The Dow Chemical Company
Midland, Michigan 48674

February 4, 2003

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

RE: Draft "Guidance for Industry: Drugs, Biologics, and Medical Devices Derived From Bioengineered Plants for Use in Humans and Animals", 67 Fed. Reg. 57828 (Sept. 12, 2002), Docket No. 02D-0324

Dear Sir or Madam:

The Dow Chemical Company ("Dow") and Dow AgroSciences LLC ("Dow AgroSciences"), a wholly owned subsidiary of Dow, appreciate the opportunity to submit comments on the above-referenced draft guidance document. We have two primary interests in this area: plant-made pharmaceuticals, an emerging Dow business, and animal health products, a business interest of Dow AgroSciences. We present below some general comments and recommendations regarding the regulation of bioengineered plants for human and animal therapeutic purposes, and specific comments relative to the draft guidance document.

Dow is a leading science and technology company that provides innovative chemical and plastic products and services to many essential consumer markets, such as transportation, health and medicine, food, building maintenance and construction materials, and personal and home care. Dow's biotechnology endeavors include plant-made pharmaceuticals and industrial enzymes, among others.

Dow AgroSciences is a global leader in providing pest management and biotechnology products that improve the quality of the food supply and contribute to the safety, health, and quality of life of the world's growing population. Dow AgroSciences' Plant Genetics and Biotechnology business is centered on providing solutions that improve crop production and deliver new and improved agricultural outputs for a multitude of food and non-food uses. We are developing plant-made vaccines for use in animal disease prevention. We are also exploring the use of plant-made antibodies to improve food safety by reducing the presence of disease-causing bacteria in livestock prior to slaughter. Additionally, we are pursuing research in the area of therapeutic antibodies, which may have a role in reducing the use of livestock antibiotics. We believe that developing these solutions through biotechnology is critical to ensuring an adequate and safe food supply.

General Comments

We support the efforts of FDA and USDA to utilize a science-based coordinated regulatory framework for the proper development and implementation of plant biotechnology derived pharmaceutical and animal health products. The draft guidance document provides useful suggestions in a number of critical areas and control points that address potential environmental and human health effects of these regulated products. We encourage the extension of this approach to plant-made industrial products that are also intended for uses other than food or feed.

In addition to a sound regulatory approach, we support mandatory oversight and compliance enforcement by the appropriate agencies. We are committed to working cooperatively with FDA and USDA to advance the regulatory scheme needed to bring about this promising beneficial technology while protecting human health and the environment.

Universities and governmental agencies involved in the production or processing of bioengineered plants for development of drugs, biologics, or medical devices should be subject to the same requirements and guidance as industry.

Specific Comments

§ I.B - Regulatory Responsibility

The U.S. Coordinated Framework for the Regulation of Biotechnology broadly defines roles and responsibilities. Clearly, the draft guidance document concerns a number of issues that have broad implications for regulators and regulated parties. Many issues can be addressed through maintenance or modification of existing regulatory processes (e.g., permitting, FDA guidance on current good manufacturing practices ("cGMPs")). Where aspects of this guidance would be implemented via new regulation, we support utilization of existing legislative authority, established rulemaking procedures, and adaptation of current regulatory processes to the extent feasible.

While the safety of many intermediate and final products are well regulated in existing FDA and USDA processes, there are few regulations applicable to the early stages of development of drugs, biologics, and medical devices derived from bioengineered plants. For example, FDA's cGMP regulations in 21 CFR Part 211 apply to finished drugs, not to plants, which, when harvested and processed, yield an active pharmaceutical ingredient. It is appropriate for FDA to refer to its cGMP and other regulations as sources of guidance. Nevertheless, care should be taken to avoid transposing requirements written with industrial settings in mind to the development of transgenic plants expressing pharmaceutically-active proteins and precursors.

With regard to animal health products, the development of recombinant veterinary biologics is already a well-established process. Many of the specific considerations necessary to regulate recombinant veterinary biologics, including plant-made biologics,

have already been established through existing processes in 9 CFR Parts 101-124 and issuance of guidance documents. We encourage a continuation of the successful utilization of the existing regulations as much as possible. We request that any changes made to the existing regulatory structure occur only when there are no other viable alternatives.

Additionally, the current mechanisms and practices designed to protect confidential business information should be included in any new regulatory processes concerning plant-made pharmaceuticals or animal health products.

§ II.C - Bioengineered Source Plants

The expression pattern of the introduced protein(s) and its distribution throughout the plant is primarily of interest to assess the potential environmental or human health implications resulting from the adventitious presence of the plant-made pharmaceutical in food, feed, or the environment. We request that the agencies provide clarification on the need for such data if the plant-made pharmaceutical will be grown only under greenhouse conditions or other fully contained environments.

