Plant-Made Pharmaceutical Confinement Systems

Agricultural Outlook Forum 2004

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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

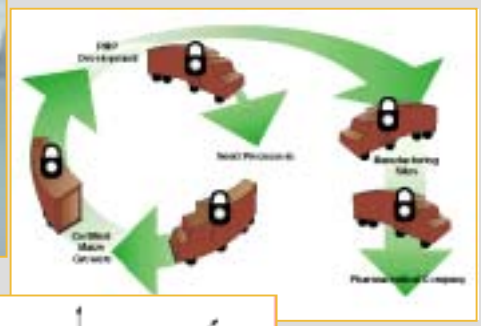
- Regulatory requirements for PMP production
- Closed loop system
- Confinement/Containment system for PMP

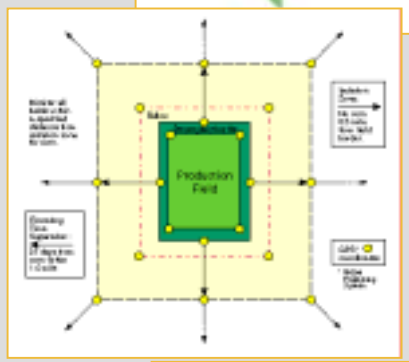
Pharmaceutical Product Requirements*

- **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

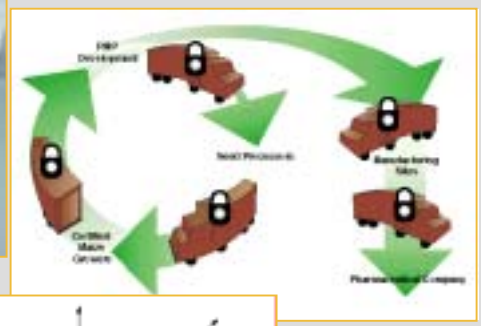


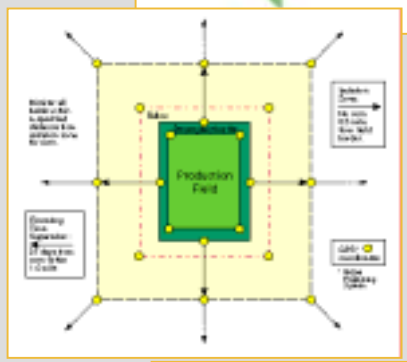


Field Operations

** 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

Field Operations

Regulatory

1. **PMP production is highly regulated and monitored by USDA and FDA**

Field Operations

Regulatory

Multiple containment strategies

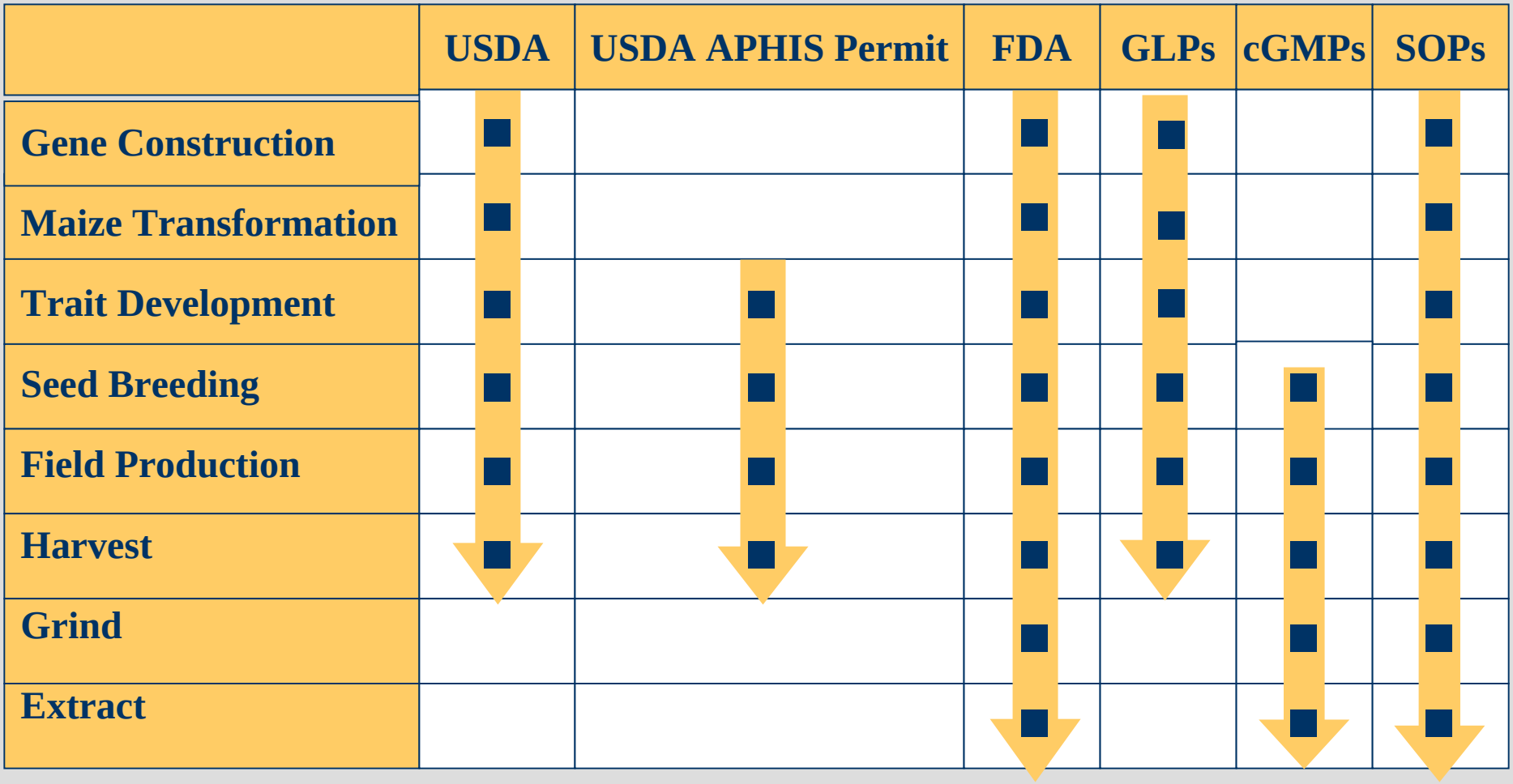
Frequent auditing:

