

Michael Phillips

Biotechnology Industry Organization



Michael J. Phillips is Vice President for Food and Agriculture, Science and Regulatory Policy of the Biotechnology Industry Organization (BIO). With over 1000 members, BIO is the largest trade organization to serve the life sciences industry. Representing biotechnology companies, academic institutions, state biotechnology centers and affiliated organizations in all 50 states and 34 nations, BIO members are involved in the research and development of health care, agricultural, industrial and environmental biotechnology products. Dr. Phillips joined BIO in 1999.

Prior to joining BIO, Dr. Phillips was the Executive Director of the Board on Agriculture and Natural Resources for the National Academy of Sciences. In this capacity, he was responsible for providing leadership to the Board and overseeing the conduct of studies including their external peer reviews and release to government agencies and the public.

Before working for the Academy, Dr. Phillips was the Director of the W.K. Kellogg Foundation program for Food, Agricultural and Natural Resource Issues for the 21st Century. He was also Director of the Food and Agriculture program of the Office of Technology Assessment (OTA) of the United States Congress where he developed and directed food and agricultural policy studies for congressional committees. Prior to his work at OTA, Dr. Phillips was on the faculty at Purdue University and was a senior staff member in the Secretary's office at the U.S. Department of Agriculture.

Dr. Phillips has M.S. and Ph.D. degrees in food and agricultural policy from The Ohio State University and Purdue University respectively, specializing in research and science policy. He has authored and supervised numerous reports and studies on food and agriculture with a special focus on agricultural biotechnology. Dr. Phillips received his B.S. degree with distinction in agricultural economics and animal sciences from The Ohio State University. He was raised on his family's grain and dairy farm in northwest Ohio and today provides the management for it as a grain operation.

Plant-Made Pharmaceutical Confinement Systems

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Risk Assessment Symposium
Biosafety Institute for Genetically Modified
Agricultural Products

Iowa State University
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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**

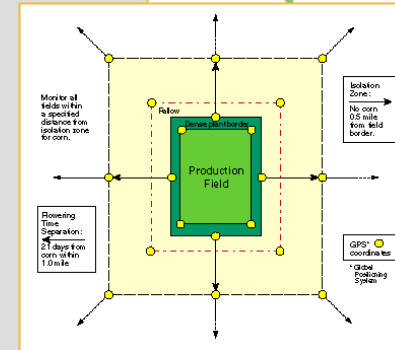
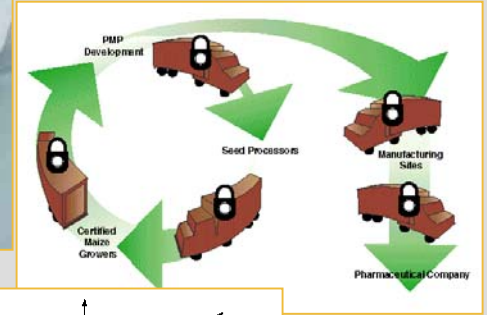


Pharmaceutical Product Requirements*

- **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



	USDA	USDA APHIS PERMIT	FDA	GLPs	cGMPs	SOPs
Gene construction	■		■	■		■
Maize transformation	■		■	■		■
Trait development	■	■	■	■		■
Seed breeding	■		■	■		■
Field production	■	■	■	■	■	■
Harvest	■	■	■	■	■	■
Grind	■	■	■	■	■	■



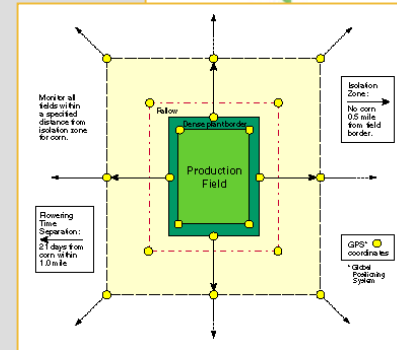
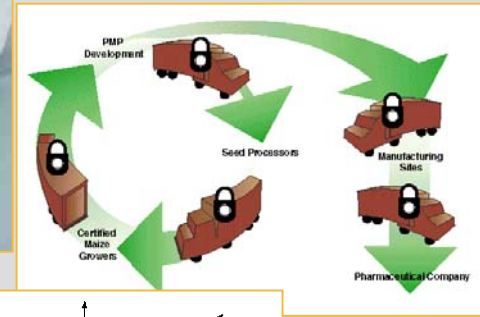
Field Operations

** 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



	USDA	USDA APHIS PERMIT	FDA	GLPs	cGMPs	SOPs
Gene construction	■		■	■		■
Maize transformation	■		■	■		■
Trait development	■	■	■	■		■
Seed breeding	■	■	■	■	■	■
Field production	■	■	■	■	■	■
Harvest	■	■	■	■	■	■
Grind	■	■	■	■	■	■



