FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

September 12, 2018

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Pharmacy Compounding Advisory Committee (advisory committee). We are bringing certain compounding issues to this advisory committee to obtain the committee's advice. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division, Office, or Agency.

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I. Introduction

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the following three sections of the FD&C Act: section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)); section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements).

Bulk Drug Substances That Can Be Used by Compounders under Section 503A

One of the conditions that must be met for a compounded drug product to qualify for the exemptions in section 503A of the FD&C Act is that a licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that meet one of the following criteria:

> (1) Comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding;
> (2) If such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or
> (3) If such a monograph does not exist and the drug substances are not components of drugs approved by the Secretary, appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A.

(*See* section 503A(b)(1)(A)(i) of the FD&C Act.)

FDA is considering those substances nominated for inclusion on the list of bulk drug substances that can be used to compound drug products under section 503A of the FD&C Act (503A Bulks List). As discussed at the February 2015 PCAC meeting, and as proposed in the Notice of Proposed Rulemaking published in the *Federal Register* of December 16, 2016 (81 FR 91071), FDA has proposed the following criteria to evaluate the nominated substances:

> (1) The physical and chemical characterization of the substance;

(2) Any safety issues raised by the use of the substance in compounded drug products;
(3) The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
(4) Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

In evaluating the candidates for the 503A Bulks List under these criteria, the Agency has proposed to use a balancing test. Specifically, the Agency has proposed to consider each criterion in the context of the others and to balance them, on a substance-by-substance basis, to decide whether a particular substance is appropriate for inclusion on the list.

II. Substances Nominated for Inclusion on the 503A Bulks List (in order of discussion at the meeting)

A. Alpha Lipoic Acid (Tab 1)

1. Nominations (**Tab 1a**)
    a. Alliance for Natural Health USA
    b. American Association of Naturopathic Physicians
    c. American College for Advancement in Medicine
    d. International Academy of Compounding Pharmacists
    e. McGuff Compounding Services, Inc.

2. Nomination Clarification (**Tab 1b**)
    a. Alliance for Natural Health USA
    b. American Association of Naturopathic Physicians
    c. McGuff Compounding Services, Inc.

3. FDA Review (**Tab 1c**)

B. Coenzyme Q_{10} (Tab 2)

1. Nominations (**Tab 2a**)
    a. Professional Compounding Centers of America

2. Nomination Clarification (**Tab 2b**)
    a. Professional Compounding Centers of America

3. FDA Review (**Tab 2c**)

C. Creatine Monohydrate (Tab 3)

1. Nominations (**Tab 3a**)
    a. Professional Compounding Centers of America

2. Nomination Clarification (**Tab 3b**)
    a. Professional Compounding Centers of America

3. FDA Review (**Tab 3c**)

D. Pyridoxal 5 Phosphate (Tab 4)

1. Nominations (**Tab 4a**)
    a. Fagron
    b. International Academy of Compounding Pharmacists
    c. National Community Pharmacists Association

2. Nomination Clarification (**Tab 4b**)
    a. Fagron
    b. International Academy of Compounding Pharmacists
    c. National Community Pharmacists Association

3. FDA Review (**Tab 4c**)

E. Quercetin Dihydrate (Tab 5)

1. Nominations (**Tab 5a**)
    a. Alliance for Natural Health
    b. American Association of Naturopathic Physicians
    c. American College for Advancement in Medicine
    d. Integrative Medical Consortium
    e. McGuff Compounding Services, Inc.

2. Nomination Clarification (**Tab 5b**)
    a. Alliance for Natural Health
    b. American Association of Naturopathic Physicians
    c. Integrative Medical Consortium

3. FDA Review (**Tab 5c**)

III. Points to Consider

A. September 12, 2018, a.m. session

Points for the PCAC to Consider Regarding Whether to Include Certain Bulk Drug Substances on the 503A Bulks List

1. FDA is proposing that alpha lipoic acid solid oral dosage forms be INCLUDED on the 503A Bulks List. Should alpha lipoic acid solid oral dosage forms be placed on the list?

2. FDA is proposing that coenzyme Q_{10} (ubiquinone) for oral administration be INCLUDED on the 503A Bulks List. Should coenzyme Q_{10} (ubiquinone) for oral administration be placed on the list?

B. September 12, 2018, p.m. session

Points for the PCAC to Consider Regarding Whether to Include Certain Bulk Drug Substances on the 503A Bulks List

3. FDA is proposing that creatine monohydrate solid oral dosage forms be INCLUDED on the 503A Bulks List. Should creatine monohydrate solid oral dosage forms be placed on the list?

4. FDA is proposing that pyridoxal 5 phosphate monohydrate (intravenous and oral dosage forms) be INCLUDED on the 503A Bulks List. Should pyridoxal 5 phosphate monohydrate be (intravenous and oral dosage forms) placed on the list?

5. FDA is proposing that quercetin dihydrate NOT be included on the 503A Bulks List. Should quercetin dihydrate be placed on the list?

Tab 1

Alpha Lipoic Acid

Tab 1a

Alpha Lipoic Acid Nominations

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September 30, 2014

VIA ELECTRONIC SUBMISSION

Division of Dockets Management [HFA-305]
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: 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

Docket No. FDA-2013-N-1525

Dear Sir/Madam:

The Alliance for Natural Health USA ("ANH-USA") submits this comment on the Notice: "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" published in the Federal Register of July 2, 2014 by the Food and Drug Administration ("FDA" or the "Agency").

ANH-USA appreciates this opportunity to comment on the list of bulk drug substances that may be used to compound drug products pursuant to Section 503A of the FD&C Act ("FDCA"), 21 U.S.C. §353a (hereinafter the "503A List"). This list of ingredients is crucial to patients who require compounded substances, in particular those substances that are available only across state lines. ANH-USA therefore write to request that the Agency:

A) Extend the deadline for nominations by at least 90 days;
B) Maintain the 1999 List; and
C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List.

As discussed in detail below, in the interest compiling a comprehensive 503B List, more time is needed to provide the required information. This will benefit both FDA, by reducing the subsequent number of petitions for amendments, and consumers, by allowing continued access to important substances.

Organizational Background of Commenter Alliance for Natural Health USA

ANH-USA is a membership-based organization with its membership consisting of healthcare practitioners, food and dietary supplement companies, and over 335,000 consumer advocates. ANH-USA focuses on the protection and promotion of access to healthy foods, dietary nutrition, and natural compounded medication that consumers need to maintain optimal health. Among ANH-USA's members are medical doctors who prescribe, and patients who use, compounded medications as an integral component of individualized treatment plans.

ANH-USA's Request and Submissions Regarding Docket No. FDA-2013-N-1525

A) Extend the deadline for nominations by at least 90 days

This revised request for nominations follows the initial notice published in the Federal Register of December 4, 2013. Like the initial notice, this revised request provides only a 90 day response period. However, FDA is requiring more information than it sought originally and yet providing the same amount of time for the submission of nominations. The September 30, 2014 deadline for such a complex and expansive request is unreasonably burdensome and woefully insufficient.

The task set forth by FDA to nominate bulk drug substances for the 503A List places an undue burden on those who are responding. The Agency requires highly technical information for each nominated ingredient, including data about the strength, quality and purity of the ingredient, its recognition in foreign pharmacopeias and registrations in other countries, history with the USP for consideration of monograph development, and a bibliography of available safety and efficacy data, including any peer-reviewed medical literature. In addition, FDA is requiring information on the rationale for the use of the bulk drug substance and why a compounded product is necessary.

For the initial request for nomination, it was estimated that compiling the necessary information for just one nominated ingredient would require five to ten hours. With the revised request requiring more information, the time to put together all of the data for a single nomination likely will be higher. Given that it is necessary to review all possible ingredients and provide the detailed support, or risk losing important therapeutic ingredients, this task requires more time than has been designated by the Agency. While ANH-USA recognizes there will be additional opportunities to comment and petition for amendments after the 503A List is published, the realities of substances not making the list initially makes this request for more time imperative. For example, if a nomination for a substance cannot be completed in full by the current September 30, 2014 deadline, doctors and patients will lose access to such clinically important substances and face the

administrative challenges in obtaining an ingredient listing once the work of the advisory committee is completed. There is no regulatory harm in providing additional time to compile a well-researched and comprehensive initial 503A List.

B) Rescind the withdrawal of the ingredient list published on January 7, 1999

In the revised request for nomination, the Agency references in a footnote its withdrawal of the proposed ingredient list that was published on January 7, 1999. ANH-USA argued against this in its March 4, 2014 comment and would like to reiterate its opposition to the withdrawal. There is no scientific or legal justification to require discarding the work that lead to the nominations and imposing the burden on interested parties to begin the process all over again.

C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List

ANH-USA submits the following ingredients for nomination for the 503B list:

1. The attached Excel spreadsheets for 21 nominated ingredients prepared by IACP in support of its petition for the nomination of these ingredients; and
2. The submissions for Copper Hydrosol and Silver Hydrosol from Natural Immunogenics Corp.,[1] with their Canadian Product Licenses as proof of safety and efficacy.

In conclusion, Alliance for Natural Health USA requests that FDA provide a more realistic time frame, adding at least 90 days to the current deadline; rescind the withdrawal of the ingredient list published on January 7, 1999; and accept the ingredient nominations for approval for use.

Sincerely,

Gretchen DuBeau, Esq.
Executive and Legal Director
Alliance for Natural Health USA

[1] As of October 1, 2014, the address for Natural Immunogenics Corp. will be 7504 Pennsylvania Ave., Sarasota, FL 34243.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Alpha Lipoic Acid
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please access this article: Therapeutic applications of lipoic acid: a patent review (2011 - 2014). Koufaki M. Expert Opin Ther Pat. 2014 Sep;24(9):993-1005. doi: 10.1517/13543776.2014.937425. Epub 2014 Aug 7.
Is the ingredient listed in any of the three sections of the Orange Book?	No
Were any monographs for the ingredient found in the USP or NF monographs?	Dietary Supplement monograph in USP Dietary Lipoic Acid Capsule Monograph available in the USP. Dietary Lipoic Acid Tablet Monograph available in the USP.
What is the chemical name of the substance?	1,2-Dithiolane-3-pentanoic acid; 1,2-Dithiolane-3-valeric acid
What is the common name of the substance?	Alpha Lipoic Acid
Does the substance have a UNII Code?	73Y7P0K73Y
What is the chemical grade of the substance?	Not graded
What is the streng h, quality, stability, and purity of the ingredient?	Lipoic acid can be supplied by a 510-FDA Registered facility A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Lipoic acid is supplied as yellow crystalline powder.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	The proposed product can be compounded in various streng hs ranging from 25 mg/mL (750 g/30 mL) to 40 mg/mL (1200 mg/30 mL).
What are the anticipated route(s) of administra ion of the compounded drug product(s)?	Slow Intravenous
Are there safety and efficacy data on compounded drugs using the nominated substance?	**SAFETY:** POSSIBLY SAFE ...when used orally and appropriately. Oral alpha-lipoic acid has been used safely in clinical trials lasting from 4 months to 4 years (3540,3541,3542,10148,20479). ...when used topically and appropriately. A 5% alpha-lipoic acid cream has been used safely in clinical trials lasting up to 12 weeks (12021). ...when used intravenously and appropriately. Intravenous alpha-lipoic acid has been used safely in clinical trials lasting up to 3 weeks (3540,3557,10148,12106). PREGNANCY AND LACTATION Insufficient reliable information available; avoid using. Effectiveness **POSSIBLY EFFECTIVE** Coronary artery bypass graft (CABG) surgery. In clinical research, taking a combination product containing alpha-lipoic acid up to 2 months prior and fo month after surgery seems to decrease plasma troponin levels as well as reduce the average postoperative hospital stay by 1.2 days in patients undergoing elective CABG surgery (21651). The combination product contained CoQ10, magnesium orotate, omega-3 fatty acids, and selenium. The effect of alpha-lipoic acid alone is not known. Diabetes. Alpha-lipoic acid used orally or intravenously seems to improve insulin sensitivity, fasting blood glucose levels, and glucose disposal in patients with type 2 diabetes (3545,3874,3875,3876,20490,20493). Patients who took alpha-lipoic acid 300-1800 mg orally or 500-1000 mg intravenously daily sign ficant improvements in insulin resistance and glucose effectiveness after 4-8 weeks of oral treatment or after 1-10 days of intravenous administration (3545,3874,3875,3876,20493). However, alpha-lipoic acid doesn't seem to significantly lower glycosylated hemoglobin (HgbA1c) levels (20490,20492,20495,20496).
Has the bulk drug substance been used previously to compound drug product(s)?	Yes
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Orally, alpha-lipoic acid is used for diabetes, peripheral neuropathy, cardiac autonomic neuropathy, retinopathy, cataracts, and glaucoma. Alpha-lipoic acid is also used orally for dementia, chronic fatigue syndrome (CFS), HIV/AIDS, cancer, liver disease, Wilson's disease, cardiovascular disease, peripheral arterial disease (PAD), intermittent claudication, Lyme disease, and lactic acidosis caused by inborn errors of metabolism. Intravenously, alpha-lipoic acid is used for improving insulin-resistance and glucose disposal in type 2 diabetes, diabetic neuropathy, and Amanita mushroom poisoning. Topically, alpha-lipoic acid is used to reduce facial wrinkles, lines, and sun damage.
What is the reason for use of a compounded drug product ra her than an FDA-approved product?	There is no FDA-approved product for preventing and treating diabetic neuropathy. Many patients have shown improvement with alpha Lipoic acid treatment when the conventional FDA-approved drug products were not successful for neuropathy, diabetic polyneuropathy, prevention of neuropathy. Over 7,000 plus patients annually have improved outcomes.
Is there any other relevant information?	105 Sabeel AI, Kurkus J, Lindholm T. Intensive Hemodialysis and Hemoperfusion Treatment of Amanita Mushroom Poisoning. Mycopathologia 1995;131:107-14. View abstract.
	391 Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. Oncology 1999;13:1003-8. View abstract. 1280 Baur A, Harrer T, Peukert M, et al. Alpha-lipoic acid is an effective inhibitor of human immuno-deficiency virus (HIV-1) replication. Klin Wochenschr 1991;69:722-4. View abstract. 1547 Anon. Alpha-lipoic acid. Altern Med Rev 1998;3 308-10. View abstract. 1548 Berkson BM. Thioctic acid in treatment of hepatotoxic mushroom (Phalloides) poisoning (letter). N Engl J Med 1979;300:371. 1549 Roldan EJ, Perez Lloret A. Thioctic acid in Amanita poisoning (letter). Crit Care Med 1986;14:753-4. 1550 Biewenga GP, Haenen GR, Bast A. The pharmacology of the antioxidant lipoic acid. Gen Pharmacol 1997;29:315-31. View abstract. 1554 Matalon R, Stumpf DA, Michals K, et al. Lipoamide dehydrogenase deficiency with primary lactic acidosis: favorable response to treatment with oral lipoic acid. J Pediatr 1984;104:65-9. View abstract. 1555 Yoshida I, Sweetman L, Kulovich S, et al. Effect of lipoic acid in patient with defective activity of pyruvate dehydrogenase, 2-oxoglutarate dehydrogenase, and branched-chain keto acid dehydrogenase. Pediatr Res 1990;27:75-9. View abstract.

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3545 Konrad T, Vicini P, Kusterer K, et al. Alpha-lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with Type 2 diabetes. Diabetes Care 1999;22:280-7. View abstract.
3546 Packer L. Antioxidant properties of lipoic acid and its therapeutic effects in prevention of diabetes complications and cataracts. Ann N Y Acad Sci 1994;738 257-64. View abstract.
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September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

> "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"

To Whom It May Concern:

The American Association of Naturopathic Physicians (AANP) appreciates the opportunity to address the FDA's request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

This is a significant issue for our members and their patients. AANP strongly supports efforts to ensure that the drug products dispensed to patients are safe and effective.

Background: AANP Submissions to Date

On January 30, 2014, we submitted comments to Docket FDA-2013-D-1444, "Draft Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Withdrawal of Guidances" relating to congressional intent in crafting HR 3204. These comments highlighted the fact that, for compounding pharmacies subject to Section 503A, Congress intended that States continue to have the authority to regulate the availability of safely compounded medications obtained by physicians for their patients. As we further noted, compounded medications that are formulated to meet unique patient needs, and that can be administered immediately in the office, help patients receive the products their physicians recommend and reduce the medical and financial burden on both the patient and

doctor that restrictions on office use would impose. Such medications, we emphasized, provide a unique benefit to patients and have an excellent track record of safety when properly produced and stored.

AANP also (on March 4, 2014) nominated 71 bulk drug substances. We identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring. We estimated, at that time, that at least 6 hours per ingredient would be needed to do so – time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP sought a 90-day extension to more completely respond to the Agency's request.

In this renomination, we have narrowed our focus to 42 bulk drug substances that are most important for the patients treated by naturopathic doctors. Twenty-one of these bulk drug substances are formally nominated in the attachments as well as noted by name in this letter. Given the limitations imposed by the fact that our physician members spend the majority of their day providing patient care, however, AANP again found that the span of time the Agency provided for renominations was insufficient to prepare the documentation needed for the remaining 21 bulk drug substances.

We now request that FDA extend the deadline for which comments are due by 120 days, so that we may provide this further documentation. We have determined that as much as 40 hours per ingredient will be needed to do so – time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP respectfully seeks an additional 120-day period for the purpose of gathering this essential information.

Naturopathic Medicine and Naturopathic Physicians

A word of background on our profession is in order. AANP is a national professional association representing 4,500 licensed naturopathic physicians in the United States. Our members are physicians trained as experts in natural medicine. They are trained to find the underlying cause of a patient's condition rather than focusing solely 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 4-year, graduate level programs at institutions recognized through the US Department of Education. There are currently 7 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. 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.

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. Currently, 20 states and territories license NDs to practice.

Naturopathic physicians provide treatments that are effective and safe. Since 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.

Characteristics of Patients Seen by Naturopathic Physicians

Individuals who seek out NDs typically do so because they suffer from one or more chronic conditions that they have not been able to alleviate in repeated visits to conventional medical doctors or physician specialists. Such chronic conditions include severe allergies, asthma, chronic fatigue, chronic pain, digestive disorders (such as irritable bowel syndrome), insomnia, migraine, rashes, and other autoimmune disorders. Approximately three-quarters of the patients treated by NDs have more than one of these chronic conditions. Due to the fact that their immune systems are often depleted, these individuals are highly sensitive to standard medications. They are also more susceptible to the numerous side effects brought about by mass-produced drugs.

Such patients have, in effect, fallen through the cracks of the medical system. This is why they seek out naturopathic medicine. Safely compounded medications – including nutritional, herbal, and homeopathic remedies – prove efficacious to meet their needs every day in doctors' offices across the country. Such medications are generally recognized as safe (GRAS), having been used safely for decades in many cases. As patients' immune function improves, and as they work with their ND to improve their nutrition, get better sleep, increase their exercise and decrease their stress, their health and their resilience improves. This is the 'multi-systems' approach of naturopathic medicine – of which compounded drugs are an essential component.

Bulk Drug Substances Nominated at this Time

Notwithstanding the concerns expressed and issues highlighted in the foregoing, AANP nominates the following 21 bulk drug substances for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A. Thorough information on these substances is presented in the spreadsheets attached with our comments. The documentation is as complete and responsive to the Agency's criteria as we can offer at this time.

The bulk drug substances nominated are:

Acetyl L Carnitine

Alanyl L Glutamine
Alpha Lipoic Acid
Artemisia/Artemisinin
Boswellia
Calcium L5 Methyltetrahydrofolate
Cesium Chloride
Choline Chloride
Curcumin
DHEA
Dicholoroacetic Acid
DMPS
DMSA
Germanium Sesquioxide
Glutiathone
Glycyrrhizin
Methylcobalamin
MSM
Quercitin
Rubidium Chloride
Vanadium

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating the patients of naturopathic doctors. AANP wishes to specify these 21 ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination. The additional bulk drug substances include:

7 Keto Dehydroepiandrosterone
Asparagine
Calendula
Cantharidin
Choline Bitartrate
Chromium Glycinate
Chromium Picolinate
Chrysin
Co-enzyme Q10
Echinacea
Ferric Subsulfate
Iron Carbonyl
Iscador
Pantothenic Acid
Phenindamine Tartrate
Piracetam
Pterostilbene

Pyridoxal 5-Phosphate
Resveratrol
Salicinium
Thymol Iodide

AANP Objects to Unreasonable Burden

AANP believes it necessary and proper to lodge an objection to FDA's approach, i.e., the voluminous data being required in order for bulk drug substances to be considered by the Agency for approval. FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of the persons most knowledgeable about and experienced in the application of compounded medications are either small business owners or busy clinicians, and given the extent and detail of information on potentially hundreds of ingredients as sought by FDA, this burden is unreasonable. The approach has no basis in the purpose and language of the Drug Quality and Security Act ("Act") – particularly for drugs that have been safely used for years, not only with the Agency's implicit acceptance, but without any indication of an unacceptable number of adverse patient reactions.

The volume of data being required in this rulemaking is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) 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 the resources to seek regulatory approvals. The FDA's analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The burden on respondents to this current rulemaking is further aggravated by the FDA's complete absence of consideration of the harm that will be caused if needed drugs are removed from the market. The "Type 2" errors caused by removing important agents from clinical use could far exceed the "Type 1" errors of adverse reactions, particularly given the strong track record of safely compounded medications. The infectious contamination that gave rise to the Act has little to do with the process set out by FDA for determining which ingredients may be compounded. Yet the Agency has offered little consideration of the respective risks and benefits of its approach. Based on the fact that compounding pharmacies and physicians are carrying the full burden of proof, as well as how much time it is likely to take for the process of documentation and evaluation to conclude, the Agency itself may well find that it has caused more harm to patients' clinical outcomes than provided a bona fide contribution to patient safety.

Conclusion

AANP appreciates the Agency's consideration of the arguments and objection presented herein, the request for an extension of time to gather the documentation that FDA is seeking, and the nominations made and referenced at this time.

We look forward to continued dialogue on these matters. As AANP can answer any questions, please contact me (jud.richland@naturopathic.org; 202-237-8150).

Sincerely,

Jud Richland, MPH
Chief Executive Officer

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Alpha Lipoic Acid
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please access this article: Therapeutic applications of lipoic acid: a patent review (2011 - 2014). Koufaki M. Expert Opin Ther Pat. 2014 Sep;24(9):993-1005. doi: 10.1517/13543776.2014.937425. Epub 2014 Aug 7.
Is the ingredient listed in any of the three sections of the Orange Book?	No
Were any monographs for the ingredient found in the USP or NF monographs?	Dietary Supplement monograph in USP Dietary Lipoic Acid Capsule Monograph available in the USP. Dietary Lipoic Acid Tablet Monograph available in the USP.
What is the chemical name of the substance?	1,2-Dithiolane-3-pentanoic acid; 1,2-Dithiolane-3-valeric acid
What is the common name of the substance?	Alpha Lipoic Acid
Does the substance have a UNII Code?	73Y7P0K73Y
What is the chemical grade of the substance?	Not graded
What is the streng h, quality, stability, and purity of the ingredient?	Lipoic acid can be supplied by a 510-FDA Registered facility A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Lipoic acid is supplied as yellow crystalline powder.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	The proposed product can be compounded in various streng hs ranging from 25 mg/mL (750 g/30 mL) to 40 mg/mL (1200 mg/30 mL).
What are the anticipated route(s) of administra ion of the compounded drug product(s)?	Slow Intravenous
Are there safety and efficacy data on compounded drugs using the nominated substance?	**SAFETY:** POSSIBLY SAFE ...when used orally and appropriately. Oral alpha-lipoic acid has been used safely in clinical trials lasting from 4 months to 4 years (3540,3541,3542,10148,20479). ...when used topically and appropriately. A 5% alpha-lipoic acid cream has been used safely in clinical trials lasting up to 12 weeks (12021). ...when used intravenously and appropriately. Intravenous alpha-lipoic acid has been used safely in clinical trials lasting up to 3 weeks (3540,3557,10148,12106). PREGNANCY AND LACTATION Insufficient reliable information available; avoid using. Effectiveness **POSSIBLY EFFECTIVE** Coronary artery bypass graft (CABG) surgery. In clinical research, taking a combination product containing alpha-lipoic acid up to 2 months prior and fo month after surgery seems to decrease plasma troponin levels as well as reduce the average postoperative hospital stay by 1.2 days in patients undergoing elective CABG surgery (21651). The combination product contained CoQ10, magnesium orotate, omega-3 fatty acids, and selenium. The effect of alpha-lipoic acid alone is not known. Diabetes. Alpha-lipoic acid used orally or intravenously seems to improve insulin sensitivity, fasting blood glucose levels, and glucose disposal in patients with type 2 diabetes (3545,3874,3875,3876,20490,20493). Patients who took alpha-lipoic acid 300-1800 mg orally or 500-1000 mg intravenously daily sign ficant improvements in insulin resistance and glucose effectiveness after 4-8 weeks of oral treatment or after 1-10 days of intravenous administration (3545,3874,3875,3876,20493). However, alpha-lipoic acid doesn't seem to significantly lower glycosylated hemoglobin (HgbA1c) levels (20490,20492,20495,20496). Some research is conflicting, finding no significant effect of alpha-lipoic acid on glucose levels, including fasting blood glucose, or insulin sensitivity compared to placebo in type 2 and type 1 diabetic patients (20494,20495,20496,20498). **Please see References listed in Relevant Information section below.**
Has the bulk drug substance been used previously to compound drug product(s)?	Yes
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Orally, alpha-lipoic acid is used for diabetes, peripheral neuropathy, cardiac autonomic neuropathy, retinopathy, cataracts, and glaucoma. Alpha-lipoic acid is also used orally for dementia, chronic fatigue syndrome (CFS), HIV/AIDS, cancer, liver disease, Wilson's disease, cardiovascular disease, peripheral arterial disease (PAD), intermittent claudication, Lyme disease, and lactic acidosis caused by inborn errors of metabolism. Intravenously, alpha-lipoic acid is used for improving insulin-resistance and glucose disposal in type 2 diabetes, diabetic neuropathy, and Amanita mushroom poisoning. Topically, alpha-lipoic acid is used to reduce facial wrinkles, lines, and sun damage.
What is the reason for use of a compounded drug product ra her than an FDA-approved product?	There is no FDA-approved product for preventing and treating diabetic neuropathy. Many patients have shown improvement with alpha Lipoic acid treatment when the conventional FDA-approved drug products were not successful for neuropathy, diabetic polyneuropathy, prevention of neuropathy. Over 7,000 plus patients annually have improved outcomes.
Is there any other relevant information?	105 Sabeel AI, Kurkus J, Lindholm T. Intensive Hemodialysis and Hemoperfusion Treatment of Amanita Mushroom Poisoning. Mycopathologia 1995;131:107-14. View abstract. 391 Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. Oncology 1999;13:1003-8. View abstract. 1280 Baur A, Harrer T, Peukert M, et al. Alpha-lipoic acid is an effective inhibitor of human immuno-deficiency virus (HIV-1) replication. Klin Wochenschr 1991;69:722-4. View abstract. 1547 Anon. Alpha-lipoic acid. Altern Med Rev 1998;3 308-10. View abstract. 1548 Berkson BM. Thioctic acid in treatment of hepatotoxic mushroom (Phalloides) poisoning (letter). N Engl J Med 1979;300:371. 1549 Roldan EJ, Perez Lloret A. Thioctic acid in Amanita poisoning (letter). Crit Care Med 1986;14:753-4.

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September 30, 2014

Division of Dockets Management (HFA-305)
Food And Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Re: Docket FDA-2013-N-1525

"Bulk Drug Substances That May Be Used to compound Drug Products in Accordance With Section 503A of Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations"

To Whom It May Concern:

The American College for Advancement in Medicine (ACAM) is a prominent and active medical education organization involved in teaching physicians in the proper use of oral and intravenous nutritional therapies for over forty years. We have also been involved in clinical research sponsored by the National Heart Lung and Blood Institute. As such, we have a vested interest in maintaining the availability of compounded drug products.

We appreciate the opportunity to address the FDA's request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products. To meet what appear to be substantial requirements involved in this submittal, the FDA has given compounding pharmacists (in general a small business operation) and physicians very limited time to comply with onerous documentation. The Agency has requested information for which no single pharmacy or physician organization can easily provide in such a contracted time frame. As such this time consuming process requires significant coordination from many practicing professionals for which adequate time has not been allotted.

This issue is of great importance and has the potential to drastically limit the number of available compounded drugs and drug products thus limiting the number of individualized treatments that compounded medicines offer to patients.
ACAM and its physician members have not had the time to collect, review and assess all documentation necessary to submit for the intended list of compounded drugs required to assure all patient therapies are represented in our submission. We respectfully seek an additional 120 day period to educate and coordinate our physicians on the issue at hand and to gather the essential information necessary to provide the Agency with the most comprehensive information.
In an attempt to comply with the current timeframe established, a collaborative effort resulted in the attached nominations prepared for bulk drug substances that may be used in pharmacy compounding under Section 503A.

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It is not clear whether the current submission will be the final opportunity to comment or communicate with the Agency. Will a deficiency letter be provided if the initial nomination information was inadequate or will a final decision to reject a nominated substance be made without the opportunity to further comment? ACAM respectfully requests that the FDA issue a deficiency letter should the submitted documentation for a nomination be considered inadequate.

Sincerely,

Neal Speight, MD
(Immediate Past President) for
Allen Green, MD
President and CEO
The American College for Advancement in Medicine

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Alpha Lipoic Acid
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please access this article: Therapeutic applications of lipoic acid: a patent review (2011 - 2014). Koufaki M. Expert Opin Ther Pat. 2014 Sep;24(9):993-1005. doi: 10.1517/13543776.2014.937425. Epub 2014 Aug 7.
Is the ingredient listed in any of the three sections of the Orange Book?	No
Were any monographs for the ingredient found in the USP or NF monographs?	Dietary Supplement monograph in USP Dietary Lipoic Acid Capsule Monograph available in the USP. Dietary Lipoic Acid Tablet Monograph available in the USP.
What is the chemical name of the substance?	1,2-Dithiolane-3-pentanoic acid; 1,2-Dithiolane-3-valeric acid
What is the common name of the substance?	Alpha Lipoic Acid
Does the substance have a UNII Code?	73Y7P0K73Y
What is the chemical grade of the substance?	Not graded
What is the streng h, quality, stability, and purity of the ingredient?	Lipoic acid can be supplied by a 510-FDA Registered facility A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Lipoic acid is supplied as yellow crystalline powder.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.
Has information been submitted about the substance to the USP for consideration of monograph development?	There are USP Dietary Supplement monographs for drug substance, tablet, and capsule.
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	The proposed product can be compounded in various streng hs ranging from 25 mg/mL (750 g/30 mL) to 40 mg/mL (1200 mg/30 mL).
What are the anticipated route(s) of administra ion of the compounded drug product(s)?	Slow Intravenous
Are there safety and efficacy data on compounded drugs using the nominated substance?	**SAFETY:** POSSIBLY SAFE ...when used orally and appropriately. Oral alpha-lipoic acid has been used safely in clinical trials lasting from 4 months to 4 years (3540,3541,3542,10148,20479). ...when used topically and appropriately. A 5% alpha-lipoic acid cream has been used safely in clinical trials lasting up to 12 weeks (12021). ...when used intravenously and appropriately. Intravenous alpha-lipoic acid has been used safely in clinical trials lasting up to 3 weeks (3540,3557,10148,12106). PREGNANCY AND LACTATION Insufficient reliable information available; avoid using. Effectiveness **POSSIBLY EFFECTIVE** Coronary artery bypass graft (CABG) surgery. In clinical research, taking a combination product containing alpha-lipoic acid up to 2 months prior and fo month after surgery seems to decrease plasma troponin levels as well as reduce the average postoperative hospital stay by 1.2 days in patients undergoing elective CABG surgery (21651). The combination product contained CoQ10, magnesium orotate, omega-3 fatty acids, and selenium. The effect of alpha-lipoic acid alone is not known. Diabetes. Alpha-lipoic acid used orally or intravenously seems to improve insulin sensitivity, fasting blood glucose levels, and glucose disposal in patients with type 2 diabetes (3545,3874,3875,3876,20490,20493). Patients who took alpha-lipoic acid 300-1800 mg orally or 500-1000 mg intravenously daily sign ficant improvements in insulin resistance and glucose effectiveness after 4-8 weeks of oral treatment or after 1-10 days of intravenous administration (3545,3874,3875,3876,20493). However, alpha-lipoic acid doesn't seem to significantly lower glycosylated hemoglobin (HgbA1c) levels (20490,20492,20495,20496). Some research is conflicting, finding no significant effect of alpha-lipoic acid on glucose levels, including fasting blood glucose, or insulin sensitivity compared to placebo in type 2 and type 1 diabetic patients (20494,20495,20496,20498). **Please see References listed in Relevant Information section below.**
Has the bulk drug substance been used previously to compound drug product(s)?	Yes
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Orally, alpha-lipoic acid is used for diabetes, peripheral neuropathy, cardiac autonomic neuropathy, retinopathy, cataracts, and glaucoma. Alpha-lipoic acid is also used orally for dementia, chronic fatigue syndrome (CFS), HIV/AIDS, cancer, liver disease, Wilson's disease, cardiovascular disease, peripheral arterial disease (PAD), intermittent claudication, Lyme disease, and lactic acidosis caused by inborn errors of metabolism. Intravenously, alpha-lipoic acid is used for improving insulin-resistance and glucose disposal in type 2 diabetes, diabetic neuropathy, and Amanita mushroom poisoning. Topically, alpha-lipoic acid is used to reduce facial wrinkles, lines, and sun damage.
What is the reason for use of a compounded drug product ra her than an FDA-approved product?	Many patients have shown improvement with alpha Lipoic acid treatment when the conventional FDA-approved drug products were not successful. Over 7,000 plus patients annually have improved outcomes
Is there any other relevant information?	105 Sabeel AI, Kurkus J, Lindholm T. ntensive Hemodialysis and Hemoperfusion Treatment of Amanita Mushroom Poisoning. Mycopathologia 1995;131:107-14. View abstract. 391 Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. Oncology 1999;13:1003-8. View abstract. 1280 Baur A, Harrer T, Peukert M, et al. Alpha-lipoic acid is an effective inhibitor of human immuno-deficiency virus (HIV-1) replication. Klin Wochenschr 1991;69:722-4. View abstract. 1547 Anon. Alpha-lipoic acid. Altern Med Rev 1998;3 308-10. View abstract. 1548 Berkson BM. Thioctic acid in treatment of hepatotoxic mushroom (Phalloides) poisoning (letter). N Engl J Med 1979;300:371. 1549 Roldan EJ, Perez Lloret A. Thioctic acid in Amanita poisoning (letter). Crit Care Med 1986;14:753-4. 1550 Biewenga GP, Haenen GR, Bast A. The pharmacology of the antioxidant lipoic acid. Gen Pharmacol 1997;29:315-31. View abstract.

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September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA's request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created an series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency's activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee ***prior*** to the implementation and issuance of regulations including the creation of the bulk ingredient list.

> (2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

> General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

David G. Miller, R.Ph.
Executive Vice President & CEO

Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Thioctic Acid
Chemical/Common Name	Lipoic acid; alpha lipoic acid
Identifying Codes	1200-22-2
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies *(including foreign recognition)*	Not Listed in USP/NF for this specific salt/form

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography *(where available)*	
Past and Proposed Use	The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

McGUFF
COMPOUNDING
PHARMACY
SERVICES, INC.

Re: Docket FDA-2013-N-1525

"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"

To Whom It May Concern:

McGuff Compounding Pharmacy Services, Inc. (McGuff CPS) appreciates the opportunity to address the FDA's request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products.

Request for Extension

The Agency has indicated the majority of compounding pharmacies are small businesses. McGuff CPS is a small business and has found that the requirements to assemble the requested documentation have been particularly onerous. The 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.

This is an issue of great importance which will limit the number of available compounded drugs products available to physicians and, therefore, will limit the number of individualized treatments to patients. McGuff CPS and physician stakeholders have not had the time to collect, review, and collate all documentation necessary to submit the intended list of compounded drugs required to assure all patient therapies are represented in our submission. McGuff CPS respectfully seeks an additional 120 day period for the purpose of coordinating the various stakeholders and gathering the essential information necessary to provide the Agency with the most comprehensive information.

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The Agency has not announced the process of follow on communication or failure e.g. what happens if a nominated substance needs more detailed information of a particular nature? Will the whole effort be rejected or will a "deficiency letter" be issued to the person or organization that submitted the nomination? The Agency issues "deficiency letters" for NDA and ANDA submissions and this appears to be appropriate for compounded drug nominations. McGuff CPS respectfully requests the FDA issue "deficiency letters" to the person or organization that submitted the nomination so that further documentation may be provided.

Nominations

To comply with the current time limits established by the Docket, attached are the nominations prepared to date for bulk drug substances that may be used in pharmacy compounding under Section 503A.

Sincerely,

Ronald M. McGuff

Ronald M. McGuff
President/CEO
McGuff Compounding Pharmacy Services, Inc.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Alpha Lipoic Acid
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please access this article: Therapeutic applications of lipoic acid: a patent review (2011 - 2014). Koufaki M. Expert Opin Ther Pat. 2014 Sep;24(9):993-1005. doi: 10.1517/13543776.2014.937425. Epub 2014 Aug 7.
Is the ingredient listed in any of the three sections of the Orange Book?	No
Were any monographs for the ingredient found in the USP or NF monographs?	Dietary Supplement monograph in USP Dietary Lipoic Acid Capsule Monograph available in the USP. Dietary Lipoic Acid Tablet Monograph available in the USP.
What is the chemical name of the substance?	1,2-Dithiolane-3-pentanoic acid; 1,2-Dithiolane-3-valeric acid
What is the common name of the substance?	Alpha Lipoic Acid
Does the substance have a UNII Code?	73Y7P0K73Y
What is the chemical grade of the substance?	Not graded
What is the streng h, quality, stability, and purity of the ingredient?	Lipoic acid can be supplied by a 510-FDA Registered facility A valid Certificate of Analysis accompanies each lot of raw material received.
How is the ingredient supplied?	Lipoic acid is supplied as yellow crystalline powder.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.
Has information been submitted about the substance to the USP for consideration of monograph development?	Information not known
What dosage form(s) will be compounded using the bulk drug substance?	Injection
What strength(s) will be compounded from the nominated substance?	The proposed product can be compounded in various streng hs ranging from 25 mg/mL (750 g/30 mL) to 40 mg/mL (1200 mg/30 mL).
What are the anticipated route(s) of administra ion of the compounded drug product(s)?	Slow Intravenous
Are there safety and efficacy data on compounded drugs using the nominated substance?	**SAFETY:** POSSIBLY SAFE ...when used orally and appropriately. Oral alpha-lipoic acid has been used safely in clinical trials lasting from 4 months to 4 years (3540,3541,3542,10148,20479). ...when used topically and appropriately. A 5% alpha-lipoic acid cream has been used safely in clinical trials lasting up to 12 weeks (12021). ...when used intravenously and appropriately. Intravenous alpha-lipoic acid has been used safely in clinical trials lasting up to 3 weeks (3540,3557,10148,12106). PREGNANCY AND LACTATION Insufficient reliable information available; avoid using. Effectiveness **POSSIBLY EFFECTIVE** Coronary artery bypass graft (CABG) surgery. In clinical research, taking a combination product containing alpha-lipoic acid up to 2 months prior and fo month after surgery seems to decrease plasma troponin levels as well as reduce the average postoperative hospital stay by 1.2 days in patients undergoing elective CABG surgery (21651). The combination product contained CoQ10, magnesium orotate, omega-3 fatty acids, and selenium. The effect of alpha-lipoic acid alone is not known. Diabetes. Alpha-lipoic acid used orally or intravenously seems to improve insulin sensitivity, fasting blood glucose levels, and glucose disposal in patients with type 2 diabetes (3545,3874,3875,3876,20490,20493). Patients who took alpha-lipoic acid 300-1800 mg orally or 500-1000 mg intravenously daily sign ficant improvements in insulin resistance and glucose effectiveness after 4-8 weeks of oral treatment or after 1-10 days of intravenous administration (3545,3874,3875,3876,20493). However, alpha-lipoic acid doesn't seem to significantly lower glycosylated hemoglobin (HgbA1c) levels (20490,20492,20495,20496). Some research is conflicting, finding no significant effect of alpha-lipoic acid on glucose levels, including fasting blood glucose, or insulin sensitivity compared to placebo in type 2 and type 1 diabetic patients (20494,20495,20496,20498). **Please see References listed in Relevant Information section below.**
Has the bulk drug substance been used previously to compound drug product(s)?	Yes
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Orally, alpha-lipoic acid is used for diabetes, peripheral neuropathy, cardiac autonomic neuropathy, retinopathy, cataracts, and glaucoma. Alpha-lipoic acid is also used orally for dementia, chronic fatigue syndrome (CFS), HIV/AIDS, cancer, liver disease, Wilson's disease, cardiovascular disease, peripheral arterial disease (PAD), intermittent claudication, Lyme disease, and lactic acidosis caused by inborn errors of metabolism. Intravenously, alpha-lipoic acid is used for improving insulin-resistance and glucose disposal in type 2 diabetes, diabetic neuropathy, and Amanita mushroom poisoning. Topically, alpha-lipoic acid is used to reduce facial wrinkles, lines, and sun damage.
What is the reason for use of a compounded drug product ra her than an FDA-approved product?	There are many patients hat choose or may benefit from Lipoic acid treatment when the conventional FDA-approved drug products fail or are not appropriate. One physician, an expert in lipoic acid therapy, administers lipoic acid intravenous infusions to**7,000 plus patients annually.**
Is there any other relevant information?	105 Sabeel AI, Kurkus J, Lindholm T. Intensive Hemodialysis and Hemoperfusion Treatment of Amanita Mushroom Poisoning. Mycopathologia 1995;131:107-14. View abstract. 391 Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. Oncology 1999;13:1003-8. View abstract. 1280 Baur A, Harrer T, Peukert M, et al. Alpha-lipoic acid is an effective inhibitor of human immuno-deficiency virus (HIV-1) replication. Klin Wochenschr 1991;69:722-4. View abstract. 1547 Anon. Alpha-lipoic acid. Altern Med Rev 1998;3 308-10. View abstract. 1548 Berkson BM. Thioctic acid in treatment of hepatotoxic mushroom (Phalloides) poisoning (letter). N Engl J Med 1979;300:371.

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30966 VIATRIS GmbH. NATHAN II Study, data on file.

Tab 1b

Alpha Lipoic Acid
Nomination Clarification

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January 26, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Avenue
Building 51, Room 3249
Silver Spring, MD 20903

RE: Docket FDA-2015-N-3534

Dear Ms. Hallman:

The Alliance for Natural Health USA (ANH-USA) is responding to FDA's questions regarding the nomination of **Alpha lipoic acid** for inclusion on the 503A bulk drug substances list.

ANH-USA is an independent, nonprofit watchdog organization of more than 550,000 members nationally that protects consumer access to natural health services, practitioners, and resources. Safely compounded medications, as provided by integrative physicians, fulfill an important clinical need for many of our members. These are patients who have not found relief for their health conditions through conventional means. Such patients often have an adverse reaction to mass-manufactured drugs, and require a more individualized treatment regimen.

Before providing our responses, we wish to object to what has apparently evolved into a new request for a disease indication rather than simply a use for the ingredient. The implication is that FDA approval will be based upon a disease indication when functional and nutraceutical uses have substantial clinical value and are plainly lawful under the Food, Drug, and Cosmetic Act.

Responses:

Q1. Does Alliance for Natural Health USA still want to pursue review by the FDA and consideration by the PCAC of alpha lipoic acid for inclusion on the 503A bulks list?

A. Yes

Q2. Please explain whether the nominated molecule is enantiomerically pure or a racemic mixture.

A. Racemic mixture

Q3. Alpha lipoic acid is minimally soluble in water and unstable unless protected from air and light. Please provide any information available about how these issues are addressed for compounded products, especially intravenous formulations.

A. ANH-USA cites the response of McGuff Compounding Pharmacy Services and the American Association of Naturopathic Physicians, both of which possess the necessary expertise on this matter.

Q4. Please confirm in writing the proposed uses identified in your nomination. For those uses of the nominated substance that you want FDA to review, provide at least one scientific article supporting each use, and identify the dosage form and strength/concentration for each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.

A. ANH-USA cites the response of McGuff Compounding Pharmacy Services and the American Association of Naturopathic Physicians, both of which possess the necessary expertise on this matter.

Q5. In your nomination, you propose alpha lipoic acid for numerous uses including three conditions treated with intravenous administration, three conditions treated with topical administration, and seventeen conditions treated with oral administration. Please prioritize the uses for which you seek review, placed in order of strongest to weakest scientific support.

A. ANH-USA cites the response of McGuff Compounding Pharmacy Services and the American Association of Naturopathic Physicians, both of which possess the necessary expertise on this matter.

ANH-USA appreciates the FDA's and its Pharmacy Compounding Advisory Committee's (PCAC) consideration of this further information in support of the nomination of Alpha lipoic acid for inclusion on the 503A bulk drug substances list. We would like to reiterate that the Agency's original request asked only for ingredients' proposed use, not the disease condition or indication.

If you have further questions, please contact me.

Sincerely,

Michael Jawer
Deputy Director

Email: mike@anh-usa.org
Phone: 240-396-2171

VIA EMAIL
toni.hallman@fda.hhs.gov

Toni Hallman, MS, BSN, RN
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Re: Response to Requests for More Information on Nominations for Alpha Lipoic Acid, Methyl B12 and Choline Chloride
Docket FDA-2015-N-3534

Dear LT. Hallman:

I write on behalf of the American Association of Naturopathic Physicians ("AANP") and its partner in these submissions, the Integrative Medicine Consortium ("IMC"), in response to your requests for more information about the nominations of the three above-named ingredients. It is correct that IMC and AANP maintain these nominations as ingredients that should be placed on the 503A positive list. In addition to providing what material we can in the short time provided, I write to object to the unreasonably short time allowed and request and extension to file a more complete response. Of more import, we also object to what has evolved into a new request for a disease indication rather than simply a use for an ingredient, and its implication that approval must be based upon a disease indication when functional uses have great clinical utility and are plainly lawful under the language of the Food, Drug and Cosmetic Act ("FDCA").

Enclosed please find three submissions addressing the questions raised for response by today, though we intend to supplement these filings. We also are in support of submissions made by co-nominators the Pharmacy Compounding Centers of America and McGuff Compounding Pharmacy.

Objection As to Insufficient Notice

IMC and AANP appreciate that FDA is seeking additional information as it weighs our nominations, but the due date of January 26, 2018 for much of the information was only submitted to our organizations on January 16th. A ten-day window, particularly for physicians and pharmacists engaged in full-time practices, is not reasonable. We appreciate that staff would

like time to review clinical materials prior to the as yet unannounced PCAC meeting, but the requests are quite extensive. We are therefore providing what we can in the limited time allowed but request until February 23, 2018 to supplement our responses along with the other questions requested by that date.

The request regarding alpha lipoic acid, for example, asks for at least one study for the 23 proposed indications that were submitted for that ingredient. Submissions by AANP, IMC and co-nominators McGuff Compounding Pharmacy and the Professional Compounding Centers of American have previously provided citations to over 280 articles, the indication for most which can plainly be seen in the titles as referring to diabetic neuropathy or other conditions. The statement that indications will not be reviewed unless we submit additional materials, and in a ten-day window, given the extent of the materials already provided, is concerning. Given, as well, the FDA's evident policy on ingredients under review that a single study is insufficient to gain approval, the actual burden for all three ingredients made in these requests is much higher.

Further, the request to break down the dosage and form by each proposed use is not contained in the Federal Register Notice (2015-27271) but constitutes a new request, as is the request to provide supportive statements from the materials of professional medical societies and to prioritize all uses. Further, while we appreciate that the FDA is following up on our previous submissions, the original request only asks for the "proposed use" and does not ask for the disease indication or condition. These are all significant requests that cannot be reasonably accomplished in ten days.

Objection as to Requirements of a Disease Indication

IMC and AANP object to the requirement that an ingredient demonstrate that it has an indication for a disease or condition to sustain a nomination. Such a requirement is neither clinically required nor lawful 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. While our nominations state and we believe evidence and experience show 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 positive list even if there may be proper and legitimate functional or nutritional uses as their sole basis is not clinically or legally grounded.

While we understand that FDA is focused on the disease model and this language might at first reading have unintentionally excluded functional uses of ingredients, FDA's briefing documents have thus far excluded consideration of functional uses. Further, the request for information for choline chloride specifically asks, for example, for the "disease state(s) or health condition(s)" we are proposing, and states that "neuropathic disorder" is insufficiently precise, suggesting not only that a disease state is required but that it must even be presented with ICD-10 or similar

specificity. 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 within the scope of their training seeks to apply an improperly high threshold to matters that fall within the purview of state overseen medical and compounding practice. While we appreciate the effort to focus the review of the clinical evidence, to the extent that a disease indication were the basis for use, as long as choline chloride, in this example, is shown to have a valid role in any form of neuropathy that should be sufficient to allow a physician to the ability access for their patients as guided by his or her knowledge and experience. While I won't burden this letter with the extensive citations available on the topic, the FDA's regulatory authority and jurisdiction is limited by the right of physicians to practice medicine. Compounding pharmacies are not permitted to market their ingredients with therapeutic claims in any event. Finally, the request for specificity seems plainly contrary to the lack of FDA authority to limit the use of a compounded ingredient placed on the positive list to certain indications.

The Legal Requirement for Ingredient "Use"

Imposing a disease model on compounding practice is expressly contrary to the FDCA, which defines a drug as including products that affect the function of the body. 21 U.S.C. § 321(g)(C). Nothing in that definition limits either the definition or proper use of a drug to the disease claim listed separately at 21 U.S.C. § 321(g)(B).[1] If one markets an ingredient with the sole claim that it affects physiologic function without first obtaining NDA approval, the FDA can and routinely does issue warning letters or take enforcement actions to remove such products from the market. The converse is also 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. Whether an oversight or intentional effort to remove an entire basis for use, the FDA cannot have it both ways in its interpretation of its enabling legislation.

Where a pharmacist compounds on lawful scripts for the prescriber's purpose of affecting physiologic function, such as to provide a high level of antioxidant or anti-inflammatory activity, and no claim made about disease treatment, the FDA's criteria imposes a burden of proof for a claim that was not undertaken by the pharmacist or physician and improperly restricts an entire basis for clinically proper and lawful use. Further, assessing claims has always been based upon manufacturer's intent, which is not applicable to physician prescribing.

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[1] "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..C. § 321(g).

Nothing in the language of the Drug Quality and Security Act ("DQSA") (P.L. 113-54) or the Food and Drug Administration Modernization and Accountability Act of 1997 (P.L. 105-115) ("FDAMA") limits this definition of a "drug" nor provides any basis for restricting compounded drugs to disease indications.

Functional Uses

Support for optimal function or therapeutic support are legitimate purposes undertaken by medical and naturopathic care that are completely missing from FDA consideration. Clinical modeling and evidence of the role of antioxidants, for example, in optimal functioning are less susceptible to controlled study but the evidence for many of these ingredients for such use is nonetheless ample. Alpha lipoic acid is a potent anti-oxidant, which is a valuable support for healthy functioning. The health effects of antioxidants are well-recognized, and as an ingredient in a compounded formulation could have obvious value. Ingredients that have recognized anti-inflammatory effects[2] have been recommended for denial by FDA because of its position that physicians should not be able to offer such support to their patients unless the evidence reaches the additional threshold of evidence that it can treat a disease. The FDA did not make that part of its request of nominators in its original request, nor has not subjected the wisdom of this health policy to notice and comment, as it is but one of many major health policy decisions that are completely absent[3] from its December 16, 2015 Anticipated Notice of Proposed 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," failing both in its legal duties and obligations to understand the arena it is regulating.

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[2] The FDA recommended the denial of resveratrol, for example, which it considered for both for the treatment of pain and impaired glucose tolerance. In its briefing paper the 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. While the FDA was concerned about bioavailability and bimodal dosing responses, this was within the context of managing disease and not an assessment of the role it can play as an antioxidant in prevention and functional support for wellness. Other examples of the complete disregard for functional purposes thus far include N-acetyl-D-glucosamine, 5-HTP (oxitriptan), alanyl-L-glutamine, acetyl-L-carnitine, and N-acetyl-D-glucosamine (recommended for disapproval for oral use).

[3] *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.

This omission of functional care considerations has been pervasive in the ingredient review process as many of the ingredients reviewed have been ingredients marketed as dietary supplements for functional purposes. Physician prescribed combinations of nutrients may be used by physicians practicing functional medicine pursuant to schools of medical or naturopathic thought, taught in properly recognized universities or credentialed educational programs that receive ACCME Category I CME certification. 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, and made no findings. Our submissions of these three products provide examples of such uses and FDA should not impose a disease claim requirement where actual practice is not based on such claims. The rejection without comment of a field of recognized care is arbitrary and capricious as a legal matter and poor practice as a matter or public health policy.

Nutritional Uses

Some compounded products may also provide convenient, tailored nutrient support specific to the health needs of a patient. This promotes convenient use, avoids allergens and contaminants, and in some cases may include prescription items as part of an overall treatment and support approach. Patients may require compounded ingredients due to 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 nutraceuticals can increase patient compliance, maximize synergistic effects and assist in treating difficulties with absorption or other digestive issues. Sublingual routes of administration may also be of help with ingredients which present absorption issues in certain patients.

This is a form of compounding practice about which the FDA has taken no cognizance and thus has not addressed its value.

The Role of the United States Pharmacopeia Dietary Ingredient Monographs

The rejection of the United States Pharmacopeia ("USP") dietary ingredient monographs generally, and of specific nutraceuticals as the process moves forward, threatens to eliminate these entire methods of practice. Whether or not this is by design, the FDA has shown no signs that it is aware of this practice or the impact it's regulatory course is having upon it. There has been no discussion in the Compliance Policy Guidance documents, federal register, PCAC briefing documents or in the PCAC meetings about this practice. No voting member of the PCAC Committee has any training or experience in this form of practice. Compounding pharmacists have always been free to compound items listed in the USP and for the purposes described in this letter are an important practice that should continue.

However these issues are ultimately addressed, the FDA's requirement for a disease indication and restrictive reviews of ingredients based on a concern that physicians may use a dietary supplement for functional or therapeutic purposes ignores areas of medical and naturopathic practice outside of FDA's expertise. Physicians with training and experience in such use, whether because of anticipated therapeutic effects or unique assimilation issues should be legally allowable without each nutrient having to go through disease indication levels of scrutiny.

We would appreciate it if you would share this letter with the members of the PCAC so that our concerns may be considered directly by the Committee.

Sincerely,

Alan Dumoff

Enclosures
AANP / IMC submission for alpha-lipoic acid
AANP / IMC submission for choline chloride
AANP / IMC submission for methylcobalamin

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Alpha Lipoic Acid
Submitted January 26, 2018

The American Association of Naturopathic Physicians ("AANP") and the Integrative Medicine Consortium ("IMC") submit this response to the FDA's questions regarding the nomination of Choline inclusion on the 503A bulk drug substances requested due by Jan. 26, 2018.

Q. Do our organization still want to pursue review by the FDA and consideration by the PCAC of alpha lipoic acid for inclusion on the 503A bulk list?

A. Yes.

Q. Please explain whether the nominated molecule is enantiomerically pure or a racemic mixture.

A. Racemic mixture.

Q. Alpha lipoic acid is minimally soluble in water and unstable unless protected from air and light. Please provide any information available about how these issues are addressed for compounded products, especially intravenous formulations.

A. Co-nominator McGuff Compounding Pharmacy has performed a stability study on for its alpha lipoic acid compounded preparations to demonstrate formulation stability through the assigned Beyond-Use Date.

The following parameters were examined and/or tested as part of the stability program:

i. Appearance, seal
ii. Appearance, vial
iii. Appearance, preparation
iv. Foreign matter, visible particulate
v. pH
vi. Potency assay, HDLC
vii. Sterility
viii. Antitoxin
ix. Method suitability, sterility test
x. Container closure integrity
xi. Preservative effectiveness (for multi-dose vial)
xii. Preservative concentration (for multi-dose vial)

Q. Please confirm in writing the proposed uses identified in your nomination. For those uses of the nominated substance that you want FDA to review, provide at least one scientific

article supporting each use, and identify the dosage form and strength/concentration for each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.

A. The routes of administration and compounded dosage form is a oral capsules ranging from 100 to 500 mg, topical use and parenteral injection of 25 mg/mL or 40 mg/mL concentration. The listing below includes some of the known uses for alpha lipoic acid:

Diabetic neuropathic pain [For e.g., ICD-10 E13.40; Ideopathyic Neuropathy ICD-10G60.9]. ALA is an approved treatment for diabetic neuropathy in Germany.

a. "Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy." Reljanovic M, Reichel G, Rett K, Lobisch M, Schuette K, Möller W, Tritschler HJ, Mehnert H. Free Radic Res 1999 Sep; 31(3): 171-9.

b. "Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy." Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schütte K, Kerum G, Malessa R. Diabetes Care. 1999 Aug;22(8):1296-301.

c. "Alpha lipoic acid: a new treatment for neuropathic pain in patients with diabetes?" A Review by Mijnhout, A. Alkhalaf, N. Kleefstra, HJG. Neth J Med 2010 Apr; 68(4):158-62.

d. "Preventing complications and treating symptoms of diabetic peripheral neuropathy." Comparative Effectiveness Review Number 187. Johns Hopkins University Evidence-based Practice Center.

e. "Predictors of improvement and progression of diabetic polyneuropathy following treatment with a-lipoic acid for 4 years in the NATHAN 1 trial." Ziegler D, Low PA, Freeman R, Tritschler H, Vinik AI. J Diabetes Complications. 2016 Mar;30(2):350-6.

Pancreatic cancer [For e.g., ICD-10 D01.7]

a. "The long-term survival of a patient with stage iv renal cell carcinoma following an integrative treatment approach including the intravenous alpha-lipoic acid/low-dose naltrexone protocol." Berkson, BM and Calvo, RF. Integr Cancer Ther 2017 Dec 1 epub.

b. "Revisiting the ALA/N (a-lipoic acid/low-dose naltrexone) protocol for people

with metastatic and nonmetastatic pancreatic cancer: a report of 3 new cases." Berkson BM, Rubin DM, Berkson AJ. Integr Cancer Ther 2009 8: 416.

Hepatitis C [For e.g., ICD-10 B17.10]

a. "A conservative triple antioxidant approach to the treatment of hepatitis c combination of alpha lipoic acid (thioctic acid), silymarin, and selenium: three case histories." Berkson BM. MEd Klin (Munich) 1999: Oct 15;94 Suppl 3:84-9.

Liver Disease, Cirrhosis and Toxic Disease [For e.g., ICD-10 K71.8]

a. "Alpha lipoic acid and liver disease." Berkson, BM. Townsend Letter, Dec 2007.

b. "Lipoic acid in liver metabolism and disease" Bustamente, J. Lodge, JK, Marcocci L, Tritschler HJ, Packer L, Rihn BH. Free Radic Biol Med. 1998 Apr; 24(6):1023-39.

Mushroom Poisoning [For e.g., ICD-10 T62.0X1A]

a. "Thioctic acid in the treatment of poisoning with alpha-amanita." Barter and Berkson.

Fibromyalgia and Muscle Pain [For e.g., M78.7]

a. "Innovations in the management of musculoskeletal pain with alpha-lipoic acid (impala trial): study protocol for a double-blind, randomized, placebo-controlled crossover trial of alpha-lipoic acid for the treatment of fibromyalgia pain." Gilron L, Tu D, Holden R, Towheed T, Ziegler D, Wang L, Milev R, Gray C. AMIR Res Protoc 2017 Mar 28;6(3).

Q. Prioritize the uses of alpha lipoic acid in order of strongest to weakest scientific support.

A. The following conditions are prioritized for the uses of alpha lipoic acid from strongest to weakest scientific support: diabetic neuropathy, hepatitis, fibromyalgia and pancreatic cancer.

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Methylcobalamin
Submitted January 26, 2018

The American Association of Naturopathic Physicians ("AANP") and the Integrative Medicine Consortium ("IMC") submit this response to the FDA's questions regarding the nomination of Methylcobalamin inclusion on the 503A bulk drug substances requested due by Jan. 26, 2018.

Q. Do our organizations still wish to pursue review by the FDA and consideration by the PCAC of Methylcobalamin for inclusion on the 503A bulk list?

A. Yes.

Q. Please confirm in writing the proposed uses identified in your nomination. For those uses of the nominated substance that you want FDA to review, provide scientific articles supporting each use, and identify the dosage form and strength/concentration for each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.

A. The routes of administration include oral, ranging from 500 to 5000 mcg; sublingual, ranging from 500 mcg to 5000 mcg troche or liquid; nasal, ranging from 250-500 mcg/spray 0.1 ml; and parenteral subcutaneous injection or infusions ranging from 0.5 mg/mL to 12.5 mg/mL for all listed uses for methylcobalamin below:

Autistic Spectrum Disorder [For e.g., ICD-10 F84.0]

a. "Treatments for biomedical abnormalities associated with autism spectrum disorder." Frye RE, Front Pediatr 2014 June 27;2:66.

b. "Randomized, placebo-controlled trial of methyl b12 for children with autism." Hendren RL." James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S. J Child Adolesc Psychopharmacol. 2016 Nov, 26(9):774-783.

c. "Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism." James SJ, Melnyk S, Fuchs G, et al. Am J Clin Nutr. 2009;89(1):425-30.

d. "Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism." James SJ, Cutler P, Melnyk S, et al. Am J Clin Nutr. 2004 Dec;80(6):1611-7.

e. "Effectiveness of methylcobalamin and folinic acid treatment on adaptive behavior in children with autistic disorder is related to glutathione redox status." Frye, RE, Melnyk S, Fuchs G, Reid T, Jernigan S, Pavliv O, Hubanks A, Gaylor DW, Walters, L, James SJ. Autism Res Treat. 2013 Oct 12:epub.

Diabetic and Idiopathic Neuropathy [For e.g., ICD-10 E13.40; Idiopathic Neuropathy G60.9; Neualgia and neuritis M79.2]

a "Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials." Sun Y. Acta Neurol Taiwan. 2005; June 14(2): 48-54.

b. "Intravenous methylcobalamin treatment for uremic diabetic neuropathy in chronic hemodialysis patients." S. Kuwabara. Intern Med. 1999. Jun; 38(6):472-5.

Pain Management [For e.g. ICD-10 G89.4]

a. "Intravenous and intrathecal methylcobalamin: a potential vitamin of pain killer." Zhang. Neuro Plast 2013 Epub 2013 Dec 26.

Amyotrophic Lateral Sclerosis [For e.g., ICD-10 G12.21]

a. "Effect of ultrahigh-dose methylcobalamin on compound muscle action potentials in amyotrophic lateral sclerosis: a double-blind controlled study." Kaji R, Kodama M, Imamura A, et al. Muscle Nerve. 1998;21(12):1775-8.

b. "Neuroprotective effect of ultra-high dose methylcobalamin in wobbler mouse model of amyotrophic lateral sclerosis." Ikeda K, Iwasaki Y, Kaji R. J Neuro Sci. 2015 Jul 15;354(1-2:70-4.

Genetic Metabolic Disorders, such as MTHFR [For e.g., ICD-10 Z15.89]

a. "Anxiety and Methylenetetrahydrofolate Reductase Mutation Treated With S-Adenosyl Methionine and Methylated B Vitamins." Anderson S, Panka J, Rakobitsch R, Tyre K, Pulliam K. Integrative Medicine: A Clinician's Journal. 2016;15(2):48-52.

Q. Provide additional information you believe would be useful for us to consider.

A. There is an FDA registered medical food, METANX, with Methyl B-12 as a primary ingredient. The claim is for usefulness in multiple disorders and lists numerous references. *See* http://www.metanx.com/pdf/METANXCapsulesPIStatement.pdf
It has safety data and has been in use over 5 years. It has common allergens [MILK AND SOY] which provides an additional reason that it should be available to compound PO.

STATED INDICATIONS: METANX® is indicated for the distinct nutritional requirements of individuals with endothelial dysfunction who present with loss of protective sensation and neuropathic pain associated with diabetic peripheral neuropathy. METANX® is also indicated for the distinct nutritional requirements of patients with endothelial dysfunction and/or hyperhomocysteinemia who present with lower extremity ulceration(s).

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Choline Chloride
Submitted January 26, 2018

The American Association of Naturopathic Physicians ("AANP") and the Integrative Medicine Consortium ("IMC") submit this response to the FDA's questions regarding the nomination of Choline inclusion on the 503A bulk drug substances requested due by Jan. 26, 2018.

Q. Do our organizations still wish to pursue review by the FDA and consideration by the PCAC of choline for inclusion on the 503A bulk list?

A. Yes.

Q. Please submit in writing the disease state(s) or health condition(s) that you are proposing for the FDA's review, the dosage form and strength/concentration proposed for each use, and scientific articles in support of each use.

