Appendix - Pharmaceutical, Industrial and Phytoremediation Permits

In 2003, APHIS modified its permit confinement measures and procedures to verify compliance and to enhance the transparency for permits intended for pharmaceutical and industrial use to include: a larger perimeter fallow zone (50 ft); cleaning of field equipment and storage facilities using APHIS-approved procedures; dedicated planting and harvesting equipment and storage facilities; planting restrictions in the subsequent growing season; APHIS approved training; and additional compliance and inspection oversight by APHIS (68 FR 11337-11340).

As part of a government-wide effort to increase transparency, APHIS posts to its website a NEPA document (including EA and EIS) and the Supplemental Permit Conditions for Pharmaceutical, Industrial, and Phytoremediation permits, see http://www.aphis.usda.gov/brs/ph_permits.html.

Additional Data Requirements

Additional information is required for the submission of permits intended for pharmaceutical and industrial use as follows:

- Provide a one to two page description of the gene product and its current or potential use.
- If the gene leads to a product intended for an industrial or other non-food/feed use, indicate if it is the gene product or a down-stream product.
- If the gene product is for therapeutic use (e.g., an antibody or vaccine) provide the type of antibody (IgG, IgM, etc.) the epitope or antigen, and the disease and target component of the immune system.
- Indicate if the gene product is new to the plant or is commonly found in plants used for food or feed.
- Provide an assessment of gene sequence homology to known toxicants or proteins known to or likely to harm non-target organisms.
- Indicate if the cloning procedure has altered the amino acid sequence of the protein and indicate if this change is expected to change the biological properties of the protein.
- Compare the properties of the engineered protein/enzyme with the native molecule.
- Compare levels produced in the engineered plant with those of known, naturally occurring toxic compounds and address possible non-target exposure routes (groundwater, foraging animals, pollen dispersal, etc.).
- Address whether the engineered protein is expected to affect worker safety or to have effects (dermal, inhalation, toxicity, etc.) on non-target invertebrates (earthworms, bees, etc.) and vertebrates (birds, rabbits, rodents, etc.).
- Indicate whether engineering has or is likely to affect biological properties related to confinement measures (e.g., dormancy, pollen viability, etc.).
- Indicate where the product is in the regulatory review process with other agencies.

Additional information is required for the submission of permits intended for phytoremediation use as follows:

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- Data or references to show whether the engineering has altered, or would be expected to alter, the levels of any naturally occurring toxicant in the plant or the accumulation or the release of toxic compounds recovered during phytoremediation.
- Would any compounds that accumulate or result from breakdown be expected to affect worker safety or to have toxic effects on non-target organisms: invertebrates (earthworms, bees, etc.) and vertebrates (birds, rabbits, rodents, etc.).
- Indicate whether engineering has or is likely to affect biological properties related to confinement measures like seed dormancy, pollen viability, etc.
- Indicate where the product is in the regulatory review process with other agencies.

Confinement Measures

APHIS will institute the following changes in field test permit conditions for pharmaceutical corn.
A. APHIS will require that there will be no corn grown within 1 mile (5,280 feet) of the field test site throughout the duration of any field test which involves open-pollinated corn. This establishes a physical isolation distance that is eightfold greater than the isolation distance required for the production of foundation seed (660 feet). When pollen flow is controlled by placing bags around the corn tassels there will be no other corn within 2,640 feet of the field test site and the pharmaceutical corn must be planted no less than 28 days before or 28 days after any corn growing in a zone extending from 2,640 to 5,280 feet from the field test site ensuring there is no overlap in anthesis.
B. With the establishment of isolation distances of 1 mile for open pollinated corn and one-half mile for controlled pollination corn field tests, APHIS will not allow the use of border rows to reduce these isolation distances. APHIS believes that other methods are available and do not pose the difficulties inherent in using border rows. For example, by eliminating the use of border rows/buffer strips there will be a reduction in the amount of plant material that must be disposed of after the field test is terminated (border rows are handled the same as the regulated article as their proximity to the plots make them possible pollen recipients). This should reduce the possibility of inadvertent mixing of regulated articles with nonregulated plant material. 68 FR 11337-11340 (II)(2)(A)

APHIS requires greater confinement measures for pharmaceutical and industrial corn.

