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NATIONAL CENTER FOR NATURAL PRODUCTS RESEARCH

a division of The Research Institute of Pharmaceutical Sciences, School of Pharmacy

December 5, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 00D-1392
Draft Guidance for Industry on Botanical Drug Products

The National Center for Natural Products Research in the School of Pharmacy at The University of Mississippi conducts basic and applied research to discover and develop natural products for use as pharmaceuticals and agrochemicals and to characterize the biological and chemical properties of medicinal plants. The Center's scientists therefore understand not only how to discover and develop single entity pharmaceutical products but also how to handle the unique challenges offered by multi-component botanical extracts and products.

The Center supports FDA's initiative to develop guidelines for botanical drug products and shares the agency's desire to encourage the clinical study of well-characterized botanical products. The Center respectfully offers the following comments on the draft guidance document entitled "Draft Guidance for Industry on Botanical Drug Products" [Docket No. 00D-1392].

Our initial comments are related to the amount of chemistry, manufacturing and control information that should be contained in an IND for marketed botanical products, even during early stage clinical research studies. Although we agree that information from the literature should be used to support and streamline wherever possible the safety and efficacy trials, we also believe that minimal quality control standards need to be in place prior to undertaking human clinical trials. We would not encourage any sponsor or clinical research organization to conduct a clinical trial without characterizing the clinical supplies. As with all other drugs, we believe that sponsors should continue to characterize the drug substance and drug product throughout the clinical development program. We offer the following specific suggestions:

1. Section VI.B.6 Chemistry, Manufacturing and Controls – it is stated on page 10 that “the IND sponsor should, to the extent possible, obtain sufficient quantities of the botanical drug product in a single batch from a single source of the botanical drug substance and/or raw materials to sustain the initial clinical trials”. We encourage the FDA to encourage sponsors to obtain and analyze multiple lots of raw materials early in the development program. The lot-to-lot variation in multiple component botanicals is higher than in single entity drug substances. Sponsors should be advised to study and understand the inherent variability of both the raw material and the clinical supplies so that good scientific judgment can be used to select appropriate clinical batches for testing and to start developing NDA specifications. If the clinical program is completed with a single lot of raw material and a single batch of product, the sponsor is establishing a “gold standard” that may or may not be representative of the botanical product, and the formulation and process used to prepare the botanical product may not be reproducible. If the sponsor or manufacturer does not characterize this "gold standard" until near the end of the clinical trials, then they are characterizing aged raw materials and finished products. A sponsor who does not have the capability to determine batch to batch differences should work with suppliers who have that capability early in the development program. Waiting until late stage clinical studies is too late.
2. Section VII. B.2 – this section calls for inclusion of the type of manufacturing process in the IND *if available*. Again, a sponsor and the FDA should know how the botanical drug substance was processed. A brief description of the manufacturing process for the botanical drug substance should be included in all INDs, regardless of the stage of the clinical trial. If a sponsor does not know this information, they should find it out. Failure of a sponsor to obtain this information early in a project may lead to inability to explain future lot to lot differences.
3. Section VII. B.3 a – we believe that a quantitative description of the formulation, including the amount of each ingredient used in the formulation should be included just as for all other drug products. Both the sponsor and the agency should know this information at all stages of clinical studies.
4. Section VII. B.3 c – we believe that a certificate of analysis should be required regardless of the source of the product. This should not be optional. Botanical material from a supplier who cannot supply this information should not be used in a clinical study even if the product is on the market in the U.S.

We would also like to comment on the definitions of a *botanical drug substance*, a *botanical ingredient* and a *botanical raw material* as they relate to a combination drug. It appears to us that a **single botanical drug substance** as defined in the draft guidance document would include **one or more** plants, algae or macroscopic fungi. Thus, as defined, a **single botanical drug substance** could contain several different plants, some algae and some fungi that

could be processed together or blended together after separate processing. We believe a *botanical drug substance* should be comparable to an active pharmaceutical ingredient. Just like other drug products, a botanical drug product should contain a well-defined drug substance. More than one drug substance should be considered to be a combination drug. We therefore encourage the agency to restrict the definition of a *botanical drug substance* to being from a single plant, algae or fungus species.

Section III.D states that a *botanical drug* composed of multiple parts of a single plant species, or of parts from different species is currently subject to the combination drug requirements. This definition of a combination drug may be confusing because it does not refer to a *botanical raw material*, a *botanical ingredient* or a *botanical drug substance*. We offer the following suggestion to clarify what constitutes a combination drug: "A *botanical drug* composed of more than one *botanical raw material* (or *botanical drug substances* if the agency agrees with our revised definition) is considered to be a combination drug". As previously stated, we agree that a *botanical drug* containing two different plants should be considered to be a combination drug. However, as currently defined, a *botanical raw material* must be from only one part of a plant. We believe that this restriction is not necessary if the sponsor can demonstrate that the plant was traditionally processed by using more than one plant part together (e.g. leaves and stems) to prepare the medicinal agent. In those cases, a company should be allowed to process more than one plant part to produce a **single** *botanical drug substance*. If the one plant part restriction remains, then alternate plant parts will be considered as contaminants or impurities and limits will have to be developed.

Sincerely,



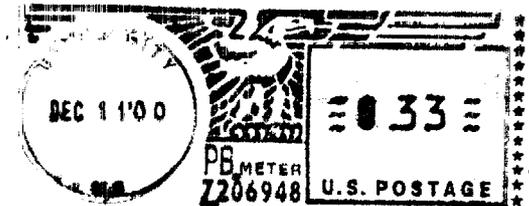
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