA's regulatory scheme is health practitioner-prescribed combinations of nutrients for the purpose of providing convenient, tailored nutrient support specific to the health needs of a patient. This has been legally acceptable but is no longer authorized for many key ingredients without any recognition of the clinical impacts of this issue. This practice that does not appear to be on FDA's radar. The impact of this is even greater given FDA's apparent reversal of prior statements that compounding pharmacists could at least use finished, off-the-shelf dietary supplement products in compounding products. At the November 2017 and September 2018 PCAC meetings,⁹⁹ FDA now states that even this is not allowable, leaving patients in need for

⁹⁸ Dr. DiGiovanna: "To use in the equation that the expanded IND is an acceptable alternative really suggests to me that that's coming from someone who hasn't tried to get an expanded IND." From discussion on Domperidone, October 2015 "Are we trying to convert every potential compounded drug into an IRB roadmap where that's the only way that they are available?" PCAC discussion on Quinacrine Hydrochloride, March 2016.

⁹⁹ MS. DAVIDSON: Or a prescription medication for an individual patient, could the pharmacists go use a dietary supplement, not the pure bulk substance, but a dietary supplement, as the source of the compound? I believe Jane Axelrad told us that that was the case in a previous meeting.

MS. BORMEL: If you're purely compounding something as a dietary supplement --

MS. DAVIDSON: No. It would be a prescription medication.

MS. BORMEL: Then the substance that you're using has to be on the bulks list.

MS. DAVIDSON: That is a significant detour from our previous understanding, and I can pull up our notes.

MS. BORMEL: I don't believe so, but we can look at that. But I remember the discussion several committee meetings ago about what happens if a pharmacy wants to compound a dietary supplement from dietary supplement ingredients. Our jurisdiction is only over the compounding of a drug product under 503A. And under 503A, we have a scheme set out that you have to use bulk substances that are components of FDA-approved products subject to an applicable USP monograph or on the bulks list. It's talking about making a drug product, but when you use something that is available as a dietary supplement over the counter and you're compounding it to make a drug product, that ingredient has to be on the bulks list or subject to an applicable USP

special formulations with no options. It is best done by a licensed compounding pharmacy who has the proper skill and establishment, rather than under a food establishment license.

Many compounded nutrients are given for the same reason as a consumer would take a supplement under DSHEA rather than for a drug indication. Such compounding addresses important health needs. It promotes convenient use and, in some cases, may include some prescription items as part of an overall treatment and support approach. Patients may require compounded ingredients due to allergens in products, difficulties consuming whole foods or specific kinds of foods or benefit from dietary supplementation which provides nutrients otherwise not readily available due to special or limited diets. Creating mixtures of formulated dietary supplements can increase patient compliance, maximize synergistic effects and assist in treating difficulties with absorption or other digestive issues. They may be prescribed because a school of medical or naturopathic thought, taught in properly accredited educational programs, is of the view that nutrients can themselves have functional or therapeutic effects. There are all appropriate and safe practices.

FDA has evidenced no awareness of such practice, and the process of review by indication does not allow reasonable consideration of these methods of using compounding as a legitimate activity. Making customized dietary supplement compounds for oral consumption based upon a physician script is a legitimate state-authorized act that is being disturbed without consideration of the activity.

The rejection of the USP dietary ingredient monographs generally, and of specific dietary ingredients specifically as this process moves forward, is eliminating this entire method of practice. There has been no discussion in the CPGs, federal register, PCAC briefing documents or in the PCAC meetings about this practice. Compounding pharmacists have historically been free to compound items listed in any USP monographs and this is an important practice that should continue. FDA's restrictions on access due to concern that physicians may use a dietary supplement for a therapeutic purpose ignores areas of medical and naturopathic practice outside of FDA or PCAC's expertise. Physicians with training and experience in such use, whether because of unique assimilation issues patients have or because of anticipated therapeutic effects which, as noted, are often taught in Category I CME ACCME recognized courses and should be legally allowable without each nutrient having to go through drug-based levels of scrutiny.

B. Nutrient Compounding is an Appropriate Activity Under State Law.

Pharmacists compound oral dietary supplements according to the standards set out in the USP dietary supplement monographs and in compliance with state law. A state licensed pharmacist is widely allowed by state law to compound nutraceutical substances, are qualified by training to do so, have facilities appropriate to the task. It is done routinely and a significant part of some pharmacies' practice. Pharmacy facilities have the capacity to work with bulk dietary supplement ingredients, many of which are compliance with USP Monograph specifications, which are safe and manufactured in GMP-compliant facilities. Compounded nutritional products, unlike OTC dietary supplements sales, are prescribed by a physician and taken with supervision and thus provided this additional safety factor.

monograph, or has to be a component of an FDA-approved product. I don't think that's ever changed.

November 20, 2017 a.m. transcript at 152-153.

C. The Interference in State Compounding Practices and the Practice of Medicine and Pharmacy is Particularly Egregious with regard to Compounding Dietary Ingredients.