Perimeter Fallow Zone

APHIS will increase the size of the perimeter fallow zone (not in production) around the field test site from 25 to 50 feet. This measure is designed to ensure that test plants are not inadvertently commingled with plants to be used for food or feed. APHIS currently prohibits the use of the field test site and its perimeter fallow zone to be used to produce food or feed crops during the tests. APHIS increased the size of the perimeter fallow zone around the test site to allow farm machinery to move around the site and yet still prevent physical mixing of the regulated plants with surrounding plants that may be used for food or feed. 68 FR 11337-11340 (II)(1)(A)

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To prevent regulated plants from inadvertently commingling with plants to be used for food or feed, a perimeter fallow zone of at least 50 ft. must be maintained around the release site in which no crops are grown to be harvested or used for food or feed. Plants may be grown in the 50 ft. fallow zone, as long as they are not used for food or feed.

SOPs and Cleaning of Field Equipment and Seed Cleaning and Drying Equipment

APHIS will require cleaning procedures to be submitted and approved to minimize the risk of seed movement by field operations or equipment (movement of seed on tires of tractors, etc.) from the authorized test site.

APHIS will require procedures to be submitted and approved for seed cleaning and drying in order to confine the plant material and minimize the risk of seed loss or spillage. 68 FR 11337-11340 (II)(1)(E-F)

Submit Standard Operating Procedures (SOPs) that describe how a particular task or operation will be carried out. Processes described in the SOPs should be followed for the duration of the permit and post-harvest monitoring period. If the permit is a renewal, indicate what changes were made and what additional equipment was added to the SOP. SOPs must be dated or have a version number. SOPs must be submitted and approved by APHIS for equipment cleaning.

Provide the following information in the SOPs for Cleaning of Field Equipment and Seed Cleaning and Drying Equipment:

- Methods for cleaning equipment used for planting/inoculation and harvesting, as well as other field equipment (e.g. tractors and tillage attachments, such as disks, plows, harrows, subsoilers, etc.) used from the time of planting/inoculation through the post-harvest monitoring period.
- Field equipment cleaning should be carried out in the release site, fallow zone, building or other regulated area designated in the permit or SOPs. Indicate where cleaning will take place.
- Equipment used to transport seeds or harvested material must be cleaned after transportation.

SOPs and Restrictions for Dedicated Planting and Harvesting Equipment

APHIS will require that planters and harvesters be dedicated to use in the permitted test site(s) for the duration of the tests. In addition, while tractors and tillage attachments, such as disks, plows, harrows, and subsoilers, do not have to be dedicated, they must be cleaned in accordance with protocols approved by APHIS (see item II.1.E). To ensure the regulated articles are not inadvertently removed from the site, APHIS authorization will be required before the machinery is used elsewhere. 68 FR 11337-11340 (II)(1)(C)

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To prevent the regulated article from being inadvertently removed from the site, planting and harvesting equipment must be dedicated for use in the permitted release site(s) from the time of planting through the end of harvesting. After use in the pharma release(s) is complete, dedicated planters and harvesters must be thoroughly cleaned and inspected by APHIS before being returned to general use.

After harvest, the permittee will not be required to obtain APHIS authorization to use this equipment on APHIS -permitted sites (same sites or different sites) planted with the same regulated crop, with the target protein(s) authorized under this permit, in subsequent growing seasons under an extension of this permit or a different permit. A harvester does not have to be dedicated for the season as long as the pharma releases are harvested last and the harvester is then inspected by APHIS before being returned to general use.

Permission must be granted by APHIS (with a determination made by the APHIS inspector) before planting and harvesting equipment can be used on any sites planted to crops not included under this permit. The permittee must submit a notice to APHIS and the State Regulatory Official at least 21 calendar days in advance of cleaning this equipment so that APHIS can complete an inspection to ensure that the equipment has been cleaned appropriately. This is done by submitting a Cleaning notice (Return to General Use Notice) through ePermits, email, FAX or mail.

In addition to the information required for Cleaning of Field Equipment and Seed Cleaning and Drying Equipment SOPs, provide the following information in the SOPs for dedicated equipment (i.e., planters and harvesters):

- If the equipment is moved between release sites, provide the method(s) used to prevent the release of the regulated article (e.g., seed) between release sites.
- Provide the make, model and Vehicle Identification Number (VIN), serial number or any other way to uniquely identify the dedicated field equipment. SOPs should be applicable to the specific make and model of the equipment.
- Indicate the final disposition of material recovered during cleaning operations. Viable plant material should be destroyed or handled appropriately to maintain containment. Non-viable material may be disposed of through appropriate waste disposal methods, depending on the constructs and where in the plant the protein is expressed.
- This equipment must be posted as restricted to authorized personnel only. When not in use, it needs to be locked or secured to prevent use by unauthorized personnel or all dedicated equipment must be labeled indicating for NON-FOOD/ NON-FEED USE ONLY.
- If the permit is a renewal, indicate what changes were made and what additional equipment was added to or removed from the SOPs.