A, Without waiving the objections contained in the accompanying letter, at the compounded dosage and delivery of a parenteral injection of 50 mg/mL concentration as a chloride salt, the listing below includes some of the known uses for choline:

Liver Diseases; Hepatic Steatosis [For e.g., ICD-10 K70.0, K76.0]

a. "Studies on the Effects of Intravenously Administered Choline Chloride in Patients with and without Liver Disease." Stegmann. J. 1953.

b. "Choline supplementation protects against liver damage by normalizing cholesterol metabolism in Pemt/Ldlr knockout mice fed a high-fat diet." Rajabi A, Castro GS, da Silva RP, Nelson RC, Thiesen A, Vannucchi H, Vine DF, Proctor SD, Field CJ, Curtis JM, Jacobs RL. J Nutr. 2014 Mar;144(3):252-7.

c. "The Addition of Choline to Parenteral Nutrition." Buchman A. Gastroenterology 2009 Nov;137 (5 Suppl):S119-128 (Steatosis).

d. "Revisiting the ALA/N (a-Lipoic Acid/Low-Dose Naltrexone) Protocol for People With Metastatic and Nonmetastatic Pancreatic Cancer: A Report of 3 New Cases." Berkson BM, Rubin DM and Berkson AJ. Integr Cancer Ther 2009 8: 416.

Fetal Alcohol Spectrum Disorder

a. "Randomized, double-blind, placebo-controlled clinical trial of choline supplementation in school-aged children with fetal alcohol spectrum disorders." Nguyen TT Risbud RD, Mattson SN, Chambers CD, Thomas JD. Am J Clin Nutr. 2016 Dec;104(6):1683-1692. Epub 2016 Nov 2.

Atherosclerosis

a. Lipotropic factors and atherosclerosis; action of methionine, choline and inositol on experimental cholesterol atherosclerosis. Capretti G, Paglia G. G Clin Med. 1950 Sep;31(9):1120-37.

b. ["Action of lipotropic factors in atherosclerosis"]. Concours Med. 1954 Nov 13;76(46):4207-9. [Article in French] Millot J (French)

Functional Support [For e.g., ICD-10 G31.84]

a. "Citicoline improves memory performance in elderly subjects." Alvarez XA, Laredo M, Corzo D, Fernández-Novoa L, Mouzo R, Perea JE, Daniele D, Cacabelos R Methods Find Exp Clin Pharmacol. 1997 Apr;19(3):201-10.

February 23, 2018

VIA EMAIL
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Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
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Re: Response to Requests for More Information on Nominations for Methylcobalamin and Alpha-Lipoic Acid
Docket FDA-2015-N-3534-0001

Dear LT. Hallman:

I write on behalf of and the American Association of Naturopathic Physicians ("AANP") and its partner in these submissions, the Integrative Medicine Consortium ("IMC"), in response to your requests for more information about the nominations of the above-named ingredients.

AANP and IMC rely upon and incorporate by reference any data on the number of prescriptions or of historical use submitted by McGuff Pharmacy, the Professional Compounding Centers of America, Medisca, International Academy of Compounding Pharmacists and the Alliance for Natural Health-USA. In the enclosed materials we provide additional information about historical and current uses.

Sincerely,

Alan Dumoff

Enclosures
Additional AANP / IMC submission for methylcobalamin and alpha-lipoic acid
Full journal articles as noted in the attached bibliographies

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American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Methylcobalamin
Submitted February 23, 2018

Additional References

Tamura J, Kubota K, Murakami H et al. Immunomodulation by vitamin B12: augmentation of CD8þT lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. Clin Exp Immu- nol (1999) 116,28 - 32.

Shibuya K1, Misawa S, Nasu S et al. Safety and efficacy of intravenous ultra-high dose methylcobalamin treatment for peripheral neuropathy: a phase I/II open label clinical trial. Intern Med. 2014;53(17):1927-31. Epub 2014 Sep 1.

Prousky, JE. Understanding the Serum Vitamin B12 Level and its Implications for Treating Neuropsychiatric Conditions: An Orthomolecular Perspective. JOM 25:2 (2010).* (PDF attached).

Xu Q, Pan J, Yu J et al. Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy. Diabetes Res Clin Pract. 2013 Aug;101(2):99-105. doi: 10.1016/j.diabres. 2013.03.033. Epub 2013 May 9.*

Historical Use Data

AANP and IMC rely upon and incorporate by reference any data on the number of prescriptions or of historical use submitted by McGuff Pharmacy, the Professional Compounding Centers of America, Medisca, International Academy of Compounding Pharmacists and the Alliance for Natural Health-USA. In addition we provide the following:

Physician comments submitted to AANP about the current clinical and historical reasons for using methylcobalamin:

Note in the following physician statements the need for compounded, injectable dosages including the absorption difficulties or tolerance for oral dosing faced by many patients; the need for this form of B12 including genetic defects and specific processing problems for cyanocobalamin; specific case reports of various ailments and for proper immune function; and financial reasons why compounded versions should be available. These represent a small sample of the clinical and historical bases for use:

“I have used many of these compounded substances in my practice for a variety of patient specific needs. In fact I have never used as B12 other than methylcobalamin for IM or IV applications as the majority of the American population has an MTHFR SNP I would give the

activated form to all patients without adverse events.

I have used L-glutathione (L-GSH) IV to support detoxification as this is our bodies most powerful antioxidant, specifically in people who are detoxifying from drug/etoh use and heavy metal/chemical/mold exposures. 1000-2000 mg qwk GSH IV in Parkinson's disease has improved symptoms regardless if they are using carbidopa-levodopa or other pharmaceuticals to improve symptoms. In addition to IV GSH I typically add in oral GSH. PMID: 8938817, 19230029. I have used IV ALA, choline, and quercetin less frequently, though, with symptomatic improvements and no adverse events.

These compounded substances have been beneficial to numerous patients in my practice. It is important to maintain access for patients to these high quality compounded substances. I'm grateful to McGuff Compounding for providing outstanding service and products for our patients and continuing to stand for compounded substances.

Audrey Schenewerk, ND, MS"

"I have been a practicing ND now for 18 years. I have yet to see a medicine that provides the expedient relief that intramuscular injections of methylcobalamin does for fibromyalgia patients. Many of these patients have suffered many years with the debilitating fatigue, insomnia and pain issues characteristic of this disorder. In many cases, these patients have positive tests for the inability to process synthetic forms of B12 (cyanocobalamin). Methylcobalamin bypasses this problematic biochemistry and provides the activated nutrient essential to recovery for these patients. In addition, the injectable form bypasses the GI system, which is also often problematic with this disorder. We just do not get the results with oral dosing of methylcobalamin that we see with the injectable.

I urge the FDA to consider the many thousands of patients of this sort who would be denied access to a safe and effective medicine. Please retain methylcobalamin availablility through our local compounding pharmacies.

Joanne M. Hillary PhD, ND
Hillary's Health
9103 N. Division St.
Spokane, WA 99218"

"I am writing a patient account in support of the compounding of methylcobalamin.

I have a patient who has pernicious anemia and genetic mutations affecting her methylation. She has seen improvements since doing injectable cyanocobalamin. However, we changed her injections to methylcobalamin 2 months ago and her energy has been steadily and dramatically improving in a way we have not seen with any other form of injectable cobalamin. She has been

able to exercise and is also sleeping better since this change. This has had a profound impact on her daily life, her work, her relationships, and what she feels is possible for her future. Without the methylcobalamin, I have every reason to believe she will lose these improvements since that was the only thing in her treatment that changed to correlate with these improvements.

Kimberly Hindman, N.D., L.Ac."

"Clinical case: Parkinson's disease.
60yr female, Height: 5"0" weight 110lbs.
Patient presented with neuropathy and common PD tremors in hands and legs as well as with muscles pain and stiffness, worse in her legs. Clinical investigation with cyanocobalamin IM injections to relieve symptoms revealed that 1,000mcg/mL, 1mL total volume, gave significant improvement in symptoms within a few hours of injection. Additionally, the patient found that she had more energy to complete activities of daily living, including cooking and cleaning, than she had had in years. She was functioning near normally to her and her family's astonishment. She felt her PD symptoms were about 80% better.

In an attempt to optimize her B12 status and symptom relief, 2,000 mcg were injected. While the patient did get benefit from her neuropathy, muscle stiffness and tremors, she experienced a slight sensation of being "amped up" which meant she felt her heart rate was slightly elevated and had a feeling of being jittery. This subsided within a few hours.

Ultimately, the patient's symptoms were found to be best treated with a 12,000 - 15,000mcg dose. This is only available through compounding.

This patient deserves for her symptoms to be better than 80%, which is what a single commercially available dose provides. If compounding of cyanocobalamin is unavailable to her, she will be forced to pay double for her injectable medication (already not covered by her insurance) and discard 50% of a vial. Why should she have to waste her B12 injectable material and pay more?

Dr. Nicole Anderson"

"I have been using methylcobalamin in my practice for over a year. This compounded vitamin has changed literally hundreds of my patients lives. I have seen the following:
- reduced anxiety
- improved stress response
- weight loss
- improved sleep
- general mood improvement
- reduced aggression
- improved immune health

All of these benefits have been reported by my patients. Many of these patients had sought out pharmaceuticals to address all of the above conditions without any reprieve. Many patients had sought out cyanocobalamin or hydroxycobalamin injections previously without any benefit. We are seeing an increase in patients with methylation difficulties, and removing methylcobalamin would be incredibly detrimental to their health.

Dosing:
IM: 2.5 mg biweekly
IV: 5 mg monthly

Dr. Elisse Evans, ND
Origins Integrative Medicine
originsintegrative.com
928 Garden St. Ste. 1
Santa Barbara, CA
805-203-6877”

“This is an essential ingredient in neuro-regenerative protocols and fatigue care for many patients (fibromyalgia, epstein barr virus, etc).

As a concerned and very hard working physician I would like to tell you about a few patients I have who need the Methylcobalamin (B12) in particular. First they have genetic defects that affect their body processing B12 orally, second they have nausea and even vomiting if they take Methylcobalamin or any other B-Vitamins orally. These folks need the injectable types of B12 and B-vitamins or they will remain ill. I have a number of clients who also receive Glutathione for various health concerns and getting this again as an oral supplement is unworkable as it is very un-absorbable through the GI system.
- Methycobalamin
- Quercitin
- Reduced L-Glutathione
- Alpha Lipoic Acid
- Choline Chloride

Dr. DeeAnn G. Saber, NMD is part of Wellness First!, a collaborative, holistic community of practitioners in Tucson, AZ, dedicated to personal integrity, professionalism, and service.
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www.3861WellnessFirst.com”

“Methylcobalamin is the form of vitamin B12 that can be used immediately without modification or conversion in the body. This is especially important for people with genetic mutations that make it difficult to activate compounds in the body by methylation. Methylcobalamin is especially important for immune health. Deficiency of Methylcobalamin in humans has been shown in research to decrease lymphocytes and suppress natural killer (NK) cell activity. NK cells are a type of white blood cell that attack cells infected by viruses. Supplementation of Methylcobalamin provides patients with the defenders necessary to stay healthy. Methylcobalamin has been especially helpful in reducing homocysteine levels in many patients. It is imperative for us to allow IV and IM compounded Methylcobalamin for patients who are unable to take it orally, and for patients who have digestive issues such as Celiac disease and IBD that prevent them from absorbing oral vitamins.

Dr. Samantha Larkin, ND”

“My first patient, 20 years ago, was a 40-something artist with severe neurological impairments. She had over $50,000 in tests performed, a lot of money for tests in those days. Finally her neurologist told her to put her affairs in order as she did not have much time left to live. She gave away and sold everything for her last hurrah, a trip to Mexico. On the recommendation of a friend of hers she came to me just before taking her trip. I gave her a homeopathic remedy and started her on 5 mg IM methylcobalamin daily. Within a week she was fine. She came back from her Mexico trip and was not sure what to do as she had to find a job, a place to live, and restock with all the things she needed to live.

About 10 years ago, a woman brought her ten-year old autistic son to me. She had already begun numerous treatments which were showing promise. One of them was 5 mg methylcobalamin every other day, slowly tapering down. Another was hyperbaric oxygen therapy. With continued treatment he went on to become completely normal. As a matter of fact,
the school principal, who fancied himself an expert on learning disabilities, told the mother that her son was not autistic and could not have been. He became one of the most popular boys in his class, a magnet for girls as his mother described him.

About five years ago I had a cancer patient who was suffering severe after-effects of conventional treatments. The main thing I offered was 10 mg doses of methylcobalamin. The patient recovered very quickly from the toxic effects of the conventional treatments.”

“From: Michael Traub ND, FABNO
[Excerpt]

Dear Committee members:

I understand you are asking for additional information to defend why these following ingredients

should be reviewed and included in the 503A bulk drug substances list:

- Methylcobalamin
- Quercetin
- Reduced L-Glutathione
- Alpha Lipoic Acid
- Choline Chloride

I have been using these agents safely and successfully for many years and I would like to urge you to include these substances in the 503A bulk drug substances list. They are extremely valuable and I would like to share one anecdote that exemplifies this:

On April 25, 2016 I was consulted by a 69 year old woman complaining of pain in her hands and feet of several months duration, with erythema and dry skin, as a result of chemotherapy-induced peripheral neuropathy from Taxotere that she had received for localized inflammatory breast cancer. Two days later she returned to my clinic and received an intravenous infusion of alpha lipoid acid 250 mg and followed by an intramuscular injection of methylcobalamin 5 mg. The following day she reported that her pain, the erythema and dry skin had all completely resolved within the prior 24 hours.

To this day (February 20, 2018), there has been no recurrence of any symptoms of the peripheral neuropathy, and the patient is asymptomatic with minimal residual disease.

This case is just one of many of my patients that have benefitted from the valuable agents in questions. Please use your authority to preserved their availability.

Thank you.

Sincerely,

Michael Traub ND, DHANP, FABNO
Primary Care Medicine
Board Certified in Naturopathic Oncology
Founder and Medical Director
Lokahi Health Center
75-169 Hualalai Rd, Suite 301
Kailua Kona, HI 96740
Phone 808.329.2114
Fax 808.326.2871
mtraubnd@me.com
michaeltraubnd.com”

"To Whom It May Concern:

As a naturopathic doctor, I often use methylcobalamin as a treatment because many of my patients are truly deficient in vitamin B12. The nutrient deficiency is first confirmed via lab testing and dosing is dependent on the degree of deficiency and how well the patient tolerates the medicine. Methylcobalamin is the bioactive form of vitamin B12, therefore, is easier to absorb and I find the diverse forms (i.e. oral, IV, sublingual, etc) afford better compliance for the patient. Methylcolabamin has been key in helping me to treat fatigue, inflammation, eczema, toxic overburden, and more. Given it is also water soluble, this naturally limits the risk of overdosing as well. . .

Dr. Ray, ND MS: The People's Doctor
(Revée Barbour, CA Lic#: 868)
1215 K Street, 17th Floor
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Ph#: (916) 503-3189
Fax#: (916) 415-1979
Email: Ray@DrRayND.com
Website: www.DrRayND.com"

Patient Comments submitted to AANP about their experience with methylcobalamin
(Names withheld for privacy):

"I have used both methylcobalamine and cyanocobalamine and strongly prefer methyl. I have had weekly B12 shots for many years due to a medical condition and ask that it remain available."

"I have a genetic fault/mutation found through MTHFR DNA Analysis. The two mutations (C677T and A1298C) combine to greatly inhibit my absorption of B12 through my diet. The mutations were discovered by Tamara Trebilcock, ND about 4 years ago when I consulted her for symptoms of pernicious anemia including peripheral neuropathy, burning tongue, burning and tingling in my thighs and feet and hands. After this discovery Dr. Trebilcock suspected that I was B12 deficient and ordered weekly injections of 2.0 cc of methylcobalamin combined with 0.5 cc of Vitamin B complex. My symptoms greatly diminished over the next 2 to 4 weeks after starting the injections. On two different occasions over the past 4 years I stopped the B12/ methycobalamin injections and my symptoms returned."

"I urge the FDA and the PCAC not to restrict the availability of methylcobalamin. It is absolutely critical to my health and well being. It turns out that my body cannot convert the other available forms of cobalamin e.g. cyanocobalamin, into the methyl form which I require."

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Alpha-Lipoic Acid
Submitted February 23, 2018

Additional Indications: Improves insulin-resistance and glucose disposal in type 2 diabetes, chronic fatigue
(Natural Medicines Database)

Additional Dosing Information: Administered intravenously in dosages no greater than 600 mg. Impaired glucose tolerance: 250mL of saline solution containing 600mg ALA. Ischemia-reperfusion injury protection: A dose of 600mg of alpha-lipoic acid in 50mL of sodium chloride. Type 2 diabetes: Alpha-lipoic acid 500-600mg in saline. (Natural Medicines Database)

Attached, *see* the application to amend schedule of substances under the General Regulation of the College of Naturopaths of Ontario and the clinical study data listed there.

Additional References

Grbovic V, Jurisic-Skevin A, Djukic S et al. Comparative analysis of the effects combined physical procedures and alpha-lipoic acid on the electroneurographic parameters of patients with distal sensorimotor diabetic polyneuropathy. J Phys Ther Sci. 2016 Jan;28(2):432-7. Epub 2016 Feb 29.*

Mijnhout GS, Kollen BJ, Alkhalaf A et al. Alpha lipoic Acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. Int J Endocrinol. 2012;2012:456279. Epub 2012 Jan 26. *

Xu Q et al. Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy.Diabetes Res Clin Pract. 2013 Aug;101(2):99-105.Level:A

Grbovic V et al. Comparative analysis of the effects combined physical procedures and alpha-lipoic acid on the electroneurographic parameters of patients with distal sensorimotor diabetic polyneuropathy.J Phys Ther Sci. 2016 Jan;28(2):432-7. Level: A

Xiang G et al. a -Lipoic acid can improve endothelial dysfunction in subjects with impaired fasting glucose. Metabolism. 2011 Apr;60(4):480-5 Level: A.*

Xu Q, Pan J, Yu J et al. Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy. Diabetes Res Clin Pract. 2013 ug;101(2):99-105. doi: 10.1016/j.diabres.2013.03.033. Epub 2013 May 9.*

Historical Use Data

AANP and IMC rely upon and incorporate by reference any data on the number of prescriptions or of historical use submitted by McGuff Pharmacy, the Professional Compounding Centers of America, Medisca, International Academy of Compounding Pharmacists and the Alliance for Natural Health-USA. In addition we provide the following:

Physician comments submitted to AANP about the current clinical and historical reasons for using alpa lipoic acid:

To Whom It May Concern:

Alpha lipoic acid (ALA) is one of my miracle nutrients for treating resistant cases of diabetes type 2, drug-induced polyneuropathy, and neuro-inflammation. Recently, one of my patients reduced her HgbA1c from 7.2 to 6.2 after only 3 months of taking ALA at 600mg, BID. A couple other patients have almost complete resolution of peripheral neuropathy in their fingers and toes as a side effect of their chemotherapy.

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Jan. 26, 2018

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Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903
Email: toni.hallman@fda.hhs.gov

RE: Docket FDA-2015-N-3534

Dear Ms. Hallman,

McGuff Compounding Pharmacy Services, Inc. (MCPS) is responding to the FDA's questions to the nomination of Alpha Lipoic Acid's inclusion on the 503A bulk drug substances list due by Jan. 26, 2018.

Responses:

Q. Does MCPS still want to pursue review by the FDA and consideration by the PCAC of alpha lipoic acid for inclusion on the 503A bulk list?
A. Yes.

Q. Please explain whether the nominated molecule is enantiomerically pure or a racemic mixture.
A. Racemic mixture.

Q. Alpha lipoic acid is minimally soluble in water and unstable unless protected from air and light. Please provide any information available about how these issues are addressed for compounded products, especially intravenous formulations.
A. MCPS has performed a stability study on for its alpha lipoic acid compounded preparations to demonstrate formulation stability through the assigned Beyond-Use Date. The following parameters were examined and/or tested as part of the stability program:
   i. Appearance, seal
   ii. Appearance, vial
   iii. Appearance, preparation
   iv. Foreign matter, visible particulate
   v. pH

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vi. Potency assay, HPLC
vii. Sterility
viii. Endotoxin
ix. Method suitability, sterility test
x. Container closure integrity
xi. Preservative effectiveness (for multi-dose vial)
xii. Preservative concentration (for multi-dose vial)

Q. Please confirm in writing the proposed uses identified in your nomination. For those uses of the nominated substance that you want FDA to review, provide at least one scientific article supporting each use, and identify the dosage form and strength/concentration for each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.

A. The compounded dosage form is a parenteral injection of 25 mg/mL or 40 mg/mL concentration. The listing below includes some of the known uses for alpha lipoic acid:

Diabetic neuropathic pain

a. "Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy." Reljanovic M1, Reichel G, Rett K, Lobisch M, Schuette K, Möller W, Tritschler HJ, Mehnert H.
b. "Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy." Ziegler D1, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schütte K, Kerum G, Malessa R.
c. "Alpha lipoic acid: a new treatment for neuropathic pain in patients with diabetes?" A Review by G.S. Mijnhout, A. Alkhalaf, N. Kleefstra, H.J.G.
d. "Preventing Complications and Treating Symptoms of Diabetic Peripheral Neuropathy." Comparative Effectiveness Review Number 187. Johns Hopkins University Evidence-based Practice Center.

Pancreatic cancer

e. "The Long-Term Survival of a Patient With Stage IV Renal Cell Carcinoma Following an Integrative Treatment Approach Including the Intravenous α-Lipoic Acid/Low-Dose Naltrexone Protocol." Burton M. Berkson, MD, MS, PhD and Francisco Calvo Riera, MD.
f. "Revisiting the ALA/N (a-Lipoic Acid/Low-Dose Naltrexone) Protocol for People With Metastatic and Nonmetastatic Pancreatic Cancer: A Report of 3 New Cases." Burton M. Berkson, Daniel M. Rubin and Arthur J. Berkson, Integr Cancer Ther 2009 8: 416.

Hepatitis C

g. "A Conservative Triple Antioxidant Approach to the Treatment of Hepatitis C Combination of Alpha Lipoic Acid (Thioctic Acid), Silymarin, and Selenium: Three Case Histories." Burton M. Berkson.

Liver Disease, Cirrhosis

h. "Alpha Lipoic Acid and Liver Disease." Burton M. Berkson, MD, MS, PhD. From the Townsend Letter, December 2007.
i. "LIPOIC ACID IN LIVER METABOLISM AND DISEASE." Juanita Bustamente, John K. Lodge, Lucia Marcocci, Hans J. Tritschler, Lester Packer, and Bertrand H. Rihn.

Mushroom Poisoning

j. "Thioctic Acid in the Treatment of Poisoning with Alpha-Amanita." Barter and Berkson.

Fibromyalgia

k. "Innovations in the Management of Musculoskeletal Pain With Alpha-Lipoic Acid (IMPALA Trial): Study protocol for a Double-Blind, Randomized, Placebo-Controlled Crossover Trial of Alpha-Lipoic Acid for the Treatment of Fibromyalgia Pain." By Ian Gilron, MSc, FRCPC, MD, Dongsheng Tu, PhD, Ronald Holden, PhD, Tanveer

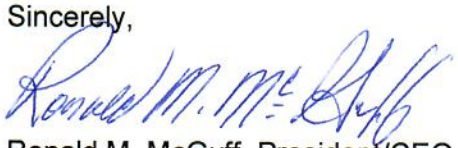
Towheed, FRCPC, MD, Dan Ziegler, Prof Dr Med, Louie Wang, MSc, FRCPC, MD, Roumen Milev, FRCPC, MD, PhD, and Christopher Gray, CCRP.

Q. Prioritize the uses of alpha lipoic acid in order of strongest to weakest scientific support.

A. Based on the parenteral IV formulations compounded by MCPS and the practitioners who have ordered our preparations over the years, the following conditions are prioritized for the uses of lipoic acid from strongest to weakest scientific support: diabetic neuropathy, hepatitis, and pancreatic cancer.

Please let us know if you are in need of any further information.

Sincerely,



Ronald M. McGuff, President/CEO
McGuff Compounding Pharmacy Services, Inc.
2921 W. MacArthur Blvd., STE 142
Santa Ana, CA 92704

Feb. 23, 2018

Toni Hallman, MS, BSN, RN
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McGUFF
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PHARMACY
SERVICES, INC.

RE: Docket FDA-2015-N-3534

Dear Ms. Hallman,

McGuff Compounding Pharmacy Services, Inc. (MCPS) is responding to the FDA's questions to the nomination of Alpha Lipoic Acid's inclusion on the 503A bulk drug substances list due by Feb. 23, 2018.

Responses:

Q. To the extent possible, we request that you submit information regarding the historical use of compounded alpha lipoic acid, such as the approximate number of prescriptions per year for compounded alpha lipoic acid and the uses associated with those prescriptions for compounded alpha lipoic acid.

A. Historically, MCPS has dispensed an average of 2,051 prescriptions annually for various compounded preparations of lipoic acid as follows:

Formulation Strength & Size	Avg Annual Prescription Dispensed
Lipoic Acid 25 mg/mL 30mL	138
Lipoic Acid 40 mg/mL 15mL	894
Lipoic Acid 40 mg/mL 30mL	1,109

Pharmacies aren't required to document the associated use with each prescription. However, some associated uses of compounded lipoic acid include diabetic neuropathic pain, pancreatic cancer, Hepatitis C, cirrhosis/liver diseases, mushroom poisoning, and fibromyalgia.

Individual Patient Statement (Name Removed To Protect Identity):
The possibility that IV Lipoic Acid would no longer be available, literally made me feel faint. I ask, respectfully, that you please consider our lengthy experience and the life changing benefits for our child and our family before acting.

Our child has been dependent on Parenteral (IV) Nutrition for almost 17 years. As this can tax the liver, our pediatrician wanted to prescribe IV Lipoic Acid for several years. We were reluctant because our child

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has a central venous catheter placed in the vein above their heart for the delivery of the IV nutrition. This puts our child at great risk for infection and potentially life threatening complications. In 2008, we were shocked when a liver biopsy revealed Stage 3 of 4 liver fibrosis and Level 2 fatty liver. Finally, we took seriously the prescription for IV Lipoic Acid. There were a number of potential suppliers. We were terrified to use any of them. At the recommendation of our child's pediatrician, we decided McGuff was the best choice. Still, given the need for absolute sterility, and wanting to take all necessary precautions, we had our expert TPN pharmacy team interview McGuff. They were impressed and agreed this was the safest choice. 9 years later, we have infused McGuff's IV Alpha Lipoic Acid thru our child's 16-year-old central venous catheter weekly *without a single issue*. Now more than 474 infusions later, we can say, without a doubt, this is the single best therapy we have ever used. Not only have the weekly IV Alpha Lipoic Acid infusions changed our child's life, but they have changed *entirely* the life of our family. 8 years of TPN related nausea, lack of appetite and poor skin pallor are now history. Thank you McGuff for providing this essential product with the required sterility and safety we need. For all those families facing the enormous physical, emotional, and financial burden of liver transplant, we pray they will find you and this product. God Bless, A 17-year TPN family (UCLA).

Q. Please provide any additional information that FDA should consider in its evaluation that may help to clarify the role of the nominated alpha lipoic acid bulk substance in compounded drugs products in current clinical practice, such as statements or guidelines from professional medical societies.

A. Professionals' Statements:

Dear Committee members:
I understand you are asking for additional information to defend why these following ingredients should be reviewed and included in the 503A bulk drug substances list:

- Methylcobalamin
- Quercetin
- Reduced L-Glutathione
- Alpha Lipoic Acid
- Choline Chloride

I have been using these agents safely and successfully for many years and I would like to urge you to include these substances in the 503A bulk drug substances list. They are extremely valuable and I would like to share one anecdote that exemplifies this:

On April 25, 2016 I was consulted by a 69 year old woman complaining of pain in her hands and feet of several months duration, with erythema and dry skin, as a result of chemotherapy-induced peripheral neuropathy from Taxotere that she had received for localized inflammatory breast cancer. Two days later she returned to my clinic and received an intravenous infusion of alpha lipoid acid 250 mg and followed by an intramuscular injection of methylcobalamin 5 mg. The following day she reported that her pain, the erythema and dry skin had all completely resolved within the prior 24 hours.
To this day (February 20, 2018), there has been no recurrence of any symptoms of the peripheral neuropathy, and the patient is asymptomatic with minimal residual disease.

This case is just one of many of my patients that have benefitted from the valuable agents in questions. Please use your authority to preserve their availability.

Thank you.

Sincerely,

Michael Traub ND, DHANP, FABNO
Primary Care Medicine
Board Certified in Naturopathic Oncology

I've used intravenous ALA for several years on pts with good success. Two impressive examples are both men with liver failure and ascites.

The one has unknown cause for the liver failure and ascites. When I first saw him in 2012 he appeared to be 10 months pregnant with the ascites and was having paracentesis done 1-2X//week just so he could breathe. He was told by mainstream providers to put his affairs in order and was given just a couple months to live. This pt sought care with Dr. Berkson in Las Cruces, NM and recovered quickly. His care was transferred closer to home to my office. We've gradually tapered the treatments and he is still alive, at age 87, and remains a productive member of his community.

The other had metastatic liver cancer from colon cancer. He too, was receiving paracentesis frequently to allow him to breathe and be able to walk. The liver tests began to normalize and he no longer needed the paracentesis. He tolerated the rest of his chemo more easily with the liver functioning better. Unfortunately, this person was being given tube feedings he was allergic to. he would get severe diarrhea and abdominal pain with each feeding. Testing showed he was lactose intolerant, and he'd known that for a long time. But his insurance wouldn't cover an organic tube feeding with no dairy and no dyes. We were able to get him that organic tube feeding and his gut issues settled down. But he has passed since of other complications.

I've used ALA in several other pt situations where liver support was needed and liver function tests normalized. Several of those pts were receiving chemo. Their LFTs would rise as they metabolized the chemo.

With intravenous ALA their LFT returned to normal. We shared the information with their oncologists who told them "I don't know anything about that, but keep doing it!"

We desperately need intravenous ALA.

Sue Peck PhD, GNP-BC, APNP, FAAO, APT, CHTP/I
Integrative Nurse Practitioner
Fellow American Academy of Ozone Therapy

Compounded Alpha Lipoic Acid has been the foundation of many of my intravenous antioxidant therapies. One of my greatest success stories with this medication was with a 62 year old female with Stage II metastatic breast cancer with metastasis to one axillary lymph node.

With a combination of intravenous administration of Alpha lipoic acid and glutathione twice per week, along with oral supplements, and dietary changes this patient survived cancer without the use of radiation and chemotherapy. Following 6 weeks of the aforementioned treatment the patient underwent surgery to have the primary tumor and affected lymph node removed. Histology reports indicated that the cancer had turned benign with no spread to nearby lymph nodes.

My patient survived cancer due to compounded Alpha Lipoic Acid. This is just one of many cases illustrating the need for compounded Alpha Lipoic Acid. Please include this life saving medication on the 503A bulk drug substances list so that future patients' lives can be saved.

Sincerely,

Bryan Dzvonick, ND

Dear Madam/Sir,

I have been using Alpha Lipoic Acid for the past 15 years for :
Neuropathic pain
Status post chemotherapy
Chronic Fatigue Syndrome
Chronic Allergies and
Chronic urticaria.

As you know Lipoic Acid is a co-factor in pyruvate dehydrogenase complex enzyme which is the component in every cell's mitochondria in the body, to produce energy.
Furthermore, it is one of the strongest antioxidants in the body due to its sulf-hydryl group.

Not having this product available to patients will be detrimental to their health.

Sincerely.

Michael Keramati, DO, DDS

To whom it may concern,

This letter is about the use of intravenous alpha lipoic acid (ALA, thioctic acid) as a treatment for various medical conditions including type 2 diabetes and its complications, various liver diseases, and other diseases associated with oxidative stress and inflammation.

Regarding my history with working with ALA, I first became aware of ALA as part of a National Institutes of Health study (1977) on the reversal of acute hepatic necrosis (hepatotoxic mushroom poisoning). FC Bartter MD (former Chief of Endocrinology and Kidney Disease, NIH), I, and others treated 79 patients with acute hepatic necrosis and 75 recovered full liver function within one month. In 1980 Dr. Bartter and I were invited to the Max Planck Institute in Heidelberg to present our studies and publish the results (1,2,3).

In 1983 I was appointed the FDA principal investigator for IV ALA as a prescription drug IND #9957. At that time, I was listed as the CDC expert consultant on the reversal of acute hepatic necrosis using ALA. I taught many how to use IV ALA, and I believe – as do the practitioners who have used this – ALA has saved many lives.

Over the years I began to use IV ALA as a treatment for chronic liver disease including hepatitis C, primary biliary cirrhosis, and progressive sclerosing cholangitis. Most patients did very well with my protocols (4,5,6,7).

Because most cancer cells are anaerobic and don't undergo mitochondrial aerobic metabolism, and because ALA is the cofactor for the production of acetyl Co enzyme A from pyruvate, it made sense that IV ALA might be an effective treatment for some malignant diseases by driving anaerobic cancer metabolism to mitochondrial aerobic metabolism, thus forcing cancer cells to undergo apoptosis.

A number of our patients had been told by their oncologists that their stage 4 cancer is terminal. I suggested to these patients that they continue with their oncologist and possibly use the IV ALA therapy as a complementary treatment.

Several patients started the IV ALA therapy and in many instances their primary tumor and metastases vanished on PET/CT scans and they returned to living normal lives (8,9,10,11).

In 2012 I was invited by the National Cancer Institute to speak in Bethesda about my cancer protocols. I presented seven stage 4 terminal cancers that were effectively treated with IV ALA and other modalities. The NCI experts reviewed each case with positive comments and sent out a NCI newsletter with their favorable opinions (https://cam.cancer.gov/docs/newsletter/nci_cam_news_spring_2012.pdf).

There have also been published positive results using IV ALA for the reversal of DM neuropathies – many not cited here (12).

In 2014, Dr. Vigil, Dr. Garcia and I published a study demonstrating what enormous doses of IV ALA can do to healthy primate mitochondria. An LD50 dose of 90mg/kg was reported. In our medical practice we never administer doses above 15mg/kg (13).

We have been very pleased with McGuff Compounding Pharmacy's IV ALA and trust the integrity of all of their products. Hundreds of our patients depend on this life saving agent for the treatment of their medical conditions and it is essential that they continue to receive this marvelous and effective healing agent.

Thank you for your consideration.

Sincerely,

Burton M. Berkson MD, MS, PhD
Integrative Medical Center of New Mexico
Adjunct Professor, Oklahoma State College of Medicine, Tulsa

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Arthur J. Berkson, MD – See accompanying letter.
Integrative Medical Center of New Mexico

Evelyn Baram-Clothier PhG, JD – See accompanying letter.
American Medical Foundation For Peer Review & Education
Executive Director

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Please let us know if you are in need of any further information.

Sincerely,

Ronald M. McGuff, President/CEO
McGuff Compounding Pharmacy Services, Inc.
2921 W. MacArthur Blvd., STE 142
Santa Ana, CA 92704

Tab 1c

FDA Review of Alpha Lipoic Acid

DATE: August 9, 2018

FROM: Ben Zhang, Ph.D.
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Senior Scientific Advisor (acting), ONDP, OPQ

Charles Ganley, M.D.
Director, ODE IV, OND

Frances Gail Bormel, R.Ph., J.D.
Director, Division of Prescription Drugs, OUDLC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Alpha Lipoic Acid for Inclusion on the 503A Bulk Drug Substances List

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

I. INTRODUCTION

Alpha lipoic acid has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for use in treatment of:

- Diabetic neuropathy and associated pain,
- acute liver toxicity from *Amanita* spp. mushroom poisoning and other toxins,
- hepatitis C,
- cancer,
- cirrhosis,
- fibromyalgia, and
- muscle pain.

Alpha lipoic acid's administration via the intravenous, topical and oral routes have been proposed.

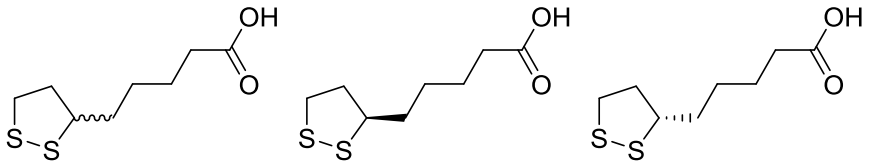
We have reviewed publicly available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh in favor of*** placing alpha lipoic acid solid oral dosage forms on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).[1]

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?[2]

[1] Inclusion 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 should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using a substance included on the list has been proven to be safe and effective under the standards required receiving Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears 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 is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act (21 U.S.C. 352(a), (bb)).

[2] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).



The UNII code provided in the nominations was 73Y7P0K73Y for thioctic acid, also known as α-lipoic acid (ALA) and as lipoic acid. ALA is a small molecule derived from octanoic acid. This UNII code refers to a mixture of two enantiomeric isomers: (R)-(+)-α-lipoic acid, the R or D form, and (S)-(-)-α-lipoic acid, the S or L form. The R form is the naturally active form and is an essential cofactor for mitochondrial enzymes. ALA is currently marketed as an antioxidant in dietary supplements, as either the R form or a mixture of the R and S forms, in capsule, powder and tablet formulations. A mixture of equal portions of R and S forms is a racemic mixture and is referred to in this review using terms from individual published literature references, such as dl-α-lipoic acid (dl-ALA) and "rac." It is also marketed in cosmetics.

Databases searched for information on α-lipoic acid in Section A of this review included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia, United States Pharmacoepia/National Formulary (USP/NF).

1. Stability of the API and likely dosage forms

ALA decomposes gradually at high temperatures and easily polymerizes at temperatures higher than its melting point, which is at 46 - 49 °C (Ikuta et al. 2013). It is also known to be sensitive to light. ALA can undergo photolysis reactions to yield dihydrolipoic acid (DHLA), the reduced form of ALA, which can be easily further polymerized (Brown and Edwards 1969). At 25 °C and 100% relative humidity, around 20% (by weight) of the ALA sodium salt sample undergoes decomposition after 48 hours, but no degradation has been observed for ALA in its acid form after 48 hours (Ikuta et al. 2013).

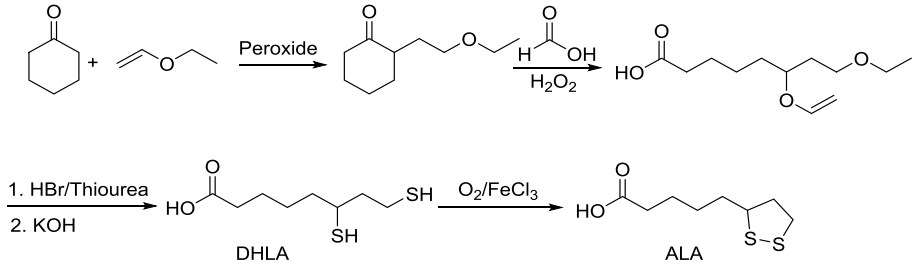
It is known that the racemic mixture is more stable than the enantiomerically pure R form. The racemic mixture may be stored in a closed and sealed amber container at room temperature for a year or longer. In contrast, the R form must be stored in a sealed amber container, refrigerated, and used within a few months (Nelson 2008). The compounded solid oral dosage forms (capsules and tablets) using the racemic mixture are likely to be stable when stored at room temperature and protected from light.

The aqueous formulations are likely to be much more unstable than the solid dosage forms. Due to the low solubility of the substance, the salt forms of the ALA are used in a lot of aqueous formulations, which has a much higher tendency for polymerization at room temperature. When compounded as aqueous solutions using the salt form, the solutions are not expected to be stable; for this reason, only freshly formulated solutions should be used for administration. Due to lack of precise stability information supporting solution formulations of ALA, the stability of the solution forms cannot be determined. Therefore, the stability of the liquid formulations of the drug substance is still of concern. More information regarding the processes used by compounding pharmacies to maintain the stability of aqueous forms of ALA is needed before we

can consider adding aqueous formulations (for intravenous or oral administration) to the 503A list. The information needed may include an example of stability study data to support a proposed expiration date for compounded solutions and directions for use.

2. Probable routes of API synthesis

There have been many reports on the synthesis of ALA, and the one shown below is an inexpensive, high-yield and efficient synthetic route.

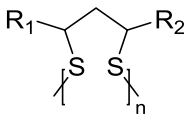


In this synthetic route, DHLA and ALA can be obtained from simple starting materials: cyclohexanone and vinyl ethyl ether. The overall yield of the synthesis is 70 - 80% (Paust et al. 1996).

3. Likely impurities[3]

Likely impurities include:

- Trace amounts of residual solvents and reagents from reactions and purification procedures, such as cyclohexanone, vinyl ethyl ether, and formic acid;
- DHLA can be generated from the photolysis of ALA or as a residue from the last step in ALA's synthesis;
- Oligomers from the polymerization of DHLA (structure shown below) (Brown and Edwards 1969).



$R_1 = R_2 = H$ or $(CH_2)_4COOH$

4. Toxicity of those likely impurities

DHLA is a metabolite of ALA which is found in humans and in animals. Further information on DHLA is discussed in section II.B.1.b.

[3] This review contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration and chronicity of dosing.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

ALA is a yellow powder that is practically insoluble in water under acidic and neutral pHs. However, the aqueous solubility can be increased by salification (using a salt form) of the substance. No further information on the influence of particle size and polymorphism on bioavailability were found in the literature.

6. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

ALA has been well characterized and can be identified with proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), Ultraviolet-visible (UV-Vis) spectroscopy and mass spectrometry (MS).

Conclusions: ALA is a small, simple molecule. The substance is very sensitive to light and heat. It is likely to be stable when compounded as solid dosage forms if strictly protected from light and stored at room temperature. However, the aqueous formulations are less stable because the salts that are used in aqueous solutions to improve solubility have a tendency to polymerize. Therefore, the drug substance is unlikely to be stable when compounded as aqueous solutions. The nominated compound is easily characterized and the synthetic strategy of this compound has been well developed.

B. Are there concerns about the safety of the substance for use in compounding?

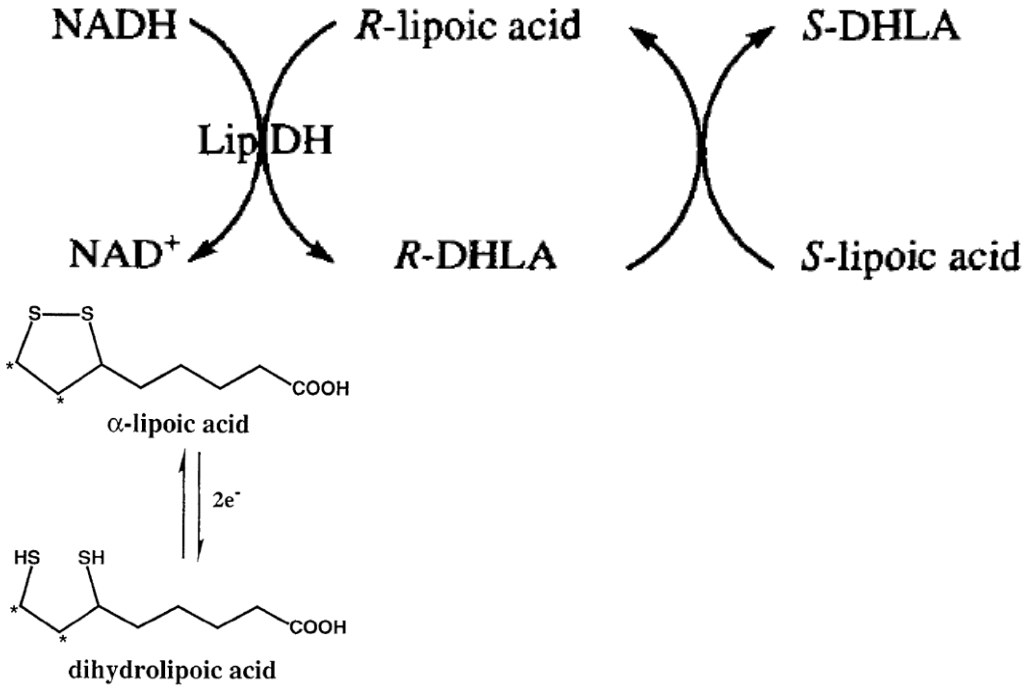
1. *Nonclinical assessment*

The following databases were consulted in the preparation of this section: PubMed, National Toxicology Program website, Embase, Web of Science, ToxNet, NIH dietary supplement label database, Google, GRAS notice inventory, and Drugs@FDA.

a. General pharmacology of the drug substance

ALA is present in all prokaryotic and eukaryotic cells. In humans, it is part of several 2-oxo acid dehydrogenases that are involved in energy production. Linked to lysine residues of the 2-oxo acid dehydrogenase multienzyme complexes, lipoic acid acts as a cofactor. It binds acyl groups and transfers them from one part of the enzyme complex to another. In this process, lipoic acid is reduced to DHLA, which is subsequently reoxidized by lipoamide dehydrogenase under the formation of nicotinamide adenine dinucleotide disodium reduced (NADH). Overall, lipoic acid and DHLA act as a redox couple, carrying electrons from the substrate of the dehydrogenase to nicotinamide adenine dinucleotide (NAD+) (Biewenga et al. 1997). See Figure 1.

Figure 1. The synthesis and metabolism of lipoic acid



b. Pharmacokinetics/Toxicokinetics

Several absorption, distribution and metabolism studies performed with ALA in animals are highlighted below (Cremer et al. 2006).

Oral, rat: ALA is an endogenous antioxidant with basal endogenous levels in control rats between 0.005 and 0.267 µM in blood and 0–0.024 µM in brain after correction for residual blood volume. Up to 93% of an orally administered dose of ALA is absorbed from the gastrointestinal system (Peter and Borbe 1995). Following its absorption, ALA undergoes reduction of the 1,2-dithiolane ring to its reduced form, DHLA, which in turn can subsequently undergo S-methylation (Schupke et al. 2001). ALA and DHLA are also subject to extensive β-oxidation (Schupke et al. 2001; Teichert et al. 2003). Pharmacokinetic profiling of ALA showed a rapid biphasic elimination in blood and poor distribution in various brain regions with levels ranging from 0.0009 to 0.0072 µM. Following an orally administered radiolabeled dose of ALA in rats, approximately 80% was detected in the urine, mainly in the form of metabolites with 4,6 bismethylmercapto-hexanoic acid as the predominant metabolite (Schupke et al. 2001).

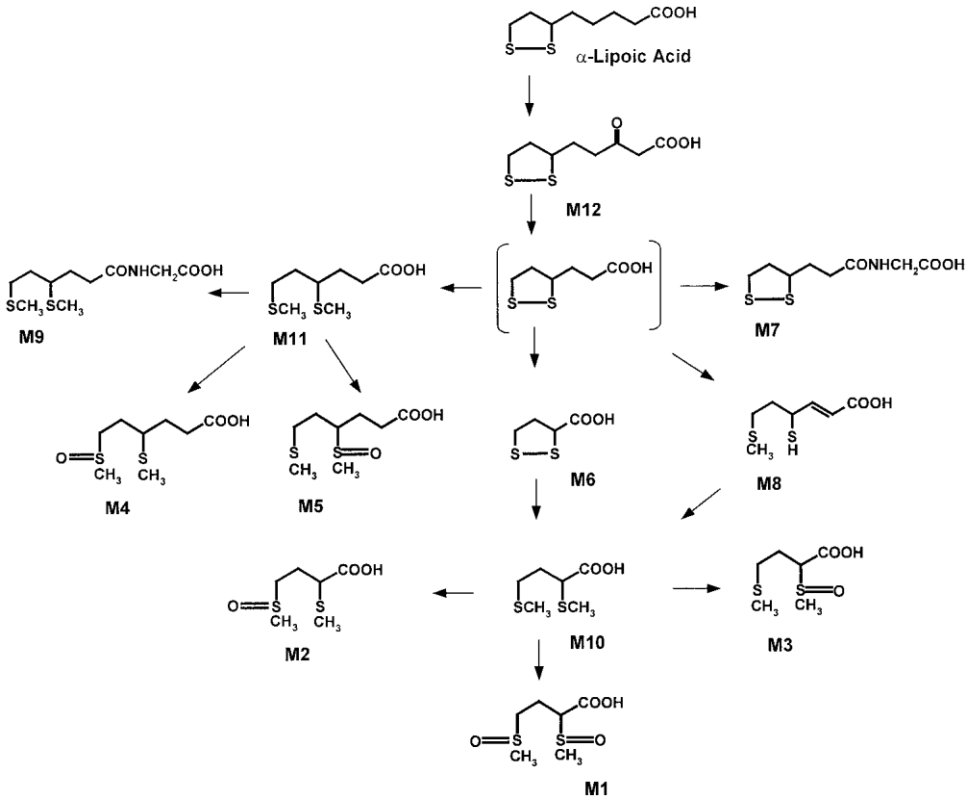
Topical, rat: The cutaneous and subcutaneous distributions of [7,8-^{14}C] rac-α-lipoic acid kinetics were assessed following topical application of a 5% solution in propylene glycol for 0.5 to 4 hrs in anesthetized hairless mice. The rate of [^{14}C]-α-lipoic acid absorption into skin was constant by 30 min (0.10 ± 0.01 nmol/cm^2/min) of topical application and maximum skin concentrations were reached 2 hrs following its application. Under the conditions of this study, [^{14}C]-α-lipoic acid penetrated the first layer of the stratum corneum and subsequently reached the inner layer of skin (corium) ($r2 = 0.96$, $P < 0.02$), thus demonstrating the percutaneous absorption of ALA.

Maximum skin concentrations were obtained within 2 hrs of topical application of ALA. Cutaneous absorption of unlabeled α-lipoic acid and its reduction to the more potent antioxidant form, DHLA, was also shown using high-performance liquid chromatography (HPLC) analysis (Podda et al. 1996).

Intraperitoneal, rat: Lipoic acid (dl[1,6 -α- ^{14}C]) was administered by intraperitoneal injection to rats (0.5 mg/100g BW). Approximately 56% of the radioactivity was recovered in the urine. Metabolites included DHLA and β-hydroxybisnorlipoate, which comprised 1.0 and 4.9%, respectively, of the radioactivity recovered in the urine (Spence and McCormick 1976).

Potential metabolic pathways of lipoic acid in the rat: All metabolites in Figure 2 below were identified in vivo except for bisnorlipoic acid (marked by brackets), which could not be identified as a metabolite (Schupke et al. 2001).

Figure 2. Metabolites of lipoic acid in rats



Oral, dog: The pharmacokinetic profile of ALA was studied in dogs (Zicker et al. 2010). When administered orally to the dogs, the pharmacokinetic parameters of ALA were significantly affected by whether a capsule or dog food was used. The inclusion of DL-ALA as an ingredient in dog food significantly decreased C_{max} and delayed T_{max}, compared with C_{max} when DL-ALA was administered orally to dogs in a capsule form (either with or without a meal following fasting for 12 hrs). The pharmacokinetic parameters of DL-ALA when administered orally in capsules were minimally affected by the fed status. ALA exposure was proportional to the oral

administered dose, regardless of whether it was administered in a capsule or included in dog food.

Summary: Pharmacokinetic profiling shows that ALA is absorbed quickly in the gastrointestinal system following oral administration. ALA exposure (area under the curve, AUC) is proportional to the administered dose in both rats and dogs. Following absorption, ALA undergoes a rapid biphasic elimination where its main metabolite, DHLA, is eliminated via the urine. Topical application of ALA in the rat shows its percutaneous absorption with maximum skin concentrations reached within 2 hours of application..

c. Acute toxicity[4]

ALA was not toxic in rats administered up to 2g/kg bw in a single oral gavage dose (using a constant volume of 10ml/kg bw) in female Sprague Dawley rats. The study followed a dose-ascending protocol starting with 175 mg/kg BW where 1 rat was dosed, followed by a monitoring period of 48 hrs then ascending to 550 mg/kg bw (n=1) and finally to 2000 mg/kg bw (n=3). The LD_{50} for oral gavage in the female rat was >2000mg/kg (Cremer et al. 2006).

When administered intraperitoneally at lower doses (20mg/kg bw), ALA was lethal to thiamine-deficient rats but death was prevented when thiamine was added to lipoic acid (Packer et al. 1995).

The LD_{50} of ALA in the rhesus monkeys was approximately 100 mg/kg via the intravenous route of administration. At such doses (90 to 100 mg/kg, IV), surviving monkeys showed hepatic necrosis (Vigil et al. 2014).

The oral LD_{50} of ALA in dogs is 400-500mg/kg (Packer et al. 1995).

ALA can cause liver toxicity in cats at doses greater than 20 mg daily (Thorne Research 2006).

The LD_{50} of ALA was obtained in toxicity studies in the rat and mouse models using various routes of administration (See Table 1 below). The rat seems to tolerate higher doses of ALA than the mouse via the oral route of administration (the LD_{50} in the rat was double that of the mouse). This difference was not observed for the other routes of administration tested (intraperitoneal, subcutaneous and intravenous).

[4] *Acute toxicity* refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). Endpoints captured in acute toxicity studies usually include mortality and gross clinical observations. Acute toxicity data are usually superseded by data obtained from longer term toxicity studies.

Table 1. LD_{50} after application of ALA via various routes of administration (Biewenga et al. 1997).

Route of administration	**LD_{50} rat**	**LD_{50} mouse**
Oral (p.o.)	1,130 mg/kg	502 mg/kg
Intraperitoneal (i.p.)	200 mg/kg	160 mg/kg
Subcutaneous (s.c.)	230 mg/kg	200 mg/kg
Intravenous (i.v.)	180 mg/kg	210 mg/kg

ALA ingestion in one dog was associated with hypoglycemia (detected within 10 hours of exposure to 191 mg/kg ALA dietary supplement), and in another case with kidney failure (detected 60 hours after ALA ingestion of 210 mg/kg). Clinical signs of lipoic acid toxicity in dogs include vomiting, ataxia, tremors, seizures, hyper salivation, lethargy, and weakness. In the first case, the dog was treated and recovered. However, in the second case the animal's health deteriorated and the dog was euthanized (Loftin and Herold 2009).

Single doses of ALA were administered to 10 healthy adult male cats at oral doses of 0 (control), 30 (low) or 60 (high) mg/kg bw. Serum enzyme activities (bile, amino acids, ammonia) and concentrations of DHLA were measured. Several tissues were examined microscopically (liver, kidney, muscles, lung, spleen, gut, and pancreas). Significant clinical toxicity with changes in ammonia and amino acid concentrations occurred in all high-dose treated cats. Oral ALA produced nonspecific acute hepatocellular toxicity (vacuoles, disrupted morphology, structures), which was seen in both low and high dose groups. The calculated single maximum tolerated dose for cats was 13 mg/kg bw, which is significantly lower than the single oral dose tolerated in humans, dogs or rats (120, 126 and 635 mg/kg bw, respectively) (Hill et al. 2004).

d. Repeat dose toxicity[5]

In a two-week dose range finding study, rats were administered daily oral gavage doses of 68, 147, 316 or 681 mg ALA/kg bw. The top two doses (316 and 681 mg/kg) were found to result in lethality while a dose of 147 mg/kg was associated with hypokinesia, coordination disturbances, sunken sides, and clonic convulsions. No adverse effects were noted at the lowest dose of 68.1 mg/kg dose (Cremer et al. 2006).

Oral gavage administration of 31.6 or 61.9 mg ALA/kg bw (body weight)/day for 4 weeks to Wistar rats (n=15/sex/group) did not show any adverse effects. There were no significant differences between control and treated animals at 31.6 or 61.9 mg/kg in terms of body weight gain, food consumption, animal behavior, hematological or clinical chemistry parameters. At the highest dose tested of 121 mg ALA/kg bw, some alterations were seen in liver enzymes at the

[5] *Repeated-dose toxicity* studies consist of in vivo animal studies that seek to evaluate the toxicity of the test substance by observing the changes that emerge in clinical observations, clinical chemistry, gross pathology, and histology endpoints when the test substance is repetitively administered daily for a predetermined period of time.

end of the 4-week period; male rats had low levels of cholesterol, total protein, triglycerides and increased alanine aminotransferase and glutamate dehydrogenase, whereas female rats showed increases in blood urea and cholesterol compared to untreated controls. Increases in liver (significant in all female dose groups and in high dose males) and kidney (significant in high dose treated males and in mid-dose and high dose treated females) weights were seen among treated rats compared to control counterparts. Histopathological changes were observed in the liver (slight increase in severity of microgranulomas among high dose treated females and males when compared to controls; increased incidence of centrilobular hypertrophy in high dose males as compared to controls) and mammary gland (increased incidence of diffuse hyperplasia in high dose treated females) (Cremer et al. 2006).

A 12-month feeding study in dogs showed that long term ALA intake of up to 52.9 mg/kg body/day (3000 ppm diet) was not associated with any toxicities (Paetau-Robinson et al. 2013).

Fuke et al. (1972) also administered ALA by subcutaneous injection at doses of 8, 16, 32, and 64 mg/kg bw/day to groups of 10 males and 10 female Sprague–Dawley rats for either 1 or 6 months.

- In the 1-month study, slightly, but significantly, increased prothrombin times were reported in males treated at concentrations above 8 mg/kg bw/day and in females treated with 32 and 64 mg/kg bw/day, respectively. The relative weights of the kidneys were increased in all treated males and in the two highest dose groups in females. Relative liver weights were reported to be significantly increased in the low-dose males and in the high-dose females. Beyond skin irritation at the site of injection, there was no effect of ALA treatment on the results of gross or microscopic examinations.
- In the 6-month study which incorporated doses of 16, 32, 64, and 125 mg ALA/kg bw/day, three females died at the highest dose level. Decreased body weight gains occurred at doses of 64 and 125 mg/kg bw/day. In the high-dose groups, decreases in hemoglobin and red blood cells (RBCs), and slight increases in white blood cells (WBCs), were reported (Fuke et al. 1972). At the 125 mg/kg bw/day dose level, alkaline phosphatase activity was significantly increased. Relative liver weights were increased in the top three dose groups in both males and in females. Relative kidney weights were increased in males dosed at 64 and 125 mg/kg bw/day and in females dosed at 125 mg/kg bw/day. Fuke et al. (1972) reported a tendency for the high-dose rats of each sex to have reduced fat content in the liver as compared to the controls.

The results of subchronic and chronic subcutaneous injection studies closely parallel the results of the 4-week oral toxicity study. As in the 4-week oral study, the 6-month subcutaneous study conducted by Fuke et al. (1972) reported mortality at doses above 120 mg/kg bw/day, mild increases in the relative organ weights of the liver and/or kidneys of rats treated at lower doses but without any significant histopathological effects of ALA under the conditions of the study.

e. Genotoxicity[6]

ALA was not mutagenic in the Ames assays conducted with various bacterial strains of *Salmonella typhimurium* when tested at concentrations up to 5000 µg/plate in the plate-incorporation assay and up to 1580 µg/plate in the preincubation assay (Cremer et al. 2006).

No evidence of genotoxic activity was seen in a mouse micronucleus assay where ALA was tested at 851 mg/kg BW in both male and female rats (Cremer et al. 2006).

f. Developmental and reproductive toxicity[7]

In a study presented in an abstract, ALA was given intraperitoneally to pregnant rats from days 2 through 6 at doses up to 100 mg/kg (presumably per day). On day 6, the rats were made diabetic with streptozotocin. ALA was reported to decrease the incidence of anomalies and growth restriction associated with streptozotocin-induced diabetes (Wiznitzer et al. 1996). The abstract does not indicate whether ALA was independently evaluated for developmental toxicity at the tested doses.

g. Carcinogenicity[8]

Rats were dosed via dietary feeding (20, 60, or 180 mg/kg/day) for 24 months. No differences were seen between control and treated animals at 20 or 60 mg/kg/day doses. ALA did not have any carcinogenic or target organ toxicity potential at doses up to 180 mg/kg/day. The only treatment-related effect was a decrease in body weight gain and reduced final body weights in rats treated at 180 mg/kg/day (a decrease of 13% in males and 22.5% in females compared to controls), which coincided with a decrease in food consumption in the 180 mg/kg dose group. The no-observed-adverse-effect-level (NOAEL) was considered by the authors to be 60 mg/kg/day (Cremer et al. 2006).

Conclusions:

- Short term oral gavage toxicity study in rats showed adverse effects in the liver and kidney when exposed to high doses of ALA (>32 mg/kg bw /day). Similarly, subchronic and chronic studies of ALA reported mild increases in the relative organ weights of the

[6] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems.

[7] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects in humans of both sexes and include females from various age groups that will be exposed to the proposed substance. *Developmental toxicity* or *teratogenicity* refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth.

[8] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to result in tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life.

liver and/or kidneys of rats without any adverse effects on the histopathology of these organs.
- No data assessing the reproductive/developmental toxicity for ALA were available.
- ALA was not mutagenic in a battery of genotoxicity tests (Ames and micronucleus assays).
- Carcinogenicity assessment (24 months dietary feeding in rats) did not result in any carcinogenic activity under the conditions of the study.

2. Human safety

The following databases were consulted in the preparation of this section: PubMed, EMBASE, ClinicalTrials.gov and Google.

a. Reported adverse reactions (FAERS, CAERS)

The Office of Surveillance and Epidemiology conducted a search of FDA's Adverse Event Reporting System (FAERS) for reports of adverse event with product terms that included alpha lipoic acid alone and in combination with other ingredients, through April 8, 2016.

Forty-six cases were reviewed in FAERS, of which forty were serious. A causal relationship to ALA could not be made in any of the cases because of other confounding factors (underlying disease, concomitant medication) or a lack of details in the reports.

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS that was conducted for adverse events associated with ALA on June 14, 2018, retrieved 73 cases. We could not assess whether a causal connection exists between the adverse events and ALA because of the concurrent use of multiple dietary supplements or drugs, or incomplete information. There were 25 cases where ALA was used alone or with an additional 1 to 2 substances (dietary supplements). The following cases are noteworthy:

- An 84-year-old self-described herbalist accidently ingested 10,000 mg of ALA and 16,000 mg of turmeric root instead of her usual "herbal concoction" containing forty capsules of different supplements. She induced vomiting but developed "seizures and cardiac instability". She died within 6 hours of the ingestion despite efforts to resuscitate.
- Other cases included diarrhea, loss of hair that resolved with stopping ALA, anaphylactic reactions, increased blood sugar in a diabetic, severe hypoglycemia, atrial fibrillation, eosinophilic myalgia syndrome, blood in the urine.

b. Clinical trials assessing safety

The FDA identified several randomized controlled studies assessing the efficacy of ALA in patients with diabetic neuropathy, several case series reporting the outcome of patients with amatoxin poisoning who received ALA, and a variety of reports describing the pharmacokinetics of ALA, its pharmacodynamic effects, or its use in other clinical indications. No randomized

trial reported an excess of toxicity in the ALA group; however, most did not appear designed to rigorously collect adverse event data. Similarly, no case series of patients treated with ALA reported any serious toxicity. The frequency of reported adverse events appears to be dose related (Ziegler 2006). At doses of 1800 mg daily, 48% of patients experienced nausea, 26% experienced vomiting and 11% experienced vertigo.

c. Other Safety Information

Health Canada posted a safety review assessing the potential risk of low blood sugar with ALA.[9] That document stated:

> This safety review was carried out by Health Canada after the publication of case reports of insulin autoimmune syndrome (IAS) causing hypoglycemic episodes linked with the use of oral alpha lipoic acid products in individuals with a genetic variation which causes the body's own defense system to attack insulin. The side effect is rare and resolves with stopping ALA. It has been reported in the literature in relation to the HLA-DRB1*0406 and HLA-DRB1*0403 HLA haplotypes.

There were no cases reported in Canada; most cases occurred in Asia where the genetic variation is more common (Yamada et al. 2007).

d. Pharmacokinetics

The pharmacokinetics (PK) of ALA has been well characterized in single (oral and intravenous) and multiple dose studies (oral) but no PK studies were found assessing topical administration.

Twelve healthy subjects were administered a single dose of 200 mg ALA in intravenous, oral liquid and oral tablet dosage forms (as a 200-mg tablet and as four 50 mg tablets). A washout period of 8 days separated the dosing and blood was collected repeatedly over a 24-hour period. Various pharmacokinetic parameters were measured. The individual enantiomers were measured. Table 2 below provides the pharmaceutic results from the study (Hermann et al. 1996).

[9] https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-alpha-lipoic-acid-assessing-potential-risk-low-blood-sugar-hypoglycemic.html, viewed July 13, 2018.

