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February 18, 2003

VIA FEDERAL EXPRESS

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

Re: **Docket 02D-0324**
Comment Number EC92

Dear Valerie,

Epicyte Pharmaceutical submitted their comments to the FDA Guidance Document (Docket 02D-0324) through the FDA web site on February 7, 2003. The comment number is EC92. During electronic transfer, all the formatting was lost and we would like to post a formatted copy. Would it be possible to post the formatted version on the web site? I am enclosing an electronic and hard copy of the response for your convenience. The text of the hard copy is unchanged from the original posting.

Thank you for time and consideration. Please feel free to call me with any questions you may have about the response.

Best regards.

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Enclosures

DR:plc

02D-0324

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Epicyte Pharmaceutical, Inc. Comments
February 7, 2003
on

FDA Guidance Document
"Drugs, Biologics and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals"

Introduction

The Food and Drug Administration published a draft guidance document entitled Drugs, Biologics and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals on September 12, 2002. The draft document provides guidance with regard to the use of bioengineered plants or plant material to produce pharmaceuticals (PMP) including intermediates, protein drugs, medical devices, new animal drugs and veterinary biologics regulated by the FDA or USDA. This document does not provide guidance for non-protein drugs or proteins designed for industrial or non-human or non-veterinary use.

The emergence of bioengineered plants as a viable manufacturing system has allowed the development of a broad spectrum of human and animal therapies by offering several important advantages over traditional drug manufacturing technologies. First, standard manufacturing technologies are limited in their inability to produce an adequate drug product for indications with large patient populations. This limitation may results in restricted patient access to treatment of many diseases. The scalable nature of plant based pharmaceutical production will change the way many diseases will be treated in the future by enabling the development of innovative therapies which either require large amounts of the drug product to treat large patient populations. Second, PMP production allows the cost-effective manufacturing of monoclonal antibodies for today's markets resulting in greater benefits to patients and more extensive therapeutic options for the health care community. Third, plant based manufacturing uniquely allows the production of certain therapeutic classes of molecules including secretory IgA antibodies. Currently, there is no effective fermentation system that allows the production of these highly stable and effective treatments for diseases requiring topical, gastrointestinal or inhaled applications. Finally, unlike many of the mammalian cell types used in traditional fermentation systems, plant cells cannot be infected with animal viruses and thereby offer an inherently safer source of drug substance.

Plant based production of pharmaceutical proteins present new challenges to the FDA and the pharmaceutical industry in cGMP and product safety. It is critical that regulators and industry work together to develop a scientifically sound regulatory policy that addresses product safety and the containment of bioengineered plants and plant material. Containment is necessary to minimize any potential persistence in the environment or inadvertent mixing with other plant products. Epicyte supports responsiveness of the FDA and the USDA and their diligence in using current regulations, and in drafting clear, concise and relevant guidance.

Despite our positive reception of the draft document, Epicyte has five main areas of concern:

- Regulatory Agency
- Best practices and cGMP
- Scope
- Product Safety
- Industrials

Regulatory Agency

As a result of several discussions with the USDA and the FDA, Epicyte believes that the regulatory oversight for the overall production process (from farm to final product) should reside with the Food and Drug Administration (CDER/CBER) for human therapeutics and the Center for Veterinary Biologics (CVB) for veterinary products. Evaluation of product safety would be best served by designating these same agencies as the primary agency of record with a required role in the USDA permitting process for importation, interstate movement and environmental release.

Best Practices and cGMP

The draft guidance document needs to clearly define specific terms and address apparent departures from current industry practices and, in some cases, current scientific data. Examples where we believe the draft guidance document is inconsistent with best practices and cGMP include:

1. Lines 238-248

In order for the agencies to assess the ability of the chosen plant to consistently manufacture your intended product, you should submit a description of the reproductive biology of the unmodified plant and production practices with regard to:

- *Growth habitat as an annual, perennial, or biennial;*
- *Timing of sexual maturity and duration of flowering; seed production and harvesting;*
- *Recognized practices for maintaining seed stock purity;*
- *Conditions of growth;*
- *Timing of harvest;*
- *Method of harvesting; and*
- *Transporting, storage and sorting of harvested materials.*

Regulators should also consider any history of safe human use or exposure when evaluating the ability of a plant host to be used consistently as the basis of manufacture of PMPs.