<u>Dedicated Storage Facilities for Equipment and Regulated Articles</u>

APHIS will require the use of dedicated facilities for the storage of equipment and regulated

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articles for the duration of the field test. Facilities must be cleaned according to APHIS approved protocols prior to general use of the facilities. 68 FR 11337-11340 (II)(1)(D)

Dedicated facilities for the storage of equipment and regulated articles (locked or secured buildings, bins, or areas) must be posted as restricted to authorized personnel only and used for storage of dedicated equipment and regulated articles. All dedicated storage facilities must be labeled indicating for NON-FOOD/ NON-FEED USE ONLY.

Before returning these facilities to general use, they must be cleaned in accordance with procedures submitted to and approved by APHIS. The permittee must submit a notice to APHIS at least 21 calendar days in advance to allow for APHIS to complete an inspection to ensure that the facilities have been cleaned appropriately. APHIS authorization (a determination by the APHIS inspector) must be received before facilities are returned to general use. This is done by submitting a Cleaning notice (Return to General Use Notice) through ePermits, email, FAX or mail.

Post Harvest Land Use Restrictions

APHIS will restrict the production of food and feed crops at the field test site and perimeter fallow zone in the following season in cases where there is a potential for volunteer plants to be inadvertently harvested with the following crop. 68 FR 11337-11340 (II)(1)(B)

Production of food and feed crops at the release site and the perimeter fallow zone is restricted during one or more growing seasons following harvest or termination of the release. This is done to ensure that volunteer plants are adequately monitored for and controlled to prevent mixing with other commodities and persistence in the environment. The same release site may be used in subsequent years for pharma production (for pharmaceutical or for industrial use) under permit. Authorization must be obtained from APHIS prior to planting any food or feed crop at the release site and perimeter fallow zone during the post-harvest monitoring period. Requests for such authorization are not encouraged and will not be granted in cases where there is a reasonable potential for the regulated articles to become mixed with the proposed food or feed crop during harvesting.

Personnel Training Program

APHIS will require the permittee to implement an approved training program to ensure that personnel are prepared to successfully implement and comply with permit conditions. 68 FR 11337-11340 (II)(1)(G)

Permittees are required to carry out an APHIS approved training program to ensure that personnel follow the confinement procedures put forth in the permit and SOPs and comply with all Permit Conditions. All personnel should be trained or work directly under the supervision of someone who has been trained, and receive instruction pertaining to the duties for which they are responsible. Records of who was trained, for what activity, and when they were trained should be maintained and be made available upon request at the time of inspection.

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If a training program has been approved with a previous permit, you must resubmit the training materials that will be used for each permit. If any changes have been made to previously approved training materials, please note this in the new application.

The training program must be submitted with the permit application and should cover all aspects related to the permitted activities and conditions at all of the intermediate and final destinations listed in the permit application. For example, these may include, but not be limited to the following:

- The regulations at 7 CFR 340 for release, interstate movement, and importation as applicable to the permittee's activities:
    - sections 7 CFR 340.4 (a)-(f), 7 CFR 340.7 and 7 CFR 340.8
        - http://www.aphis.usda.gov/biotechnology/regulations.shtml
    - FR Notice (68 FR 11337-11340) on Field Testing of plants Engineered to Produce Pharmaceutical and Industrial Compounds
        - http://www.aphis.usda.gov/brs/fedregister/BRS_20030310a.pdf
    - Plant Protection Act [7 U.S.C. 7734 (Sec. 424)] that address the consequences of noncompliance
        - http://www.aphis.usda.gov/biotechnology/regulations.shtml
- The training should include all aspects related to permit activities including those described in the permit, the standard permit conditions, the supplemental permit conditions and the SOPs.
- The training should include methods for inspecting, monitoring, and recording activities that are undertaken to meet the conditions of the permit. For example, this could include monitoring or reporting forms, seed inventory and transport forms, third party auditing, or witness verification that critical procedures were performed according to SOPs and/or permit conditions.
- The training program should be applicable to all personnel who handle, store, perform field activities with, or transport regulated articles, or who are responsible for regulatory affairs, or those who manage these activities.
- Personnel should know who has authorized access to the release site and other restricted areas. Persons having access should receive training that addresses site security and how to prevent unauthorized access to regulated articles.
- Personnel should be made aware of reporting requirements for accidental or unauthorized releases and appropriate remedial measures to address spills or loss of containment of regulated articles.