- **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



Field Operations

Regulatory

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**

APHIS Permit Regulates Field Research and Movement

Field confinement strategy for maize producing a therapeutic protein

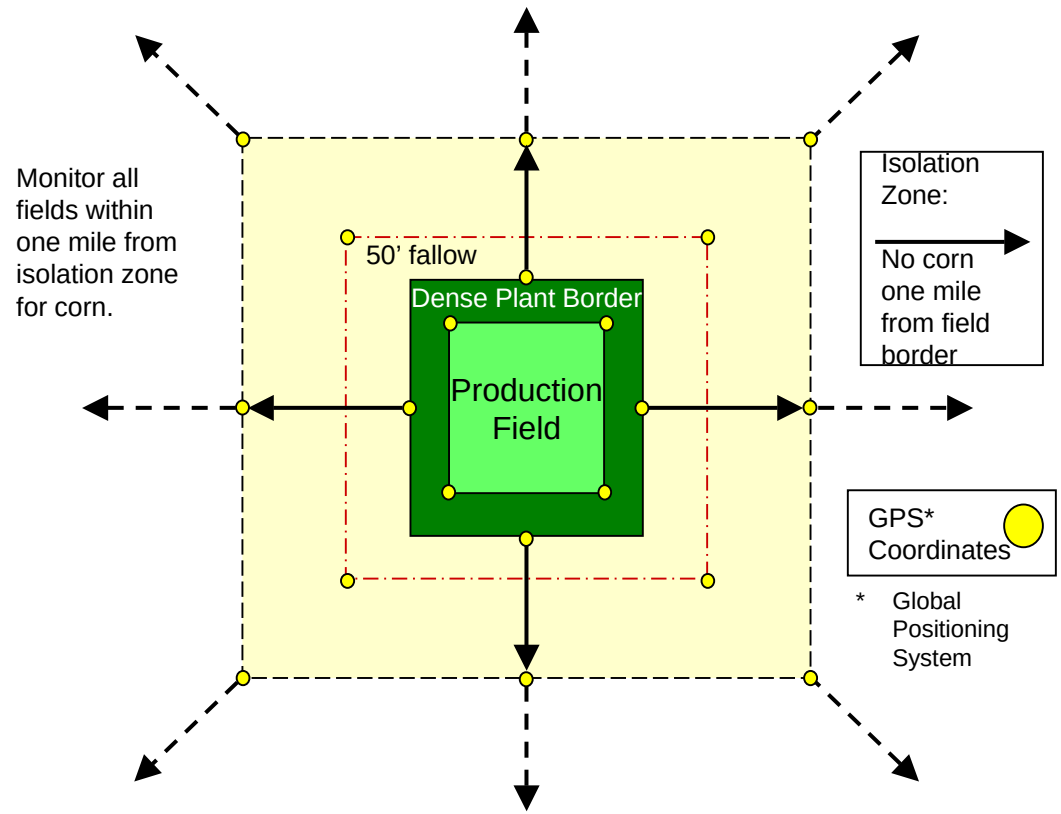


Diagram for illustration purposes only

- 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
- 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 years after crop destruction
- Contingency plans for unintentional release in place prior to planting

APHIS confinement standards for a PMP field release

Field Operations

Regulatory

USDA-APHIS must be notified prior to planting any PMP plant field to allow auditors the opportunity to be present during planting.

Field Operations

Regulatory

Internal company QA also conducts a facility audit prior to planting to insure that all compliance measures are being understood and followed.