2. Lines 272-274

We strongly recommend that you have tests available that can detect the presence of the target gene and protein in the raw agricultural commodity.

Epicyte suggests, "strongly recommend," be replaced with "required". Detection of the target gene and the primary gene product is critical to validation of containment and the manufacturing process. Such assays should have application to both the raw agricultural commodity and to partially processed agricultural products.

3. Lines 278-289

You should provide a full characterization of the recombinant DNA constructs or viral vectors used to transfer genes, including:

- *The origin and function of all component parts of the construct, including coding regions, antibiotic- or herbicide-resistance genes, origins of replication, promoters, and enhancers;*
- *Physical map of the construct(s) illustrating the position of each functional component;*
- *Method used for plasmid propagation;*
- *Any sequences required for bacterial expression of plasmid constructs;*
- *The nucleotide sequence of the intended insert up to and including the junctions at the 5'- and 3' ends; and*
- *Any changes in codons to reflect more acceptable codon usage in plants.*

Epicyte recommends that the possibility of sequencing of the intended insert be restricted to the Master Seed Banks.

4. Lines 305-307

Before preparing Master Seeds or Master Seed Banks (MSB) and Working Seeds or Working Seed Banks (WSB), we recommend that you establish a suitable transformant.

The preparation of a Master Seed Bank from a suitable transformant should be required at the time of the drug licensing. Recognizing that it may take considerable time to establish a MSB, Epicyte recommends that the filing of an IND for initial clinical trials require defined transformation event(s). Epicyte also recommends that this requirement be extended to include systems that employ propagation of individual clonal organisms.

5. Lines 344-345

Characterization of the host plant should include the information in section IIB and above.

In evaluating of the suitability of transient transfection systems, the agencies should address transient system stability, a sampling system to detect genetic drift after transfection, and a requirement to establish limits of genetic drift.

6. Lines 373-375

Regardless of whether a transient-transfection system or a stable transformation system is used, you should prepare a MSB and a WSB to ensure consistent lot-to-lot growth of the plant and expression of the regulated product.

Epicyte recommends clarification of the definition of a Master Seed Bank or Working Seed Bank relative to best agronomical practices in recombinant plant technology.

7. Lines 400-407

For all inserted coding regions, you should provide data that demonstrates whether the protein is or is not produced (describe assay methods and indicate limit of detection as intended in the expected tissues consistent with the associated regulatory sequences driving its expression (e.g. if the gene is inducible, you should determine if the gene is expressed in the expected tissues under induction conditions). You should provide quantitative data characterizing the distribution of the product in the major plant tissues (e.g. leaves, roots, stalks, seeds).

Epicyte would like clarification as to whether this requirement addresses product safety or ecological concerns such as exposure risk due to handling of the waste stream during processing or field disposal.

8. Lines 479-484

When a plant species that is used for food or feed is bioengineered to produce a regulated product, you should consider the use of strategies that allow the bioengineered pharmaceutical plant line to be readily distinguished from its food or feed counterpart. Such strategies might include the use of genetic markers that alter the physical appearance of the plant (e.g., a novel color or leaf pattern), or change the conditions under which a plant will grow (e.g., the use of an auxotrophic marker gene).

Epicyte recommends that the use phenotypic differentiation be considered as one of many possible methods to readily distinguish between transgenic and nontransgenic crop both in the field and post-harvest, where such distinction is more critical.

9. Lines 492-501

Measures should be in place to ensure that there is no inadvertent mixing of the bioengineered pharmaceutical plant with plant material intended for food or feed (including inadvertent mixing with seeds for food or feed crops). During the development of your overall production process (from farm to final product), you should determine where in the process inadvertent mixing could occur and establish appropriate control measures. We strongly recommend that you have test(s) available that can detect the presence of the target gene and the protein product in the raw agricultural commodity.

Epicyte recommends the addition of a statement that includes "a testing protocol for the target gene and protein product preferably at the time of the permit application but no later than the filing of the IND with the FDA or its equivalent with the USDA CVB". It is recommended that SOPs be established for such control measures, and that batch records reflecting good agricultural practices include such control measures to restrict unintended exposure of the PMP.

