

BEFORE
THE UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

COMMENTS OF
TRADITIONAL MEDICINALS, INC.
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ON THE FOOD AND DRUG ADMINISTRATION'S REQUEST FOR COMMENT
ON DRAFT GUIDANCE:

"GUIDANCE FOR INDUSTRY: SUBSTANTIATION FOR DIETARY
SUPPLEMENT CLAIMS MADE UNDER SECTION 403(r)(6) OF THE FEDERAL
FOOD, DRUG AND COSMETIC ACT"

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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Traditional Medicinals, Inc. submits in duplicate the following comments in response to the Food and Drug Administration Draft Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal, Food, Drug and Cosmetic Act [Docket No. 2004D-0466].

Traditional Medicinals is a manufacturer and marketer of herbal products that are regulated as "Dietary Supplement Products" by the United States Food and Drug Administration (FDA). Our same herbal products are regulated in Canada as "Natural Health Products" by the Health Canada Natural Health Products Directorate (NHPD) and will be regulated as "Traditional Herbal Medicinal Products" in EU Member States under the new Directive 2004/24/EC on Traditional Herbal Medicinal Products.

Many US companies, such as ours, market herbal products internationally and therefore must already internally harmonize various regulatory requirements including those concerning the levels of evidence required to support claims. We strongly urge FDA to review the existing guidelines in this regard that have been published by your regulatory counterparts, in particular Health Canada NHPD, the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Australian Therapeutic Goods Administration (TGA), and to make a concerted effort to harmonize certain relevant parts of the claim substantiation guidance. Such an effort will help US companies to streamline their substantiation activities. While we are cognizant that the same herbal products are regulated under food/dietary supplement regulations in the USA but under drug regulations in other western countries, we believe that close comparability of the levels of evidence requirements is reasonable, particularly in the case of traditional use claims.

The FDA Draft Guidance for Industry states that for this guidance, the agency drew on its own expertise, in addition to the Federal Trade Commission (FTC) experience with its policy on substantiating claims made for dietary supplements in advertising, and recommendations from the Commission on Dietary Supplement Labels¹. FDA further states that the guidance document is modeled on, and complements the FTC guidance document "Dietary Supplements: An Advertising Guide for Industry."² However, while the FTC guidance includes a specific section on "Claims Based on Traditional Use" (pages 20-22 of FTC document), the word 'traditional' appears only once in the FDA draft guidance, within Example 16 where it is placed in a context with testimonial experience. In this context, FDA states that neither source of evidence (testimonial and traditional use) would adequately substantiate the claim because neither source is based on scientific evidence. While we agree that testimonial evidence would be insufficient, we strongly disagree with the assertion that traditional use would be insufficient evidence. FDA should be aware that traditional use claims and the requisite levels of evidence to support them are well-defined by its regulatory counterparts in Australia, Canada and EU Member States, among others. Traditional use claims have little or nothing to do with anecdotal or testimonial statements, as is implied in the FDA document.

Concerning the statement that for this guidance FDA drew from the recommendations of the Report of the Commission on Dietary Supplement Labels, FDA's comments on the Report were published in the Federal Register on April 29, 1998.³ Specifically with regard to substantiation file content, FDA stated that the agency agreed with the Commission's guidance. The Commission Report includes guidance on what quantity and quality of evidence should be used to substantiate claims made under section 403(r)(6) of the act. The Commission Report also includes guidance on the content of substantiation files

¹ Commission on Dietary Supplement Labels. *The Report of the Commission on Dietary Supplement Labels*. Washington, DC: Commission on Dietary Supplement Labels. November 1997. Available at: <http://www.health.gov/dietsupp/cover.htm>

² Federal Trade Commission. *Dietary Supplements: An Advertising Guide for Industry*. Federal Trade Commission Bureau of Consumer Protection. April 2001. Available at: <http://www.ftc.gov/bcp/online/pubs/buspubs/dietsupp.pdf>

³ Food and Drug Administration (FDA). Dietary Supplements; Comments on Report of the Commission on Dietary Supplement Labels, *Federal Register*. April 29, 1998;63(82):23633-23637]

for statements made under section 403(r)(6) of the act, including the notification letter, identification of the product's ingredients, evidence to substantiate the statements, evidence to substantiate safety, assurances that good manufacturing practices were followed, and the qualifications of the person(s) who reviewed the data on safety and efficacy.

It is therefore important to point out that the Commission Report recommendations for evidence to substantiate the statements include the following: "Research or monographs from appropriate foreign sources may be cited, along with evidence that specific uses or claims are approved in other countries... Where historical use is cited as the evidence for a statement, the composition of the product should correspond with the material for which such claims of historical use may be made." This recommendation relates to traditional use claims because many authoritative documents and/or monographs from foreign health authorities specify traditional use claims for herbal products, particularly those published by the health authorities in Australia, Canada and EU Member States, among many others.

In the section of FDA's draft guidance entitled "What Are the Types of Evidence that May Substantiate a Claim?" traditional use evidence is unrepresented. We strongly urge FDA to include a special section on traditional use that is in line with the traditional use evidence requirements of your regulatory counterparts. If an herbal dietary supplement product label bears a traditional use statement that meets the evidence requirements of Australia, Canada and/or the UK, the FDA should accept a comparable level of evidence for the substantiation of dietary supplement structure/function claims.