Field Operations

Regulatory

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**

Field Operations

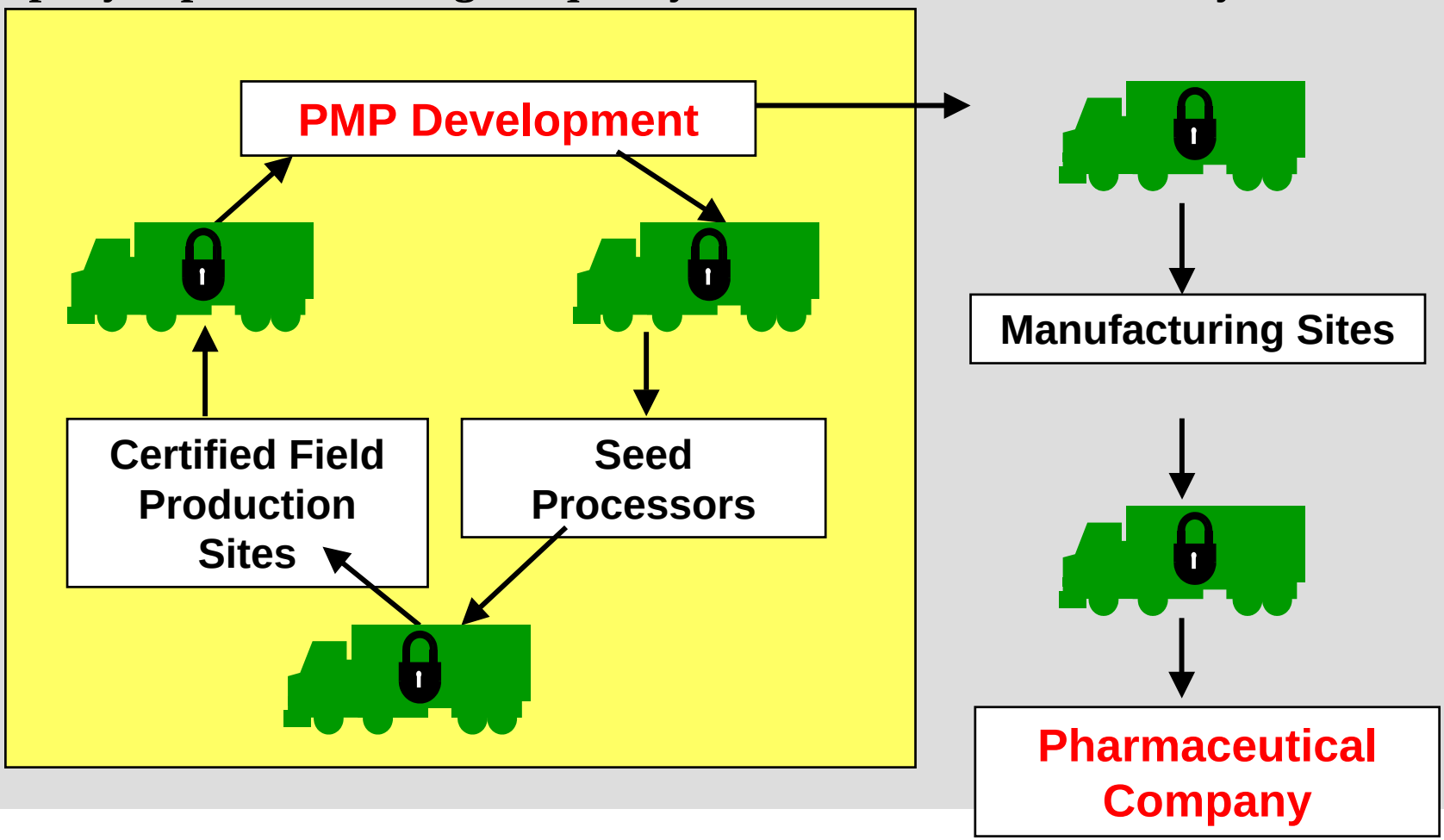
Closed-Loop Production

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.**



Field Operations

Containment Strategies

3. **PMP plants are produced using multiple containment strategies to ensure that no PMP plants enter into the food or feed channels.**

Field Operations

Containment Strategies

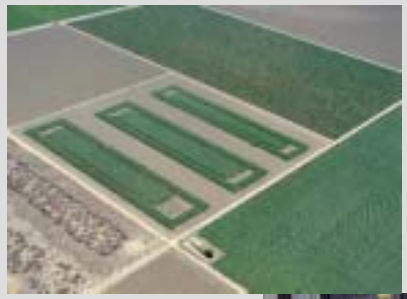
The BIO PMP Working Group has developed a Containment Analysis and Critical Control Point (CACCP) Plan for PMP production.

Field Operations

Containment Strategies

Containment Strategies have been developed for :

- **Field Production**
- **Seed Conditioning and Storage facilities**
- **Volunteer Monitoring**



Containment Strategies

Containment Strategies

Field Operations

Field Operations

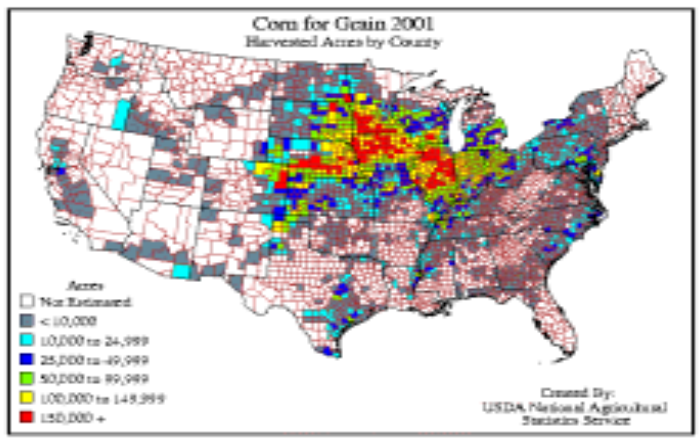
Containment Strategies - Field

PMP companies may use up to four levels of control for PMP production to ensure containment.

