

Notifications and Related Issues” (available at <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/ucm257563.htm>). Some comments argued that FDA underestimated the burden of the notification procedures under § 190.6 because it failed to take into account the provisions of the new draft guidance. (Response) FDA disagrees that we underestimated the burden of the

notification procedures under § 190.6. The collection of information analysis in the June 3, 2011, notice was limited to the sole collection of information contained in § 190.6; that is, the regulation itself and not the provisions of the new draft guidance. The notification requirements set forth in § 190.6 remain unchanged. The notice of availability for the new draft guidance (76 FR 39111, July 5, 2011) states that FDA will estimate the paperwork

burden of the draft guidance document and submit it for OMB review under the PRA in a future issue of the **Federal Register**. Comments on the new draft guidance and any information collection provisions therein are outside the scope of the comment request in the June 3, 2011, notice, and will not be discussed in this document.

FDA estimates the burden of this collection of information as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN ¹

21 CFR Section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
190.6	55	1	55	20	1,100

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

As previously discussed, the Agency believes that there will be minimal burden on the industry to generate data to meet the requirements of the premarket notification program because the Agency is requesting only that information that the manufacturer or distributor should already have developed as the basis for its conclusion that a dietary supplement containing an NDI will reasonably be expected to be safe. Therefore, the Agency estimates that extracting and summarizing the relevant information from the company's files, and presenting it in a format that will meet the requirements of section 413(a) of the FD&C Act and § 190.6 will require a burden of approximately 20 hours of work per submission.

The estimated number of premarket notifications and hours per response is an average based on the Agency's experience with notifications received during the last 3 years and information from firms that have submitted recent premarket notifications. FDA received 77 notifications in 2008, 39 notifications in 2009, and 48 notifications in 2010, for an average of 55 notifications. Accordingly, we estimate that 55 respondents will submit 1 premarket notification each and that it will take a respondent 20 hours to prepare the notification, for a total of 1,100 hours.

Dated: August 15, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-N-0403]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Substantiation for Dietary Supplement Claims Made Under the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by September 19, 2011.

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7285, or e-mailed to oir_submission@omb.eop.gov. All comments should be identified with the OMB control number 0910-0626. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Denver Presley, Jr., Office of Information Management, Food and Drug Administration, 1350 Piccard Dr., PI50-

400B, Rockville, MD 20850, 301-796-3793.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Substantiation for Dietary Supplement Claims Made Under the Federal Food, Drug, and Cosmetic Act—21 U.S.C. 343(r)(6)—(OMB Control Number 0910-0626)—Extension

Section 403(r)(6) of the Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 343(r)(6)) requires that a manufacturer of a dietary supplement making a nutritional deficiency, structure/function, or general well-being claim have substantiation that the statement is truthful and not misleading. Under section 403(r)(6)(A) of the FD&C Act, such a statement is one that “claims a benefit related to a classical nutrient deficiency disease and discloses the prevalence of such disease in the United States, describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, or describes general well-being from consumption for a nutrient or dietary ingredient.”

The guidance document entitled “Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act” provides FDA's recommendations to manufacturers about the amount, type, and quality of evidence they should have to substantiate a claim under section 403(r)(6) of the FD&C Act. The guidance does not discuss the types of claims that can be made concerning

the effect of a dietary supplement on the structure or function of the body, nor does it discuss criteria to determine when a statement about a dietary supplement is a disease claim. The guidance document is intended to assist manufacturers in their efforts to comply with Section 403(r)(6). Persons with access to the Internet may obtain the guidance at <http://www.cfsan.fda.gov/~dms/guidance.html>.

Dietary supplement manufacturers collect the necessary substantiating information for their product as required by section 403(r)(6) of the FD&C Act. The guidance provides information to manufacturers to assist them in doing so. The recommendations contained in the guidance are voluntary. Dietary supplement manufacturers will only need to collect information to substantiate their product's nutritional deficiency, structure/function, or general well-being claim if they choose to place a claim on their product's label.

The standard discussed in the guidance for substantiation of a claim on the labeling of a dietary supplement is consistent with standards set by the Federal Trade Commission for dietary supplements and other health-related products that the claim be based on competent and reliable scientific evidence. This evidence standard is broad enough that some dietary supplement manufacturers may only need to collect peer-reviewed scientific journal articles to substantiate their claims; other dietary supplement manufacturers whose products have properties that are less well documented may have to conduct studies to build a body of evidence to support their claims. It is unlikely that a dietary supplement manufacturer will attempt to make a claim when the cost of obtaining the evidence to support the claim outweighs the benefits of having the claim on the product's label. It is likely that manufacturers will seek substantiation for their claims in the scientific literature.