Dietary ingredients compounded for oral use are not the manufacture of a drug and widely allowed under state law. Compounding dietary ingredients for oral use are not provided for a different route of administration than intended and within the intended reach of dietary supplement regulation allowing for such use. As compounding is not manufacturing, allowing dietary ingredients to be compounded to meet the specific nutritional needs of a physician's patient would be more consistent with the overall scheme of drug and supplement regulation.

Particularly because dietary supplements are available over the counter, the removal of these ingredients from the positive list directly interferes with the practice of medicine. *See Linder v. United States*, 268 U.S. 5, 18 (1925) (direct control of medical practice in the states is beyond the power of the federal government). The Food, Drug and Cosmetic Act "disclaims any intent to directly regulate the practice of medicine." *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 350-51 (2001). Where state pharmacy boards allow the practice, Petitioner's ask FDA not curtail the practice, either intentionally or inadvertently.

While FDA is concerned that a substance may present some risk, FDA may be harming the patient by compelling access outside of the physician-patient relationship and without the help of an educated pharmacist. Ironically, safety risks will increase. At very least, the patient is compelled to use a product that may not precisely fit their specific needs, in contrast with the compounded product.

Where a physician prescribes an ingredient from a compounding pharmacy for a functional or therapeutic purpose, FDA is seeking to apply the customary intent element to determine that the product is a drug. Disallowing compounding of an otherwise legal product is an extraordinary step that requires direct findings on the issue. FDA is determining that because these ingredients are prescribed it is appropriate for it to assert jurisdiction and eliminate an important, historically state authorized practice. Petitioner asks FDA not to act upon this position without engaging in fact-finding about the practice, rather than basing its view on the technical distinctions of how it regulates a "drug" versus a "dietary supplement" as a basis to disallow a state regulated form of compounding practice rather.

VI. FDA's Recognition that it's Rule Will Have a Significant Impact on Small Businesses under the Regulatory Flexibility Act Requires it to Use Means that Minimize the Economic Disruption of Compounding Practice While Meeting Legitimate Public Health Goals, Which it Has Not Done.

Petitioners appreciate that the FDA Office of Planning in the Office of the Commissioner has now recognized that the 2019 Final Rule will have a significant impact on small business under its required analysis pursuant to the Regulatory Flexibility Act (RFA) (5 U.S.C. §§ 601-612). Final Regulatory Impact Analysis Final Regulatory Flexibility Analysis and Unfunded Mandates Reform Act Analysis (hereinafter "Final RFA Analysis") at 3, 15. *Cf.* 2016 NPRM, 81 FR at 91081 (Proposing that it would not have a significant economic impact). Given this finding, it is incumbent on FDA to provide "a description of the steps the agency has taken to minimize the significant economic impact on small entities consistent with the stated objectives of applicable statutes, including a statement of the factual, policy, and legal reasons for selecting

the alternative adopted in the final rule and why each one of the other significant alternatives to the rule considered by the agency which affect the impact on small entities was rejected.” 5 U.S.C. § 604(6).

A. The FDA Has Not Identified a Market Failure Requiring Resolution.

Given the Agency's position that it cannot certify no significant impacts on small businesses, it must demonstrate a market failure requiring Agency action. In its Final RFA Analysis, the Agency argues that the difference between the new drug approval process and the regulation of compounded drugs requires that it take additional regulatory action. The difference between these two regulatory pathways was set forth by Congress; it is not a defect, it is by design. The Agency next says that it must change historical use to resolve an information asymmetry between consumers and the Agency, an issue discussed *infra* at 69-71, that is not sensible for prescription items that are not available for selection by consumers. That the ingredient review process is disconnected from the NECC and other contamination issues is addressed *supra* at 51-53. The FDA has offered no findings of actual harm by the use of ingredients merely because they are subject to professional disagreements between FDA and Petitioners' and other medical professionals. The FDA has offered no basis upon which there is a market failure requiring this Rule.

B. The Agency has Not Fulfilled Its Obligation Under the RFA to Explain its Rationale and Consider Alternative Means With Less Economic Impact.

FDA's sole effort to address its obligation under the RFA was to discuss considerations with regard to one ingredient, tranilast, which it had considered for possible recommendation for topical use only. Final RFA Analysis at 15. FDA is completely silent on the other ingredients in the 2019 Final Rule, but of greater import, offers no comment on regulatory alternatives to its reset of the entire field contained in the 2019 Final Rule. FDA has thus failed to meet its obligations under the RFA. It has adopted criteria in the Rule and its ongoing decision-making that create strong presumptions against the inclusion of over 420 ingredients. Responding to this point, which Petitioners made in their comments on the 2016 NPRM, the Agency says that it disagrees:

with comments suggesting we include the full costs of the criteria for all nominated bulk drug substances in the economic analysis for this rule. *We recognize that the criteria we use to evaluate bulk drug substances for the 503A Bulks List will affect the markets for bulk drug substances considered in future rulemakings.* However, we cannot predict how the criteria will affect which bulk drug substances will be on the 503A Bulks List in the future.”
Final RFA Analysis at 4 (Response 1) (Emphasis added).