Field Operations

Containment Strategies - Field

1. Field production may be conducted outside the main crop producing regions.



Field Operations

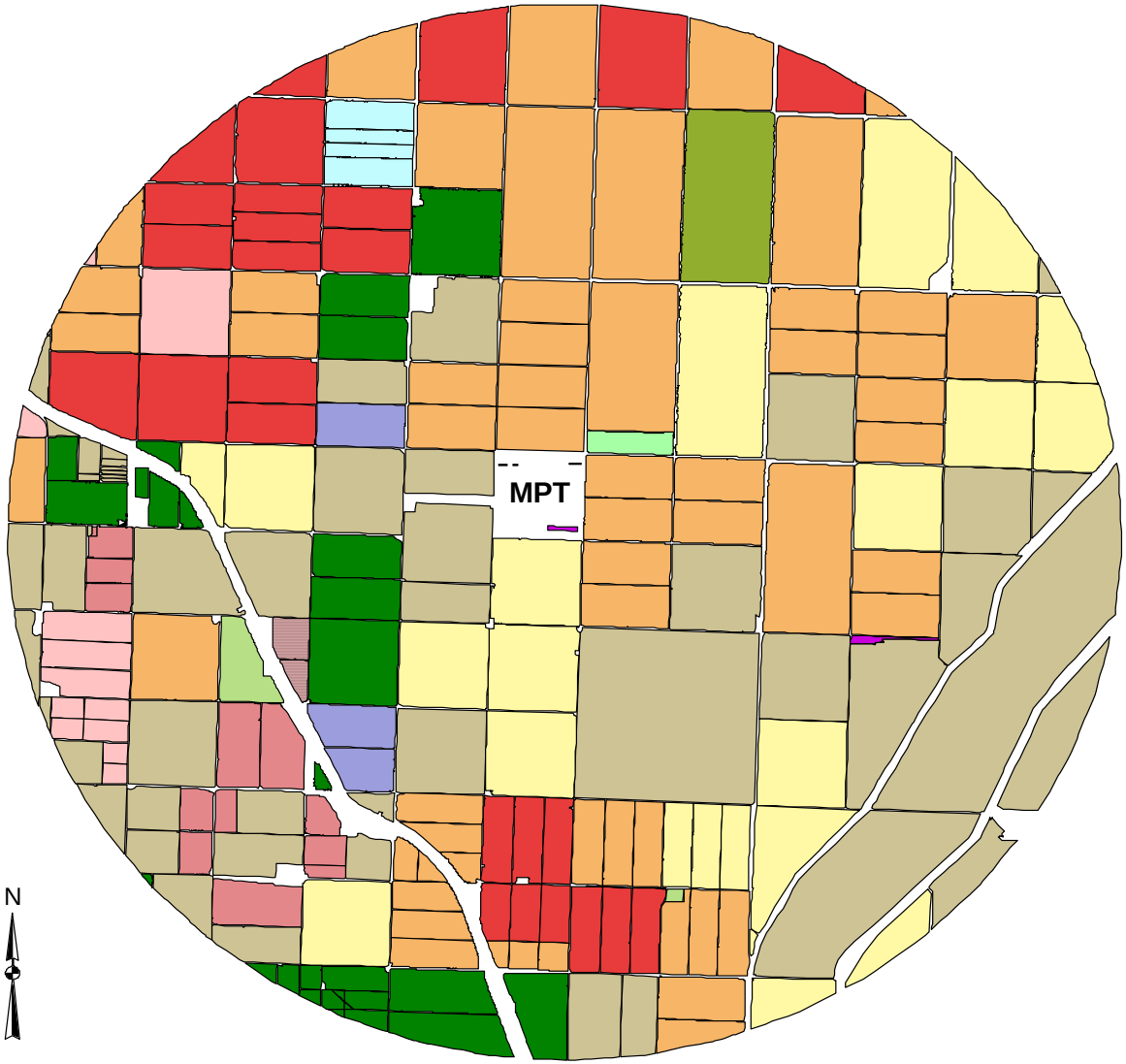
Containment Strategies - Field

2. **USDA PMP regulations are strictly followed, with a required isolation distance from commercial crop counterpart.**

