ANIMAL HEALTH INSTITUTE
Representing manufacturers of animal health products

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

Re: Docket No. 02D–0324; Draft Guidance for Industry: Drugs, Biologics, and Medical Devices Derived From Bioengineered Plants for Use in Humans and Animals.

The Animal Health Institute (AHI) provides the following comments on Docket No. 02D-0324; Draft Guidance for Industry: Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals. AHI is the national trade association that represents manufacturers of veterinary biologics and pharmaceuticals. Our member companies represent the vast majority of the domestic veterinary biologics and pharmaceutical market, as well as a significant portion of the global market. Several of our member companies are actively involved in developing new products utilizing plant-based production platforms. As such, we have a tremendous interest in the draft guidance document under development.

We offer the following comments delineated under the corresponding heading contained in the draft guidance document:

I Introduction

- The document should clarify the types of products regulated through specific agencies. Furthermore, the guidance should delineate the oversight of the various agencies with respect to particular types of products. This would facilitate a product sponsors' initiating contact with the appropriate agency.

- There is a very strong need for continued interagency communication and coordination, once a sponsor begins to navigate the regulatory process. The best approach would be for the sponsor to initiate regulatory oversight with the agency that will ultimately be charged with making the approval decision. This agency, with ultimate authority over the product, should have oversight over the product throughout the entire registration / approval process and shepherd it through the envisioned interagency process. This would entail a "lead agency" concept as utilized under NEPA. The result would be a linear process that starts with the agency ultimately responsible for approval decisions, that navigates the interagency process under the guidance of the responsible agency, and ends with the responsible agency making the approval determination and continued oversight.

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- A more extensive supportive glossary of terms should be developed. Throughout the document, we recommend against using the terms "master seeds," "master seed banks," "working seeds," and "working seed banks," etc.... These are terms in frequent use in the development of biologics. However, our experience shows that they do not conceptually flow to plant-based production platforms, and, indeed, cause confusion. Better terms are ones like "stable transformed plant stock" to replace terms like "master seed" which, although currently in use for biologic production become confusion and make less sense with plant-based production systems. Some of the terms to potentially be included in a glossary are:

    - "Stable transformed plant stock" to replace "master seed"
    - "Expanded stable transformed plant stock" to replace "working seed"
    - Production stable plant stock: may replace production seed
    - Multiple site or Multiple flock/herd/ study: may replace field study

- 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 § 101, *et. seq.* and issuance of guidance documents such as APHIS' Veterinary Services Memoranda. We encourage continued use of the existing regulations as much as possible. Any changes made to the existing regulatory structure should occur only when needed to address unique aspects of plant-based production systems and where there are no other viable alternatives.

- The current mechanisms and practices designed to protect confidential business information should be included in any new guidelines or regulations.

II Host and Source Plant Characterization

- The consequences of misuse should be addressed, with information about who to notify, when and how remediation will be addressed. Such considerations should be incorporated into the regular development process rather than supplanting it if there should ever be an issue.

II(C)(2) Characterization of the Recombinant DNA

- We want clarification that the full characterization applies only to the construct. All components of the plant genome may not or cannot be known. However, all such information would be available for the construct, the

recombinant DNA-derived plasmids used for the construct, and the method used to introduce and screen for the construct in the target plant..

II(C)(3) Stable Transformation Systems

- The last sentence of the first paragraph should be changed by deleting "could be" after "protein," and inserting the word "is." The real issue is whether a fusion protein is being expressed, not theoretically whether one could be produced.

- In the last paragraph, where a complete description is required to be submitted, it should be noted that the diagrams, maps and formats will provide the most useful information.

II(C)(4) Transient Transfection Systems

- Stability and the potential for reversion to virulence should be addressed. These types of studies will be required prior to approval and should be incorporated into the early development phases.

III(B) National Environmental Policy Act (NEPA)

- For clarification, it should be pointed out that there are actually two NEPA procedures. The first one performed via APHIS / BRS with respect to production. The second performed with respect to the final product by the agency with ultimate regulatory responsibility.

III(C) Confinement Measures

- There are a number of instances where the guidance document indicates that a sponsor "should" institute particular controls. We understand the legalese used when an agency pretends that guidance documents such as these do not become de facto regulation. However, measures such as ensuring no inadvertent mixing with food or feed, and control over inventory and disposition of viable seed are examples of items that should be mandatory, with use of words like "must" rather than "should." It is clear that such necessary control measures will be required and must meet the agency's criteria. Making it clear that such controls are mandatory, not permissive, will help assure the public of the stringent regulatory oversight of plant-based production platforms.

