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3. *Field-grown Plants*

You must have a permit from APHIS/BRS to grow bioengineered pharmaceutical plants in the field (7 CFR 340.4) and must have control over the growing process from planting through harvesting and over the disposition of remaining crops and/or crop residue and, if required, over the subsequent use of the field if for growth of food or feed or as a pasture during subsequent seasons. All persons involved in field growth of the product should be adequately trained to perform the duties for which they are responsible. Control measures should include an accounting of seed that is transferred from seed bank storage to the field for planting, or for archiving. Documentation of the size and location of all sites where the bioengineered pharmaceutical plants will be grown, of the control of pollen spread, and of the subsequent use of the field and destruction of volunteer plants in subsequent growing seasons should be maintained and provided to the FDA and CVB, as appropriate. Fields should be unambiguously identified, such as by Global Position Satellite (GPS) markers. We recommend that you consider the use of perimeter fencing to help exclude wildlife and escaped livestock. All fields used to grow source bioengineered pharmaceutical plants are subject to inspection by the USDA (7 CFR 340.4; 9 CFR 101-108) and/or by the FDA (42 U.S.C. 262; 21 U.S.C. 374).

4. *Control of Harvested Material*

APHIS requires that appropriate confinement procedures be in place for transport of the source material from the field or greenhouse to the production facility (7 CFR 340.4(b)(10-12)). During transport, containers of harvested material should carry a label that clearly indicates that the material, including but not limited to seeds, leaves, roots, and stems, is not to be used for food or feed or for any purposes in which residual materials could be used for food or feed (such as ethanol production). Reconciliation of the quantities of material leaving the growing facility and arriving at the processing facility should be made. In manufacturing of a regulated product, records must be kept to document control over harvested material in accordance with 21 CFR part 211 subpart J, 21 CFR part 226 subpart E, 7 CFR 340.4, or 9 CFR part 116 and made available for inspection by the FDA or CVB, as appropriate.

5. *Control at Processing Facilities*

As stated in section III.C.1., you should implement appropriate procedures to ensure that bioengineered pharmaceutical plants or plant materials do not unintentionally mix with other plant products, particularly those used as food or feed. Source plant materials should not be processed in facilities that also are used for the production of food or feed, such as grain mills, without prior consultation with USDA/APHIS/BRS and FDA.

6. *Control of Waste Material*

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. Waste material from the manufacture of human drug and biological products, or animal drugs should be disposed of in a safe and sanitary manner (21 CFR 211.50). Veterinary biologic materials should be disposed of in a manner consistent with 9 CFR 114.15, Disposal of Unsatisfactory Products and By-products, following Veterinary Services Memorandum 800.56. If, rather than disposal, the residual material is to be used for a secondary purpose other than a food or feed product, there should be clear procedures in place to verify the disposition of this material and by-products and to document that it will not be used for food or feed.

IV. **MANUFACTURING AND PROCESS-RELATED CONSIDERATIONS**

A. **General Considerations**

Facilities and procedures used for the manufacturing of regulated products should be designed to prevent contamination and cross-contamination during harvest and processing of source material. The flow of personnel, material, product, and waste into and out of the facility should be designed to prevent contamination of the product. You should establish written procedures for appropriate cleaning, maintenance, and sanitization of equipment and utensils to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug products beyond established requirements (21 CFR 211.67). In controlled areas with specified air classifications, a program for monitoring the environment for viable and non-viable particulates should be established based on the criticality of the manufacturing process involved and should include active monitoring of critical manufacturing processes as they are performed. For FDA-regulated products, manufacturing controls, including process validation, should be appropriate for the type of product and stage of development. The regulations governing facilities requirements are listed in section IV.C., Applicable FDA and USDA Regulations.

Because microbiological contaminants can have an adverse effect on product safety, quality, and stability, we recommend that you establish processing steps to decrease bioburden levels as the material moves through the manufacturing process (21 CFR 211.80(b)). The validation activities described in this section should be phased in during the investigational phase, as the clinical studies progress toward submission of a regulated product application. It should be noted however that assurance of sterility or limits on bioburden in the final product may be required as appropriate, depending on the final form and intended use of the product (e.g., parenteral vs. whole fruit or vegetable). (21 CFR 211.80, 211.100-103, and

609 211.113; 21 CFR parts 226, 514, 610, and 820; and 9 CFR part 113.)

610

611 You should only use source materials with appropriate quality attributes for manufacture of
612 the product. Each lot of source material should be assessed for the presence of foreign
613 matter. Care should be taken to minimize contaminants (e.g., molds and other agents that
614 may be present in the source material) that could lead to the inadvertent exposure of
615 recipients of regulated products to undesirable impurities or could affect product quality
616 (e.g., microbial proteases).

