



## Global Research & Development

October 9, 2000

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

RE: Draft Guidance for Industry on Botanical Drug Products  
Docket No. 00D-1392, 65 Fed. Reg. 49247 (8/11/2000)

Dear Dockets Management:

Pfizer Inc submits these comments on the *Draft Guidance for Industry – Botanical Drug Products*, published in the *Federal Register* on August 11, 2000.

### General Comments:

We welcome guidance from FDA on the development and regulatory approval of botanical drugs. Overall, we believe that the draft guidance represents a thorough and practical approach that will significantly improve the understanding of FDA's philosophy and requirements for botanicals in the industry and elsewhere. In particular, we support:

- The application of equivalent standards of quality, safety and efficacy, and of the data to support these attributes, for both prescription and non-prescription botanicals.
- The indication that FDA will consider the supporting data with some flexibility, according to whether or not the botanical drug has been marketed in the US as a constituent of a dietary supplement, or is otherwise known.
- The statement that a sponsor may characterize the clinical effects of a botanical drug as the sum of its parts, and need not differentiate the effects of each molecular species.
- The confirmation that the Combination Drug Regulation (21 CFR 300.50) will not be applied to botanical drugs from a single part of a plant, alga or macroscopic fungus. We welcome also FDA's expressed intent to revise its regulations, to exempt drugs prepared from different parts of the same plant from this Regulation under some circumstances.

We have the following specific comments:

### Section I, Introduction, page 1, paragraph 1

The text states, "...marketed as foods and dietary supplements...". We suggest that this be changed to "...foods or dietary supplements . . ."

### Section III A, Marketing Under OTC Monograph Versus Approved NDA, page 4, paragraph 1

The text states, "...when a product is approved under an NDA, the approval is specific to the drug product that is the subject of the application (the applicant's drug product), and the applicant may be eligible for marketing exclusivity for either 5 years (if it is a new chemical entity) or 3 years from the time of approval...". We believe it would be more accurate to say: "the applicant may be eligible for a period of data exclusivity (rather than "market exclusivity"),

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up to five years if the product is a new chemical entity". It may also be helpful to indicate that, since many botanicals will have little or no patent protection, their exclusivity may be open to challenge by generic competitors after only 4 years (21 CFR 314.108).

Section III B, CMC Information for Botanical Drug Products, page 4

The text states, "...active constituents in a botanical drug might not need to be identified during the IND stage or in an NDA submission if this is shown to be infeasible". It is not stated what criteria should be used to determine "unfeasibility". Depending on the plant part used, it might be technically difficult to determine a botanical's active ingredients; under what circumstances does "difficulty" become "unfeasibility"? Also, if the activity is from a combination of actives it may be difficult to identify single actives - does this make it infeasible? Active constituents may be identified by chromatographic fingerprinting and strength by weight. The guidance does not specify the use of dry weight, wet weight or water content. Plants can vary greatly in wet weight, and in some cases the plant material may not be dried completely. More specific information would allow batches to be compared appropriately.

Section V, Marketing a Botanical Drug Under an NDA, page 6

We suggest that it be made clear that, in principle, all of the regulatory mechanisms available to small molecule NCEs are also available to botanical NCEs when a full NDA is submitted. These mechanisms would include provisions for expedited review of botanical drugs for serious or life-threatening conditions, treatment INDs and orphan drug status.

Section VI B, Basic Format for INDs, page 8, paragraph 2

The text states, "*For most conditions potentially treated by botanical drugs (generally mildly symptomatic), active control equivalence designs would not be credible.*" We believe that it is quite reasonable that botanicals might have valuable activity against serious or life-threatening conditions, and would therefore suggest the following wording: "*For generally mild symptomatic conditions, or for those conditions for which objective endpoints or validated surrogate endpoints are unavailable, active control studies would generally not be credible and placebo-controlled studies are recommended.*"

Section VI B 6, Chemistry, Manufacturing and Controls, page 9, paragraph 2

This paragraph states, "*To ensure that a botanical drug product is made consistently with good quality, the sponsor should have, in addition to final product testing, appropriate quality controls for the botanical raw materials and adequate in-process controls during manufacturing and final process validation, especially for the drug substance.*" We believe that further details should be given in the guidance as to the minimal quality controls that should be in place. We see the derivation of drugs from plant material as in some ways analogous to the derivation of drugs from transgenic animals (and, indeed, it seems likely that botanical drugs will be derived from transgenic plants at some time in the future). The "*Points To Consider In The Manufacture And Testing Of Therapeutic Products For Human Use Derived From Transgenic Animals*" (1995) describes in greater detail the controls that should be in place in this situation, and it would be helpful if the current guidance described the necessary controls for plants to be at least an equivalent level.

