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Docket Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Milan, October 10, 2000

Re: Guidance for Industry: Botanical Drug Products: Draft Guidance Docket No. 00D-1392

Dear Madam or Sir,

These comments are submitted by Indena s.p.a., v. le Ortles 12, Milan 20139, Italy (Indena), in response to the Federal Register publication of a draft guidance document entitled "Guidance for Industry: Botanical Drug Products (Fed. Reg. 65: 49247- 2000).

Indena has read the draft guidance with great interest and, in general, appreciates the new vision that allows the developing of new botanical drug products. In particular, Indena appreciates the concept that a botanical product can be clinically tested through an IND approval and registered (after NDA approval) as a new drug product.

Considering the FDA effort to improve safety and efficacy of botanicals, Indena believes that to ensure the quality of these products, starting from the raw material, is fundamental. IND should be submitted for well defined botanical drug which, because they are considered as active principle in its entirety, need to be well characterized and of constant composition. The only way to guarantee constancy of the extract is to have a specified manufacturing process, including defined botanical raw materials, and adequate specifications for the botanical drug substance.

Specifically, in regards with the draft guidance, Indena recommends specific wording changes, deletions and additions:

1. On the basis of the above mentioned concepts, Indena proposes that the CMC criteria for the non marketed botanical products should be added to the marketed ones. In other words, to substitute the content of paragraph VII, B with the content of paragraph VIII, B.
2. In paragraph VII, B, 2, deletion of the words "...if available.";
3. In paragraphs VII, B, 2, and VIII, B, 2, d, addition of the words: "The manufacturing process should be submitted in full with the specifications of the production starting materials (e.g. solvents) and critical in process controls to guarantee the constant quality of the obtained extract".
4. In paragraph VIII, B, 2, e, Chemical assay, deletion of the words "..., if available."
5. In paragraph VIII, B, 2, e, biological assay, addition of the words "The bioassay must be linked to the desired quality of the product."



6. In paragraph IX, B, 1, a, Quality control tests, addition of the words "In the case the botanical raw material will not be used as a botanical drug substance itself (pulverization), periodic or skip testing of the starting botanical raw material used for the preparation of the botanical drug substance, on preselected batches or at predetermined intervals, should be accepted if justified. This concept may be applicable to the determination, for example, of heavy metals, aflatoxins, microbiological controls and pesticides, provided that there are no concerns about these controls."
7. In paragraph IX, B, 2, e: after "....the mass balance of the test sample" addition of the words "if this is shown to be feasible".
8. Paragraph IX, B, 2, g: substitution with the following "Since the botanical raw material or botanical drug substance in its entirety is regarded as the active substance, a mere determination of the stability of the constituents with known therapeutic activity may not be sufficient. When feasible, appropriate analytical techniques should be used to check the overall stability of botanical drug substance or botanical drug product".

Regarding toxicological requirements in general, Indena recommends that FDA should take into consideration, even if on a case by case basis, the toxicological studies performed outside United States that meet modern criteria.

In conclusion, Indena believes that the Botanical Drug Guidance has added flexibility to the IND requirements and has given to FDA the possibility to take into consideration the peculiar aspects of botanical sourcing of drug products.

Sincerely Yours,

A handwritten signature in black ink, appearing to read "E.M. Martinelli", written over a horizontal line.

E.M. MARTINELLI

(QUALITY ASSURANCE MANAGER)

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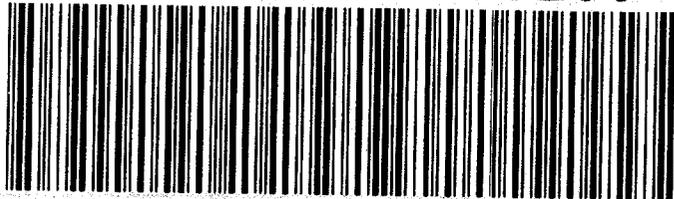
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