617

618 For veterinary biologics, manufacturing must be in accordance with an Outline of
619 Production filed with CVB as required by 9 CFR 114.8 and 114.9. For all other regulated
620 products, you must document the manufacturing procedure and lot-specific data (21 CFR
621 part 211 subpart F, 226.102, part 514, and 820.184). You should ensure that source material
622 is propagated, harvested, and processed in accordance with written standard operating
623 procedures that will ensure the adequate processing of the plant derived material and specify
624 the acceptable limits and kinds of contaminants that may be present. Specifications should
625 be established regarding the health status of the plants at the time of viral infection and/or
626 harvest.

627

628 **B. Special Considerations for Whole Fruit or Vegetable Products**

629

630 One of the challenges in the use of whole vegetables and/or fruits as the delivery system for
631 edible biologics is the demonstration of batch uniformity and consistency of dose. A
632 homogenization step to produce a uniform bulk drug substance, such as a puree, juice, or
633 milled grain may be necessary. Testing could then be conducted on this homogenized
634 product to demonstrate potency. In addition, if the plant line used for production is known
635 to be allergenic, you should consult with FDA or CVB, as appropriate, to discuss the safety
636 and regulatory issues.

637

638 • Packaging for regulated products must comply with applicable regulations. For
639 FDA-regulated products, packaging should be consistent with 21 CFR parts 210,
640 211, 226, 314, 514, 600, 610, and 820. Packaging for APHIS/CVB-regulated
641 products should comply with 9 CFR part 112. Although edible products for
642 pharmaceutical use in humans, such as whole fruit or vegetable vaccines, are
643 regulated as biologics, not foods, we generally recommend that you package your
644 edible biological products in material that conforms to food packaging regulations
645 (21 CFR 174.5). The plant source must be clearly identified in the label or
646 packaging material for biologics for use in humans (21 CFR 610.61(p)) or animals
647 (9 CFR 112). The plant source should be clearly identified in the labeling of both
648 oral and non-oral prescription drugs (21 CFR 201.57(a)(2); see also 21 CFR
649 201.100(b)(4) and (5)). For products containing viable seeds, you should consult
650 with FDA or CVB, as appropriate.

651

652 **C. Applicable FDA and USDA Regulations**

653

654 The specific regulations applicable to the manufacture of a regulated product derived from

655 bioengineered pharmaceutical plants are based on: the intended recipient of the product (i.e.,
 656 human or animal); the intended use of the product (e.g., biologic, drug, or device); and the
 657 intended route of administration (e.g., parenteral vs. oral). The Table below includes, but is
 658 not limited to, the following applicable regulations for specific classes of regulated products
 659 for use in humans or animals.
 660

Planned use	Applicable regulations
Human drug or biologic for parenteral administration	7 CFR part 340, 21 CFR parts 210, 211, 312, 314, 600, 601, 610
Human drug or biologic for oral administration	7 CFR part 340, 21 CFR 174.5, parts 210, 211, 312, 314, 600, 601, 610
Biologic device for human use	7 CFR part 340, 21 CFR parts 600, 601, 610, 812, 814, 820
Animal drug: Type A medicated articles and Type B and C medicated feed	7 CFR part 340, 21 CFR parts 225, 226, 500, 510, 511, 514, 515, 558
Animal drug	7 CFR part 340, 21 CFR parts 210, 211, 500, 510, 511, 514
Veterinary biologic	7 CFR part 340, 9 CFR parts 101-118

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We encourage you to refer to FDA and CVB guidance documents for additional information and recommendations specific to the product class. Any exceptions to the regulatory requirements must be obtained as provided by regulation. For example, the general safety, sterility, and mycoplasma tests prescribed in 21 CFR 610.11-12 and 610.30 (for biologics for use in humans) or 9 CFR 113.26-28 (for veterinary biologics) may be inappropriate for some products (e.g., edible plant material intended for use as an oral dosage form) and modifications or alternative, but equivalent, methods of demonstrating a product's safety and sterility may be permitted in accordance with 21 CFR 610.9 or the product may be exempted in accordance with 9 CFR 113.4 (see Table, above).

D. Product Manufacturing Procedures

1. General Considerations

Your application should include a description of each step of the purification process including analytical tests to demonstrate identity, purity, and concentration, and the levels of product related and non-product related impurities. This is particularly important if the impurities are related to be toxins, allergens, teratogens, or carcinogens. For each process that is not intended to be sterile, you should describe the procedures to be followed to control extraneous bioburden and the in-process testing used to monitor the level of bioburden (see, 21 CFR 211.113, 226.102, 312.23, 314.50(d), 514.1(b), 820.70, 820.181, and 820.184). 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). You should consult with the appropriate agency regarding the applicability of these considerations to device components.