The time it takes to assemble the necessary scientific information to support their claims depends on the product and the claimed benefits. If the product is one of several on the market making a particular claim for which there is adequate publicly available and widely established evidence supporting the claim, then the time to gather supporting data will be minimal; if the product is the first of its kind to make a particular claim or the evidence supporting the claim is less publicly available or not widely established, then gathering the appropriate scientific evidence to substantiate the claim will be more time consuming.

In the **Federal Register** of June 3, 2011 (76 FR 32215), FDA published a 60-day notice requesting public comment on the proposed extension of this collection of information. FDA received five letters in response to the notice, each containing multiple comments. Several comments were generally supportive of the necessity of the information collection provisions of the guidance. Additional comments were outside the scope of the four collection of information topics on which the notice solicits comments, and will not be discussed in this document.

(Comment 1) Several comment letters noted the accuracy of FDA's estimate of the burden hours, which ranges from 44 to 120 hours per claim depending upon the nature of the claim.

(Response) FDA agrees. As discussed in this notice, if the product is one of several on the market making a particular claim for which there is adequate publicly available and widely established evidence supporting the claim, then the time to gather supporting data will be minimal; if the product is the first of its kind to make a particular claim or the evidence supporting the claim is less publicly available or not widely established, then gathering the appropriate scientific evidence to substantiate the claim will be more time consuming.

(Comment 2) One comment stated that FDA incorrectly estimated that there are no capital costs associated with developing information that meets the guidance's recommendations to manufacturers about the amount, type, and quality of evidence they should have to substantiate a claim under section 403(r)(6) of the FD&C Act. The comment argued that FDA did not fully consider that manufacturers invest significant capital resources in subscriptions to scientific journals and libraries to gain access to full-text scientific literature, consultants to develop appropriate wording for claims, and legal review of claims.

(Response) FDA disagrees. The comment mischaracterizes the significant costs associated with hiring consultants, obtaining reference materials, and securing legal review of a notification as capital costs. For purposes of information collection requests under the Paperwork Reduction Act, capital costs are costs for equipment, machinery, and construction that, if not for FDA's request or requirement, the respondent would not incur. This includes: Buying new software and new computer equipment; monitoring, sampling, drilling and testing equipment; record storage facilities; the cost of purchasing

or contracting out information collection services; and postage costs to mail in a report. Capital costs do not include costs to achieve regulatory compliance with requirements not associated with the information collection. Subscriptions to scientific journals and libraries to gain access to full-text scientific literature, hiring consultants to develop appropriate wording for claims, and legal review of claims are costs associated with developing information that the manufacturer uses to satisfy itself that it has met the guidance's recommendations to manufacturers about the amount, type, and quality of evidence they should have to substantiate a claim under section 403(r)(6) of the FD&C Act; thus, these costs are not capital costs because they are costs associated with achieving regulatory compliance with requirements of the FD&C Act, not costs associated specifically with equipment, machinery, and construction needed to retain appropriate substantiating evidence. FDA notes that it has added a reference to these costs as "Costs to Respondent" in section 12(b) of the supporting statement component of the Information Collection Request that it has submitted to OMB.

(Comment 3) One comment suggested that, to enhance the quality, utility and clarity of the information as well as minimize the burden of collection on manufacturers, FDA explore options for electronic submission and a digital, interactive database so the information can be easily reviewed, collated, analyzed and reported.

(Response) FDA notes that dietary supplement manufacturers making a nutritional deficiency, structure/function, or general well-being claim are required by section 403(r)(6) of the FD&C Act to have substantiation that the claim is truthful and not misleading. There is no requirement in the FD&C Act or recommendation in the guidance document that manufacturers submit the substantiation information to FDA. The information is retained by the manufacturers in their records. The guidance does not specifically prescribe the use of automated, electronic, mechanical, or other technological techniques or other forms of information technology as necessary for use by dietary supplement manufacturers. Companies are free to use whatever forms of information technology that may best assist them in developing substantiation information.