Table 2. Pharmacokinetics of intravenous ALA

Pharmacokinetic parameters of the α-lipoic acid enantiomers after an intravenous 4 min constant rate infusion and single administration of different oral dosage forms

Rac-α-LA enantiomer		Intravenous		Oral solution		4 × 50 mg tablets		200 mg tablet	
(200 mg)		R(+)	S(−)	R(+)	S(−)	R(+)	S(−)	R(+)	S(−)
AUC (μg·h ml^{-1})	Geometric mean	1.82	1.44	0.65	0.37	0.41	0.25	0.39	0.23
	Arithmetic mean	1.86	1.48	0.68	0.39	0.45	0.28	0.41	0.25
	SD	±0.41	±0.37	±0.24	±0.14	±0.20	±0.13	±0.13	±0.09
F_{abs} (%)	Geometric mean	–	–	35.6	25.5	22.4	17.2	21.6	16.2
	Arithmetic mean	–	–	38.2	28.3	25.9	20.9	24.1	19.1
	SD	–	–	±15.2	±14.4	±17.1	±16.6	±12.7	±12.8
C_{max} (μg ml^{-1})	Geometric mean	13.0	11.6	1.95	1.17	0.46	0.28	0.44	0.28
	Arithmetic mean	13.5	12.2	2.24	1.32	0.60	0.38	0.49	0.31
	SD	±3.90	±3.94	±1.21	±0.69	±0.41	±0.28	±0.27	±0.16
t_{max} (h)	Arithmetic mean	–	–	0.21	0.21	0.70	0.70	0.90	0.90
	SD	–	–	±0.07	±0.07	±0.41	±0.41	±0.74	±0.74
$t_{1/2}$ (h)	Arithmetic mean	0.37	0.32	0.24	0.15	0.71	0.82	0.33	0.33
	SD	±0.25	±0.14	±0.29	±0.08	±0.68	±0.99	±0.20	±0.24
				(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)
CL (ml min^{-1} kg^{-1})	Arithmetic mean	12.2	15.6	–	–	–	–	–	–
	SD	±2.62	±4.18	–	–	–	–	–	–
V_z (ml kg^{-1})	Arithmetic mean	419	471	–	–	–	–	–	–
	SD	±369	±338	–	–	–	–	–	–

n = 12, unless stated otherwise.

Source: Hermann et al. 1998

The half-life ($t_{1/2}$) of the drug is approximately 30 minutes. The absolute bioavailability of the tablets is approximately 20%. In this study, the bioavailability of the liquid dosage form is higher than the tablet dose form. Significant first pass metabolism by the liver accounts for the low bioavailability. First pass metabolism is also observed in other studies with absolute bioavailability between 20 – 30% (Teichert et al. 1998; Teichert et al. 2003).

Following absorption, ALA undergoes reduction of the 1,2-dithiolane ring to form DHLA that can subsequently undergo S-methylation (Schupke et al. 2001). ALA and DHLA each also are subject to extensive β-oxidation (Teichert et al. 2003). ALA is excreted in the urine in humans mainly in the form of metabolites, with 4,6-bismethylmercapto-hexanoic acid as the predominant form (Teichert et al. 2003). The pharmacokinetic parameters are not significantly changed with repeat oral dosing.

The oral administration of DL-ALA in fifteen male subjects at dosages between 50 and 600 mg resulted in a dose proportional increase in Cmax and AUC and no change clearance or elimination half-life (Breithaupt-Grogler et al. 1999).

Table 3. Pharmacokinetics of oral ALA

Pharmacokinetic data of *R*-(+)- and *S*-(−)-enantiomers of thioctic acid[a]

rac-TA dose (mg)	t_{max} (h)		C_{max} (ng/ml)		$t_{1/2}$ (h)		AUC (h*ng/ml)		CL/f (ml/min/kg)	
	R	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*	*S*
50	0.50	0.50	71.78	42.74	0.50	0.56	110.23	65.51	48.52	81.64
100	0.33	0.33	302.98	182.23	0.50	0.47	261.73	147.89	40.87	72.33
200	0.50	0.50	429.28	231.27	0.67	0.69	506.77	282.67	42.22	75.69
300	0.50	0.50	473.74	235.08	0.58	0.60	752.76	393.69	42.63	81.52
600	1.00	1.00	1135.10	591.33	0.60	0.64	1814.81	929.34	35.37	69.06

[a] Analysis of pooled plasma samples following single oral doses of racemic thioctic acid in the dose range of 50 to 600 mg (n=15)
t_{max}: time to maximum plasma concentration; C_{max}: maximum plasma concentration; $t_{1/2}$: terminal half-life; AUC: area under the plasma concentration time curve, linear trapezoidal rule; CL/f: oral total plasma clearance.

Source: Breithaupte-Grögler et al. 1999

We conducted a search for potential drug interactions with ALA and noted the following:

- Some websites mentioned the possibility of drug interactions with various medications but did not provide source references. For example, insulin, oral hypoglycemic drugs and levothyroxine were identified as possible drugs interacting with ALA.[10] ALA may cause hypoglycemia and lower thyroid hormone levels when used with these medications. The low blood sugars may be attributable to the effect of alpha lipoic acid on glucose metabolism and transport and an increase in insulin sensitivity (Bustamante et al. 1998).
- ClinicalTrials.gov lists a completed study (NCT01808300) that evaluated the interaction between pregabalin and ALA. No results are posted.
- We did not find any studies that evaluated the potential interaction with cytochrome P450 enzymes.

c. Availability of alternative approved therapies that may be as safe or safer

ALA appears to be relatively nontoxic at doses up to 1800 mg daily, as described in Section B(2)(b) above. For some of the nominated conditions, however, there is little evidence that ALA is effective. For an approved drug which has established benefit for the nominated conditions, many are well tolerated. See Table 4.

Table 4. FDA-Approved Therapies for Nominated Conditions

Condition	Approved Therapies
Diabetic neuropathy and associated pain	Duloxetine hydrochloride and pregabalin are approved for the treatment of diabetic neuropathy. Drugs commonly used for symptomatic treatment of diabetic neuropathy include topical capsaicin, anticonvulsants, and serotonin-norepinephrine reuptake inhibitors.
Acute liver toxicity from *Amanita* spp. mushroom poisoning	Atropine is approved for the treatment of muscarinic mushroom poisoning. Activated charcoal is indicated for poisoning related to oral ingestions.
Hepatitis C	There are several drugs and drug combinations that have been established to be curative for the treatment of hepatitis C. These

[10] http://pennstatehershey.adam.com/content.aspx?productId=107&pid=33&gid=000940, viewed July 13, 2018.

Condition	Approved Therapies
	drugs are administered over several months and are generally well tolerated.
Cancer	There are many drugs and biologics approved for the treatment of cancer. The toxicity profile varies greatly but the benefit risk profile justifies their use.
Cirrhosis	Ursodiol is indicated for the treatment of primary biliary cirrhosis.
Fibromyalgia	Duloxetine, pregabalin, and milnacipran hydrochloride are approved for the treatment of fibromyalgia. Each drug has been associated with a variety of adverse events.
Muscle pain	Many drugs, both topical and oral, are approved for the treatment of muscle pain or aches. They have a wide variety of adverse effects some of which are serious but generally because the drugs are for short durations of use they are well tolerated.

Conclusions:
There has been extensive literature reporting clinical evaluation of ALA, and there do not appear to be significant adverse effects associated with its use. There are potential drug interactions that have not been fully characterized. The most concerning involves the potential interactions with oral hypoglycemic drugs which may represent a pharmacodynamic interaction.

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, EMBASE, and ClinicalTrials.gov.

1. *Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance*

a. Reports in patients with diabetic neuropathy

The clinical setting in which ALA has been best studied is in the treatment of symptomatic diabetic sensorimotor polyneuropathy, a common condition that tends to respond poorly to standard analgesic medications. The rationale for studying ALA in patients with diabetes is strong, since ALA normally functions as a cofactor in the tricarboxylic acid cycle and as an antioxidant, and ALA has been reported to improve insulin sensitivity in patients with type 2 diabetes.

We identified 10 published randomized, controlled studies and three meta analyses evaluating the effects of ALA on diabetic peripheral neuropathy. These included oral administration (4 studies), intravenous administration (3 studies), or both (3 studies). Although five of these studies were conducted by the same German group of investigators, there is no evidence of overlap between patient populations. In these studies, intravenous ALA was given for three weeks, and oral administration varied between three weeks and four years. While the results of these studies varied, several of these trials and all three meta analyses concluded that ALA

administered orally or intravenously at doses between 100 and 1800 mg/day led to modest short-term improvement in neuropathic symptoms or nerve conduction parameters. Caveats are:

- Few clinical trials of ALA included patients with type 1 diabetes; most were limited to patients with type 2 diabetes (T2DM)
- No trial has shown ALA to improve diabetic autonomic neuropathy.
- ALA may provide some symptomatic improvement over several weeks. Some studies suggest a benefit (Ziegler et al. 1995) and others do not (Ziegler et al. 1999).
- The data does not support ALA providing effectiveness on the progression of neuropathy or nerve conduction.
- The NATHAN 1 trial (Ziegler et al. 2011) was the a long-term study in which ALA was administered for 4 years; for the primary endpoint (a composite endpoint NIS-LL+7), there was no significant difference between ALA and placebo ($p = 0.105$). There were many secondary endpoints some of which were reported as statistically significant. But, given that the study failed on its primary endpoint, it is difficult to interpret the relevance of the p values calculated for the secondary endpoints.

The primary outcome measure in six of the studies of peripheral diabetic neuropathy was the total symptom score (TSS). The TSS questionnaire asks patients to assess the intensity (absent, mild, moderate, severe) and frequency (now and then, often, continuous) of four symptoms (pain, burning, paresthesia, numbness), resulting in a total score in which 0 means no symptoms and 14.64 means that all four symptoms are severe and continuously present. Most trials that used the TSS defined a clinically relevant improvement in neuropathic symptoms as a 30% to 50% change or a decrease in 3 points in the total score.

In aggregate, seven of these 10 studies concluded that ALA improved neuropathic symptoms and/or objective nerve conduction parameters, whereas three studies were unable to detect a significant treatment effect. See Table 5.

Table 5. Randomized Clinical Trials of ALA in Adults with Diabetic Neuropathy

Author	**Trial**	**Population**	**Treatment**	**Result**
Ziegler et al. (1995)	ALADIN	Type 2 DM and symptomatic neuropathy (n = 328)	ALA (100, 600, or 1200 mg IV daily) vs. placebo x 3 weeks	ALA at 600 and 1200 mg was superior to placebo in improving TSS at 19 days.
Reljanovic et al. (1999)	ALADIN 2	Type 1 or 2 DM and symptomatic neuropathy (n = 65)	ALA (600 or 1200 mg) vs. placebo IV daily x 5, then PO daily x 2 years	There were major flaws in the electrophysiological assessments for a large number of patients and there was a high rate of drop-outs. 299 patients were randomized but the final analysis in the publication only included 65 patients which makes the study uninterpretable.

Ziegler et al. (1999)	ALADIN 3	Type 2 DM and symptomatic neuropathy (n = 503)	ALA 600 mg IV daily x 3 weeks, then 600 mg PO TID x 6 mo (n = 167) vs. ALA 600 mg IV daily x 3 weeks, then placebo x 6 mo (n = 174) vs. placebo IV daily x 3 weeks, then placebo x 6 mo.	No significant difference in TSS was demonstrated.
Ruhnau et al. (1999)	ORPIL	Type 2 DM and symptomatic neuropathy (n = 24)	ALA 600 mg PO TID vs. placebo x 3 weeks	ALA improved some elements of TSS and secondary symptom scores at 19 days.
Ametov et al. (2003)	SYDNEY	Diabetic with symptomatic neuropathy (n = 120)	ALA 600 mg IV daily 5 days/weeks for 14 treatments vs. placebo	ALA improved TSS at 3 weeks. No toxicity was seen.
Ziegler et al. (2006)	SYDNEY 2	Diabetic with symptomatic neuropathy (n = 181)	ALA 600, 1200, or 1800 mg PO daily x 5 weeks vs, placebo	ALA improved TSS at 5 weeks. AEs included nausea, vomiting, and vertigo.
Vijayakumar et al. (2014)	Vijayakumar	Type 2 DM with symptomatic neuropathy (n = 20)	Oral hypoglycemic ± ALA 600 mg PO daily	ALA improved 6 of 15 parameters of nerve conduction.
Garcia-Alcala et al. (2015)	Garcia-Alcala	Type 2 DM with symptomatic neuropathy responding to 4 weeks of ALA 600 mg TID (n = 33)	ALA 600 mg PO daily x 16 weeks vs. ALA withdrawal	ALA improved TSS; ALA withdrawal led to higher use of rescue analgesic drugs.
Grbovic et al. (2016)	Grbovic	Type 2 DM with symptomatic neuropathy (n = 60)	ALA 600 mg IV daily x 14 d, then 600 mg PO daily x 6 mo vs. physical therapy	Both groups had similar improvements in nerve conduction at 6 months
Ziegler et al. (2011)	NATHAN 1	Diabetic with symptomatic neuropathy (n = 460)	ALA 600 mg PO daily vs. placebo x 4 years	ALA failed to improve the NIS-LL+7 neuropathy score compared to placebo

ALADIN: Alpha-Lipoic Acid in Diabetic Neuropathy; NATHAN: Neurological Assessment of Thioctic Acid in Diabetic Neuropathy; SYDNEY: symptomatic diabetic neuropathy; NIS-LL+7: Neuropathy Impairment Score – Lower Limbs + 7

Three meta analyses of randomized controlled studies evaluating ALA in adults with diabetic neuropathy concluded that ALA improved neuropathic symptoms (Table 6).

Table 6.
Meta Analyses of Randomized Controlled Studies of ALA in Adults with Diabetic Neuropathy

Author	Trials Included	Treatment	Result
Ziegler et al. (2004)	ALADIN, ALADIN III, SYDNEY, and NATHAN II (total n = 1258; ALA n = 716; placebo n = 542)	ALA 600 mg IV daily x 3 weeks vs. placebo	ALA improved neuropathic symptoms. Adverse event rates were similar in both groups.
Mijnhout et al. (2012)	ALADIN I, ORPIL, SYDNEY, and SYDNEY 2 (total n = 361; ALA n = 180; placebo n = 181)	ALA 600 mg IV or PO daily x 3 weeks vs. placebo x 14-21 days	ALA improved neuropathic symptoms.
Han et al. (2012)	15 RCTs (total n = 1058; ALA n = 536; placebo n = 522)	ALA 300-600 mg IV vs. control	ALA improved nerve conduction velocities and neuropathic symptoms. No SAEs or discontinuations for AEs were reported.

b. Reports in patients with mushroom poisoning

The FDA identified six nonrandomized case series, involving a total of 410 patients with amatoxin poisoning during the period from between 1971 and 2003. ALA (listed as thioctic acid) was included as part of the treatment which included other medications, intravenous support and other supportive measure (e.g. gastric lavage) as necessary. Of these 410 patients, 352 (86%) survived (Table 7).

Table 7. Published case series of amatoxin poisoning

Author	Time Period	Patient Survival
Moroni et al. (1976)	Before 1976	33 of 33 (100%)
Bartter et al. (1978)	Aug 1974 to Nov 1978	67 of 75 (89%)
Dluholucky et al. (2006)	1977 to 2003	34 of 34 (100%)
Fantozzi et al. (1986)	Autumn 1981	40 of 44 (91%)
Sabeel et al. (1995)	1979 to 1994	19 of 19 (100%)
Floersheim et al. (1982)	1971 to 1980	159 of 205 (78%)

The case series published by Floersheim et al. 1982 concluded that the use of ALA (thioctic acid) did not appear to confer benefit:

> "With the aid of multiple regression analysis taking into account age, latency period and the effects of all the other measures, penicillin and hyperbaric oxygenation were found to contribute independently to a higher overall survival rate. As compared to penicillin the combination of penicillin with silybin was associated with still further increased survival. On the other hand, several measures, including exchange transfusion, thioctic acid, sulfamethoxazole, plasma expanders, hemodialysis, treatment of the hemorrhagic diathesis and THAM/sodium bicarbonate were administered most often to patients who did not survive. For the remaining 20 therapeutic measures, our analysis revealed neither a positive nor a negative correlation with the clinical outcome."

The FDA also identified five additional reports describing a total of seven patients with amatoxin poisoning, all of whom survived following treatment with comprehensive treatment protocols that included ALA (Becker et al. 1976; Teutsch and Brennan 1978; Plotzker et al. 1982; Piering and Bratanow 1990; Nagy et al. 1994).

A limitation to interpreting these reports is the inability to isolate the treatment effect of ALA. Patients with amatoxin are typically treated in the intensive care setting, where ALA is administered as part of comprehensive treatment protocols that include other hepatoprotective drugs (e.g., benzylpenicillin, silybin), procedures to accelerate the elimination of amatoxin (e.g., charcoal lavage, forced diuresis, hemodialysis), supportive care measures (e.g., vitamin K), and ultimately liver transplantation if necessary.

A second limitation to the interpretation of these reports is the use of historical controls for comparison. Patients hospitalized and given aggressive support therapy almost immediately after ingestion of amanitin-containing mushrooms have expected mortality rates as low as 10%, whereas those admitted 60 or more hours after ingestion have a 50–90% mortality rate. Also, some mushrooms contain less toxic compounds and, therefore, are less poisonous than the Amanitas.

Micromedex was searched in August 2018 for the treatment of mushroom poisoning[11]. In addition to intravenous fluid, activated charcoal and other supportive care, the following description of drugs therapies does not include alpha lipoic acid (thioctic acid) as demonstrating benefit.

From Micromedex "Mushroom -Cyclopeptides"

1) There are several drugs that have been proposed as antidotes in the management of cyclopeptide containing mushroom poisoning. None has been proven to have clinical efficacy in humans, but since the toxicity of these agents is limited, they are often used in suspected cyclopeptide mushroom ingestion. In studies, silibinin and NAC both administered as monotherapy, and silibinin with benzylpenicillin as bi-, tri-, and polytherapies were associated with the lowest mortalities. Overall, NAC and silibinin were the most effective agents.
2) N-ACETYLCYSTEINE: High doses of N-acetylcysteine have been used in humans in the setting of amatoxin poisoning. The dose most often used is 150 mg/kg infusion over 60 minutes followed by 50 mg/kg infusion over 4 hours followed by 6.25 mg/kg/hour infusion which is continued until the patient has clinically improved.
3) SILIBININ: Silibinin is being studied as a potential antidote for amatoxin. It is an extract from milk thistle and thought to inhibit the uptake of amatoxin into hepatocytes. The most common dose is 5 mg/kg IV loading dose followed by 20 mg/kg/day via continuous infusion. There is some human data showing promise of silibinin as an antidote, and it is currently available as part of an open label, multicenter clinical trial. To obtain silibinin, contact 866-520-4412.

[11] http://www.micromedexsolutions.com/micromedex2/librarian/CS/E5A14A/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/59595B/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=53&contentSetId=134&title=MUSHROOMS-CYCLOPEPTIDES&servicesTitle=MUSHROOMS-CYCLOPEPTIDES#

4) PENICILLIN G: Penicillin G appears to displace amatoxin from plasma protein binding sites and possibly inhibit its uptake into hepatocytes. The dose with some evidence of effectiveness is 300,000 to 1,000,000 units/day, though mortality is not significantly affected in preliminary studies.
5) THIOCTIC ACID: Thioctic acid is a coenzyme in the Krebs cycle used in Eastern Europe for the treatment of amatoxin poisoning with some data showing a possible reduction in mortality. The dose is 50 to 150 mg every 6 hours. Its efficacy remains unproven. It has been reported to cause hypoglycemia and is not readily available in the US.

In summary, several retrospective case series and case reports suggest that the addition of ALA to comprehensive intensive supportive care and other treatments may improve overall survival of patients with amatoxin poisoning. However, the limitations of these reports include an inability to isolate the contribution of ALA to complex treatment protocols, the use of historical controls for comparing outcomes, and possible reporting bias (i.e., selective reporting of positive studies). It has been used in the United States to treat amatoxin poisoning. Nonetheless, ALA appears to be a component or has been a component of protocols for this life-threatening condition, and its risks seem to be minimal.

c. Published reports in other nominated conditions

The FDA identified no convincing reports that ALA has clinical activity in pancreatic cancer, liver disease, or fibromyalgia. No additional studies of ALA treatment of muscle pain were identified.

Berkson, of the Integrative Medical Center of New Mexico, reported one patient with pancreatic adenocarcinoma metastatic to liver who had stable disease for six years and three who had complete responses while receiving ALA and low-dose naltrexone (Berkson 2007).

Guais reported the case of an 80-year-old woman with advanced pancreatic adenocarcinoma who received gemcitabine in combination with several nutritional supplements including ALA, and survived for 8 months (Guais et al. 2012).

Marshall randomized 40 patients with non-cirrhotic alcoholic liver disease to ALA 100 mg TID vs. placebo. Histological improvement at 24 weeks correlated with alcohol abstention, but not with treatment assignment (Marshall et al. 1982).

Basu randomized 155 patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis to no therapy, ALA, vitamin E, or ALA plus vitamin E for 6 months. A publication in abstract form concluded that ALA and vitamin E had additive effects with respect to improving biomarkers of inflammation (Basu et al. 2011; Basu et al. 2014).

Bettoni treated 33 patients with fibromyalgia and dyspareunia with a combination of ALA, cyanocobalamin, and methylsulfonylmethane. Some patients experienced symptomatic improvement (Bettoni et al. 2010).

Beltran randomized 24 women with fibromyalgia to 8 weeks of ALA versus placebo. Overall, no differences between treatment groups were demonstrated (Beltran et al. 2011).

A randomized clinical trial comparing pregabalin plus ALA versus each monotherapy for fibromyalgia is planned (Gilron et al. 2017).

2. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Some of the proposed uses are serious or life-threatening.

- Diabetic neuropathy seriously impacts quality of life, and in severe cases, can lead to life-threatening complications, such as nonhealing foot ulcers.
- Amatoxin poisoning is a serious and life-threatening disease that requires prompt intensive intervention.
- Hepatitis C can cause cirrhosis and liver cancer leading to death.
- Cancer and cirrhosis are serious diseases.
- Fibromyalgia can cause significant impairment for patients that impacts on their quality of life.
- Muscle pain in most cases is not life-threatening.

3. Whether there are any alternative approved therapies that may be as effective or more effective

See section II.B.2.d.

Conclusions:

- Based on the information reviewed, ALA appears to show symptom improvement with treatment for several weeks in the treatment of diabetic neuropathy. The evidence for improvement of nerve conduction and affecting progression of disease was not compelling. Studies of several years duration did not show a difference from placebo for progression of neuropathy.
- ALA has been used as part of comprehensive treatment protocols for amatoxin poisoning. The contribution of ALA to the improvement in survival amatoxin poisoning has not been evaluated.
- For the other conditions evaluated, there are no clinical data that support effectiveness.

D. Has the substance been used historically as a drug in compounding?

We searched the following databases searched for historical information on the compounding of ALA: PubMed, Natural Medicines, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and Google.

1. Length of time the substance has been used in pharmacy compounding

ALA was discovered in 1937 by Snell et al. who found that certain bacteria needed a compound from potato extract for growth (Snell et al. 1937; Vallianou et al. 2009). It was later isolated from beef liver in 1951 (Reed et al. 1951). ALA has been used in pharmacy compounding since at least 1999 (Karolchyk 1999).

2. The medical condition(s) it has been used to treat

The Natural Medicines Database (2018) indicates that ALA is used orally for diabetes and prediabetes, diabetic neuropathy, and diabetic retinopathy, among other conditions. It is used intravenously for improving insulin-resistance and glucose disposal in type 2 diabetes, diabetic neuropathy, and Amanita mushroom poisoning. Topically, it is used to reduce facial wrinkles, lines, and sun damage (Natural Medicines 2018).

Results from a Google search using the terms *alpha lipoic acid compounding pharmacy* indicate that ALA is/has been compounded as an injection, suppository, topical product, and troche. It appears that the injection is used in treating diabetes and diabetic neuropathy, among other conditions, while the topical product is used for "anti-aging."

The International Journal of Pharmaceutical Compounding (IJPC) published a recipe for lipoic acid 200 mg chewable troches (Loyd 2000). In addition, in an IJPC article describing compounded IV nutrition, authors state that lipoic acid is usually prepared as a 50 mg/mL injection with a usual IV dose of 50 to 100 mg (Karolchyk 1999).

3. How widespread its use has been

Insufficient data are available from which to draw conclusions about the extent of use of alpha lipoic acid in compounded drug products.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

A search of the British Pharmacopoeia (BP 2018), the European Pharmacopoeia (9th Edition, 2018, 9.4), and the Japanese Pharmacopoeia (16th Edition) did not show any monograph listings for alpha lipoic acid.

Conclusions: Based on internet searches and the published literature, ALA has been used in pharmacy compounding for at least 19 years and is/has been compounded as an injection, suppository, topical product, and troche. It appears that it is used in compounded injectable products for treating diabetes and diabetic neuropathy, among other conditions.

III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate alpha lipoic acid for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs in favor of*** alpha lipoic acid solid oral dosage forms being placed on that list based on the following:

1. ALA is well characterized chemically and physically. The substance is very sensitive to light and heat. It is likely to be stable when compounded as solid dosage forms if strictly protected from light and temperatures above 40 degrees Celsius. However, the aqueous formulations are less stable because the salts used in aqueous formulations to improve solubility have a tendency to polymerize. Therefore, the drug substance is unlikely to be stable when compounded as aqueous solutions.

2. The clinical and non-clinical data reviewed do not suggest significant safety concerns with ALA. Possible drug-drug interactions with ALA have not been explored. This may be relevant because of the many approved drugs used in the treatment of diabetes.

3. There have been numerous investigations of ALA in the treatment of diabetic neuropathy. Several studies suggest some effectiveness in the treatment of symptoms over several weeks but studies of disease progression and nerve conduction do not indicate a benefit. The data reviewed for amatoxin poisoning fails to establish effectiveness. However, ALA is used in some treatment protocols for amatoxin poisoning in addition to other interventions. We did not find evidence of effectiveness of ALA in the treatment of hepatitis C, cancer, cirrhosis, fibromyalgia or muscle pain.

4. ALA has been used historically in pharmacy compounding for at least 19 years.

Based on this information the Agency has considered, a balancing of the four evaluation criteria ***weighs in favor of*** alpha lipoic acid solid oral dosage forms being added to the 503A Bulks List. The clinical studies of ALA for the treatment of diabetic peripheral neuropathy usually involves the administration of intravenous ALA for the first 3 weeks and then switching to oral therapy. We were not able to find sufficient information and the information provided by the nominator was not adequate to assure the stability of aqueous ALA. For this reason, the intravenous route of administration is not recommended.

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Tab 2

Coenzyme Q10

Tab 2a

Coenzyme Q10

Nominations

May 23, 2017

Julie Dohm, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

[Docket No. FDA-2015-N-3534]

RE: Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A

Dear Dr. Dohm:

I am writing on behalf of PCCA in reference to FDA's Interim Guidance on Bulk Substances Under Section 503A. Currently coenzyme Q10 is listed on Category 3: Bulk Drug Substances Nominated Without Adequate Support, and FDA has cited violations by 503A pharmacies on Form 483s for compounding with this substance.

Attached for your consideration is a nomination for it to be placed on FDA's Category 1 list of bulk substances that can be lawfully compounded. Due to the nature of metabolic diseases and the regulatory implications for patient care, PCCA respectfully requests that coenzyme Q10 be immediately placed on Category 1 – Bulk Drug Substances Under Evaluation. There are no suitable alternative manufactured products for many patients with mitochondrial disorders, and we wish to avoid disruptions in care.

If you have questions about this nomination, I can be reached at 800.331.2498, ext 1223, or at jsmith@pccarx.com. Thank you for your prompt consideration of this request.

Sincerely,

Jim R. Smith

Jim Smith
PCCA President

Ingredient Name	Co-Q10 USP
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No, though it has been granted FDA orphan drug status for treatment of mitochondrial cytopathies
Does it have a USP or NF Monograph	Yes
Chemical Name	2,5-Cyclohexadiene-1,4-dione, 2-[(2E,6E,10E,14E,18E,22E,26E,30E,34E)-3,7,11,15,19,23,27,31,35,39-decamethyl-2,6,10,14,18,22,26,30,34,38-tetracontadecaenyl]-5,6-dimethoxy-3-methyl; 2-[(all-E)-3,7,11,15,19,23,27,31,35,39-Decamethyl-2,6,10,14,18,22,26,30,34,38-tetracontadecaenyl)-5,6-dimethoxy-3-methyl-p-benzoquinone
Common Name(s)	Coenzyme Q10; ubidecarenone; ubiquinone
UNII Code	EJ27X76M46
Chemical Grade	USP
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmcopeias or registered in other countries	Japanese Pharmacopoeia; European Pharmacopoeia; OTC in US as dietary supplement
Submitted to USP for monograph consideration	Already included in USP Dietary Supplement section
Compounded Dosage Forms	Oral capsules, troches, liquid, gel
Compounded Strengths	15 mg - 1200 mg
Anticipated Routes of Administration	Oral
Saftey & Efficacy Data	Bhagavan, H. N., & Chopra, R. K. (2006). Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radical Research* , 40(5), 445-453. doi:10.1080/10715760600617843 Parikh, S, et al. A Modern Approach to the Treatment of Mitochondrial Disease. Curr Treat Options Neurol. 2009;11(6): 414-430. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3561461/#R17 Parikh, S, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med. 2015;17(9): 689-701. https://www.ncbi.nlm.nih.gov/pubmed/25503498 Camp K, et al. Nutritional interventions in primary mitochondrial disorders: Developing an evidence base. Mol Genet Metab. 2016:119(3): 187-206. https://www.ncbi.nlm.nih.gov/pubmed/27665271 Desbats, M, et al. Genetic bases and clinical manifestations of coenzyme Q10 (CoQ 10) deficiency. J Inherit Metab Dis. 2015;38(1): 145-56. https://www.ncbi.nlm.nih.gov/pubmed/?term=25091424 Emmanuele V, et al. Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. Arch Neurol. 2012;69(8): 978-83. https://www.ncbi.nlm.nih.gov/pubmed/22490322 Bonakdar, R. A., & Guarneri, E. (2005). Coenzyme Q10. American Family Physician, 72(6), 1065-1070. Saini, R. (2011). Coenzyme Q10: The essential nutrient. Journal of Pharmacy and Bioallied Sciences, 3(3), 466–467. doi:10.4103/0975-7406.84471 Glover E, et al. A Randomized Trial of Coenzyme Q10 in Mitochondrial Disorders. Muscle Nerve. 2010;42(5):739-48. https://www.ncbi.nlm.nih.gov/pubmed/?term=20886510 Stamelou M, et al. Short-term effects of coenzyme Q10 in progressive supranuclear palsy: a randomised, placebo-controlled trial. Mov Disord. 2008;23(7) 942-9. https://www.ncbi.nlm.nih.gov/pubmed/?term=18464278 Abe K, et al. Effect of coenzyme Q10 in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): evaluation by noninvasive tissue oximetry. J Neurol Sci. 1999;162(1) 65-8. https://www.ncbi.nlm.nih.gov/pubmed/?term=10064171 Chan A, et al. Metabolic changes in patients with mitochondrial myopathies and effects of coenzyme Q10 therapy. J Neurol. 1998;245(10):681-5. https://www.ncbi.nlm.nih.gov/pubmed/?term=9776469 Chen RS, et al. Coenzyme Q10 treatment in mitochondrial encephalomyopathies. Short-term double-blind, crossover study. Eur Neurol. 1997;37(4):212-8. https://www.ncbi.nlm.nih.gov/pubmed/?term=9208260

Barbiroli B, et al. Coenzyme Q10 improves mitochondrial respiration in patients with mitochondrial cytopathies. An in vivo study on brain and skeletal muscle by phosphorous magnetic resonance spectroscopy. Cell Mol Biol. 1997;43(5):741-9. https://www.ncbi.nlm.nih.gov/pubmed/?term=9298596
Gold R, et al. Phosphorus magnetic resonance spectroscopy in the evaluation of mitochondrial myopathies: results of a 6-month therapy study with coenzyme Q. Eur Neurol. 1996;36(4):191-6. https://www.ncbi.nlm.nih.gov/pubmed/?term=8814419
Bendahan D, et al. 31P NMR spectroscopy and ergometer exercise test as evidence for muscle oxidative performance improvement with coenzyme Q in mitochondrial myopathies. Neurology. 1992;42(6):1203-8. https://www.ncbi.nlm.nih.gov/pubmed/?term=1603348
Bresolin N, et al. Ubidecarenone in the treatment of mitochondrial myopathies: a multi-center double-blind trial. J Neurol Sci. 1990;100(1-2):70-8. https://www.ncbi.nlm.nih.gov/pubmed/?term=2089142
Bresolin N, et al. Clinical and biochemical correlations in mitochondrial myopathies treated with coenzyme Q10. Neurology. 1988;38(6):892-9. https://www.ncbi.nlm.nih.gov/pubmed/?term=3368070
Ogasahara S, et al. Treatment of Kearns-Sayre syndrome with coenzyme Q10. Neurology. 1986;36(1):45-53. https://www.ncbi.nlm.nih.gov/pubmed/?term=3941783

Used Previously to compound drug products	Yes
Proposed use	Treatment of Mitochondrial Disorders
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	Estevez P, et al. Coenzyme Q10 stability in pediatric liquid oral dosage formulations. Farm Hosp. 2012;36(6): 492-7. https://www.ncbi.nlm.nih.gov/pubmed/23461442

Tab 2b

Coenzyme Q10
Nomination Clarification

February 26, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

LT Hallman:

Thank you for contacting PCCA as the nominator of coenzyme Q10 for inclusion on the 503A Bulk Drug Substances list. Below is our response to FDA's questions #1 and #2.

1. PCCA does want to pursue review by the FDA and consideration by the PCAC of coenzyme Q10 (CoQ10; ubidecarenone; ubiquinone) for inclusion on the 503A Bulks list. Please note that coenzyme Q10 does have a monograph in the current USP/NF, and thus meets the statutory requirement for use as an Active Pharmaceutical Ingredient under section 503A of the DQSA.

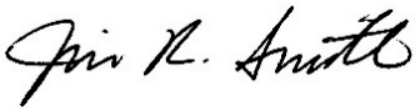
2. Compounded CoQ10 is nominated for use in the care of patients with mitochondrial disease, which is a large group of metabolic disorders. While CoQ10 may not specifically be used in each of the more than 200 individual variants of mitochondrial metabolic disorder, as a category these conditions do share many clinical and biochemical similarities and CoQ10 is the most commonly prescribed antioxidant for children and adults with mitochondrial diseases. As with all medications, treatment outcomes are patient specific. FDA has issued Orphan Drug Designation to ubiquinone oral gel for the "treatment of mitochondrial cytopathies," although FDA has not approved a ubiquinone product for that orphan indication (see Appendix A).

Proposed Use	**Dosage Form & Strength/Concentration**
Mitochondrial disorders	Oral dosage forms (capsules, troches, liquid, gel) Dosing is weight-based (Mitochondrial Medicine Society recommends 5 mg/kg/day to 30 mg/kg/day) Doses typically range between 15 mg and 1200 mg

Literature citations for the treatment of mitochondrial disorders with oral CoQ10 are listed in Appendices B and C.

We look forward to providing you further information as requested in the coming weeks.

Sincerely,



Jim Smith
PCCA President

APPENDIX A

[Accessed February 26, 2018]

Secure | https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=125099

Search Orphan Drug Designations and Approvals

Generic Name:	Ubiquinone
Trade Name:	Ubi-Q-Gel
Date Designated:	12/14/1999
Orphan Designation:	Treatment of mitochondrial cytopathies.
Orphan Designation Status:	Designated
FDA Orphan Approval Status:	Not FDA Approved for Orphan Indication
Marketing Approval Date:	N/A
Approved Labeled Indication:	
Exclusivity End Date:	N/A
Sponsor:	Gel-Tec, Division of Tishcon Corp. 30 New York Avenue P. O. Box 331 Westbury, New York 11590 USA *The sponsor address listed is the last reported by the sponsor to OOPD.*

APPENDIX B

Bhagavan, H. N., & Chopra, R. K. (2006). Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radical Research*, 40(5), 445-453. doi:10.1080/10715760600617843

Parikh, S, et al. A Modern Approach to the Treatment of Mitochondrial Disease. Curr Treat Options Neurol. 2009;11(6): 414-430. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3561461/#R17

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Camp K, et al. Nutritional interventions in primary mitochondrial disorders: Developing an evidence base. Mol Genet Metab. 2016:119(3): 187-206. https://www.ncbi.nlm.nih.gov/pubmed/27665271

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Glover E, et al. A Randomized Trial of Coenzyme Q10 in Mitochondrial Disorders. Muscle Nerve. 2010;42(5):739-48. https://www.ncbi.nlm.nih.gov/pubmed/?term=20886510

Stamelou M, et al. Short-term effects of coenzyme Q10 in progressive supranuclear palsy: a randomised, placebo-controlled trial. Mov Disord. 2008;23(7):942-9. https://www.ncbi.nlm.nih.gov/pubmed/?term=18464278

Abe K, et al. Effect of coenzyme Q10 in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): evaluation by noninvasive tissue oximetry. J Neurol Sci. 1999;162(1):65-8. https://www.ncbi.nlm.nih.gov/pubmed/?term=10064171

Chan A, et al. Metabolic changes in patients with mitochondrial myopathies and effects of coenzyme Q10 therapy. J Neurol. 1998;245(10):681-5. https://www.ncbi.nlm.nih.gov/pubmed/?term=9776469

Chen RS, et al. Coenzyme Q10 treatment in mitochondrial encephalomyopathies. Short-term double-blind, crossover study. Eur Neurol. 1997;37(4):212-8. https://www.ncbi.nlm.nih.gov/pubmed/?term=9208260

Barbiroli B, et al. Coenzyme Q10 improves mitochondrial respiration in patients with mitochondrial cytopathies. An in vivo study on brain and skeletal muscle by phosphorous magnetic resonance spectroscopy. Cell Mol Biol. 1997;43(5):741-9. https://www.ncbi.nlm.nih.gov/pubmed/?term=9298596

Gold R, et al. Phosphorus magnetic resonance spectroscopy in the evaluation of mitochondrial myopathies: results of a 6-month therapy study with coenzyme Q. Eur Neurol. 1996;36(4):191-6. https://www.ncbi.nlm.nih.gov/pubmed/?term=8814419

Bendahan D, et al. 31P NMR spectroscopy and ergometer exercise test as evidence for muscle oxidative performance improvement with coenzyme Q in mitochondrial myopathies. Neurology. 1992;42(6):1203-8. https://www.ncbi.nlm.nih.gov/pubmed/?term=1603348

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Bresolin N, et al. Clinical and biochemical correlations in mitochondrial myopathies treated with coenzyme Q10. Neurology. 1988;38(6):892-9. https://www.ncbi.nlm.nih.gov/pubmed/?term=3368070

Ogasahara S, et al. Treatment of Kearns-Sayre syndrome with coenzyme Q10. Neurology. 1986;36(1):45-53. https://www.ncbi.nlm.nih.gov/pubmed/?term=3941783

APPENDIX C

VMP, LLC
expanding genetic horizons...

Voice: 404.793.7800
Fax: 866.744.5665
www.vmpgenetics.com

February 22, 2018

Re: COENZYME Q-10 and FDA REVIEW

We are clinical biochemical geneticists, trained at Harvard University and certified by the American Board of Medical Genetics and Genomics. We have undergone formal training in the area of metabolic and mitochondrial disease, and are among 100 or so practicing clinical biochemical geneticists in this country. We are both experts in the area of metabolic disease, published in the field, and have worked with and/or served as board members of the Mitochondrial Medicine Society, the United Mitochondrial Disease Foundation, and MitoAction.

We are writing in support of maintaining Coenzyme Q10 as a Category-A compound, eligible for compounding.

As background, mitochondrial disease is a large group of metabolic disorders, representing over 200 (and counting) some individual defects. These disorders are typically inherited (either by nuclear DNA mutations or by mitochondrial DNA mutations), and represent problems in the body's ability to generate energy on a cellular level. Without adequate energy, tissues and organ systems slow down and sometimes fail, resulting in a diverse set of symptoms, including muscle weakness, muscle fatigue, cognitive decline, developmental disorders, seizures, vision loss, hearing loss, cardiac dysfunction, and endocrine dysfunction. There is considerable clinical and biochemical overlap between these disorders.

Coenzyme Q-10 is the most commonly prescribed antioxidant for children and adults with mitochondrial disease, and has been recognized by the FDA for the treatment of these energy disorders. Coenzyme Q-10 is a fat-soluble, natural substance present in almost all body cells, serving as a coenzyme or helper molecule for several key enzymatic steps in the production of energy within the cell. Also, as an antioxidant, it protects against the accumulation of harmful, disease-causing free radicals within the cell.

There are many reports in the medical literature documenting the clinical benefits of Coenzyme Q-10 in mitochondrial disease. A number of studies have shown that the use of Coenzyme Q10 results in increased energy production and improvement in clinical symptoms (see below). One such article (Euro J of Neurol, 2008 Dec;15(12):1371-9) showed much improvement in clinical symptoms in individuals with Friedrich's ataxia, a type of mitochondrial disease, after the patient was started on Coenzyme Q10. For such disorders, associated with significant morbidity and mortality, and for which other treatments are not available, the use of Coenzyme Q10 helps support the patient and in many cases helps optimize care.

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Of note, some patients actually have inherited defects in the endogenous synthesis of Coenzyme Q-10. In these cases, treatment with Coenzyme Q-10 is analogous to treating patients who have a deficiency in vitamin B12 or folate. These patients are particularly sensitive to treatment with the deficient vitamin. In this respect, Coenzyme Q-10 is not at all a supplement, but rather replacement of a naturally-occurring body substance.

Treated patients are followed clinically and by assessment of Coenzyme Q10 levels using objective measures of improvement. Follow up is guided by the patient's clinical manifestations of mitochondrial disease. Treatment with Coenzyme Q-10 represents the standard of care for most patients with mitochondrial disease.

Selected References:

1. Treatment of Mitochondrial Disorders: Antioxidants and Beyond. Journal of Child Neurology. 2014, Vol. 29(9) 1235-1240
2. Treatment of Mitochondrial Disorder. Pediatric Neurology Curr Treat Options Neurol. 2014 16:292
3. The myopathic form of coenzyme Q10 deficiency is caused by mutations in the electrontransferring- flavoprotein dehydrogenase (ETFDH) gene. Brain. 2007 Aug;130(Pt 8):2037-44
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13. Coenzyme Q10 deficiency and isolated myopathy. Neurology. 2006 Jan 24; 66(2):253-5.
14. The effect of coenzyme Q10 on idiopathic chronic dilated cardiomyopathy in children. PediatrCardiol. 2005 Jul-Aug; 26(4):361-6.
15. Infantile encephalomyopathy and nephropathy with CoQ10 deficiency: a CoQ10-responsive condition. Neurology. 2005 Aug 23;65(4):606-8

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16. Coenzyme Q-10 treatment of patients with a 7445A--->G mitochondrial DNA mutation stops the progression of hearing loss. Acta Otolaryngol. 2005 May; 125(5):510-2.
17. Coenzyme Q and mitochondrial disease. Dev Disabil Res Rev 2010;16:183–188.

Sincerely,

Fran D. Kendall, M.D.
Founder, Managing Director
Clinical Biochemical Geneticist
Adjunct Assistant Professor, University of Georgia

Mark S. Korson, M.D.
Director of Physician Support
Director of Education

March 16, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

LT Hallman:

Thank you for contacting PCCA as the nominator of coenzyme Q10 for inclusion on the 503A Bulk Drug Substances list. Below is our response to FDA's questions #1 and #2.

> The information provided here is not to be considered all-inclusive. Some clinicians may have further information that we were not able to collect by the due date requested. Also, please note that coenzyme Q10 does have a USP monograph, and thus meets the statutory requirements for use as an Active Pharmaceutical Ingredient under section 503A of the DQSA.

Below are our responses to FDA's questions #3 and #4:

3. To the best of our abilities, approximately 12,000 to 20,000 prescriptions of compounded CoQ10 are estimated to be dispensed per year in the U.S. in the treatment of metabolic disorders.

4. Coenzyme Q10 is just one part of the treatment regimen for patients with mitochondrial diseases. Dosing is weight-based and adjusted to the functional status of individual patients.

   The United Mitochondrial Disease Foundation (UMDF) lists CoQ10 as a part of the treatment plan for patients with variations of mitochondrial diseases, including OXPHOS. CoQ10 is considered a "First Tier Supplement," pending approval from the treating physician. Dosing protocols are found on its webpage: http://www.umdf.org/what-is-mitochondrial-disease/treatments-therapies/

   A detailed explanation of the role of CoQ10 in mitochondrial disease, with dosing and references, is provided in Appendix A. This information is consistent with the recommendations and protocols of UMDF, MitoAction and the Mitochondrial Medicine Society.

It is important to note that coenzyme Q10 is not a cure for metabolic diseases. There are no cures, and the goals of treatment are to alleviate symptoms and slow progression of the disease. There are no FDA-approved products to replace the role of compounded CoQ10. Clinicians at The Johns Hopkins Hospital note that the overall number of patients with mitochondrial disease is small, and for those individuals, CoQ10 significantly improves quality of life. CoQ10 is an essential component of the vast majority of treatment plans for their patients with various mitochondrial diseases.

We hope this information aids the Agency in your review of compounded coenzyme Q10. If you require further information, please contact us at your convenience.

Sincerely,

Jim Smith
PCCA President

APPENDIX A

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February 22, 2018

Re: COENZYME Q-10 and FDA REVIEW

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Selected References:

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3. The myopathic form of coenzyme Q10 deficiency is caused by mutations in the electrontransferring- flavoprotein dehydrogenase (ETFDH) gene. Brain. 2007 Aug;130(Pt 8):2037-44
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6. Beneficial effects of creatine, CoQ10, and lipoic acid in mitochondrial disorders. Muscle Nerve. 2007 Feb;35(2):235-42
7. The impact of coenzyme Q10 on systolic function in patients with chronic heart failure. J Card Fail. 2006 Aug;12(6):464-72.
8. Clinical trials of coenzyme Q10 in neurological disorders. Biofactors. 2005;25(1-4):117-26
9. Neuroprotective agents for clinical trials in ALS: a systematic assessment. Neurology. 2006 Jul 11;67(1):20-7
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13. Coenzyme Q10 deficiency and isolated myopathy. Neurology. 2006 Jan 24; 66(2):253-5.
14. The effect of coenzyme Q10 on idiopathic chronic dilated cardiomyopathy in children. PediatrCardiol. 2005 Jul-Aug; 26(4):361-6.
15. Infantile encephalomyopathy and nephropathy with CoQ10 deficiency: a CoQ10-responsive condition. Neurology. 2005 Aug 23;65(4):606-8

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Sincerely,

Fran D. Kendall, M.D.
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Director of Physician Support
Director of Education

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Tab 2c

FDA Review of Coenzyme Q10

DATE: August 9, 2018

FROM: Ben Zhang, Ph.D.
Staff Fellow, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)

Nour Debiat
ORISE Fellow, Office of Drug Evaluation IV (ODE IV), Office of New Drugs (OND)

Yen-Ming Chan, Ph.D.
ORISE Fellow, ODE IV, OND

Wafa Harrouk, Ph.D.
Senior Pharmacology/Toxicology Reviewer, ODE IV, OND

Susan Johnson, Pharm.D., Ph.D.
Associate Director, ODE IV, OND

Elizabeth Hankla, PharmD
Consumer Safety Officer, Office of Compliance, Office of Unapproved Drugs and Labeling Compliance (OUDLC)

THROUGH: Ramesh K. Sood, Ph.D.
Senior Scientific Advisor (acting), ONDP, OPQ

Charles Ganley, M.D.
Director, ODE IV, OND

Frances Gail Bormel, R.Ph., J.D.
Director, Division of Prescription Drugs, OUDLC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Coenzyme Q_{10} for Inclusion on the 503A Bulk Drug Substances List

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

I. INTRODUCTION

Coenzyme Q_{10} (ubiquinone, ubidecarenone, CoQ_{10}) has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). It has been proposed for use in the treatment of mitochondrial diseases. The proposed route of administration is oral.

We have reviewed publicly available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh in favor of*** placing ubiquinone for oral administration on the list of bulk drug substances that can be used to compound drug products for oral use in accordance with section 503A of the FD&C Act (503A Bulks List).[1]

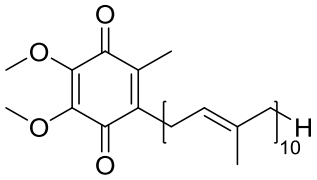
II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?[2]

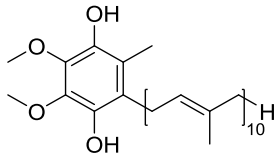
The term "coenzyme Q_{10} (CoQ_{10})" can be used to refer to two different molecules that are benzoquinone derivatives with 10 isoprenoid units in their side chains. Ubiquinone is the fully oxidized form of CoQ_{10} whose structure is shown below. Per the nomination, the all-trans (all-"E") isomer has been identified as the bulk substance that is the subject of the nomination.

[1] Inclusion 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 should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using a substance included on the list has been proven to be safe and effective under the standards required receiving Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears 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 is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act (21 U.S.C. 352(a), (bb)).

[2] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).



Ubiquinol is the fully reduced form of CoQ_{10}. Ubiquinol is not the subject of this review;[3] its structure is shown below.



Ubiquinol
Fully Reduced Form of CoQ_{10}

For the purposes of this review, consistent with the nomination, the term "CoQ_{10}" will refer to ubiquinone. We use those two terms interchangeably in this document. CoQ_{10} is currently available as a dietary ingredient in dietary supplement capsules (30 mg, 50 mg, 60 mg, 100 mg, 200 mg, and 400 mg), and as an oral liquid. It is proposed for oral administration as compounded oral capsules, troches, liquid, or gel in strengths of 15 to 1200 mg.

Databases searched for information on ubiquinone regarding this section: PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and USP/NF.

1. Stability of the API and likely dosage forms

No issues concerning the stability of ubiquinone have been reported in the literature. Based on its chemical structure, ubiquinone is likely to be stable under normal storage conditions in the proposed dosage forms.

While we did not find information about stability issues with CoQ_{10}, there are stability concerns reported for the fully reduced form of CoQ_{10}, ubiquinol. Ubiquinol undergoes oxidation of the hydroquinol moiety into benzoquinone (Yamamoto and Yamashita 2002). Other than the oxidation issues, ubiquinol is stable under ordinary storage conditions. As the fully oxidized form of CoQ_{10}, ubiquinone is unlikely to undergo further oxidation, and it is likely to be stable under ordinary storage conditions.

2. Probable routes of API synthesis

[3] Ubiquinol, 30% powder, was proposed for use in adjunctive therapy for glycemic control as orally administered capsules. FDA reviewed available data on the physiochemical characteristics, safety, effectiveness, and historical use in compounding of the substance and proposed that ubiquinol not be included on the 503A Bulks List at the May 8-9, 2017 Pharmacy Compounding Advisory Committee (PCAC) meeting. We intend to take into consideration this review and consultation with the PCAC as we move forward with the rule making for ubiquinol.

CoQ_{10} can be obtained by chemical synthesis or semi-synthesis (West 2001; Lipshutz et al. 2002; Negishi et al. 2002), but such synthetic routes involve tedious manufacturing procedures, and the yield is usually low. Instead, industrial production of CoQ_{10} is usually carried out via fermentation technology using microbes, such as *Agrobacterium tumefaciens, Paracoccus denitrificans or Rhodobacterosphaeroides* (Yoshida et al. 1998; Pfaller and Leonhartsberger 2004; Choi et al. 2005; Yajima et al. 2005; Kumar et al. 2012). The crude fermentation product can be then isolated and purified by extraction, chromatography and other purification techniques.

3. Likely impurities[4]

Likely impurities may include:

- Bioburden from the fermentation process
- Residual solvents and reagents used in the separation and purification processes.

4. Toxicity of those likely impurities

Potential impurities are unlikely to be significantly toxic.

5. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

CoQ_{10} is a yellow solid. It is practically insoluble in water. Intravenous administration would require a complex formulation made under tight controlsNo further information on the influence of particle size and polymorphism on its bioavailability was found in the literature.

6. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

CoQ_{10} is easily characterized with proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and mass spectrometry (MS).

Conclusions: CoQ_{10} is a small organic molecule, and it is likely to be stable under ordinary storage conditions. The nominated substance is easily characterized with various analytical techniques and the preparation of this compound has been well developed. It is not recommended that CoQ_{10} be compounded for intravenous administration.

[4] This review contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing.

B. Are there concerns about the safety of the substance for use in compounding?

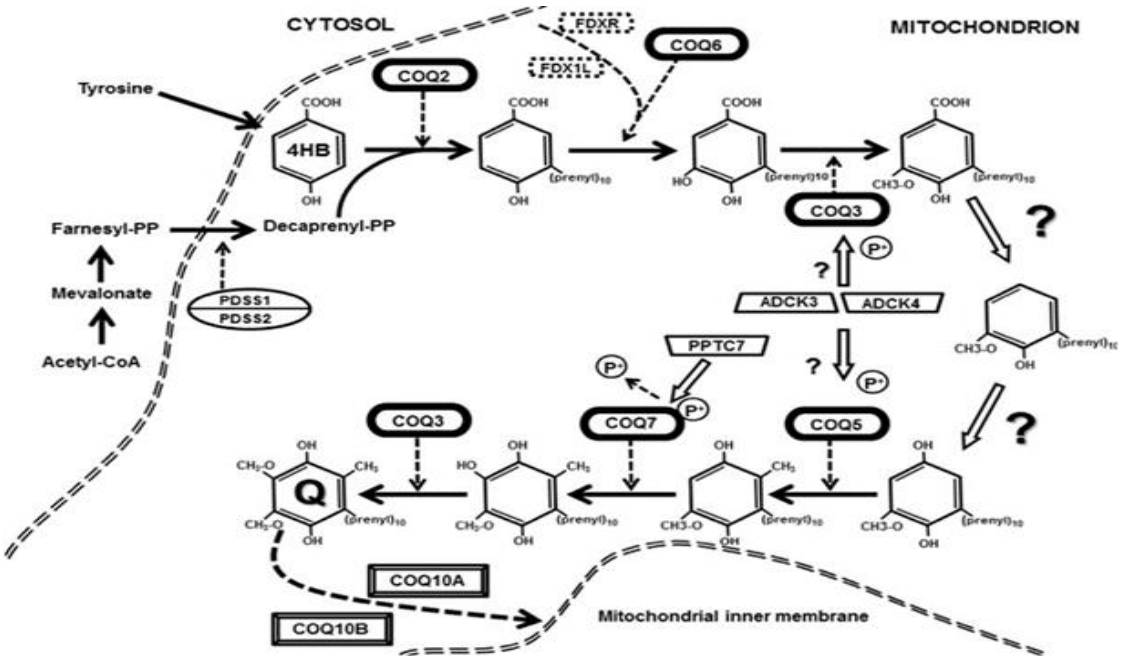
1. Nonclinical assessment

The following databases were consulted in the preparation of this section: PubMed, National Toxicology Program website, Google Scholar, GRAS notice inventory, US Pharmacopeia/NF monographs, and Drugs@FDA.

a. General pharmacology of the drug substance

CoQ_{10} has been identified in all plants and animals, as well as in many microorganisms. It is found in many foods, including meats (e.g., beef, chicken) and fish (e.g., herring, rainbow trout). It is estimated that humans consume an average of 2–20 mg/day of ubiquinone per day (Kitano et al. 2007). Humans also synthesize CoQ_{10} in cytoplasmic organelles, mitochondria, in which a sequential process takes place to add 10 isoprene repeats to a quinone unit (Figure 1).

Figure 1. Synthesis of CoQ_{10} in Humans (Acosta et al. 2016)



Mitochondria also generate ATP through oxidative phosphorylation (OXPHOS) under aerobic conditions, creating more than 90% of the energy needed by the body and affecting almost all human cells and organ systems (Acosta et al. 2016). Mitochondrial functions also include roles in calcium homeostasis, apoptosis, cellular stress response, heme biosynthesis, sulfur metabolism, and cytosolic protein degradation (Rahman and Rahman 2018).

CoQ_{10} serves as an electron transporter in OXPHOS as follows (Rahman and Rahman 2018); see also, Figure 2.

The OXPHOS system involves five multimeric enzymes, named complexes I to V, and two mobile electron carriers, cytochrome c and CoQ_{10}. Complex I (NADH:ubiquinone oxidoreductase) pumps four protons across the inner mitochondrial membrane into the intermembrane space through the oxidation of NADH and reduction of CoQ_{10}. Complex II (Succinate-CoQ oxidoreductase) transfers electrons from FAD-dependent sources through the reduction of CoQ_{10}. However, no protons are pumped across the inner mitochondrial membrane by this enzyme. Complex III (ubiquinol-cytochrome c oxidoreductase) oxidizes CoQ_{10} and reduces cytochrome c, releasing a total of four protons into the intermembrane space.

In summary, CoQ_{10} is responsible for shuttling electrons from Complex I and II to Complex III (Hirano et al. 2006). The next steps in OXPHOS do not require CoQ_{10}. Complex IV catalyzes a reaction to release four electrons accepted by molecular oxygen to form water. Proton transfer to the intermembrane space is used by Complex V to phosphorylate ADP to ATP.

Figure 2. CoQ_{10}'s Role as an Electron Transporter in Oxidative Phosphorylation

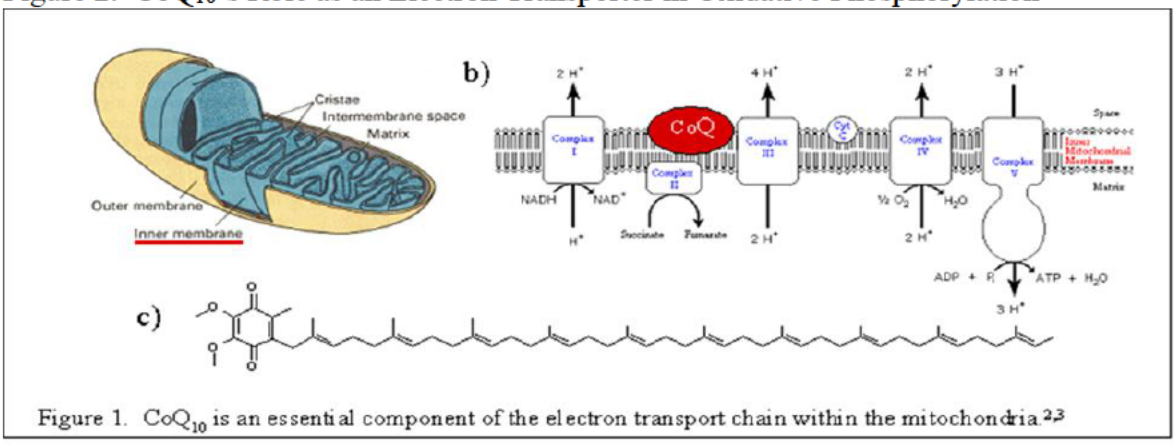


Figure 1. CoQ_{10} is an essential component of the electron transport chain within the mitochondria.[2,3]

CoQ_{10} has may functions in addition to electron transfer in OXPHOS. It is a cofactor for uncoupling proteins, another part of the OXPHOS system, and for several mitochondrial dehydrogenases involved in fatty acid beta oxidation. It is a main cellular antioxidant, contributes to pyrimidine biosynthesis, and is a modulator of the mitochondrial permeability transition pore controlling apoptosis (Parikh et al. 2009; Desbats et al. 2015).

b. Pharmacokinetics/Toxicokinetics

The pharmacokinetic profile of CoQ_{10} was studied in rats following a single oral dose where various formulations of CoQ_{10} were studied (Hatanaka et al. 2008). Although the time to maximum concentration (T_{max}) did not differ significantly among the various formulations, the area under the curve (AUC) and the maximum concentration (C_{max}) were higher among the various formulations when compared to the crystalline form of CoQ_{10} (e.g., the nano-formulation showed a 1.7-fold higher AUC and C_{max} than the crystalline CoQ_{10}; see Figure 3 and Table 1).

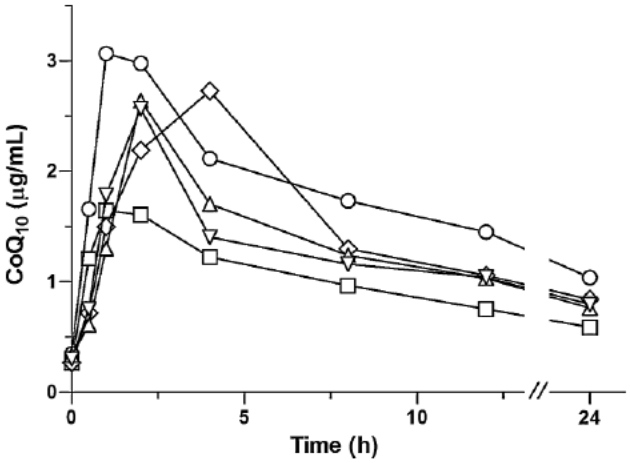


Fig. 3. Mean CoQ_{10} concentrations in blood of rats after oral administration of CoQ_{10} formulations (60 mg CoQ_{10}/kg body weight of rat as a single dose). Each value represents the mean from six experiments. The lines represent the following: (square □) crystalline, (circle ○) CoQ_{10} –NE (nano- emulsion), (triangle ∧) CoQ_{10} –PDE (primary dry-emulsion), (inverted triangle ∨) CoQ_{10} –HDE (homogenized dry-emulsion), and (diamond ◊) CoQ_{10} –CD (cyclodextrin inclusion complex).

Table 1: Pharmacokinetic parameters of CoQ_{10} formulations following oral administrations of 60 mg/kg of CoQ_{10}

	AUC (µg/mL h)	T1/2 (h)	Cmax (µg/mL)	Tmax (h)
Crystalline CoQ_{10}	43.3 ± 20.2	23.0 ± 13.9	1.9 ± 0.5	1.7 ± 1.2
CoQ_{10} formulations:				
CoQ_{10} –NE	71.3 ± 10.8*	21.4 ± 6.0	3.2 ± 0.6**	1.5 ± 0.5
CoQ_{10} –PDE	55.0 ± 16.1	23.3 ± 10.7	2.7 ± 0.6*	2.7 ± 1.0
CoQ_{10} –HDE	58.4 ± 12.5	26.4 ± 5.4	2.6 ± 0.4*	1.7 ± 0.5
CoQ_{10} –CD	50.9 ± 9.2	15.4 ± 4.6	2.9 ± 0.8*	2.8 ± 1.3

Values are expressed as means ± S.D. from six experiments. T1/2: half-life; Tmax: time to maximum concentration; Cmax: maximum concentration; AUC: area under the curve of plasma concentration versus time from t =0 to t = ∞ after oral administration. * $P < 0.05$, ** $P < 0.01$ versus crystalline CoQ_{10}.

Exposure to CoQ_{10} for 13 weeks in dogs showed a trend towards an increase in C_{max} and AUC values when comparing data from day 1 to week 7 (see ubiquinone values in Table 2 below). However, this increase seems to be transient as CoQ_{10} levels seem to have reached their peak at week 7, and plateaued afterwards since levels from week 13 were lower than those seen in week 7. Accumulation does not seem to be a concern over subchronic exposure period (week 13) to CoQ_{10} in dogs under the conditions of this study. A similar pattern of exposure was seen in males and females (Kitano et al. 2008).

Table 2

Summary of pharmacokinetic parameters in dog plasma (mean ± *SD*)

	Test chemical	Level (mg/kg)	No. of animals examined	C_{max} (μg/ml)			AUC_{0-24h} (μg·h/ml)		
				Day 1	Week 7	Week 13	Day 1	Week 7	Week 13
Males	Ubiquinol	150	3	3.54 ± 0.20	9.71 ± 0.16	8.20 ± 1.23	65.85 ± 9.98	175.50 ± 18.24	167.86 ± 22.84
	Ubiquinol	300	3	5.20 ± 0.13	8.58 ± 1.05	9.57 ± 0.34	94.97 ± 9.22	174.12 ± 29.11	181.77 ± 12.88
	Ubiquinol	600	3	6.79 ± 0.93	11.90 ± 2.02	8.55 ± 0.06	129.81 ± 15.53	213.02 ± 27.04	164.41 ± 14.41
	Ubiquinone	600	3	4.35 ± 0.68	8.03 ± 1.09	6.06 ± 0.53	86.46 ± 13.73	164.87 ± 19.74	122.41 ± 8.37
Females	Ubiquinol	150	3	4.51 ± 1.66	8.02 ± 1.80	7.17 ± 0.72	66.60 ± 26.04	139.87 ± 51.89	144.18 ± 32.89
	Ubiquinol	300	3	5.23 ± 0.20	8.87 ± 1.08	8.80 ± 0.98	89.99 ± 6.74	184.17 ± 24.32	185.27 ± 35.06
	Ubiquinol	600	3	6.19 ± 1.03	7.60 ± 1.12	5.76 ± 0.74	102.44 ± 13.26	146.20 ± 14.24	119.03 ± 21.80
	Ubiquinone	600	3	3.58 ± 0.37	5.96 ± 2.26	5.63 ± 1.76	74.27 ± 3.21	126.72 ± 53.66	108.68 ± 28.05

c. Acute toxicity[5]

Exposure to single doses of CoQ_{10} in mice and rats when administered orally (po), subcutaneously (sc), intramuscularly (im), or intravenously (iv) did not result in deaths or any morbidities when animals were observed for a week following dosing with CoQ_{10}. The maximum tolerated doses of CoQ_{10} were estimated to be higher than: 4,000 mg/kg (po) for mice and rats, 500 mg/kg (iv) for mice, and 250 mg/kg (iv) for rats, 500 mg/kg (im) for mice and rats, and 500 mg/kg (sc) for mice and rats (Hatakeyama et al. 2006; Hidaka et al. 2008). Testing of another formulation of CoQ_{10} produced by Kaneka Q10™ using a single oral dose of 1250, 2500 or 5000 mg/kg CoQ_{10} dissolved in corn oil was not associated with any deaths (LD^{6}_{50} > 5000 mg/kg in male and female rats).

d. Repeat dose toxicity[7]

Rabbits: No toxicities were identified when male and female white rabbits were orally dosed with CoQ_{10} for 23 days at a daily dose of 0, 6, 60 or 600 mg/kg. The parameters that were evaluated included hematological analyses, biochemical tests on blood and urine samples, gross and histopathological examinations (Hidaka et al. 2008).