2. *Growth Conditions*

The Chemistry, Manufacturing, and Controls (CMC) section or the Outline of Production should include information regarding the location of source plant propagation. For greenhouse-grown material, you should include in the description the types of containers, the soil mix composition and qualification criteria, and the greenhouse growth conditions. For field grown material, the description should include the previous uses of the land (e.g., agricultural and/or industrial use). We recommend that you establish specification/acceptance criteria/limits for the soil composition and potential soil contaminants that may affect the source material. In addition, you should describe the agricultural methods utilized during crop growth, including specifications regarding the use of chemicals and limits on specific agricultural practices (e.g., the use of specified fertilizers, pesticides, or herbicides, and irrigation practices relative to a specified harvest time frame, etc.). You should provide in your application a list of expected pests that will require control during the growth of the bioengineered pharmaceutical plants. All pest-control measures implemented should be in accordance with good agricultural practices for the growth of food crops in the United States. The Pesticide Product Information System (Ref. 5) contains information concerning all pesticide products registered in the United States. In order to evaluate the purity of the product, all pest-control interventions should be described in appropriate SOPs and should be documented in the Batch Record (for FDA-regulated products) or Outline of Production (for veterinary biologics). We recommend that you follow current Good Agricultural Practices (e.g., Ref. 6). If product expression is induced, either chemically or physically, you should establish criteria to ensure that induction is performed consistently from batch to batch. (See generally, 21 CFR parts 210, 211, 226, 312, 314, 514, 601, 610, and 820; see e.g., 21 CFR 211.84, 211.186, 312.23(a)(7), 314.50(d), 514.1, 820.50, and 9 CFR parts 101-118.)

3. *Harvest*

You should describe the method of harvesting the source material in written procedures and document the process in production records. You should have procedures for determining when the harvest will occur in order to ensure lot-to-lot consistency of the source material. You should establish specifications for the harvested material with regard to the levels of active component, process-derived contaminants, significant endogenous impurities, and adventitious agents. For example, you should describe agricultural practices and training of harvesting personnel regarding plant source material quality (e.g., assessment of the disease status of plant for manual harvesting operations, etc.) (21 CFR part 211 subpart B). You should have written procedures for establishing the necessary training of personnel engaged in harvesting plants to ensure the quality of the harvested material (21 CFR 211.25). 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 (21 FR 211.67). In addition,

735 you should consider measures to prevent the contamination of the harvested
736 source material with equipment lubricants during processing. (21 CFR part 211
737 subparts F and J; 21 CFR part 226; 21 CFR 314.50(d)(1), 514.(b)(5); 21 CFR part
738 814 subpart B; 21 CFR 820.70, 820.75, 820.181, 820.250; and 9 CFR parts 101-
739 118).

740
741 The description of the harvesting process in the CMC section or Outline of
742 Production should include specifications regarding acceptable conditions of the
743 plants and a listing of equipment used to harvest the source material, including
744 power equipment, hand tools, and transport equipment (see Table, above, for
745 applicable regulations and refer to applicable FDA and CVB guidance
746 documents). If the equipment is not dedicated to harvesting only the source
747 material, other uses should be documented.
748

749 4. *Transfer and Storage Conditions*

750
751 Of special concern is the transfer of source material from the field or greenhouse
752 to the manufacturing facility (see section III.C.1., Confinement Measures; for
753 authorities concerning the movement of plant materials). The source material
754 should be transported in such a way as to exclude introduction of insects, vermin,
755 or potential surface contaminants, which may be carried from the farm field or
756 greenhouse environment, and to ensure that plant material remains confined
757 within the container during transport. We recommend that during transport,
758 containers of regulated product material should carry a label that clearly indicates
759 that the material is not to be used for food or feed.
760

761 If the harvested source material is to be stored prior to further processing, the
762 storage conditions (e.g., temperature, humidity, volume, density, storage time,
763 etc.) should be fully described in your application. The material to be stored
764 should be characterized and all properties that may be reasonably expected to
765 affect product quality should be identified and appropriate controls should be
766 specified (e.g., stability of the product, ability to support growth of
767 microorganisms, residual soil content, presence of foreign material, insects,
768 vermin). Source material should be stored under appropriate conditions to ensure
769 that decomposition processes do not increase the concentration of contaminants
770 above specified levels or adversely affect the desired active pharmaceutical
771 ingredient. (21 CFR parts 211, 226, 314, 514, 601, and 820, and 9 CFR parts
772 101-118).
773

774 5. *Initial Processing of Source Material*

775
776 Procedures used to process harvested material should be validated. Harvested
777 material may be processed to lower bioburden or viability, improve its handling
778 characteristics, bulk consistency, and/or its extractability using various
779 procedures, including washing, sanitizing, milling of grain, shredding of leaves,
780 and homogenization of source plant material, fruits or vegetables. The material

781 produced by these processes may be intended for further processing or for use as
782 the final product (e.g., as an oral vaccine). (21 CFR 211.110, 211.186, 226.40,
783 and 820.75, and 9 CFR parts 101-118).