- Control and confinement measures will vary and depend upon the characteristics of the construct, expression characteristics, growth characteristics, the crop, the protein of interest, etc.... The ultimate decision

about the level of necessary control rests with the agency that will approve the product.

- For control and confinement measures, the product sponsor should be required to submit standard operating procedures (SOPs) to the agency. Such SOPs should identify personnel (including qualifications, experience and numbers), and identify the particular steps address the particular control or confinement measure. For example, a sponsor would submit SOPs for control of viable seeds, control of fields for field grown plants, control of harvested material, controls at processing facilities, and controls over waste material. Requiring such detailed SOPs will ensure appropriate levels of control, government oversight, and will facilitate acceptance and the ability to exploit these promising technologies.

III(C)(3) Field-grown plants

- We recommend clarification of the statement regarding the use of perimeter fencing. The use of fencing may be in conflict with security measures based on concealment. In our experience fencing is ineffective with regard to birds, insects, and small mammals. Any issue regarding fencing should be based on specific product review regarding toxicity, environmental impact, etc. and specific issues should dictate the level of fencing (containment).

- The use of dedicated land is recommended in the field-testing and production of plant made pharmaceuticals and industrials. Dedicated land will help ensure that transgenic protein from these crops does not enter the food or feed supply. Dedicated land for the testing or production must have a USDA-approved plant-back process for subsequent growing seasons. This process may entail physical, chemical or genetic controls, restricted crop rotations or the requirement for the land lie fallow for a minimum of one growing season (or longer if scientifically supported) before it can be used in the production of crops intended for use as food or feed.

III(C)(5) Control at Processing Facilities

- Sponsors must implement measures to ensure that bioengineered plants do not unintentionally mix with other plant products. Source plant 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 product, which would not be appropriate. For processing and purification in the manufacturing of a product, we believe that use of dedicated facilities and equipment should be

required. This will minimize the opportunity for inadvertent contamination and facilitate acceptance of the technology.

III(C)(6) Control of Waste Material

- The use of vendors acceptable to the agency should be allowed.

- The term "regulated product" should be clarified to clearly refer to non-viable plant material. There are many instances where manufacturing in-process wastes such as column wash solutions do not go through a true inactivation process prior to disposal. Should the final test material be considered the "regulated product" whereas materials leading up to the final product be referred to by another descriptor?

IV(A) Manufacturing and Process-Related Controls – General Considerations

- Again, the development of written procedures for cleaning, maintenance, and sanitation of equipment is something that must be required of a product sponsor – not something that "should" be done. Even though, in practice, the agencies would never approve a plant-based manufacturing process without detailed SOPs, use of permissive terms fails to communicate to the public the strict regulatory control that will be exerted over such products.

- The industry needs further guidance as to the type of sanitization and / or validation procedures that will be acceptable to the agencies.

- The guidance states that the bioburden of microbiological contaminants should be decreased during the manufacturing process. Of course, the guidance does acknowledge that different types of plant-based products will have different requirements (e.g. a parenteral product versus a feed top dressing). However, some additional guidance as to the acceptable bioburden levels is needed to assist the product sponsor in developing SOPs.

IV(B) Special Considerations for Whole Fruit or Vegetable Products

- The section on special considerations for whole fruit or vegetable products mentions that for products containing viable seeds that the sponsor should contact the agency. At this stage of the development of the technology of plant-based production platforms, we believe that it would not be appropriate to consider approval of final product forms containing viable seeds. We believe, this should be stated clearly, to facilitate acceptance of the technology.

IV(D) Product Manufacturing Procedures

- Many of the considerations for product manufacturing procedures will be the same as for any type of product, regardless of the production platform. For example, a veterinary biologic must be demonstrated to be pure, safe, potent and efficacious regardless of the production platform. A veterinary pharmaceutical must be shown to be safe and effective, regardless of the production platform.

- The section on growth conditions requires detailed SOPs for the manufacturing process. This is really the same as for any product, regardless of production platform.