The inability to predict the economic consequences of a rule and set forth the economic costs is moot now that the Agency has acknowledged that it cannot certify the Rule will not have a significant impact on small businesses. Given that, FDA has an obligation to consider alternatives to the entire Rule, not one ingredient. That Agency acknowledges that the Rule will affect markets and that its criteria in this Rule includes the methods by which decision-making is going forward and thus the impacts must be addressed as required under the RFA. That the

economic costs are uncertain does not relieve the Agency of this obligation. Inability to predict the scope of economic impact is not a shield allowing the Agency to exercise discretion without looking for regulatory alternatives, especially where it has acknowledged that its actions will disadvantage the compounding industry while favoring pharmaceutical manufacturers. *Ibid.* The FDA has a statutory obligation pursuant to 5 U.S.C.S. § 609(d)(2) to consider alternative means to making decisions about inclusion on the bulk ingredient list, which is within the scope of the 2019 Final Rule. It has not done so.¹⁰⁰ As part of correcting this, Petitioners ask FDA to follow the provisions of the RFA and notify the Chief Counsel for Advocacy of the Small Business Administration (SBA) detailing information regarding the economic impacts for an independent assessment of the Agency's actions.¹⁰¹

As but one consequence of FDA's actions, compounding pharmacies have discontinued manufacture of many of the ingredients FDA and PCAC have recommended be withdrawn even though they have not been noticed as proposed rules in the Federal Register. This is occurring both because FDA inspectors are citing pharmacies in Form 483 write-ups on some ingredients even though they are still under a safe harbor and because of the legal liability resulting from compounding of ingredients FDA has listed for denial. Of the total nominated ingredients, the List 1 and List 3 ingredients constitute well over 300 ingredients. This limitation is effectively in force now and already having economic impacts.

C. The FDA Economic Analysis Minimizes the Nature and Extent of Economic Impacts and Fails to Address its Required Consideration of Alternative Means of Regulating Compounded Drugs.

There are a number of alternatives means of regulating the field that would have less adverse economic and health impacts. These alternatives would include adopting proper criteria that do not undermine the economics of the industry and patient care, dedicating greater resources and participation FDA's review process, and at the very least an analysis of the comparative costs and benefits of use. While physicians, pharmacists and suppliers who use these ingredients are better informed than the Agency has presumed to be the case in the absence of any finding on the matter, Agency concerns about specific ingredients can be addressed through the less restrictive means of communication by FDA to physicians, bulk ingredient

¹⁰⁰ The failure to perform a proper regulatory flexibility analysis is not harmless and has to be corrected. *See for e.g. U.S. Telecom Assn*, 400 F.3d at 41 and the cases cited therein. Upon the final rule that FDA, small businesses will be entitled to judicial review pursuant to 5 U.S.C. § 611. The available remedies for the violation of the RFA include:

- remand the rule to the agency
- defer the enforcement of the rule against small entities.
- stay the effective date of any rule or provision thereof under any other provision of law or to grant any other appropriate relief

5 U.S.C.S. § 611(a)(4).

¹⁰¹ A certification of small business representatives is required to be involved in the process to minimize impacts, 5 U.S.C.S. § 609(b) which was not done because the analysis was limited to the six ingredients listed in the 2019 Final Rule. That same law requires the Agency to obtain advice and recommendations from affected small businesses, which was not done because the analysis was limited to a few ingredients and the overreaching restrictions on an entire industry created by the actual criteria in place was not considered.

suppliers and compounding pharmacists using available means other than labeling. Such lines of communication are already in place, as bulk ingredient suppliers include notices of concerns in their bulk shipments to the compounding pharmacies, physicians and compounding pharmacists are aware of and can track interactions and do inform patients. Compounding pharmacists can include patient information leaflets informing patients of a concern, such as interactions between 5-HTP and SSRIs. State laws, in fact, generally place responsibility on the compounding pharmacist to ensure that the patient understands how to use the drug.¹⁰² Interactions or other safety information of concern can be including in interaction checker software.

As a matter of health policy, an important question is at what point in the chain of supply presents the most effective point to alert patients and the public about such concerns. Grapefruit juice, for example, does not have to carry a warning label about its interactions with atorvastatin (Liptor), felodipine (Plendil), ranolazine (Ranexa) or hundreds of other drugs. The appropriate point of information for the patient about potential interactions is from their medication prescriber and dispensing pharmacist. In the case of dietary supplements, such as 5-HTP, the proper point of education about any potential for serotonin syndrome would be from the prescriber of the SSRI. In the case of compounding 5-HTP, the physician prescriber and the compounding pharmacist would be aware of and able to check for and follow any possible side effects. Compounding pharmacists, as par of state law pharmacy requirements, provide patient leaflets that give patients such information. This system could be enhanced, if needed. In extreme cases, FDA could use special controls such as the Risk Evaluation and Mitigation Strategies (REMS) guidance, 21 USC § 355-1, currently applicable to 503B outsourcing facilities. 21 USC § 353b(a)(7). This could be done by rule and would allow access while providing information to ensure safety issues raised by FDA can be kept in mind. Despite the REMS program having been raised by PCAC members, *see for e.g.*, Transcript November 20, 2017 p.m. at 121-22, 140, it has not been adopted in any recommendation to-date nor in the RFA analysis. There is no evidence that FDA has considered these alternatives.