784
785 6. *Extraction*
786

787 The extraction process should be designed to efficiently concentrate the active
788 component or separate it from the rest of the plant material. As with any
789 purification procedure, the extraction method should not introduce contaminants
790 into the process intermediate. Acceptance criteria for relevant parameters (e.g.,
791 product concentration, total protein concentration) should be established in order
792 to verify lot-to-lot consistency. If the drug or biologic is extracted into a soluble
793 form, it is advisable to implement sterilizing filtration procedures early in the
794 process. (See generally, 21 CFR 226.40, 312.23(a)(7), 314.50, 514.1(b)(5)(iv),
795 820.75 and 9 CFR parts 101-118.)
796

797 7. *Aseptic Processing*
798

799 For those products for which sterility is required, sterility of protein products is
800 usually achieved through the use of appropriately validated filtration steps.
801 However, for products for which sterile filtration is not feasible, we recommend
802 that you use a validated aseptic process. For FDA-regulated products, refer to 21
803 CFR 211.113, 610.12(g)(4), and 820.75, and current guidance, such as the
804 Guideline on Sterile Drug Products Produced by Aseptic Processing (Ref. 7) and
805 Guidance for Industry: For the Submission of Documentation for Sterilization
806 Process Validation in Applications for Human and Veterinary Drug Products
807 (Ref. 8). For veterinary biologics, refer to 9 CFR 113.26 and 113.28 for further
808 information.
809

810 8. *Changeover Procedures*
811

812 Changeover procedures designed to prevent contamination between harvests of
813 source material should be in place and documented (21 CFR 211.67, 226.30, and
814 820.75). These procedures should include clearance of all materials and waste
815 from the receiving area and plant material processing equipment, and
816 cleaning/sanitization of surfaces. Pieces of equipment used for harvesting (e.g.,
817 scythe bars, harvested material transportation vehicles) and initial source material
818 processing (e.g., maceration equipment) are of particular concern in terms of
819 cross-contamination. We recommend that only one lot of source material be
820 processed at a time. If multiple lots of source material are to be processed at one
821 time, segregation procedures should be developed and implemented. Integrity of
822 processing equipment should be demonstrated or closed systems employed, when
823 possible. Product contact equipment should be sufficiently cleaned between each
824 lot operation to prevent product carry-over contamination of subsequent lots.
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9. *Process Validation*

All processes used to manufacture the product should be validated prior to marketing the regulated product. Laboratory studies may help to establish appropriate operating and process parameters and may be used in support of the formal validation study. You should include information and data from validation protocols and executed validation studies in your application. (21 CFR 211.110, 211.165, 211.194(a)(2), and 226.40)

E. Characterization of the Product

You should provide a complete characterization of the regulated product. For purified drug substances and drug products provide a characterization sufficient to ensure its identity, strength, quality, and purity (21 CFR 211.160-165, 211.186, 226.58, 312.23(a)(7), 314.50(d)(1)(i), 601.2(a), 820.60, 820.70, 820.75, 820.80-86, and 820.181). You should include both physicochemical as well as functional assessments. For purified protein products, the physicochemical description should also include molecular weight, subunit composition, isoelectric point, post-translational modifications, impurity profile, and other relevant parameters. Functional assays should evaluate clinically relevant activities of the product. You should provide a description of the potency assay for the active component. You should submit information on the sensitivity, specificity, and variability of all assays, including the data from the material used to prepare clinical/pre-clinical lots and prelicense serials that were used to set the acceptance limits for the assay.

In your application, you should provide specifications for the product, including identity, purity, potency, physicochemical measurements, and measures of stability (21 CFR 211.160(b) or 9 CFR 114.9). If test results are reported for final release of the product, you should establish estimates of variability and upper and lower limits for each specification. If the purified drug substance is held prior to further processing, a description of the storage conditions and verification of its stability under the conditions described should be included (see section V.). For FDA-regulated biological products, you are encouraged to consult related guidance documents for general product characterization guidance (Refs. 9, 10). For new animal drugs, consult with CVM and for veterinary biologics, CVB.

You should give special consideration to the characterization of edible plant biologics as noted above (section IV.B.) especially for measurements of identity of the active drug or biologic, bioburden limits, dose considerations and final presentation of the product (e.g., juice, puree, whole fruit, etc.).

F. Product Stability

Your application should include a stability protocol containing, but not limited to, testing for:

- potency;
- physicochemical measurements that are stability-indicating;
- moisture, if lyophilized;

- 872 • pH, if appropriate;
- 873 • sterility or control of bioburden;
- 874 • pyrogenicity, if applicable; and
- 875 • general safety, if applicable.