California Site

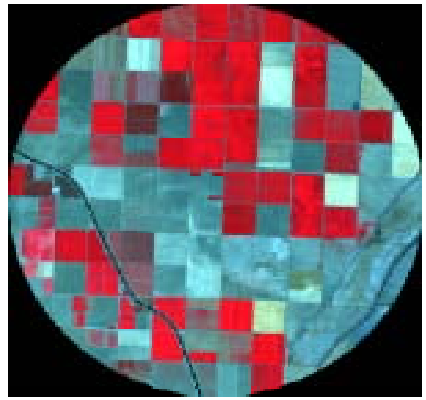
July 2002

MONSANTO
Protein Technologies



Land Cover

- Asparagus
- Bedded
- Corn
- Cotton
- Fallow
- Garbonzo Beans
- Garlic
- Grapes
- Lettuce
- Melon
- Onion
- Tomato
- Trees
- Vines
- Volunteer Wheat
- Wheat
- Worked Fallow



Field Operations

Containment Strategies - Field

3. Large scale protein production plantings of corn can be conducted with male sterile transgenic plants that do not produce pollen.

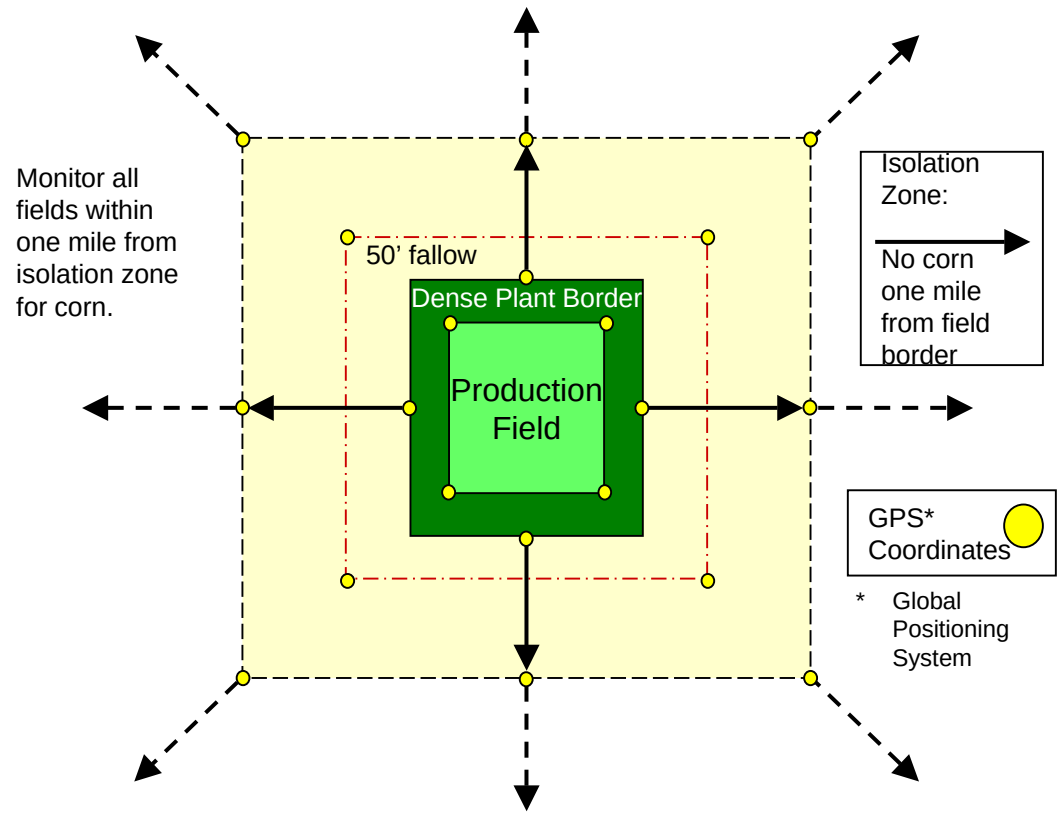
Field Operations

Containment Strategies - Field

4. Large scale protein production field plantings are additionally detasseled (if corn is used) to remove any chance of release of transgenic pollen.