As part of addressing these alternatives in more detail, a better understanding of the economic impacts than offered in the Final RFA Analysis is helpful. While Petitioners understand the difficulty forecasting the economic impacts of the Rule, there are a number of clear impacts FDA has not addressed.¹⁰³ Many of Petitioner's concerns about the underestimates of economic impacts are now moot given FDA's recognition that it cannot certify the Rule under RFA but understanding some of these impacts better frames the need and nature of regulatory alternative Petitioners ask FDA to consider.

First, FDA now recognizes that the costs to nominators has been significant, Final RFA

¹⁰² *See for e.g.*, Wisconsin: Wis. Adm. Code Phar 15.10. Patient training. A pharmacist is responsible for documenting the patient's training and competency in managing the type of therapy provided by the pharmacist to the patient if administered by the patient or a caregiver. A pharmacist is responsible for the provision of or supervision of the patient training process in any area that relates to drug compounding, administration, labeling, storage, stability or incompatibility. A pharmacist shall be responsible for seeing that the patient's competency in the above areas is reassessed on an ongoing basis.

¹⁰³ During an initial review, the OMB noted that "FDA has not been significantly involved in the regulation of pharmacy compounding and does not have any economic data on the industry at this time. FDA needs to work with OMB and develop a proper analysis and response to the economic impacts of this regulation and Guidance." *See* 65 FR 73302, 73362 (November 30, 2000)

Analysis at 11-12. While still underestimating the costs, for example making the astonishing estimate that some nominations took just 0.5 hours and without consideration of the costs to nominators preparing and traveling to FDA for PCAC meetings among many other expenses, the issue is ultimately the quality of information that could realistically be presented to the Agency. Unlike pharmaceutical companies, which have enormous budgets and financial incentives to prepare clinical materials, Petitioners organizations are primarily dependent upon the clinical expertise of physicians who are extremely busy with patient care.¹⁰⁴

The burden created by FDA's approach creates an asymmetry between the data available for review and the standards employed by the Agency. Petitioner McGuff CPS Pharmacy, one of the larger 503A compounding pharmacies, as an example, is a small business that noted in its comments, "[t]he Agency has requested information for which no one particular pharmacy, physician or physician organization can easily assemble and must be sought through coordination with the various stakeholders. To collect the information required is a time-consuming process for which many practicing professionals have indicated that the time allotted for comment to the Docket has been too limited."¹⁰⁵ Despite allowances for additional time, this has created a bias against fair consideration on economic grounds.

While Petitioner recognizes that the Agency has clearly committed staff resources to ingredient review, the submission requirements and review process stand in contrast to the Agency's commitment of resources on similar issues. For example, to accomplish the DESI review program, the Agency contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. Unlike the compounding industry, most pharmaceuticals under review were manufactured by pharmaceutical companies with far greater resources and financial incentives to seek regulatory approvals. An alternative means the Agency might have considered is contracting for additional technical and practice support, as it did on its OTC review, rather than shifting so much of the nomination burden onto the industry and professions. FDA might have recognized that the impacts that burden would place on the nature and depth of information that could be provided as it set its thresholds for review, including attention to physician's clinical experience.

Second, FDA has briefly noted that there will likely be economic costs from displacement to the therapies it prefers but has not noted lost treatment opportunities in the form of lost productivity, added health care costs, malpractice actions and other costs resulting from the loss of previously available drugs. We recognize the Agency has confidence that it has not excluded effective drugs, but as we have set forth in detail, FDA is making a risk assessment based on the evidence before it and the presumptions include a disregard for the treatment failures and adverse events of medications to which it intends to limit physicians. FDA's

¹⁰⁴ This is not simply an issue under the RFA; the Agency has placed an unreasonable burden on already overtaxed health professionals to provide the voluminous information necessary to support the nomination of bulk drug substances. The approach has no basis in the purpose and language of the Act. Given that many of the persons most knowledgeable about and experienced in the application of compounded medications are either small business owners or over-burdened clinicians, the manner in which FDA has created the nomination process itself, as well as the criteria it has imposed internally, is unreasonable and has not led to a productive consideration.

¹⁰⁵ McGuff Pharmacy letter to FDA dated September 30, 2014, reproduced in FDA PCAC Briefing Materials dated October 27-28, 2015 at 27.

confidence that this process is more reliable than the clinical judgment of physicians seeking to provide functional support to patients with chronic conditions is misplaced and cannot support ignoring downstream health costs due to lack of access to these drugs. The reduced availability of compounded medications will cause increased costs due to shifts toward more expensive pharmaceutical drugs, as well as lowering price pressures on approved drugs. In addition to calculating the costs upon the pharmacy industry, the economic impact of removing compounded drugs from the market on patients and their insurers in higher costs of prescription pharmaceuticals, which often are long-term requirements to manage chronic conditions, should be considered as part of an analysis of the economic impact of FDA's actions.

Given these concerns, one regulatory alternative would have been to first understand the spectrum of use of compounded medications, including how they are used for metabolic and functional support and whether they are used adjunctively, rather than reducing its consideration to the single ingredient tested against discrete disease entity model. Another regulatory alternative would have been to include the limitations on effectiveness of the approved alternative medication and its adverse effects so as to be able actually weight the economic and health impacts of criteria that remove ingredients from the market, which, while a seeming prerequisite to the decision-making FDA has undertaken, was not done.