876

877 For products intended for use in humans and for new animal drugs, you should submit
878 information on the stability of the final product and any in-process material at each holding
879 step (21 CFR 211.166, 226.58(d), 312.23(a)(7)(iv), 314.50(d)(1), 601.2(a), and 820.75).

880 Additional information for human drugs and biologics can be found in ICH and FDA
881 guidance documents (Refs. 9, 10), in 21 CFR part 514, and a CVM specific guidance
882 document for new animal drugs (Ref. 11). FDA has also published a draft guidance
883 document issued for public comment and an ICH document on human drug and biological
884 product stability (Refs. 12, 13). For veterinary biologics, you should establish the stability
885 of the product prior to licensure.

886

887 You should propose an expiration dating period for the final product and designate the
888 recommended storage conditions. Also, you should define the procedure for determining
889 the date from which the expiration dating period begins.

890

891 A plan for an ongoing stability program should be provided in your application. This should
892 include the protocol to be used, number of final lots/serials to be entered into the stability
893 protocol each year, and how such lots/serials will be selected.

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**V. PRE-CLINICAL CONSIDERATIONS FOR BIOENGINEERED
PHARMACEUTICAL PLANT-DERIVED PRODUCTS FOR USE IN HUMANS**

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The extent of pre-clinical testing will be determined by the known attributes of the product, the donor genetic material, the host plant, and the extent of structurally and pharmacologically comparable products for which there is clinical experience. Guidance for the pre-clinical testing of various biological products is available (Refs. 14-16). Additional consideration given to pre-clinical testing of the bioengineered pharmaceutical plant source material includes the presence and identity of potentially harmful constituents such as: toxicants, pathogens, pesticides, herbicides, fungicides, heavy metals, anti-nutrients, and allergens. Both in vitro and in vivo studies may contribute to this characterization.

For plant lines derived from a host plant or related species having a known potential to produce toxins, anti-nutrients, or allergens, you should perform sensitive tests early in

918 product development to demonstrate whether the levels of these components have changed
919 in the bioengineered source plant. If the donor of the DNA is known to be a source of
920 allergens or toxicants, then you should perform appropriate allergenicity or toxicity testing.
921

922 **B. Evaluation of Impurities**

923 Impurities and contaminants include: source-plant-derived impurities, pesticides, herbicides,
924 fungicides, bacterial or fungal-derived impurities, and downstream processing-derived
925 impurities. Product-related impurities include degradation products, aggregates, or other
926 modified forms of the desired product (e.g., deamidated, isomerized, mismatched disulfide-
927 linked, oxidized, or altered conjugated forms). You should give special attention to post-
928 translational modifications unique to plant expression systems, for example the presence of
929 xylose in glycoproteins.
930

931 Further information on this topic is provided in the ICH; Technical Requirements for
932 Registration of Pharmaceuticals for Human Use - Guideline Q6B Specifications: Test
933 Procedures and Acceptance Criteria for Biotechnological/Biological Products (Ref. 9).
934

935 *1. Toxicants*

936 If the host species is known to contain toxicants (e.g., protease inhibitors,
937 hemolytic agents, neurotoxins), analytical tests, animal tests, or validation of
938 removal may be appropriate to establish that the toxicant levels are in a safe range
939 in the final product. Consult with FDA for further guidance.
940

941 *2. Evaluation of Pesticide, Herbicide, and Fungicide Levels*

942 You should use only pesticides, herbicides and/or fungicides registered by the
943 Environmental Protection Agency (EPA) for use on the crop you are using. With
944 regard to the final pharmaceutical product, you should specify the maximum
945 amount of any pesticide, herbicide, and/or fungicide residues anticipated to be
946 present, justify the safety of those amounts under conditions of anticipated use of
947 the pharmaceutical, and demonstrate that the final product does not exceed those
948 limits. A developer who has a new plant that expresses both a bioengineered
949 biologic product and a bioengineered pesticide should consult with EPA regarding
950 the safety of the pesticide. In some instances, validation of removal of the
951 pesticide from the preparation may be an acceptable alternative to final product
952 safety tests. This document only addresses FDA and USDA guidance; if you
953 have questions regarding the use or safety of pesticides, you should contact EPA.
954

955 *3. Evaluation of Metal Toxicants*

956 You should evaluate both the presence and levels of toxic heavy metals.
957 Consideration should be given to the host plant and whether it stores or
958 accumulates these metals.
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C. Allergenicity

As part of the pre-clinical evaluation, you should consider the allergenicity or immunogenicity of the intended biological product or drug. Appropriate testing protocols depend upon the intended effect of the product, the intended use (route of administration of the product), and the purity of the product. You should assess the need for allergenicity testing for each product on an individual basis and take into account production methods that might introduce allergens into the final product (e.g., from inadvertent contamination by mold, animal dander, animal excrement, or dust mite due to field or storage conditions), in addition to the potential allergenicity of the bioengineered pharmaceutical plant, itself. Consult with FDA for further guidance.