(Comment 4) One comment stated that FDA should provide clarity on what type of evidence is needed to substantiate a traditional use claim. The

comment argued that Canada, the European Union, and Australia recognize traditional use evidence to support appropriate claim statements. The comment stated that several authoritative labeling standards monographs for herbal products specify traditional use claim statements, such as Health Canada Natural Health Products Directorate (NHPD) monographs, European Medicines Agency (EMA) European Community Herbal Monographs, and World Health Organization (WHO) Monographs on Selected Medicinal Plants. The comment recommended that FDA allow such monographs as acceptable pieces of evidence to substantiate a traditional use claim. The comment concluded that FDA's acceptance of label claim statements listed in appropriate monographs and clear guidance on other types of evidence that could be used to substantiate traditional use claims would significantly reduce the burden of collecting such information.

(Response) FDA disagrees that traditional use evidence is sufficient to meet the substantiation standard of competent and reliable scientific evidence applied by FDA in "Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act." A claim based on historical or traditional use is not a claim that is substantiated by scientific evidence. Claims permitted by foreign and international monographs do not always have to be substantiated by

scientific studies but may be acceptable if, in some cases, they are accompanied by disclosures that the claim is not scientifically established or are deemed appropriate merely by their history of use for a particular intended use. Therefore, FDA does not believe that these monographs are adequate to meet the substantiation standard applied by FDA.

(Comment 5) One comment suggested that FDA should identify monographs that are already recognized in other countries as substantiation for claims made for products that are manufactured in strict conformity to these monographs. The comment identified two specific compendia of monographs and recommended that FDA recognize these monographs as "constituting in and of themselves substantiation for a pre-existing widely established claim that may be made for a dietary supplement under section 403(r)(6) of the FD&C Act, so long as the claim is not a drug claim and is significantly similar to the use or purpose described in a monograph, and the conditions and level of use of the ingredient(s) that is the basis of the claim is within the dosage range described in the monograph."

(Response) FDA disagrees that foreign or other third-party monographs assure that a claim is substantiated by competent and reliable scientific evidence, which is the standard applied by FDA. Claims that may be permitted by foreign and international monographs do not always have to be substantiated by scientific studies but

may be acceptable if substantiated, in whole or in part, by evidence not deemed adequate for a claim made for a dietary supplement in the United States, such as animal data or traditional medicinal use. Therefore, FDA does not believe that these monographs are adequate to meet the substantiation standard applied by FDA

(Comment 6) One comment argued that FDA overestimated the burden of the information collection by overestimating the number of respondents. The comment noted that FDA's website contains a list of notifications submitted in compliance with the requirements of 21 CFR 101.93 (a)(1) and stated that their review of the notices submitted between December 2007 and August 2010 indicates that the Agency has received an average of approximately 1,600 to 1,650 annually during this time, not the 2,001 per year estimated by FDA.

(Response) FDA disagrees that it has overestimated the number of respondents and stands by the estimate of 2,001 annual respondents for the next 3 years. The number of such notifications received by FDA in any given year can vary quite widely (by up to 300). In addition, the number of firms keeping records in anticipation of submitting a notification may be greater than the number of notification submitted. Thus, FDA believes retaining the estimate of 2,001 from the prior submission is appropriate.

FDA estimates the burden of this collection of information as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN ¹

Claim type	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Widely known, established	667	1	667	44	29,348
Pre-existing, not widely established	667	1	667	120	80,040
Novel	667	1	667	120	80,040
Total					189,428

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

FDA assumes that it will take 44 hours to assemble information needed to substantiate a claim on a particular dietary supplement when the claim is widely known and established. FDA believes it will take closer to 120 hours to assemble supporting scientific information when the claim is novel or when the claim is pre-existing but the scientific underpinnings of the claim are not widely established. These are claims that may be based on emerging science, where conducting literature searches and understanding the literature takes

time. It is also possible that references for claims made for some dietary ingredients or dietary supplements may primarily be found in foreign journals and in foreign languages or in the older, classical literature where it is not available on computerized literature databases or in the major scientific reference databases, such as the National Library of Medicine's literature database, all of which increases the time of obtaining substantiation.

