

Docket No. 00D-1392

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**BEFORE THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

COMMENTS OF THE
AMERICAN HERBAL PRODUCTS ASSOCIATION

Related to
DRAFT GUIDANCE FOR INDUSTRY ON BOTANICAL DRUG PRODUCTS

October 20, 2000

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The American Herbal Products Association (“AHPA”) is the national trade association and voice of the herbal products industry, comprised of companies doing business as growers, importers, manufacturers, and marketers of herbs and herbal products. AHPA serves its members by promoting the responsible commerce of products that contain herbs. Most AHPA members sell botanicals as dietary supplements or as OTC monograph drug products. Some are also interested in the development of new botanical drug products. In this regard AHPA appreciates the publication of the Draft *Guidance for Industry – Botanical Drug Products* (the Guidance).

Background

The Guidance provides important information regarding botanical products intended for use as drugs. In the Guidance, the Agency has represented its current thinking on a number of issues relevant to such products, including:

- amending an over-the-counter (OTC) drug monograph and marketing a botanical drug under an OTC monograph
- the criteria that would constitute the need for FDA to approve a new drug application (NDA) for a botanical drug
- specific issues related to investigational new drug applications (INDs) for botanical drugs, including botanical products that are currently lawfully marketed as foods and dietary supplements in the United States, those that have been previously marketed but not in the United States, and those that have not been lawfully marketed anywhere or that have known safety issues.

In its discussion of each of these topics, the agency identified areas in which it “finds it may be appropriate to apply regulatory policies that differ from those that apply to synthetic, semisynthetic, or otherwise highly purified or chemically

modified drugs.” At the same time, the Guidance makes it clear that most policies that govern OTC monograph, NDAs and INDs will be the same for botanical drugs as they currently are for all other drugs.

AHPA agrees that it is sometimes appropriate to apply different regulatory policies to botanical drugs than to synthetic or highly purified drugs. AHPA agrees with most but disagrees with some of the specific differences identified in the Guidance. AHPA also agrees that most policies that govern the areas that are the subject of the Guidance should be the same for botanical drugs as for all other drugs.

One area in which the agency identifies a different regulatory policy is seemingly based on the acknowledgment of the Guidance that botanical drugs “are usually prepared as complex mixtures.” The agency states its intention to refrain from treating botanical drug products derived from a single part of one species as combination drugs and further states its intention to propose revisions that will allow similar exemptions under certain circumstances for botanical drugs derived from multiple parts of one species, or from parts of different plant species. AHPA agrees that such exemptions should be made so that most botanical drugs will not be treated as combination drugs.

Botanicals as OTC Drugs

The Guidance discusses the criteria by which a botanical drug might qualify as an OTC drug and describes the process whereby an amendment to an OTC monograph can be requested. In most of the described elements, the agency refers to the relevant sections of Title 21 of the *Code of Federal Regulations*, thus implying that such requests for botanical drugs would be no different than those for other drugs. The one difference that is described is the statement that, although OTC monographs do not ordinarily contain information on chemistry, manufacturing, and controls (CMC), “tests and specifications” for a botanical drug product should be part of the OTC monograph “either directly or by cross-reference.” No explanation is offered for this seeming higher standard to which botanical OTC drug products will be held.

AHPA strongly opposes any position that would require CMC information for new botanical OTC drug products if such information is not required for non-botanical OTC drugs. The listings of active ingredients in current OTC monographs usually state only the name of each drug substance, whether or not that substance is botanical in origin. For example, in the OTC monograph for Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products (21 CFR 341), a total of 43 active ingredients are listed without any further specifications. In addition, we are aware that certain of the botanical OTC drugs currently approved for use do not include "tests and specifications" as part of the monograph. One such example can be found in the monograph for Astringent Drug Products (21 CFR 347, Subpart A) where "Witch hazel" is listed as one of the three approved active ingredients, without further specification.

At the same time, AHPA believes that accurate identification of all OTC drug substances, including botanical drug substances, should be assured. In the case of botanical drug substances, this can be accomplished by choosing specific methods and references that are relevant to the particular species as well as to the form of the plant at the time that the botanical raw material comes into possession of a manufacturer (e.g., whole; cut; powdered; extracted).

It is possible that the our perception that the Guidance intends to establish a different regulatory policy for CMC information for botanical OTC drug products is based on a misunderstanding of the intent of this section of the Guidance. We therefore request clarification of the need for any different standard for botanical OTC drug products.

