Plant-Made Pharmaceutical Confinement Systems

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Rachel G. Lattimore

Arent Fox
Plant-Made Pharmaceuticals

*Plant-made pharmaceutical production:*

*Is like any other pharmaceutical production system:*
- Regulated and subject to mandatory conditions
- Well characterized
- Stable
- Productive
- Produces safe, pure, potent, consistent product

*Is not a commodity agricultural production system:*
- Contained process
- Outside commercial grain or respective crop channel
- Limited acreage, location
- Controlled articles
Plant-Made Pharmaceuticals (PMPs)
Presentation Overview

- Regulatory requirements for PMP production
- Closed loop system
- Confinement/Containment system for PMP
Pharmaceutical Product Requirements*

- Safe
- Pure
- Potent
- Well Characterized
- Validated Manufacturing Process
- Assure Consistent Supply

* Regardless of production method used: synthetic, microbial fermentation, mammalian cell culture, PMP
Plant-Made Pharmaceutical

Field Operations

*Maize as an illustrative example*
Field Operations

The PMP production process

1. Is very highly regulated

2. Is produced and processed in a closed-loop system outside of the commercial grain channel

3. Uses multiple containment strategies to insure that no PMP plant material (corn seed, rice grains, tobacco leaves etc.) enters into the food or feed channels
1. PMP production is highly regulated and monitored by USDA and FDA
Multiple containment strategies

Frequent auditing:
• by internal company QA
• by government regulatory agencies

Goal to ensure:
• no PMP plant material enters the food chain
• medical products are safely and consistently produced
**Significant Regulatory Oversight with Multiple, Overlapping Responsibilities**

<table>
<thead>
<tr>
<th>Process</th>
<th>USDA</th>
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<tbody>
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<td>Gene Construction</td>
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For every field planted to PMP plants, a permit must be pre-approved by USDA-APHIS that contains:

- the proposed location
- acreage
- field design
- containment procedures
Field confinement strategy for maize producing a therapeutic protein

Monitor all fields within one mile from isolation zone for corn.

Isolation Zone:
- No corn one mile from field border
- 50 foot fallow ground surrounding the test site
- One mile physical isolation from all other maize.
- Equipment cleaning in field, with pre-approved SOP
- Crop destruction of field post-harvest
- Field not followed with same crop in the next planting season
- Rotational crops must be pre-approved
- Volunteer monitoring for one year after crop destruction
- Contingency plans for unintentional release in place prior to planting

Diagram for illustration purposes only

Notify agency 7 days prior to planting and 21 days before harvest/crop destruct
- Detailed plot maps, acreage, isolation monitoring data, etc., to be submitted

APHIS confinement standards for a PMP field release
USDA-APHIS must be notified prior to planting any PMP plant field to allow auditors the opportunity to be present during planting.
Internal company QA also conducts a facility audit prior to planting to insure that all compliance measures are being understood and followed.
PMP field productions are conducted according to pre-approved written field plan that specifies:

- the objectives and conduct of the field production
- references the Standard Operating Procedures that will be followed
2. PMP plants are produced and processed in a closed-loop system outside of the commercial grain/respective commodity channel.
Closed Loop Production System

- Closed loop production system completely outside of commodity grain channels means no cross-over of facilities, critical equipment or personnel.

- PMP seed is not sold: growing, handling, transport under contract and company supervision -- higher quality standards, chain of custody.
3. PMP plants are produced using multiple containment strategies to ensure that no PMP plants enter into the food or feed channels.
The BIO PMP Working Group has developed a Containment Analysis and Critical Control Point (CACCP) Plan for PMP production.
Containment Strategies have been developed for:

- Field Production
- Seed Conditioning and Storage facilities
- Volunteer Monitoring
Field Operations
Containment Strategies

Containment Strategies
Field Operations
PMP companies may use up to four levels of control for PMP production to ensure containment.
1. Field production may be conducted outside the main crop producing regions.
2. USDA PMP regulations are strictly followed, with a required isolation distance from commercial crop counterpart.
3. Large scale protein production plantings of corn can be conducted with male sterile transgenic plants that do not produce pollen.
4. Large scale protein production field plantings are additionally detasseled (if corn is used) to remove any chance of release of transgenic pollen.
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**APHIS confinement standards for a PMP field release**
Containment Strategies

Seed Conditioning and Storage Facilities
1. PMP host plants are grown at facilities that are dedicated only for the production of PMP.

Use of the same facilities for crops intended for feed or food is prohibited.
2. PMP facilities are controlled access facilities, enclosed by fencing, and monitored by security guards.
3. All movement of PMP plant material (seed, grain, leaves) is triple contained to prevent loss of plant material during shipment.

All shipments are labeled “Not for Food or Feed Use”
Transport of PMP Grain Under Triple Containment
Transport of PMP Grain Under Triple Containment
4. All PMP plant material shipments are controlled by a chain of custody system.
5. All planting and harvesting equipment used in PMP production is cleaned and inspected prior to leaving the field according to USDA–approved procedures.
6. All equipment used to clean and bag PMP plant material is dedicated equipment, cleaned and inspected after each use according to USDA–approved procedures.
Field Operations

Containment Strategies

Containment Strategies

Volunteer Monitoring
1. All PMP fields are monitored during the following season to ensure the absence of volunteers from previous PMP plants.
2. A minimum of 12 months of monitoring in rotational crops is required.
3. Only rotational crops that are pre-approved by USDA are permitted during the season following PMP production.
Field Operations

The goal of the containment strategy is to insure that no PMP plant material will enter the food chain.
PMP production is very highly regulated and monitored.

PMPs are produced and processed in a closed-loop system outside of the commercial grain channel.

PMP production uses multiple containment strategies suited to the plant host.
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