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 insure:

- **no PMP plant material enters the food chain**
- **medical products are safely and consistently produced**

Significant Regulatory Oversight with Multiple, Overlapping Responsibilities

	USDA	USDA APHIS Permit	FDA	GLPs	cGMPs	SOPs
Gene Construction	■		■	■		■
Maize Transformation	■		■	■		■
Trait Development	■	■	■	■		■
Seed Breeding	■	■	■	■	■	■
Field Production	■	■	■	■	■	■
Harvest	■	■	■	■	■	■
Grind			■		■	■
Extract			■		■	■

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*

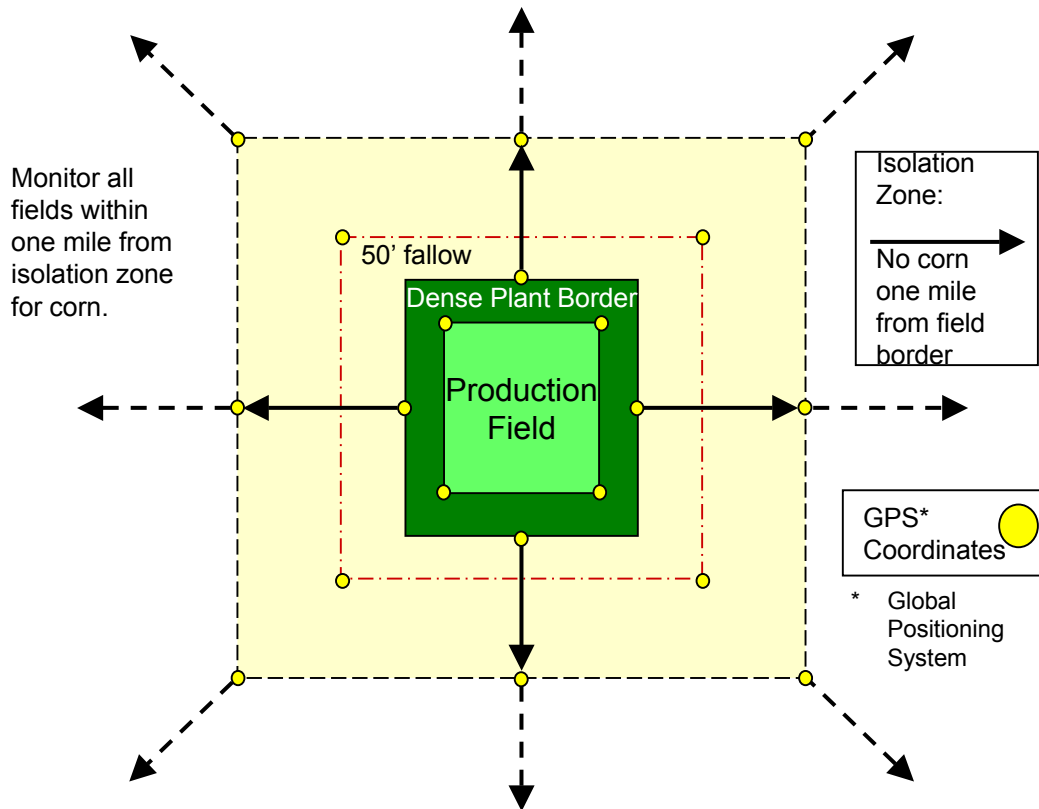


Diagram for illustration purposes only

*** Note, each plant has specific field requirements**

- Notify agency 7 days prior to planting and 21 days before harvest/crop destruct
- Detailed plot maps, acreage, monitoring data, etc., to be submitted
- 50 foot fallow ground surrounding the test site
- One mile physical isolation from all other maize (MPT implementation)
- Equipment cleaning in field, with pre-approved SOP
- Crop destruction of field post-harvest
- Field not followed with corn 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**