10. Lines 565-571

In-process wastes (e.g. column wash solutions, diafiltration solutions, etc.), rejected in-process material, and residual source plant material from the purification process should be treated to inactivate the regulated product prior to disposal, as appropriate. They should be disposed in a manner to ensure that the material will not enter the human or animal food chain unless you have specifically consulted with FDA for the use of this material in food or feed products. Disposal should conform to local and state regulations.

Epicyte recommends that language be inserted to define "in-process waste". We suggest that inviable plant host or inviable plant material does not need to be treated to inactivate the regulated product.

11. Lines 684-686

A summary of the manufacturing, including propagation of the source material, should be available at the site where the manufacturing occurred (21 CFR 211 subpart J).

Pharmaceutical field crops often employ multiple growing sites. Epicyte recommends that the requirement be amended to indicate that in a field environment, original documentation be available for inspection at a locally accessible site.

12. Lines 732-734

We recommend the use of dedicated equipment. We recommend that equipment-cleaning procedures be developed and that cleaning agents used on harvesting equipment be described (21FR 211.67).

Epicyte suggests that definition of "dedicated equipment" include the exclusive use of the equipment in the production and processing of plant made pharmaceuticals use only and not for use in processing food or feed materials. The term "recommend" should be replaced with "require".

13. Lines 751-772

Transfer and Storage Conditions.

Epicyte suggests the addition of a statement requiring the use of "dedicated equipment" in transfer and storage of PMP materials. Dedicated use includes the exclusive use in the transfer and storage of plant made pharmaceuticals and not for use in processing food or feed materials.

14. Lines 928-930

You should give special attention to post-translational modifications unique to plant expression systems, for example the presence of xylose in glycoproteins.

Epicyte suggests that post-translational modification or any other property unique to plant expression systems do not represent any additional level of concern to product safety and should be removed from the guidance. Preclinical pharmacology and toxicology and appropriately designed and conducted clinical trials provide the best strategy for determining product safety.

Scope

The focus of the draft guidance document is clearly directed towards bioengineered plants grown in the field. Epicyte strongly recommends that the guidelines clearly define "contained" plant based manufacturing methods and examine whether the guidelines adequately apply to issues surrounding physical containment, waste stream disposal and nontarget organism exposure.

15. Lines 196-199

APHIS/BRS regulates the importation, interstate movement, and release into the environment (e.g., field testing) of all such bioengineered pharmaceutical plants, under the Plant Protection Act (7 USC 7701-7772).

Currently, a general APHIS categorical exclusion exists for contained or non-field (greenhouse) planting. Epicyte recommends that a "contained or non-field" planting be better defined before the industry supports the continuation of this policy for plant made pharmaceutical products. Specifically, the definition of containment should include a description of an acceptable structure, acceptable (if any) levels of exposure of PMPs to nontarget organisms and the designation of the "loss of containment" (e.g. disposal of waste stream).

16. Line 428-433

Bioengineered pharmaceutical plants that are grown exclusively in and enclosed building (greenhouse) generally will be considered to be confined during the growing period if there are control measures in place to eliminate the spread of pollen or seeds outside of

the facility. Growing plants in such an enclosed building does not require a USDA/ APHIS permit, however the importation or interstate movement of bioengineered pharmaceutical plants would require a permit.

As previously suggested, Epicyte recommends that a "contained or non-field" planting be clearly defined. Specifically, the definition of containment should include a description of an acceptable structure, acceptable (if any) levels of exposure of PMPs to nontarget organisms and the designation of the "loss of containment" (e.g. disposal of waste stream).

Product Safety

17. Lines 452

Confinement Considerations

As a general comment, Epicyte recommends that the guidance be clear as to their intent. Issues of confinement related product quality or safety should be clearly addressed under Manufacturing and Process-Related Considerations. Confinement regulations designed to protect food and/or feed sources from contamination should be addressed under ecological consideration.

Industrials

Epicyte strongly recommends that a separate guidance document be prepared for plant made industrial proteins and peptides.