Third, physicians not only face lost business but have to take the time to find replacement medications and modify protocols that have been well-established. In many cases, physicians have taken special training in the use of medications, some attending certification programs in ingredients that may no longer be available.¹⁰⁶ Ingredients that are physiologic treatments simply cannot be replaced; physiology is simply what it is. Such costs could include physician retraining, diverted expenditures into other pharmaceutical markets or increased health care costs due to failure to prevent or treat disease. The disruption of methods of treatment are not trivial and while FDA is aware of the profit-shift to pharmaceutical manufacturers, Final RFA Analysis at 14, the effects on the medical and naturopathic professions have not been acknowledged by FDA it has not considered these economic and health effects.

Fourth, an error that has pervaded the decision process is FDA's misrepresentation that the Expanded Use IND process is a reasonable substitute for approval. As discussed at length, *supra* at 54-60, the burden of such an application creates a very high barrier to its use at the expense of patient care. While the Final RFA Analysis attempts to improve its grasp of the financial burdens and limits of IND as an alternative approach, the report continues to radically overestimate the availability and underestimate the costs of an IND application. Final RFA Analysis at 13-14. The report ultimately concludes it does not have enough information to project costs, even though this is uniquely within the ambit of the Agency that works with physicians to review them. The error Petitioner asks FDA to correct in this instance is offering the Expanded Use IND as an alternative means of access as part of its RFA analysis and as part of influencing PCAC decisions.

Errors in the Final RFA Analysis include basing its estimates that completing a Form

¹⁰⁶ To make sure a central point of this Petition has been made, physician members of Petitioners' organizations do not generally agree with the proposition that SSRI drugs are the optimal choice for patients with depressive symptoms, that COX-2 inhibitors are the best choice for patients with arthritis or other similar determinations being made by the Agency. FDA's foray into practicing medicine and imposing these choices upon trained physicians not only has consequences on the quality of care but economic consequences on the costs, financing and outcomes of therapy that have not been considered.

3926¹⁰⁷ would be \$166.14 per patient, so gross an underestimate that it is difficult to find a good faith basis for it. Form 3926¹⁰⁸, as just one matter, is only appropriate if the physician only wants to give the drug to one patient.¹⁰⁹ FDA Guidances make clear that intermediate size populations require the far more extensive form 1571 or 1572 pursuant to 21 CFR §§ 312.315 or 312.320, forms which are estimated to take 40 to 80 hours to complete. Petitioners addressed this in our comments but the Agency took no notice. These forms require IRB approval, a sponsor, justification statement, numerous regulatory checks on investigators, facilities, environmental impacts and first require extensive research and review of regulations and guidance documents to determine what is applicable. It is a significant and largely prohibitive investment of time; the FDA analysis continues to be wildly inaccurate.

Given the odyssey described by Dr. Day in an effort to get an IND for domperidone described *supra* at 55-58, there is considerable groundwork that would have to be done. The physician would first have to draft a basis for Institutional Review Board Approval, requiring human consent consistent with 21 CFR Parts 50 and 52 as well as a setting out a protocol that may have to include inclusion and exclusion criteria or at least compile clinical data showing a basis for use. IRBs are generally only available for physicians practicing within an institutional setting, where layers of approval might first be required. The FDA's analysis does not take the real costs of developing an Expanded Use IND into account, and the short answer to FDA's question about whether physicians would use this process is only in extraordinary circumstances given that the costs of obtaining such INDs are prohibitive. The Agency's estimates are wildly inaccurate and will discourage most physicians from being able to provide this care for their patients.¹¹⁰

To require each physician in the US with an interest in a denied ingredient to attempt to undertake these hurdles is unrealistic and an enormous waste of critical and limited resources that are not accounted for in the RFA analysis. Expanded Use INDs are not a reasonable alternative, and while not formally stated as an alternative analysis it is set forth in the Final

¹⁰⁷ Assuming this is the correct form, contacts with FDA staff trying to determine if FDA Form 1571, 1572 or 3926 were the correct form, as noted *supra*, did not lead to a clear decision. See discussion *supra* at 56.

¹⁰⁸ Individual Patient Expanded Access Applications: Form FDA 3926, Guidance for Industry. June 2016.

¹⁰⁹ A physician who wishes to use 5-HTP for a subpopulation of depressed patients, for example, would need to complete a different form 3926 for every patient and it is unclear whether this would be acceptable as this might in fact be an intermediate size population. Even more restricting, the FDA Guidance states that the Expanded Use IND for individual patients is only available where the patient is suffering a life-threatening condition, making this use uncertain at best and eliminating its use in many contexts. It should also be clear that even were it true that Form 3926 was sufficient and it only took 45 minutes per patient, if a physician wanted to treat a subpopulation like depression with a compounded version of 5-HTP, if it were true that adding 30-45 minutes to each patient would suffice, the exercise serves no actual purpose but makes the exercise prohibitively expensive as a practical matter.