If the source plant producing the product is allergenic or immunogenic, you should test the product for those substances. Consideration should be given to plant-specific modifications, such as altered glycosylation (e.g., xylose), with regard to potential effects on immunogenic and allergic responses to the intended product.

You should evaluate the final product for allergenic determinants, such as N-glycans. Specific serum screening of the expressed protein could be evaluated using sera derived from patients allergic to the source material. Any positive outcome from specific serum screening would define the product as likely to be allergenic.

D. Immunogenicity

You should evaluate your product for plant specific modifications that may contribute to unintended immunogenicity. Standard immunogenicity testing for these products should be performed according to existing guidance (Refs. 14, 15) and consultation with FDA.

VI. CLINICAL TESTING FOR FDA-REGULATED PRODUCTS AND PRE-LICENSE TESTING FOR USDA-REGULATED PRODUCTS

We recommend that you refer to existing guidance(s) for conduct of clinical studies for drugs and biologics for humans and contact CDER or CBER, respectively if you have further questions. The potential residues of animal drugs (derived from bioengineered plants) in edible food animal tissues may be of concern, and you should contact CVM directly for guidance. You should contact CVM or CVB before animal drugs or veterinary biologics are tested on non-laboratory animals.

1003 **VII. DEFINITIONS**

1004

1005 **APHIS** – Animal and Plant Health Inspection Service of the USDA.

1006

1007 **Batch** – a specific quantity of a drug or other material that is intended to have uniform character
1008 and quality, within specified limits, and is produced according to a single manufacturing order
1009 during the same cycle of manufacture.

1010

1011 **Bioengineered pharmaceutical plant** – a plant manipulated by recombinant DNA technology
1012 to express a gene encoding a biologic or drug product.

1013

1014 **BLA** – Biologics License Application.

1015

1016 **BRS** – Biotechnology Regulatory Services Division of the USDA/APHIS.

1017

1018 **CFR** – Code of Federal Regulations.

1019

1020 **Coding region** – protein coding regions contain an open reading frame which can be transcribed
1021 into messenger RNA to direct the synthesis of a protein product.

1022

1023 **Confinement** – measures implemented to control the co-mingling of bioengineered
1024 pharmaceutical plants with non-bioengineered plants or to limit the distribution of an introduced
1025 gene to a defined area.

1026

1027 **Construct** – an engineered DNA fragment that contains, but is not limited to, the DNA
1028 sequences to be integrated into a target plant's genome.

1029

1030 **CBER** – Center for Biologics Evaluation and Research of the FDA.

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1032 **CDER** – Center for Drug Evaluation and Research of the FDA.

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1034 **CDRH** – Center for Devices and Radiological Health of the FDA.

1035

1036 **CFSAN** – Center for Food Safety and Applied Nutrition of the FDA.

1037

1038 **CVB** – Center for Veterinary Biologics of the USDA/APHIS.

1039

1040 **CVM** – Center for Veterinary Medicine of the FDA.

1041

1042 **Direct delivery systems** – gene delivery systems that do not use biological agents to introduce
1043 foreign genes into plants. Examples include electroporation, the chemical polyethylene glycol,
1044 microprojectile bombardment, and injection via a capillary tube or pipette.

1045

1046 **Drug** – human protein drug and new animal drug.

1047

1048 **FDA** – United States Food and Drug Administration.

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- 1049
1050 **Genetic stability** – the ability of the introduced DNA to be inherited in a predictable fashion and
1051 the introduced trait to be expressed in the transformed plant line and plant lines derived
1052 therefrom in a consistent, reliable, and predictable manner.
1053
1054 **Host Plant** – the parent plant prior to insertion of the gene encoding the regulated product.
1055
1056 **ICH** – International Conference on Harmonisation.
1057
1058 **IDE** – Investigational Device Exemption.
1059
1060 **INAD** – notice of claimed investigational exemption for a New Animal Drug that must be
1061 submitted prior to shipment of a new animal drug for clinical tests; establishes an Investigational
1062 New Animal Drug file, if one has not already been established for the new animal drug.
1063
1064 **IND** – Investigational New Drug Application.
1065
1066 **Indirect delivery systems** – indirect delivery systems use a biologic agent to introduce the
1067 foreign genes into the plant's genome.
1068
1069 **Lot** – a batch, or a specific identified portion of a batch, having uniform character and quality
1070 within specified limits; or, in the case of a process, it is a specific identified amount produced in
1071 a unit of time or quantity in a manner that assures its having a uniform character and quality
1072 within specified limits.
1073
1074 **Marketing application** – a BLA, NDA, NADA, PMA, 510(k), or VBPLA.
1075
1076 **MSB** – Master Seed Bank (or Master Seed for veterinary biologics).
1077
1078 **NADA** – New Animal Drug Application.
1079
1080 **NDA** – New Drug Application.
1081
1082 **NEPA** – National Environmental Policy Act.
1083
1084 **New animal drug** – are articles other than food intended for therapeutic, preventative,
1085 mitigation or diagnostic purposes OR alter the structure and function of the animal.
1086
1087 **Non-coding region** – DNA sequences that lie outside of an open reading frame and which are
1088 not translated to become part of a protein. These might include scaffold attachment regions,
1089 promoters, leader sequences, enhancers, introns, terminators, and any other sequences that are
1090 used for gene expression either in the plant or other hosts.
1091
1092 **Outline of Production** – a detailed protocol of methods of manufacture to be followed in the
1093 preparation of a veterinary biological product.
1094