Section IV B 6, Chemistry, Manufacturing and Controls, page 10, paragraph 2

The text states, "*More important, 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 believe that the "single batch" requires greater definition or clarification, since the harvest of a large field might occur over days or even weeks, with processing also occurring over that time. It would be more practical to document the source of drug to the field, rather than the batch.

Section VII D, *Bioavailability*, page 16, line 7

It is unclear what is meant by "*representative markers*". It is also not explained how concentrations of drug in the blood should be monitored when there may be several actives or major chemical constituents. Are such situations automatically exempt from the requirement to monitor blood levels?

Section VIII B, *Chemistry, Manufacturing and Controls*, page 18

This section is said to relate to products "*...for which there are known safety issues*". It should be clarified what is meant by this phrase, and particularly the extent to which the assessment of the drug's safety will depend upon its potential for interaction with other drugs or foods.

Section VIII B 1, *Botanical Raw Material*, page 18, paragraph 2

The text states, "*A voucher specimen of the plant or plant parts should be retained for each batch.*" The guidance mentions plant samples and voucher specimens at several points. Some plants can be readily identified from leaves, stems and roots, but many plants cannot be reliably identified by examination of these parts only, and the flowers and/or fruit are needed to make a definitive identification. We believe that collection of the flowers and/or fruit should be expressly required. If the leaves or stems are used and the plants are collected before they flower or fruit, then a sample may not be definitive for identification purposes. This may also be a problem for wild collections, since if the leaves of different species were similar, it would be easy to make a mistake, even for a trained botanist. This is more of a problem for annual plants, than for perennial, since it would be easy to mark a perennial during flowering or fruiting to ensure that it is the correct plant when, for example, leaves are collected in early spring. Also, for how long do the specimens need to be retained? Are the storage arrangements liable to GMP inspection? This could pose a formidable storage problem, especially for a multiple-herb product.

Likewise, the guidance does not request information about stage of plant growth, presence of damage, etc. Plant secondary compounds (compounds not produced in general metabolism) are often responsible for medicinal activity. These compounds are often produced at different stages of the plant life cycle and sometimes in response to certain stimuli (such as insect damage, drought, etc.)

Section IX B 1 a, sixth bullet, page 26

The text mentions that reference standards of the plant should be retained, but does not describe the conditions under which they should be kept, or how the conditions should be validated.

Section IX B 2 c, *Batch-to-batch consistency*, page 30

The text states that this "*should be demonstrated for the botanical drug substance and drug product based on results from all chemical, physical, and biological tests on all relevant batches. All chemical constituents present in the drug substance batches should be qualitatively and quantitatively comparable based on spectroscopic and/or chromatographic fingerprinting.*" We

believe that spectroscopic and chromatographic methods will not characterize the compositions of botanical products appropriately in every case, so some looser form of reference to these methods should be used in the text. Further, we believe that it is important that some guidance be given on the ranges of product specifications that will be accepted as constituting consistency between batches. For example, the stems and leaves of many plants contain grossly variant proportions of soluble carbohydrate, depending upon the time of day at which they are harvested. Plants harvested early in the morning may contain essentially no soluble carbohydrate. Without further explanation, according to the text it would not be possible for batches harvested early in the morning to be consistent with batches harvested in the evening, which could contain a substantial proportion of soluble carbohydrate. It is not clear what range of variability of compositions would be accepted.

Sincerely,

A handwritten signature in cursive script, appearing to read "Cheryl Fossum Graham".

Cheryl Fossum Graham, M.D.  
Senior Vice President  
Pfizer Global Research and Development  
Worldwide Regulatory Affairs