A further concern to AHPA and its members is the seemingly higher standard for establishment of efficacy envisioned by the Guidance than that currently required for other OTC drug products. The Guidance states that "For a botanical drug substance to be included in an OTC monograph, there must be published data establishing general recognition of safety and effectiveness, including results of adequate and well-controlled clinical studies." By comparison, the existing procedures for classifying OTC drugs as generally recognized as safe and effective are found in 21 CFR 330.10, and state greater flexibility, as follows:

Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.126(b) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

In addition to this existing regulation, the Commission on Dietary Supplement Labels discussed its perspective on the relevance of OTC monographs for botanical products in its Final Report of November 24, 1997. The Commission provided examples of amendments to OTC monographs that were approved with a waiver by FDA of the narrowest requirement for controlled clinical investigations. The Commission also encouraged manufacturers "wishing to make claims that go beyond those allowed by NLEA or DSHEA to submit them for OTC review." Addressing the fact that many products now sold as OTC drugs may have been held to a different standard than is now assumed for new drugs, the Commission recommended that "the type of evidence that was required for OTC drugs already approved for certain uses should be the benchmark for determining what is generally recognized as sufficient evidence for botanical products intended for the same uses now. If a higher standard is deemed to be required today than was required historically, justification should be provided by FDA to show that such a higher standard is in the best interest of consumers who are currently using OTC drugs approved under a different standard." The Commission further stated support for an "assumption that there would be equity in the OTC review process and that it would apply equally to currently approved OTC drugs and to any botanical product covered by a new review."

AHPA agrees with the conclusions of the Commission cited above, and requests that FDA address the issues addressed in their findings, and specifically define any justification for failing to provide equity in the OTC amendment process that would apply equally to any newly submitted amendments for botanical OTC drugs and currently approved OTC drugs.

INDs for Botanical Drugs

Most of the Guidance is concerned with the process of submitting investigational new drug applications (INDs) for botanical drugs. The Guidance identifies particular areas where the agency has determined that it may be appropriate to apply regulatory policies for botanical drugs that differ from those that apply to other drugs. At the same time, the Guidance makes it clear that most policies that govern INDs should be assumed to be the same for botanical drugs as they currently are for all other drugs.

The primary difference that is identified by the Guidance is in the area of the relevance of historical use in evaluation of safety in early phases of botanical drug investigation. The Guidance provides the agency and its review division personnel with discretion to waive various requirements that are routine for the review and approval of new chemical entities. In particular, Sections VI. A., VII. C., VIII. C. indicate that previous human experience may be sufficient to demonstrate the safety of a botanical product for initial (phase 1 and phase 2) clinical studies. AHPA believes that such an approach accurately represents the usefulness of taking historical usage of a botanical drug substance into account when evaluating safety for initial clinical studies.

On the other hand, Section IX. C. states that previous human experience may be *insufficient* to support safety for expanded (phase 3) clinical studies. AHPA reads this as permitting the presentation of data regarding previous human use even into the later phase of clinical study of a botanical drug product. AHPA further reads this as an indication that the agency and its review division personnel are not foreclosing such presentations with respect to the need for additional toxicity

data, and may, in fact, consider such prior use data to be sufficient to support safety throughout a clinical study.

AHPA is also aware of comments filed by Botanical Enterprises, Inc. (BEI), and specifically of that section of BEI's comments entitled "Preclinical Safety Assessment." Those comments urge FDA to "carefully consider the appropriateness of using animal data to predict human safety for products with a significant history of human use" and suggest that "previous safe human exposure should be used as the primary indicator of human safety where available, with scientific data from animal testing being required only when relevant human use data is unavailable." AHPA joins BEI in these recommendations.

Specific Issues

- The weight-to-weight ratios given as examples in describing the composition of the botanical drug products are inconsistent with the established use of these ratios. AHPA's Botanical Extract Committee has recently completed a paper (in press) entitled *Guidance for the Retail Labeling of Dietary Supplements Containing Soft or Powdered Botanical Extracts*, in which the standard commercial use of these expressions is defined to conform to the following convention: "The first number shall represent the amount of dried botanical starting material, the second number shall represent the amount of finished total extract. For example, a 4:1 extract is one in which each kilogram (or other unit) of finished total extract represents the extractives from four kilograms (or other unit) of dried botanical starting. Where fresh rather than dried starting material is used in determining the ratio, this fact must be disclosed."
- The Guidance states in Section VIII. A. that the description of the botanicals used should indicate whether the species is determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Flora and Fauna (CITES). AHPA believes that, while it is essential to refrain from the use of wild

harvested populations of species listed as endangered by the Endangered Species Act or in Appendix I of CITES, the Guidance should clarify that cultivation of these species provides relief to potential environmental pressure.