Rats: A four-week repeated oral dose toxicity study with CoQ_{10} (1000 mg/kg/day) was conducted in male and female rats, neither CoQ_{10} nor its 2Z isomer produced any toxic effects. No alterations were seen in body weight, food consumption, blood chemistry, select organ weights, and histopathology when comparing control animals to those treated with CoQ_{10} (Hatakeyama et al. 2006).

A 28-day repeated dose oral toxicity study was conducted in rats using a water-miscible (i.e., drug and water formed a homogeneous mix), emulsified preparation of CoQ_{10} (Q10EP40: CoQ_{10}

[5] *Acute toxicity* refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). Endpoints captured in acute toxicity studies usually include mortality and gross clinical observations. Acute toxicity data are usually superseded by data obtained from longer term toxicity studies.

[6] LD_{50}: dose of the drug at which 50% of animals die.

[7] *Repeated-dose toxicity* studies consist of in vivo animal studies that seek to evaluate the toxicity of the test substance by observing the changes that emerge in clinical observations, clinical chemistry, gross pathology, and histology endpoints when the test substance is repetitively administered daily for a predetermined period of time.

content, 40w/w% at 0, 500, 1000, or 2000 mg/kg/day). No adverse effects were observed and the no-observed-adverse-effect level (NOAEL) for Q10EP40 was estimated to be 2000 mg/kg/day (equivalent to 800 mg/kg/day of CoQ_{10}) for both males and females (Tanaka et al. 2005).

A 13-week oral gavage toxicity study was conducted in rats where CoQ_{10} was dosed daily at 300, 600 or 1200 mg/kg/day. No adverse effects were observed in body weights, food consumption, ophthalmoscopy, clinical chemistry, organ weights or histopathology. A NOAEL of 1200 mg/kg/day was estimated under the conditions of the study (Honda et al. 2007).

A 90-day oral gavage toxicity study was conducted in rats where CoQ_{10} was dosed daily at 500, 1500 or 3000 mg/kg/day. A 15-day recovery period was included in the study. The following observations were noted:

- A slight reduction in body weight was seen among treated males dosed with 1500 mg/kg/day.
- A reduction in food consumption was seen among females treated with 3000 mg/kg/day.
- A change in triglyceride (among females dosed with 1500 & 3000 mg/kg/day) and cholesterol (a trend towards a dose-dependent decrease in males and an increase in females, neither was statistically significant) was seen. These changes were not accompanied by changes in liver histopathology.
- An increase in Na^+ was seen among male rats treated with 1500 and 3000 mg/kg/day.
- A decrease in ovarian weight (relative to body weight) was seen among females dosed with 1500 mg/kg/day and an increase in uterine weight (relative to body weight) was noted among females dosed with 3000 mg/kg/day. Body weight changes seen in the ovary and uterus did not correlate with histopathological changes.

A 52-week study with a 4-week recovery period was conducted in rats using CoQ_{10} at 100, 300, 600, and 1200 mg/kg day via oral gavage administration. The following observations were noted:

- No deaths or adverse changes in clinical signs, body weight, food consumption, or clinical pathology results were reported, except for some increase in alanine aminotransferase, decrease in mean corpuscular volume which were seen among females treated with $\geq$ 600 mg/kg/day and a decrease in mean corpuscular hemoglobin in females at the 53-week time point (which was reversed after the 4-week recovery period). These clinical pathology findings did not have a corollary with histopathological findings.
- At 1200 mg/kg/day, a high incidence of exudates was seen in the nasal turbinates of treated rats. This finding correlated with microscopic findings of affected rats where small granulomas within lung alveoli were observed at the end of the main study (52 weeks) and was still apparent after the recovery period (week 57). The authors hypothesized that the nasal turbinate and lung findings were possibly secondary to incidental exposure to crystallized test material.
- Other findings reported included a dose-related increase in the incidence of vacuolated macrophages (mesenteric lymph nodes) and vacuolated hepatic periportal cells among treated rats (Williams et al. 1999).

Dogs: In a 13-week toxicity study in beagle dogs, three dose groups of ubiquinol and a single dose of ubiquinone were assessed. Ubiquinone (600 mg/kg) was dissolved in corn oil and orally administered daily to Beagle dogs (n= 3/sex). The following observations were noted:

- No deaths occurred in any group during the study period.
- No toxicologically significant abnormalities were noted in body weight, food consumption, ophthalmology, electrocardiogram, urinalysis, hematology, or clinical chemistry.
- Dose related effects could not be assessed for ubiquinone as only one dose was included.
- No effects related to the administration of ubiquinone were seen in gross pathology or histopathological examinations (Kitano et al. 2008).

e. Genotoxicity[8]

No evidence of genetic toxicity was seen for CoQ_{10} synthesized by bacterial fermentation in a standard panel of genotoxicity assays. The panel included the bacterial reverse mutation assay (Ames), mouse bone marrow micronucleus and chromosomal aberration assays which were conducted to evaluate the in vitro and in vivo mutagenic potential of CoQ_{10} (Kitano et al. 2007).

In the Ames test, CoQ_{10} did not induce reverse mutations in Salmonella typhimurium or Escherichia coli at concentrations up to 5000 µg/plate (Yamaguchi et al. 2009). CoQ_{10} was also negative for clastogenic activity when administered orally to mice at doses up to 2000 mg/kg/day. In the *in vitro* chromosome aberration test, CoQ_{10} did not induce chromosomal aberration in Chinese hamster lung (CHL/IU) cells exposed to concentrations up to 5.0 mg/ml (Kitano et al. 2007). These findings suggest that CoQ_{10} manufactured by bacteria fermentation has no potential for genotoxic activities (Yamaguchi et al. 2009).

f. Developmental and reproductive toxicity[9]

A review describing the reproductive toxicity aspects of CoQ_{10} in rats and mice reported that CoQ_{10} did not show any adverse effects when pregnant dams were given doses up to 600 mg/kg/day by oral gavage during the organogenesis stage of fetal development (Notake et al. 1972; Hidaka et al. 2008). The quality of these data cannot be evaluated because the original data are not available for review.

[8] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems.

[9] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects in humans of both sexes and include females from various age groups that will be exposed to the proposed substance. *Developmental toxicity* or *teratogenicity* refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth.

g. Carcinogenicity[10]

In a study where CoQ_{10} was investigated for its impact on senescence in mice, lifelong CoQ_{10} supplementation did not prolong or shorten the lifespan of exposed mice. Based on pathologic examinations of a subgroup of mice, the cancer incidence was not different between CoQ10 and placebo treated mice in middle-aged senescence-accelerated mouse prone (SAMP1) mice (Yan et al. 2006).

Conclusions: Available repeat dose toxicity studies for CoQ_{10} do not show toxicities associated with the use of CoQ_{10}. In a standard panel of genotoxicity assays, CoQ_{10} did not show evidence of genetic toxicity activity. Reproductive toxicity information available in the public literature lacks sufficient detail to assess the quality of the studies. No developmental studies were found in the public literature for CoQ_{10}. In a senescence study conducted in mice, CoQ_{10} did not seem to impact (increase or decrease) the lifespan or the incidence of tumor formation.

2. Human safety

The following databases were consulted in the preparation of this section: PubMed, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov.

Mitochondrial Disorders

CoQ_{10} is nominated for the treatment of mitochondria disorders. A brief background regarding mitochondrial disorders is provided here to assist in the interpretation of safety and efficacy information associated with CoQ_{10} treatment. Normal mitochondrial biogenesis, function, and inheritance requires the integrated activity of an estimated 3000 genes and 1500 gene products. While energy production is an important component of mitochondrial function, over 95% of these 3000 genes are related to the specific functions of differentiated cells. Most genes affecting mitochondrial function are encoded in the cell nucleus (nDNA), but mitochondria contain their own small genome (mtDNA) consisting of 37 genes. Proper mitochondrial functioning is dependent on the proper integration of nuclear DNA protein products and mtDNA protein products. Primary mitochondrial diseases have been linked so far to mutations in more than 200 nDNA genes and 37 mtDNA genes (Rahman 2015).

Mitochondrial disorders can originate from inherited or spontaneous mutation of either nDNA or mtDNA. The myriad of mitochondrial functions forms the basis for the complex physiologic abnormalities associated with nDNA or mtDNA aberrations. The term 'mitochondrial disease' currently includes several hundred different diseases (Rahman 2015). Among these diseases, patients with the same genotype may not present clinically similar symptoms. And, the same genetic mutation or deletion can produce varied phenotypes (Davison and Rahman 2017). Diagnosis of mitochondrial disease in adults is further complicated because mtDNA changes occur as part of normal aging, presenting a wider array of possible age-associated mitochondrial

[10] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to result in tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life.

function abnormalities. Clusters of symptoms and features are recognized as phenotypic mitochondrial syndromes; a listing of the most common syndromes and their most frequently associated mtDNA mutations appears in Appendix 1 (Skorecki and Behar 2015).

One example of genetic diversity in the presence of phenotypic similarity occurs in Leigh syndrome. Leigh syndrome is characterized by bilaterally symmetrical MRI abnormalities in the brain stem, cerebellum, and basal ganglia, and often accompanied by elevated lactic acid levels in the blood or cerebrospinal fluid. However, this syndrome has now been shown to stem from pathogenic mutations in more than 75 nDNA or mtDNA genes. Not all children with these mutations go on to develop the disease (Lake et al. 2016). The field of mitochondrial disease research is exponentially expanding, with nearly 30 of the Leigh syndrome genes characterized in the approximately five years prior to 2015. While the Leigh syndrome population is considered clinically heterogeneous, onset is generally prior to 2 years of age following a period of normal development, with symptoms appearing during infection or illness, and results in death by 3 years of age. Adult onset is infrequent. Genotype-phenotype correlations are being investigated, helping to provide insight into links among biochemical defects, characteristic disease features, and affected ethnicities (e.g., the population of the Saguenay-Lac-Saint-Jean region of Quebec, Canada).

Schaefer et al. (2008) estimated the minimum point prevalence for 2001 of mitochondrial diseases (mtDNA only) in the North East of England as 9.2 in 100,000 people between the ages of 16 years and 60 years (for females) or 65 years (for males). It was also estimated that an additional 16.5 in 100,000 children and adults younger than 60 (or 65) were at risk for the development of mtDNA disease. Studies of the frequency of specific phenotypes, or population based reports of disease, have been conducted in northern Finland, Japan, Switzerland, and Australia (Chinnery and Turnbull 2001). The estimates of prevalence are highly varied based on geographic locale and the disease or mutation of interest.

There are no drugs that have been FDA approved for the treatment of any mitochondrial disorders, although 14 substances have received orphan designation.[11]

a. Reported adverse reactions (FAERS, CAERS)

The Office of Surveillance and Epidemiology conducted a search of FDA Adverse Event Reporting System (FAERS) for reports of adverse events with the product terms "coenzyme q10," "ubiquinol," "ubidecarenone," and ubiquinone" through June 14, 2018. A total of 19 reports of serious events were identified as being possibly related to CoQ_{10}. Among these, there were two deaths reported, both in pediatric patients with mitochondrial disorders. Both appear to be related to the underlying condition and unrelated to CoQ_{10} use. Comorbidities and use of

[11] https://www fda.gov/forindustry/developingproductsforrarediseasesconditions/howtoapplyfororphanproductdesignation/ucm333718.htm; downloaded June 14, 2018.

concomitant medications are confounders that limit the ability to determine whether there is a causal relationship between CoQ_{10} and the reported events.

CAERS

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for adverse events associated with CoQ_{10} and dietary supplements on June 15, 2018 and retrieved 837 reports.

- Eight deaths reported. Two deaths were due to cerebrovascular accidents (strokes), two were due to cancer, one was due to a myocardial infarction, one was due to a pulmonary embolism, and in one case the cause was not specified. Further interpretation of these cases is confounded by the use of multiple dietary supplements and medications and lack of information.
- There were 22 cases in which CoQ_{10} was the only dietary supplement or drug mentioned in the report, although not necessarily the only product being used by the patient. Reported events included: blotches in field of vision, dizziness, hives (n = 2), allergic reaction (n = 2), swollen hands, irregular heartbeat (n = 2), diarrhea (n = 3), vaginal yeast infection, product contamination (glass), ataxia, renal disorder (resolved), "abdominal bleeding" (unclear what this means), dyspepsia, vertigo, weight gain, constipation, emotional sensitivity, syncope, abdominal pain/nausea, eye floater, "hands and feet turned black."

b. Clinical trials assessing safety

The safety of CoQ_{10} has been evaluated in healthy volunteers during trials of CoQ_{10} formulations designed to help improve absorption of CoQ_{10} from the gastrointestinal tract. The studies include:

- Kaneka Q10 is an all-*trans* form of CoQ_{10}, created by yeast fermentation (Ikematsu et al. 2006). The all-*trans* form of CoQ_{10} is the isomeric form that has been nominated and is the subject of the United States Pharmacopeia dietary supplement monograph.[12] The authors state that the all-*trans* form is the physiologically active form and differs from CoQ_{10} produced by chemical synthesis, which produces a largely *tran*s substance with minor quantities of the *cis* isomer. Kaneka Q10 was taken for four weeks by 12 volunteers at 300 mg per day, 20 volunteers at 600 mg per day, and 16 volunteers at 900 mg per day. Adverse events included common cold symptoms, abdominal pain, soft feces as well as minor changes in hematology, blood biochemistry, and urinalysis. None of these changes were found to be dose related or attributed to CoQ_{10} treatment.
- A "water-soluble type CoQ_{10} powder" formulation was given at doses of 900 mg per day of CoQ_{10} to 23 healthy volunteers (Nukui et al. 2007). No "significant changes in symptoms or clinical laboratory results" were observed.
- Hathcock and Shao (2006) conducted a risk assessment to evaluate the safety of CoQ_{10} based on trials conducted in a variety of disease conditions. Maximum exposures were

[12] http://www.usp.org/products/dietary-supplements-compendium

reported as doses of 3000 mg daily in an uncontrolled, open-label study of 31 amyotrophic lateral sclerosis patients and a 16-month trial of 80 Parkinson's disease patients taking 1200 mg daily. Nausea and other gastrointestinal effects have been reported at doses from 60 to 1200 mg daily and do not appear to be more frequent or severe at higher doses. The authors conclude that this finding limits the ability to make a causal assessment. In addition, the authors of this study conclude that data for doses above 1200 mg per day are insufficient to evaluate risk.

No studies were found specifically designed to assess the safety of CoQ_{10} in mitochondrial disorders. In the clinical studies and case reports of CoQ_{10} use in the treatment of mitochondrial diseases, two studies were found to have significant safety findings, described below. Additional details of these studies are in Section II.C. Other studies reported that there were no adverse events, or none related to CoQ_{10} (see Appendix 2).

Glover et al. (2010) did not describe adverse event data. However, at doses of 600 mg twice daily for 60 days, CoQ_{10} treatment was found to be positively associated with urinary levels of 8-hydroxy-2-deoxyguanosine. The authors presume that this is a marker of oxidative stress and suggest that higher doses of CoQ_{10} taken for prolonged periods may be "deleterious."

Remes et al. (2002) reported that no changes in "blood chemistry or other safety measures were observed" among the seven MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; 3243A>G mutation) patients studied. However, the sudden death of a female patient with multiorgan disease on the 39th day of treatment with 3 mg/kg daily of CoQ_{10} occurred. It was reported that the clinical evaluation of this patient conducted one week before her death was unremarkable, but electrocardiogram changes had been observed at some (unspecified) point in her prior examinations. Autopsy revealed cardiomyocyte degeneration and active fibrotic changes in the myocardium. The death was considered unrelated to CoQ_{10}. Sudden death of a second patient was reported in this trial. The patient had taken 3 mg/kg daily of CoQ_{10} for six months, followed by a three-month washout period, and then 20 days of dosing with 50 mg/kg daily of nicotinamide. This patient was also reported to have previously had electrocardiogram changes and was found on autopsy to have had ">50% stenosis in the left anterior descending coronary artery, abundant fibrosis of the myocardium and mild glomerular sclerosis." The death was not considered related to nicotinamide or CoQ_{10}. Three additional patients died shortly after the 24-month trial. Authors conclude that the overall high mortality rate of 0.22/year was likely related to the severity of patients enrolled in the study; however, it was also suggested that CoQ_{10} and/or nicotinamide could be harmful in patients with severely disturbed mitochondrial function.

c. Pharmacokinetic data

CoQ_{10} is synthesized de novo in all tissues such that humans are generally not dependent on an exogenous supply (Bhagavan and Chopra 2006). Without supplementation, the total body pool of CoQ_{10} is estimated to be 0.5 – 1.5 g in normal adults. Plasma levels are approximately 0.4 - 1.72 µmol/L but appear to be variable based on race and ethnicity. CoQ_{10} is found in all human tissues as shown in Table 3, with higher concentrations in tissues that have greater energy requirements.

Table 3 Distribution and redox state of CoQ10 in human tissues.

Tissue	CoQ10 (nmol/g)	Redox state (% reduced)
Heart	132.0	61.0
Kidney	77.0	75.0
Liver	63.6	95.0
Muscle	46.0	65.0
Brain	15.5	23.0
Intestine	13.3	95.0
Lungs	9.2	25.0
Plasma (μmol/l)	1.1	96.0*

Reviews by Miles (2007) and Bhagavan and Chopra (2006) highlight the available information regarding the pharmacokinetics of supplemental CoQ_{10} (ubiquinone) in healthy individuals. CoQ_{10} has low solubility in aqueous solutions because of its lipophilic 10 carbon chain and high molecular weight. Orally administered exogenous CoQ_{10} is incorporated into chylomicrons for transport from the gut into the lymph and peripheral blood. Absorption in animal models is highest in the duodenum and is likely both a passive and active process (Miles 2007). In a rat model, only 2-3% of orally administered CoQ_{10} was absorbed (Bhagavan and Chopra 2006). It is anticipated that human absorption mechanisms and extent of absorption are similar to that found in animals. Inter-product and inter-individual variability in the extent of absorption in humans are high. Time to peak plasma levels (Tmax) is approximately 6-8 hours following a dose and is generally more consistent with solubilized (e.g., emulsified) dosage forms (Miles 2007). Other factors, such as the effects of age, gender, disease, presence of food in the gastrointestinal tract, especially lipids, CoQ_{10} source (dietary supplement or natural food source), and chronicity of dosing, require further study. Over 95% of an ingested CoQ_{10} dose is excreted in the feces.

CoQ_{10} absorbed from the intestine is taken up by liver cells, incorporated with lipoproteins as transporters, and released into the blood (Miles 2007). Enterohepatic circulation also occurs and is thought to contribute to the wide variability in plasma concentrations resulting from different product formulations. In vitro studies with human Caco-2 cells have confirmed animal findings that ubiquinone is reduced to ubiquinol during or following absorption and about 95% of circulating CoQ_{10} has been converted to ubiquinol (Bhagavan and Chopra 2006). A three-compartment pharmacokinetic model best fits the concentration-time curve, with a 6-12 hour phase of distribution to peripheral tissues following T_{max}. The terminal elimination half-life is approximately 33 hours. This is thought to be due to the slow release of CoQ_{10} from peripheral tissues back in the plasma. Steady state is reached after 3-4 weeks of consistent dosing and plasma concentrations range from 5-10 µg/mL at adult dosages of 1200 mg per day. CoQ_{10} metabolism has not been well established.

Optimal plasma levels of CoQ_{10} for clinical effects have not been established (Miles 2007). However, with numerous factors affecting the bioavailability of CoQ_{10}, it is recommended that CoQ_{10} plasma levels be monitored where verification of dosing adherence and systemic exposure is of interest. Many studies discussed in Section II.C. compared pre-treatment and post-treatment plasma levels and found that CoQ_{10} levels increased with treatment (Nishikawa et al.

1989; Bresolin et al. 1990; Chen et al. 1997; Suzuki et al. 1998; Remes et al. 2002; Glover et al. 2010).

Studies of CoQ_{10} analogues idebenone, mitoquinone, and benzoquinone are being conducted to assess whether they may provide improved bioavailability, particularly for intracellular targets such as mitochondria (Finsterer and Bindu 2015).

d. Availability of alternative approved therapies that may be as safe or safer

There are no drugs approved by FDA to treat mitochondrial disorders. Various dietary supplements and approved and investigational drugs are used in treatment, as discussed in Section II.C.

Conclusions: Available safety data for CoQ_{10} suggest that the substance is associated with non-serious adverse events, particularly gastrointestinal symptoms. However, it is noted that most safety data have been derived from healthy individuals. There is minimal information available to establish CoQ_{10} safety in patients with various types of mitochondrial disorders and it is possible that the safety profile in patients may differ from that of healthy subjects.

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov.

1. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

Treatment Guidelines

Treatment for mitochondrial diseases is mostly supportive (i.e., does not cure or modify the disease process) and determined by phenotypic symptom expression (Kisler et al. 2010; Rahman 2015; Davison and Rahman 2017). For example, physical therapy and mobility aids are the mainstay of treatment for myopathy as a predominant symptom; anticonvulsants are used to control seizures; sodium bicarbonate is indicated to correct lactic acidosis; and various visual aids or surgery are used to improve visual dysfunction or ptosis.

CoQ_{10} has been researched in the treatment of mitochondrial diseases and various neurological disorders since the 1980s (Shults and Haas 2005). A consensus statement from the Mitochondrial Medicine Society (MMS) (Parikh et al. 2015) provides recent recommendations for diagnosis and treatment. In 2012, the MMS surveyed North American physicians and nurse practitioners who, based on the organization that they worked for, were identified as practitioners of mitochondrial medicine (Camp et al. 2016). MMS estimated that the "practice patterns" of at least 90% of U.S. mitochondrial centers were captured by the surveys (Parikh et al. 2013). Concerned about the variability in approaches to diagnoses and treatment, MMS developed consensus recommendations

based on existing evidence (Parikh et al. 2015). The evidence for use of CoQ_{10} in mitochondrial diseases is described as "sparse" and specific dose recommendations are not provided. Nevertheless, the MMS states the following (Parikh et al. 2015).

> CoQ_{10} should be offered to most patients with a diagnosis of mitochondrial disease, and not exclusively for primary CoQ_{10} deficiency. Reduced CoQ_{10} (ubiquinol) is the most bioavailable form, and when used, dosing should be modified relative to other forms. Leukocyte CoQ_{10} levels are helpful to monitor absorption and adherence to treatment whereas plasma levels are more variable and less reflective of tissue levels.

The American Academy of Pediatrics offers diagnostic information for primary physicians, without specific drug treatment recommendations (Haas et al. 2007), but a number of treatments other than CoQ_{10} and creatine have been identified with various proposed mechanisms of action and amounts of supportive scientific evidence (Avula et al. 2014; Enns 2014; Finsterer and Bindu 2015; El-Hattab et al. 2017). These include idebenone (a CoQ_{10} analogue), riboflavin, thiamine, niacin, succinate, l-carnitine, vitamin C, vitamin K, dichloroacetate, creatine, cysteine, N-acetyl cysteine, dimethylglycine, lipoic acid, arginine, EPI-743 (a vitamin E analog), benzafibrate, resveratrol, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), dimethylglycine, bendavia, (-)-epicatechin, RTA 408, nucleoside bypass therapy, potential gene therapies, and liver or stem cell transplantation.

Distinct from the general recommendations, CoQ_{10} is considered a standard, effective treatment for one mitochondrial disorder, primary CoQ_{10} deficiency (Parikh et al. 2015), which will be discussed in the next section.

Primary CoQ_{10} Deficiency

Primary CoQ_{10} deficiencies are autosomal recessive rare diseases in which genetic defects exist that are directly related to CoQ_{10} biosynthesis (Yubero et al. 2018). Although no controlled clinical trials have been conducted, primary CoQ_{10} deficiency is considered to be a treatable mitochondrial disorder, as patients have a response to oral CoQ_{10} supplementation (Montini et al. 2008; Parikh et al. 2015; Davison and Rahman 2017). In some cases, treatment can stop disease progression of symptoms such as steroid resistant nephrotic syndrome and encephalopathy (Desbats et al. 2015).

Ogasahara et al. (1986) described a familial syndrome of lactacidemia, mitochondrial myopathy, and encephalopathy in sisters age 14 and 12 years. Measurement of CoQ_{10} levels in their muscle mitochondria was 3.7% of the mean observed in 10 healthy controls. Levels of complexes I-III and II-III, which require CoQ_{10}, were found to be low. This deficiency was tissue-specific and not found in serum or cultured fibroblasts. Concluding that the CoQ_{10} deficiency was caused by a familial defect in CoQ_{10} biosynthesis, the girls were treated with 50 mg of CoQ_{10} three times daily. After three months of therapy, they appeared "to fatigue less rapidly on physical exertion" and be "generally more alert." These cases have since been associated with a predominantly myopathic form of a primary idiopathic CoQ_{10} deficiency (Sobreira et al. 1997; Di Giovanni et al. 2001).

The number of recognized phenotypes expanded to three (Salviati et al. 2005) and currently five main clinical phenotype groups are recognized (Quinzii et al. 2007; Emmanuele et al. 2012):

- Encephalomyopathic, characterized by recurrent myoglobinuria, brain involvement (e.g., seizures), and ragged red fibers
- Isolated myopathy (Horvath et al. 2006; Gempel et al. 2007)
- Cerebellar ataxia, associated with cerebellar atrophy (Musumeci et al. 2001; Lamperti et al. 2003; Artuch et al. 2006; Hirano et al. 2006)
- Leigh syndrome with growth retardation, ataxia, and deafness
- Severe infantile disease, with potentially fatal multisystemic involvement including corticosteroid resistant nephrotic syndrome (Salviati et al. 2005; Montini et al. 2008)

Each of the phenotype groups is associated with one or more of the nine gene mutations that have been identified to date among the affected patients (Acosta et al. 2016).

The infantile form of primary CoQ_{10} deficiency has been identified in only three families (Salviati et al. 2005). In a case report, a 33-month old boy was described who had suffered a progressive decline since the age of 18 months experienced seizures, corticosteroid-resistant nephrotic syndrome, encephalopathy with stroke-like episodes, dysphagia, vomiting, psychomotor regression, tremor, loss of the ability to walk, and hemiplegia with myoclonus. His CoQ_{10} levels in muscle were found to be decreased (12 mg/g; compared to a mean of 32 mg/g from n = 118 controls) and cultured skin fibroblasts. At 22 months, oral CoQ_{10} supplementation of 30 mg/kg daily was initiated generating a "prompt and dramatic" improvement in the patient's muscle tone and strength. The patient continued to improve, regaining the ability to walk and eat. However, his renal function did not improve and he continued to require dialysis. Montini et al. (2008) reported that the patient received a renal transplant at 3 years of age and at 7 years of age continues to have encephalopathy, including cognitive impairment, seizures, and hemiplegia. The patient's sister received a diagnosis of primary CoQ_{10} deficiency at the age of 12 months, before developing symptoms. Immediately after diagnosis she developed nephrotic syndrome. Treatment with CoQ_{10} 30 mg/kg daily was initiated, but her renal function did not improve and she experienced an episode of acute renal failure during the first two weeks of treatment. After 20 days of CoQ_{10} treatment, her renal function began to improve and ultimately became normal. She did not develop neurologic damage, which was attributed to CoQ10 treatment.

Secondary CoQ_{10} deficiency has also been identified and occurs more frequently than primary CoQ_{10} deficiency (Desbats et al. 2015). The causal gene defects are not related to CoQ_{10} biosynthesis. Treatment with CoQ_{10} can be beneficial, but, compared to treatment of primary disease, does not produce as "striking" results.

CoQ_{10} in Other Mitochondrial Disorders

Evidence of the effectiveness of CoQ_{10} in mitochondrial diseases other than primary CoQ_{10} deficiency is lacking. It has been emphasized; however, that there is a need to overcome the difficulties associated with "obtaining high-quality evidence for rare disorders" to collect reliable evidence of drug treatment effects (Pfeffer et al. 2013). The National Institute of Neurological

Disorders and Stroke Common Data Element Project has defined a Mitochondrial Disease Data Standards list to assist researcher in accruing critical and consistent information among studies of mitochondrial disorders (Karaa et al. 2017).

A search of "coenzyme Q_{10}," "CoQ_{10}," and "ubiquinone" in ClinicalTrials.gov retrieved one trial of CoQ_{10} in the treatment of mitochondrial disease. There is an associated publication describing the "design and implementation of the first randomized controlled trial of coenzyme Q_{10} in children with primary mitochondrial diseases" (Stacpoole et al. 2012). The website states that the trial was completed in 2013, but no associated publication of results was found. Studies of CoQ_{10} in the treatment of chronic fatigue syndrome/myalgic encephalomyelitis and Gulf War Illness/Syndrome were listed due to potential relationships between these disorders and mitochondrial deficiency.

In a 2012 Cochrane review of the treatment for mitochondrial disorders (Pfeffer et al. 2012), one randomized, double blind, placebo-controlled crossover trial of CoQ_{10} treatment of mitochondrial disease was included. Glover et al. (2010) compared the effects of CoQ_{10} at doses of 600 mg twice daily (1200 mg per day) for 60 days with placebo dosing for 60 days, separated by a washout period of approximately 70 days. A total of 30 patients, with varied diagnoses, were enrolled:

- N = 15 MELAS. This syndrome is thought to be caused in the majority of cases by the same mtDNA mutation (m.3243A>G) (Davison and Rahman 2017).
- N = 11 CPEO (chronic progressive external ophthalmoplegia), with single or multiple mtDNA deletions.
- N = 1 LHON (Leber's hereditary optic neuropathy), caused by an mtDNA mutation (14459G>A).
- N = 1 NARP (neuropathy, ataxia, and retinitis pigmentosa), a mitchondrial myopathy due to complex I deficiency (8993G>A).
- N = 1 ataxia-neuropathy (9035T>C).

Diagnoses were confirmed with a combination of clinical symptoms, fasting serum lactate concentration, muscle biopsy, and mtDNA analysis. Most patients had been on CoQ_{10} (120-200 mg/day) and other supplements for several years prior to the study; all supplements were stopped six weeks prior to the start of the study.

A variety of endpoints were assessed after 60 days on each treatment (i.e., endpoints were not assessed prior to the initiation of either treatment) and included: height, weight, lean-body mass (LBM), bone mineral density, forearm fatigue testing with near-infrared spectroscopy (NIRS), (exer)cycle ergometry, brain magnetic resonance spectroscopy (MRS), venous blood sampling (collected at rest, analyzed for creatine kinase, bilirubin, gamma-glutamyltransferase, and CoQ_{10} concentration; collected after exercise, analyzed for lactate, glucose, and partial pressure of oxygen and carbon dioxide) and urine collection (analyzed for creatinine, 8-isoprotanes, and 8-hydroxy-2-deoxyguanosine, employed by the authors as urinary markers of oxidative damage). Patient reported visual-analog scales were used to collect information about activities of daily living and quality-of-life.

Following the 60-day treatment with CoQ_{10}, mean plasma CoQ_{10} levels had risen 5-fold compared to 60 days on placebo, but otherwise the authors conclude that "there was a lack of

effect on most measured variables." Lactate levels were significantly lower after 5 minutes of cycling in association with CoQ_{10} treatment in the 15 of 30 patients who were able complete this duration of testing. CoQ_{10} treatment was also associated with a statistically greater increase in mean oxygen uptake compared to placebo (19.3 vs 17.4 ml/kg LBM/m, $p<0.05$) following 15, but not 5, minutes of cycling in the 11 of 30 patients who completed this duration of cycling. The mean concentration of creatine-containing compounds was estimated by modeling with MRS and was statistically lower in gray matter, but not in basal ganglia or periventricular white matter, than with placebo (0.166 vs 0.217, $p<0.05$) among the 19 of 30 patients who completed both MRS evaluations.

The Cochrane review identified additional studies and case reports that were included only in the reference list of their review, as these evaluations failed to meet the Cochrane criteria (Pfeffer et al. 2012). These publications are addressed below, along with various clinical reports that were not identified in the Cochrane review.

Remes et al. (2002) found no significant benefit in treating five patients, diagnosed with the 3243A>G mutation and MELAS, with 3 mg/kg daily CoQ_{10} for six months in an open-label study. CoQ_{10} treatment was followed by a three-month washout and then 50 mg/kg daily of nicotinamide in three of the previous five patients and two additional patients. Nicotinamide also showed no benefit. Blood lactate and pyruvate, and the seven-point Clinician's Interview Based Impression of Change, were the primary outcome measures.

Suzuki et al. (1998) evaluated the use of CoQ_{10} in treatment of MIDD (maternally inherited diabetes mellitus and deafness) patients. MIDD is associated with an mtDNA mutation (3243A>G). A treatment group of 28 MIDD patients, 7 patients with mutant DNA and impaired glucose tolerance, and 15 patients with mutant DNA but normal glucose tolerance were compared to 16, 5, and 5 patients in the same classifications, respectively. The first group received 150 mg oral CoQ_{10} daily for 3 years and the other patients did not receive CoQ_{10} (or placebo). Insulin secretory response was assessed annually in each group by glucagon-induced C-peptide secretion and 24-hour urinary C-peptide excretion. MIDD patients who had taken CoQ_{10} had a significantly higher mean insulin response after 3 years than control MIDD patients, but there were no differences between mutant patients with impaired or normal glucose tolerance based on CoQ_{10} treatment. There were no differences between groups with respect to MIDD patients' diabetic complications or clinical symptoms. MIDD patients who had taken CoQ_{10} were also reported to have had less progressive hearing loss and improved blood lactate after exercise. This open label trial suggests potential benefit of CoQ_{10} benefit in MIDD but does not provide definitive information regarding the identification of patients who may be responsive to CoQ_{10} treatment, dosing or long term efficacy, particularly given the lack of apparent CoQ_{10} effect on diabetic complications and clinical symptoms.

Chen et al. (1997) enrolled 8 patients with one of three different mitochondrial disorders, each associated with encephalomyopathies: MELAS, CPEO or MERRF (myoclonus epilepsy with ragged-red fibers). In a crossover study, comprising CoQ_{10} therapy at 160 mg per day orally for 3 months and placebo for one month, patients were randomized to treatment order and, if CoQ_{10} treatment was assigned first, a one month washout period was allowed between treatments. One patient did not complete the trial due to a fatal intracerebral hemorrhage. Assessments were

made at monthly intervals: subjective scoring of fatigability in activities of daily living was provided by patients, two blinded neurologists provided index scores from Medical Research Council (MRC) assessment of functionality of various muscle groups, objective scoring of sustained endurance strength, and collection of serum samples for lactate and pyruvate assessment. Only the global MRC index score was statistically significantly improved in association with CoQ_{10} treatment. Perhaps due in part to the small number of heterogenous patients, the short duration or selected endpoints, this study does not provide substantive evidence of the effect of CoQ_{10}.

In a two-phase study, Bresolin et al. (1990) attempted to identify a subset of CoQ_{10} responder patients for focused study. The first phase included 44 patients, with diagnoses of Kearns-Sayre syndrome, CPEO, MERRF or mitochondrial myopathy without ophthalmoplegia, and was a six month, open label period in which patients received 2 mg/kg/day of CoQ_{10}. A fall in serum lactate following exercise of 25% or more compared to pre-dosing levels was deemed a response and the 16 patients who met this criterion were enrolled in the second phase of the trial. A blinded, placebo controlled trial that was 3 months in duration, during which patients were treated with either 2 mg/kg/day of CoQ_{10} or placebo. No significant differences were seen between the two groups. The authors conclude that they were unsuccessful in identifying a CoQ_{10} responder population, or the duration of the second phase was insufficient to demonstrate differences between groups.

Many literature reports were found of uncontrolled, observational assessments of symptoms in a small number of patients representing one or more mitochondrial disorders. Each evaluation suggests a potential role for CoQ_{10} in clinical treatment, most often due to evidence of improvement of particular physiologic measures or clinical chemistries, but these reports do not provide definitive information regarding the effectiveness of CoQ_{10}. This review does not address a comprehensive list of these reports, as treatment guidelines and other clinical reviews best reflect the totality of clinical science in this field. Two example reports are described in the following:

- Angeli et al. (2005) identified three patients with the 7445A>G mitochondrial mutation who had associated SNHL (sensorineural hearing loss). Two were treated with 75 mg CoQ_{10} twice daily for one year. The third patient refused treatment. The authors report that the two patients who received CoQ_{10} did not show any additional deterioration of their SNHL while the patient who refused treatment exhibited an 11-db deterioration of his hearing thresholds.
- Papadimitriou et al. (1996) reported that CoQ_{10} replaced treatment with alfacalcidol in two patients with Kearns-Sayre syndrome and hypoparathyroidism to maintain normal total serum calcium concentrations. The authors propose that CoQ_{10} improved the capacity of the mitochondria in the proximal tubules to produce an active form of Vitamin D.

Early studies of the effects of CoQ_{10} with mitochondrial disease often used bicycle ergometer exercise to help assess OXPHOS function (Ogasahara et al. 1986; Nishikawa et al. 1989; Abe et al. 1991; Bendahan et al. 1992; Gold et al. 1996; Barbiroli et al. 1997; Chan et al. 1998; Abe et al. 1999). These studies included a small number of patients (n = 1 to 9) and included treatment from 120 to 300 mg CoQ_{10} daily for periods of 2 weeks to 2 years. Endpoints were assessed

before and after exercise throughout treatment and included measures such as noninvasive tissue oximetry; near-infrared spectroscopy or ^{31}P magnetic resonance spectroscopy with assessment of phosphocreatine levels compared to inorganic phosphate in muscle, and both serum and CSF lactate, pyruvate, and pH. Patients' diagnoses were heterogeneous among these studies, and many studies included patients with various diagnoses. These studies contributed significantly to the understanding of OXPHOS dysfunction in mitochondrial disorders, and provided physiologic assessment tools for potential drug effect metrics, but generally showed only minor, sporadic associations between CoQ_{10} treatment and OXPHOS improvement.

CoQ_{10} has been studied in combination with other agents for the treatment of mitochondrial diseases. The contribution of CoQ_{10} to the effects seen cannot be discerned. Examples of combination studies include:

- Rodriguez et al. (2007) assessed the combination of creatine, $CoQ_{1,0}$ and lipoic acid in the treatment of 16 patients with various mutations and/or mitochondrial disease diagnoses. The authors conclude that combination therapies may target multiple common pathways of mitochondrial dysfunction, but larger studies of combination therapies in homogeneous populations are needed.
- Ihara et al. (1989) report that a 64-year old female diagnosed with MELAS was given 210 mg of CoQ_{10} daily for three months and was reported to have had some improvement in symptoms of sensory disturbance and ataxia. Idebenone was added to the CoQ_{10} regimen at a dose of 90 mg per day. Her sensory disturbance and ataxia improved further. In addition, her electroencephalogram became nearly normal (reduction of high-voltage slow wave bursts), her dementia improved, and protein levels in her CSF decreased. The authors conclude that while CoQ_{10} may improve peripheral symptoms in MELAS, the addition of idebenone may be needed for effective treatment of MELAS damage to the CNS.

2. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

There are numerous mitochondrial disorders, as explained above. Most are serious diseases and many are life-threatening.

3. *Whether there are any alternative approved therapies that may be as effective or more effective*

There are no drugs approved by FDA to treat mitochondrial disorders.

Conclusions: There are no compelling data establishing the effectiveness of CoQ_{10} for the treatment of mitochondrial diseases. Mitochondrial diseases encompass a wide variety of conditions related to genetic mutations in nDNA and mtDNA, with different phenotypic presentations. Based on a small amount of clinical data, clinical guidelines that recommend the use of ubiquinone in the treatment of primary CoQ_{10} deficiency and, in the absence of FDA approved therapies, therapeutic experts recommend CoQ_{10} for the treatment of other mitochondrial disorders. The results of CoQ_{10} therapy have been described in numerous

publications, but do not appear to definitively support effectiveness for particular uses other than primary CoQ10 deficiency or in particular doses.

D. Has the substance been used historically as a drug in compounding?

Databases searched for information on CoQ_{10} in regard to Section II.D. of this consultation included PubMed, Natural Medicines, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and Google.

1. Length of time the substance has been used in pharmacy compounding

Coenzyme Q10 has been used in pharmacy compounding since at least 1999 (Hudson 1999).

2. The medical condition(s) it has been used to treat

According to the Natural Medicines Database, CoQ_{10} is used orally for congestive heart failure, angina, dilated cardiomyopathy, hypertrophic cardiomyopathy, diabetes, hypertension, periodontal disease, cardiotoxicity associated with doxorubicin chemotherapy, breast cancer, bipolar disorder, Huntington's disease, Parkinson's disease, muscular dystrophy, increasing exercise tolerance, chronic fatigue syndrome, Lyme disease, pre-eclampsia, warfarin-induced alopecia, autism, and numerous other conditions (Natural Medicines 2018).

Results from a Google search using the terms *coenzyme Q10 compounding pharmacy* indicate that CoQ_{10} is/has been compounded as an injection and topical cream by at least one pharmacy.

In addition, CoQ_{10} is advertised as a component of the "Mito Cocktail," which according to MitoAction,[13] is a cocktail[14] of various vitamins and supplements commonly used in adults and children who have been diagnosed with mitochondrial disease. See http://www.mitoaction.org/blog/mito-cocktail.

According to CompoundingToday.com, ubidecarenone is/has been compounded as a troche, chewable troche, capsule, oral solution, and a sublingual suspension. See https://compoundingtoday.com/Formulation/SearchByKeyword.cfm. It appears that these oral and sublingual formulations have been used for the treatment of heart disease (Hudson 1999; Loyd 2008; Bramwell 2010), Raynaud's disease (Glassnap 2003), and chronic fatigue syndrome (Hudson 1999).

3. How widespread its use has been

Insufficient data are available from which to draw conclusions about the extent of use of CoQ_{10} in compounded drug products.

[13] According to mitoaction.org, MitoAction is a patient advocacy organization within the mitochondrial disease community.

[14] This "cocktail" appears to be for oral administration. Per the guide for patients available at http://www.mitoaction.org/files/mito%20cocktail%20brochure%202010.pdf, doses should be taken with a meal and plenty of fluids.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

"Ubidecarenone," a synonym for ubiquinone and CoQ_{10}, (Ph. Eur monograph 1578) is listed in the British Pharmacopoeia (BP 2018) and the European Pharmacopoeia (9^{th} Edition, 2018, 9.4). Ubidecarenone is also listed in the Japanese Pharmacopoeia (16^{th} Edition).

Conclusions: Based on internet searches and the published literature, CoQ_{10} has been used in pharmacy compounding for at least 19 years and is/has been compounded as an injection, topical cream, various oral formulations, and as a sublingual suspension. It appears that it is used in compounded products for the treatment of heart disease, Raynaud's disease, chronic fatigue syndrome, and for mitochondrial disease. Ubidecarenone is listed in the British, European, and Japanese Pharmacopeia.

III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate CoQ_{10} for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs in favor of*** ubiquinone for oral administration being placed on that list for oral use based on the following:

1. CoQ_{10} is a well characterized substance that is likely to be stable under ordinary storage conditions for oral dosage forms. Due to solubility concerns, it is not appropriate for compounding for IV administration.

2. Available safety data for CoQ_{10} suggest that the substance is primarily associated with non-serious gastrointestinal adverse events; however, there is a minimal amount of information to assess the safety profile of CoQ_{10} in patients with mitochondrial disorders.

3. There are no compelling data establishing the effectiveness of CoQ_{10} for the treatment of mitochondrial diseases. Mitochondrial diseases encompass a wide variety of conditions related to genetic mutations in nDNA and mtDNA, with different phenotypic presentations. Based on a small amount of clinical data, clinical guidelines that recommend the use of ubiquinone in the treatment of primary CoQ_{10} deficiency and, in the absence of FDA approved therapies, therapeutic experts recommend CoQ_{10} for the treatment of other mitochondrial disorders. The results of CoQ_{10} therapy have been described in numerous publications, but do not appear to definitively support effectiveness for particular uses other than primary CoQ_{10} deficiency or in particular doses.

4. CoQ_{10} has been compounded in oral and other dosage forms, including for injection, for the treatment of various disorders, including mitochondrial disease since at least 1999. It is also found in the British and European Pharmacopoeia.

Based on this information the Agency has considered, a balancing of the four evaluation criteria ***weighs in favor of*** ubiquinone for oral administration being added to the 503A Bulks List.

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APPENDIX 1: ILLUSTRATIVE MITOCHONDRIAL DISORDERS

Mitochondrial Diseases Due to mtDNA Point Mutations and Large-Scale Rearrangements

Disease	Phenotype	Most Frequent mtDNA Mutations	Homoplasmic (usually)	Maternal
NARP, Leigh disease	Loss of central vision leading to blindness in young adult life	m.1778G>A, m.14484T>C, m.3460G>A	Heteroplasmic	Maternal
MELAS	*M*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes; may manifest only as diabetes mellitus	Point mutation in $tRNA^{leu}$	Heteroplasmic	Maternal
MERRF	*M*yoclonic *e*pilepsy, *r*agged *r*ed *f*ibers in muscle, ataxia, increased CSF protein, sensorineural deafness, dementia	Point mutation in $tRNA^{lys}$	Heteroplasmic	Maternal
Deafness	Progressive sensorineural deafness, often induced by aminoglycoside antibiotics	m.1555A>G mutation in 12S rRNA	Homoplasmic	Maternal
	Nonsyndromic sensorineural deafness	m.7445A>G mutation in 12S rRNA	Homoplasmic	Maternal
Chronic progressive external ophthalmoplegia (PEO)	Late-onset bilateral ptosis and ophthalmoplegia, proximal muscle weakness, and exercise intolerance	Single deletions or -duplications	Heteroplasmic	Mostly sporadic, somatic mutations
Pearson syndrome	Pancreatic insufficiency, pancytopenia, lactic acidosis	Large deletion	Heteroplasmic	Sporadic, somatic mutations
Kearns-Sayre syndrome (KSS)	External ophthalmoplegia, heart block, retinal pigmentation, ataxia	The 5-kb "common deletion"	Heteroplasmic	Sporadic, somatic mutations

Abbreviations: CSF, cerebrospinal fluid; NARP, neuropathy, ataxia, and retinitis pigmentosa.

APPENDIX 2: SUMMARY OF SAFETY INFORMATION FROM SMALLER MITOCHONDRIAL DISORDER STUDIES

Authors	Patients treated with CoQ10	CoQ10 dose & duration	Safety Information
Bresolin et al. 1990	N = 59, open label phase N = 8, double blind phase	2 mg/kg daily x 6 months 2 mg/kg daily x 3 months	15 of 59 patients dropped out of the initial phase of the trial "not due to side effects of the drug." "No side effects of the drug were observed."
Suzuki et al. 1998	N = 50; Having mutation associated with MIDD	150 mg daily x 3 years	"There were no side effects during therapy."
Chen et al. 1997	N = 8; MELAS, CPEO or MERRF	160 mg daily x 3 months	"There were no side effects during therapy." One MERRF patient did not complete the trial due to a fatal intracerebral hemorrhage but the report did not provide information about whether the patient was receiving CoQ10 treatment at the time of the event.
Angeli et al. 2005	N = 2; Mitochondrial DNA mutation 7445 A>G, SNHL	75 mg twice daily X 1 year	"There were no side effects related to treatment with CoQ10."
Papadimitriou et al. 1996	N = 2 Kearns-Sayre	100 mg daily x 2 months	No safety information was reported.
Abe et al. 1999	N = 2; MELAS	200 mg daily x 2 weeks	No safety information was reported.
Bendahan et al. 1992	N = 2 Partial defects in Complex I and IV of the electron transport chain	150 mg daily x 10 months	"There was no adverse reaction to drug therapy."
Abe et al. 1991	N = 1 MELAS	Increasing doses of 120 – 300 mg daily X 3 months	No safety information was reported.
Nishikawa et al. 1989	N = 1 Kearns-Sayre	150 mg daily x 2 years	"We found no adverse drug reactions."
Ogasahara et al. 1986	N = 5; Kearns-Sayre	60 mg for 1 month followed by 120 – 150 mg daily for a year or longer	CoQ10 "did not cause any detectable side effects."

Tab 3

Creatine Monohydrate

Tab 3a

Creatine Monohydrate Nominations

September 20, 2017

Julie Dohm, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

[Docket No. FDA-2015-N-3534]

RE: Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A

Dear Dr. Dohm:

I am writing on behalf of PCCA to formally submit two new nominations to the open docket (ID: FDA-2015-N-3534-0001) for consideration of melatonin and creatine monohydrate to the 503A Bulks List. The patients who rely on these materials to be compounded are primarily those with autism spectrum disorders and mitochondrial disorders affecting muscle, heart and brain function. Please note that the nomination includes safety studies in the bibliography, and while those may be designed for clinical outcomes other than the nominated uses, we included them to assist FDA in your thorough evaluation of the substance. We respectfully ask that this nomination be considered for placement in Category 1 of the 503A Bulks List with urgency. There are no suitable alternative manufactured products for many patients with these serious conditions, and we wish to avoid disruptions in care.

Both melatonin and creatine monohydrate are currently on the 503A Category 3 list. Per FDA's Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act, section 3B, "FDA generally expects to categorize bulk drug substances nominated to the October docket and to publish updated categories on its website on the first business day of each month." We understand FDA likely has a detailed internal review process for these types of nominations, and we hope the urgency of the patient need prioritizes this request. We look forward to hearing from you soon.

Sincerely,

Jim Smith
PCCA President

PCCA USA: 9901 S. Wilcrest Drive Houston, Texas 77099 | 800.331.2498 (f) 800.874.5760 | www.pccarx.com
PCCA Canada: 744 Third Street London, ON Canada N5V 5J2 | 800.668.9453 (f) 800.799.4537 | www.pccarx.ca
PCCA Australia: Unit 1, 73 Beauchamp Road Matraville NSW 2036 Australia | 02.9316.1500 (f) 02.9316.7422 | www.pccarx.com.au

Ingredient Name	Creatine Monohydrate
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	N-(Aminoiminomethyl)-N-methylglycine
Common Name(s)	Creatine; Creatine Monohydrate
UNII Code	9603LN7R2Q
Chemical Grade	NA
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of PCCA Certificate of Analysis for this chemical is attached.
How supplied	Powder
Recognition in foreign pharmcopeias or registered in other countries	NA
Submitted to USP for monograph consideration	No
Compounded Dosage Forms	Oral formulations as requested by prescribers
Compounded Strengths	Up to 20gm daily in divided doses in oral formulations
Anticipated Routes of Administration	Oral
Saftey & Efficacy Data	1. Klopstock T, Querner V, Schmidt F, et al. A placebo-controlled crossover trial of creatine in mitochondrial diseases. Neurology. 2000;55(11):1748-51.

2. Komura K, Hobbiebrunken E, Wilichowski EK, et al. Effectiveness of creatine monohydrate in mitochondrial encephalomyopathies. Pediatr Neurol. 2003;28(1):53-8.

3. Pfeffer G, Majamaa K, Turnbull DM, et al. Treatment for mitochondrial disorders. Cochrane Database Syst Rev. 2012;(4):CD004426. doi: 10.1002/14651858.CD004426.pub3.

4. Tarnopolsky MA, Roy BD, MacDonald JR. A randomized, controlled tiral of creatine monohydrate in patients with mitochondrial cytopathies. Muscle Nerve. 1997; 20(12):1502-9.

5. Kornblum C1, Schröder R, Müller K, et al. Creatine has no beneficial effect on skeletal muscle energy metabolism in patients with single mitochondrial DNA deletions: a placebo-controlled, double-blind 31P-MRS crossover study. Eur J Neurol. 2005;12(4):300-9.

6. Rodriguez MC, MacDonald JR, Mahoney DJ, et al. Beneficial effects of creatine, CoQ10, and lipoic acid in mitochondrial disorders. Muscle Nerve. 2007;35(2):235-42.

Used Previously to compound drug products	Yes
Proposed use	Treatment of Mitochondrial Disorders
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	

Tab 3b

Creatine Monohydrate Nomination Clarification

May 11, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

Thank you for contacting PCCA as the nominator of creatine monohydrate (creatine) for inclusion on the 503A Bulk Drug Substances list. Below is our response to FDA's question #1.

1. PCCA does want to pursue review by the FDA and consideration by the PCAC of creatine for inclusion on the 503A Bulks list.

   The nominated use of compounded creatine is adjunctive therapy in the management of mitochondrial disorders. Creatine is found to be beneficial in several subtypes of mitochondrial disorders where patients' bodies need alternative energy sources and to assist with maintaining or improving muscle strength. Due to varied dosing needs over time for individual patients, and combination therapies for mitochondrial diseases, patient-specific compounding of creatine formulations is often necessary. We request creatine monohydrate be placed on the 503A Bulks list and that a USP monograph be developed.

   Dosing is up to 20 grams daily in divided doses, most commonly as oral liquid.

   a. National Institutes of Health Office of Dietary Supplements. Dietary Supplements for Primary Mitochondrial Disorders – Fact Sheet for Health Professionals. Updated April 24, 2018. https://ods.od.nih.gov/factsheets/PrimaryMitochondrialDisorders-HealthProfessional/ Accessed May 10, 2018.

   b. Klopstock T, Querner V, Schmidt F, et al. A placebo-controlled crossover trial of creatine in mitochondrial diseases. *Neurology*. 2000;55(11):1748-51.

   c. Komura K, Hobbiebrunken E, Wilichowski EK, et al. Effectiveness of creatine monohydrate in mitochondrial encephalomyopathies. *Pediatr Neurol.* 2003;28(1):53-8.

d. Pfeffer G, Majamaa K, Turnbull DM, et al. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev.* 2012;(4):CD004426. doi: 10.1002/14651858.CD004426.pub3.

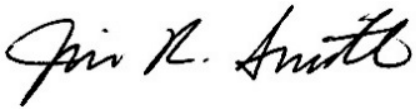
e. Tarnopolsky MA, Roy BD, MacDonald JR. A randomized, controlled trial of creatine monohydrate in patients with mitochondrial cytopathies. *Muscle Nerve.* 1997; 20(12):1502-9.

f. Rodriguez MC, MacDonald JR, Mahoney DJ, et al. Beneficial effects of creatine, CoQ10, and lipoic acid in mitochondrial disorders. *Muscle Nerve.* 2007;35(2):235-42.

g. Parikh S, Saneto R, Falk MJ, et al. A Modern Approach to the Treatment of Mitochondrial Disease. *Curr Treat Options Neurol.* 2009 Nov;11(6):414-30.

We look forward to providing you further information as requested in the coming weeks.

Sincerely,



Jim Smith
PCCA President

May 25, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

LT Hallman:

Thank you for contacting PCCA as the nominator of creatine for inclusion on the 503A Bulk Drug Substances list. The information provided here is not to be considered all-inclusive. Some clinicians may have further information that we were not able to collect by the due date requested.
The number of patients affected by mitochondrial disorders is relatively small, and only a subset of those patients require creatine supplementation. For some patients, commercially available creatine products are suitable. For others, the excipients and concentrations of the manufactured creatine products are not appropriate, which necessitates compounding of their dosages.

Below are our responses to FDA's questions #2 and #3:

2. To the best of our abilities, approximately 2,000 prescriptions of compounded creatine per year are estimated to be dispensed as adjunctive therapy in the management of mitochondrial disorders. The patients receiving creatine often require frequent dose adjustments due to changes in muscle and organ function, which are closely monitored.

3. The scientific literature provided in PCCA's response to FDA's Request for Clarification Question #1, dated May 11, 2018, includes analyses from leading researchers in the field, as well as practicing clinicians and the 2018 NIH Fact Sheet on Dietary Supplements for Primary Mitochondrial Disorders.

There are no FDA-approved products which address the conditions for which creatine is nominated.

We hope this information aids the Agency in your review of compounded creatine. If you require further information, please contact us at your convenience.

Sincerely,

Jim Smith
PCCA President

Tab 3c

FDA Review of
Creatine Monohydrate

DATE: August 9, 2018

FROM: Ben Zhang, Ph.D.
Staff Fellow, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)

Yen-Ming Chan, Ph.D.
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SUBJECT: Review of Creatine Monohydrate for Inclusion on the 503A Bulk Drug Substances List

I. INTRODUCTION

Creatine monohydrate has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). It has been proposed for use in treatment of mitochondrial disorders. The proposed route of administration is oral. In addition to the use of creatine monohydrate for mitochondrial disorders, this review considers the oral use of creatine monohydrate for treatment of creatine deficiency syndromes.[1]

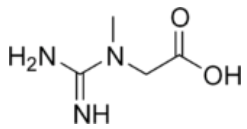
We have reviewed publicly available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh in favor of*** placing creatine monohydrate solid oral dosage forms 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 (503A Bulks List).[2]

[1] Consistent with its practice as stated in the Notice of Proposed Rulemaking entitled *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*, published in the Federal Register of December 16, 2016 (81 FR 91071, 91075), FDA in its discretion opted to review the unnominated use of creatine deficiency syndromes. Creatine deficiency syndrome is considered a serious condition.

[2] Inclusion 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 should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using a substance included on the list has been proven to be safe and effective under the standards required receiving Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears 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 is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act (21 U.S.C. 352(a), (bb)).

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?[3]



Creatine (N-(aminoiminomethyl)-N-methyl glycine) monohydrate is a nonprotein amino acid. Creatine monohydrate is nominated for use in oral formulations (in divided doses up to 20 g/day), and the nominator has identified that compounders most often create oral liquid formulations. This substance is currently marketed in oral formulations as a dietary supplement. As a dietary supplement, creatine monohydrate is available in powdered, tablet, and liquid forms.

Creatine monohydrate is one of the crystal forms of creatine and is considered the same active pharmaceutical ingredient as creatine. For the purposes of this review, we will consider data for both creatine and creatine monohydrate, which will be referred to as creatine except when providing the doses of substances.

Databases searched for information presented in Section II.A. of this review included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia, and USP/NF.

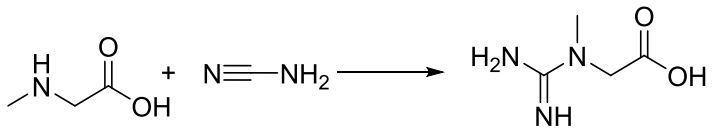
1. Stability of the API and likely dosage forms

Creatine is likely to be stable at room temperature in its solid form. However, it is known that this substance is unstable in aqueous solutions. Intramolecular cyclization of creatine will occur to give inactive creatinine as the product. This reaction is accelerated under acidic conditions (pH < 4) (Edgar and Shiver 1925; Cannan and Shore 1928). One study on the aqueous formulations of creatine reported that, at room temperature, 5 – 20% of creatine degraded after 4 days and 15 – 55% degradation was observed after one week. The pH value also increased from 3.6 to 4.5 (Ganguly et al. 2003). Therefore, creatine is unlikely to be stable when compounded as aqueous formulations, including those intended for oral administration.

2. Probable routes of API synthesis

[3] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

Currently, creatine is mainly obtained from chemical synthesis, which involves the reaction between cyanamide with N-methylglycine (sarcosine) (An et al. 2001; Kessel et al. 2004). The synthetic scheme is shown below:

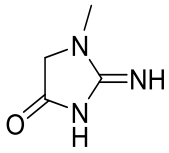


The reaction can be carried out either in acidic or basic conditions in aqueous solutions. Thus, different reagents can be used (i.e., HCL, H_3PO_4 for acidic conditions, and NH_4OH for basic conditions) depending on different reaction conditions chosen by the manufacturers.

3. Likely impurities[4]

Likely impurities may include:

- Residual starting materials and reaction intermediates, including cyanamide and N-methylglycine, dicyanamide, dihydro-1,3,5-triazine and arsenic (Persky and Brazeau 2001; European Food Safety Authority 2004).
- The cyclization byproduct, creatinine. The structure of creatinine is shown below:



4. Toxicity of those likely impurities

Levels of impurities such as cyanimide, dicyanamide, and dihydro-1,3,5-triazine, need to be carefully controlled. Other impurities are unlikely to be significantly toxic.

5. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

Creatine is a white crystalline solid, which is slightly soluble in water. No further information on the influence of particle size and polymorphism on bioavailability were found in the literature.

6. Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize

[4] This review contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing.

Creatine is easily characterized with proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, UV-Vis spectroscopy, Fourier transform infrared spectroscopy (FT-IR), and mass spectrometry (MS).

Conclusions: Creatine monohydrate is physically and chemically well characterized. Creatine is a small organic molecule. Under ordinary storage conditions, when kept away from moisture, solid oral formulations of creatine are likely to be stable; however, aqueous formulations, including aqueous oral formulations, are unlikely to be stable. The nominated substance is easily characterized with various analytical techniques and the preparation of this substance has been well developed.

B. Are there concerns about the safety of the substance for use in compounding?

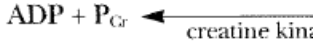
1. Nonclinical assessment

The following databases were consulted in the preparation of Section II.B. of this review: PubMed, National Toxicology Program website, Embase, ToxNet, NIH dietary supplement label database, Google, GRAS notice inventory, US Pharmacopeia, and Drugs@FDA.

a. General pharmacology of the drug substance

Creatine is an endogenous substance which is found in many human organs, with the highest concentrations found in the skeletal muscle (approximately 95% of the body's total creatine pool) and in the cardiac muscle (Snow and Murphy 2003). The remaining 5% is found in brain, liver, kidney, and testis (Nasrallah et al. 2010). It is also found in foods such as meat, fish, and other animal products.

Creatine functions in the human body to help supply energy to exercising muscle (Culpepper 1998). Under conditions of submaximal exercise, adenosine triphosphate (ATP) is generated from adenosine diphosphatase (ADP) through aerobic glycolysis. However, during intense exercise, when demand for ATP increases beyond the rate of generation via aerobic metabolism, anaerobic glycogenolysis employs the transfer of high energy phosphate bonds from intracellular phosphocreatine (creatine phosphate, PCr) to ADP to form ATP. When in a resting state, the high-energy bond of ATP is transferred at the mitochondrial membrane to creatine to produce a PCr store. The creatine phosphate shuttle is diagrammed below:



Creatine can be endogenously synthesized using the basic amino acids glycine, arginine, and methionine at the rate of 1-2 g/day (Persky and Brazeau 2001; European Food Safety Authority 2004) (see Figure 1 below). In the kidney and pancreas, L-arginine:glycine amidinotransferase catalyzes the transamidation of a guanidine group from arginine to glycine, yielding guanidinoacetic acid and ornithine. Guanidinoacetic acid enters the circulation to reach the liver where it is methylated by N-guanidinoacetate methyltransferase to yield creatine. Creatine is then transported out of the liver into the blood circulation where it is distributed into different

creatine-requiring target tissues (e.g., muscle, brain, heart, etc.) through an active Na^+/Cl^- dependent creatine transporter system. Creatine is transformed in target tissues to PCr. Any creatine that exceeds the amount needed for storage in muscle is converted to creatinine, which is excreted in the urine. Urinary creatinine level is a commonly used marker of kidney function.

