BIOLEX

January 6, 2003

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

Re: Docket 02D-0324

Dear Sir/Madam

Pursuant to Docket 02D-0324, Guidance for Industry – Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals, Biolex, Inc. would like to submit comments to this document for your consideration. Biolex is an early stage biopharmaceutical company located in the Research Triangle region of North Carolina. Biolex' proprietary protein manufacturing platform, the Lemna System™, uses the aquatic plant *Lemna* (duckweed) to express human therapeutic proteins. *Lemna* is an aquatic plant that propagates clonally (vegetatively) and production of therapeutic proteins using the Lemna System™ is performed under closed conditions. Biolex' comments are as follows:

Section II.B
Line 244 refers to "recognized practices for maintaining seed stock purity".
This section makes no mention of vegetative archival plant lines. We recommend that the statement be changed to:
... recognized practices for maintaining seed stock and/or archival plant line purity.

Section II.C.3
Lines 305 – 307 state:
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.

We feel that this statement does not recognize alternative banking systems to seed banking systems. We suggest that this be changed to:
Before preparing master banks or working banks we recommend that you establish a suitable transformant.

02D-0324 C 242

158 Credle Street
Pittsboro, NC 27312
www.biolex.com
tel 919.542.9901
fax 919.542.9910

Section II.C.5
Lines 373 – 375 state:
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.

We recommend that this be changed to:
Regardless of whether a transient-transfection system or a stable transformation system is used, you should prepare a banking system that ensures consistent lot-to-lot growth of the plant and expression of the regulated product.

Lines 388 – 391 state:
For plants that are infertile or for which it is difficult to produce seed (such as vegetatively propagated male-sterile potatoes), you should provide data to demonstrate that the trait is stably maintained and expressed during vegetative propagation over a number of cycles that is appropriate to the crop.

This section refers specifically to crops and doesn't take into consideration non-crop plants and makes no reference to plants that normally propagate asexually (clonal propagation). We recommend that this be changed to:
For plants that are infertile, are propagated asexually or for which it is difficult to produce seed (such as vegetatively propagated male-sterile potatoes), you should provide data to demonstrate that the trait is stably maintained and expressed during vegetative propagation over a number of manufacturing cycles that is appropriate to the plant.

Section II.C.6
We agree with the provisions of this section for systems where the product is derived from the plant tissue and/or where isolation of the expressed product to selected tissues is necessary for confinement of the expressed product. However, these data are not relevant where the product is secreted or the transformed plant is grown in containment. We recommend that lines 400 - 401 be changed to:
Where expressed product is extracted from plant tissue or isolated to selected tissues for the purpose of isolation of the expressed product, you should provide data for all inserted coding regions that demonstrates whether the protein is or is not produced...

Section III.A
In general, we support this section as written; however, we do not believe that greenhouses, or even advanced greenhouses, provide adequate control over the spread of pollen or seeds. Unlike truly contained systems, such as the Lemna System™, that are grown under controlled conditions in secure pharmaceutical grade facilities, pollen and seeds can still escape through greenhouse ventilation systems and by the movement of personnel, birds, insects and vermin.

Section III.C.1
We support this section as written.

Section III.C.2
We support this section as written.

Section III.C.3
In general, we support this section as written; however, even perimeter fencing will not be able to exclude wildlife from sites where transgenic field crops are grown.

Section III.C.4
We support this section as written.

Section III.C.5
In general we support this section however, we recommend that dedicated facilities be required to process bioengineered pharmaceutical plants where the plant species is also used for food or feed.

Section III.C.6
Lines 565 – 571 state:
"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 the material will not enter the human or animal food chain unless you have specifically consulted with the FDA for the use of this material in food or feed products"
It is unclear in this section whether the reference to "regulated product" refers only to the presence of the active ingredient in the source plant or whether the intent is to include regulated product in the waste stream that is not contained in the source plant. A requirement to inactivate regulated product not part of the source plant would not be consistent with 21 CFR 25. We recommend that this statement be changed to clearly reflect a requirement for inactivation of the source plant material only.

Section IV.A
We support this section as written.

Section IV.D.2
In general we agree with this section, however, we believe that this section should include controls for field crops to prevent cross-contamination of pharmaceutical plants and source material by transgenic crop plants previously grown on the land. Since different transgenic lines of the same crop species would likely be indistinguishable from each other, we recommend that the following controls be considered for inclusion into this document:

- Rotation of transgenic crops of different species between production of different PMPs
- Validated product specific assays to detect contamination by previously produced PMPs.
- Fields used to grow pharmaceutical plants lay fallow for at least one growing season between plantings of different transgenic lines.

Section IV.D.3
In general we agree with this section, however, we feel that the discretionary tone of some items such as: "You should establish specifications for the harvested material with regards to the level of active component, process derived contaminants, significant endogenous impurities and adventitious agents", "You should have written procedures for establishing the necessary training of personnel ... ", "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", and "you should consider measures to prevent the contamination of harvested source material with equipment lubricants during processing." should be strengthened to make these items mandatory. While we understand that guidance documents are not intended to create new requirements, we believe that these issues be mandatory since the requirements for training procedures, cleaning procedures and removal of lubricants and other manufacturing materials are well established in 21 CFR 211 and 21 CFR 820.

Section IV.D.4
In general, we support this section as written, however, we believe that a requirement for dedicated transport equipment be included and that the discretionary tone of the statement "Source material should be stored under appropriate conditions to ensure that decomposition processes do not increase the concentration of contaminants above specified levels or adversely affect the desired active pharmaceutical ingredient." should be strengthened to make the statement mandatory. Requirements for storage and handling of materials are well established in 21 CFR 211 and 21 CFR 820.

Section IV.D.5
We support this section as written.

Section IV.D.6
We support this section as written. However, this section proceeds directly to aseptic processing. We feel that a section on purification should be added. Although purification will generally be similar to traditional biotech purification schemes, field grown plants will have their own special needs such as the removal of pesticide, herbicide, fungicide, toxoid and fertilizer residues. We believe that this should be addressed in a purification section with a requirement for validated procedures for the removal of these residues.

Section IV.D.8
We support this section as written.

SectionIV.D.9
In general we support this section as written, however we feel the discretionary tone of the statement be strengthened to make it mandatory. The requirements for process validation are well established in 21 CFR 211.

Section V.A
We support this section as written.

Section V.B.2
In general we support this section as written, however, we believe that validation of removal of pesticides is a necessary step and should be stated as a requirement in Section IV.

We would like to thank you for this opportunity to comment on this document and we appreciate any consideration you might give to our recommendations.

Sincerely,

Eugene B. Johnston
Director Regulatory Affairs/Quality Assurance
Biolex, Inc.