¹¹⁰ The regulation is not cost-neutral, and also appears to be a violation of Executive Order 13771 (January 30, 2017) Section 2(b), which requires proper certification that the net effect of regulations will be cost neutral, or if not, per Section 2(c), any costs shall be offset.

RFA Analysis as an option for denied ingredients. But the Agency's description of this alternative is not accurate. This is even heightened for ingredients that have been reviewed and not listed by FDA and PCAC, as that denial makes IND approval unlikely. Were ingredient reviews done properly, ingredients that would be approved under an IND should have been approved in the PCAC review process. Physicians and pharmacists should have reasonable discretion without bureaucratic obstacles that would have to be replicated at every site, a result which does not have a reasonable justification. If the Agency believes that Expanded Use IND's would offer additional protections that are necessary, those protections could be put in place under REMS or other special controls such as informed consent requirements that would be a less onerous approach economically and clinically.

D. The Agency Rationale Based On Information Asymmetry with Consumers is Completely at Odds with the Regulation of Prescription Items.

The Agency's rationale stated in its Final RFA Analysis confirms that the Agency is basing its determinations on concerns about consumers choice and an information asymmetry between information held by FDA and consumers of compounded drugs. This is an inappropriate standard given that compounded drugs are prescription items selected by the learned intermediaries of the physician and compounding pharmacist. The Final RFA Analysis describing the reason for FDA's Rule begins with this discussion:

The availability of drug products compounded using these bulk drug substances may lead consumers to believe that we have approved these compounded drugs. Because we have more information about the bulk drug substances used to compound drug products than the average consumer of the compounded drugs, an information asymmetry may exist between us and the average consumer. With an information asymmetry, consumers may make choices they would not have made if they were better informed. Without this final rule, consumers may not have access to information about bulk drug substances that might influence their choice to use compounded drug products. Moreover, section 503A, which the DQSA clarified is applicable nationwide, directs us to create the 503A Bulks List by rulemaking. This final rule will fulfill this statutory requirement
Final RFA Analysis at 6.

This rationale undergirds essential errors Petitioners have detailed throughout this Petition; FDA is treating compounded medications as if they are OTC products and a matter of consumer choice. Yet there is no information asymmetry to account for between the FDA and the consumer as the consumer is a patient of a trained physician. This Petition is filed on behalf of thousands of physicians well-trained in the use of these ingredients and an information asymmetry between themselves and FDA is not grounded in fact. FDA has made no inquiry or findings into whether professionals misunderstand the risks, benefits and proper uses of compounded drugs, yet FDA has predicated its entire approach on that presumption.

The Final RFA Analysis continues to frame the selection of prescription items as an issue of consumers making choices based upon the allegedly incomplete advice of their prescriber:

Consumers choose compounded drug products based on the advice of their prescriber because the consumer may prefer these drugs to alternative treatments.

However, consumers may have incomplete information about the risks and benefits of the compounded drug product. We expect that the final rule will indirectly provide consumers with additional information about the risks and benefits of the compounded drug product. Once consumers and their prescribers become aware of this additional information, consumers may prefer alternative treatments to the compounded drug product. If consumers and their prescribers opt for alternative treatments, these alternative treatments may be safer or more effective than drug products compounded using the bulk drug substances. These consumers may experience better health outcomes than they currently experience with the compounded drug product. Such consumers will benefit from the final rule.

Ibid.

Petitioners' organizational members are in fact trained in and aware of the risks and benefits of these ingredients. Their information is not based on the incomplete literature reviews and criterion heavily weighted against compounded ingredients in use by FDA but on the decades of actual shared clinical experience noted throughout this Petition. While informed patient involvement is a key principle in the practices of Petitioner's organizational members, framing the issues as a matter of consumer choice is contrary to the very definition of a prescription drug as one that cannot be adequately labeled to allow consumers to make such choices. Petitioners note that there are profound differences of professional viewpoints between themselves and FDA, and to the extent that the information asymmetry between FDA and physicians using ingredients is at issue deserving of additional discussion, that is the only issue and the issue of consumer choice is ill-framed.

FDA could take steps to promulgate consent requirements as a less economically adverse means of addressing its concerns, but as a threshold matter must correctly identify the proper regulatory context. These are ultimately decisions that are made by or with the physician. As the Agency itself frames the prescription requirement:

One important regulatory distinction between OTC and prescription drug products involves the requirement for "adequate directions for use." All drugs must have labeling that bears "adequate directions for use." Prescription drugs, however, by definition, require the intervention of a licensed healthcare professional. Since these products require the intervention of a healthcare professional, also known as a "learned intermediary," "adequate directions for use" for OTC drug products should not include those uses which require a prescription.¹¹¹

The concern FDA has about proper labeling of compounded drugs is contrary to the statutory scheme of prescription drugs, which by definition means that they cannot be properly labeled for consumer choice and require a physician as a learned intermediary. FDA is using the very fact that the statutory scheme relied on the physician, rather than labeling, as a basis in and of itself to deny ingredients. It is doing this by holding, inaccurately and without any finding, that physicians are unable to understand the use of these products. To the extent that such

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https://www.accessdata.fda.gov/scripts/cder/training/otc/topic2/topic2/da_01_02_0090.htm (last accessed March 3, 2019).

concerns were true, the public would be better served if that was addressed directly rather than erecting consumer protections arguments inconsistent with the statutory scheme that has skewed this entire process.