Figure 1. Creatine synthesis and metabolism (Persky and Brazeau 2001)

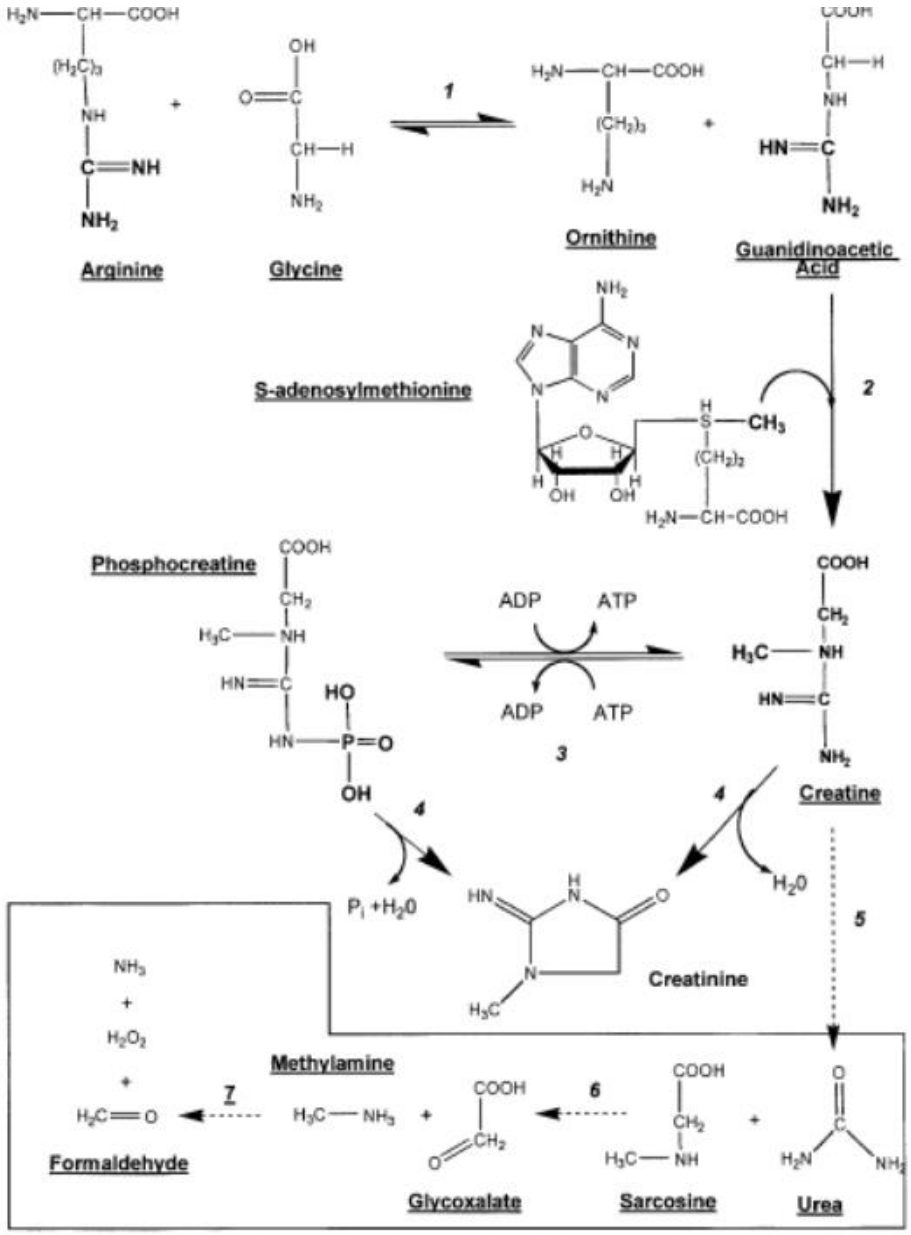


FIG. 1. Pathway of creatine metabolism. Catalyzed by AGAT (*1*), catalyzed by GAMT (*2*), catalyzed by creatine kinase (CK) (*3*), spontaneous (*4*), catalyzed by creatine amidohydrolase (*5*), catalyzed by glycine oxidase (*6*), and catalyzed by semicarbazide-sensitive amine oxidase (SSAO) (*7*). Dotted pathway indicates recently hypothesized toxic formation of formaldehyde by Yu and Deng (2000).

Creatine supplementation has been associated with increased muscle strength and performance in healthy people (Culpepper 1998). Quantitative evaluations of phosphate-containing metabolites (e.g., ATP and phosphocreatine) using ^{31}P nuclear magnetic resonance have been conducted to assess biomarkers of mitochondrial diseases that are associated with muscle fatigue and weakness due to impaired oxidative phosphorylation (Radda et al. 1995). Such studies have suggested that patients experience a shift in their bioenergetic processes toward increased reliance on compensatory anaerobic glycogenolytic ATP synthesis and conversion of phosphocreatine to ATP. It is hypothesized that creatine supplementation can support these compensatory processes and improve the ability of patients' skeletal muscles to perform during exercise and recover from exercise.

The addition of creatine has been shown to augment the anticancer effect of methylglyoxal plus ascorbic acid in in vitro models. These studies have shown that sarcoma tissue has low levels of creatine and creatine kinase while levels were significantly elevated in association with tumor regression (Patra et al. 2012).

b. Pharmacokinetics/Toxicokinetics

Absorption: Creatine is rapidly absorbed from the gastrointestinal tract (T_{max} < 2hrs) where it has been tracked in the ileum and jejunum of rodents (McCall and Persky 2007). Rats dosed orally with low (10 mg/kg) or high dose (70 mg/kg) ^{13}C-labeled creatine monohydrate showed a higher absolute oral bioavailability in the low dose group (53%) compared to the high dose (16%) treated rats (Alraddadi et al. 2018); this observation was explained by the potential saturation binding sites of creatine. In the same study, using a physiologically based pharmacokinetic (PBPK) model for creatine monohydrate, a dose of 70 mg/kg creatine hydrochloride (CHCL) had an improved aqueous solubility compared to creatine monohydrate where CHCL had an estimated C_{max} of approximately 35 µg/mL compared to 14 µg/mL for creatine monohydrate. The predicted oral bioavailability for CHCL was 66% compared to 17% with creatine monohydrate (Alraddadi et al. 2018). Endogenous creatine levels have been detected in blood samples of various species where the highest levels of detection are seen in dogs, followed by the rat, mouse, and rabbits; with the rabbit creatine levels being the closest to those in humans (Persky and Brazeau 2001) (see Table 1 below).

TABLE 1
Values for blood levels of creatine and creatine transporter K_M across species

Species	Blood Cr	K_m
	μM	μM
Bovine		187[a] (Dodd et al., 1999)
Dog	30,000 (Lowe et al., 1998), 50–100 (Harris and Lowe, 1995)	
Human	50–100 (Harris et al., 1992; Marescau et al., 1986)	15,[a] 20,[f] 30[c] (Ku and Passow, 1980; Loike et al., 1986; Sora et al., 1994)
Mouse	200 (Marescau et al., 1986)	45,[d] 110[e] (Moller and Hamprecht, 1989; Odoom et al., 1996)
Rabbit	150 (Marescau et al., 1986)	35[a] (Guimbal and Kilimann, 1993)
Rat	500–600 (Horn et al., 1998; Marescau et al., 1986) 140 (Fitch and Shields, 1966)	22,[a] 46,[a] 73,[b] 160,[b] 500,[b] 40–60,[c] 45 (Fitch and Shields, 1966; Fitch et al., 1968; Moller and Hamprecht, 1989; Schloss et al., 1994; Willott et al., 1999)

[a] Cloned transporter.
[b] Intact muscle.
[c] White blood cell.
[d] Astroglia.
[e] Cell culture (L6 or G8).
[f] Red blood cell.

Distribution: Creatine is distributed throughout the body with the highest distribution in skeletal muscle cells where it seems to be concentrated due to the nature of the restrictive transport process in muscle cells. Creatine has a high volume of distribution due to its low binding activity to plasma proteins (<10% is bound). Because creatine is a potential treatment for various neurological disorders, the ability of creatine to cross the blood–brain barrier has been studied (Perasso et al. 2003). After a single intraperitoneal injection of 160 mg/kg creatine, radioactively labelled creatine (C-creatine) entered the rat brain to a limited extent, it reached its maximum concentration within 30 min of injection (~1 mM), followed by a decrease where it reached half of the peak concentration ~60 min after the initial injection. Creatine does not seem to accumulate in the brain after repeated exposure (see Table 2).

Table 2. Brain concentrations of creatine and phosphocreatine after single or repeated intraperitoneal injections of exogenous creatine (160 mg/ kg rat weight) and controls

Treatment	*N*	Creatine (mM)	Phosphocreatine (mM)	Total creatine pool (creatine] phosphocreatine, mM)	Phosphocreatine (% of total creatine pool)
Control (saline)	11	5.7561.17	1.6660.56	7.4161.70	21.9062.90
Creatine, single injection	9	6.5161.27	2.0060.61	8.5161.84	23.0063.00
Creatine, six repeated injections	7	5.6360.72	1.3960.31	7.0160.90	20.0063.00

A comparison of the pharmacokinetic parameters (theoretical/simulated and observed) of a single dose ^{13}C creatine monohydrate (intravenous injection or oral suspension) was conducted in the rat (Alraddadi et al. 2018). The data show that its oral bioavailability is limited and that it is distributed and eliminated slowly under the conditions of the study.

Table 3 Comparison between predicted CM pharmacokinetic parameters and observed values following iv and oral dose of CM.

Parameter	IV Injection of CM (10 mg/kg)		Oral Suspension of CM (70 mg/kg)	
	Simulated	Observed	Simulated	Observed
C_{max} (μg/mL)	122	76.18 ± 15.23	14.07	13.72 ± 3.57
T_{max} (min)	3	3	87	60
V_d (L/kg)	0.208	0.304 ± 0.087	-	-
$T_{1/2}$ (min)	64.08	69.3 ± 3.7	-	-
CL (L/hr)	0.039	0.051 ± 0.01	-	-
$AUC_{0-\infty}$ (μg·h/mL)	2279.36	2450.01 ± 110	2286.1	2501.33 ± 378
F (%)	-	-	16.8	15.69 ± 4.3
R^2 value (model vs. observed)	0.99	-	0.84	-

CM = creatine monohydrate

Conclusion: Pharmacokinetic/toxicokinetic studies of creatine in animals show that it is quickly absorbed from the gastrointestinal tract and reaches its maximum concentrations within 2 hrs. Upon oral ingestion, creatine has low bioavailability and slow distribution throughout the body with the highest concentrations found in skeletal muscle cells and excretion in the urine and feces. Creatine is metabolized to creatinine in various organ systems where the highest concentrations found in the skeletal muscle cells.

c. Acute toxicity[5]

Acute toxicity studies of creatine monohydrate in the rat show an LD_{50} between 1,535 mg/kg to >2 g/kg. Adverse effects following exposure to high doses of creatine monohydrate include musculoskeletal effects (Sigma-Aldrich).

d. Repeat dose toxicity[6]

Toxicology studies conducted in several animal models (mice, rats, guinea pigs, dogs) in which animals were treated with doses of creatine ranging from 0.05 to 2 g/kg body weight (bw)/day for durations ranging between 2 and 8 weeks did not report any changes in creatine concentrations in the serum, muscle or various organs, and no adverse effects were reported (Shao and Hathcock 2006).

A 15-day toxicity study was conducted in rats and chickens in which creatine monohydrate was dosed in drinking water at 0.25 or 0.50 g/kg/day. While no change in body weight was noted among the treated rats, an increase in body weight (without a concomitant increase in food conversion rate[7]) was noted among chickens treated with 0.50 g/kg bw/day creatine. No changes in the histology assessment of the liver, kidney, or skeletal muscle were noted among either treated rats or chickens (Moghadam et al. 2008).

A 28-day toxicity study was conducted in rats where creatine monohydrate was dosed via food at doses up to 2 g/kg bw/day and did not result in any treatment-related adverse effects (European Food Safety Authority 2004).

Kidney: Because of the high content of nitrogen in creatine, the potential for renal toxicity due to excess exposure to creatine via the diet has been studied in animal models. Conflicting data have been reported in terms of the effect of creatine supplementation on rat kidneys. In one study in Sprague–Dawley rats with a pre-existing condition of cystic kidney disease by Edmunds et al. (2001) where creatine was used in a loading dose, followed by a maintenance dose (human equivalent of 20 g/day for 1 week followed by 5 g/day for 5 weeks), reduced renal function (increased kidney weight, increased serum urea level, lower creatinine clearances) was observed. These results do not corroborate with another study reported by Taes et al. (2003) where sham-operated and partially nephrectomized (mimicking renal failure) rats were either given a control diet, or creatine-enriched diet (providing 0.9 g/kg bw creatine/day; equivalent to approximately 50 g/day in a 60 kg adult human for four weeks). In the latter study, creatine supplementation

[5] *Acute toxicity* refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). Endpoints captured in acute toxicity studies usually include mortality and gross clinical observations. Acute toxicity data are usually superseded by data obtained from longer term toxicity studies.

[6] *Repeat-dose toxicity* studies consist of in vivo animal studies that seek to evaluate the toxicity of the test substance by observing the changes that emerge in clinical observations, clinical chemistry, gross pathology, and histology endpoints when the test substance is repetitively administered daily for a predetermined period of time.

[7] In animal husbandry, feed conversion rate is a rate measuring the efficiency with which the bodies of livestock convert animal feed into the desired output (e.g. milk in cows, eggs in chickens, etc.).

did not adversely affect kidney function in rats with pre-existing renal failure. Creatine exposure did not change levels of inulin and creatinine clearance rates, urinary protein excretion, and urea clearance.

Liver: Conflicting data were also seen regarding the toxicity of the liver, using the histological assessment endpoints. While inflammation was noted in two different strains of mice, rats seem to be resistant to such impact after exposure to creatine monohydrate. Clinical chemistry endpoints were assessed in a study in which adult male Wistar rats were treated with creatine for 14 days at 0, 0.5, 1 and 2 g/kg/day. An increase in liver biomarkers (ALT and AST) was seen, although the difference from controls was not statistically significant (see Table 4 below). This study was limited in its significance because it did not include a histological assessment of the liver to better interpret the clinical chemistry findings (Baracho et al. 2015). The authors concluded that exposure to creatine for 14 days under the conditions of the study did not result in hepatic or renal toxicities.

Table 4**.** Plasma levels of the parameters assessed for control group and creatine groups (Results are expressed as average and standard deviation)

		0.5 g/kg/day	1 g/kg/day	2 g/kg/day
PARAMETERS	CONTROL	CREATINE	CREATINE	CREATINE
Glucose (mg/dl)	185.3 ± 29.9	197.3 ± 33.5	190.0 ± 21.0	181.7 ± 26.7
Creatinine (mg/dl)	0.3 ± 0.1	0.2 ± 0.2	0.3 ± 0.1	0.3 ± 0.1
Total Cholesterol (mg/dl)	59.5 ± 18.0	53.3 ± 8.4	54.2 ± 15.8	40.2 ± 6.4
Triglycerides (mg/dl)	43.2 ± 13.3	41.5 ± 11.0	39.0 ± 15.8	35.0 ± 7.0
HDL-C (mg/dl)	13.8 ± 7.7	10.8 ± 4.1	12.0 ± 5.2	8.3 ± 4.3
LDL-C (mg/dl)	37.0 ± 12.2	34.2 ± 11.0	34.3 ± 11.8	24.8 ± 9.2
VLDL-C (mg/dl)	8.6 ± 2.7	8.3 ± 2.2	7.8 ± 3.2	7.0 ± 1.4
AST (U/L)	111.2 ± 31.8	153.5 ± 84.2	144.0 ± 96.0	177.3 ± 91.3
ALT (U/L)	13.2 ± 4.3	19.2 ± 6.9	25.8 ± 32.0	22.2 ± 11.6
Alkaline Phosphatase (U/L)	155.8 ± 71.4	219.3 ± 68.0	185.5 ± 66.1	165.5 ± 32.5
Total Protein (g/dl)	6.0 ± 0.7	6.8 ± 0.5	6.4 ± 0.5	6.6 ± 0.4
Albumin (g/dl)	3.6 ± 0.2	3.8 ± 0.2	3.8 ± 0.3	3.8 ± 0.3
Urea (mg/dl)	8.6 ± 4.2	7.1 ± 4.9	8.0 ± 3.5	9.5 ± 3.1
Creatinine Clearance	0.4±0.4	0.6±0.8	0.5 ± 0.5	0.2 ± 0.1

In a separate study, histological assessment (18–20 organs/tissues) was performed on transgenic mice (G93A[8]) after 159 days, and in Sprague-Dawley (SD) rats after 365 days of creatine monohydrate supplementation (2% wt/wt) compared with control feed (Tarnopolsky et al. 2003). No inflammatory lesions were observed among the panel of observed tissues except for presence of hepatitis in the transgenic mice. No inflammation was noted among the treated rats.

[8] The SOD1 G93A transgenic mouse has a mutation in the Cu/Zn-superoxide dismutase gene that results in an increase in oxidative stress. This mouse model is a good animal model to evaluate the potential for creatine monohydrate tissue toxicity under conditions of increased oxidative stress.

In the same paper, the authors reported on a second study of the effect of creatine monohydrate exposure on the histopathology of the liver. Liver histology was evaluated in CD-1 mice after exposure to low doses of creatine monohydrate supplementation (0.025 and 0.05 g/kg/day) for 56 or 300 days and in SD rats supplemented for 52 days with creatine monohydrate (2% wt/wt) with and without prednisolone (Tarnopolsky et al. 2003). Similar to the G93A group described above, significant hepatic inflammation marked by the appearance of a diffuse inflammatory infiltration of the liver was noted in the CD-1 mouse group when compared to the placebo control. No difference was noted among SD rats treated with creatine when compared to a creatine-supplemented diet. No other organ lesions were noticed in the kidneys, heart or skeletal muscles where creatine is highly expressed, and no neoplasia was seen in any tissue or organ, under the conditions of this study (Tarnopolsky et al. 2003).

The Tarnopolsky studies seem to suggest a species-specific effect and that mice are more susceptible than rats to liver inflammation after exposure to creatine monohydrate. Rats seem to be resistant to such adverse effects under the conditions of this study.

e. Genotoxicity[9]

Creatine monohydrate was tested in the Ames assay and was found to be negative for mutagenic potential (European Food Safety Authority 2004).

In recent years, creatine, along with other amino acids that are found in meats, were identified as precursors to mutagenic compounds when meats (red meat, fish) are cooked at high temperatures. The positive mutagenicity signal seen in the Ames assay seems to be associated with the formation of heterocyclic amino-imidazo compounds during heating. Creatine is naturally present in meats at about 0.5% of the total weight. When added during the cooking process at 10 times the naturally available level, creatine increased the mutagenic activity between 2- and 17-fold (Marsh et al. 1990; Knize et al. 1991). However, given the temperature at which creatine is proposed to be prepared and administered in compounding, and the route of administration, it is unlikely that mutagenic concerns are pertinent to drug compounding for clinical use.

f. Developmental and reproductive toxicity[10]

No developmental or reproductive toxicity data were found for creatine.

[9] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems.

[10] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects in humans of both sexes and include females from various age groups that will be exposed to the proposed substance. *Developmental toxicity* or *teratogenicity* refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth.

g. Carcinogenicity[11]

No animal carcinogenicity data were found for creatine. Several public health organizations (IARC, ACGIH, NTP, and OSHA) have concluded that at levels less than or equal to 0.1%, creatine is not associated with a potential for human carcinogenicity.

Conclusions: Exposure to high doses of creatine (at doses up to 2 g/kg body weight) for up to 8 weeks of duration was associated with adverse effects in the liver and the kidney. In terms of the kidney findings, reduced renal function (increased kidney weight, increased serum urea level, lower creatinine clearances) was reported in a rat disease model with a pre-existing condition of cystic kidney disease. However, in another disease model, where partially nephrectomized rats were studied, exposure to creatine did not adversely affect kidney function in rats. A species-specific effect on the liver was seen after exposure to creatine monohydrate, where mice were more susceptible to liver inflammation than rats under the conditions of the studies conducted. Creatine was negative in a bacterial mutation study, the Ames test; this was the only genotoxic assay which was conducted with creatine. No data were found for the reproductive and developmental effects of creatine or for its its potential to be carcinogenic when taken chronically or for lifetime exposure.

2. Human safety

The following databases were consulted in the preparation of this section: PubMed, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov.

Creatine was proposed for use in the treatment of mitochondrial disorders. A brief background regarding mitochondrial disorders is provided here to assist in the interpretation of safety and effectiveness information associated with creatine treatment. Normal mitochondrial biogenesis, function, and inheritance requires the integrated activity of an estimated 3000 genes and 1500 gene products. While energy production is an important component of mitochondrial function, over 95% of these 3000 genes are related to the specific functions of differentiated cells. Most genes affecting mitochondrial function are encoded in the cell nucleus (nDNA), but mitochondria contain their own small genome (mtDNA) consisting of 37 genes. Proper mitochondrial functioning is dependent on the integration proteins from nuclear DNA and from mtDNA. Primary mitochondrial diseases have been linked so far to mutations in more than 200 nDNA genes and 37 mtDNA genes (Rahman 2015).

Mitochondrial disorders can originate from inherited or spontaneous mutation of either nDNA or mtDNA. The myriad of mitochondrial functions forms the basis for the complex physiologic abnormalities associated with nDNA or mtDNA aberrations. The term 'mitochondrial disease' currently includes several hundred different diseases (Rahman 2015). Among these disease, patients with the same genotype may not present clinically similar symptoms. And the same

[11] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to result in tumors when used by humans on a chronic basis. Carcinogenicity studies are conduct if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life.

genetic mutation or deletion can produce varied phenotypes (Davison and Rahman 2017). Diagnosis of mitochondrial disease in adults is further complicated because mtDNA changes occur as part of normal aging, presenting a wider array of possible age-associated mitochondrial function abnormalities. Clusters of symptoms and features are recognized as phenotypic mitochondrial syndromes; a listing of the most common syndromes and their most frequently associated mtDNA mutations appears in Appendix 1 (Skorecki and Behar 2015).[12] Many mitochondrial disorders are named with an acronym representing the primary symptoms (e.g., the disorder MELAS is mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes.)

One example of genetic diversity in the presence of phenotypic similarity occurs in Leigh syndrome. Leigh syndrome is characterized by bilaterally symmetrical MRI abnormalities in the brain stem, cerebellum, and basal ganglia, and is often accompanied by elevated lactic acid levels in the blood or cerebrospinal fluid. However, this syndrome has now been shown to stem from pathogenic mutations in more than 75 nDNA or mtDNA genes. Not all children with these mutations go on to develop the disease (Lake et al. 2016). The field of mitochondrial disease research is exponentially expanding, with nearly 30 of the Leigh syndrome genes characterized in the approximately five years prior to 2015. While the Leigh syndrome population is considered clinically heterogeneous, onset is generally prior to 2 years of age following a period of normal development, with symptoms appearing during infection or illness, and results in death by 3 years of age. Adult onset is infrequent. Genotype-phenotype correlations are being investigated, helping to provide insight into links among biochemical defects, characteristic disease features, and affected ethnicities (e.g., the population of the Saguenay-Lac-Saint-Jean region of Quebec, Canada).

Schaefer et al. (2008) estimated that in 2001, the minimum point prevalence of mitochondrial diseases (mtDNA only) in the North East of England was 9.2 in 100,000 people between the ages of 16 years and 60 years (for females) or 65 years (for males). It was also estimated that an additional 16.5 in 100,000 children and adults younger than 60 (or 65) were at risk for the development of mtDNA disease. Studies of the frequency of specific phenotypes, or population based reports of disease, have been conducted in northern Finland, Japan, Switzerland, and Australia (Chinnery and Turnbull 2001). The estimates of prevalence are highly varied based on geographic locale and the disease or mutation of interest.

Although creatine was not proposed by the nominator for use in the treatment of creatine deficiency syndromes, FDA is aware of this clinical use and has therefore included it in this review. Creatine deficiency syndromes include three autosomal recessive inborn errors of creatine synthesis (Nasrallah et al. 2010). Two of these disorders are related to creatine synthesis, L-arginine-glycine amidinotransferase (AGAT) deficiency and guanidinoacetate methyl-transferase (GAMT) deficiency (see Figure 1). One creatine deficiency syndrome is related to transport of creatine across cell membranes (discussed in Section II.B.1.a.), creatine transporter deficiency (SLC6A8 defect). These syndromes are associated with depletion of brain

[12] Mitochondrial disorders are commonly referred to by acronyms based on the numerous symptoms. See Appendix 1 for an explanation of the disorders and the associated terminology.

creatine pool. Clinical features include mental retardation, autism, movement disorders, and early-onset epilepsy, and the syndromes are sometimes misdiagnosed as mitochondrial disorders.

There are no FDA-approved drugs for the treatment of any of the mitochondrial disorders or creatine deficiency syndromes. However, there are 14 substances that have received orphan designation for mitochondrial disorders and one that has received orphan drug designation for creatine transporter deficiency.[13]

a. Reported adverse reactions (FAERS, CAERS)

FAERS

The Office of Surveillance and Epidemiology conducted a search of FDA Adverse Event Reporting System (FAERS) for reports of adverse events with the product terms "creatine" and "creatine monohydrate" through June 19, 2018. Four cases were identified, two non-serious and two serious events.

There was one death reported of a 42 year old male who visited an emergency department (ED) after having taken a loading dose of creatine followed by a 5 g per day maintenance dose for an unspecified period of time. He was diagnosed with diabetes mellitus (Type 1 or 2 was not specified) with a blood glucose of 290 mg/dL (normal < 100 - 120). He was prescribed metformin, but returned to the ED four weeks later with a blood glucose of 493 mg/dL, urea = 77 mg/dL (normal < 20), creatinine = 3.5 mg/dL (normal < approximately 1.2 and 1.4 at first ED visit), and lactate = 17.2 mmol/L (normal < 2.2). He died from cardiac arrest while on hemodialysis for acute renal failure. Although the company that reported this case concluded that creatine played a role in the development of renal failure, lactic acidosis is an adverse event known to be associated with metformin, and it is possible that diabetic nephropathy existed prior to the first ED visit.

In the second serious event case, a 38 year old male was reported to have been diagnosed with drug-induced cholestatic hepatitis after having taken methyl masterdol and methyl 1-D (no longer marketed), both reported by the manufacturer to contain anabolic "prohormones" that are converted to testosterone, intermittently for most of the 3 month period prior to the event. He had also taken a creatine-containing supplement for the past several years. Liver injury was considered attributable to the anabolic steroids.

A search of the literature identified four additional cases. One of these cases is described in Section II.B.2.b. (Barisic et al. 2002):

- A 30 year old male diagnosed with atrial fibrillation during two sequential visits to an ED while routinely taking "vitamins, amino acids and creatine" (Kammer 2005). Although there appears to be a temporal relationship between initiation of creatine supplementation

[13] https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/howtoapplyfororphanproductdesignation/ucm333718.htm; downloaded June 14, 2018.

and the cardiac events, there is insufficient information about his use of other substances to establish whether a causal relationship with creatine exists.

- A 26 year old male was treated in a military facility in Afghanistan after experiencing a thalamic hemorrhagic stroke less than 12 hours after taking a "performance enhancing" supplement and completing weight lifting training (Young et al. 2012). It is unclear if this was the first dose of the product, which contains numerous ingredients, among these caffeine and another sympathomimetic, 1,3-dimethylamylamine. As such, it is not possible to establish the role of creatine in this event.
- A 24 year old man diagnosed with acute kidney injury reported having taken 52 different dietary supplements during the prior 6 months, including 5 g of creatine three times a week (Thorsteinsdottir et al. 2006). Although the authors stated that they found creatine to be the only nephrotoxic substance among the supplements, it is not possible based on the available information to establish whether a causal link with creatine exists.

CAERS

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for adverse events associated with the terms "creatine" and "dietary supplements" on June 14, 2018. There were a total of 139 reports found, including four deaths due to pneumonia, cardiac arrest (n=2) and a traffic accident, respectively. These cases were reported in association with consumers who used creatine supplementation products marketed for improvement of athletic performance. There were 52 hospitalizations reported, four included life threatening events. Frequently reported adverse events included seizures, renal disorders, dyspnea, and rash. There were eight reports in which creatine was reported as the only supplement or medication taken. These cases did not include reports of renal toxicity and do not appear to have any clinical commonalities. No cases reported use in patients with mitochondrial disorders or creatine deficiency syndromes. We could not assess whether a causal connection exists between the adverse events and creatine in any of the CAERS reports because of the concurrent use of multiple dietary supplements or drugs, or incomplete information.

b. Clinical trials assessing safety

No studies were found specifically designed to assess the safety of creatine in patients with mitochondrial disorders or creatine deficiency syndromes. Studies of the effectiveness of creatine in treating mitochondrial disorders are discussed in more detail in Section II.C. Safety findings from these studies include:

- Tarnopolsky et al. (1997) stated that the study had "demonstrated the lack of side effects from this regimen" (i.e., 5 g creatine monohydrate orally twice a day for 2 weeks followed by 2 g creatine monohydrate orally twice a day for 1 week).
- Klopstock et al. (2000) reported that two patients on creatine treatment experienced muscle cramps, which were not considered to be "major side effects." Otherwise, creatine was considered to have been "well tolerated."

- Kornblum et al. (2005) found that creatine was "well tolerated in all patients without major side effects." Three patients reported flatulence during creatine treatment and one patient reported flatulence during placebo treatment. Increased appetite and mild weight gain were reported by one patient during creatine treatment and one patient during placebo treatment.
- Komura et al. (2003) reported that the side effects of creatine supplementation used in their study "were negligible."

We found no reports of clinical trials of creatine in patients with AGAT deficiency syndrome. Long term supplementation with creatine monohydrate is reported to have been well tolerated (Stockler-Ipsiroglu et al. 2015). One case of urinary creatine crystals was reported in an AGAT deficiency syndrome patient using 800 mg/kg/day, which resolved with dose reduction.

Safety data for use of creatine in GAMT deficiency syndrome were not identified in the reviewed literature.

Creatine is generally considered to be safe in humans and common adverse events include minor weight gain and gastrointestinal distress (Persky and Brazeau 2001). Hepatic function has been monitored in various studies and significant abnormalities have not been reported (Juhn and Tarnopolsky 1998). However, use of creatine to enhance athletic performance became associated with a number of significant renal toxicity events, beginning with the deaths of three American college wrestlers in the late 1990s. It was concluded that these deaths were due to the consequences of the athletes' attempts at extreme rapid weight loss.[14] Because one of the individuals was reported to have been using creatine supplementation, it was speculated that creatine may have be associated with renal toxicity. No confirmation of a causal relationship was identified in the literature search conducted for this review.

Subsequent to the three weight loss cases, Pritchard and Kalra (1998) reported that a 25 year old male with an eight year history of focal segmental glomerulosclerosis, and frequently relapsing steroid-responsive nephrotic syndrome that had been minimized with cyclosporin treatment for the previous five years, experienced a substantial decline in renal function over approximately a four month period. Between June and October 1997, the patient's serum creatinine rose from 103 µmol/L to 180 µmol/L and his creatinine clearance fell from 93 mL/min to 54 mL/min. The patient reported having taken creatine beginning in mid-August at a dose of 5 g three times a day for one week, followed by 2 g per day for the next seven weeks until he was seen by his physicians in October. Creatine was discontinued and the patient's glomerular filtration rate was assessed using an injected radioisotope (isotopic GFR). One month later, his serum creatinine had dropped to 128 µmol/L and his creatine clearance was 115 mL/min.

Gualano et al. (2012) reviewed the extensive literature that followed the initial cases of creatine association with renal toxicity. While the dose and duration of treatments in various animal studies and human case reports and studies differ greatly, in general, doses of approximately 2 - 5 g/day over a period of months do not appear to be associated with renal toxicity in patients

[14] https://www.cdc.gov/mmwr/preview/mmwrhtml/00051388.htm

with normal renal function. The authors state in their conclusion that elderly patients and patients with Type 2 diabetes, who have normal renal function, may also use creatine safely at these doses. A risk assessment based on a similar evaluation of the published literature recommends a dose limit of 5 g/day for chronic supplementation (e.g., up to one year) (Shao and Hathcock 2006). Use at higher doses or longer durations, and studies in special populations including children, adolescents, pregnant women, geriatric patients, individuals on high protein diets, and those with disease states that may affect renal function, have not been adequately studied (Gualano et al. 2012).

One published case report has linked creatine supplementation and renal dysfunction in a patient with MELAS (Barisic et al. 2002). This 18 year old male had experienced previous episodes of cerebral stroke and recurrent seizures and had preexisting nephropathy. He was given creatine 20 g daily for 12 days followed by 5 g daily for 28 months. Although his neurologic symptoms improved, his renal insufficiency worsened over the treatment period, with increasing urea retention and impaired creatinine clearance. Because the decline in renal function occurred gradually, the authors felt that the deterioration was due to the natural course of his underlying disease rather than creatine use. However, they caution that creatine supplementation should be used with caution in mitochondrial disease patients who have preexisting nephropathy.

c. Pharmacokinetic data

In a 2007 review of the pharmacokinetics of creatine, McCall and Perksy report that "very little is known about the disposition of creatine after supraphysiologic doses" in humans. Absorption from the gastrointestinal tract in humans is thought, based on animal data, to involve transporters that mediate flux through the intestinal wall. The portion of an administered oral dose that is absorbed has not been established. Gastrointestinal absorption may be limited for a number of reasons: degradation of creatine in the acidic gastric pH, degradation due to gut bacteria, limits in transportation across the intestinal wall, or factors related to dosage form. In a comparison of the ingestion of creatine from various sources, C_{max} was found to be higher from a 2 g creatine dose delivered in an oral solution than from 2 g of creatine in meat (Harris et al. 2002). Mean T_{max} was longer with meat ingestion (1.5 hours) than with the solution (1 hour), but AUCs were approximately the same.

In a study of six healthy males, a dose of 71 mg/kg was given for six days and pharmacokinetics were assessed after a single dose and at steady state (Persky et al. 2003). In addition to plasma measurements, microdialysis was used to assess the creatine content of interstitial muscle space. The results are below in Table 5.

Table 5 Noncompartmental Analysis of Plasma and Muscle Data (mean ± *SD*)

	Plasma (n = 6)		Muscle (n = 3)	
	Single	Steady State	Single	Steady State
C_{max} (mg L^{-1})	102.1 ± 11.2	162.2 ± 30.0**	47.9 ± 16.2	52.3 ± 30.3
t_{max} (h)	1.9 ± 0.88	1.9 ± 0.58	2.1 ± 0.76	1.92 ± 0.29
AUC (mg h L^{-1})[a]	392 ± 97.8	585 ± 77.7*	162 ± 64.3	197 ± 125.3
$t_{1/2}$ (h)	2.0 ± 0.68	2.7 ± 0.63	1.8 ± 0.46	2.0 ± 0.34
CL/F (L h^{-1} kg^{-1})	0.20 ± 0.066	0.12 ± 0.016*	—	—
Mean residence time (h)	3.7 ± 0.86	4.0 ± 0.9	3.2 ± 0.65	4.2 ± 0.41
R_{ss}	—	1.60 ± 0.35	—	—
C_{ss} (mg L^{-1})	—	97.4 ± 13.0	—	32.9 ± 20.9
F	—	—	0.47 ± 0.09	0.37 ± 0.27

a. AUC calculated as $AUC_{0-\infty}$ on Day 1 and AUC_{ss} on Day 8 (steady-state for one dosing interval).
*$p < 0.05$ when compared to Day 1 values. **$p < 0.01$ when compared to Day 1 values.

Plasma protein binding is believed to be low due to the hydrophilicity of creatine and, although creatine can distribute to various tissues such as the brain, cardiac muscle, and the retina, creatine is predominantly taken up by skeletal muscle (Persky et al. 2003). A creatine transporter (CreaT) has been identified using in vitro, nonclinical and ex vivo human models and is responsible for cellular uptake of creatine in humans (Snow and Murphy 2001; Snow and Murphy 2003). Transporter activity is influenced by total creatine content, various hormones such as thyroid and insulin, and exercise (Persky et al. 2003). CreaT has been shown to be diminished in heart failure and various myopathies, although no studies have established specifics for mitochondrial diseases (Tarnopolsky and Beal 2001). Intracellular creatine is cleared very slowly from skeletal muscle (e.g., through metabolism to creatinine) such that only approximately 2 g of creatine needs to be synthesized or ingested daily to maintain whole body stores (Snow and Murphy 2003). Creatine uptake by skeletal muscle is a saturable process. Excess creatine is cleared through renal elimination at a rate that is close to glomerular filtration rate (Pitts 1934). Ropero-Miller et al. (2000) dosed 4 healthy adult volunteers with 5 g creatine monohydrate four times daily for five days, then 5 g per day for a total of 14 days and collected an aliquot of urine during all voids. The authors concluded that short term oral creatine supplementation does not affect urinary creatinine, pH or specific gravity values.

No information was found regarding the pharmacokinetics of creatine in patients with mitochondrial disorders or creatine deficiency syndromes.

d. Availability of alternative approved therapies that may be as safe or safer

There are no drugs approved by FDA to treat mitochondrial disorders. Various dietary supplements and approved and investigational drugs are used in treatment, as discussed in Section II.C.

There are no drugs approved by FDA to treat AGAT or GAMT deficiency disorders. Creatine is the primary treatment, as discussed in Section II.C.

Conclusions: Creatine is commonly associated with non-serious events, such as nausea, and safe doses have been identified for healthy adults. However, nonclinical data suggest potential toxicity in the liver and kidney when creatine is used at high doses. Some data support the

potential for creatine to be associated with renal toxicity, particularly in patients who have, or are at risk of, renal impairment. Many mitochondrial disorders are commonly associated with renal impairment and we did not find adequately designed safety evaluations to provide data on which to identify safe doses for mitochondrial disease patients. One case of urinary creatine crystals was reported in a patient with AGAT deficiency taking 800 mg/kg/day of creatine monohydrate.

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov.

1. *Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance*

Treatment Guidelines for Mitochondrial Disorders

Treatment for mitochondrial diseases is mostly supportive and determined by phenotypic symptom expression (Kisler et al. 2010; Rahman 2015; Davison and Rahman 2017). For example, physical therapy and mobility aids are the mainstay of treatment for myopathy as a predominant symptom; anticonvulsants are used to control seizures; sodium bicarbonate is indicated to correct lactic acidosis; and various visual aids or surgery are used to improve visual dysfunction or ptosis.

A consensus statement from the Mitochondrial Medicine Society (MMS) provides recent recommendations for diagnosis and treatment (Parikh et al. 2015). In 2012, the MMS surveyed North American physicians and nurse practitioners who, based on the organization that they worked for, were identified as practitioners of mitochondrial medicine (Camp et al. 2016). MMS estimated that the "practice patterns" of at least 90% of U.S. mitochondrial centers were captured by the surveys (Parikh et al. 2013). Of 32 practitioner respondents, 75% reported that creatine is among their "most often used" vitamins or xenobiotics. Concerned about the variability in approaches to diagnoses and treatment observed among the survey responses, MMS developed consensus recommendations based on existing evidence (Parikh et al. 2015). No recommendation was provided for the use of creatine.

The American Academy of Pediatrics offers diagnostic information for primary physicians, without specific drug treatment recommendations (Haas et al. 2007), but a number of treatments other than CoQ10 and creatine have been identified with various proposed mechanisms of action and amounts of supportive scientific evidence (Avula et al. 2014; Enns 2014; Finsterer and Bindu 2015; El-Hattab et al. 2017). These include idebenone (a CoQ_{10} analogue), riboflavin, thiamine, niacin, succinate, l-carnitine, vitamin C, vitamin K, dichloroacetate, cysteine, N-acetyl cysteine, dimethylglycine, lipoic acid, arginine, EPI-743 (a vitamin E analog), benzafibrate, resveratrol, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), dimthylglycine, bendavia, (-)-epicatechin, RTA 408, nucleoside bypass therapy, potential gene therapies, and liver or stem cell transplantation.

Studies in Mitochondrial Disorders

Although supplemental creatine was the first intervention for mitochondrial disorders to be assessed in a controlled clinical study (Kerr 2013), evidence of the effectiveness of creatine is minimal. It has been emphasized, however, that there is a need to overcome the difficulties associated with "obtaining high-quality evidence for rare disorders" to collect reliable evidence of drug treatment effects (Pfeffer et al. 2013). The National Institute of Neurological Disorders and Stroke Common Data Element Project has defined a Mitochondrial Disease Data Standards list to assist researcher in accruing critical and consistent information among studies of mitochondrial disorders (Karaa et al. 2017).

A search of "creatine" and "creatine monohydrate" in ClinicalTrials.gov retrieved no trials in the treatment of mitochondrial disease.

In a 2012 Cochrane review of the treatment for mitochondrial disorders (Pfeffer et al. 2012), three placebo-controlled crossover trials of creatine treatment of mitochondrial disease were included. In a study by Tarnopolsky et al. (1997) seven patients with MELAS or mitochondrial myopathy were randomized to receive 5 g creatine monohydrate orally twice a day for 2 weeks followed by 2 g creatine monohydrate orally twice a day for 1 week, or placebo for 3 weeks. Patients were crossed over to receive the alternate treatment after a 5 week washout. Evaluations were made at the end of each 3 week treatment period including:

- a visual analog scale assessment of the physical demand of activities of daily living
- blood sampling for lactate levels following a 2 minute walk test and subsequent 75 minutes of rest
- ischemic isometric handgrip strength (1 minute)
- evoked and voluntary contraction strength of the dorsiflexors
- nonischemic, isometric, dorsiflexion torque (NIDFT) (2 minutes)
- aerobic cycle ergonometry with pre- and post-lactate levels.

Creatine treatment was associated with significantly increased handgrip strength, NIDFT, and postexercise lactate after both isometric grip and cycle ergonometry. No effects of treatment were observed with other assessments. The authors concluded that creatine's effects were limited to high-intensity aerobic and anaerobic activities and there was no effect on lower intensity aerobic activities. It is noted that Tarnopolsky and Martin (1999) later reported on creatine supplementation effects in a group of 81 patients with various neuromuscular diseases, but the heterogeneity of this group was too great to assess the impact of creatine on the mitochondrial disease patients (n = 17).

Sixteen patients with CPEO (chronic progressive external ophthalmoplegia) or myocardial myopathy were randomized in a double-blind, crossover study by Klopstock et al. (2000) to receive 20 g creatine (given as 5 g 4 times a day) or placebo daily for 4 weeks separated by a washout period of approximately 29 days. No significant differences were observed between treatments for exercise performance (including a variety of assessments of strength, torque, aerobic cycle ergonometry, plasma lactate, ataxia, and symptom scores), eye movements or activities of daily life.

Kornblum et al. (2005) conducted a randomized double-blind crossover study in 15 patients with CPEO or Kearns-Sayre syndrome (patients experience retinitis pigmentosa at an early age, ataxia, heart block and other conduction defects, sensorineural deafness, elevated protein in cerebral spinal fluid, and seizures) comparing 6-week treatments with 150 mg/kg per day of creatine monohydrate and placebo. The authors found that based on ^{31}P magnetic resonance spectroscopy, creatine treatment showed no effects (e.g., on phosphocreatine or ATP status). In addition, creatine treatment showed no effects on clinical scores or laboratory tests, with the exception that creatine plasma levels were increased during creatine treatment.

In an uncontrolled study of five patients between the ages of 7 and 19 years with mitochondrial encephalopathy from Kearns-Sayre syndrome, NARP (neuropathy, ataxia, retinitis pigmentosa syndrome) or MELAS, the effects on exercise performance were assessed following creatine monohydrate supplementation with doses between 0.08 g/kg and 0.35 g/kg per day (Komura et al. 2003). This retrospective study compared exercise performance prior to treatment and after variable periods of dosing (between 9 months and nearly 5 years). A skeletal muscle power analysis based on cycle ergonometer performance showed an increase in performance compared to baseline of between 4 and 30%. Design considerations of this study, such as lack of a control group, and the variability of patients, doses and treatment duration, limit the ability to generalize from these findings.

Creatine has been studied in combination with other agents for the treatment of mitochondrial diseases. The contribution of creatine to the effects seen cannot be discerned. Rodriguez et al. (2007) assessed the combination of creatine, $CoQ_{10,}$ and lipoic acid in the treatment of 16 patients with various mutations and/or mitochondrial disease diagnoses. The authors conclude that combination therapies may target multiple common pathways of mitochondrial dysfunction, but larger studies of combination therapies in homogeneous populations are needed.

Studies in Creatine Deficiency Syndromes

ClinicalTrials.gov lists two studies of creatine deficiency syndromes, one for biomarker identification (NCT02934854, which was terminated due to change in study sponsorship) and one study of the natural history of creatine transporter deficiency (NCT02931682, ongoing). Neither reports evaluated the effects of creatine treatment.

In a review of clinical features and long term outcomes of AGAT deficiency, it was reported that 16 patients, within 8 families, worldwide were known to have been diagnosed with AGAT deficiency by 2015 (Stockler-Ipsiroglu et al. 2015). Early diagnosis of three of these patients and treatment with creatine beginning at ages 4, 16 and 24 months, respectively, has been associated with normal development. Other patients, who received treatment after the onset of symptoms have continued to have various cognitive and functional disabilities. Eight patients also have myopathy or proximal muscle weakness. Treatment with creatine is reported to have improved or restored brain creatine levels and improved a variety of symptoms. Creatine doses used in creatine treatment range from 100 to 800 mg/kg/day. At 800 mg/kg/day, one patient was found to have urinary creatine crystals which were reversible upon dose reduction. We found no clinical trials reported for the use of creatine in treatment of AGAT deficiency.

GAMT deficiency is a creatine deficiency syndrome that, while rare, is somewhat more prevalent than AGAT deficiency. While prospective clinical trials of creatine treatment were not identified, there are various publications confirming the effects of creatine in patients with GAMT deficiency.

- Stockler-Ipsiroglu et al. (2014) reviewed data on 48 patients with GAMT deficiency from 38 families worldwide and identified developmental delay/intellectual disability affected in 44 patients. Epilepsy was present in 33 patients and 13 had movement disorders. Treatments consisted of creatine monohydrate (doses of 300 – 800 mg/kg/day) with various other substances including L-ornithine, sodium benzoate and protein/arginine restricted diets to control brain and plasma levels of related metabolic products. Treatment duration was between 11 and 192 months. Clinical improvement had been reported in "the majority of patients" across all symptoms. Thirty of the 38 patients who had magnetic resonance imaging (MRI) or proton magnetic resonance spectroscopy (MRS) at baseline, showing creatine deficiency in the brain, also had followup MRI/MRS that established creatine treatment had increased brain creatine levels to "considerably higher" levels.
- Viau et al. (2013) retrospectively documented the course of treatment with creatine (doses of 250 – 1000 mg/kg/day) for five patients with GAMT deficiency. Four were diagnosed after the appearance of symptoms and one was diagnosed at birth. The patient treated from birth remained asymptomatic and was reported to be developmentally normal at 12 months of age. Other patients were diagnosed between ages 10 months and 5 years and showed improvement in seizures and development, as well as increases in brain creatine based on MRS assessments.
- Clark and Cecil (2015) created recommendations for treatment of AGAT deficiency which include oral creatine supplementation at doses of 100 – 800 mg/kg/day administered in divided doses three or four times a day. For GAMT deficiency, they recommend the same creatine therapy, to be given with supplementation of ornithine and sodium benzoate for control of various metabolic products.
- Notably, creatine therapy is considered so effective when given early in the course of the disease, it has been suggested that newborn screening should include testing for GAMT deficiency. Initial assessment could include a blood spot test followed by genetic sequencing in potentially affected patients (Viau et al. 2013; Braissant 2014; Stockler-Ipsiroglu et al. 2014; Clark and Cecil 2015).

2. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

There are numerous mitochondrial disorders, as explained above. Most are serious diseases and many are life-threatening. AGAT and GAMT deficiency syndromes are serious diseases.

3. *Whether there are any alternative approved therapies that may be as effective or more effective*

There are no drugs approved by FDA to treat mitochondrial disorders or creatine deficiency syndromes.

Conclusions: There are no compelling data that establish effectiveness in the support the treatment of mitochondrial diseases with creatine. Mitochondrial diseases encompass a wide variety of conditions related to genetic mutation in nDNA and mtDNA with different phenotypic presentations. Recommendations for creatine supplementation do not appear in treatment guidelines. The theoretical action for creatine in the treatment of mitochondrial disorders, to help support alternative ATP synthesis mechanisms in the context of dysfunctional oxidative phosphorylation, suggest a mechanism of action, and there is some indication that creatine may improve aspects of exercise performance. However, well-designed clinical trials have not demonstrated creatine's efficacy, and there are no trials which appear to support definitive indications or dosing.

Creatine is an effective treatment for two creatine deficiency syndromes, AGAT deficiency and GAMT deficiency. The identified biochemical mechanism of action is supported by clearly documented clinical outcomes.

D. Has the substance been used historically as a drug in compounding?

Databases searched for information on creatine and creatine monohydrate in regard to Section II.D. of this review included PubMed, Natural Medicines, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and Google.

1. Length of time the substance has been used in pharmacy compounding

Insufficient information is available to determine how long creatine or creatine monohydrate have been used in pharmacy compounding.

2. The medical condition(s) it has been used to treat

According to the Natural Medicines Database, creatine is used orally for improving athletic performance and increasing muscle strength, chronic obstructive pulmonary disease, congestive heart failure, depression, diabetes, exercise tolerance, fibromyalgia, Huntington's disease, idiopathic inflammatory myopathies (polymyositis, dermatomyositis), Parkinson's disease, mitochondrial myopathies, multiple sclerosis, muscle atrophy, muscle cramps, and numerous other conditions. Topically, it is used for aging skin (Natural Medicines Comprehensive Database 2018).

Results from a Google search using the terms *creatine compounding pharmacy* indicate that creatine may been included as a component of the "Mito Cocktail," which according to MitoAction,[15] is a cocktail[16] of various vitamins and supplements commonly used in adults and children who have been diagnosed with mitochondrial disease. See

[15] According to mitoaction.org, MitoAction is a patient advocacy organization within the mitochondrial disease community.

[16] This "cocktail" appears to be for oral administration. Per the guide for patients available at http://www.mitoaction.org/files/mito%20cocktail%20brochure%202010.pdf, doses should be taken with a meal and plenty of fluids.

http://www.mitoaction.org/blog/qa-compounding-pharmacists. Otherwise, we did not find evidence of any compounded creatine or creatine monohydrate products for clinical use in the United States.

3. How widespread its use has been

Insufficient data are available from which to draw conclusions about the extent of use of creatine or creatine monohydrate in compounded drug products.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

A search of the British Pharmacopoeia (BP 2018), the European Pharmacopoeia (9th Edition, 2018, 9.4), and the Japanese Pharmacopoeia (16th Edition) did not show any monograph listings for creatine or creatine monohydrate.

Conclusions: Based on internet searches, it appears that creatine is/has been compounded along with various other ingredients into a cocktail for use in patients with mitochondrial disease. There is insufficient information available to determine how long creatine had been used in pharmacy compounding.

III. RECOMMENDATION

We have balanced the criteria described in Section II above to evaluate creatine monohydrate for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs in favor of*** creatine monohydrate solid oral dosage forms being placed on that list based on the following:

1. Creatine monohydrate is easily characterized, and its preparation has been well developed. It is likely to be stable under ordinary storage conditions in its solid form and in solid oral dosage forms when kept away from moisture. However, aqueous formulations, including aqueous oral formulations, are unlikely to be stable.

2. Creatine monohydrate is generally associated with non-serious adverse events, and safe doses have been identified for healthy adults. We did not find adequately designed safety evaluations to provide data with which to identify safe doses for mitochondrial disease patients or other patients having, or at risk of having, renal impairment. Some data support the potential for creatine to be associated with renal toxicity, particularly in patients who have, or are at risk of, renal impairment. One case of urinary creatine crystals was reported in an AGAT patient using 800 mg/kg/day, which resolved with dose reduction. Safety data were not identified in the reviewed literature regarding GAMT deficiency.

3. Mitochondrial disorders encompass a wide variety of conditions, genetic mutations, and phenotypic presentations. There are no compelling data that establish the effectiveness of creatine monohydrate in the treatment of mitochondrial diseases. Recommendations for creatine supplementation do not appear in treatment guidelines, no well-designed clinical trials have demonstrated creatine monohydrate's efficacy, and there are no trials which

appear to support definitive uses or dosing.

Oral supplementation with creatine, such as the monohydrate, is standard, effective treatment for creatine deficiency syndromes AGAT and GAMT.

4. It appears that creatine monohydrate is/has been compounded along with various other ingredients into a cocktail for treatment of patients with mitochondrial disease. There is insufficient information available to determine how long creatine had been used in pharmacy compounding.

Based on this information the Agency has considered, a balancing of the four evaluation criteria ***weighs in favor of*** creatine monohydrate solid oral dosage forms being added to the 503A Bulks List.

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APPENDIX 1: ILLUSTRATIVE MITOCHONDRIAL DISORDERS

Mitochondrial Diseases Due to mtDNA Point Mutations and Large-Scale Rearrangements

Disease	Phenotype	Most Frequent mtDNA Mutations	Homoplasmic (usually)	Maternal
NARP, Leigh disease	Loss of central vision leading to blindness in young adult life	m.1778G>A, m.14484T>C, m.3460G>A	Heteroplasmic	Maternal
MELAS	*M*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes; may manifest only as diabetes mellitus	Point mutation in $tRNA^{leu}$	Heteroplasmic	Maternal
MERRF	*M*yoclonic *e*pilepsy, *r*agged *r*ed *f*ibers in muscle, ataxia, increased CSF protein, sensorineural deafness, dementia	Point mutation in $tRNA^{lys}$	Heteroplasmic	Maternal
Deafness	Progressive sensorineural deafness, often induced by aminoglycoside antibiotics	m.1555A>G mutation in 12S rRNA	Homoplasmic	Maternal
	Nonsyndromic sensorineural deafness	m.7445A>G mutation in 12S rRNA	Homoplasmic	Maternal
Chronic progressive external ophthalmoplegia (PEO)	Late-onset bilateral ptosis and ophthalmoplegia, proximal muscle weakness, and exercise intolerance	Single deletions or -duplications	Heteroplasmic	Mostly sporadic, somatic mutations
Pearson syndrome	Pancreatic insufficiency, pancytopenia, lactic acidosis	Large deletion	Heteroplasmic	Sporadic, somatic mutations
Kearns-Sayre syndrome (KSS)	External ophthalmoplegia, heart block, retinal pigmentation, ataxia	The 5-kb "common deletion"	Heteroplasmic	Sporadic, somatic mutations

Abbreviations: CSF, cerebrospinal fluid; NARP, neuropathy, ataxia, and retinitis pigmentosa.

Tab 4

Pyridoxal 5 Phosphate

Tab 4a

Pyridoxal 5 Phosphate Nominations

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

> "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"

Dear Sir or Madam,

Fagron appreciates the opportunity to address the FDA's request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

We hereby nominate the bulk drug substances in the attached spreadsheets for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

None of these items appear on an FDA-published list of drugs that present demonstrable difficulties for compounding. In addition, none are a component of a drug product that has been withdrawn or removed from the market because the drug or components of the drug have been found to be unsafe or not effective.

We include references in support of this nomination for your consideration.

Thank you for your consideration. If Fagron can answer any questions, please contact me (j.letwat@fagron.com; 847-207-6100).

Respectfully submitted,

Julie Letwat, JD, MPH
Vice-President, Regulatory and Government Affairs

Re: Docket FDA-2013-N-1525

Substances submitted (see corresponding .xlxs file)

7-Keto Dehydroepiandrosterone
Acetyl-D-Glucosamine
Aloe Vera 200:1 Freeze Dried
Astragalus Extract 10:1
Beta Glucan (1,3/1,4 –D)
Boswellia Serrata Extract
Bromelain
Cantharidin
Cetyl Myristoleate Oil
Cetyl Myristoleate 20% Powder
Chrysin
Citrulline
Dehydroepiandrosterone
Deoxy-D-Glucose (2)
Diindolylmethane
Domperidone
EGCg
Ferric Subsulfate
Glycolic Acid
Glycosaminoglycans
Hydroxocobalamin Hydrochloride
Kojic Acid
Methylcobalamin
Nicotinamide Adenine Dinucleotide
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)
Ornithine Hydrochloride
Phosphatidyl Serine
Pregnenolone
Pyridoxal 5-Phosphate Monohydrate
Pyruvic Acid
Quercetin
Quinacrine Hydrochloride
Ribose (D)
Silver Protein Mild
Squaric Acid Di-N-Butyl Ester
Thymol Iodide
Tranilast
Trichloroacetic Acid
Ubiquinol 30% Powder

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What is the name of the nominated ingredient?	**Pyridoxal-5-Phosphate Monohydrate**
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?	Yes, Pyridoxal 5-Phosphate Monohydrate is an active ingredient as defined in 207.3(a)(4) because when added to a pharmacologic dosage form it produces a pharmacological effect. References for Pyridoxal 5-Phosphate Monohydrate pharmacological actions are provided Evans, M., Sharma, P., & Guthrie, N. (2010). A randomized, double-blind, crossover study on the pharmacokinetics of a novel formulation of coq_{10} with pyridoxal 5'-phosphate and phosphatidyl choline. Journal of Dietary Supplements, 7(4), 314-24. doi:10.3109/19390211.2010.522551 Kuo, M. F., & Wang, H. S. (2002). Pyridoxal phosphate-responsive epilepsy with resistance to pyridoxine. Pediatric Neurology, 26(2), 146-7. Nakamura, S., Li, H., Adijiang, A., Pischetsrieder, M., & Niwa, T. (2007). Pyridoxal phosphate prevents progression of diabetic nephropathy. Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association, 22(8), 2165-74. doi:10.1093/ndt/gfm166 Ohtsuka, Y., Matsuda, M., Ogino, T., Kobayashi, K., & Ohtahara, S. (1987). Treatment of the west syndrome with high-dose pyridoxal phosphate. Brain & Development, 9(4), 418-21. Porri, S., Fluss, J., Plecko, B., Paschke, E., Korff, C. M., & Kern, I. (2014). Positive outcome following early diagnosis and treatment of pyridoxal-5'-phosphate oxidase deficiency: A case report. Neuropediatrics, 45(1), 64-8. doi:10.1055/s-0033-1353489 Tardif, J. C., Carrier, M., Kandzari, D. E., Emery, R., Cote, R., Heinonen, T., . . . MEND-CABG Investigators. (2007). Effects of pyridoxal-5'-phosphate (MC-1) in patients undergoing high-risk coronary artery bypass surgery: Results of the MEND-CABG randomized study. The Journal of Thoracic and Cardiovascular Surgery, 133(6), 1604-11. doi:10.1016/j.jtcvs.2007.01.049 Wang, H. S., Kuo, M. F., Chou, M. L., Hung, P. C., Lin, K. L., Hsieh, M. Y., & Chang, M. Y. (2005). Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. Archives of Disease in Childhood, 90(5), 512-5. doi:10.1136/adc.2003.045963
Is the ingredient listed in any of the three sections of the Orange Book?	The nominated substance was searched for in all three sections of the Orange Book located at http://www.accessdata.fda.gov/ scripts/cder/ob/docs/queryai.cfm. The nominated substance does not appear in any section searches of the Orange Book.
Were any monographs for the ingredient found in the USP or NF monographs?	The nominated substance was searched for at http://www.uspnf.com. The nominated substance is not the subject of a USP or NF monograph.
What is the chemical name of the substance?	(4-Formyl-5-hydroxy-6-methyl-3-pyridinyl)methyl dihydrogen phosphate hydrate (1:1)
What is the common name of the substance?	Pyridoxal Phosphate; P5P; PLP; Vitamin B6 Phosphate; Codecarboxylase
Does the substance have a UNII Code?	73R90F7MQ8
What is the chemical grade of the substance?	no grade

What is the strength, quality, stability, and purity of the ingredient?	Description: Slightly yellow or off-white powder Identification: Posi ive Particle Size: 100% through 30 mesh Bulk Density: (report) Tapped Density: (report) Solubility: Sparingly soluble in water Soluble in alkali-OH solution: (report) Melting Point: 140.0°C - 145.0°C pH (0.25% Water): 2.6 - 3.0 Heavy Metal: ≤ 10 ppm Arsenic: ≤ 2 ppm Cadmium: ≤ 2 ppm Lead: ≤ 2 ppm Mercury: ≤ 2 ppm Residual Solvents: - Ethanol: ≤ 5000 ppm - Toluene: ≤ 890 ppm Loss on Drying: ≤ 10.0% Purity by HPLC: ≥ 99.0% Assay (Dried): 98.5% - 101.0% Assay (as is): ≥ 90.0% Total Plate Count: ≤ 1000 cfu/gram Yeast and Mold: ≤ 100 cfu/gram Coliforms: ≤ 10 cfu/gram E. Coli: Negative Staph. Aureaus: Nega ive Salmonella: Negative
How is the ingredient supplied?	Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	Active-B6 Chin Teng, TW Aderoxal Zonnebode Seiyaku, JP Behzex Taiho Yakuhin, JP
Has information been submitted about the substance to the USP for consideration of monograph development?	No USP Monograph submission found.
What dosage form(s) will be compounded using the bulk drug substance?	Capsules
What strength(s) will be compounded from the nominated substance?	25-100mg
What are the anticipated route(s) of administration of the compounded drug product(s)?	Oral
Are there safety and efficacy data on compounded drugs using the nominated substance?	Dill, P., Schneider, J., Weber, P., Trachsel, D., Tekin, M., Jakobs, C., . . . Blau, N. (2011). Pyridoxal phosphate-responsive seizures in a patient with cerebral folate deficiency (CFD) and congenital deafness with labyrinthine aplasia, microtia and microdontia (LAMM). Molecular Genetics and Metabolism, 104(3), 362-8. doi:10.1016/j.ymgme.2011.05.019 Evans, M., Sharma, P., & Guthrie, N. (2010). A randomized, double-blind, crossover study on the pharmacokinetics of a novel formulation of coq_{10} with pyridoxal 5'-phosphate and phosphatidyl choline. Journal of Dietary Supplements, 7(4), 314-24. doi:10.3109/19390211.2010.522551 Kuo, M. F., & Wang, H. S. (2002). Pyridoxal phosphate-responsive epilepsy with resistance to pyridoxine. Pediatric Neurology, 26(2), 146-7. Nakamura, S., Li, H., Adijiang, A., Pischetsrieder, M., & Niwa, T. (2007). Pyridoxal phosphate prevents progression of diabetic nephropathy. Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association, 22(8), 2165-74. doi:10.1093/ndt/gfm166
Has the bulk drug substance been used previously to compound drug product(s)?	Capsules
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Supplementation with bioactive form of pyridoxine in cases of deficiency
What is the reason for use of a compounded drug product rather than an FDA-approved product?	No FDA approved preparation for Pyridoxal 5- Phosphate Monohydrate (PLP). PLP deficiency is a metabolic disorder causing refractory neonatal seizures. These children have poor outcome unless treated with PLP. (S. Porri, J. Fluss, B. Plecko, Paschke, CM. Kroff, I.Kern (2014) Positive Outcome Following Early Diagnosis and Treatment of Pyridoxal-5-Phosphate Oxidase Defeciency: A Case Report. Neuropediatrics Feb;45(1):64-8) PLP also helps patients with peritoneal dialysis. It prevents glycation of proteins hat can collect in the peritoneal cavity. This can help lessen thickening and accumulation of glycenated proteins in the peritoneal cavity leading to less complications with dialysis patients. (S. Nakamura and T. Niwa(2005) Pyridoxal Phosphate and Hepatogrowth factor Prevent Dialysate-Induced Peritoneal Damage J. Am. Soc. Nephrol Jan:16(1):144-5) With no PLP FDA options available, patient outcomes can be compromised.
Is there any other relevant information?	All relevant information was expressed in the above questions

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

[Docket No. FDA-2013-N-1525]

Re: FDA-2013-N-1525; List of Bulk Drug Substances That May Be Used in Pharmacy Compounding in Accordance with Section 503A

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on FDA's request for a list of bulk drug substances that may be used in pharmacy compounding as defined within Section 503A of the Federal Food, Drug and Cosmetic Act. As FDA receives these lists from the public, the medical and pharmacy practice communities, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to identify and share drug substances which are commonly used in the preparation of medications but which have neither an official USP (United States Pharmacopeia) monograph nor appear to be a component of an FDA approved drug product.

IACP is an association representing more than 3,600 pharmacists, technicians, academicians students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Working in tandem with the IACP Foundation, a 501(c)(3) non-profit organization dedicated to enhancing the knowledge and understanding of pharmacy compounding research and education, our Academy is submitting the accompanying compilation of 1,215 bulk drug substances which are currently used by compounding pharmacies but which either do not have a specific USP monograph or are not a component of an FDA approved prescription drug product.

These drug substances were identified through polling of our membership as well as a review of the currently available scientific and medical literature related to compounding.

Although the information requested in FDA-2013-N-1525 for each submitted drug substance is quite extensive, there are many instances where the data or supporting research documentation does not currently exist. IACP has provided as much detail as possible given the number of medications we identified, the depth of the information requested by the agency, and the very short timeline to compile and submit this data.

ISSUE: The Issuance of This Proposed Rule is Premature

IACP is concerned that the FDA has disregarded previously submitted bulk drug substances, including those submitted by our Academy on February 25, 2014, and created an series of clear obstructions for the consideration of those products without complying with the requirements set down by Congress. Specifically, the agency has requested information on the dosage forms, strengths, and uses of compounded preparations which are pure speculation because of the unique nature of compounded preparations for individual patient prescriptions. Additionally, the agency has developed its criteria list without consultation or input from Pharmacy Compounding Advisory Committee. Congress created this Advisory Committee in the original and reaffirmed language of section 503A to assure that experts in the pharmacy and medical community would have practitioner input into the implementation of the agency's activities surrounding compounding.

As outlined in FDCA 503A, Congress instructed the agency to convene an Advisory Committee ***prior*** to the implementation and issuance of regulations including the creation of the bulk ingredient list.

> (2) Advisory committee on compounding.--Before issuing regulations to implement subsection (a)(6), the Secretary shall convene and consult an advisory committee on compounding. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

Despite a call for nominations to a Pharmacy Compounding Advisory Committee (PCAC) which were due to the agency in March 2014, no appointments have been made nor has the PCAC been formed to do the work dictated by Congress. Additionally, the agency provides no justification in the publication of criteria within FDA-2013-N-1525 which justifies whether this requested information meets the needs of the PCAC.