- AHPA is concerned that the recognition by FDA of one or more botanical drugs may result in an assumption, either by the agency or by the company who successfully completes an NDA, that products that contain the same botanical ingredient will no longer be allowed to be legally sold as dietary supplements. This concern exists whether a newly approved botanical drug is for a novel use, never before ascribed to that particular botanical, or for a traditionally recognized use. This concern also applies to the approval of an amendment to an OTC monograph to include a botanical ingredient not now listed in that monograph.

AHPA is aware, and the Guidance states, that the Federal Food, Drug, and Cosmetic Act (the Act) characterizes a product primarily based on its intended use. AHPA is also aware that the Dietary Supplement Health and Education Act (DSHEA) allows the marketing of herbs and other botanicals and extracts and concentrates of herbs and other botanicals as dietary ingredients in dietary supplements, and that DSHEA specifically states that articles approved as new drugs under Section 505 of the Act that were marketed as dietary supplements prior to such approval are allowed to continue to be marketed as dietary supplements.

AHPA believes that there may be great benefit to consumers in requesting amendments to OTC monographs and submitting NDAs for botanical drugs, whether for novel or traditional uses. Nevertheless, AHPA believes that it would be an unfair detriment to companies that now sell, and a potentially unfair financial burden on consumers that now use such a botanical in a dietary supplement product if the letter and spirit of this protection to access under DSHEA is not maintained. Further, in the event that a company seeks an NDA for a use that is established by tradition for a specific botanical, it is essential that there be some assurance that that company does not gain

“ownership” of knowledge and use that is, in fact, owned by the public, or a portion of the public. AHPA therefore recommends that language be added to the Guidance that clarifies and specifically states that the approval of either an OTC monograph or an NDA for a botanical drug derived from any particular botanical does not limit legal sale of dietary supplements or other food products derived from the same botanical ingredient.

- AHPA is also aware of comments filed by Botanical Enterprises, Inc. (BEI), and specifically of that section of BEI’s comments entitled “Chemistry, Manufacturing, and Control Issues.” Those comments identify concerns regarding requirements for bioassays stated in the Guidance and regarding the requirement for multiple quality control tests, consisting of chemical and biological assays, for a botanical drug substance and a botanical drug product.

BEI’s comments suggest that requirement for bioassays are “not necessary or even particularly useful for adequate characterization of botanical drug products and merely adds unwarranted expense to the manufacturing process,” and so “should be removed or made optional rather than mandatory.” BEI’s comments also request that the agency provide a rationale for requiring multiple quality control tests. AHPA joins BEI in these recommendations.

Conclusion

Again, AHPA appreciates the publication of this draft Guidance and the information it provides to the botanical products industry. Our presentation of specific criticisms here is offered in the spirit of assuring that the Final Guidance will provide useful direction to researchers and manufacturers of botanical drugs, and so assure consumer access to a greater variety of well-characterized drugs that are derived from botanicals.

We are aware that FDA had requested that these comments be filed by October 10, 2000. Given the complexity of the issues raised in the Guidance and the diversity of our membership, we were not able to complete our review within that

time. We regret any inconvenience caused by our delay, and request that the agency admit these comments as the expression of our members review and suggestions as they relate to the Draft *Guidance for Industry – Botanical Drug Products*.

Respectfully submitted,



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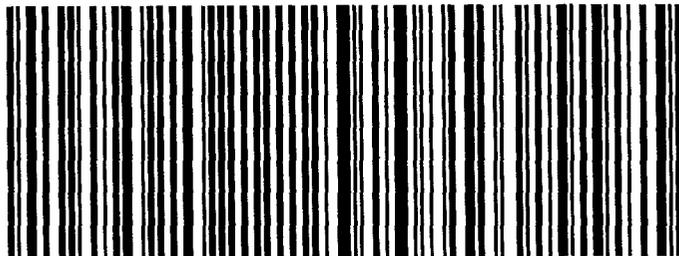
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