- It is important to recognize that this technology is merely a production platform to create a beneficial product. Of course, there are unique considerations to plant-based production platforms, just as there are with production platforms that utilize recombinant bacteria. Viewed in this manner, most of the regulatory requirements for approval of products will apply to the development of plant-based products. What is necessary to address are the aspects unique to development in a plant-based production platform. We believe this view will facilitate acceptance of the technology, will require sponsors to approach the technology in an appropriate manner, and will allow the beneficial use of the promise of plant-based products.

- We strongly believe that all equipment used in the harvest and processing of plant-based products should be dedicated to such use. That is, it should never be appropriate to utilize equipment used in food or feed preparation at any level. This is the best manner to prevent cross contamination and inadvertent mixing of biologic / pharmaceutical material and food or feed material. Just as it would be unthinkable for a fermenter used in the production of a biologic or pharmaceutical product to also be used to brew commercial beer, it should be unthinkable for equipment used to harvest and process plant-based biologics and pharmaceuticals to also be used in commercial food or feed preparation. The only distinction to be made would be for final products intended to be mixed into animal feed, as some pharmaceuticals are used, in a feed mill licensed to carry out such activity. The end result is that the product sponsor will be required to have a dedicated grain mill or similar facility and dedicated equipment for use in the production of the plant-based product located at a licensed or approved facility. This is no different than the existing requirements for production of biologics and pharmaceuticals by other methods.

- The sections on transfer and storage conditions, initial processing of source material, extraction, aseptic processing, changeover procedures, and process

validation really point out considerations that must be taken into account for any product, regardless of production platform. The manufacturing process involves a licensed or approved establishment, a controlled, validated manufacturing process that is scrutinized and approved by agency reviewers, with equipment and facilities dedicated to biologic / pharmaceutical production, and the use of detailed SOPs. For example, if a manufacturer desired to transport bulk fluids from a fermenter to another facility for storage or further processing, the agency would have to be satisfied that appropriate, validated controls were in place before such would be allowed. The same should be true for plant-based production platforms.

CONCLUSION / FURTHER RECOMMENDATIONS

The use of plant-based production platforms to manufacture veterinary biologicals and drugs is an exciting prospect, with the potential to offer tremendous benefits for animal and human health. The technology will ultimately complement existing traditional and biotechnological production methods. For certain complex proteins, it will be plant-based production that allows their commercialization for the veterinary market. Other production methods are either impracticable, not feasible, or simply too costly. This innovative technology will allow the development of new solutions to animal health and human health needs, particularly through the development of vaccines and antibodies.

- Plant-based production of vaccines presents the opportunity for mass immunization of animals with less handling. The decreased need for handling animals would be a major benefit to livestock producers, as it would decrease the stress and costs associated with handling and administering parenteral vaccines.

- Plant-based production of antibodies provides the opportunity for development of novel and innovative antimicrobials.

- Plant-based production of vaccines and antibodies for use in animals that are targeted against food-borne pathogens have the potential to decrease the incidence of these agents and subsequent human illness.

- Plant-based production systems do not utilize serum or ingredients of biologic origin, eliminating the potential for transmission of extraneous agents of mammalian significance. Further, the potential extraneous agents of plant-based production systems are not of consequence to mammals.

- Vaccines and antibodies manufactured via plant-based production systems (as well as contemplated packaging) are biodegradable, eliminating concerns about environmental persistence.

In order to reap the benefits of plant-based production systems, it is imperative that the regulation of their use in producing drugs and biologics be science based, risk based, comprehensive and appropriate to the situation. It is imperative that the regulatory scheme consider and be designed to prevent accidental cross-contamination with food materials. This type of regulatory oversight will foster public confidence in the use of the technology.

Overall, the Guidance document is a good effort. We do believe it can be improved through incorporation of the items set forth above and the following recommendations:

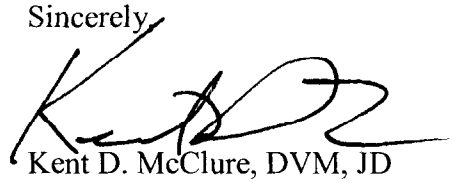
- The guidance document should include specified guidance parameters for the known plant species under development for field use in a plant-based production system, delineating such items as buffer zone, wild life protection parameters, required replant restrictions, fallow time frame requirements, storage, etc....

- The guidance document should include specific guidance parameters for processing.

- The guidance document should include specific guidance parameters for residue levels on "sanitized" processing equipment (e.g. non-detectable, below minimum detectable levels, zero tolerance)

- The guidance document should include specific guidance parameters for transport and shipping of bulk materials.

Sincerely,



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