In summary, IACP believes that the absence of the PCAC in guiding the agency in determining what information is necessary for an adequate review of a bulk ingredient should in no way preclude the Committee's review of any submitted drug, regardless of FDA's statement in the published revised call for nominations that:

> General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

IACP requests that the Pharmacy Compounding Advisory Committee review each of the 1,215 drug substances we have submitted for use by 503A traditional compounders and we stand ready to assist the agency and the Committee with additional information should such be requested.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

David G. Miller, R.Ph.
Executive Vice President & CEO

Bulk Drug Substances for Consideration by the FDA's Pharmacy Compounding Advisory Committee

Submitted by the International Academy of Compounding Pharmacists

General Background on Bulk Drug Substance

Ingredient Name	Pyridoxal-5-Phosphate, Monohydrate
Chemical/Common Name	Codecarboxylase; 3-Hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde 5'-Phosphate; Pyridoxal Phosphate
Identifying Codes	41468-25-1
Chemical Grade	Provided by FDA Registered Supplier/COA
Description of Strength, Quality, Stability, and Purity	Provided by FDA Registered Supplier/COA
How Supplied	Varies based upon compounding requirement
Recognition in Formularies *(including foreign recognition)*	Not Listed in USP/NF for this specific salt/form

Information on Compounded Bulk Drug Preparation

Dosage Form	Varies based upon compounding requirement/prescription
Strength	Varies based upon compounding requirement/prescription
Route of Administration	Varies based upon compounding requirement/prescription
Bibliography *(where available)*	
Past and Proposed Use	The very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription. FDA's request for this information is an insurmountable hurdle that has not been requested by the PCAC.

Submitted electronically via www.regulations.gov

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No.: FDA-2013-N-1525: *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*

Dear Sir or Madam:

The National Community Pharmacists Association (NCPA) is writing today to nominate specific bulk drug substances that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. As the FDA considers which drugs nominated will be considered for inclusion on the next published bulk drugs list, NCPA is committed to working with the FDA and other interested stakeholders on these critical issues.

NCPA represents the interests of pharmacist owners, managers and employees of more than 23,000 independent community pharmacies across the United States. Independent community pharmacies dispense approximately 40% of the nation's retail prescription drugs, and, according to a NCPA member survey, almost 89% of independent community pharmacies engage in some degree of compounding.

Regarding specific nominations, NCPA would like to reference the attached spreadsheet as our formal submission of bulk drug substances (active ingredients) that are currently used by compounding pharmacies and are not, to the best of our knowledge, the subject of a USP or NF monograph nor are components of approved products.

All nominated substances on the attached spreadsheet are active ingredients that meet the definition of "bulk drug substance" to the best of our knowledge, and we have searched for the active ingredient in all three sections of the Orange Book, and the substances did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product. In addition, we have searched USP and NF monographs, and the substances are not the subject of such monographs to our best knowledge.

100 Daingerfield Road
Alexandria, VA 22314-2888
(703) 683-8200 PHONE
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Regarding the request for chemical grade information pertaining to the submitted ingredients, NCPA would like to stress that chemical grades of bulk active products vary according to manufacturing processes, and products are often unassigned. When compounding products for patient use, pharmacists use the highest grade ingredients available, typically USP/NF, USP/GenAR, ACS, or FCC, among others, depending on the chemical. The same standard applies for all of the bulk active ingredients submitted on the attached list.

Related to rationale for use, including why a compounded drug product is necessary, NCPA would like to stress that many of the attached listed products are unavailable commercially in traditional dosage forms and must therefore be compounded using bulk ingredients. For other listed products, the use of bulk ingredients allows compounders to create an alternate dosage form and/or strength for patients who are unable to take a dosage form that is commercially available.

NCPA would like to strongly recommend that FDA institute a formal process by which the list is updated and communicated to the compounding community. We would recommend an annual process that can be anticipated and acted upon in order to ensure maximum understanding and adherence to the list. The FDA should issue such request via *The Federal Register* and review and consider all updates to the list with the Pharmacy Compounding Advisory Committee (PCAC). No changes to the list should occur without the input and review of the PCAC.

NCPA is very disappointed that despite a call for nominations to the PCAC which we submitted in March 2014, no appointments have been made nor has the Committee been formed to do the work that Congress requires of the Agency. Without formation of this Committee, FDA is unable to consult the Committee regarding the submitted lists. NCPA strongly recommends that FDA consult with the PCAC related to every single submission the Agency receives in relation to FDA-2013-N-1525. It is only through complete consultation with the PCAC that each substance can be appropriately evaluated.

NCPA is committed to working with the FDA and other stakeholders regarding these important matters. We appreciate your consideration of our comments.

Sincerely,

Steve Pfister
Senior Vice President, Government Affairs

Attachment

Ingredient Name	Chemical Name	Common Name	UNII Code	Description of strength, quality, stability and purity	Ingredient Format(s)	Recognition in Pharmacopeias	Final Compounded Formulation Dosage Form(s)	Final Compounded Formulation Strength	Final Compounded Formulation Route(s) of Administration	Final Compounded Formulation Clinical Rationale and History of Past Use
Pyridoxal-5-phosphate, Monohydrate	co-decarboxylase; 3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde 5'-Phosphate	Pyridoxal phosphate	5V5IOJ8338	From PCCA Database MSDS: Product is 100% by weight and stable. Should be protected from strong oxidizing agents.	powder	Not USP; sold OTC in US as a dietary supplement.	Capsule	Capsule: 182 - 822mg	Oral	Vitamin supplement Helps the body to build and break down amino acids and to change amino acids from one to another

Tab 4b

Pyridoxal 5 Phosphate Nomination Clarification

March 2, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager
CDER/OC/OPRO
10903 New Hampshire Ave. Bldg 51, Rm 3249
Silver Spring, MD 20903

Regarding Docket No.: FDA-2015-N-3534

Toni Hallman:

Thank you for contacting Fagron, Inc., IACP, and NCPA the nominators of pyridoxal 5'-phosphate to the 503A Bulk Drug Substances that can be used in compounding list. Please find the answers to questions 1 and 2 to the clarification questions regarding pyridoxal 5'-phosphate below. Responses to questions 3 and 4 will be provided by March 16, 2018 as called for.

1. Yes, Fagron, Inc., IACP and NCPA would like to continue to pursue consideration of pyridoxal 5'-phophate for inclusion on the 503A bulk substances list.

2. Upon review of additional scientific literature, Fagron, Inc., IACP and NCPA would like to propose the use of pyridoxal 5'-phophate (PLP) for the treatment of neonatal and pediatric seizure disorder, infantile spasms, Intractable neonatal epileptic encephalopathy, Pyridox(am)ine-5-phosphate oxidase deficiency and PLP dependent epilepsy.

-Dosing range: 10-50 mg/kg/day
-Route: IV and Oral

Scientific Literature:

1. Porri S, Fluss J, Plecko B, Paschke E, Korff CM, Kern I. Positive outcome following early diagnosis and treatment of pyridoxal-5'-phosphate oxidase deficiency: a case report. *Neuropediatrics.* 2014 Feb;45(1):64-8.
2. Takuma Y, Seki T. Combination therapy of infantile spasms with high-dose pyridoxal phosphate and low-dose corticotropin. J *Child Neurol.* 1996 Jan;11(1):35-40.
3. Guerin A, Aziz AS, Mutch C, Lewis J, Go CY, Mercimek-Mahmutoglu S. Pyridox(am)ine-5-Phosphate Oxidase Deficiency Treatable Cause of Neonatal Epileptic Encephalopathy With Burst Suppression: Case Report and Review of the Literature. J *Child Neurol.* 2015 Aug;30(9):1218-25.

4. Wang, H., Kuo, M., Chou, M., Hung, P., Lin, K., Hsieh, M., & Chang, M. (2005). Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. *Archives of Disease in Childhood*, *90*(5), 512–515.
5. Mills PB, Struys E, Jakobs C, Plecko B, Baxter P, Baumgartner M, Willemsen MA,Omran H, Tacke U, Uhlenberg B, Weschke B, Clayton PT. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. *Nat Med.* 2006 Mar;12(3):307-9.
6. Gospe SM Jr. Neonatal vitamin-responsive epileptic encephalopathies. *Chang Gung Med J.* 2010 Jan-Feb;33(1):1-12. Review.

Fagron, Inc., IACP and NCPA greatly appreciate the opportunity to work with FDA in this matter and looks forward to continued collaboration.

Sincerely,

Ronna Hauser, PharmD
NCPA Vice President of
Pharmacy Affairs

Erik Tosh, BS, DPh,
FIACP, FACA
IACP President

Alex Govze
Fagron Legal Counsel

Tab 4c

FDA Review of
Pyridoxal 5 Phosphate

DATE: August 9, 2018

FROM: Ben Zhang, Ph.D.
Staff Fellow, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)

Yen-Ming Chan, Ph.D.
Nour Debiat
Farjad Khan, Pharm.D.
ORISE Fellow, Office of Drug Evaluation IV (ODE IV), Office of New Drugs (OND)

Wafa Harrouk, Ph.D.
Senior Pharmacology/Toxicology Reviewer, ODE IV, OND

Elizabeth Hankla, Pharm.D.
Consumer Safety Officer, Office of Compliance, Office of Unapproved Drugs and Labeling Compliance (OUDLC)

THROUGH: Ramesh K. Sood, Ph.D.
Senior Scientific Advisor (acting), ONDP, OPQ

Charles Ganley, M.D.
Director, ODE IV, OND

Frances Gail Bormel, R.Ph., J.D.
Director, Division of Prescription Drugs, OUDLC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Pyridoxal-5-Phosphate Monohydrate for Inclusion on the 503A Bulk Drug Substances List

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

I. INTRODUCTION

Pyridoxal-5-phosphate monohydrate has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). This review considers pyridoxal-5-phosphate (PLP) monohydrate for the treatment of epilepsy and seizure disorders. [1] PLP monohydate's administration via the intravenous and oral routes have been proposed.

We have reviewed publicly available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh in favor*** *of* placing pyridoxal-5-phosphate monohydrate (intravenous and oral dosage forms) 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 (503A Bulks List).[2]

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?[3]

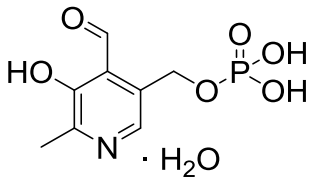
PLP is the metabolically active form of vitamin B6. PLP is a synonym for (4-formyl-5-hydroxy-6-methylpyridin-3-yl) methoxyphosphonic acid (IUPAC name). The molecular formula for the PLP monohydrate is $C_8H_{10}NO_6P \cdot H_2O$ and the molecular weight is 265.16 Daltons.

[1] PLP monohydrate was nominated for the treatment of neonatal and pediatric seizure disorder, infantile spasms, intractable neonatal epileptic encephalopathy, Pyridox(am)ine-5-phosphate [sic] oxidase deficiency, and PLP dependent epilepsy, all of which are conditions associated with epilepsy in the pediatric population. Because of the close relationship of the proposed uses, and the fact that there is evidence of effectiveness of PLP monohydrate for the treatment of pediatric seizure disorders, we are not individually evaluating each of the related proposed uses.

[2] Inclusion 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 should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using a substance included on the list has been proven to be safe and effective under the standards required receiving Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears 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 is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act (21 U.S.C. 352(a), (bb)).

[3] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

The chemical structure for the PLP monohydrate form is shown below:



PLP and PLP monohydrate will be considered the same for the purposes of this review. The acronym PLP will be used to designate either compound.

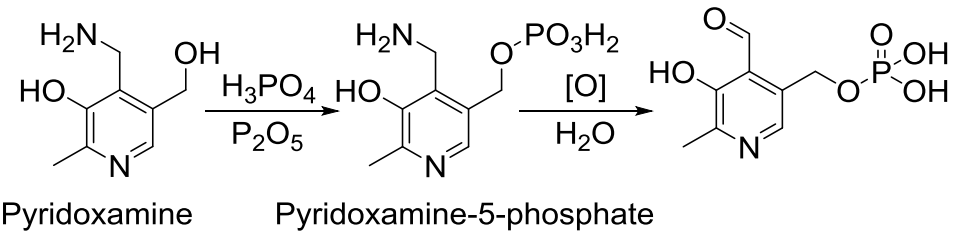
1. *Stability of the API and likely dosage forms*

PLP is a small molecule with a simple chemical structure. It is currently marketed as a dietary ingredient in dietary supplements as tablets and capsules. The aqueous solution of this compound is sufficiently stable at neutral and weak acidic and alkaline conditions (5.0 – 8.0) up to 98°C. The hydrolysis of the compound appears to be accelerated at pH lower than 5.0 (Kozlov and L'Vova 1977). No other stability issues have been reported in the literature for either the solid form or the aqueous solution of this compound.

2. *Probable routes of API synthesis*

PLP can be synthesized from pyridoxamine. Pyridoxamine dihydrochloride is treated with a mixture of phosphorus pentoxide and 85% phosphoric acid to give pyridoxamine-5-phosphate. Pyridoxamine-5-phosphate is then oxidized with manganese dioxide which results in the formation of PLP after purification (Wilson and Harris 1951; Peterson and Sober 1954).

Synthesis of PLP from pyridoxamine.



3. *Likely impurities*

Possible impurities may include:

- Trace amounts of manganese from the oxidation step
- Byproducts from the oxidation step
- Trace amounts of pyridoxal from the hydrolysis of pyridoxal-5-phosphate

4. *Toxicity of those likely impurities*

Manganese, which is present in the oxidation step for PLP, is a generally recognized micronutrient that has an upper intake limit in adults of 11 mg/day.[4] Other impurities, like pyridoxal, are unlikely to exhibit high toxicity.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

PLP is a light yellow solid, and is sparingly soluble in water. There is insufficient information in the literature about the impact of the particle size and polymorphism on the bioavailability and bioactivity of the substance.

6. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

The chemical structure of PLP is simple and it has been well characterized with nuclear magnetic resonance (NMR) spectroscopy, Fourier transform infrared (FT-IR) spectroscopy, mass spectrometry (MS) and Ultraviolet-visible (UV/Vis) spectroscopy.

Conclusions: PLP is a well characterized small molecule. Its synthesis is straightforward under current technical conditions. The compound is stable under ordinary storage conditions as a solid or in neutral or weak acidic and alkaline aqueous solutions.

B. Are there concerns about the safety of the substance for use in compounding?

1. *Nonclinical assessment*

The following databases were consulted in the preparation of this section: PubMed, National Toxicology Program website, Embase, Web of Science, ToxNet, NIH dietary supplement label database, Google Scholar, GRAS notice inventory, US Pharmacopeia/NF monographs, and Drugs@FDA.

Because we were not able to locate nonclinical data (pharmacology/toxicology) which were exclusive for PLP, we widened our search to include all forms of vitamin B6 that were available.

a. General pharmacology of the drug substance

PLP is a vitamer of vitamin B6. Vitamin B_6 is the collective term for a family of chemical substances that are structurally related and includes pyridoxine (PN), pyridoxine 5'-phosphate (PNP), pyridoxal (PL), pyridoxal-5-phosphate (PLP, pyridoxamine (PM), and pyridoxamine 5'-phosphate (PMP), each of which can be converted into one another.

PLP is found in animal food sources. The European Food Safety Authority (EFSA) has set the tolerable upper intake levels of PLP when used in food supplements at 25 mg/day for adults and

[4] https://www.ncbi nlm nih.gov/books/NBK222332/.

5-20 mg for children depending on their body weight (European Food Safety Authority 2008). The US Food and Drug Administration (FDA) has set the tolerable upper limit for vitamin B6 in food at 100 mg/day (Food and Nutrition Board 1998; Food and Nutrition Board 2000).

PLP is the active form of vitamin B6 and is an essential cofactor for over 100 different enzyme reactions involved in amino acid metabolism, heme and neurotransmitter synthesis, and the metabolism of glycogen, lipids, steroids, vitamins, and the conversion of tryptophan to niacin (Russell and Suter 2015). This review will not focus on the many important reactions which require PLP but will limit the discussion to its role in the treatment of seizures.

The role of PLP in the treatment of seizures involves primarily inborn errors of metabolism that lead to vitamin B-6 dependent epilepsy (Plecko 2013). PLP dependent epilepsy is the result of a mutation in the pyridox(am)ine 5' phosphate oxidase (PNPO) gene, which leads to a deficiency of PNPO. PNPO is an enzyme essential for the conversion of PN and PM to PLP, the active form of vitamin B6. Attributes of the PLP dependent epilepsy (also called PNPO deficiency) include (Plecko 2013):

- Present within the first 2 weeks of life
- Seizures are myoclonic and may become status epilepticus
- Patients are often encephalopathic (eye deviations, screaming for hours, automatisms and abnormal posturing)
- Unresponsive to approved anticonvulsants and pyridoxine
- Treatment with PLP results in cessation/amelioration of seizures quickly
- Dose ranges from 10 mg/kg/day to 100 mg/kg/day divided into four to six doses
- Early treatment is critical to avoid irreversible neurologic damage

b. Pharmacokinetics/Toxicokinetics

No animal pharmacokinetics or toxicokinetics data were found for PLP.

c. Acute toxicity[5]

While no toxicity data were found for PLP, the literature contained data for pyridoxine, one of the naturally occurring forms of vitamin B6. The toxicity of consuming large doses of vitamin B6 has been evaluated by several groups (Scientific Committee on Food 2000; Expert Group on Vitamins and Minerals 2003; Hathcock 2004). The principal toxicities of concern associated with excess intakes of vitamin B6 (as pyridoxine hydrochloride) are neuronal damage and sensory and motor effects, which have been reported in humans and animals. In the rat, neurotoxicity due to pyridoxine was dose and duration dependent (Krinke and Fitzgerald 1988). Rats administered single high doses (1200 mg/kg) of pyridoxine were observed to have neuronopathy (damage to the cell body), whereas those administered lower chronic doses (200 mg/kg for 12 weeks) were observed to have axonopathy to the distal portion of sensory nerves.

[5] *Acute toxicity* refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). Endpoints captured in acute toxicity studies usually include mortality and gross clinical observations. Acute toxicity data are usually superseded by data obtained from longer term toxicity studies.

When used in large doses in rats and dogs, pyridoxine (1-7 g/kg) results in pronounced ataxia, weakness and degeneration of the spinal cord roots, posterior ganglia, and peripheral nerves. Doses up to 1g/kg were tolerated in rats, rabbits, and dogs (Unna 1954). An overview of acute toxicity findings is shown in Table 1 below.

Table 1. Acute toxicity data for PLP [6]

Species	Test	Route	Reported Dose	Effect	Source
cat	LD_{50}	intramuscular	250 mg/kg	gastrointestinal: changes in structure or function of salivary glands; hypermotility, diarrhea behavioral: convulsions or effect on seizure threshold	Kraft et al. (1961)
mouse	LD_{50}	oral	4640 mg/kg	behavioral: convulsions, effect on seizure threshold other: dyspnea of lungs, thorax, or respiration	Kraft et al. (1961)
mouse	LD_{50}	subcutaneous	870 mg/kg	behavioral: convulsions; effect on seizure threshold other: dyspnea of lungs, thorax, effects on respiration	Kraft et al. (1961)
rat	LD_{50}	oral	5900 mg/kg	behavioral: excitement; convulsions or effect on seizure threshold	Kraft et al. (1961)
rat	LD_{50}	subcutaneous	850 mg/kg	behavioral: excitement, convulsions or effect on seizure threshold	Kraft et al. (1961)

d. Repeat dose toxicity[7]

Overdosing of vitamin B6 results in species-specific toxicities (Xu et al. 1989). Briefly, the toxicity most often observed consisted of neuronal abnormalities, which were observed in the following species when administered high doses of pyridoxine: rats (600-1200 mg/kg/day for 6-10 days), guinea pigs (1800 mg/kg/day for 10 days), and mice (1800 mg/kg/day for 7 days; 1200 mg/kg/day for 6 weeks; other studies tested higher doses covering shorter time periods). Neuropathy with necrosis of sensory neurons in dorsal root ganglia, accompanied by axonal atrophy and breakdown of peripheral and central sensory axons, was observed in rats. Lower doses in rats (150-300 mg/kg/day) exposed to vitamin B6 for up to 12 weeks produced minor effects to the dorsal root ganglia and neuropathy with axonal atrophy and degeneration. Mice

[6] Adapted from https://chem.nlm.nih.gov/chemidplus/rn/41468-25-1#toxicity, viewed July 13, 2018.
[7] *Repeat-dose toxicity* studies consist of in vivo animal studies that seek to evaluate the toxicity of the test substance by observing the changes that emerge in clinical observations, clinical chemistry, gross pathology, and histology endpoints when the test substance is repetitively administered daily for a predetermined period of time.

were resistant to such changes. Rats dosed with 2.5 mg/kg vitamin B6 for three generations did not have any toxicities (Unna 1954).

Below is a brief overview of the available toxicity data conducted with various vitamin B6 compounds in different species:

- Dosing of single doses of pyridoxine in rats (25mg/kg), dogs (20 mg/kg), and monkeys (10mg/kg) did not show any toxic signals or pathological changes in examined tissues (Unna 1954).
- Rats fed a diet containing between 7-2100 mg/kg of pyridoxine in their diet (equivalent to approximately 0.28-84 mg vitamin B6/kg body weight/day) for 7 weeks experienced attenuation of a startle response which represents a central nervous system reflex (Schaeffer 1993).
- In the dog, a comparison of the available data on exposure to vitamin B6 indicates a possible inverse relationship between dose and time to effect.
    - Krinke et al. (1981) reported on the effects of the oral administration of pyridoxine (300 mg/kg/day for 78 days) on beagle dogs. Animals developed swaying gait within 4 to 9 days of start of treatment and severe ataxia between 8-30 days. Morphological examination of affected dogs revealed widespread neuronal degeneration in the dorsal root ganglia and the Gasserian ganglia, degeneration of sensory nerve fibers in peripheral nerves, in dorsal columns of the spinal cord, and in the descending spinal tract of the trigeminal nerve.
    - Phillips et al. (1978) administered pyridoxine hydrochloride orally in gelatin capsules (0, 50 or 200 mg/kg/day) to 3 groups of female beagle dogs (4 in the control group, and 5 per treatment group) for 100-112 days. Four of the 5 animals in the high dose group (200 mg/kg/day) showed ataxia and loss of balance after 45 days of treatment, whereas the rest of the animals showed clinical signs after 75 days. Histological examination of tissues at termination showed bilateral loss of myelin and axons in the dorsal funiculi and loss of fibers in the dorsal roots. Animals in the low dose group (50 mg/kg/day) showed no clinical signs, but histological examination revealed loss of myelin in the dorsal nerve roots in all five dogs.
    - Hoover and Carlton (1981) reported that all dogs (5 male and 5 female) treated with 150 mg pyridoxine/kg/day for 100-112 days developed neurologic disease characterized by ataxia involving predominantly the hind limbs at first, followed by the fore limbs. Tests of postural reactions reflected proprioceptive abnormalities. Hind limb flexor reflexes were mildly reduced in two dogs and pain perception (pinprick) was mildly reduced in four. However, all dogs remained alert and cranial nerve and the ophthalmologic tests did not show any abnormalities.

e. Genotoxicity[8]

No information was found for the genotoxicity of PLP.

f. Developmental and reproductive toxicity[9]

In normal pregnant rats, about 15% of an intraperitoneal dose of PN is initially taken up by the uterus, placenta, and fetus, suggesting a direct transport of PLP to the fetus (Contractor and Shane 1971).

The effects of vitamin B6 administration on spermatogenesis has been described in several animal studies (Mori et al. 1989; Kaido et al. 1991; Ide et al. 1992; Mori et al. 1992). Administration of vitamin B6 (125-1000 mg/kg/day) injected intraperitoneally to rats for 6 weeks resulted in a decrease in the weight of the epididymides and a decrease in the number of sperm (Mori et al. 1989; Mori et al. 1992).

Daily oral doses of between 20-80 mg pyridoxine/kg to pregnant rats during gestation days 6-15 did not produce any evidence of teratogenicity in the offspring (Khera 1975). No changes were seen in the number of implantations, corpora lutea or number of live pups. At higher doses (100-800 mg/kg), the number of implantations, live pups and corpora lutea in treated animals were increased in comparison with controls. However, doses of either 400 or 800 mg/kg significantly reduced the body weights of the pups.

No data exist for effect of PLP on female fertility or on pre- and postnatal development.

g. Carcinogenicity[10]

Long-term studies in animals to evaluate the carcinogenic potential of PLP have not been performed.

Conclusions: PLP is one of the naturally occurring forms of Vitamin B_6, which includes PN, PNP, PL, PLP, PM, and PMP. Exposure to high doses of vitamin B6 is associated with neuronal abnormalities which included dose related neuronal abnormalities as seen in several

[8] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems.

[9] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects in humans of both sexes and include females from various age groups that will be exposed to the proposed substance. *Developmental toxicity* or *teratogenicity* refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth.

[10] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to result in tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life.

species (dogs, rats, guinea pigs, and mice). In rats, neuropathy with necrosis of sensory neurons in dorsal root ganglia, accompanied by axonal atrophy and breakdown of peripheral and central sensory axons, was observed. Toxicities observed in dogs dosed with pyridoxine included widespread neuronal degeneration in the dorsal root ganglia and the Gasserian ganglia, and degeneration of sensory nerve fibers in peripheral nerves in dorsal columns of the spinal cord and in the descending spinal tract of the trigeminal nerve. At high doses, vitamin B6 resulted in a decrease in the weight of the epididymides and a decrease in the number of sperm in male rats. Exposure to pyridoxine during the mid-gestational period in rats did not result in fetal toxicities. No data were found for the potential genotoxicity or carcinogenicity of PLP.

2. Human safety

The following databases were consulted in the preparation of this section: PubMed, Embase, Web of Science, and ClinicalTrials.gov.

a. Reported adverse reactions (FAERS, CAERS)

FAERS

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for PLP and related terms for the period of January 2000 to May 2017. Twenty cases were identified.

Twelve of the 20 cases were likely related to concomitant medication or underlying disease states and do not suggest an association with PLP. The cases included six cases related to isoniazid or rifampin hepatotoxicity, thrombocytopenia/neutropenia related to rifampin, breast cancer complications, liver injury with lapatinib, and pneumonia and influenza related Reye's syndrome.

Eight of the 20 cases were not assessable because of limited information available in the cases, including 7 literature reports. These eight cases did not provide adequate details for causality assessment. Six deaths were reported but none appeared to be related to PLP.

CAERS

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for adverse events associated with PLP and dietary supplements on June 14, 2018 and retrieved 98 reports. There were no deaths reported. The patient in each case visited an emergency department and/or was hospitalized, most for serious events. Use of multiple ingredient supplements was reported in each case so the relationship between the event and PLP cannot be established.

b. Clinical trials assessing safety

Most of the clinical trials evaluating pyridoxine or PLP included dosing close to the recommended daily dose or slightly higher amounts. Pyridoxine and PLP are well tolerated in this dose range. We found one study where eleven patients with schizophrenia or schizoaffective disorder were treated with vitamin B6 at 1200 mg/day orally for 12 weeks. There was no report of safety endpoints in the publication (Miodownik et al. 2007).

c. Published case reports

The principal toxicity of concern associated with excessive ingestion of vitamin B6 (as pyridoxine hydrochloride) is neuronal damage, as well as sensory and motor effects, which has been reported in humans and animals (Food and Nutrition Board 1998; Food and Nutrition Board 2000). A similar affect would be expected for high doses of PLP.

In a case series of seven patients ingesting large doses of PN, peripheral neuropathy presented as a gradual progressive sensory ataxia and a distal limb impairment of position and vibratory senses (Schaumburg et al. 1983). Touch, temperature and pain were less affected. The daily dose ranged from two to six grams per day and symptoms presented after 2 months to 40 months. Once the pyridoxine was stopped, symptoms resolved gradually.

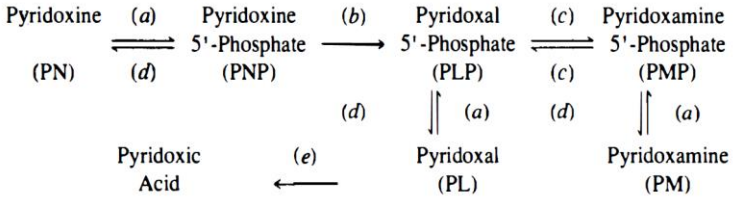
Other cases reported in the literature included:

- An 8-year boy with PNPO deficiency related to a mutation in the PNPO gene and a diagnosis of mild hemophilia A developed multiple spontaneous hemarthrosis after his PLP dose was increased (up to 43 mg/kg/day; 1050 mg/day) for better seizure control. It was determined that the higher PLP dose interfered with platelet function. High doses of PLP can interfere with platelet function (van Wyk et al. 1992; Borst and Tchapyjnikov 2018).
- Painful and disfiguring dermatological lesions were reported in humans after consumption of 2 to 4 g/day of pyridoxine for more than 1 year (Friedman et al. 1986; Schaumburg and Berger 1988). However, the limited data fail to demonstrate a relationship between this endpoint and the dose or duration of treatment. The mechanism of pyridoxine dermatoses remains unclear (Schaumburg and Berger 1988).
- A retrospective review of children receiving oral PLP reported that 2 patients developed gastrointestinal symptoms, diarrhea in one and vomiting/epigastric pain in the other, which prompted discontinuing the PLP (Cortes-Saladelafont et al. 2016).

d. Pharmacokinetic data

The hydrolysis of PLP to PL and PMP to PM occurs in the intestinal lumen and is catalyzed by intestinal phosphatases. The non-phosphorylated forms of vitamin B6 (PL, PM, and PN) are the absorbed forms of vitamin B6. Absorption of these forms is rapid (PL, 40%; PN, 23%; and PM, 18% within 10 min) in humans (Ink and Henderson 1984). The various forms of vitamin B6 (pyridoxine, pyridoxal, and pyridoxamine) can be enzymatically converted into each other as shown below (Holtz and Palm 1964).

The metabolism of B6 vitamers in animals is shown below:



The enzymes involved are (*a*) PL kinase, (*b*) PMP (PNP) oxidase, (*c*) amino-transferase, (*d*) phosphatase, and (*e*) PL oxidase; aldehyde dehydrogenase.

The European Food Safety Authority (European Food Safety Authority 2008) and the Expert Group on Vitamins and Minerals panel (Expert Group on Vitamins and Minerals 2003) have reported on the pharmacokinetic aspects of PLP.

The bioavailability of vitamin B_6 requires hydrolysis through the action of alkaline phosphatases of the phosphate group before absorption through the intestinal layer may occur. Once vitamin B_6 in food is dephosphorylated in the intestinal lumen, PN, PL, and PM are taken up from the small intestine by an energy dependent process (Merrill and Henderson 1990). The three forms, PN, PL, and PM, are converted to PLP in the tissues (Expert Group on Vitamins and Minerals 2003).

PLP is the metabolically active phosphorylated form of vitamin B_6. The phosphorylation of vitamin B_6 to PLP is catalyzed by pyridoxal kinase which is found in all cells with the liver being the major site for its oxidation (Expert Group on Vitamins and Minerals 2003; European Food Safety Authority 2008).

The EFSA Panel concluded in their opinion paper that bioavailability and safety of PLP will not be significantly different from those of other forms of vitamin B_6. As a result, the EFSA determined that the safe upper limit level of vitamin B_6 is identical to that of PLP (European Food Safety Authority 2008).

The plasma concentrations of PL and its phosphate form rise rapidly after a single oral dose of PL, followed by a rapid decrease in PL levels due to tissue uptake and phosphorylation. Blood levels decrease to baseline levels within 12 hours of exposure (Speitling et al. 1990).

Metabolism: The liver and intestines, where B6 vitamers are metabolized, are very active organs. When PN is taken up by these cells, it is rapidly acted on by PL kinase and then converted to PLP by pyridoxine phosphate oxidase. These two enzymes along with phosphohydrolase convert dietary PN to circulating PL, which can then serve as a source of the coenzyme PLP in all tissues that contain pyridoxal kinase, whether they contain PNP oxidase or not (Ink and Henderson 1984).

Excretion: In humans, excess PN is mainly metabolized to 4-pyridoxic acid, which is eliminated mostly unchanged in the urine. Following oral administration of PL, PM, or PN (100 mg doses) in humans, most of the ingested dose is found unchanged in the urine (36 hours after dosing).

When physiological doses are given, most of the excretion of pyridoxic acid occurs within 3 hours after dosing (Ink and Henderson 1984).

A schematic overview of the metabolic profile of PLP is shown in Appendix 1 (Ebadi et al. 1982).

Drugs that can react with carbonyl groups have the potential to interact with PLP. Isoniazid, which is used in the treatment of tuberculosis, and L-DOPA, which is metabolized to dopamine, have been reported to reduce plasma PLP concentrations (Bhagavan 1985; Weir et al. 1991).

Some studies have reported decreases in vitamin B6 status indicators in women receiving high-dose oral contraceptives (Shane and Contractor 1975; Rose 1978).

e. Availability of alternative approved therapies that may be as safe or safer

There are numerous drugs approved for the treatment of seizure disorders. They are often used in the initial efforts to control seizures in both neonates and adults. They are associated with side effects, some serious, that are balanced against their effectiveness in the treatment and prevention of seizures. In neonates with a suspected diagnosis of PNPO deficiency, PLP may be administered prior to genetic testing or when a neonate with seizures fails to adequately respond to anti-epileptic medications.

Conclusions:
PLP is generally a safe substance at doses within the recommended daily dose, but may be associated with peripheral nerve injury at higher doses.

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, EMBASE, and Web of Science.

1. *Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance*

The following excerpt related to pyridoxine dependent epilepsy is from the World Health Organization guidelines for that treatment of neonatel seizures (World Health Organization 2011).

Empirical pyridoxine treatment

Pyridoxine dependent epilepsy is a rare disease with an incidence of definite and probable cases of 1:396,000 (Been et al., 2005) compared to the overall incidence of NS between 1:71 to 1:1000. Other treatable neonatal epileptic encephalopathies with metabolic causes, such as pyridoxal-phosphate dependent epilepsy probably are even less frequent; only case reports and small series of patients have been published and an incidence cannot be calculated. Diagnosis of pyridoxine dependent epilepsy can be established clinically by a positive response to treatment with pyridoxine. Failure to diagnose this condition may have deleterious effects on affected neonates, but delay in treatment of other underlying etiologies may also cause harm. A benefit *vs.* harm ratio cannot be calculated.

The General Pharmacology section of this memo described the condition known as Pyridoxal-5'-Phosphate Dependent Epilepsy which is caused by PNPO deficiency. According to the National Institutes of Health (NIH), PLP-dependent epilepsy is a rare genetic metabolic disorder that involves seizures beginning soon after birth, or in some cases, before birth. Anticonvulsants are ineffective in this group of patients. Instead, patients are treated with large doses of PLP (NIH Genetics Home Reference 2008; NIH Genetics and Rare Diseases Information Center 2016). According to Blau et al. (2014), PLP-dependent epilepsy is treated with 30-60 mg/kg/day of PLP given in 4-6 single doses as an oral suspension. Currently, Nationwide Children's Hospital, located in Columbus, OH, has a recipe on their website for a compounded 25 mg/mL oral suspension of PLP (Nationwide Children's 2018).

There are numerous summary articles in the literature describing pyridoxine dependent seizures and the effectiveness of PLP in the treatment of patients with PNPO deficiency but the number of cases are few. Treatment with PLP is essential to reduce the seizures and prevent irreversible neurologic injury. Although some of the cases are identified shortly after birth, the following case illustrates a later diagnosis

> A case report of female patient who developed intractable seizures shortly after birth. She had a normal cranial ultrasound and EEG showed generalized burst suppression. The patient was treated with pyridoxine, carnitine, phenobarbital, phenytoin, topiramate and thiopental infusion but seizures persisted. The patient died at 31 days of age from gram negative sepsis. Post mortem sequence analysis of the coding region of the PNPO gene was conducted and a homozygous missense mutation was identified.
>
> The patient had an older brother, age 3, who had treatment resistant, pyridoxine non-responsive epilepsy starting 48 hours after birth. He had severely delayed psychomotor development and almost constant "epileptic phenomena." He had sequence analysis testing of the PNPO gene and he was found to have a homozygous missense mutation. He was treated with PLP 50 mg/kg/day which "markedly reduced seizure activity" (Bagci et al. 2009). The testing of these

children was done shortly after the first cases of PNPO deficiency was reported. There are likely unreported cases of PNPO deficiency but this case is supportive of the effectiveness of PLP in PNPO deficiency.

The use of PN or PLP for the treatment of seizures in adults is not generally recommended. There are some reports, however, suggesting that a deficiency of vitamin B6 may contribute to seizures refractory to treatment under certain circumstances (Dave et al. 2015; Lee et al. 2015). In these cases, supplementation with PN or PLP may improve the response to antiseizure medication

2. *Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease*

Pyridoxine deficient epilepsies, including PNPO deficiency, are serious diseases, and if left untreated can result in significant neurological deficits.

3. *Whether there are any alternative approved therapies that may be as effective or more effective*

As stated above, there are other therapies that are approved for the treatment of epilepsy. However, typically, patients with pyridoxine deficient epilepsies have inborn errors of metabolism and have failed to control the seizures with other FDA approved, conventional anti-seizure medications.

Conclusions:
PNPO deficiency leading to neonatal seizures is a rare condition that may be responsive to therapy with PLP.

D. Has the substance been used historically as a drug in compounding?

Databases searched for information on PLP monohydrate in Section II.D. of this consultation included PubMed, Natural Medicines, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and Google.

1. *Length of time the substance has been used in pharmacy compounding*

PLP has been used in pharmacy compounding since at least 2010 (Nationwide Children's 2018).

2. *The medical condition(s) it has been used to treat*

Results from a Google search using the terms *pyridoxal-5-phosphate compounding pharmacy* indicate that PLP is/has been compounded as an oral suspension, an injectable, and a transdermal.

As described above, PLP is used to treat PLP-dependent epilepsy and at least one pediatric hospital has a recipe on their website for a compounded 25 mg/mL oral suspension of PLP (Nationwide Children's 2018).

According to an article published in American Pharmacist,[11] vitamins and minerals, including PLP, are commonly compounded for pediatric patients as an adjunct therapy for autism spectrum disorders (Heitman 2014). Based on a Google search, at least one pharmacy offers transdermal pyridoxal-5-phosphate for pediatric patients with autism spectrum disorder.

3. How widespread its use has been

Insufficient data are available from which to draw conclusions about the extent of use of PLP in compounded drug products.

4. Recognition of the substance in other countries or foreign pharmacopeias

A search of the British Pharmacopoeia (BP 2018), the European Pharmacopoeia (9th Edition, 2018, 9.4), and the Japanese Pharmacopoeia (16th Edition) did not show any monograph listings for "pyridoxal-5-phosphate monohydrate." From a review of PN and PLP dependent epilepsies (Plecko 2013), the following was noted: "PLP is unlicensed outside of Japan and only available as an oral, chemical powder from naturopathic stores or via pharmaceutical companies."

Conclusions: PLP is used as for the treatment of pyridoxal-5-phosphate-dependent epilepsy. In addition, it appears that transdermal PLP is compounded for use in pediatric patients with autism spectrum disorder. PLP has been used in pharmacy compounding since at least 2010.

III. RECOMMENDATION

We have balanced the criteria described in section II above to evaluate pyridoxal-5-phosphate monohydrate for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs in favor of*** pyridoxal-5-phosphate monohydrate (intravenous and oral dosage forms) being placed on that list based on the following:

1. PLP is well characterized and stable.

2. The available data indicate that PLP is a relatively safe substance at doses within the range of the recommended daily intake. High doses may be associated with peripheral neuronal disease.

3. Published reports have indicated that neonatal seizures related to PNPO deficiency may be responsive to PLP.

4. Information about the history of compounding is limited, but it is evident that the use of this substance for the treatment of neonatal seizures would have required a

[11] According to the website https://www.ncpanet.org/newsroom/america%27s-pharmacist, American Pharmacist is the official magazine of the National Community Pharmacists Association (NCPA).

compounded substance. PLP has been used in pharmacy compounding since at least 2010.

Based on this information the Agency has considered, a balancing of the four evaluation criteria ***weighs in favor of*** pyridoxal-5-phosphate monohydrate (intravenous and oral dosage forms) being added to the 503A Bulks List.

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Appendix 1. Metabolic Profile of PLP (Ebadi et al. 1982)

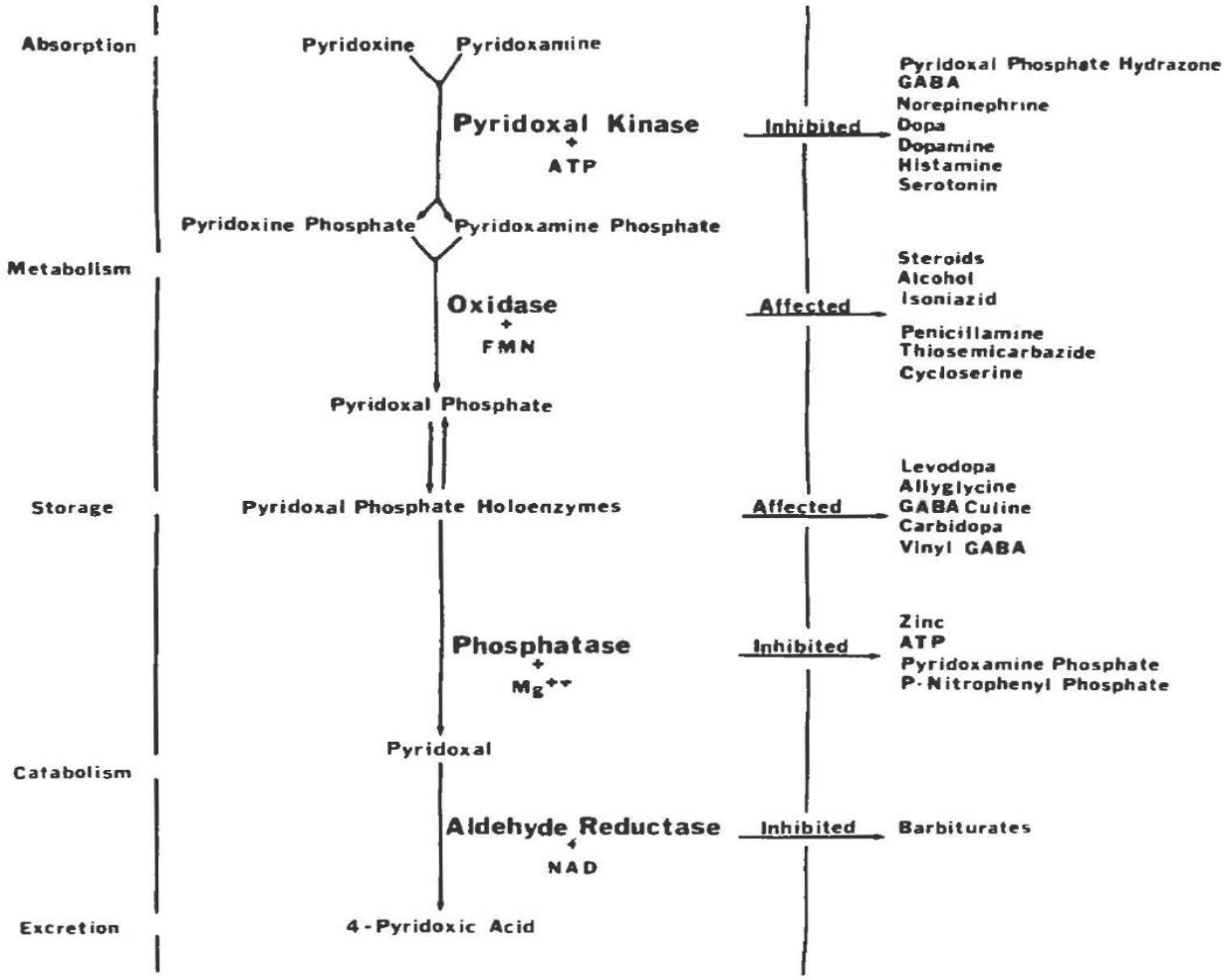

Fig. 1. The pharmacokinetics of pyridoxine and the synthesis of pyridoxal phosphate. Drugs may alter the metabolism and function of pyridoxal phosphate by inhibiting the activity of pyridoxal kinase, such as levodopa (Ebadi and Govitrapong, 1979a); by inhibiting the binding of pyridoxal phosphate to apoenzymes and/or proteins, such as alcohol (Lumeng, 1978; Shane, 1982); by inhibiting the activity of L-aromatic amino acid decarboxylase, which requires pyridoxal phosphate, such as carbidopa (Sandler, 1980); by inhibiting the activity of pyridoxal phosphate phosphatase, such as zinc (Ebadi and Govitrapong, 1979b); and by inhibiting the activity of aldehyde reductase, such as barbiturates (Erwin et al., 1971).

Tab 5

Quercetin Dihydrate

Tab 5a

Quercetin Dihydrate Nominations

Alliance for Natural Health USA
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INTERNATIONAL
anhinternational.org

September 30, 2014

VIA ELECTRONIC SUBMISSION

Division of Dockets Management [HFA-305]
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: 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

Docket No. FDA-2013-N-1525

Dear Sir/Madam:

The Alliance for Natural Health USA ("ANH-USA") submits this comment on the Notice: "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" published in the Federal Register of July 2, 2014 by the Food and Drug Administration ("FDA" or the "Agency").

ANH-USA appreciates this opportunity to comment on the list of bulk drug substances that may be used to compound drug products pursuant to Section 503A of the FD&C Act ("FDCA"), 21 U.S.C. §353a (hereinafter the "503A List"). This list of ingredients is crucial to patients who require compounded substances, in particular those substances that are available only across state lines. ANH-USA therefore write to request that the Agency:

A) Extend the deadline for nominations by at least 90 days;
B) Maintain the 1999 List; and
C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List.

As discussed in detail below, in the interest compiling a comprehensive 503B List, more time is needed to provide the required information. This will benefit both FDA, by reducing the subsequent number of petitions for amendments, and consumers, by allowing continued access to important substances.

Organizational Background of Commenter Alliance for Natural Health USA

ANH-USA is a membership-based organization with its membership consisting of healthcare practitioners, food and dietary supplement companies, and over 335,000 consumer advocates. ANH-USA focuses on the protection and promotion of access to healthy foods, dietary nutrition, and natural compounded medication that consumers need to maintain optimal health. Among ANH-USA's members are medical doctors who prescribe, and patients who use, compounded medications as an integral component of individualized treatment plans.

ANH-USA's Request and Submissions Regarding Docket No. FDA-2013-N-1525

A) Extend the deadline for nominations by at least 90 days

This revised request for nominations follows the initial notice published in the Federal Register of December 4, 2013. Like the initial notice, this revised request provides only a 90 day response period. However, FDA is requiring more information than it sought originally and yet providing the same amount of time for the submission of nominations. The September 30, 2014 deadline for such a complex and expansive request is unreasonably burdensome and woefully insufficient.

The task set forth by FDA to nominate bulk drug substances for the 503A List places an undue burden on those who are responding. The Agency requires highly technical information for each nominated ingredient, including data about the strength, quality and purity of the ingredient, its recognition in foreign pharmacopeias and registrations in other countries, history with the USP for consideration of monograph development, and a bibliography of available safety and efficacy data, including any peer-reviewed medical literature. In addition, FDA is requiring information on the rationale for the use of the bulk drug substance and why a compounded product is necessary.

For the initial request for nomination, it was estimated that compiling the necessary information for just one nominated ingredient would require five to ten hours. With the revised request requiring more information, the time to put together all of the data for a single nomination likely will be higher. Given that it is necessary to review all possible ingredients and provide the detailed support, or risk losing important therapeutic ingredients, this task requires more time than has been designated by the Agency. While ANH-USA recognizes there will be additional opportunities to comment and petition for amendments after the 503A List is published, the realities of substances not making the list initially makes this request for more time imperative. For example, if a nomination for a substance cannot be completed in full by the current September 30, 2014 deadline, doctors and patients will lose access to such clinically important substances and face the

administrative challenges in obtaining an ingredient listing once the work of the advisory committee is completed. There is no regulatory harm in providing additional time to compile a well-researched and comprehensive initial 503A List.

B) Rescind the withdrawal of the ingredient list published on January 7, 1999

In the revised request for nomination, the Agency references in a footnote its withdrawal of the proposed ingredient list that was published on January 7, 1999. ANH-USA argued against this in its March 4, 2014 comment and would like to reiterate its opposition to the withdrawal. There is no scientific or legal justification to require discarding the work that lead to the nominations and imposing the burden on interested parties to begin the process all over again.

C) Accept the ingredients set forth herein and in the attached submissions as nominations for inclusion in the 503A List

ANH-USA submits the following ingredients for nomination for the 503B list:

1. The attached Excel spreadsheets for 21 nominated ingredients prepared by IACP in support of its petition for the nomination of these ingredients; and
2. The submissions for Copper Hydrosol and Silver Hydrosol from Natural Immunogenics Corp.,[1] with their Canadian Product Licenses as proof of safety and efficacy.

In conclusion, Alliance for Natural Health USA requests that FDA provide a more realistic time frame, adding at least 90 days to the current deadline; rescind the withdrawal of the ingredient list published on January 7, 1999; and accept the ingredient nominations for approval for use.

Sincerely,

Gretchen DuBeau, Esq.
Executive and Legal Director
Alliance for Natural Health USA

[1] As of October 1, 2014, the address for Natural Immunogenics Corp. will be 7504 Pennsylvania Ave., Sarasota, FL 34243.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Quercetin
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please search for keyword: Quercetin.
Is the ingredient listed in any of the three sections of the Orange Book?	No.
Were any monographs for the ingredient found in the USP or NF monographs?	Dietary Supplement monograph in USP
What is the chemical name of the substance?	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H -1-benzopyran-4-one
What is the common name of the substance?	Quercetin
Does the substance have a UNII Code?	53B03V78A6 (Quercetin dihydrate)
What is the chemical grade of the substance?	Dietary Supplement
What is the streng h, quality, stability, and purity of he ingredient?	A valid Certificate of Analysis accompanies each lot of material received.
How is the ingredient supplied?	Bright yellow to greenish crystal solid.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	WHMIS (Canada): Class D-1B, material causing immediate and toxic effects. DSCL (EEC): R20/22: Harmful by inhalation and if swallow.
Has information been submitted about the substance to the USP for consideration of monograph development?	Dietary Supplement monograph in USP
What dosage form(s) will be compounded using the bulk drug substance?	Oral capsule
What strength(s) will be compounded from the nominated substance?	50 mg to 500 mg per capsule
What are the anticipated route(s) of administra ion of the compounded drug product(s)?	Oral capsule, injection
Are there safety and efficacy data on compounded drugs using the nominated substance?	Select item 25241191 1.Quercetin suppresses insulin receptor signaling through inhibition of the insulin ligand-receptor binding and therefore impairs cancer cell proliferation Wang F, Yang Y. Biochem Biophys Res Commun. 2014 Sep 18. pii S0006-291X(14)01655-6. doi 10.1016/j.bbrc.2014.09.039. [Epub ahead of print] PMID 25241191[PubMed - as supplied by publisher] Related c tations Select item 25211642 2.Direct binding of Bcl-2 fam ly proteins by quercetin triggers its pro-apoptotic activity. Primikyri A, Chatziathanasiadou MV, Karali E, Kostaras E, Mantzaris MD, Hatzimichael E, Shin JS, Chi SW, Briasoulis E, Kolettas E, Gerothanassis IP Tzakos AG. ACS Chem Biol. 2014 Sep 11. [Epub ahead of print] PMID 25211642[PubMed - as supplied by publisher]
Has the bulk drug substance been used previously to compound drug product(s)?	Yes.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Allergenic reactions, Histamine reactions and intolerance, and Food intolerances make up the bulk of the patients who utilize Quercetin. Quercetin can also be used with hypertension, adjunctive cancer treatment, hyperlipidemia, and liver conditions
What is the reason for use of a compounded drug product ra her than an FDA-approved product?	FDA-approved products are: Anti-histamines, oxidase monoamine, cortisone topically or orally. Hypertension- beta blockers, diuretics, ACE inhibitors, calcium channel blockers, etc. High Cholesterol- statins. antihistamines often do not relieve chronic allergies,patients develop tolerance or adverse side effects. Quercetin can stabilize mast cells and decrease allergy reactions. It is noted that allergies can permanently improve after a season or two of regular Quercetin dosing. Histamine intolerance cannot be treated with anti-histamines, developing further degradation of the condition. Monoamine oxidase from porcine is an experimental treatment, not readily available but the only treatment available. Quercetin is the a better option available for these patients. Quercetin is safe and has no unknown side effects even at very high doses, derived from food sources.

Is there any other relevant information?	many patients can improve their allergies by improving their diet. **An estimated 20-40% of patients** will use Quercetin at some time in their life to alleviate the annoying symptoms of allergies. **Three to five percent of patients** have histamine intolerance and will benefit from access to Quercetin since they become unresponsive to the available FDA drugs. This is a review of the use of Quercetin in allergy: J Biol Regul Homeost Agents. 2006 Jul-Dec;20(3-4):47-52. Role of quercetin (a natural herbal compound) in allergy and inflammation. Shaik YB1, Castellani ML, Perrella A, Conti F, Salini V, Tete S, Madhappan B, Vecchiet J, De Lutiis MA, Caraffa A, Cerulli G. Its use in allergy is well known and accepted; therefore most newer research is about other topics. Cancer: Nutr Cancer. 2013;65(3):494-504. doi: 10.1080/01635581 2012.725194. Resveratrol and quercetin in combination have anticancer activity in colon cancer cells and repress oncogenic microRNA-27a. Del Follo-Martinez A1, Banerjee N, Li X, Safe S, Mertens-Talcott S. Food Funct. 2014 Aug 28. [Epub ahead of print] Quercetin, a natural dietary flavonoid, acts as a chemopreventive agent against prostate cancer in an in vivo model by inhibiting the EGFR signaling pathway. Firdous AB1, Sharmila G, Balakrishnan S, RajaSingh P, Suganya S, Srinivasan N, Arunakaran J. Blood pressure: Adv Nutr. 2012 Jan;3(1) 39-46. doi: 10 3945/an.111.001271. Epub 2012 Jan 5. Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. Larson AJ1, Symons JD, Jalili T. Hyperlipidemia (High Cholesterol) : PLoS One. 2014 May 23;9(5) e97901. doi: 10.1371/journal.pone.0097901. eCollection 2014. Luteolin and quercetin affect the cholesterol absorption mediated by epithelial cholesterol transporter niemann-pick c1-like 1 in caco-2 cells and rats. Nekohashi M1, Ogawa M1, Ogihara T2, Nakazawa K3, Kato H3, Misaka T4, Abe K5, Kobayashi S1. One of many recent studies demonstrating liver protective constituent of polyphenol in Quercetin: World J Gastroenterol. 2014 Jun 21;20(23):7366-80. doi: 10.3748/wjg.v20.i23.7366.

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525

> "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"

To Whom It May Concern:

The American Association of Naturopathic Physicians (AANP) appreciates the opportunity to address the FDA's request for nominations of bulk drug substances that may be used to compound drug products that are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs.

This is a significant issue for our members and their patients. AANP strongly supports efforts to ensure that the drug products dispensed to patients are safe and effective.

Background: AANP Submissions to Date

On January 30, 2014, we submitted comments to Docket FDA-2013-D-1444, "Draft Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Withdrawal of Guidances" relating to congressional intent in crafting HR 3204. These comments highlighted the fact that, for compounding pharmacies subject to Section 503A, Congress intended that States continue to have the authority to regulate the availability of safely compounded medications obtained by physicians for their patients. As we further noted, compounded medications that are formulated to meet unique patient needs, and that can be administered immediately in the office, help patients receive the products their physicians recommend and reduce the medical and financial burden on both the patient and

doctor that restrictions on office use would impose. Such medications, we emphasized, provide a unique benefit to patients and have an excellent track record of safety when properly produced and stored.

AANP also (on March 4, 2014) nominated 71 bulk drug substances. We identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring. We estimated, at that time, that at least 6 hours per ingredient would be needed to do so – time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP sought a 90-day extension to more completely respond to the Agency's request.

In this renomination, we have narrowed our focus to 42 bulk drug substances that are most important for the patients treated by naturopathic doctors. Twenty-one of these bulk drug substances are formally nominated in the attachments as well as noted by name in this letter. Given the limitations imposed by the fact that our physician members spend the majority of their day providing patient care, however, AANP again found that the span of time the Agency provided for renominations was insufficient to prepare the documentation needed for the remaining 21 bulk drug substances.

We now request that FDA extend the deadline for which comments are due by 120 days, so that we may provide this further documentation. We have determined that as much as 40 hours per ingredient will be needed to do so – time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, AANP respectfully seeks an additional 120-day period for the purpose of gathering this essential information.

Naturopathic Medicine and Naturopathic Physicians

A word of background on our profession is in order. AANP is a national professional association representing 4,500 licensed naturopathic physicians in the United States. Our members are physicians trained as experts in natural medicine. They are trained to find the underlying cause of a patient's condition rather than focusing solely 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 4-year, graduate level programs at institutions recognized through the US Department of Education. There are currently 7 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. 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.

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. Currently, 20 states and territories license NDs to practice.

Naturopathic physicians provide treatments that are effective and safe. Since 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.

Characteristics of Patients Seen by Naturopathic Physicians

Individuals who seek out NDs typically do so because they suffer from one or more chronic conditions that they have not been able to alleviate in repeated visits to conventional medical doctors or physician specialists. Such chronic conditions include severe allergies, asthma, chronic fatigue, chronic pain, digestive disorders (such as irritable bowel syndrome), insomnia, migraine, rashes, and other autoimmune disorders. Approximately three-quarters of the patients treated by NDs have more than one of these chronic conditions. Due to the fact that their immune systems are often depleted, these individuals are highly sensitive to standard medications. They are also more susceptible to the numerous side effects brought about by mass-produced drugs.

Such patients have, in effect, fallen through the cracks of the medical system. This is why they seek out naturopathic medicine. Safely compounded medications – including nutritional, herbal, and homeopathic remedies – prove efficacious to meet their needs every day in doctors' offices across the country. Such medications are generally recognized as safe (GRAS), having been used safely for decades in many cases. As patients' immune function improves, and as they work with their ND to improve their nutrition, get better sleep, increase their exercise and decrease their stress, their health and their resilience improves. This is the 'multi-systems' approach of naturopathic medicine – of which compounded drugs are an essential component.

Bulk Drug Substances Nominated at this Time

Notwithstanding the concerns expressed and issues highlighted in the foregoing, AANP nominates the following 21 bulk drug substances for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A. Thorough information on these substances is presented in the spreadsheets attached with our comments. The documentation is as complete and responsive to the Agency's criteria as we can offer at this time.

The bulk drug substances nominated are:

Acetyl L Carnitine

Alanyl L Glutamine
Alpha Lipoic Acid
Artemisia/Artemisinin
Boswellia
Calcium L5 Methyltetrahydrofolate
Cesium Chloride
Choline Chloride
Curcumin
DHEA
Dicholoroacetic Acid
DMPS
DMSA
Germanium Sesquioxide
Glutiathone
Glycyrrhizin
Methylcobalamin
MSM
Quercitin
Rubidium Chloride
Vanadium

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating the patients of naturopathic doctors. AANP wishes to specify these 21 ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination. The additional bulk drug substances include:

7 Keto Dehydroepiandrosterone
Asparagine
Calendula
Cantharidin
Choline Bitartrate
Chromium Glycinate
Chromium Picolinate
Chrysin
Co-enzyme Q10
Echinacea
Ferric Subsulfate
Iron Carbonyl
Iscador
Pantothenic Acid
Phenindamine Tartrate
Piracetam
Pterostilbene

Pyridoxal 5-Phosphate
Resveratrol
Salicinium
Thymol Iodide

AANP Objects to Unreasonable Burden

AANP believes it necessary and proper to lodge an objection to FDA's approach, i.e., the voluminous data being required in order for bulk drug substances to be considered by the Agency for approval. FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of the persons most knowledgeable about and experienced in the application of compounded medications are either small business owners or busy clinicians, and given the extent and detail of information on potentially hundreds of ingredients as sought by FDA, this burden is unreasonable. The approach has no basis in the purpose and language of the Drug Quality and Security Act ("Act") – particularly for drugs that have been safely used for years, not only with the Agency's implicit acceptance, but without any indication of an unacceptable number of adverse patient reactions.

The volume of data being required in this rulemaking is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) 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 the resources to seek regulatory approvals. The FDA's analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The burden on respondents to this current rulemaking is further aggravated by the FDA's complete absence of consideration of the harm that will be caused if needed drugs are removed from the market. The "Type 2" errors caused by removing important agents from clinical use could far exceed the "Type 1" errors of adverse reactions, particularly given the strong track record of safely compounded medications. The infectious contamination that gave rise to the Act has little to do with the process set out by FDA for determining which ingredients may be compounded. Yet the Agency has offered little consideration of the respective risks and benefits of its approach. Based on the fact that compounding pharmacies and physicians are carrying the full burden of proof, as well as how much time it is likely to take for the process of documentation and evaluation to conclude, the Agency itself may well find that it has caused more harm to patients' clinical outcomes than provided a bona fide contribution to patient safety.

Conclusion

AANP appreciates the Agency's consideration of the arguments and objection presented herein, the request for an extension of time to gather the documentation that FDA is seeking, and the nominations made and referenced at this time.

We look forward to continued dialogue on these matters. As AANP can answer any questions, please contact me (jud.richland@naturopathic.org; 202-237-8150).

Sincerely,

Jud Richland, MPH
Chief Executive Officer

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Quercetin
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please search for keyword: Quercetin.
Is the ingredient listed in any of the three sections of the Orange Book?	No.
Were any monographs for the ingredient found in the USP or NF monographs?	Dietary Supplement monograph in USP
What is the chemical name of the substance?	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H -1-benzopyran-4-one
What is the common name of the substance?	Quercetin
Does the substance have a UNII Code?	53B03V78A6 (Quercetin dihydrate)
What is the chemical grade of the substance?	Dietary Supplement
What is the streng h, quality, stability, and purity of he ingredient?	A valid Certificate of Analysis accompanies each lot of material received.
How is the ingredient supplied?	Bright yellow to greenish crystal solid.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	WHMIS (Canada): Class D-1B, material causing immediate and toxic effects. DSCL (EEC): R20/22: Harmful by inhalation and if swallow.
Has information been submitted about the substance to the USP for consideration of monograph development?	Dietary Supplement monograph in USP
What dosage form(s) will be compounded using the bulk drug substance?	Oral capsule
What strength(s) will be compounded from the nominated substance?	50 mg to 500 mg per capsule
What are the anticipated route(s) of administra ion of the compounded drug product(s)?	Oral capsule, injection
Are there safety and efficacy data on compounded drugs using the nominated substance?	Select item 25241191 1.Quercetin suppresses insulin receptor signaling through inhibition of the insulin ligand-receptor binding and therefore impairs cancer cell proliferation Wang F, Yang Y. Biochem Biophys Res Commun. 2014 Sep 18. pii S0006-291X(14)01655-6. doi 10.1016/j.bbrc.2014.09.039. [Epub ahead of print] PMID 25241191[PubMed - as supplied by publisher] Related c tations Select item 25211642 2.Direct binding of Bcl-2 fam ly proteins by quercetin triggers its pro-apoptotic activity. Primikyri A, Chatziathanasiadou MV, Karali E, Kostaras E, Mantzaris MD, Hatzimichael E, Shin JS, Chi SW, Briasoulis E, Kolettas E, Gerothanassis IP Tzakos AG. ACS Chem Biol. 2014 Sep 11. [Epub ahead of print] PMID 25211642[PubMed - as supplied by publisher]
Has the bulk drug substance been used previously to compound drug product(s)?	Yes.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Allergenic reactions, Histamine reactions and intolerance, and Food intolerances make up the bulk of the patients who utilize Quercetin. Quercetin can also be used with hypertension, adjunctive cancer treatment, hyperlipidemia, and liver conditions
What is the reason for use of a compounded drug product ra her than an FDA-approved product?	FDA-approved products are: Anti-histamines, oxidase monoamine, cortisone topically or orally. Hypertension- beta blockers, diuretics, ACE inhibitors, calcium channel blockers, etc. High Cholesterol- statins. antihistamines often do not relieve chronic allergies,patients develop tolerance or adverse side effects. Quercetin can stabilize mast cells and decrease allergy reactions. It is noted that allergies can permanently improve after a season or two of regular Quercetin dosing. Histamine intolerance cannot be treated with anti-histamines, developing further degradation of the condition. Monoamine oxidase from porcine is an experimental treatment, not readily available but the only treatment available. Quercetin is the a better option available for these patients. Quercetin is safe and has no unknown side effects even at very high doses, derived from food sources.

