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

Reference: Comments in response to the draft Guidance for Industry: Botanical Drug Products (Docket # 00D-1392)

Standardized, well-characterized formulations of botanical products have not occurred in the US market, greatly impeding research on safety and efficacy. Before clinical trials on botanical products can begin in earnest, a number of issues regarding the characterization of botanical products must first be addressed including: whether to use whole extract or a specific fraction; the method of extraction (e.g., alcoholic, tea, pressed juice); and the chemical and genetic standardization of the product. Reliable and well-characterized products are necessary for high-quality research. The recent release of draft **FDA Guidance for Industry: Botanical Drug Products** should help guide development of reliable products for research. However, we believe there are a number of inconsistencies or vagaries in the document that should be addressed before the final release.

The document, as written, may greatly discourage rigorous research exploring the health effects of botanicals. The document gives the false impression that the chemical composition of botanicals can be closely and easily reproduced from batch-to-batch. Batch-to-batch chemical consistency of many botanicals is extremely difficult to achieve despite compliance with rigorous GMP. This requirement is more relevant to classical single-entity synthetic drug development than to botanicals that may contain multiple constituents. Chromatographic and/or DNA fingerprinting and content analysis should be sufficient if an investigation can be completed using a single lot of product.

The Guidance dictates that investigators document "substantial evidence of effectiveness." It is unrealistic to expect that such evidence will already exist. First, there are rarely pre-clinical data of the type that helps propel proprietary drugs into the clinic.

Second, the biologic effects of botanical products are likely to be modest and may require much larger or more complex studies than had been performed in the past. Whether true or not, the US Public prefers botanicals because of the perceived low side effects associated with "natural products." Alternative study designs that emphasize safety as well as efficacy should be encouraged.

The FDA regulates botanical products based upon their intended use. Within the FDA, CDER regulates botanicals intended for use as drugs, while CFSAN regulates other uses of botanicals. Will CFSAN use the Guidance document for botanicals that are regulated as dietary supplements, since these are by DSHEA definition, not intended for use as drugs? The Guidance is unclear as to which of the FDA Divisions and Centers it is considering.

The Guidance correctly states that interactions with other medicines should be investigated extensively. However, no additional guidance is provided as to the type of research that is required, and the guidance does not address whether interactions with other botanicals need to be addressed.

Moreover, the document does not adequately delineate when it is necessary to seek an IND for clinical studies. For example, no guidance is provided as to how the intended use of a product for a particular study impacts on the decision to seek an IND. An investigator might not seek an IND for phase I/II studies because there is no intention to make disease claims; later on, the decision may be reached to explore disease-related questions, which would require an IND. Does this mean that the early studies may then not be used to support the disease claim, since they were not performed using the IND product? Furthermore, there is nothing in the Guidance that discusses how previously collected Phase I/II data can be used as part of an IND/NDA submission. To address these concerns, the Guidance should contain information about how to obtain input from the FDA as to whether an IND is needed. Included in this information should be the types of information the FDA will need to make a decision.

Besides these general issues, comments on specific sections of the document are noted below:

Focus on Section VII.

INDs for Phase 1 and Phase 2 Clinical Studies of Lawfully Marketed Botanical Products (i.e., food and dietary supplements)

General: The Guidance addresses "lawfully marketed products that do not raise safety issues." However, one should not assume that a botanical product does not have safety concerns simply because it is lawfully marketed (e.g., comfrey, ephedra, pennyroyal, etc.)

Section VII A: Description of Product and Documentation of Human Use.

In this section, the investigator is given the choice to identify active constituent(s) OR a characteristic marker.

However, while the latter approach will be less expensive, it may be irrelevant to clinical efficacy (e.g., hypericin in St. John's Wort). This specific option (active constituent versus biochemical marker) is repeated throughout the document.

Section VII B: CMC

The Guidance states that a certificate of authenticity should be provided, "if available." This is inadequate; an accurate identification of the botanical material should be required, not optional.

The Guidance also states that the study product should be from a single source and where feasible, from a single batch. This is unreasonable for any sustained research endeavor. It may take years to proceed from Phase I through Phase III trials; it is unlikely that a single batch would provide a sufficient source of product through all three phases.

Section VII C: Pharmacology/Toxicology Information.

As described in the Guidance, Phase I and Phase II requirements are less rigorous than those for Phase III studies. If an investigator follows the less rigorous guidelines for the early testing and then wants to proceed to Phase III, the Phase I /II work may need to be repeated. This problem appears throughout the document.

The requirements for U.S.-based and foreign-based manufacturers should be consistent. The Guidance states that marketing data is required from foreign manufacturers but not U.S. manufacturers. It is possible that a product may be marketed to only a small number of people, which may not realistically reflect safety concerns that would be evident in a larger pool.

Section VII D: Bioavailability

While appropriate for single-entity drugs, the guidance in this section is probably unfeasible for many botanicals because of their chemical complexity. The Guidance also suggests that bioavailability is solely reflected in blood levels of products. In some situations, monitoring for blood levels of some botanicals (e.g., fiber as a prebiotic) is not logical. Other alternatives should be allowed as appropriate.

Section VIII A: Description of Product and Documentation of Human Use

The Guidance states that "products that have not previously been lawfully marketed in the United States or elsewhere or that have known safety issues" must comply with the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora. These same guidelines should also apply to lawfully marketed products.

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VIII B and IX B: Chemistry, Manufacturing, and Controls

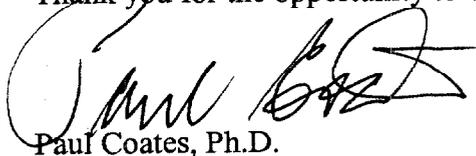
The CMC requirements for quality control standard should be identical whether the product is used in Phase I/II trials or Phase III trials for the following two reasons: The integrity and safety of the product must be assured in all studies using humans regardless of the scientific question being addressed.

Lack of product uniformity across trial phases (I-III) could impede research progress and lead to incomparable results scientifically. Production in the United States is no guarantee that these appropriately high standards are met. Thus, the same standards should apply for all botanicals.

Attachment B: IND for a botanical drug product

There is a missing element in the flow chart. In the second tier, the two boxes on "Initial clinical trial of a marketed, (Sec. VII) and non-marketed botanical product, (Sec. VIII)" should include "or products with safety issues".

Thank you for the opportunity to comment on the draft Guidance.



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