APHIS Permit Regulates Field Research and Movement

Field confinement strategy for maize producing a therapeutic protein



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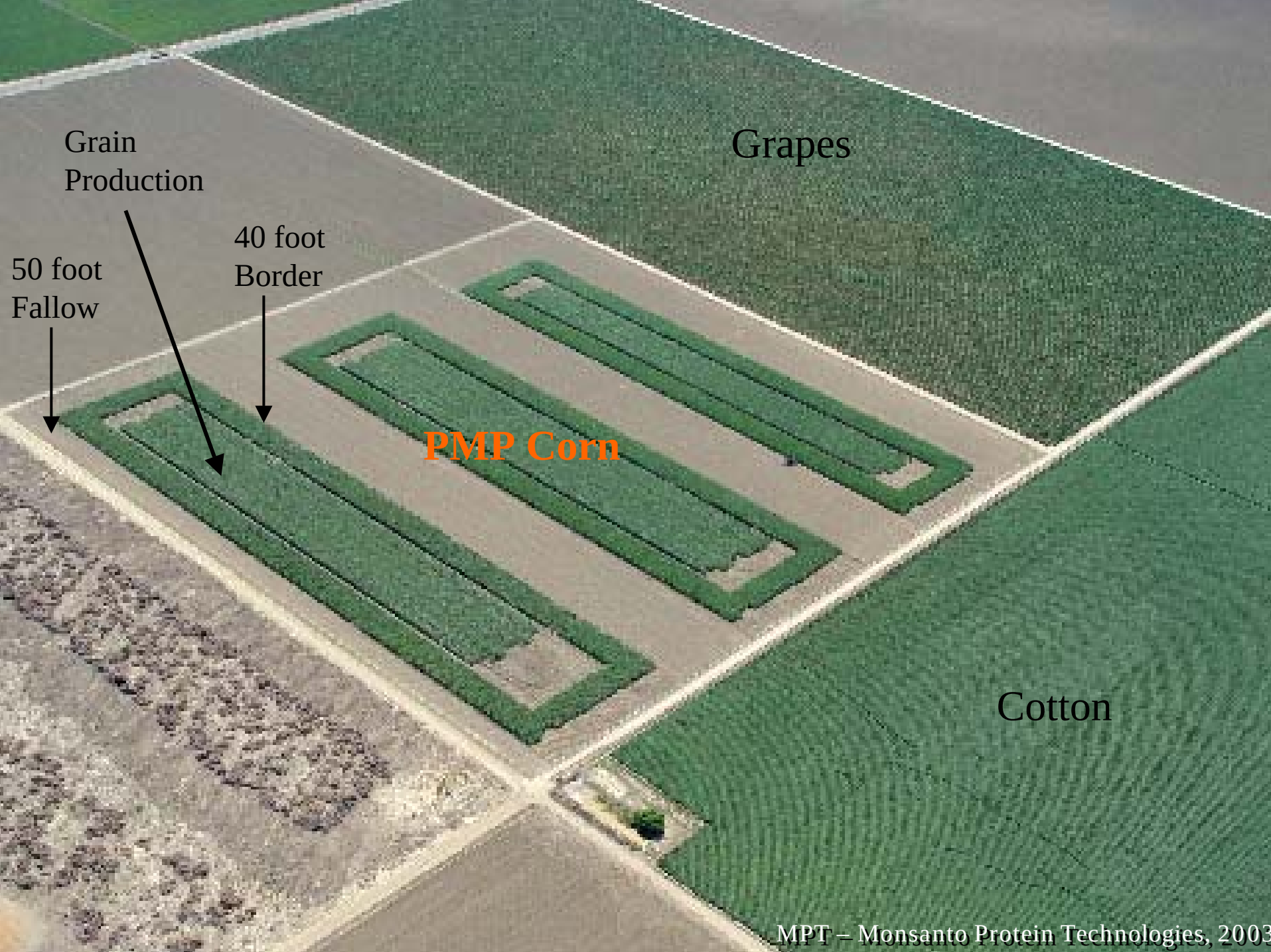