Is there any other relevant information?	many patients can improve their allergies by improving their diet. **An estimated 20-40% of patients** will use Quercetin at some time in their life to alleviate the annoying symptoms of allergies. **Three to five percent of patients** have histamine intolerance and will benefit from access to Quercetin since they become unresponsive to the available FDA drugs. This is a review of the use of Quercetin in allergy: J Biol Regul Homeost Agents. 2006 Jul-Dec;20(3-4):47-52. Role of quercetin (a natural herbal compound) in allergy and inflammation. Shaik YB1, Castellani ML, Perrella A, Conti F, Salini V, Tete S, Madhappan B, Vecchiet J, De Lutiis MA, Caraffa A, Cerulli G. Its use in allergy is well known and accepted; therefore most newer research is about other topics. Cancer: Nutr Cancer. 2013;65(3):494-504. doi: 10.1080/01635581 2012.725194. Resveratrol and quercetin in combination have anticancer activity in colon cancer cells and repress oncogenic microRNA-27a. Del Follo-Martinez A1, Banerjee N, Li X, Safe S, Mertens-Talcott S. Food Funct. 2014 Aug 28. [Epub ahead of print] Quercetin, a natural dietary flavonoid, acts as a chemopreventive agent against prostate cancer in an in vivo model by inhibiting the EGFR signaling pathway. Firdous AB1, Sharmila G, Balakrishnan S, RajaSingh P, Suganya S, Srinivasan N, Arunakaran J. Blood pressure: Adv Nutr. 2012 Jan;3(1) 39-46. doi: 10 3945/an.111.001271. Epub 2012 Jan 5. Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. Larson AJ1, Symons JD, Jalili T. Hyperlipidemia (High Cholesterol) : PLoS One. 2014 May 23;9(5) e97901. doi: 10.1371/journal.pone.0097901. eCollection 2014. Luteolin and quercetin affect the cholesterol absorption mediated by epithelial cholesterol transporter niemann-pick c1-like 1 in caco-2 cells and rats. Nekohashi M1, Ogawa M1, Ogihara T2, Nakazawa K3, Kato H3, Misaka T4, Abe K5, Kobayashi S1. One of many recent studies demonstrating liver protective constituent of polyphenol in Quercetin: World J Gastroenterol. 2014 Jun 21;20(23):7366-80. doi: 10.3748/wjg.v20.i23.7366.

ACAM
American College for Advancement in Medicine

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www.acam.org

September 30, 2014

Division of Dockets Management (HFA-305)
Food And Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Re: Docket FDA-2013-N-1525

"Bulk Drug Substances That May Be Used to compound Drug Products in Accordance With Section 503A of Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations"

To Whom It May Concern:

The American College for Advancement in Medicine (ACAM) is a prominent and active medical education organization involved in teaching physicians in the proper use of oral and intravenous nutritional therapies for over forty years. We have also been involved in clinical research sponsored by the National Heart Lung and Blood Institute. As such, we have a vested interest in maintaining the availability of compounded drug products.

We appreciate the opportunity to address the FDA's request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products. To meet what appear to be substantial requirements involved in this submittal, the FDA has given compounding pharmacists (in general a small business operation) and physicians very limited time to comply with onerous documentation. The Agency has requested information for which no single pharmacy or physician organization can easily provide in such a contracted time frame. As such this time consuming process requires significant coordination from many practicing professionals for which adequate time has not been allotted.

This issue is of great importance and has the potential to drastically limit the number of available compounded drugs and drug products thus limiting the number of individualized treatments that compounded medicines offer to patients.
ACAM and its physician members have not had the time to collect, review and assess all documentation necessary to submit for the intended list of compounded drugs required to assure all patient therapies are represented in our submission. We respectfully seek an additional 120 day period to educate and coordinate our physicians on the issue at hand and to gather the essential information necessary to provide the Agency with the most comprehensive information.
In an attempt to comply with the current timeframe established, a collaborative effort resulted in the attached nominations prepared for bulk drug substances that may be used in pharmacy compounding under Section 503A.

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It is not clear whether the current submission will be the final opportunity to comment or communicate with the Agency. Will a deficiency letter be provided if the initial nomination information was inadequate or will a final decision to reject a nominated substance be made without the opportunity to further comment? ACAM respectfully requests that the FDA issue a deficiency letter should the submitted documentation for a nomination be considered inadequate.

Sincerely,

Neal Speight, MD
(Immediate Past President) for
Allen Green, MD
President and CEO
The American College for Advancement in Medicine

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Quercetin
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please search for keyword: Quercetin.
Is the ingredient listed in any of the three sections of the Orange Book?	No.
Were any monographs for the ingredient found in the USP or NF monographs?	Dietary Supplement monograph in USP
What is the chemical name of the substance?	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H -1-benzopyran-4-one
What is the common name of the substance?	Quercetin
Does the substance have a UNII Code?	53B03V78A6 (Quercetin dihydrate)
What is the chemical grade of the substance?	Dietary Supplement
What is the streng h, quality, stability, and purity of he ingredient?	A valid Certificate of Analysis accompanies each lot of material received.
How is the ingredient supplied?	Bright yellow to greenish crystal solid.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	WHMIS (Canada): Class D-1B, material causing immediate and toxic effects. DSCL (EEC): R20/22: Harmful by inhalation and if swallow.
Has information been submitted about the substance to the USP for consideration of monograph development?	Dietary Supplement monograph in USP
What dosage form(s) will be compounded using the bulk drug substance?	Oral capsule
What strength(s) will be compounded from the nominated substance?	50 mg to 500 mg per capsule
What are the anticipated route(s) of administra ion of the compounded drug product(s)?	Oral capsule, injection
Are there safety and efficacy data on compounded drugs using the nominated substance?	Select item 25241191 1.Quercetin suppresses insulin receptor signaling through inhibition of the insulin ligand-receptor binding and therefore impairs cancer cell proliferation Wang F, Yang Y. Biochem Biophys Res Commun. 2014 Sep 18. pii S0006-291X(14)01655-6. doi 10.1016/j.bbrc.2014.09.039. [Epub ahead of print] PMID 25241191[PubMed - as supplied by publisher] Related c tations Select item 25211642 2.Direct binding of Bcl-2 fam ly proteins by quercetin triggers its pro-apoptotic activity. Primikyri A, Chatziathanasiadou MV, Karali E, Kostaras E, Mantzaris MD, Hatzimichael E, Shin JS, Chi SW, Briasoulis E, Kolettas E, Gerothanassis IP Tzakos AG. ACS Chem Biol. 2014 Sep 11. [Epub ahead of print] PMID 25211642[PubMed - as supplied by publisher]
Has the bulk drug substance been used previously to compound drug product(s)?	Yes.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Allergenic reactions, Histamine reactions and intolerance, and Food intolerances make up the bulk of the patients who utilize Quercetin. Quercetin can also be used with hypertension, adjunctive cancer treatment, hyperlipidemia, and liver conditions
What is the reason for use of a compounded drug product ra her than an FDA-approved product?	FDA-approved products are: Anti-histamines, oxidase monoamine, cortisone topically or orally. Hypertension- beta blockers, diuretics, ACE inhibitors, calcium channel blockers, etc. High Cholesterol- statins. antihistamines often do not relieve chronic allergies,patients develop tolerance or adverse side effects. Quercetin can stabilize mast cells and decrease allergy reactions. It is noted that allergies can permanently improve after a season or two of regular Quercetin dosing. Histamine intolerance cannot be treated with anti-histamines, developing further degradation of the condition. Monoamine oxidase from porcine is an experimental treatment, not readily available but the only treatment available. Quercetin is the a better option available for these patients. Quercetin is safe and has no unknown side effects even at very high doses, derived from food sources.

Is there any other relevant information?	many patients can improve their allergies by improving their diet. **An estimated 20-40% of patients** will use Quercetin at some time in their life to alleviate the annoying symptoms of allergies. **Three to five percent of patients** have histamine intolerance and will benefit from access to Quercetin since they become unresponsive to the available FDA drugs. This is a review of the use of Quercetin in allergy: J Biol Regul Homeost Agents. 2006 Jul-Dec;20(3-4):47-52. Role of quercetin (a natural herbal compound) in allergy and inflammation. Shaik YB1, Castellani ML, Perrella A, Conti F, Salini V, Tete S, Madhappan B, Vecchiet J, De Lutiis MA, Caraffa A, Cerulli G. Its use in allergy is well known and accepted; therefore most newer research is about other topics. Cancer: Nutr Cancer. 2013;65(3):494-504. doi: 10.1080/01635581 2012.725194. Resveratrol and quercetin in combination have anticancer activity in colon cancer cells and repress oncogenic microRNA-27a. Del Follo-Martinez A1, Banerjee N, Li X, Safe S, Mertens-Talcott S. Food Funct. 2014 Aug 28. [Epub ahead of print] Quercetin, a natural dietary flavonoid, acts as a chemopreventive agent against prostate cancer in an in vivo model by inhibiting the EGFR signaling pathway. Firdous AB1, Sharmila G, Balakrishnan S, RajaSingh P, Suganya S, Srinivasan N, Arunakaran J. Blood pressure: Adv Nutr. 2012 Jan;3(1) 39-46. doi: 10 3945/an.111.001271. Epub 2012 Jan 5. Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. Larson AJ1, Symons JD, Jalili T. Hyperlipidemia (High Cholesterol) : PLoS One. 2014 May 23;9(5) e97901. doi: 10.1371/journal.pone.0097901. eCollection 2014. Luteolin and quercetin affect the cholesterol absorption mediated by epithelial cholesterol transporter niemann-pick c1-like 1 in caco-2 cells and rats. Nekohashi M1, Ogawa M1, Ogihara T2, Nakazawa K3, Kato H3, Misaka T4, Abe K5, Kobayashi S1. One of many recent studies demonstrating liver protective constituent of polyphenol in Quercetin: World J Gastroenterol. 2014 Jun 21;20(23):7366-80. doi: 10.3748/wjg.v20.i23.7366.

VIA WWW.REGULATIONS.COM

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket FDA-2013-N-1525
Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations.

To Whom It May Concern:

The Integrative Medicine Consortium (IMC) appreciates the opportunity to address the Food and Drug Administration's request for the submission of ingredients to be listed as allowed for compounding by compounding pharmacies pursuant to Section 503A of the Food Drug and Cosmetic Act. IMC represents the interests of over 6,000 medical and naturopathic physicians and their patients. As we noted in our submission of March 4, 2014, we know from extensive experience that the appropriate availability of compounded drugs offers significant clinical benefits for patients and raise certain objections to the manner in which the FDA is proceeding on these determinations.

First, we note that we are in support of and incorporate by reference the comments and proposed ingredients submitted by our member organization, the American Association of Naturopathic Physicians (AANP), as well as the International Association of Compounding Pharmacists (IACP), and the Alliance for Natural Health-USA (ANH-USA). We also write on behalf of the Academy of Integrative Health and Medicine (AIHM), a merger of the American Holistic Medical Association and the American Board of Integrative and Holistic Medicine.

We also write to raise objections to:

A) The ingredient submission process the FDA is following on this docket, which places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the

process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Further, we write to ask that FDA:

D) Keep the record open for an additional 120 days for the submission of additional materials.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

F) Accept the attached nominations.

G) Accept allergenic extracts as a class without requiring individual nominations and approval.

Commenter Organizational Background: The Integrative Medicine Consortium

The Integrative Medicine Consortium (IMC) 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. Our comment is based on the collective experience of over 6,000 doctors from the following seven organizations:

American Academy of Environmental Medicine (AAEM) www.aaemonline.org
American Association of Naturopathic Physicians (AANP) www.naturopathic.org
American College for Advancement in Medicine (ACAM) www.acam.org
International College of Integrative Medicine (ICIM) www.icimed.com
International Hyperbaric Medical Association (IHMA) www.hyperbaricmedicalassociation.org
International Organization of Integrative Cancer Physicians (IOIP) www.ioipcenter.org

The IMC has been involved in the assessment of risk as applied to the integrative field generally, including participation in the 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 subject to Category

I CME credit. Our collective experience on these matters is thus profound, well-credentialed and well-documented.

IMC Objections and Requests Regarding Docket FDA-2013-N-1525

A) The ingredient submission process the FDA is following on this docket, inappropriately places the burden entirely on small industry and practicing physicians to review and support ingredient nominations rather than devoting Agency resources to the task.

We wish to lodge our objection to FDA's approach to its data collection about drugs that will be placed on the list of permitted ingredients. The FDA is placing the entire burden of documentation of every element in support of the clinical rationale and scientific evidence on already overtaxed health professionals. Given that many of those knowledgeable and experienced in compounded pharmaceuticals are either small businesses or busy physicians, and given the significant quality and quantity of information on potentially hundreds of ingredients requested by FDA, this burden is unreasonable. This approach has no basis in the purpose and language of the Drug Quality and Security Act ("Act"), particularly for drugs that have been in use for years, not only with FDA's at least implicit acceptance, but without any indication of an unacceptable level of adverse reactions.

This is contrary to the manner in which FDA has approached such reviews in the past. For example, to accomplish the Drug Efficacy Study Implementation (DESI) program, FDA 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 the resources to seek regulatory approvals.

B) The withdrawal of approval for bulk ingredients that had been previously allowed until the process is completed, leaving a void whose harm far outweighs the risks presented by these ingredients.

Given that the Act arose from Good Manufacturing Practice violations and not concern for any specific drug ingredient, the requirement that ingredients not the subject of a USP monograph or a component of approved drugs be withdrawn pending these proceedings has no legislative basis or rationale. The hiatus in availability and inappropriate shift of burden to the compounding industry is further aggravated by the complete absence of consideration by the FDA of the harm caused by the removal of needed drugs from practice. The "Type 2" errors caused by removing important agents from clinical use could far exceed the "Type 1" errors of adverse reactions, particularly given the

track record in this industry. This is particularly true given that the infectious contamination that gave rise to the Act has little to do with the approval process for which ingredients may be compounded. Yet FDA has offered little consideration of the respective risks and benefits of its approach, and with pharmacies and physicians carrying the full burden of proof and the time expected for the advisory process to conclude, the FDA will likely itself cause more patient harm than provide a contribution to safety.

C) The lack of findings of the economic impact of this regulation with regard to the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) or the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

The FDA's analysis of the costs of regulatory compliance did not appear to include an examination of the impacts on the industry. The initial or continuing notice for nominations did not analyze this under the Executive Regulatory Flexibility Act (5 U.S.C. 601-612) nor the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). While the FDA made this assessment for "Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness," 79 FR 37687, in which 25 drugs were added to the list of barred drugs, it has not done so for the much broader issue of upending the compounding pharmaceutical industry, which bears costs both in preparation of detailed submissions on potentially hundreds of ingredients, loss of sales of ingredients no longer approved, the economic consequence to physicians of not being to prescribe these drugs, and the economic impacts of health difficulties and added expense that will result from the withdrawal of drugs from clinical use. The Agency needs to address these concerns.

D) Extend the deadline for which comments are due by 120 days.

IMC's March 4, 2014 submission, along with AANP and ANH-USA nominated 71 bulk drug substances. IMC identified 21 more where we did not have the capacity to research and present all the necessary documentation within the timeframe the Agency was requiring.[1] We had determined that at least 6 hours per ingredient would be needed to do so, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC sought a 90

[1] For example, other nominations would include 7 Keto Dehydroepiandrosterone; Asparagine; Calendula; Cantharidin; Choline Bitartrate; Chromium Glycinate; Chromium Picolinate; Chrysin; Co-enzyme Q10; Echinacea; Ferric Subsulfate; Iron Carbonyl; Iscador; Pantothenic Acid; Phenindamine Tartrate; Piracetam; Pterostilbene; Pyridoxal 5-Phosphate; Resveratrol; Thymol Iodide.

day extension to more completely respond to the Agency's request.

In the renomination, we have narrowed our focus to the attached 21 bulk drug substances given restraints on available resources. These bulk drug substances are documented in the attachment. Given the limitations imposed by the fact that our physician members spent the majority of their day providing patient care, however, we have found that the span of time the Agency provided for renominations was insufficient.

We now request that FDA extend the deadline for which comments are due by at least 120 days, so that we may provide additional documentation. The FDA can certainly begin work on those nominations it has received, but nominations should remain open. We have determined that as much as 40 hours per ingredient will be needed to do, particularly given the lack of resources being offered by the Agency, time that our physician members simply do not have in their day-to-day business of providing patient care. Thus, IMC respectfully seeks an additional 120 day period - if not greater - for the purpose of gathering this essential information. If such an extension is not granted, we will explore the prospect of submitting a Citizen's Petition along with AANP and other interested parties.

E) Address the outstanding issues we raised in our submission of March 4, 2014.

In our submission of March 4, 2014, we raised a number of additional considerations, in particular citing a number of monographs, compendia and other authoritative sources that should be considered proper sources for authorized compounding in addition to the U.S. Pharmacopeia. We urge FDA to reach this issue as a means of allowing substances in long use on the market without undue delay or ambiguity.

F) Accept the attached nominations.

Notwithstanding the concerns expressed and issues highlighted in the foregoing, IMC nominates the bulk drug substances in the attachment for FDA's consideration as bulk drug substances that may be used in pharmacy compounding under Section 503A.

G) Accept allergenic extracts as a class without requiring individual nominations and acceptance.

In addition, we ask the FDA clarify its view of, and accept as appropriate for use, the category of materials that have been long used in the compounding of allergenic extracts for immunotherapy.

This should particularly be the case where such substances are compounded in manner consistent, where appropriate under its terms, with USP Monograph 797. Given both long-standing safe use, the nature of the materials and methods of clinical use,[2] and the safety assurances contained in this monograph, we believe that individual nominations and approval should not be imposed upon this form of treatment.

As explained above, we did not have sufficient opportunity to provide all the required information for many of the bulk drug substances identified as essential for treating patients. IMC wishes to identify these additional ingredients so that we may, with sufficient opportunity to carry out the extensive research required, provide the necessary documentation to support their nomination.

Sincerely,

Michael J. Cronin, N.D.
Chair, Integrative Medical Consortium

Enclosures:
Nominations

[2] Such as environmental and body molds, dust mites, grasses, grass terpenes, weeds, trees, foods, as well as hormone, neurotransmitter, and chemical antigens that are used in various forms of immunotherapy and desensitization.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Quercetin
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please search for keyword: Quercetin.
Is the ingredient listed in any of the three sections of the Orange Book?	No.
Were any monographs for the ingredient found in the USP or NF monographs?	Dietary Supplement monograph in USP
What is the chemical name of the substance?	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H -1-benzopyran-4-one
What is the common name of the substance?	Quercetin
Does the substance have a UNII Code?	53B03V78A6 (Quercetin dihydrate)
What is the chemical grade of the substance?	Dietary Supplement
What is the streng h, quality, stability, and purity of he ingredient?	A valid Certificate of Analysis accompanies each lot of material received.
How is the ingredient supplied?	Bright yellow to greenish crystal solid.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	WHMIS (Canada): Class D-1B, material causing immediate and toxic effects. DSCL (EEC): R20/22: Harmful by inhalation and if swallow.
Has information been submitted about the substance to the USP for consideration of monograph development?	Dietary Supplement monograph in USP
What dosage form(s) will be compounded using the bulk drug substance?	Oral capsule
What strength(s) will be compounded from the nominated substance?	50 mg to 500 mg per capsule
What are the anticipated route(s) of administra ion of the compounded drug product(s)?	Oral capsule, injection
Are there safety and efficacy data on compounded drugs using the nominated substance?	Select item 25241191 1.Quercetin suppresses insulin receptor signaling through inhibition of the insulin ligand-receptor binding and therefore impairs cancer cell proliferation Wang F, Yang Y. Biochem Biophys Res Commun. 2014 Sep 18. pii S0006-291X(14)01655-6. doi 10.1016/j.bbrc.2014.09.039. [Epub ahead of print] PMID 25241191[PubMed - as supplied by publisher] Related c tations Select item 25211642 2.Direct binding of Bcl-2 fam ly proteins by quercetin triggers its pro-apoptotic activity. Primikyri A, Chatziathanasiadou MV, Karali E, Kostaras E, Mantzaris MD, Hatzimichael E, Shin JS, Chi SW, Briasoulis E, Kolettas E, Gerothanassis IP Tzakos AG. ACS Chem Biol. 2014 Sep 11. [Epub ahead of print] PMID 25211642[PubMed - as supplied by publisher]
Has the bulk drug substance been used previously to compound drug product(s)?	Yes.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Allergenic reactions, Histamine reactions and intolerance, and Food intolerances make up the bulk of the patients who utilize Quercetin. Quercetin can also be used with hypertension, adjunctive cancer treatment, hyperlipidemia, and liver conditions
What is the reason for use of a compounded drug product ra her than an FDA-approved product?	FDA-approved products are: Anti-histamines, oxidase monoamine, cortisone topically or orally. Hypertension- beta blockers, diuretics, ACE inhibitors, calcium channel blockers, etc. High Cholesterol- statins. antihistamines often do not relieve chronic allergies,patients develop tolerance or adverse side effects. Quercetin can stabilize mast cells and decrease allergy reactions. It is noted that allergies can permanently improve after a season or two of regular Quercetin dosing. Histamine intolerance cannot be treated with anti-histamines, developing further degradation of the condition. Monoamine oxidase from porcine is an experimental treatment, not readily available but the only treatment available. Quercetin is the a better option available for these patients. Quercetin is safe and has no unknown side effects even at very high doses, derived from food sources.

Is there any other relevant information?	many patients can improve their allergies by improving their diet. **An estimated 20-40% of patients** will use Quercetin at some time in their life to alleviate the annoying symptoms of allergies. **Three to five percent of patients** have histamine intolerance and will benefit from access to Quercetin since they become unresponsive to the available FDA drugs. This is a review of the use of Quercetin in allergy: J Biol Regul Homeost Agents. 2006 Jul-Dec;20(3-4):47-52. Role of quercetin (a natural herbal compound) in allergy and inflammation. Shaik YB1, Castellani ML, Perrella A, Conti F, Salini V, Tete S, Madhappan B, Vecchiet J, De Lutiis MA, Caraffa A, Cerulli G. Its use in allergy is well known and accepted; therefore most newer research is about other topics. Cancer: Nutr Cancer. 2013;65(3):494-504. doi: 10.1080/01635581 2012.725194. Resveratrol and quercetin in combination have anticancer activity in colon cancer cells and repress oncogenic microRNA-27a. Del Follo-Martinez A1, Banerjee N, Li X, Safe S, Mertens-Talcott S. Food Funct. 2014 Aug 28. [Epub ahead of print] Quercetin, a natural dietary flavonoid, acts as a chemopreventive agent against prostate cancer in an in vivo model by inhibiting the EGFR signaling pathway. Firdous AB1, Sharmila G, Balakrishnan S, RajaSingh P, Suganya S, Srinivasan N, Arunakaran J. Blood pressure: Adv Nutr. 2012 Jan;3(1) 39-46. doi: 10 3945/an.111.001271. Epub 2012 Jan 5. Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. Larson AJ1, Symons JD, Jalili T. Hyperlipidemia (High Cholesterol) : PLoS One. 2014 May 23;9(5) e97901. doi: 10.1371/journal.pone.0097901. eCollection 2014. Luteolin and quercetin affect the cholesterol absorption mediated by epithelial cholesterol transporter niemann-pick c1-like 1 in caco-2 cells and rats. Nekohashi M1, Ogawa M1, Ogihara T2, Nakazawa K3, Kato H3, Misaka T4, Abe K5, Kobayashi S1. One of many recent studies demonstrating liver protective constituent of polyphenol in Quercetin: World J Gastroenterol. 2014 Jun 21;20(23):7366-80. doi: 10.3748/wjg.v20.i23.7366.

September 30, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

McGUFF
COMPOUNDING
PHARMACY
SERVICES, INC.

Re: Docket FDA-2013-N-1525

"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"

To Whom It May Concern:

McGuff Compounding Pharmacy Services, Inc. (McGuff CPS) appreciates the opportunity to address the FDA's request for nominations of bulk drug substances that may be used by compounding facilities to compound drug products.

Request for Extension

The Agency has indicated the majority of compounding pharmacies are small businesses. McGuff CPS is a small business and has found that the requirements to assemble the requested documentation have been particularly onerous. The 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.

This is an issue of great importance which will limit the number of available compounded drugs products available to physicians and, therefore, will limit the number of individualized treatments to patients. McGuff CPS and physician stakeholders have not had the time to collect, review, and collate all documentation necessary to submit the intended list of compounded drugs required to assure all patient therapies are represented in our submission. McGuff CPS respectfully seeks an additional 120 day period for the purpose of coordinating the various stakeholders and gathering the essential information necessary to provide the Agency with the most comprehensive information.

McGUFF
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877.444.1155
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EMAIL: answers@mcguff.com
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The Agency has not announced the process of follow on communication or failure e.g. what happens if a nominated substance needs more detailed information of a particular nature? Will the whole effort be rejected or will a "deficiency letter" be issued to the person or organization that submitted the nomination? The Agency issues "deficiency letters" for NDA and ANDA submissions and this appears to be appropriate for compounded drug nominations. McGuff CPS respectfully requests the FDA issue "deficiency letters" to the person or organization that submitted the nomination so that further documentation may be provided.

Nominations

To comply with the current time limits established by the Docket, attached are the nominations prepared to date for bulk drug substances that may be used in pharmacy compounding under Section 503A.

Sincerely,

Ronald M. McGuff

Ronald M. McGuff
President/CEO
McGuff Compounding Pharmacy Services, Inc.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Quercetin
Is the ingredient an active ingredient that meets the definition of ''bulk drug substance'' in § 207.3(a)(4)?	Yes. There is ample information in PubMed. Please search for keyword: Quercetin.
Is the ingredient listed in any of the three sections of the Orange Book?	No.
Were any monographs for the ingredient found in the USP or NF monographs?	Dietary Supplement monograph in USP
What is the chemical name of the substance?	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H -1-benzopyran-4-one
What is the common name of the substance?	Quercetin
Does the substance have a UNII Code?	53B03V78A6 (Quercetin dihydrate)
What is the chemical grade of the substance?	Dietary Supplement
What is the streng h, quality, stability, and purity of he ingredient?	A valid Certificate of Analysis accompanies each lot of material received.
How is the ingredient supplied?	Bright yellow to greenish crystal solid.
Is the substance recognized in foreign pharmacopeias or registered in other countries?	WHMIS (Canada): Class D-1B, material causing immediate and toxic effects. DSCL (EEC): R20/22: Harmful by inhalation and if swallow.
Has information been submitted about the substance to the USP for consideration of monograph development?	Dietary Supplement monograph in USP
What dosage form(s) will be compounded using the bulk drug substance?	Oral capsule
What strength(s) will be compounded from the nominated substance?	50 mg to 500 mg per capsule
What are the anticipated route(s) of administra ion of the compounded drug product(s)?	Oral capsule
Are there safety and efficacy data on compounded drugs using the nominated substance?	Select item 25241191 1.Quercetin suppresses insulin receptor signaling through inhibition of the insulin ligand-receptor binding and therefore impairs cancer cell proliferation Wang F, Yang Y. Biochem Biophys Res Commun. 2014 Sep 18. pii S0006-291X(14)01655-6. doi 10.1016/j.bbrc.2014.09.039. [Epub ahead of print] PMID 25241191[PubMed - as supplied by publisher] Related c tations Select item 25211642 2.Direct binding of Bcl-2 fam ly proteins by quercetin triggers its pro-apoptotic activity. Primikyri A, Chatziathanasiadou MV, Karali E, Kostaras E, Mantzaris MD, Hatzimichael E, Shin JS, Chi SW, Briasoulis E, Kolettas E, Gerothanassis IP Tzakos AG. ACS Chem Biol. 2014 Sep 11. [Epub ahead of print] PMID 25211642[PubMed - as supplied by publisher]
Has the bulk drug substance been used previously to compound drug product(s)?	Yes.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Allergenic reactions, Histamine reactions and intolerance, and Food intolerances make up the bulk of the patients who utilize Quercetin. Quercetin can also be used with hypertension, adjunctive cancer treatment, hyperlipidemia, and liver conditions
What is the reason for use of a compounded drug product ra her than an FDA-approved product?	FDA-approved products are: Anti-histamines, oxidase monoamine, cortisone topically or orally. Hypertension- beta blockers, diuretics, ACE inhibitors, calcium channel blockers, etc. High Cholesterol- statins. Many patients find antihistamines do not help with chronic allergies, hey wear off; patients become tolerant or there are adverse side effects. Quercetin can stabilize mast cells and decrease allergy reactions of all sorts. Many patients find their allergies are permanently improved after a season or two of regular Quercetin dosing. Histamine intolerance cannot be treated with anti-histamines and actually worsens the condition. Steroids are a temporary relief and also cause a rebound effect. Monoamine oxidase from porcine is an experimental treatment, not readily available but the only treatment available. Quercetin is the best tool available for these patients. Quercetin is safe and has no unknown side effects even at very high doses, derived from food sources.

Is there any other relevant information?	many patients can improve their allergies by improving their diet. **An estimated 20-40% of patients** will use Quercetin at some time in their life to alleviate the annoying symptoms of allergies. **Three to five percent of patients** have histamine intolerance and will benefit from access to Quercetin since they become unresponsive to the available FDA drugs. This is a review of the use of Quercetin in allergy: J Biol Regul Homeost Agents. 2006 Jul-Dec;20(3-4):47-52. Role of quercetin (a natural herbal compound) in allergy and inflammation. Shaik YB1, Castellani ML, Perrella A, Conti F, Salini V, Tete S, Madhappan B, Vecchiet J, De Lutiis MA, Caraffa A, Cerulli G. Its use in allergy is well known and accepted; therefore most newer research is about other topics. Cancer: Nutr Cancer. 2013;65(3):494-504. doi: 10.1080/01635581 2012.725194. Resveratrol and quercetin in combination have anticancer activity in colon cancer cells and repress oncogenic microRNA-27a. Del Follo-Martinez A1, Banerjee N, Li X, Safe S, Mertens-Talcott S. Food Funct. 2014 Aug 28. [Epub ahead of print] Quercetin, a natural dietary flavonoid, acts as a chemopreventive agent against prostate cancer in an in vivo model by inhibiting the EGFR signaling pathway. Firdous AB1, Sharmila G, Balakrishnan S, RajaSingh P, Suganya S, Srinivasan N, Arunakaran J. Blood pressure: Adv Nutr. 2012 Jan;3(1) 39-46. doi: 10 3945/an.111.001271. Epub 2012 Jan 5. Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. Larson AJ1, Symons JD, Jalili T. Hyperlipidemia (High Cholesterol) : PLoS One. 2014 May 23;9(5) e97901. doi: 10.1371/journal.pone.0097901. eCollection 2014. Luteolin and quercetin affect the cholesterol absorption mediated by epithelial cholesterol transporter niemann-pick c1-like 1 in caco-2 cells and rats. Nekohashi M1, Ogawa M1, Ogihara T2, Nakazawa K3, Kato H3, Misaka T4, Abe K5, Kobayashi S1. One of many recent studies demonstrating liver protective constituent of polyphenol in Quercetin: World J Gastroenterol. 2014 Jun 21;20(23):7366-80. doi: 10.3748/wjg.v20.i23.7366.

Tab 5b

Quercetin Dihydrate
Nomination Clarification

Alliance for Natural Health USA
3525 Piedmont Road NE
Building 6, Suite 310
Atlanta, GA 30305

email: office@anh-usa.org
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202.803.5119
fax: 202.315.5837
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ANH-USA is a regional office of ANH-Intl
INTERNATIONAL
anhinternational.org

February 21, 2018

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
10903 New Hampshire Avenue
Building 51, Room 3249
Silver Spring, MD 20903

RE: Docket FDA-2015-N-3534

Dear Ms. Hallman:

The Alliance for Natural Health USA (ANH-USA) is responding to FDA's questions regarding the nomination of Quercetin for inclusion on the 503A bulk drug substances list.

ANH-USA is an independent, nonprofit watchdog organization of more than 550,000 members nationally that protects consumer access to natural health services, practitioners, and resources. Safely compounded medications, as provided by integrative physicians, fulfill an important clinical need for many of our members. These are patients who have not found relief for their health conditions through conventional means. Such patients often have an adverse reaction to mass-manufactured drugs, and require a more individualized treatment regimen.

Before providing our responses, we wish to object to what has apparently evolved into a new request for a disease indication rather than simply a use for the ingredient. The implication is that FDA approval will be based upon a disease indication when functional and nutraceutical uses have substantial clinical value and are plainly lawful under the Food, Drug, and Cosmetic Act.

Responses:

Q1. Does Alliance for Natural Health USA still want to pursue review by the FDA and consideration by the PCAC of quercetin for inclusion on the 503A bulks list?

A. Yes

Q2. Please confirm in writing the proposed uses identified in your nomination that you wish for FDA to review, provide scientific articles supporting each use, and identify the dosage form and

strength/concentration for each use. If this information is not provided for a proposed use, FDA does not intend to review that use. Please note that the uses "antioxidant" and "clinical therapeutic potential for other conditions" are sufficiently imprecise to guide FDA's review.

A. ANH-USA cites the response of the American Association of Naturopathic Physicians and the Integrative Medicine Consortium, both of which possess the necessary expertise on this matter.

ANH-USA appreciates the FDA's and its Pharmacy Compounding Advisory Committee's (PCAC) consideration of this further information in support of the nomination of quercetin for inclusion on the 503A bulk drug substances list. We would like to reiterate that the Agency's original request asked only for ingredients' proposed use, not the disease condition or indication.

If you have further questions, please contact me.

Sincerely,

Michael Jawer
Deputy Director

Email: mike@anh-usa.org
Phone: 240-396-2171

February 21, 2018

VIA EMAIL
toni.hallman@fda.hhs.gov

Toni Hallman, MS, BSN, RN
LT USPHS
Project Manager, PCAC
CDER/OC/OPRO
Food and Drug Administration
10903 New Hampshire Ave., Bldg 51, Rm 3249
Silver Spring, MD 20903

Re: Response to Requests for More Information on Nominations for Quercetin
Docket FDA-2015-N-3534

Dear LT. Hallman:

I write on behalf of and the American Association of Naturopathic Physicians ("AANP") and its partner in these submissions, the Integrative Medicine Consortium ("IMC"), in response to your requests for more information about the nominations of the above-named ingredient. It is correct that IMC and AANP maintain this nomination as an ingredient that should be placed on the 503A positive list. In addition to providing what material we can in the short time provided, I once again must object to the unreasonably short time allowed and request and extension to file a more complete response. We have not heard back on our previous requests under similar circumstances. As FDA likely has a work plan that sets forth a schedule under which the outstanding nominations will be considered, it would be helpful if we could have some advance notice so that we can begin our responses with some reasonable notice.

Enclosed please find our submission regarding quercetin in which we address the questions raised for today's date, though we intend to supplement these filings. We also are in support of submissions made by co-nominators the Pharmacy Compounding Centers of America, Alliance for Natural Health and McGuff Compounding Pharmacy.

Objection As to Insufficient Notice

IMC and AANP appreciate that FDA is seeking additional information as it weighs this nomination, but the due date of February 21, 2018 for much of the information was only submitted to our organizations on February 7th. A two-week window, particularly for physicians

and pharmacists engaged in full-time practices, is not reasonable. We have raised this previously yet this same practice continues and FDA does not appear to respect the time demands on professionals engaged in the care of their patients. We appreciate that staff would like time to review clinical materials prior to the as yet unannounced PCAC meeting, but patient care is at risk given FDA's approach to these questions and sufficient time should be provided.

As noted in our previous response, we note that the request to break down the dosage and form by each proposed use is not contained in the Federal Register Notice (2015-27271) but constitutes a new request, as is the request to provide supportive statements from the materials of professional medical societies and to prioritize all uses. Further, while we appreciate that the FDA is following up on our previous submissions, the original request only asks for the "proposed use" and does not ask for the disease indication or condition. These are all significant requests that cannot be reasonably accomplished in two weeks.

Objection as to Requirements of a Disease Indication

As we noted in our letter of January 26 with regard to three other nominated ingredients, we also object to what has evolved into a new request for a disease indication rather than simply a use for an ingredient, and its implication that approval must be based upon a disease indication when functional uses have great clinical utility and are plainly lawful under the language of the Food, Drug and Cosmetic Act ("FDCA"). Rather than restate the details of our objections to the requirement that an ingredient be used for a disease indication, I incorporate by reference the objections we made in my letter of January 26, 2018 in response to questions about choline chloride, alpha lipoic acid and methylcobalamin.

In the request for more information the Agency states that use as an "antioxidant" is insufficiently precise. If a physician wishes to provide an antioxidant for medical reasons that, in his or her judgment is medically indicated, that should be sufficient without the FDA adding a requirement to prove claims that are not even being made, nor should FDA interfere in the practice of medicine.

Sincerely,

Alan Dumoff

Enclosures
AANP / IMC submission for quercetin

American Association of Naturopathic Physicians and the Integrative Medicine Consortium
Additional Information supporting Ingredient Nomination of
Quercetin
Submitted February 21, 2018

The American Association of Naturopathic Physicians ("AANP") and the Integrative Medicine Consortium ("IMC") submit this response to the FDA's questions regarding the nomination of Quercetin for inclusion on the 503A bulk drug substances requested due by Jan. 26, 2018.

Q. Do our organization still want to pursue review by the FDA and consideration by the PCAC of quercetin for inclusion on the 503A bulk list?

A. Yes.

Q. Please confirm in writing the proposed uses identified in your nomination. For those uses of the nominated substance that you want FDA to review, provide at least one scientific article supporting each use, and identify the dosage form and strength/concentration for each use. If this information is not submitted for a proposed use, FDA does not intend to review the nominated substance for that use.

A. Allergenic and histamine reactions, asthma and intolerance; treatment and support for cancer patients, anti-inflammatory and antioxidant effects make up the bulk of the patients who utilize quercetin.

We intend to supplement this submission with regard to route and dosing information, but intend to preserve for its nomination all routes until adequate time is allowed to prepare a response, including but not limited to oral, intravenous, intramuscular and sublingual uses.

Asthma

Joskova M, Franova S, Sadlonova V. Acute bronchodilator effect of quercetin in experimental allergic asthma. Bratisl Lek Listy. 2011;112(1):9-12. (Study showed that quercetin (20 mg/kg) caused significant bronchodilation, both in vivo and in vitro. Quercetin proved in laboratory conditions its ability to reduce hyperreactivity of airways as one of the main attribute of allergic asthma.

Allergy and Related Reactions

Mlcek J, Jurikova T, Skrovankova S, Sochor J. Quercetin and Its Anti-Allergic Immune Response. Molecules. 2016 May 12;21(5).

Shaik YB, Castellani ML, Perrella A, Role of quercetin (a natural herbal compound) in allergy and inflammation. J Biol Regul Homeost Agents. 2006 Jul-Dec;20(3-4):47-52.

Cancer Prevention, Treatment and Support

Ranganathan S, Halagowder D, Sivasithambaram ND. Quercetin Suppresses Twist to Induce Apoptosis in MCF-7 Breast Cancer Cells. PLoS One. 2015 Oct 22;10(10).

Baron BW, Thirman MJ, Giurcanu MC, Baron JM. Quercetin Therapy for Selected Patients with PIM1 Kinase-Positive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: A Pilot Study. Acta Haematol. 2018 Feb 14;139(2):132-139.

Primikyri A, Chatziathanasiadou MV, Karali E, et al. Direct binding of Bcl-2 family proteins by quercetin triggers its pro-apoptotic activity. ACS Chem Biol. 2014 Dec 19;9(12):2737-41. Epub 2014 Oct 9.

Han Y, Yu H, Wang J et al. Quercetin alleviates myocyte toxic and sensitizes anti-leukemic effect of adriamycin. Hematology. 2015 Jun;20(5):276-83.

Cincin ZB, Unlu M, Kiran B et al. Molecular mechanisms of quercitrin-induced apoptosis in non-small cell lung cancer. Arch Med Res. 2014 Aug;45(6):445-54.

Sharma G, Park J, Sharma AR et al. Methoxy poly(ethylene glycol)-poly(lactide) nanoparticles encapsulating quercetin act as an effective anticancer agent by inducing apoptosis in breast cancer. Pharm Res. 2015 Feb;32(2):723-35.

Del Follo-Martinez A, Banerjee N, Li X et al. Resveratrol and quercetin in combination have anticancer activity in colon cancer cells and repress oncogenic microRNA-27a. Nutr Cancer. 2013;65(3):494-504.

Firdous AB, Sharmila G, Balakrishnan S, et al. Quercetin, a natural dietary flavonoid, acts as a chemopreventive agent against prostate cancer in an in vivo model by inhibiting the EGFR signaling pathway. Food Funct. 2014 Aug 28.

Anti-inflammatory Effects

Mahomoodally F1, Suroowan S1. Herbal products for common auto-inflammatory disorders - Novel approaches. Comb Chem High Throughput Screen. 2018 Feb 12.

Le NH, Kim CS, Park T, et al. Quercetin protects against obesity-induced skeletal

muscle inflammation and atrophy. Mediators Inflamm. Epub 2014 Dec 28.

D'Andrea G. Fitoterapia. Quercetin: A flavonol with multifaceted therapeutic applications? 2015 Oct;106:256-71. Epub 2015 Sep 21.

Giacosa A, Barale R, Bavaresco L, et al. Mediterranean Way of Drinking and Longevity. Crit Rev Food Sci Nutr. 2016;56(4):635-40.

Hypertension

Larson AJ1, Symons JD, Jalili T. Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. Adv Nutr. 2012 Jan;3(1):39-46.

Safety

Harwood M, Danielewska-Nikiel B, Borzelleca JF et al. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. Food Chem Toxicol. 2007 Nov;45(11):2179-205.

Okamoto T. Safety of quercetin for clinical application (Review). Int J Mol Med. 2005 Aug;16(2):275-8.

Tab 5c

FDA Review of
Quercetin Dihydrate

DATE: August 9, 2018

FROM: Ben Zhang, Ph.D.
Staff Fellow, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)

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Consumer Safety Officer, Office of Compliance, Office of Unapproved Drugs and Labeling Compliance (OUDLC)

THROUGH: Ramesh K. Sood, Ph.D.
Senior Scientific Advisor (acting), ONDP, OPQ

Charles Ganley, M.D.
Director, ODE IV, OND

Frances Gail Bormel, R.Ph., J.D.
Director, Division of Prescription Drugs, OUDLC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Review of Quercetin Dihydrate for Inclusion on the 503A Bulk Drug Substances List

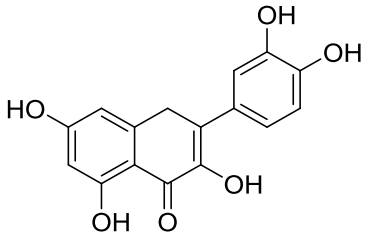
I. INTRODUCTION

Quercetin dihydrate has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Quercetin was proposed for use in the treatment of asthma, allergy, hypertension and cancer prevention and treatment.[1] The proposed routes of administration are oral, sublingual, intravenous and intramuscular.

We have reviewed publicly available data on the physicochemical characteristics, safety, effectiveness, and historical use in compounding of this substance. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing quercetin dihydrate 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 (503A Bulks List).[2]

II. EVALUATION CRITERIA

A. Is the substance well-characterized, physically and chemically, such that it is appropriate for use in compounding?[3]



[1] 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.

[2] Inclusion 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 should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using a substance included on the list has been proven to be safe and effective under the standards required receiving Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears 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 is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act (21 U.S.C. 352(a), (bb)).

[3] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

Quercetin is a naturally occurring flavonol found in many fruits and vegetables. It has a bitter flavor and is used as an additive in beverages and food products. This compound is also currently marketed as a dietary ingredient in dietary supplement products.

Quercetin dihydrate is one of the crystal forms of quercetin and is considered the same active pharmaceutical ingredient as quercetin. For the purposes of this review, we will consider data for both quercetin and quercetin dihydrate, which will be referred to as quercetin except when providing the doses of substances.

Databases searched for information on quercetin in Section A of this review included PubMed, SciFinder, Analytical Profiles of Drug Substances, the European Pharmacopoeia, British Pharmacopoeia, and Japanese Pharmacopoeia, and USP/NF.

1. *Stability of the API and likely dosage forms*

Quercetin is stable in its solid states when protected from strong oxidants. Thermal stability of its crystals is dependent on the degree of hydration, and the quercetin dihydrate crystal is more thermodynamically stable than other crystal forms with higher degrees of hydration (Borghetti et al. 2012). It is very likely to be stable when compounded as a solid oral dosage form when protected from oxygen (i.e., through the addition of antioxidants). However, aqueous solutions of quercetin seem to be less stable. Multiple studies suggest that oxidation and other degradations occur under basic conditions very rapidly (Dechene 1951; Ramesova et al. 2012). Therefore, this compound is unlikely to be stable when compounded as an aqueous solution.

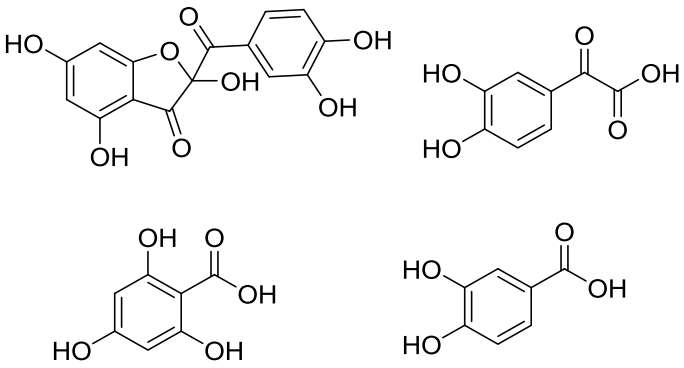
2. *Probable routes of API synthesis*

Quercetin is usually obtained from extraction of plant tissues. It can be produced from rapid extraction of powdered quercetin bark with dilute ammonia and boiling of the extract of sulfuric acid. Rhododendron cinnabarinum Hook, Ericaceae, and bark of fir trees can also be the sources of this compound (International Agency for Research on Cancer 1983; O'Neil 2006).

3. *Likely impurities*

Likely impurities may include:

- Residual solvents and reagents used in the extraction processes.
- Trace amount of inorganic salts generated from the extraction and purification processes, such as sodium sulfate.
- Degradation products of quercetin, such as the impurities shown below (Ramesova et al. 2012).



4. *Toxicity of those likely impurities*

Impurities are unlikely to be significantly toxic.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

Quercetin is a yellow crystalline solid chemical that is soluble in water. Depending on the degree of hydration, quercetin has at least three different crystalline structures. Being the most stable crystalline structure, quercetin dihydrate, the nominated substance, may have the lower bioavailability (Borghetti et al. 2012).

6. *Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize*

Quercetin is easily characterized with proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, Fourier transform infrared spectroscopy (FT-IR), UV-Vis spectroscopy, and mass spectrometry (MS).

Conclusions: Quercetin is a naturally occurring flavonol. Quercetin dihydrate is likely to be stable as a solid dosage form when protected from oxygen. However, the aqueous formulations are unlikely to be stable. The nominated substance is easily characterized with various analytical techniques and the preparation of this substance has been well developed.

B. Are there concerns about the safety of the substance for use in compounding?

1. *Nonclinical Assessment*

The following databases were consulted in the preparation of this section: PubMed, National Toxicology Program website, ToxNet, NIH dietary supplement label database[4], Google Scholar, GRAS notice inventory and Drugs@FDA.

a. General pharmacology of the drug substance

[4] https://pubchem.ncbi nlm nih.gov/compound/quercetin#section=Top: PubChem Open chemistry Database by NIH National Center for Biotechnology information

Quercetin is a naturally available flavonol found in several fruits, vegetables and nuts, with high doses found in onions and apples. It is estimated that the average dietary intake of quercetin for all age groups ranges from 25- 205 mg/person/day. An exercising adult, with a high intake of fruits and vegetables, may potentially consume up to 1250 mg/day (20.8 mg/kg body weight (bw)/d) of quercetin. In its natural form, quercetin exists as quercetin glycoside or rutinoside, which breaks down once ingested to quercetin aglycone[5] and sugar moieties (glucose or rutinose) (Guo and Bruno 2015).

Several therapeutic claims have been made for quercetin where it has been hypothesized that a higher dietary intake of quercetin is associated with a decrease in cardiovascular disease risk and anticancer effects. However, experimental findings examining these claims have not shown conclusive evidence of effectiveness (See Section C of this review for further details).

Based on in vitro and in vivo models, quercetin has been hypothesized to have a variety of potential beneficial effects in the treatment of cancer through antioxidant, anti-inflammatory, anti-proliferative, and anti-angiogenic activities, some of which are outside the scope of this memo. Simply because a model may suggest an antioxidant effect, for example, providing doses much greater than those ingested in a normal diet does not readily translate into a demonstrable added benefit in humans for a specific disease.

Flavonoids, such as quercetin, have been shown to have some effects in in vitro and in vivo animal studies suggestive of a beneficial effect in the treatment of allergy or asthma. A review article on flavonoids and their potential effect in allergy (Castell et al. 2014) summarized some of the data that led some to speculate that these chemicals may provide beneficial effects in the treatment of allergy or asthma. Some of the potential mechanisms of effect, which are discussed exhaustively in the review article, are listed below:

- The oral administration of an extract of Kalanchoe pinnata containing flavonols such as quercetin, quercitrin and kaempferol to ovalbumin sensitized mice reduced the production of OVA-specific IgE antibodies
- In mice, an extract of Camellia japonica containing quercetin showed passive cutaneous anaphylaxis inhibitory effect
- Quercetin protected against fatal anaphylactic shock in mice
- Quercetin inhibited the asthma reaction in mice and decreased eosinophils and cytokines in bronchoalveolar lavage fluid
- Quercetin decreased hyper-responsiveness and inflammation in rats
- Suppress histamine release by suppressing mast cell degranulation

In Guinea pigs, quercetin (20 mg/kg) resulted in bronchodilation, in vivo and in vitro, demonstrating its ability to reduce hyperreactivity of airways in tested animals (Joskova et al. 2011).

[5] Aglycone or aglyca is the name given to flavonoids without attached sugars.

b. Nonclinical Pharmacokinetics/Toxicokinetics

The bioavailability of quercetin is generally poor and variable. Upon its ingestion, quercetin is metabolized to several byproducts, which vary depending on the site and manner by which quercetin is absorbed. For example, in situ studies using an intestinal perfusion rat model show that while quercetin glycoside is not absorbed from the stomach, its breakdown product, quercetin aglycone, is absorbed from the stomach and small intestine.

The relative bioavailability, distribution, metabolism and excretion of quercetin was studied in rats following oral administration. When [^{14}C] quercetin was administered orally, around 20% of the dose was absorbed from the digestive tract, >30% was decomposed to yield $^{14}CO_2$ and around 30% was excreted unchanged in the feces. The absorbed [^{14}C] quercetin was rapidly excreted into the bile and urine within 48 hours as the glucuronide and sulfate conjugates of [^{14}C] quercetin, 3'-O-monomethyl [^{14}C] quercetin and 4'-O-monomethyl [^{14}C] quercetin. Autoradiographic analysis conducted 6 hours after receiving a single oral dose of quercetin (2.3 mg/kg) in rats showed that most of the radioactivity remained in the digestive tract, liver and kidney with low levels seen in other tissues such as the blood, lung, and ribs (Ueno et al. 1983). In another study, it was reported that ingested radiolabeled quercetin was rapidly eliminated via feces and urine in rats (Mullen et al. 2008).

In a longer repeat dose pharmacokinetic study, the tissue distribution of quercetin and its metabolites was studied in rats (after 11 weeks of exposure to a 0.1 or 1% quercetin diet at 50 or 500 mg/kg bw/day) and in pigs (after 3 days of exposure to a high dose of quercetin in the diet at 500 mg/kg bw/day). Under the conditions of this study, quercetin and quercetin metabolites were widely distributed in rat tissues, with the highest concentrations seen in lungs (3.98 and 15.3 nmol/g tissue for the 0.1 and 1% quercetin diet, respectively) and the lowest in brain, white fat, and spleen. In the 3-day pig study, the liver (5.87 nmol/g tissue) and kidney (2.51 nmol/g tissue) contained the highest concentrations of quercetin and quercetin metabolites, whereas the brain, heart, and spleen had low concentrations (de Boer et al. 2005).

The route of administration is another factor that determines the bioavailability of quercetin. In a study conducted in rats, the pharmacokinetics and mean time tissue distribution parameters were compared after a single 50 mg/kg dose of quercetin administered as an intravenous bolus, oral solution, or oral suspension. Following intravenous administration, the elimination rate constant and the elimination half-life were found to be 0.0062 min and 111 min, respectively. Following oral administration, the extent of absorption was greater for the solution with shorter T_{max} and a higher C_{max} than the suspension dosage form. The absolute bioavailability was also higher for the solution (0.275 compared to 0.162 for the suspension). The mean residence time and the mean absorption time were higher for the suspension, reflecting the need to dissolve the drug for it to be absorbed (Khaled et al. 2003).

The low bioavailability of quercetin was also shown in pigs after a single intravenous (0.4 mg/kg bw) or oral dose (50 mg/kg) of quercetin. The calculated apparent bioavailability of free, unchanged quercetin after intake of 50 mg quercetin/kg bw was 0.54 ± 0.19%. Bioavailability was increased to 8.6 ± 3.8% when the conjugated quercetin was added and further increased to 17.0 ± 7.1% when other quercetin metabolites were added (Ader et al. 2000). This example

highlights the importance of the formulation used in the clinical setting for estimating the absorption and bioavailability of quercetin.

In animal models, quercetin was shown to be metabolized to three main metabolites, 3,4-dihydroxyphenylacetic 3-methoxy-4-hydroxy- acid, phenylacetic (homovanillic acid), and m-hydroxyphenyl acetic acid, all of which have been detected in the urine following oral administration of quercetin to rabbits and rats (Booth et al. 1956; Petrakis et al. 1959). These metabolites are thought to be formed in the liver after fissure of the heterocylic pyrone ring. The induction of the cytochrome P450 enzymes (CYP1A or CYP2B monooxygenases) was studied in rat liver where liver extracts were exposed to quercetin using a cytochrome P450 induction assay (CYP IA test). Quercetin (3×80 mg/kg) was not a potent inhibitor of CYP1A but was potent in inhibiting the CYP2B isoenzyme (Rahden-Staron et al. 2001).

The effect of quercetin on the absorption and disposition of digoxin was studied in pigs, which were orally administered a single dose of digoxin (0.02 mg/kg) with and without quercetin in a crossover design study. The coadministration of 50 mg/kg quercetin unexpectedly resulted in sudden death of two out of three pigs within 30 min after digoxin administration. The coadministration of 40 mg/kg quercetin significantly elevated the C_{max} of digoxin by 413% and increased the AUC0-t by 170% (Wang et al. 2004). Digoxin is extensively metabolized in rats and its metabolism seems to be mediated by the CYP3A enzyme family. Based on these two studies, it is possible that people who are exposed simultaneously to quercetin and to drugs that are metabolized by the CYP2B and CYP3A enzymes may be prone to potential toxicities caused by drug-drug interactions.

Summary of nonclinical pharmacokinetics/toxicokinetics: Quercetin is a naturally occurring flavonol with poor oral absorption and distribution when administered to animals. Efforts have been made to improve its bioavailability when used in clinical settings. Once absorbed, quercetin is quickly metabolized and is rapidly excreted via the urine and feces. Quercetin may have a potential for drug-drug interactions with drugs that are metabolized by the cytochrome P450 pathway, notably the CYP2B and CYP3A enzymes.

c. Acute toxicity[6]

The oral LD_{50} of quercetin was reported to be 160 mg/kg in the mouse and 161 mg/kg in the rat. The subcutaneous LD_{50} of quercetin in the mouse was reported as 97 mg/kg (Sullivan et al. 1951). No toxicities were reported in rabbits that were administered a single intravenous dose of quercetin at 100-150 mg/kg bw (Ambrose et al. 1952).

d. Repeat dose toxicity[7]

[6] *Acute toxicity* refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). Endpoints captured in acute toxicity studies usually include mortality and gross clinical observations. Acute toxicity data are usually superseded by data obtained from longer term toxicity studies.

[7] *Repeat-dose toxicity* studies consist of in vivo animal studies that seek to evaluate the toxicity of the test substance by observing the changes that emerge in clinical observations, clinical chemistry, gross pathology, and histology endpoints when the test substance is repetitively administered daily for a predetermined period of time.

No toxicities were reported in rabbits that were administered quercetin orally (1% in diet) for 410 days (Ambrose et al. 1952).

In the rat (n=15/sex), oral administration of quercetin in the diet at a concentration of 0.1% for 540 days did not increase the incidence of tumors when compared to controls (International Agency for Research on Cancer 1983; Takanashi et al. 1983).

In a 2-year carcinogenicity study conducted by the National Toxicology Program (NTP), quercetin was tested at doses of 0, 1000 ppm, 10,000 ppm and 40,000 ppm in rats (National Toxicology Program 1992). Clinical signs included decreases in body weight gain among animals (both males and females) given 40,000 ppm quercetin compared to controls. The decrease in body weight gain was not accompanied by a decrease in food consumption. Among mid- and high-dose treated animals, a yellowish coloration of the hair coat, especially in the perineal area, was present, presumably due to the urinary and/or fecal excretion of quercetin and/or its metabolites, which have a yellow color. This yellowish coloration was also noted in viscera of treated animals. Toxicity findings associated with dietary administration of quercetin for 2 years were mainly seen in the kidney of male rats where dose-related mild increases in the severity of chronic nephropathy (control, 2.7; low-dose, 2.7; mid-dose, 3.0; high-dose, 3.2) and a slight increase in the incidence of focal hyperplasia of the renal tubule epithelium (1/50; 2/50; 3/50; 4/50) were seen. Parathyroid hyperplasia, indicative of renal secondary hyperparathyroidism, also increased in incidence among male rats (1/43, 6/45, 6/43,17/43) (National Toxicology Program 1992).

An interim analysis was included in the 2 year NTP study where subgroups of animals were examined after 6 months and 15 months of exposure to quercetin. Findings included a significantly greater increase in relative kidney and liver weights of male and female rats treated with the highest dose (40,000 ppm) relative to the control groups. For high dose treated females, these differences were linked to the reduced body weights observed in this group. No biologically significant changes in hematology or clinical chemistry parameters were observed. The only abnormality noted in the urinalyses was the presence of calcium oxalate crystals in 7/ 10 high-dose treated males at 15 months without histopathological correlates.

e. Genotoxicity[8]

Quercetin has been studied extensively to evaluate its ability to induce mutations and chromosomal damage. Available data seem to point to conflicting conclusions between the in vitro and in vivo data. In vitro studies generally tended to show a positive signal for mutagenesis, whereas in vivo studies were mostly negative.

- In the Ames assay, an in vitro test, quercetin induced gene mutations in Salmonella typhimurium strains TA100 and TA98 with and without exogenous metabolic activation (S9) (Bjeldanes and Chang 1977). A mutagenic signal was also obtained in other in vitro

[8] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems.

tests with and without S9 for induction of sister chromatid exchanges (SCE) and chromosomal aberrations (CA) in Chinese hamster ovary cells (National Toxicology Program 1992).

- Paradoxically, quercetin exhibits a protective effect from oxidative damage in vitro as was shown in a caco-2 cell line, human peripheral blood lymphocytes and murine leukemia cells (Okamoto 2005).
- In vivo, quercetin injected intraperitoneally at 2.79, 27.9, 279 and 558 mg/kg bw, did not induce the formation of micronuclei in bone marrow erythrocytes of male and female mice (Caria et al. 1995).
- In the micronucleus assay, an in vivo assay, quercetin used up to a maximum dose of 1,000 mg/kg did not induce micronuclei in bone marrow erythrocytes of mice exposed either by intraperitoneal injection or by oral gavage (Aeschbacher et al. 1982; Carver et al. 1983).

This data point to a discrepancy between in vitro findings (positive in Ames, CA and SCE) and in vivo results (negative in micronuclei, SCE). This could be explained by the observation that in vivo the absorption and bioavailability of quercetin are limited. This coupled with a fast and extensive intestinal degradation and enzymatic metabolism, along with active DNA repair mechanisms available in vivo but not in vitro, could contribute to the apparent conflicting results obtained in the two systems. Another theory that has been proposed is that quercetin can produce hydroxyl radicals which induce strand breakage in vitro and can give rise to oxygen radicals which contribute to the formation of chromosomal aberrations (Okamoto 2005). The free radicals produced by quercetin are probably repaired by anti-oxidative mechanisms available in vivo. When using a weight of evidence approach, the in vivo data tend to be more reliable in terms of predicting potential genotoxicity findings in humans.

f. Developmental and reproductive toxicity[9]

To study the effect of quercetin on male fertility, quercetin was administered orally to male Swiss albino mice at doses up to 150 mg/kg bw/day. Under the conditions of the study, quercetin did not induce any significant increases in the frequency of abnormal sperm (Nandan and Rao 1983).

To study the effect of quercetin on male and female fertility, male and female F344 rats were fed diets containing 0.1% (~ 58 mg/kg/day) or 0.2% (~ 76 mg/kg/day) quercetin from birth until postnatal week 12 or 13 of age but not during the gestation period. Quercetin had no effect on mean viable litter size, live birth index, survival of pups up to 3 days after birth, lactation index, or weight of pups at birth or at postnatal day 21(Stoewsand et al. 1984).

[9] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects in humans of both sexes and include females from various age groups that will be exposed to the proposed substance. *Developmental toxicity* or *teratogenicity* refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth.

When 0, 20, 200, or 2,000 mg/kg quercetin was administered to Sprague-Dawley rats from gestational days (GD) 6 through 15, no overt signs of toxicity were seen in the dams at any of the tested doses. No malformations were noted among pups treated with quercetin when exposed for a single day (GD 9) or between GD 6 -15 except for a decrease in the average fetal weight in the 2,000 mg/kg treated group when compared to the controls (Willhite 1982).

Quercetin did not show adverse effects on the reproductive or developmental aspects under the conditions of the studies reported in the literature.

g. Carcinogenicity[10]

Based on an NTP study which resulted in an increased incidence of gastrointestinal tumors in rats that were fed a diet containing 0.1% quercetin for about a year (see below for details), the carcinogenicity potential of quercetin has been studied extensively in various rodent models using various routes of administration. Several attempts using longer periods of exposure (up to 2 years) and higher doses of quercetin have not been able to reproduce the positive NTP tumorigenicity results. In addition, other studies have shown that a life time exposure to quercetin was associated with a decrease in the incidence of skin neoplasm formation compared to vehicle controls. A summary of carcinogenicity studies conducted with quercetin is shown below (more details can be found in Appendix 1):

- In an NTP study where albino rats were fed a diet containing 0.1% quercetin for 58 weeks, the incidence of renal tubular cell adenoma was increased among high dose treated males compared to controls (See table 1 below). The NTP report concluded that there was no evidence of carcinogenic activity in lower dose group males or in female rats dosed up to 40,000 ppm quercetin. Other findings included two cases of squamous cell carcinomas of the tongue in high-dose treated females. However, these were deemed to be unrelated to quercetin exposure because their incidence was within the historical control range in this strain of rats (Pamukcu et al. 1980).

[10] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to result in tumors when used by humans on a chronic basis. Carcinogenicity studies are conduct if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life.

Table 1
Incidence of renal tubule lesions in F344/N rats in the 2-year feed study of quercetin conducted by the National Toxicology Program (NTP)

	0 ppm (control)	1000 ppm	10000 ppm	40000 ppm
Males				
Initial evaluation (single sections)				
Hyperplasia	1/50 (2%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adenoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adenocarcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adenoma or adenocarcinoma[a]	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Evaluation of step sections				
Hyperplasia	2/50 (4%)	2/50 (4%)	6/50 (12%)	8/50 (16%)
Adenoma	1/50 (2%)	2/50 (4%)	7/50 (14%)	6/50 (12%)
Combined (Single and Step Sections)[b]				
Hyperplasia	3/50 (6%)	3/50 (6%)	8/50 (16%)	11/50 (22%)
Adenoma	1/50 (2%)	2/50 (4%)	7/50 (14%)	8/50 (16%)
Adenoma or adenocarcinoma	1/50 (2%)	2/50 (4%)	7/50 (14%)	9/50 (18%)*
Females				
Initial evaluation (single sections)				
Hyperplasia	1/49 (2%)	1/49 (2%)	3/50 (6%)	1/50 (2%)
Adenoma[c]	0/49 (0%)	0/49 (0%)	1/50 (2%)	0/50 (0%)
Evaluation of step sections				
Hyperplasia	1/49 (2%)	–[d]	–	3/50 (6%)
Adenoma	1/49 (2%)	–	–	0/50 (0%)
Combined				
Hyperplasia	2/49 (4%)	–	–	4/50 (8%)
Adenoma	1/49 (2%)	–	–	0/50 (0%)

Table adapted from NTP (1992).
* $p \leq 0.01$ pair-wise comparison between control and dose group.
[a] Historical incidence for 2-year NTP feed studies with untreated control groups 4/499 (0.8% ± 1.1%), range 0–4%.
[b] Where the combined incidence of lesions identified in the single and step-section evaluations are less than the addition of both, it is because the same lesion was identified in both examinations.
[c] Historical incidence for 2-year NTP feed studies with untreated control groups 1/499 (0.2% ± 0.6%), range 0–2%.
[d] Step sections not conducted at the 1000 and 10000 ppm dose levels.

- In a separate 2-year feeding carcinogenicity study where quercetin was administered to F44/N rats at up to 40,000 ppm (equivalent to 1,900 g/kg/day), an increase in the incidence of renal tubular neoplasm was observed (see Table 3 from reference below). However, no gastrointestinal neoplasms were seen in this study among treated rats of any dose (Dunnick and Hailey 1992).

