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21 December 2000

Ref: AW

Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852
USA

Dear Dockets Management:

Re: [Docket No.00D-1392] Botanical Drug Products (Published in Federal Register August 11, 2000).

Phytopharm is pleased to have the opportunity to provide comments on the Draft Guidance for Industry on Botanical Drug Products.

We commend FDA's efforts to regulate botanical drug products, since it will ensure that botanical drug products are controlled in terms of quality, safety and efficacy. In particular Phytopharm welcomes the proposal of the FDA to accept previous human experience as a means of supporting the safety of the product and that such data may be sufficient to initiate 'more definitive (Phase II) trials'. To improve the consistency and workability, the proposed draft needs further clarification in a number of areas. Specific comments under the headings of pre-clinical safety, chemistry, manufacturing and control and clinical are provided below. These are followed by a comment on lawfully marketed botanical products and comments on ANDA submissions.

Pre-Clinical Safety – (page 31)

Section IX C – To assist in the avoidance of unnecessary testing in animals further guidance is required on the type of previous human experience data that would be deemed to support the safety of a botanical product for expanded clinical studies.

Further guidance is required on the criteria that should be applied in deciding on the appropriate animal models to establish the safety of a product, when a product's active moieities are not known, and standard pharmacokinetic measurements to demonstrate systemic exposure of the product in animals and/or humans is infeasible.

Chemistry, Manufacturing And Controls

Section III B CMC Information for Botanical Drug Products (page 4) – Guidance is required on the circumstances under which the identification of the active constituents in a botanical drug would be considered to be 'infeasible'. This guidance should include examples of botanical drugs for which the FDA considers the identification of the active constituents in an NDA submission would be 'infeasible'.

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Section III D - Applicability of Combination Drug Regulations (page 5) – Guidance is required on the circumstances under which botanical drugs could be exempt from combination drug requirements. In particular clarification is required on:

1) Whether lawfully marketed combination drugs and traditional medicines, which invariably consist of a complex mixture of several herbal drugs, would be exempt from the combination drug regulations.
2) The likely timeframe for the proposed revisions and whether there will be dispensations from the combination requirements until such a time as the exemptions is in place.

Section IX – B. Chemistry, Manufacturing and Controls

b. Botanical drug substance & c. Botanical drug product - page 27 & 29

For botanical drug substance and botanical drug product the requirement for a biological assay is accepted, but guidance on the criteria to assess the clinical relevance of the bioassay should be provided.

c. Botanical drug product – page 30

Guidance is required on the qualitative and quantitative limits that would be acceptable to demonstrate batch-to-batch consistency.

Clinical

Phytopharm plc accept the clinical considerations presented in this guideline.

Additional Comments

SECTION VII - INDS FOR PHASE 1 AND PHASE 2 CLINICAL STUDIES OF LAWFULLY MARKETED BOTANICAL PRODUCTS

A definition of lawfully marketed (**Section VII**) as it applies in this guideline is required and in particular in cases of dispute, guidance on the evidence the FDA would require as proof that a product or the botanical ingredient was lawfully marketed.

III – GENERAL REGULATORY APPROACHES

A. Marketing Under OTC Monograph Versus Approved NDA

Footnote 4 – page 3

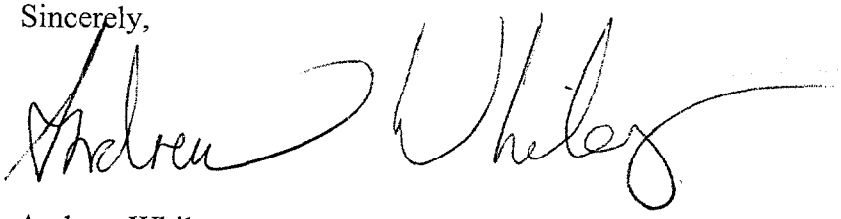
The FDA acknowledges the unique nature of botanicals, and has produced this document detailing specific regulatory policies. As stated in this document botanical drug products have unique characteristics that cannot be defined. In some cases where the active principles remain undefined, without replicating the method of manufacture it maybe impossible to ensure the identity, purity, quality, strength, potency and consistency of the botanical drug. Clarification is required as to whether the FDA anticipate that for some botanical drug products it maybe impossible to produce a generic version and guidance on the data needed to demonstrate pharmaceutical equivalence and bioequivalence for botanical generic products is required.

Footnote 5 –page 3

Definition of material extent and material time is required.

It is of paramount importance that as this document evolves it provides a framework for ensuring the botanical drug products meet standards of quality, safety and efficacy that are equivalent to the standards demanded of all drug products.

Sincerely,



Andrew Whiles
Director of Regulatory Affairs

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