Grain
Production
40 foot
Border
50 foot
Fallow
Grapes
PMP Corn
Cotton

Field Operations

Containment Strategies

Containment Strategies

Seed Conditioning and Storage Facilities

Field Operations

Containment Strategies - 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.

Field Operations

Containment Strategies - Facilities

2. **PMP facilities are controlled access facilities, enclosed by fencing, and monitored by security guards.**

Field Operations

Containment Strategies - Facilities

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

Field Operations

Containment Strategies - Facilities

4. All PMP plant material shipments are controlled by a chain of custody system.

Field Operations

Containment Strategies - Facilities

5. All planting and harvesting equipment used in PMP production is cleaned and inspected prior to leaving the field according to USDA – approved procedures.

Field Operations

Containment Strategies - Facilities

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.

Containment Strategies

Containment Strategies

Volunteer Monitoring

Field Operations

Containment Strategies - Volunteer

1. **All PMP fields are monitored during the following season to ensure the absence of volunteers from previous PMP plants.**

Field Operations

Containment Strategies - Volunteer

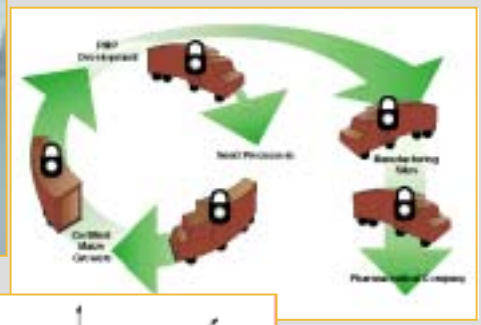
2. A minimum of 12 months of monitoring in rotational crops is required.

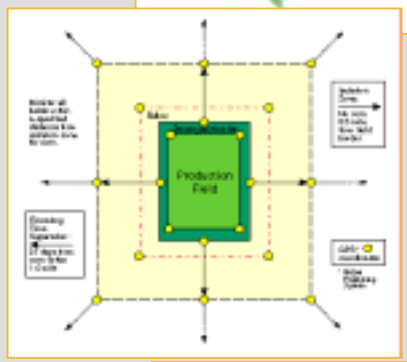
Field Operations

Containment Strategies - Volunteer

3. **Only rotational crops that are pre-approved by USDA are permitted during the season following PMP production.**

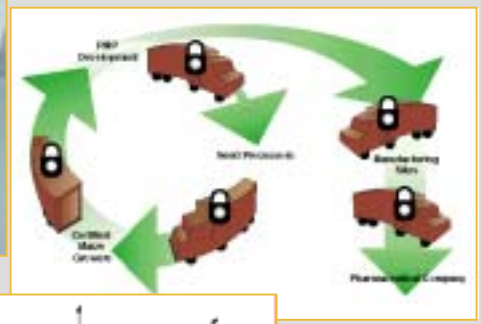
Field Operations

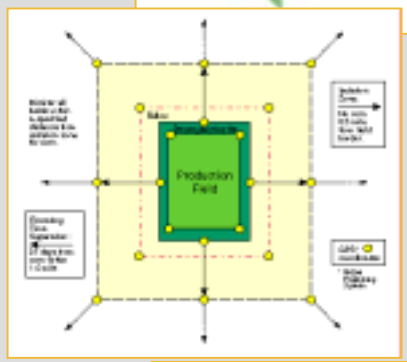




The goal of the containment strategy is to insure that no PMP plant material will enter the food chain.

Field Operations





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.

Conclusions

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- **Well characterized**
- **Stable**
- **Productive**
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