Our suggestion is that FDA explicitly state that traditional use evidence can be sufficient to substantiate a claim and that certain existing guidelines are acceptable for US companies to follow for determination of levels of evidence to support traditional use claims. For example, any of the following authoritative sources of information could be referenced by FDA in this regard:

- Health Canada Natural Health Products Directorate (NHPD). **Evidence to Support Traditional Use.** In: Evidence for Safety and Efficacy of Finished Natural Health Products. Ottawa, Ontario: NHPD. 2003. Available at: http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/evidence_for_safety_efficacy_finished_nhp_e.pdf
- Medicines and Healthcare products Regulatory Agency (MHRA). **Briefing note: sources of evidence of traditional use under the proposed Directive on Traditional Herbal Medicinal Products.** United Kingdom: MHRA. August 2004. Available at: http://medicines.mhra.gov.uk/ourwork/licensingmeds/herbals/meds/dir_evidtraduse.pdf
- Therapeutic Products Administration (TGA). **How to use evidence of traditional use to support claims.** In: Guidelines for Levels and Kinds of Evidence to Support Indications and Claims. Woden, Australia: TGA. October 2001. Available at: <http://www.tga.gov.au/docs/pdf/tgaccevi.pdf>

As a specific example to illustrate our main point, we provide a traditional use claim for peppermint leaf tea and/or tincture for alleviating flatulence and bloating. In the preamble of FDA's Final Rule (January 2000), "Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body",⁴ FDA states: "All of the claims listed in the comment from the "Antiflatulents" (antigas) monograph are acceptable structure/function claims, because the symptoms in the claims are not sufficiently characteristic of specific diseases: "Alleviates the symptoms referred to as gas," "alleviates bloating," "alleviates pressure," "alleviates fullness," and "alleviates stuffed feeling." In the case of peppermint leaf tea or tincture, there are a number of authoritative monographs available that indicate its traditional use for minor digestive disorders such as bloating, flatulence, fullness or gas. Assuming that the quality of the peppermint leaf (e.g. USP-NF- or Ph Eur- grade) and the single- and daily dosage recommendations conform to the requirements of the specified monograph, it is our view that such monographs should be specified in FDA's guidance as allowable types of evidence to substantiate a dietary supplement structure/function claim statement. This is also in keeping with the recommendations of the Report of the

⁴ Food and Drug Administration. Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body; Final Rule. Federal Register. January 6, 2000;65(4):999-1050. Available at: <http://www.cfsan.fda.gov/~lrd/fr000106.html>

Commission on Dietary Supplement Labels. For example, any of the following authoritative sources of information should be specifically allowed to substantiate a claim statement for peppermint leaf tea or tincture:

- The Health Canada NHPD Peppermint monograph⁵ indicates its use as “Traditionally used as a digestive aid,” “Traditionally used for the relief of flatulence and/or bloating due to excess gas production” and “Traditionally used for symptomatic treatment of digestive disorders.”
- The World Health Organization (WHO) Peppermint leaf monograph⁶ indicates the traditional use of peppermint tea infusion for “symptomatic treatment of dyspepsia, flatulence and intestinal colic.”
- The German BfArM “standard license” monograph for peppermint leaf tea⁷ indicates its use for spasmodic complaints of the gastrointestinal tract as well as of the gallbladder and biliary ducts.
- The European Agency for the Evaluation of Medicinal Products (EMA) Peppermint leaf monograph⁸ indicates the use of peppermint leaf tea and/or tincture as an: “Herbal medicinal product for the symptomatic relief of minor digestive disorders.”

With regard to the Supplementary Information, Section II (Federal Register, November 9, 2004;69(216):64962-64964) FDA states: “FDA assumes that it will take only about an hour to assemble information needed to substantiate a claim on a particular dietary supplement when the claim is widely known and established,” and goes on to state: “FDA believes it will take close 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.” We seek further clarification on the one-hour estimate, specifically in the context of traditional use claims. FDA should clarify that if the traditional

⁵ Health Canada Natural Health Products Directorate (NHPD). Peppermint—Draft Monograph. Ottawa, ON: NHPD. January 19, 2004. Available at: http://www.hc-sc.gc.ca/hpfb-dqpsa/nhpd-dpsn/mono_peppermint_e.pdf

⁶ World Health Organization (WHO). Folium Menthae Piperitae. In: WHO Monographs on Selected Medicinal Plants, Volume 2. Geneva, Switzerland: WHO. 2002;199-205. Available at: <http://www.who.int/medicines/library/trm/medicinalplants/vol2/199to205.pdf>

⁷ Braun R, Surmann P, Wendt R, Wichtl M, Ziegenmeyer J (eds.) Pfefferminzblätter. In: Standardzulassungen für Fertigarzneimittel Text und Kommentar, 11. Ergänzungslieferung. Stuttgart, Germany: Deutscher Apotheker Verlag. February 1996; Zulassungsnummer: 1499.99.99.

⁸ European Agency for the Evaluation of Medicinal Products (EMA). Final Proposal for a Core-Data For Peppermint Leaf. London, UK: EMA Working Party on Herbal Medicinal Products (HMPWP). 17 December 2003;EMA/HMPWP/1418/02. Available at: <http://www.emea.eu.int/pdfs/human/hmpwp/141802en.pdf>

use claim is widely known and established, for example evidenced by the fact that the claim is published in two or more separate authoritative monographs (e.g. EMEA, German Commission E, Health Canada NHPD, WHO, etc...), the estimated one-hour to access copies of those monographs and reference them in the substantiation file will satisfy the substantiation requirement.

Up until this point, our company has been preparing its product substantiation files based on the guidance provided in the Report of the Commission on Dietary Supplement Labels. Based on our experience thus far, having prepared about 50 substantiation files, the preparation of substantiation files for single-herb or traditional two- or three-herb combination products has ranged between 18 and 24 labor hours per file, plus an additional 2-4 hours of independent expert reviewer time before finalizing the file. For proprietary multi-herb formulas, our average has been closer to 40 labor hours per file, plus the additional independent peer review hours.

Respectfully submitted,

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