TABLE 3
Kidney Lesions of the Renal Tubules in Rats in the 2-Year Feed Study of Quercetin

	Dose (ppm)			
	0	1000	10,000	40,000
Male rats				
Initial evaluation				
Hyperplasia	1/50	2/50	3/50	4/50
Adenoma	0/50	0/50	0/50	3/50*
Adenoma or adenocarcinoma	0/50	0/50	0/50	4/50*
Step section[a] evaluation				
Hyperplasia	2/50	1/50	5/50	7/50*
Adenoma	1/50	2/50	7/50	5/50*
Single and step section combined				
Hyperplasia	3/50	3/50	8/50	11/50*
Adenoma	1/50	2/50	7/50	8/50*
Adenoma or adenocarcinoma[b]	1/50	2/50	7/50	9/50*
Female rats				
Initial evaluation				
Hyperplasia	1/49	1/49	3/50	1/50
Adenoma	0/49	0/49	1/50	0/50
Step section[a] evaluation				
Hyperplasia	1/49	—	—	3/50
Adenoma	1/49	—	—	0/50
Single and step section combined				
Hyperplasia	2/49	—	—	4/50
Adenoma	1/49	—	—	0/50

[a] Additional animals identified with kidney lesions.
[b] NTP historical incidence for renal tubule adenoma or adenocarcinoma control male F344/N rats: 3/99 (3.0%, range 0–6%) at this laboratory, 8/499 (1.6%, range 0–6%) for all laboratories. —, not evaluated.
* Trend test $p < 0.05$ (significant by all tests used); tumors randomly distributed among animal cages.

- In a third rat carcinogenicity study where F344 rats were fed a diet containing 1.25 and 5% quercetin for 104 weeks, followed by 8 weeks of treatment-free period (recovery), no tumors were observed in the urinary bladder of any of the treated rats. Non-neoplastic findings included an increased incidence of hyperplastic polyps of the colon which was observed in animals treated with 5% quercetin of both sexes. A decrease in the incidence of cystic changes and fibroadenomas of the mammary gland, and a decrease in the proliferation of the liver bile duct were noted in quercetin-treated rats when compared to controls (Ito et al. 1989).

- Feeding carcinogenicity studies in mice (2% quercetin) and hamsters (up to 4% quercetin) were negative for neoplasms (see Appendix 1) (Saito et al. 1980; Morino et al. 1982).

- Topical studies show that quercetin may inhibit the promotion of skin neoplasms in the mouse (Appendix 1) (Nishino et al. 1984).

- When quercetin was injected intraperitoneally for 6 days at a dose of 500 mg/kg/day in hepatectomized rats followed by treatment with a liver tumor promotor, phenobarbital, there was no increase in liver neoplasms in rats treated with quercetin when compared to control rats when animals were followed up to 16 months after the initial exposure to quercetin (Appendix 1) (Kato et al. 1985).

The International Agency for Research on Cancer (IARC) (1999) review on quercetin concluded that there is *limited evidence* in experimental animals for the carcinogenicity of quercetin and that there is *inadequate evidence* in humans for the carcinogenicity of quercetin. Overall, the IARC opined that quercetin is not classifiable as to its carcinogenicity to humans.

Based on the above cited references (where most carcinogenicity studies were found to be negative) and the pharmacokinetic profile of quercetin (low absorption, quick metabolism, rapid excretion), it is unlikely that quercetin poses a risk for an increase in carcinogenic potential in humans.

Conclusions

- Quercetin is a naturally available flavonol found in fruits and vegetables.
- When taken orally, quercetin is quickly metabolized and only a small portion (~20% in rats) of the dose is absorbed from the digestive tract. Excretion into the bile and urine occurs within 48 hours as glucuronide or sulfate conjugates. Autoradiographic analysis in rats shows that most of the dose remains in the digestive tract. Quercetin may have a potential for drug-drug interactions with drugs that are metabolized via the cytochrome P450 pathway, notably the CYP2B and CYP3A enzymes.
- Repeat dose toxicity studies in rats show the kidney as a target toxicity organ as seen in male rats which had increases in the severity of chronic nephropathy and a slight increase in focal hyperplasia of the renal tubule epithelium. The incidence of parathyroid hyperplasia was also increased among dosed male rats.
- Quercetin did not show adverse effects on the reproductive or developmental aspects in fertility studies, embryofetal or pre/postnatal toxicity studies.
- While quercetin showed a positive response in some in vitro mutagenicity assays (Ames and chromosomal aberration), several other in vitro as well as the in vivo genotoxicity testing (micronuclei and sister chromatid exchange) showed negative mutagenic response, thus shifting the weight of evidence towards an overall negative potential for genotoxicity for quercetin.
- In a 58-week chronic oral toxicity study, quercetin was associated with an increased incidence of renal tubular cell adenoma among males treated with 5% quercetin. In a 2-year carcinogenic study, quercetin was associated with an increased incidence of hyperplastic polyps of the colon but no tumors were observed in the kidney in this study. Since the publication of the NTP report in 1980, several chronic studies have been conducted to confirm (or refute) the positive carcinogenic finding using equivalent (or higher) doses for the same (or longer) durations have not been able to reproduce the positive finding. Paradoxically, quercetin was shown to reduce the incidence of skin

neoplasms in the mouse and the incidence of cystic changes and fibroadenomas of the mammary gland in the rat, and a decrease in the proliferation of the liver bile duct in the rat. The overall evidence available (majority of animal studies being negative and quercetin's pharmacokinetic profile) does not seem to implicate quercetin as a potential carcinogen in humans.

2. Human safety

The following databases were consulted in the preparation of this section: PubMed, EMBASE, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov.

a. Reported adverse reactions (FAERS, CAERS)

FAERS

The Office of Surveillance and Epidemiology conducted a search of FDA Adverse Event Reporting System (FAERS) for reports of adverse events for quercetin/quercetin dihydrate from January 1, 2000 to January 30, 2018. Seven (six US) nonduplicated cases were identified that reported both exposure to quercetin/quercetin dihydrate and at least one adverse event. These reports were submitted to the FDA because they listed a co-suspect drug that was approved by the FDA. It should be noted that three of the seven reports were coded with a serious outcome.

FAERS Case #13251227, Expedited, Foreign
A 72-year old male was admitted to the hospital with moderate sick sinus syndrome. He was enrolled in a randomized controlled clinical trial evaluating the effects of ticagrelor on cardiovascular endpoints. He had a history of sinus node dysfunction, hypertension, coronary artery disease and congestive heart failure. He was on 15 medications, including quercetin, ticagrelor, lisinopril, amlodipine, and valsartan. The ticagrelor was continued; however, no information was provided regarding whether his other medications were continued or stopped. He was discharged about a week after the admission. Because he had a history of sinus node dysfunction and was on multiple cardiovascular agents, and, it is considered unlikely that the quercetin was the cause of his hospital admission.

FAERS Case #14170737, Expedited, US
A 10-year old male was admitted to the hospital for treatment of anxiety after an infusion of deflazacort. He had a history of anxiety, attention deficit hyperactivity disorder, Duchenne muscular dystrophy (DMD), dyslexia, elevated triglycerides, insulin resistance, obesity, osteopenia and scoliosis. He was enrolled in a Phase 2 study for DMD. His medications included alendronate, deflazacort, fish oil and tocopherol, fluoxetine, lisinopril, lorazepam, metformin, quercetin (for unspecified indication), quetiapine, ubidecarenone and arginine (for unspecified indication), an unknown study drug, vitamin D and Calcium. He was treated with intravenous lorazepam and quetiapine. While his physician included quercetin in his list of six drugs that he considered to have caused the aggravated anxiety, it is considered unlikely that the

quercetin was the cause of his hospital admission because of his history of anxiety and multiple other medications.

FAERS Case #977288 Expedited, US
A 55-year old male patient diagnosed with mast cell activation syndrome was found to be "intolerant" to quercetin, as well as to other medications that had been given in serial trials to relieve his symptoms. The patient's symptoms eventually started to improve with off-label use of low dose dasatinib. Because such minimal information was provided regarding the reaction of this patient to quercetin, no clinical assessment is possible.

The remaining four non-serious cases are summarized as follows:

- A 77-year old male reported running nose and sneezing after beginning varenicline for smoking cessation. The report stated that the quercetin and Datura metel that he was also taking did not affect him. It appears unlikely that the patient's symptoms were due to the quercetin; however, the minimal information provided was insufficient to make any conclusion.
- A male of unknown age reported drug ineffectiveness with apremilast and an unspecified drug interaction between apremilast and quercetin. The minimal information provided was insufficient to make any conclusion.
- A 29-year old female experienced anxiety, aches, bladder tenderness, bloating, gassiness, increased estrogen levels, and painful breasts while on therapy with norgestimate/ethinyl estradiol, alprazolam (0.125 mg as needed) and quercetin. It is likely that the birth control pills contributed to her painful breasts.
- A 51-year old female who experienced dry eyes, dry skin, dry mouth, anxiety, constipation, joint pain, hair loss, insomnia and increased thyroid stimulating hormone while on therapy with calcium citrate, fish oil, levothyroxine, L-theanine, magnesium, melatonin, probiotics, quercetin and vitamin D. It was the physician's opinion that the patient's symptoms were <u>not</u> related to the patient's levothyroxine therapy. The patient's hypothyroidism is a confounder.

CAERS

The Center for Food Safety and Nutrition (CFSAN) collects reports of adverse events involving food, cosmetics, and dietary supplements in the CFSAN Adverse Event Reporting System (CAERS). A search of CAERS was conducted for adverse events associated with quercetin dihydrate in June 2018 based on the term "quercetin". Twenty cases were spontaneously reported from April 2009 to January 2018 with quercetin listed as the suspected product in 11 reports and as a concomitant product in 9 reports. The age of the person consuming the quercetin was provided in only five reports. None of the seven cases that involved hospitalization appeared directly related to taking quercetin (i.e., hospitalized for peri-tonsillar abscess, exacerbation of asthma, headache and dizziness ("all tests normal"), faint (observed overnight), "mini stroke" (consumer told to discontinue her 12+ dietary supplements), "allergic reaction to shrimp" and 75 year old "falling down a pyramid." The majority of cases were

confounded by multiple medications and/or underlying disease or there was insufficient information for assessment.

b. Clinical trials assessing safety

Many clinical trials have been conducted with oral quercetin and the table below provides a sample of them. In the publications included in the table below, the authors generally report that no adverse events were reported by the subjects or the authors failed to provide any safety data.

Author	Subjects	Dose	Endpoints	Results
Egert et al. (2008)	35 healthy subjects	50 mg/d, 100 mg/d, 150 mg/d (3 arms) for 2 weeks	To evaluate the effects of oral supplementation of quercetin dihydrate at 3 different doses	No adverse effects of quercetin were reported by subjects.
Moon et al. (2008)	10 healthy humans	500 mg three times daily with meals for 7 days	To evaluate the pharmacokinetics of quercetin aglycone	No safety data provided.
Heinz et al. (2010)	120 female humans	500 mg/d, 1000 mg/d or placebo for 12 weeks	To evaluate the effects of long-term (12 weeks) quercetin supplementation on innate immune and inflammation	No safety data provided.
Talirevic and Sehovic (2012)	400 healthy persons with dyslipidemia (200 in quercetin and 200 in control arms)	Quercetin (dose not provided in publication) and control arm (treatment duration not provided study duration was two months)	To evaluate the effects of regular consumption of quercetin on blood lipid values	No patients had any undesired side effects necessitating cessation of therapy or exclusion from study.
Kanzaki et al. (2012)	40 adult patients with symptomatic knee osteoarthritis (OA)	Six supplement tablets or placebo/d with each supplement tablet containing glucosamine HCl 1200 mg, chondroitin sulfate 60 mg & quercetin glycosides 45 mg; duration 16 weeks	Quercetin effects on knee OA	Comparable numbers of subjects in both groups reported experiencing one or more adverse event(s) during the treatment. Relatively frequent adverse events (AEs) included cold symptoms, myalgia/muscle stiffness, arthralgia, gastric distress, and diarrhea. No appreciable differences between AEs in the two groups. No significant lab abnormalities.
Boots et al. (2011)	18 patients with sarcoidosis	Quercetin 500 mg four times per day (n=12) versus placebo (n=6) for 24 hours	To evaluate the effects of quercetin supplementation on markers of oxidative stress and inflammation	No safety data provided.
Katske et al. (2001)	22 patients with interstitial	Quercetin 500 mg/ twice daily (Cysta-Q Complex	Quercetin effects on interstitial cystitis	None of the patients experienced any negative side effects.

Author	Subjects	Dose	Endpoints	Results
	cystitis; no control group	equivalent to 500 mg quercetin; also contained bromelain and papain) for 4 weeks		
Edwards et al. (2007)	19 patients with prehypertension; 22 patients with stage 1 hypertension	Two phase crossover design with Quercetin 730 mg/d or placebo for 4 weeks in each phase (2-week washout between phases)	Blood pressure responses in patients	No safety data provided.
Olson et al. 2010	57 healthy subjects	Single oral dose of quercetin 2,000 mg (N = 20), caffeine 200 mg (N = 19) or placebo (N = 18)	Profile of Mood States questionnaire	No adverse effects occurred during the study.

Source: Cai et al. (2013) and above individual publications
OA: osteoarthritis; LDL: low density lipoprotein; HDL: high density lipoprotein; d: day

It should be noted that the safety of intravenous quercetin is quite different from oral quercetin. Ferry et al. 1996 reported multiple, serious adverse events that occurred after administration of high dose intravenous quercetin to patients with cancer no longer responding to standard treatments. Fifty-one patients with cancer no longer amenable to standard therapies were treated with escalating intravenous doses of quercetin administered at three-week or one-week intervals. The dose range was 60 mg/m^2 to 2000 mg/m^2. Pain at the site of injection was noted at all dose levels and was worse at higher doses. Dyspnea was noted starting at 1400 mg/m^2 and was severe at 2000 mg/m^2. Vomiting occurred at 1700 mg/m^2 and was grade 4. Significant renal toxicity was noted at doses as low as 630 mg/ m^2 and became dose limiting at 1700 mg/m^2 (grade 1 to grade 4) with some patients having residual renal toxicity after treatment was stopped (Ferry et al. 1996).

c. Published case reports

We did not find any safety related case reports in the literature.

d. Pharmacokinetics

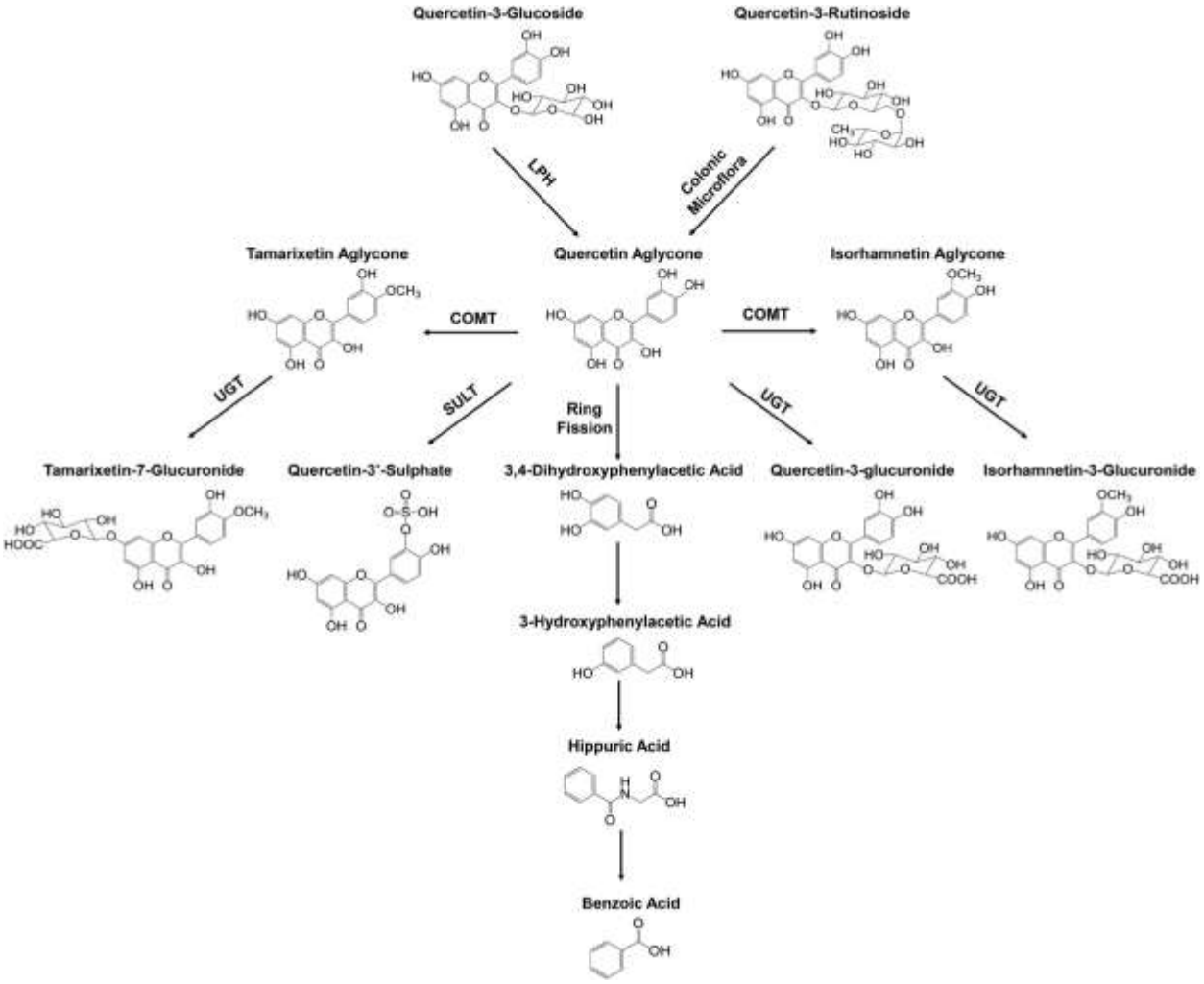
The bioavailability of quercetin requires knowledge of the form. Most quercetin in plants is bound to sugars as O-glycosides but aglycone forms can develop with storage. Approximately 150 glycosides of quercetin have been described and the sugar moiety can be mono, di, or oligosaccharides. Quercetin is lipophilic and may passively diffuse through cell wall membranes. Quercetin glycosides are polar, less likely to be absorbed, may be transported by a sodium dependent glucose transporter and require β-glucosidase to cleave the sugar to form the aglycone in the intestinal cell. Removal of the sugar also occurs in the gut for 3-O-linked glucosides by the brush border enzyme, lacrase-phloridzin hydrolase (LPH). Different quercetin forms (e.g. dihydrate vs. glucoside) will be absorbed from different sections of the gastrointestinal tract depending on the sugar link (e.g. glycosides, glucose, galactose) (Lesser and

Wolffram 2006). Quercetin dihydrate, as noted in the chemistry section, is a stable molecule which may affect its bioavailability.

In a review of quercetin bioavailability (Guo and Bruno 2015), the key pharmacokinetic issues are:

- Quercetin has poor and highly variable bioavailability.
- Quercetin metabolism is complex and involves intestinal uptake and/or deglycosylation, glucuronidation, sulfation, methylation, possible degluronidation and ring fission.
- Various metabolites are generated following its biotransformation.
- Ingested quercetin is rapidly eliminated via feces and urine.
- Absolute bioavailability of quercetin in humans was estimated at 44.8% when radiolabeled quercetin aglycone solubilized in ethanol was administered prior to measuring total radioactivity of plasma. The estimated bioavailability is probably overestimated since ethanol enhances quercetin absorption.
- Pharmacokinetic studies routinely indicate low absorption of quercetin, e.g., healthy subjects ingesting grape juice containing 10 mg quercetin aglycone had quercetin Cmax of 0.16µM, which represents ~1.4% of ingested dose.
- Marked inter-subject variability exists in quercetin bioavailability, e.g., quercetin AUC 0-24h in adults was 8.9-89.1 µM·h following ingestion of onion-derived quercetin glucosides at a dose equivalent to 100 mg quercetin aglycone.

The following figure illustrates the biotransformation of various forms of quercetin. The glycoside forms are depicted as the starting material and are converted to the aglycone form in the gut or the intestinal cell. Quercetin dihydrate is considered an aglycone form and its pathway for biotransformation will follow the path depicted in the schematic. Within the intestinal cell, the aglycone undergoes glucuronidation, sulfation and methylation and these are the primary forms circulating in the body. Quercetin aglycone is difficult to detect in the blood because of the rapid conversion to conjugated forms. The conjugated forms of quercetin can be excreted in the bile fluid and undergo enterohepatic circulation. Small amounts may be excreted in the urine or they can deconjugate and undergo ring fission to form 3-hydroxyphenylacetic acid which is converted to hippuric acid and benzoic acid for excretion by the kidneys.



Schematic representation of quercetin biotransformation. From (Guo and Bruno 2015).
Abbreviations: COMT, catechol-O-methyl transferase; LPH, lactase phlorizin hydrolase; SULT, sulfotransferase; UGT, uridine 5′-diphospho-glucuronosyltransferase.

Cai et al. (2013) state that the application of quercetin in the pharmaceutical field is limited due to its poor aqueous solubility, low bioavailability, poor permeability, rapid metabolism and instability in physiological medium. To improve the bioavailability, quercetin prodrugs, quercetin combined with inclusion complexes, quercetin nanocrystals, quercetin microemulsions and various forms of quercetin lipid formulations (e.g., liposome, lipid nanoparticle, phospholipid complex) have been developed and these alternative drug delivery systems appear to provide higher solubility and bioavailability.

In a review of herbal medicines, He et al. (2010) states:

- The urinary excretion of quercetin after intravenous (IV) administration of 100 mg to humans was 7.4% of the dose as a conjugated metabolite and 0.65% as the unchanged form.
- Total fecal recovery was 53% after oral administration of 4 grams of quercetin to humans.

- Excretion of quercetin or its conjugates in human urine ranged from 0.07 to 17.4% of intake.

In the study by Egert et al 2008, the total quercetin (unconjugated and conjugated) was measured. The following table shows that the Cmax and AUC increased in a dose dependent manner after ingestion of 50 mg, 100 mg or 150 mg of quercetin dihydrate. The elimination half-life was approximately 16 hours for total quercetin.

TABLE 3 Plasma pharmacokinetic parameters of quercetin after oral intake of 50, 100, or 150 mg quercetin in a subgroup of 15 volunteers[1]

Variable	Q50	Q100	Q150
n	5	5	5
c_{max}, *nmol/L*	189 (141, 250)[a]	295 (188, 459)[ab]	431 (242, 529)[b]
t_{max}, *min*	120 (120, 330)	180 (105, 420)	360 (210, 420)
AUC_{0-1440}, $\mu mol \cdot min \cdot L^{-1}$	76.1 (60.4, 135.0)	108.0 (77.6, 194.0)	305.8 (63.4, 382.0)
AUC_{0-480}, $\mu mol \cdot min \cdot L^{-1}$	49.3 (39.9, 55.4)[a]	65.7 (56.7, 104.6)[b]	99.2 (57.7, 161.9)[b]
Rate of absorption, $nmol \cdot min^{-1} \cdot L^{-1}$	1.2 (0.6, 1.8)	1.3 (0.9, 2.2)	1.1 (0.8, 1.9)

[1] Values are median (25th, 75th percentile). Medians in a row with superscripts without a common letter differ, $P < 0.05$.

The authors reported that pharmacokinetic results suggested a high inter-individual variability. Some patients appeared to have "reentry peaks" as exhibited in the figure below. This is suggestive of enterohepatic recirculation.

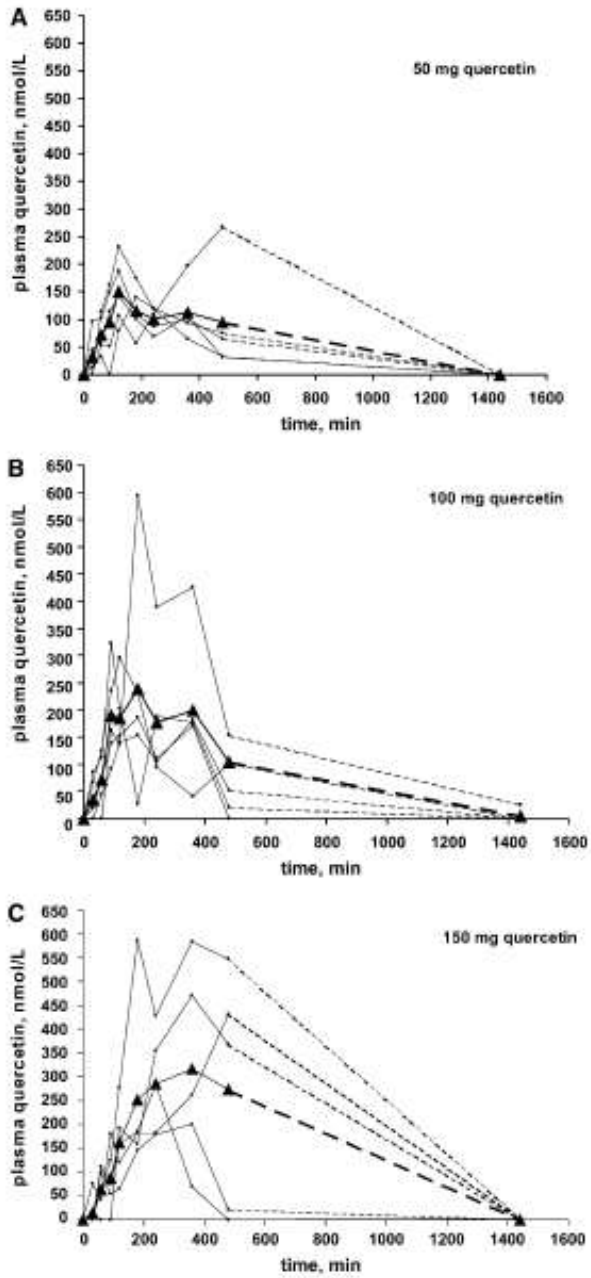


FIGURE 1 Mean (bold line) and individual (fine line) plasma concentration-time curves of quercetin after oral intake of 50 (*A*), 100 (*B*), or 150 mg (*C*) quercetin to a subgroup of 15 volunteers ($n = 5$ per dosage group). The last 2 data points are connected by a dashed line, because elimination processes during this time cannot be reliably determined.

Six subjects received an intravenous infusion (over 5 minutes) of 100 mg quercetin (in ethanol diluted in aqueous solution to pH of 8.5) and the elimination half-life of unconjugated quercetin was approximately 2.5 hours (Gugler et al. 1975). Five of the subjects received an oral dose of 4

grams; quercetin aglycone was not detected in the blood samples after ingestion (may be due to insensitive assay; the lower limit of detection was 0.1 ug/ml).

Williamson and Manach (2005) reviewed 97 polyphenol bioavailability studies and summarized the bioavailability of flavonols or flavonol-containing foods, with the majority evaluating quercetin, in the following table:

TABLE 2
Bioavailability studies of flavonols or flavanol-containing foods[1]

Source	No. of subjects	Dose	T_{max} plasma	Plasma concentration	AUC	Urinary excretion	Elimination half-life	Ref
			h	*μmol/L*	*μmol · h/L*	*% of intake*	*h*	
Pure quercetin	6	4 g		<0.33		<1		23
Onions	9 ileostomized	89 mg quercetin eq				0.31/13h		24
Pure rutin	9 ileostomized	100 mg quercetin eq				0.07/13h		24
Pure quercetin	9 ileostomized	100 mg quercetin eq				0.12/13h		24
Fried onions	2	64 mg quercetin eq	2.9	0.65			16.8	25
Onions	9	68 mg quercetin eq	0.7	0.74	7.7		28.0	26
Apples	9	107 mg quercetin eq	2.5	0.3	3.5		23.0	26
Pure rutin	9	100 mg quercetin eq	9.3	0.3	3.3			26
Complete meal	10	87 mg quercetin eq		0.37 at 3 h				27
Onions	5	186 mg quercetin eq	1.3–1.9	2.18		1.11		28
Onions	5	50 mg quercetin eq	2	0.83				29
Quercetin 4'-glucoside	9	150 mg	<0.5	3.5	18.8		21.6	30
Pure rutin	9	190 mg	6	0.18	3.7		28.1	30
Quercetin 3-glucoside	9	156 mg	0.6	5	19.1	3.6	18.5	31
Quercetin 4'-glucoside	9	160 mg	0.45	4.5	17.5	3.1	17.7	31
Pure rutin	3	500 mg	4–7	0.13–0.73				32
Pure quercetin	16	8, 20, 50 mg	2, 2.7, 4.9	0.14, 0.22, 0.29	1.74, 2.92, 3.77		17, 17.7, 15	33
Pure rutin	16	8, 20, 50 mg quercetin eq	6.5, 7.4, 7.5	0.08, 0.16, 0.30	1.26, 2.10, 3.36			33
Onions	12	100 mg quercetin eq	0.68	7.6	32.1	6.4	10.9	34
Pure quercetin 4'-glucoside	12	100 mg quercetin eq	0.7	7.0	27.8	4.5	11.9	34
Buckwheat tea	12	200 mg quercetin eq	4.3	2.1	12.6	1.0	10.3	34
Pure rutin	12	200 mg quercetin eq	7	1.1	8.3	0.9	11.8	34
Apple cider (1.1 L)	6	1.6 mg quercetin eq	0.66–1	0.14				35
Pure quercetin	12	0.14 mg/kg bw	0.5	0.15–0.42		2.9–7		36

[1] T_{max}, time to C_{max}; AUC, area under the curve; eq, equivalents; bw, body weight.

Pharmacokinetic data was collected from eleven of 51 patients with a cancer diagnosis who were treated with intravenous quercetin in DMSO in doses ranging from 60 mg/m^2 to 2000 mg/m^2 during a Phase 1 trial (Ferry et al. 1996). The median elimination half-life was 43 minutes (range: 4 – 86 minutes). The median volume of distribution was 3.7 L/m^2. (See Section "b. Clinical Trials Assessing Safety" for the safety data for all 51 patients.)

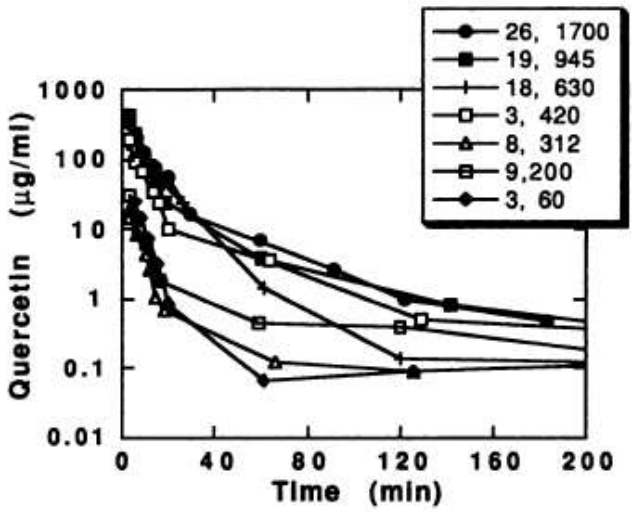
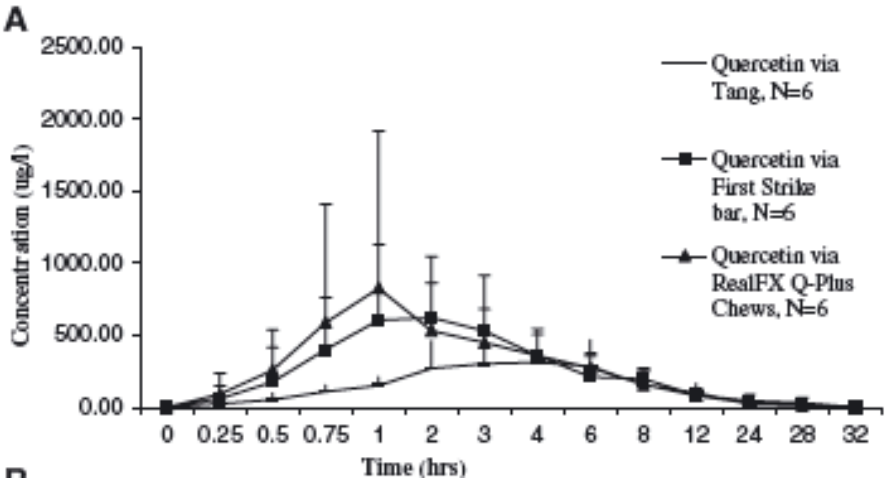


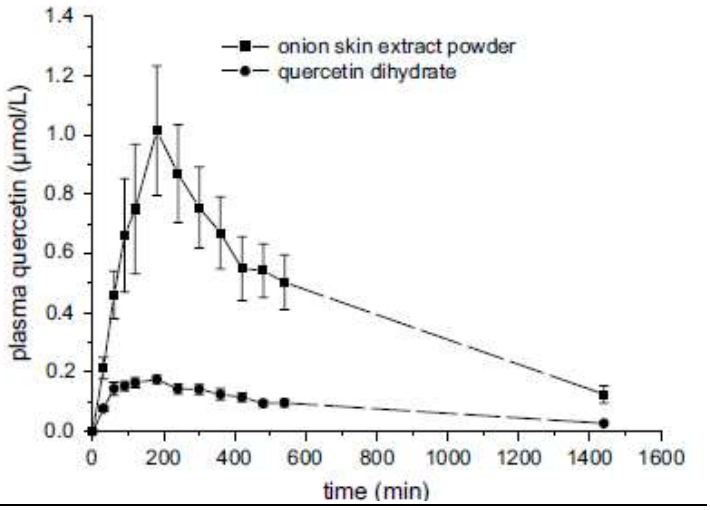
Fig. 3 Pharmacokinetics of quercetin. In the key, the first number refers to the patients' trial number and the second to the dose in mg/m^2.

The pharmacokinetics of quercetin aglycone administered as a suspension in Tang® and spring water, nutritional bars (First Strike™) and chews (RealFX™ Q-Plus™) was evaluated in 18 healthy human subjects (Kaushik et al. 2012). Three different carriers were evaluated because buccal absorption offered by chews, bars, chewing gums or lozenges, compared to conventional oral delivery, can offer more rapid uptake in the blood stream due to avoiding first pass metabolism. Subjects were divided into three groups of six individuals with each subject receiving one of the above three formulations. Subjects agreed to refrain from the use of drugs, over-the-counter medications, quercetin containing dietary supplements, and foods rich in quercetin (apples and onions) 7 days prior to and during the study.

The Cmax of quercetin was highest with RealFX™ Q-Plus™ Chews (1051.9 ± 393.1 μg/L) achieved within 3.3 hours as compared to that for First Strike™ Bars (698.1 ± 189.5 μg/L in 2.3 hours) and Tang® suspension (354.4 ± 87.6 μg/L in 4.7 hours). No safety data was provided.



In a randomized, single blind, diet-controlled crossover study conducted in 12 healthy subjects, subjects refrained from quercetin-rich food during the one-week, run-in period. During one treatment period, each subject was administered a single oral dose of approximately 163 mg quercetin (containing 95.3% of total flavonoids as quercetin aglycone) derived from onion skin extract powder contained in three capsules. In the other treatment period, each subject was administered a single oral dose of quercetin dihydrate 150 mg (equivalent to 134 mg quercetin aglycone) contained in six capsules. The systemic availability, determined by comparing the plasma concentration–time curves of quercetin, was 4.8 times higher, and the maximum plasma concentration (Cmax) was 5.4 times higher after ingestion of the onion skin extract than after ingestion of pure quercetin dihydrate. Based upon this study, the source of the quercetin can dramatically affect the bioavailability. The concentration – time curves illustrate the results. No adverse effects of the quercetin intakes were reported (Burak et al. 2017).



A double-blind, 2-arm, pharmacokinetic and risk factor study conducted in 27 healthy subjects evaluated the effects on plasma quercetin, serum/platelet fatty acid levels and risk factors for heart disease after taking four capsules daily for 28 days of placebo versus a nutritional supplement (each capsule contained quercetin anhydride 250 mg, mixed other bioflavanoids 250 mg, rutin 50 mg, bromelain 50 mg and 4.2 mg magnesium stearate) (Conquer et al. 1998). After 28 days of treatment, the selected cardiovascular risk factors were not significantly altered in either group. However, a significant increase in plasma quercetin concentrations was noted in the experimental group, with no change in the control group. No safety data was provided.

TABLE 2

Plasma quercetin concentrations in fasting subjects after placebo or quercetin supplementation for 28 d[1]

Variable	Control		Quercetin	
	ng/mL	*μmol/L*	*ng/mL*	*μmol/L*
Day 0	ND	ND	27.7 ± 25.7	0.10 ± 0.09
Day 28	18.5 ± 16.4	0.07 ± 0.06	427.1 ± 89.2*	1.5 ± 0.3*

[1] Values are means ± SEM, $n = 8$ (control) or $n = 7$ (quercetin).
* Significantly different than d 0, $P < 0.05$; ND, nondetectable.

Drug-Food Interaction Studies

Scholz and Williamson (2007) reviewed polyphenol interactions with various foods. The following interactions with quercetin described in the review are listed below:

- Quercetin and red wine resulted in increase of plasma concentration of total flavonols by 138%.
- Quercetin and black tea resulted in increase of plasma concentration of total flavonols by 169%.
- Quercetin and fried onions resulted in increase of plasma concentration of total flavonols by 288%.
- Quercetin and white wine resulted in a significant increase of plasma total quercetin AUC(4h) with tmax = 30 minutes.
- Quercetin and soybean oil (>0.75 grams/day) significantly increased plasma concentration of quercetin metabolites.

Drug Interaction Studies

Co-administration of quercetin 500 mg (once daily on Days 1-13) with midazolam 7.5 mg (one dose on Day 14 and Day 56) in CYPA5*1/*1 and CYP3A5*1/*3 individuals significantly decreased the $AUC_{0-\infty}$, shortened the t1/2 and decreased tmax significantly (Duan et al. 2012). The authors concluded that quercetin significantly induced CYP3A activity to substrate midazolam and the induction was partly related to CYP3A5 genotype. No safety data was provided.

In a study evaluating single-dose and short-term administration of quercetin on the pharmacokinetics of oral (n=10) and IV (n=3) administered midazolam, subjects were dosed per the following dosing schedule (Nguyen et al. 2015):

Table 1. Dosing Scheme of Midazolam–Quercetin Interaction Study

Period	Day 1–6	Day 7
Midazolam Per Oral (MDZ p.o.), $n = 10$		
Control (MDZ p.o.)	Baseline quercetin: 20 mg 2× daily	7.5 mg midazolam (film-coated tablet p.o.)
Quercetin single-dose (MDZ p.o.)	Baseline quercetin: 20 mg 2× daily	7.5 mg midazolam p.o. + 1500 mg quercetin
Quercetin 1-week (MDZ p.o.)	High-dose quercetin: 500 mg 3× daily	7.5 mg midazolam p.o. + 1500 mg quercetin
Midazolam Intravenous (MDZ i.v.), $n = 3$		
Control (MDZ i.v.)	Baseline quercetin: 20 mg 2× daily	1 mg midazolam (1 mg/mL solution i.v.)
Quercetin 1-week (MDZ i.v.)	High-dose quercetin: 500 mg 3× daily	1 mg midazolam i.v. + 1500 mg quercetin

The authors concluded that co-administration with a single dose of quercetin did not significantly alter the pharmacokinetics of midazolam and its 1′-hydroxymetabolite, but following short-term quercetin intake, there was a trend to reduced midazolam exposure (geometric mean ratio of test–control area under the plasma concentration–time curve (AUC0-∞: 0.82; 90% confidence interval: 0.61–1.10) and midazolam–metabolite AUC0-∞ ratios were decreased by 9.7%–47.6% from control in seven subjects. The tendency was opposite when midazolam was given intravenously. All subjects completed the study. No adverse events were reported.

In a two-phase study conducted in 12 healthy volunteers, during the control phase, a single 100 mg oral dose of diclofenac sodium was administered, while during the quercetin treatment phase, quercetin 500 mg was administered twice daily on Days 1-10 and one dose of diclofenac sodium 100 mg was administered on Day 11. Diclofenac plasma maximum concentrations (Cmax) and t1/2 were increased after quercetin treatment when compared with the control phase, due to significant inhibition of CYP2C9 mediated metabolism of diclofenac attributed to modulation of CYP450 enzymes in the liver leading to a reduction of the formation of diclofenac to 4-OH diclofenac. The following figure demonstrates the increased Cmax and $AUC_{0-\infty}$, of diclofenac when co-administered with quercetin. All subjects completed the two periods and no adverse events were reported (Bedada and Neerati 2018).

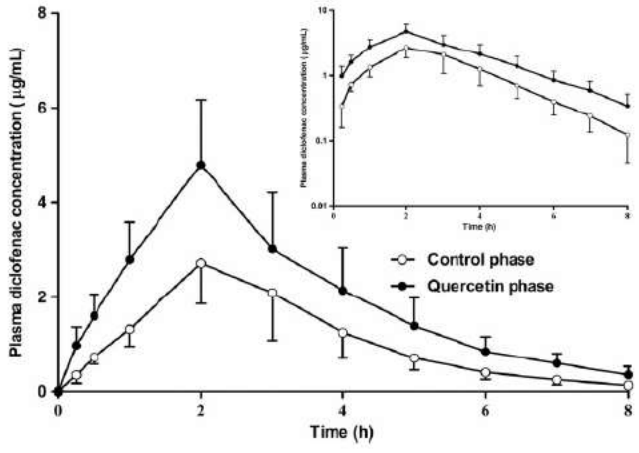


FIGURE 1 Mean plasma concentration-time plots of diclofenac sodium in 12 healthy volunteers after administration of 100 mg diclofenac sodium during control phase and after quercetin treatment phase of 500 mg quercetin twice daily for 10 days. Data are presented as mean ± SD

Quercetin interacts with multiple cytochrome P450 enzymes and ABC transporters. The clinical implication of these have not been fully characterized. For example, quercetin is a transporter

for P-glycoprotein and may have a biphasic effect in the transport of vincristine such that low concentrations will activate transport and high concentrations will inhibit it (Mitsunaga et al. 2000). Quercetin isolated from St. John's Wort has been shown to inhibit activities of cytochromes 1A2, 2C19 and 2D6 (Badal et al. 2012). It is not clear how this in vitro and cell data will translate to the clinical setting.

e. Availability of alternative approved therapies that may be as safe or safer

There are a wide variety of approved drugs for cancer, allergy, hypertension and asthma. The adverse event profile can be quite variable.

Conclusions:

- Quercetin dosing in clinical studies ranges widely but generally falls within the amounts ingested in food. Amounts in the 500-mg range would be similar to the amount consumed by someone ingesting a diet high in fruits and vegetables. There do not seem to be significant adverse events related to oral ingestion. There is limited data on intravenous exposure. In one study of intravenous exposure up to 2000 mg/m2, dyspnea ($\geq$ 1400 mg/m2) and vomiting ($\geq$ 1700 mg/m2) was observed. Significant renal toxicity was noted with doses as low as 630 mg/m2. In some cases, residual renal toxicity was observed.
- Quercetin bioavailability via the oral route is low (< 50%) and quite variable; the form of quercetin significantly influences the bioavailability. Quercetin dihydrate is poorly absorbed compared to quercetin glycosides (the form in food). In one study, quercetin glycoside (from onion skin extract) had Cmax levels that were 5-fold greater than the levels observed with quercetin dihydrate.
- Quercetin may interact with different cytochromes and ABC transporters.

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, EMBASE, Cochrane Database of Systematic Reviews.

1. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

a. Cancer

There are no compelling clinical studies evaluating the effectiveness of quercetin in the treatment or prevention of cancer. The mechanisms, described earlier, by which quercetin is thought to be relevant in treating cancer are insufficient to demonstrate benefit. There is an extensive literature on purported mechanisms by which quercetin may be an effective treatment or a preventive intervention in a wide variety of cancers. Most of the prevention information is based on dietary interventions with multiple dietary ingredients (e.g., antioxidants) and not on the use of quercetin in a clinical trial in a specific population and demonstrating some quantifiable decrease in risk of developing a certain type of cancer. The information available is primarily hypothesis generating

and not something to support its use at a specific dose. There are sporadic reports of small clinical studies in the literature. Some examples are described below:

- Three patients with chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) who had rising lymphocyte counts received quercetin 500 mg twice a day for 3 months. Lymphocyte counts which had been rising steadily for several months prior to quercetin were measured after initiation of therapy. There was no other concomitant therapy. In two of the patients, the lymphocyte count while on quercetin was stable. This was a small study of very short duration which is not sufficient to support the use of quercetin in the treatment of CLL/SLL. The authors noted that further study appeared warranted (Baron et al. 2018).
- A study of twelve patients with clear cell renal carcinoma treated with sunitinib (50 mg) and isoquercetin (either 450 mg or 900 mg) and vitamins. Isoquercetin has better bioavailability than quercetin and is converted to quercetin in the body. The isoquercetin was added to treat fatigue that is associated with sunitinib therapy. The median treatment duration was 81 days. While the study reported an improvement in fatigue over the course of treatment, this was a small, unblinded study without a control group and offers little evidence supportive of effectiveness. Isoquercetin seemed to be well tolerated (Buonerba et al. 2018).
- 51 patients with various cancers were treated with quercetin intravenously in doses ranging from 60 mg/ m^2 to 2000 mg/ m^2 for 1 – 3 cycles every 1 to 3 weeks. The number of dose cycles provided was variable for each patient and incompletely reported in the reference. No patient treated had a response by conventional radiologic evaluation. Some patients had changes in tumor markers but these results were uninterpretable because the reference provided incomplete results for all biomarkers measured for each patient (Ferry et al. 1996).

b. Allergy

Most clinical studies conducted to date have evaluated combinations or mixtures of ingredients either in the form of an herbal product or in a food substance. Despite the extensive mechanistic literature there are few studies where quercetin alone has been studied in allergic diseases and asthma. For example, a food supplement containing quercetin was evaluated in an open label study of Seasonal Allergic Rhinitis (Ariano 2015).

The following are examples of the types of clinical studies available to assess allergic conditions.

- Thirty patients with a diagnosis of oral lichen planus, a chronic autoimmune disease, were enrolled in a randomized, double blind, placebo controlled trial in Iran to evaluate the effect of quercetin (250 mg twice a day) or placebo in patients treated with background therapy consisting of a mouthwash containing dexamethasone and nystatin. Patients were treated for up to eight weeks with measurements of efficacy (pain index, severity index, visual analogue score (VAS)) obtained weekly. There was no difference between treatment groups in the VAS scores and lesion severity. Quercetin's anti-inflammatory and antioxidant effects did not provide added benefit to standard therapy for oral lichen planus (Amirchaghmaghi et al. 2015).

- A double blind, placebo controlled, study in 39 subjects with Japanese cedar pollinosis symptoms (sneezing attacks, nasal discharge, and nasal obstruction) were treated with a drink containing either 100 mg of hop water extract (HWE) or placebo daily. HWE has been shown to decrease histamine release from mast cells. The HWE contained a combination of quercetin and kaempherol aglycones. The group that received the HWE had a slight improvement in symptoms. Because the HWE contained a mixture of substances and was not limited to quercetin alone, it is difficult to extrapolate any information in this study to quercetin (Segawa et al. 2007).

There is insufficient data from clinical studies to support the effectiveness of quercetin in the treatment of allergy.

c. Hypertension

A meta-analysis of available randomized controlled trials evaluating the impact of quercetin on blood pressure (BP) was conducted (Serban et al. 2016). Not all studies included in the meta-analysis involved patients with hypertension or pre-hypertension. The meta-analysis shows a statistically significant effect of quercetin supplementation in the reduction of BP, with a greater effect of oral doses higher, rather than lower, than 500 mg/day. Seven studies were included in the meta-analysis ranging from four to 10 weeks of treatment with quercetin at oral doses from 100 to 1000 mg/day. The meta-analysis showed a statistically significant drop in systolic BP of 4.45 mmHg ($p<0.007$) and diastolic BP 2.98 mmHg ($p<0.001$) for doses of quercetin above 500 mg daily. No statistically significant effects were seen in doses less than 500 mg daily. The authors concluded that additional study was necessary to "determine the clinical relevance of these results."

One trial among the seven in the meta-analysis was focused on assessing the effect of quercetin in the treatment of hypertension (Edwards et al. 2007). This randomized, double-blind, placebo-controlled, crossover study was conducted in the U.S. and included "middle-aged, Caucasian" men and women with prehypertension (n = 19; 120–139 mm Hg systolic/80–89 mm Hg diastolic) and stage 1 hypertension[11] (n = 22; 140–159 mm Hg systolic/90–99 mm Hg diastolic). Patients who were currently using antihypertensive medications were excluded. Quercetin aglycone was dosed at 730 mg (365 mg twice a day) daily for 28 days; treatments were separated by a two-week washout. Blood pressure was not changed with quercetin therapy in prehypertension patients. In stage 1 hypertensives, mean systolic BP dropped 7 ± 2 mmHg, mean diastolic BP dropped 5 ± 2 mmHg and mean arterial pressures dropped 5 ± 2 mmHg. The study authors reported the result as statistically significant. The analysis in blood pressure was not a comparison of quercetin aglycone compared to placebo; it compared the intragroup change at 12-weeks to baseline. There was no significant difference compared to placebo. Figure 2 below is from the publication and shows that the statistical comparison was a within group comparison. The best that can be said for this study is that there may be a treatment effect on blood pressure with quercetin aglycone. This study also evaluated blood levels of quercetin and found that levels approximately doubled.

[11] As defined by 7th Report of the Joint National Committee on 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

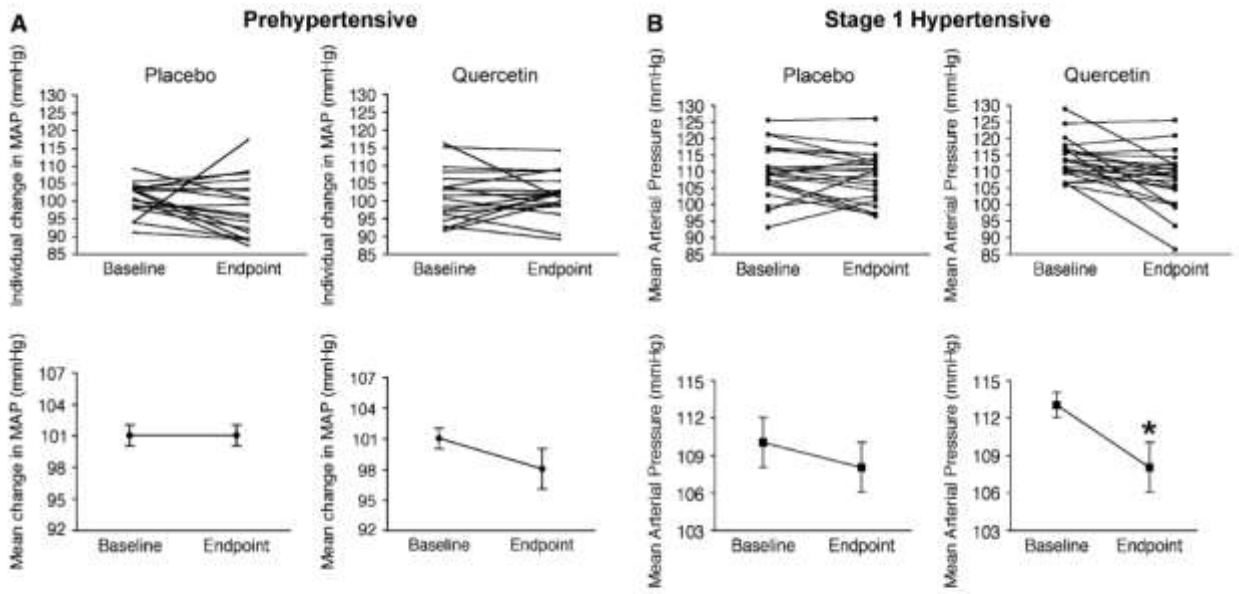


FIGURE 2 Mean arterial blood pressure at baseline and after quercetin and placebo treatments in prehypertensive (*A*, $n = 19$) and stage 1 hypertensive (*B*, $n = 22$) subjects. Upper graphs illustrate individual subject responses during each supplementation phase; the lower graphs show means ± SEM. *Different from baseline, $P < 0.05$. MAP, Mean arterial pressure.

Quercetin aglycone did not reduce systemic markers of oxidative stress in this study, which were evaluated as a hypothetical mechanism of action for quercetin.

Other studies included in the meta-analyses had design considerations that limit the ability to extrapolate their findings to the treatment of hypertensive patients.

- Egert et al. (2010) assessed 93 patients with traits of metabolic syndrome (waist circumference, elevated serum triglycerides and elevated C reactive protein). This was a randomized, double-blind, placebo controlled cross-over study of 6-week treatment duration. Elevated blood pressure or a history of hypertension was not a requirement for enrollment. Blood pressure was measured after 6 weeks of placebo and 6 weeks of 150 mg/day of quercetin dihydrate. Data were analyzed by patient subgroup, based on apolipoprotein E genotype. Only one 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
- Pfeuffer et al. (2013) enrolled healthy male subjects of the apoE3 and apoE4 genotypes. Blood pressure was not significantly decreased with quercetin dihydrate (150 mg/d). Genotypic differences were seen only on waist-circumference and body mass index measurement responses. This study did not evaluate the blood pressure effect in hypertensive patients.
- Zahedi et al. (2013) assessed numerous endpoints relating to cardiovascular risk factors (e.g., total cholesterol, low-density lipoprotein) and inflammatory biomarkers (e.g., tumor necrosis factor-α, C-reactive protein) in women with Type 2 diabetes. BP was not among the enrollment/exclusion criteria considerations. There was no significant difference in blood pressure with quercetin (Solaray brand) doses of 500 mg per day compared to

placebo and the results of other assessments were mixed. Within group changes in blood pressure were reported as significant for diastolic blood pressure by the authors but this is misleading in that it was a within group comparison.

- Lee et al. (2011) studied 92 healthy male smokers in a randomized, double blind placebo controlled study for 10 weeks duration and assessed similar parameters as the Zahedi study. BP was not among the enrollment/exclusion criteria considerations. The authors reported that both systolic and diastolic BP was significantly decreased in association with quercetin treatment. This is misleading in that the significance was a within group calculation comparing the baseline blood pressures with those obtained after 10 weeks of treatment. There was no significant difference in blood pressure effect of quercetin compared with placebo. See table 3 below from Lee et al 2011.

  (Table 3 from Lee et al. 2011)

Table 3. Blood pressure and inflammatory cytokine concentrations before and after 10 weeks of quercetin supplementation

	Placebo (n = 43)			Quercetin-rich supplementation (n = 49)			*P*-value[2]
	Baseline	10 wks	*P*-value[1]	Baseline	10 wks	*P*-value[1]	
Systolic blood pressure (mmHg)	135.5 ± 11.3	132.5 ± 12.7	NS	132.9 ± 14.9	129.3 ± 13.3	< 0.05	NS
Diastolic blood pressure (mmHg)	86.9 ± 10.4	84.0 ± 9.2	NS	88.7 ± 9.9	85.5 ± 10.0	< 0.01	NS
IL-6 (pg/mL)	1.25 ± 0.44	1.31 ± 0.48	NS	1.26 ± 0.44	1.29 ± 0.44	NS	NS
sVCAM -1 (ng/mL)	4.78 ± 0.34	4.72 ± 0.28	NS	4.85 ± 0.35	4.81 ± 0.29	NS	NS

Values are mean ± SD.
IL-6: interleukin-6; sVCAM -1 : soluble vascular cell adhesion molecule-1
[1] *P*-values for comparison between baseline and 10-wk intervention were made using the paired *t*-test in each group.
[2] *P*-values for comparing the placebo and the quercetin-rich supplementation group were made at baseline using the Student's *t*-test.

  The 10-week quercetin dose was defined as 100 mg quercetin dihydrate derived from onion peel extract and 128 mg "other mixed flavonoids (composition unknown)." It is not possible, based on this information about the test substance, to draw conclusions about the findings' relevance to quercetin. The characterization of the quercetin as the dihydrate form is inaccurate because a description regarding the extraction of quercetin from onion skins was provided and make it quercetin glycosides and not quercetin dihydrate. This is an important distinction because of the bioavailability of the glycosides being better than the dihydrate.

- In a study of 51 rheumatoid arthritis patients, for whom BP was not among their enrollment/exclusion criteria considerations, BP was assessed along with other potential indicators of quercetin's anti-inflammatory effects (Javadi et al. 2014). No significant change in systolic or diastolic BP was observed in association with quercetin doses of 500 mg/d for 8 weeks.
- Conquer et al. (1998) assessed a variety of clinical markers of potential risk factors for heart disease in healthy subjects (n = 27). BP was not identified as an enrollment/exclusion criteria. Doses of 1 g/d of quercetin anhydride (and 1.0 g bioflavonoids 200 mg rutin and 200 mg bromelain) for 28 days had no effect on resting heart rate and blood pressure.

There were also design limitations in other studies that we identified in which quercetin's potential effects on blood pressure were assessed.

- Larson et al. (2012) administered single doses of quercetin aglycone to normotensive (n = 5) and stage 1 hypertensive (n = 12) men to assess the potential mechanism of the flavonol's action. Quercetin aglycone was associated with lower BP only in hypertensives and mean systolic BP decreased approximately 5 mmHg. Based on the assessment of numerous other endpoints, the authors conclude that the mechanism is independent of changes in angiotensin converting enzyme activity, circulating endothelin-1 or nitric oxide bioavailability, or effects on vascular reactivity.
- Brull et al. (2015), as with several other identified studies, used an onion skin extract powder as the source of quercetin. Although capsules were labeled as having 54 mg of quercetin each, and a total daily dose of 162 mg, there is a potential for variability in dose based on changes in the botanical substance. The study included 68 patients with prehypertension or stage 1 hypertension, dyslipidemia and central obesity. In this crossover design, patients received doses of quercetin and placebo for 6 weeks separated by a 6-week washout. There were 10 different BP parameters considered including systolic, and diastolic for daytime and nighttime, in the ambulatory or in-office settings, plus mean arterial pressure and heart rate assessments. Among these, there was one statistically significant difference between treatment groups in the subgroup of hypertensive patients in which quercetin treatment was associated with a decreased (approximately 3 mmHg) 24-hour ambulatory systolic BP. The total study group did not show any significant intergroup differences.

Summary/Conclusion: The available effectiveness data for the use of quercetin in the treatment of hypertension are limited and do not show a significant change in blood pressure in hypertensive patients. In most of the studies, there was no significant difference from placebo and the analysis for some of the studies was a within treatment group analysis comparing baseline to the end of treatment. Although some authors reported a significant effect for the within treatment analysis, the change compared to placebo was minimal. Because of the effects on some CYP P450, more information is needed regarding the potential interaction between quercetin and FDA approved antihypertensive drugs.

d. Asthma

We were not able to identify clinical studies where quercetin was administered and evaluated for the treatment of asthma.

2. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Many cancers are serious conditions that result in life-threatening consequences if not appropriately treated. Hypertension is an asymptomatic condition for most patients but lack of adequate treatment can lead to serious cardiovascular complications. Asthma without appropriate treatment can lead to serious complications. Most allergies are not serious but can lead to significant morbidity for some patients.

3. *Whether there are any alternative approved therapies that may be as effective or more effective*

There are many approved therapies for the treatment of cancer, allergy, hypertension and asthma.

Conclusions:

There are no clinical studies supportive of the use of quercetin in the treatment of cancer, asthma and allergies. There have been some clinical studies on its use in the treatment of hypertension. Many of the studies do not show a significant difference in blood pressure compared to placebo and the data are analyzed in many cases by the authors as the within group change rather the between group change. At best, there may be a small treatment effect in some studies but it seems to be minimal compared to placebo and the data is not sufficient to support its use in the treatment of hypertension.

D. Has the substance been used historically as a drug in compounding?

Databases searched for information on quercetin in regard to Section II.D of this consultation included PubMed, Natural Medicines, European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, and Google.

1. Length of time the substance has been used in pharmacy compounding

Insufficient information is available to determine how long quercetin has been used in pharmacy compounding.

2. The medical condition(s) it has been used to treat

According to the Natural Medicines Database, quercetin is used for atherosclerosis, hypercholesterolemia, hypertension, coronary heart disease, vascular insufficiency, diabetes, cataracts, allergic rhinitis, peptic ulcers, schizophrenia, inflammation, asthma, gout, viral infections, chronic fatigue syndrome, preventing cancer, treating prostatitis, and improving function of kidney transplants, and for increasing exercise endurance and improving athletic performance. Intravenously and intraperitoneally, it is used for treating cancer (Natural Medicines Comprehensive Database 2018).

Results from a Google search using the terms *quercetin compounding pharmacy* yielded multiple dietary supplements; although we did not find evidence of any compounded quercetin products for clinical use in the United States.

3. How widespread its use has been

Insufficient data are available from which to draw conclusions about the extent of use of quercetin in compounded drug products.

4. *Recognition of the substance in other countries or foreign pharmacopeias*

A search of the British Pharmacopoeia (BP 2018), the European Pharmacopoeia (9th Edition, 2018, 9.4), and the Japanese Pharmacopoeia (16th Edition) did not show any monograph listings for quercetin.

Conclusions: Based on internet searches we did not find evidence of any compounded quercetin products for clinical use in the United States.

III. RECOMMENDATION

We have balanced the criteria described in Section II above to evaluate quercetin dihydrate for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** quercetin dihydrate being placed on that list based on the following:

1. Quercetin dihydrate is a thermodynamically stable form compared to other forms of quercetin. It should be stable in a solid oral dosage form if protected from oxygen by the addition of antioxidants. For the aqueous forms, oxidation and degradation occur under basic conditions and the aqueous solutions are unlikely to be stable. Because the dihydrate form is one of the most stable structures of the different crystalline forms, it may have lower bioavailability. Quercetin dihydrate is physically and chemically well characterized.

2. There do not appear to be serious adverse effects with oral ingestion of quercetin for doses within the range of daily intake in food. For intravenous dosing, there are limited data available, but serious adverse effects are reported, including kidney toxicity (≥ 630 mg/m2), dyspnea (≥ 1400 mg/m2) and vomiting (≥ 1700 mg/m2). Quercetin dihydrate has poor and variable bioavailability and may be associated with drug interactions through its effect on the CYP P450 system.

3. There are no clinical studies showing quercetin is effective for the treatment of cancer, asthma and allergy. For hypertension, some studies showed there may be at best a small treatment effect, but it seems to be minimal compared to placebo and the data is not sufficient to show effectiveness in the treatment of hypertension. Because of the lack of adequate effectiveness data, poor and variable bioavailability of quercetin dihydrate and its potential drug interactions, it is not a good candidate to treat any of these diseases.

4. We did not find information that quercetin is or has been compounded for clinical use in the United States.

Based on this information the Agency has considered, a balancing of the four evaluation criteria ***weighs against*** quercetin dihydrate being added to the 503A Bulks list.

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Appendix 1. Summary of Quercetin Rodent Carcinogenicity Studies (National Toxicology Program 1992)

TABLE 1
Quercetin Rodent Carcinogenicity Studies

Strain of Rodent	Route of Administration and Dose[a]	Length of Dosing	Histopathologic Findings[b]	Reference
Male and female F344/DuCrj rats	Diet 0, 1.25, 5.0%	104 weeks	Negative	Ito *et al.*, 1989
Male and female albino rats	Diet 0, 0.1% quercetin	58 weeks	Intestinal and urinary bladder neoplasms in treated groups	Pamukcu *et al.*, 1980
Male and female ACI rats	Diet 1, 5, 10%	850 days	Negative	Hirono *et al.*, 1981
Male and female F344 rats	Diet 0, 0.1%	540 days	Negative	Takanashi *et al.*, 1983
Male and female ddY mice	Diet 0, 2%	842 days	Negative	Saito *et al.*, 1980
Male and female golden hamsters	Diet 0, 1, 4%	351 to 709 days	Negative	Morino *et al.*, 1982
Female ICR/Ha Swiss mice	DMBA as initiator on skin, 25 mg quercetin applied to the skin 3 times per week for 25 weeks	368 days	Negative (no skin neoplasm induction)	Van Duuren and Goldschmidt, 1976
Male F344 rats (effects on initiation/ promotion in urinary bladder)	Diet 0, 5%	a) Quercetin given for 25 weeks after initiation with 0.01% BHBN, b) 5% quercetin given as an initiator for 4 weeks followed by 0.001% BHBN for 29 weeks	No effects on initiation/ promotion in urinary bladder	Hirose *et al.*, 1983
Female ICR mice	Skin initiated with DMBA, promoted with telocidin twice per week, quercetin (30 μmol) treatment applied topically with telocidin	20 weeks	Suppressed skin neoplasm formation	Nishino *et al.*, 1984a

(continued)

Appendix 1 (continued)

TABLE 1
Quercetin Rodent Carcinogenicity Studies (continued)

Strain of Rodent	Route of Administration and Dose	Length of Dosing	Histopathologic Findings[a]	Reference
Male and female A(A/JJms) mice[c]	Diet 0, 5%	23 weeks	Negative (no increase or decrease in lung neoplasms)	Hosaka and Hirono, 1981
Female CD-1 mice	Skin-initiated with DMBA, promoted with TPA, quercetin (30 μmol) applied topically after each TPA treatment	18 weeks	Suppressed skin neoplasm formation	Kato *et al.*, 1983

[a] DMBA = 7,12-dimethyl[a]anthracene; TPA = 12-*o*-tetradecanoylphorbol-13-acetate; BHBN = N-butyl-N-(4-hydroxylbutyl)nitrosamine
[b] Negative = no evidence for neoplasms related to administration of quercetin
[c] This strain develops lung neoplasms at a low incidence by week 23.