We recommend that the presence of the expressed protein, not the presence of DNA, be the primary focus of analytical methods used for detection as it is the protein, not DNA, that may manifest any human, animal, or environmental effects. FDA has repeatedly found that transferred genetic material (DNA) is presumed to be GRAS, i.e., it raises no safety issue. See 66 Fed. Reg. 4706, 4709 (Jan. 18, 2001) ("Premarket Notice Concerning Bioengineered Food"); 57 Fed. Reg. 22984, 22990 (May 29, 1992) ("Statement of Policy: Foods Derived From New Plant Varieties").

§ III.C - Confinement Measures

1. General Considerations

We support mandatory development and use of standard operating procedures that provide for control and confinement of crops producing pharmaceutical and animal health products. Such documentation should be a permit condition and available for inspection and compliance review by the appropriate regulatory agencies.

Development of physical markers for pharmaceutical crops, as recommended in the draft guidance document, may actually detract from overall security by calling attention to the bioengineered nature of the crop. Physical markers should be considered only when taking all aspects of security into consideration.

As part of a multiple layer confinement scheme, we support the growth of pharmaceutical crops outside the primary food and feed growing regions of those crops at this time. We also support and recommend that a test method be made available to regulatory authorities that can detect the presence of the specific expressed protein in the corresponding food or feed crop.

Total containment of bioengineered pharmaceutical plants or plant products is the goal, thereby preventing the materials from contacting food or feed supplies. Nevertheless, should inadvertent contact occur, FDA should have a mitigation plan in place, based on sound science, to determine whether the situation is potentially injurious to health, and act accordingly. One approach would be for FDA to use risk-based methodologies to determine prospectively what contaminant levels would be *de minimis*, utilizing the mechanisms set forth in 21 CFR Part 109. With such an approach, FDA would be positioned to act swiftly and authoritatively to deal with these matters, should they arise.

2. Control of Seed Stocks

Many future products derived from pharmaceutical plants will require use of field-grown plants. In some instances, however, a developer may choose to utilize systems that are fully contained throughout the duration of the production cycle. Examples of confined production systems include cell suspension cultures or greenhouses that are adjacent to the processing facility. Specific recommendations and appropriate exclusions should be detailed for the use of such production facilities.

The growth conditions described in the draft guidance document for greenhouse-grown material appear to be limited by an assumption that all plants will be grown in pots. The guidance should be expanded to consider the use of other contained production systems, such as hydroponics or cell suspension systems.

The term "stable transformed plant stock" is preferable to "master seed stocks" or "working seed" when referring to materials from plant sources. Adopting the term "stable transformed plant stock" will allow easier differentiation between master seed of a biologic of animal or viral origin and plant-made materials that may produce seeds or be developed and maintained as a callus or suspension culture.

3. Field-Grown Plants

Security measures should be required for all research and commercial plots. The control and security measures for field grown plants should take into consideration, on a case-by-case basis, the specific crop, the geographic location of the site, the physical aspects of the site, and the surrounding environment, in order to put in place optimal control and security. Specific measures such as perimeter fencing are not effective in all aspects of wildlife control and are only a temporary deterrent to persons trespassing on the site. The geographic location coordinates that are provided to the regulating authorities should remain as confidential business information in order to assure security.

4. Control During Processing

The equipment used to plant, harvest, and process plant-made pharmaceuticals and animal health products should be dedicated to those uses as a whole and not be used in the processing of food or feed products. Equipment dedicated in this regard should be

thoroughly cleaned and inspected prior to and after use for a particular plant-made pharmaceutical or animal health product.

Sponsors must implement measures to ensure that crop plants expressing biopharmaceuticals or veterinary biologics do not unintentionally mix with other food or feed products. Source materials must not be processed in facilities also used for production of food or feed. However, a distinction must be made between an approved final commercial product intended to be mixed with feed (e.g. a feed additive), where use in a commercial grain mill would be appropriate, versus use of a commercial grain mill in the purification process of manufacturing a pharmaceutical or animal health product, which would not be appropriate. For processing and purification in the manufacturing of such a product, we believe that the use of dedicated facilities and equipment should be required. This will minimize the opportunity for inadvertent contamination and facilitate acceptance of the technology.

Agency regulations or procedures should require that once production and processing of plant-made pharmaceuticals and animal health products is complete, formerly dedicated equipment must be decommissioned. Decommissioning should include thorough cleaning and inspection in adherence with appropriate regulatory guidelines.

Conclusion

We believe that plant-made pharmaceutical and animal health products can provide tremendous benefits to society. For these products to succeed, however, the public must have confidence that environmental and health considerations are adequately addressed. The draft guidance is an important step toward establishing that confidence.

Please contact the undersigned if you need additional information.

Sincerely,

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