LARGE SCALE BIOLOGY

January 08, 2003

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

Docket No. 02D-0324, Comments

"Guidance for Industry: Drugs, Biologics, and Medical Devices Derived From Bioengineered Plants for Use in Humans and Animals"

Large Scale Biology Corporation (LSBC) is a publicly traded biotechnology company, with corporate offices located in Vacaville, CA, and a current staff of 125 people. Founded in 1987, the Company's mission is to produce biopharmaceuticals using plant-based expression systems. LSBC's core capabilities include plant virus-based protein and peptide expression and the associated processes, facilities, personnel and quality systems for product extraction and purification.

LSBC has achieved significant technical milestones related to the production of biologics derived from bioengineered plants, including: (1) first use of RNA plant viruses to transiently express foreign genes systemically in non-recombinant plants (1990), (2) first introduction of a recombinant plant virus into the environment under USDA permit (1991), and (3) conducted a Phase I clinical trial under IND 9283, to treat indolent non-Hodgkin's Lymphoma patients with a virus expressed, plant derived, autologous single chain vaccine.

Large Scale Biology, a leader in the manufacturing of plant-derived therapeutics, believes that the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) have done an excellent job in capturing the unique manufacturing issues associated with the use of bioengineered plants as source material for the production of regulated pharmaceutical products. The recommendations and current thoughts addressed in the this guidance document are in congruence with current pharmaceutical regulations, Title 21 of the Code of Federal Regulations (21 CFR) and veterinary biologics regulations Title 9 of the Code of Federal Regulations (9 CFR).

After reviewing the draft guidance document, we identified three areas for the agency to consider when preparing the final document.

Lines 364-366, *Transient Transfection Systems*:

LSBC has used both primary transcripts, derived from plasmid DNA and virion, derived from either transcript inoculated plants or passaged recombinant virion as inoculum sources (inoculum source used is dependent upon the stability of the recombinant virus). Add the following item to the list of information provided regarding virus vectors:

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A description of the preparation of the Master Virion Bank (MVB), if one is used;

Line 371, Genetic Stability: Seed Banks and Vegetative Propagation

There may be manufacturing circumstances when a transgenic host plant is used in combination with a transient expression system. The transgenic host plant could express products that modify the pharmaceutical protein, enhance the expression of the viral vector or enhance a particular agronomic trait or characteristic of the host while the pharmaceutical protein is expressed via the recombinant vector. In other cases, the pharmaceutical protein might be expressed transgenically and a recombinant viral vector would express a protein-modifying enzyme or host plant enhancing product. In either of the above cases, master seed banks and working seed banks would be prepared and fully described.

Line 533, *Field-grown Plants*

The use of perimeter fencing may help in excluding wildlife and escaped livestock, but fencing may also attract undo attention to what would otherwise be viewed as just another field crop. The careful selection of field plot location should be considered in minimizing unwanted intruders while adhering to spatial and temporal requirements that would contain the genetically altered material.

We believe that the recommendations considered in this draft guidance document for the use of bioengineered plants to produce biologic products, along with established FDA and USDA regulatory authority is sufficient and requires no additional regulatory oversight. The proposed document provides the necessary controls to assure that a consistent product can be manufactured from bioengineered plant sources beginning with a thorough description of the recombinant nucleic acid, master and working seed, plasmid and vector banks, plant growth, harvest, extraction and product purification.

Sincerely,

LARGE SCALE BIOLOGY CORPORATION

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