In the **Federal Register** of January 6, 2000, FDA published a final rule on

statements made for dietary supplements concerning the effect of the product on the structure or function of the body (65 FR 1000). FDA estimated that there were 29,000 dietary supplement products marketed in the United States (65 FR 1000 at 1045). Assuming that the flow of new products is 10 percent per year, then 2,900 new dietary supplement products will come on the market each year. The structure/function final rule estimated that about 69 percent of dietary supplements have a claim on their labels, most probably a

structure/function claim (65 FR 1000 at 1046). Therefore, we assume that supplement manufacturers will need time to assemble the evidence to substantiate each of the 2,001 claims ($2,900 \times 69$ percent) made each year. If we assume that the 2,001 claims are equally likely to be pre-existing widely established claims, novel claims, or pre-existing claims that are not widely established, then we can expect 667 of each of these types of claims to be substantiated per year. Table 1 of this document shows that the annual burden hours associated with assembling evidence for claims is 189,428 (the sum of 667×44 hours, 667×120 hours, and 667×120 hours).

Dated: August 15, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2010-P-0628]

Determination That PENTETATE CALCIUM TRISODIUM (Trisodium Calcium Diethylenetriaminepentaacetate) Solution for Intravenous or Inhalation Administration, Equivalent to 1 Gram Base/5 Milliliters (Equivalent to 200 Milligrams Base/Milliliter), Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that PENTETATE CALCIUM TRISODIUM (trisodium calcium diethylenetriaminepentaacetate (Ca-DTPA)) solution for intravenous or inhalation administration, equivalent to (EQ) 1 gram (g) base/5 milliliters (mL) (EQ 200 milligrams (mg) base/mL) was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for PENTETATE CALCIUM TRISODIUM (Ca-DTPA) solution for intravenous or inhalation administration (EQ 1 g base/5 mL (EQ 200 mg base/mL)), if all other legal and regulatory requirements are met.

FOR FURTHER INFORMATION CONTACT: Alexis Reisin Miller, Center for Drug Evaluation and Research, Food and

Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6356, Silver Spring, MD 20993-0002, 301-796-3977.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the “listed drug,” which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is known generally as the “Orange Book.” Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

PENTETATE CALCIUM TRISODIUM (Ca-DTPA) solution for intravenous or inhalation administration (EQ 1 g base/5 mL (EQ 200 mg base/mL)) is the subject of NDA 21-749, held by Hameln Pharmaceuticals GmbH, and initially approved on August 11, 2004. PENTETATE CALCIUM TRISODIUM (Ca-DTPA) solution for intravenous or inhalation administration (EQ 1 g base/5 mL (EQ 200 mg base/mL)) is indicated for treatment of individuals with known or suspected internal contamination

with plutonium, americium, or curium to increase the rates of elimination.

In a letter dated June 24, 2010, Hameln Pharmaceuticals GmbH notified FDA that PENTETATE CALCIUM TRISODIUM (Ca-DTPA) solution for intravenous or inhalation administration (EQ 1 g base/5 mL (EQ 200 mg base/mL)) was being discontinued, and FDA moved the drug product to the “Discontinued Drug Product List” section of the Orange Book.

Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG submitted a citizen petition dated November 26, 2010 (Docket No. FDA-2010-P-0628), under 21 CFR 10.30, requesting that the Agency determine whether PENTETATE CALCIUM TRISODIUM (Ca-DTPA) solution for intravenous or inhalation administration (EQ 1 g base/5 mL (EQ 200 mg base/mL)) was withdrawn from sale for reasons of safety or effectiveness.

After considering the citizen petition and reviewing Agency records, FDA has determined under § 314.161 that PENTETATE CALCIUM TRISODIUM (Ca-DTPA) solution for intravenous or inhalation administration (EQ 1 g base/5 mL (EQ 200 mg base/mL)) was not withdrawn for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that PENTETATE CALCIUM TRISODIUM (Ca-DTPA) solution for intravenous or inhalation administration (EQ 1 g base/5 mL (EQ 200 mg base/mL)) was withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of PENTETATE CALCIUM TRISODIUM (Ca-DTPA) solution for intravenous or inhalation administration (EQ 1 g base/5 mL (EQ 200 mg base/mL)) from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. We have found no information that would indicate that this product was withdrawn from sale for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list PENTETATE CALCIUM TRISODIUM (Ca-DTPA) solution for intravenous or inhalation administration (EQ 1 g base/5 mL (EQ 200 mg base/mL)) in the “Discontinued Drug Product List” section of the Orange Book. The “Discontinued Drug Product List” delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to PENTETATE CALCIUM TRISODIUM (Ca-DTPA) solution for intravenous or inhalation