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- 1095 **Raw agricultural commodity** – any food in its raw or natural state, including all unprocessed
1096 fruits, vegetables, nuts, and grains.
1097
- 1098 **Regulated products** – FDA- or CVB-regulated intermediates, and biological products, vaccines,
1099 and drugs, intended for human or animal use and/or animal feed.
1100
- 1101 **Serials** – consecutive lots or batches in support of a CVB product license application.
1102
- 1103 **Source material** – plant biomass from which the regulated product is produced.
1104
- 1105 **Source plant** – bioengineered host plant.
1106
- 1107 **Source plant material** – any biomass, including seeds, from a source plant.
1108
- 1109 **Target gene** – the gene encoding the regulated product, including any linked regulatory elements
1110 and selectable markers.
1111
- 1112 **Trait(s)** – the phenotypic characteristic(s) conferred to the recipient plant by the introduced
1113 DNA.
1114
- 1115 **Transfection system** – a method for transitory gene expression using a plant virus.
1116
- 1117 **Transformation event** – the introduction into an organism of genetic material that has been
1118 manipulated in vitro. For the purpose of this document, 'organism' refers to plants.
1119
- 1120 **Transformation system** – a method for introducing new genes into plants by either direct or
1121 indirect delivery systems.
1122
- 1123 **USDA** – United States Department of Agriculture.
1124
- 1125 **VBPLA** – United States Veterinary Biological Product License Application.
1126
- 1127 **Vector** – an autonomously replicating DNA molecule into which foreign DNA is inserted and
1128 then propagated in a host cell.
1129
- 1130 **Veterinary biologic** - all viruses, serums, toxins, or analogous products at any stage of
1131 production, shipment, distribution, or sale, which are intended for the use in the treatment of
1132 animals and which act primarily through the direct stimulation, supplementation, enhancement, or
1133 modulation of the immune system or immune response.
1134
- 1135 **Viral vector** – a virus that has been modified to contain foreign genes.
1136
- 1137 **Virus** – infectious agents containing only nucleic acid and a protein coat that can enter and
1138 replicate in a cell.
1139
- 1140 **WSB** – Working Seed Bank (or Working Seed for veterinary biologics).
1141

1141 **VIII. REFERENCES**

1142

1143 1. ICH; Technical Requirements for Registration of Pharmaceuticals for Human Use - Guideline
1144 Q5B: Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used
1145 for Production of r-DNA Derived Protein Products – (1996).

1146

1147 2. FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics
1148 Applications – (1998).

1149

1150 3. FDA Guidance for Industry: Environmental Impact Assessments (EIA's) for Veterinary
1151 Medicinal Products (VMP's) - Phase I – (2001).

1152

1153 4. FDA Draft Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed
1154 Biologics – (1999).

1155

1156 5. The Pesticide Product Information System contains information concerning all pesticide
1157 products registered in the United States. (<http://www.epa.gov/oppmsd1/PPISdata/index.html>).

1158

1159 6. Guide to minimize microbial food safety hazards for fresh fruits and vegetables,

1160 <http://www.cfsan.fda.gov/~dms/guidance.html> or

1161 <http://www.foodsafety.gov/~dms/prodguid.html>

1162

1163 7. FDA Guideline on Sterile Drug Products Produced by Aseptic Processing – (1987).

1164

1165 8. FDA Guidance for Industry: For the Submission of Documentation for Sterilization Process
1166 Validation in Applications for Human and Veterinary Drug Products – (1994).

1167

1168 9. ICH; Technical Requirements for Registration of Pharmaceuticals for Human Use - Guideline
1169 Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological
1170 Products – (1999).

1171

1172 10. FDA Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products
1173 for Human Use – (1997).

1174

1175 11. FDA Guidance for Industry: Stability Guidelines. CVM Guidance #5. (1990).

1176

1177 12. FDA Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products –
1178 (1998).