Physicians who use natural ingredients have generally learned these techniques at seminars for which they have been granted Category 1 CME credits, which requires significant peer review, submission of evidence-based data and compliance with ACCME criteria. These reviews are based upon actual clinical use and experience, not by the narrow and incomplete process used by the Agency. Compounding pharmacists have extensive training and resources, including standards and reference materials from the bulk ingredient suppliers that also inform these choices. The difference between the acceptance of these therapies for CME credit and acceptance within state pharmacy practice is that FDA's findings reflect a difference in professional viewpoint and of the decision-making criteria employed rather than a clear and objective finding. It also reflects differences in the paradigm in which practice is viewed. While denying that it is overstepping into the practice of medicine, 84 FR at 4707 (Response 34), the FDA RFA Analysis intentionally sets forth the Agency's effort to direct choices within the treatment room:

[W]e expect that consumers who choose an alternative treatment will benefit from using treatments that may be safer or more effective. These consumers will also benefit by not using a treatment that, based on the evidence considered, is not safe or effective. If the health benefits are larger than the loss in utility, then these consumers will benefit from the final rule. If the loss in utility is greater than the health benefits, then these consumers will incur negative benefits from the final rule.

This is premised on the false assumption that patients are all in the same position with regard to treatment response, which is clearly false; that FDA has conducted an evaluation of the respective risks and benefits of compounded drugs and the alternative pharmaceutical option, which it has not; that medicine may only be practiced based upon literature reviews rather than medical experience, which is a crippling standard; and that the process FDA has conducted places it in a superior position to guide physician treatment choices. For the reasons outlined in this Petition, we ask the Agency to take a broader view of the important role that the ingredients nominated for the bulk list offer for patient care.

VII. Petitioners' Requests

Docket Creation

Petitioners' request that FDA promptly open a public docket and maintain it for open comment until at least such time as the Agency's provides a formal response with a time period of at least 180 days or until the Petition is addressed by the Agency, whichever is longer, for the public to respond to FDA's position on the Petition.

Petitioners' Proposed Criteria

In addition to reissuing a Notice of Proposed Rulemaking that gives notice of the actual criteria FDA is applying to ingredient nominations, Petitioners request that FDA consider the following criteria as more appropriate:

- A disease indication is not required where there is an historical or appropriate functional use; an ingredient nominated to fulfill a functional use shall be evaluated solely on whether it is safe and has a clinically valid use; following reconsideration, nominators should be given an opportunity to resubmit ingredients FDA still intends to deny inclusion on the positive list.
- An ingredient that has historically been in use to an extent that is significant in the context of the specialty or community of physicians conducting similar treatment for the indications for use should be listed unless there is reliable evidence that the ingredient presents unacceptable concerns for adulteration or adverse reactions.
- Ingredients that present a significant risk of adulteration will not be listed unless there are reasonable controls that reduce these risks to acceptable levels.
- The fact that an approved ingredient already exists for a proposed indication will not lead to the denial of listing where there is any reasonable evidence for effectiveness, including competent medical testimony, case studies or support from professional associations unless it is found that the nominated ingredient has clearly established adverse effects that make the option of its use unreasonable in the patient populations in which it is used; review shall include consideration of whether the approved medication offered as an alternative to the nominated ingredient leads to a complete cure or remission of illness or otherwise fully addresses the disease classification without significant adverse events, FDA would not accept an NDA for the indication and a review of the proposed reasons why the compounded ingredient should be available is not supportable .
- If the use of a nominated ingredient is taught in seminars that have received Category 1 CME credits, there should be a presumption in favor of inclusion on the bulks list.
- Consideration of an ingredient will include recognition that it may be used in combination with or adjunctively with other drugs rather than instead of an approved medication.
- Unless there is clear evidence that use of an ingredient as a dietary supplement has led to significant adverse events, there should be a presumption that an ingredient will be placed on the bulks list at least for oral use, and denied IV use only with cause.
- The review of an ingredient that is GRAS should have a presumption of safety for placement on the bulk ingredient list at least to the extent of dosage a found to be GRAS.
- Ingredients that are analogs of physiologic compounds will be presumed to be allowed for all compounding uses unless shown to have risks unreasonable risks that cannot be managed

- Ingredients subject to a USP dietary supplement monograph ordered for use for functional or dietary purposes be allowed if consistent with state law.

- Items on List 3 will be granted a safe harbor until proper criteria are in place, notice and comment is given, and an opportunity to correct deficiencies in the nomination are resolved. Items that are clearly used for functional purposes will be changed from List 3 to List 1.

These criteria will allow physicians the choice to use, and patients the benefits of receiving ingredients that have been seen by the professions as historically benefitting patients without undue incidents.

In addition, Petitioners ask FDA to:

- Involve the professions more directly in the review process to understand the rationale and methodology of the use of nominated ingredients including determinations that consider that some uses are adjunctive and situations in which compounded medications are used because approved drugs resulted in treatment failures and which considers the rights of patients to give informed consent and have choices in their care.