Compliance and Inspections

In order to ensure compliance with the regulations as well as all permit conditions APHIS will increase the number of field site inspections during the upcoming growing season to correspond with critical times relevant to the confinement measures. Examples might include inspection at the preplanting stage to evaluate the site location; at the planting stage to verify site coordinates

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and adequate cleaning of planting equipment; at midseason to verify reproduction isolation protocols and distances; at harvest to verify cleaning of equipment and appropriate storage; at post-harvest to verify cleanup at the field site; and for the following growing season inspections will be timed to ensure that regulated articles do not persist in the environment. For example a field test may have five inspections during the growing season and two additional inspections postharvest; however APHIS may inspect more frequently in some cases.

The permittee must as always maintain records of activities related to meeting the permitting conditions. APHIS will increase the auditing of the permittee's records to verify that required permit conditions were accomplished. APHIS will continue to require permittees to regularly inspect sites and maintain accurate records that will be available for APHIS auditing. The permittee will be required to record all efforts undertaken to meet the confinement protocols and other permit conditions. Some of this information will be related to agronomic information (i.e. detasseling, pollination time of test crop, pollination time of surrounding crops, etc.). Frequent APHIS audits will enable the Agency to identify any discrepancies and mitigate any potential adverse effects. 68 FR 11337-11340 (III)

To ensure compliance with regulations and permit conditions, APHIS's policy for pharmaceutical and industrial releases is to conduct inspections at critical control points in the production cycle of the regulated article. Generally, seven inspections of the release are performed. These inspections usually occur prior to planting/microbe inoculation, during planting/microbe inoculation, during active growth (generally at mid-season), at harvest, and after harvest. Two inspections are conducted at the same site the following season to monitor for volunteer plants.

For perennial plants, inspections may be different than that of annual plants depending on the biology of the species. Generally, sites are inspected prior to planting/release and during planting/release. The release is usually inspected during the period when volunteer plants usually emerge or when flowering is expected each year. Harvest and post-harvest inspections are performed in the year in which these activities occur. Site inspections for volunteer monitoring occur in year one or year two following the harvest of the regulated plants to ensure they do not persist in the environment.

As part of a government-wide effort to increase transparency, APHIS posts to its website redacted notices of inspection findings summarizing the results of permit inspections for Pharmaceutical, Industrial, and Phytoremediation permits, see http://www.aphis.usda.gov/brs/ph_permits.html.

Records and Record Audits

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The permittee must, as always, maintain records of activities related to meeting the permitting conditions. APHIS will increase the auditing of the permittee's records to verify that required permit conditions were accomplished. APHIS will continue to require permittees to regularly inspect sites and maintain accurate records that will be available for APHIS auditing. The permittee will be required to record all efforts undertaken to meet the confinement protocols and other permit conditions. Some of this information will be related to agronomic information (i.e., detasselling, pollination time of test crop, pollination time of surrounding crops, etc.). Frequent APHIS audits will enable the Agency to identify any discrepancies and mitigate any potential adverse effects. 68 FR 11337-11340 (III)

APHIS audits records and verifies compliance with the conditions imposed in permits. See the section on Compliance and Inspections in the Permit Guidance for further information. Records of who has been trained, for what activity, and when they were trained should be maintained.

Reports and Notices

Additional Reports and Notices are required for permits designed for pharmaceutical and industrial intent. A report is the submission of required information; a notice is the alert of some action to occur in the near future.

- For information on what reports must be submitted, when and where and how to submit the reports, refer to the permit conditions.
- For additional information on submitting planting/environmental reports refer to **Appendix –Planting/Environmental Reports** and **Appendix - Consolidated Monthly Planting/Release Report Submission Formats for Applicable Organizations**
- For information on what to include in these reports and notices and how and when to submit the reports and notices through ePermits consult the permit conditions and the guidance provided in the "ePermits BRS Reports and Notices User Guide" (see https://epermits.aphis.usda.gov/epermits/xml_schema/BRS_Reports_and_Notices_User_Guide.pdf)

Version

7/9/2008	"Guidance for APHIS Permits for Field Testing or Movement of Organisms Intended for Pharmaceutical or Industrial Use"
12/7/2011	"USDA-APHIS-BRS User's Guide Permit, Appendix - Pharmaceutical, Industrial and Phytoremediation Permits" supersedes "Guidance for APHIS Permits for Field Testing or Movement of Organisms Intended for Pharmaceutical or Industrial Use" Version 7/9/2008