1179

1180 13. ICH; Technical Requirements for Registration of Pharmaceuticals for Human Use -
1181 Guideline Q1A(R): Stability Testing of New Drug Substances and Products – (2001).

1182

1183 14. ICH; Technical Requirements for Registration of Pharmaceuticals for Human Use -
1184 Guideline S5B: Detection of Toxicity to Reproduction for Medicinal Products – (2000).

1185

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- 1186 15. ICH; Technical Requirements for Registration of Pharmaceuticals for Human Use -
1187 Guideline S6: Pre-Clinical Testing of Biotechnology-Derived Pharmaceuticals – (1997).
1188
1189 16. ICH; Technical Requirements for Registration of Pharmaceuticals for Human Use -
1190 Guideline M3: Nonclinical Safety Studies for the Conduct of Human Clinical Trials for
1191 Pharmaceuticals – (2000).
1192
1193

1193 **APPENDIX A**

1194

1195 **CONTACTS:**

1196

1197 To apply for a permit for importation, interstate movement, and field testing of bioengineered
1198 plants and plant viruses:

1199 James White, Ph.D.

1200 U.S. Department of Agriculture

1201 Animal and Plant Health Inspection Service

1202 Biotechnology Regulatory Services, Unit 147

1203 4700 River Road

1204 Riverdale, MD 20737

1205 Ph. # (301) 734-5940

1206 <http://www.aphis.usda.gov/ppq/biotech>

1207

1208 For permission to ship experimental veterinary biological products (9 CFR 103.3 authorization)
1209 or for information regarding veterinary biologics:

1210 U.S. Department of Agriculture

1211 Animal and Plant Health Inspection Service

1212 Center for Veterinary Biologics

1213 Licensing and Policy Development

1214 510 S. 17th St., Suite 104

1215 Ames, Iowa 50010

1216 Ph. # (515) 232-5785; Fax # (515) 232-7120

1217 <http://www.aphis.usda.gov/vs/cvb/>

1218

1219 For permission to import veterinary biological products:

1220 U.S. Department of Agriculture

1221 Animal and Plant Health Inspection Service

1222 Center for Veterinary Biologics

1223 4700 River Road, Unit 148

1224 Riverdale, MD 20737

1225 Ph. # (301) 734-8245; Fax # (301) 734-4314

1226 <http://www.aphis.usda.gov/vs/cvb/>

1227

1228 For information regarding therapeutic or diagnostic biologics for use in humans:

1229 U.S. Food and Drug Administration

1230 Center for Biologics Evaluation and Research

1231 Office of Therapeutics Research and Review

1232 1401 Rockville Pike

1233 Rockville, MD 20852

1234 Ph. # (301) 827-5101; Fax # (301) 827-5397

1235 www.fda.gov/cber

1236

1237 For information regarding vaccines for use in humans:

1238 U.S. Food and Drug Administration

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- 1239 Center for Biologics Evaluation and Research
1240 Office of Vaccines Research and Review
1241 1401 Rockville Pike
1242 Rockville, MD 20852
1243 Ph. # (301) 827-3070; Fax # (301) 827-3532
1244 www.fda.gov/cber
1245
1246 For information regarding animal feeds and animal drugs:
1247 U.S. Food and Drug Administration
1248 Center for Veterinary Medicine
1249 HFV-200, 7500 Standish Place
1250 Rockville, MD 20855
1251 Ph. # (301) 827-6652; Fax # (301) 827-1484
1252 www.fda.gov/cvm
1253
1254 For consultation on issues related to human food:
1255 U.S. Food and Drug Administration
1256 Center for Food Safety and Applied Nutrition
1257 HFS-013, 5100 Paint Branch Parkway
1258 College Park, MD 20740-3835
1259 Ph # (301) 436-1715; Fax # (301) 436-2637
1260 www.cfsan.fda.gov
1261
1262 For information regarding drugs for use in humans:
1263 U.S. Food and Drug Administration
1264 Center for Drug Evaluation and Research
1265 5600 Fishers Lane
1266 Rockville, MD 20857
1267 Ph.# (301) 827-4573; Fax # (301) 827-3056
1268 www.fda.gov/cder
1269
1270 For information regarding medical devices:
1271 U.S. Food and Drug Administration
1272 Center for Devices and Radiological Health
1273 Division of Small Manufacturers Assistance
1274 1350 Piccard Drive
1275 Rockville, MD 20850
1276 Ph.# (301) 443-6597; Fax # (800) 638-2041
1277 www.fda.gov/cdrh



European Medicines Agency
Evaluation of Medicines for Human Use

London, 24 July 2008
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(COMMITTEE ABBREVIATION)**

**GUIDELINE ON THE QUALITY OF BIOLOGICAL ACTIVE SUBSTANCES PRODUCED
BY STABLE TRANSGENE EXPRESSION IN HIGHER PLANTS**

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