- Devote additional resources to understanding the nature, use and rationale for compounding for 503A pharmacies, similar to its contract with the University of Maryland work on 503B ingredients that includes support for review of comparative benefit and safety with approved drugs.

- To the extent that consideration of approved drugs for an indication remain a criterion, FDA consider and inform the PCAC Committee of the adverse event reports on the approved drugs offered as fulfilling the role of proposed ingredients and other such information as will allow proper decision-making.

- Inform the PCAC Committee that obtaining an IND is not a reasonable alternative to placing an ingredient on the positive bulks list and reconsider those ingredients that were denied and reconsider its RFA analysis given that it inaccurately states the legal and economic restrictions upon use of INDs as an alternative.

- Where there are in fact documented significant adverse effects but a reasonable clinical use is shown, communicate those concerns through the supply and health care system, or, in extreme cases, uses REMS strategies to ameliorate those risks.

- Once proper criteria are in place, FDA should reconsider with the PCAC Committee all published or recommended ingredient denials in the light of new criteria and proper information.

- Once proper criteria are in place, FDA should reach out to nominators for additional submissions.

- FDA prepare an RFA analysis that addresses the actual market failure it is addressing, alternatives it considered to its entire regulatory approach including the actual criteria it is applying, and corrects its approach to prescription items as consumer choices.

HEARING REQUEST

If these matters cannot be addressed directly by the Agency, Petitioners' respectfully ask FDA to hold an administrative hearing on:

- 1) the issues with the administrative process raised in this Petition.
- 2) specific ingredients that have been proposed for denial.

ADDITIONAL REQUESTS

Petitioners' respectfully request, in addition, that:

FDA work with the Office of Management and Budget and Petitioners to more accurately determine the costs and alternative means to address its concerns with the use of compounded ingredients in medical care, the compounding industry, the medical and naturopathic physician communities.

FDA work with the Chief Counsel for Advocacy of the Small Business Administration to more accurately determine the costs and alternative means to address its concerns with the use of compounded ingredients in medical care, the compounding industry, the medical and naturopathic physician communities.

VIII. Conclusion and Request for Relief

In its pursuit of a significantly curtailed compounding formulary, FDA has made numerous errors of law as well as policy; it has denied consideration of functional uses of ingredients as an entire class of care, not provided adequate administrative notice and an opportunity for comment on the actual criteria it is in fact using for a drug's inclusion on the 503A Bulk Ingredient List, adopted standards that leave the Agency unfettered discretion contrary to the requirements of the APA, claims to offer a balanced approach but fails to consider the limited benefits or adverse affects of the approved drugs it offers as the remaining alternatives or that ingredients may be used adjunctively, based its rule on consumer choice within a regulatory framework for prescription medications, failed to properly offset its conflicts of interest under PDUFA, failed to set forth a case for market failure that needs to be resolved, failed to explore alternative means to minimize economic impacts under the RFA and improperly relied upon Expanded Use INDs as an alternative approach inaccurate on the law and with an inaccurate economic assessment. Petitioners view these actions as contrary to law.

The approach the Agency has taken has led to standards that are not justified or good policy. The actual criteria are poor science, anti-competitive and do not serve the public health. FDA has discounted the expertise of physicians prescribing these ingredients and rejected entire approaches to care recognized by appropriate accreditation bodies and authorized under state law according to practice principles and methods FDA has failed to consider. The resulting policy decisions the Agency is making are of great concern to Petitioners. We respectfully submit that decisions being reached, such as directing physicians to use medications with significant known risks over compounded medications with minor or theoretical risks, is contrary to FDA's mission.

Our recommended criteria are consistent with public health and safety. The lawful practice of pharmacy compounding, which includes compliance with state laws and best practice, is an important part of the health care system. While the Agency appears to believe that reassuring the public that it is addressing safety concerns about compounded medications requires aggressive limitations on allowed ingredients, the experience of Petitioners is that these actions will undermine important functional support and treatment. These difficulties have been very widely recognized and raised with FDA by numerous medical and other professional associations and industry health care organizations. Petitioners ask the Agency to reconsider these criteria and issue proper notice and comment to involve the professional community in the decisions about these important clinical tools. Petitioners criteria would more accurately reflect Congressional intent and the recognition that there are other approaches to health and healing would result in more sound public health policy.

D. Environmental Impact

Petitioner believes that under 21 C.F.R. § 25.30(h) and 25.31 that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required and claims a categorical exclusion.

E. Economic Impact

The only foreseeable economic effect of granting Petitioners effect would be to undo the economic impact of FDA's restriction on the compounded pharmaceutical market and restoring some certainty and access to medications.

F. Certification

On behalf of all Petitioners organizations listed below, we the undersigned certify that, to the best of Petitioners' knowledge, this Citizen's Petition is true and accurate. It includes, as reasonable given the breadth of the petition, all relevant information whether favorable or unfavorable to Petitioners' position on the matter.

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On behalf of the:

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Integrative Medicine Consortium, comprised of the AANP and the:

American Academy of Environmental Medicine

American College for Advancement in Medicine

American College of Integrative Medicine

Academy of Integrative Health and Medicine

Medisca

McGuff Compounding Pharmacy Services, Inc.