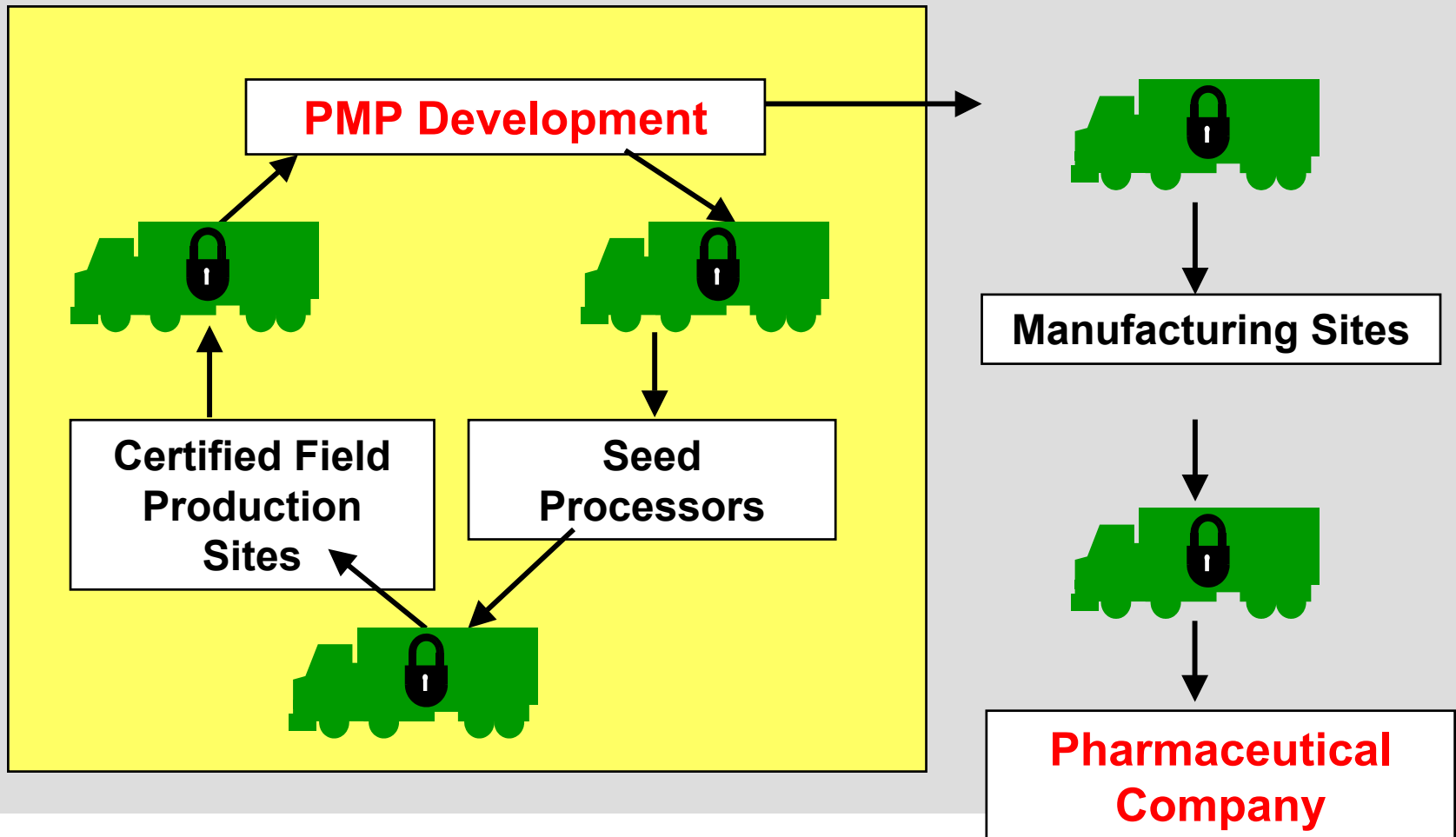
Field Operations

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

Closed-Loop Production

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

Field Operations

Containment Strategies

- 3. PMP corn and other host plants are produced using multiple containment strategies to insure that no PMP corn or other host plants enter into the food or feed channels**

Field Operations

Containment Strategies

Containment Strategies have been developed for :

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



Field Operations

Containment Strategies

Containment Strategies

Field Operations



Field Operations

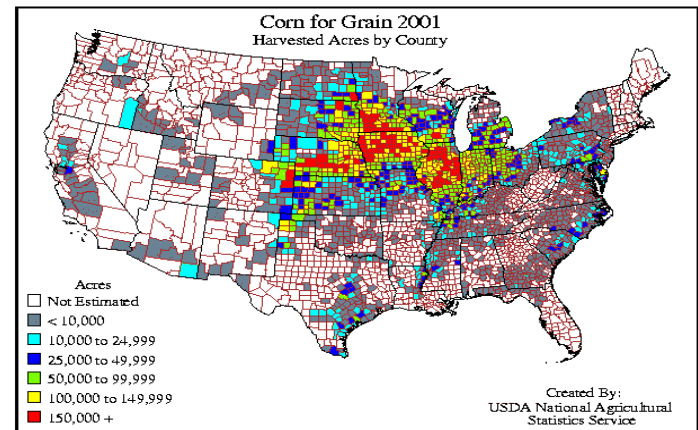
Containment Strategies - Field

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

Field Operations

Containment Strategies - Field

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



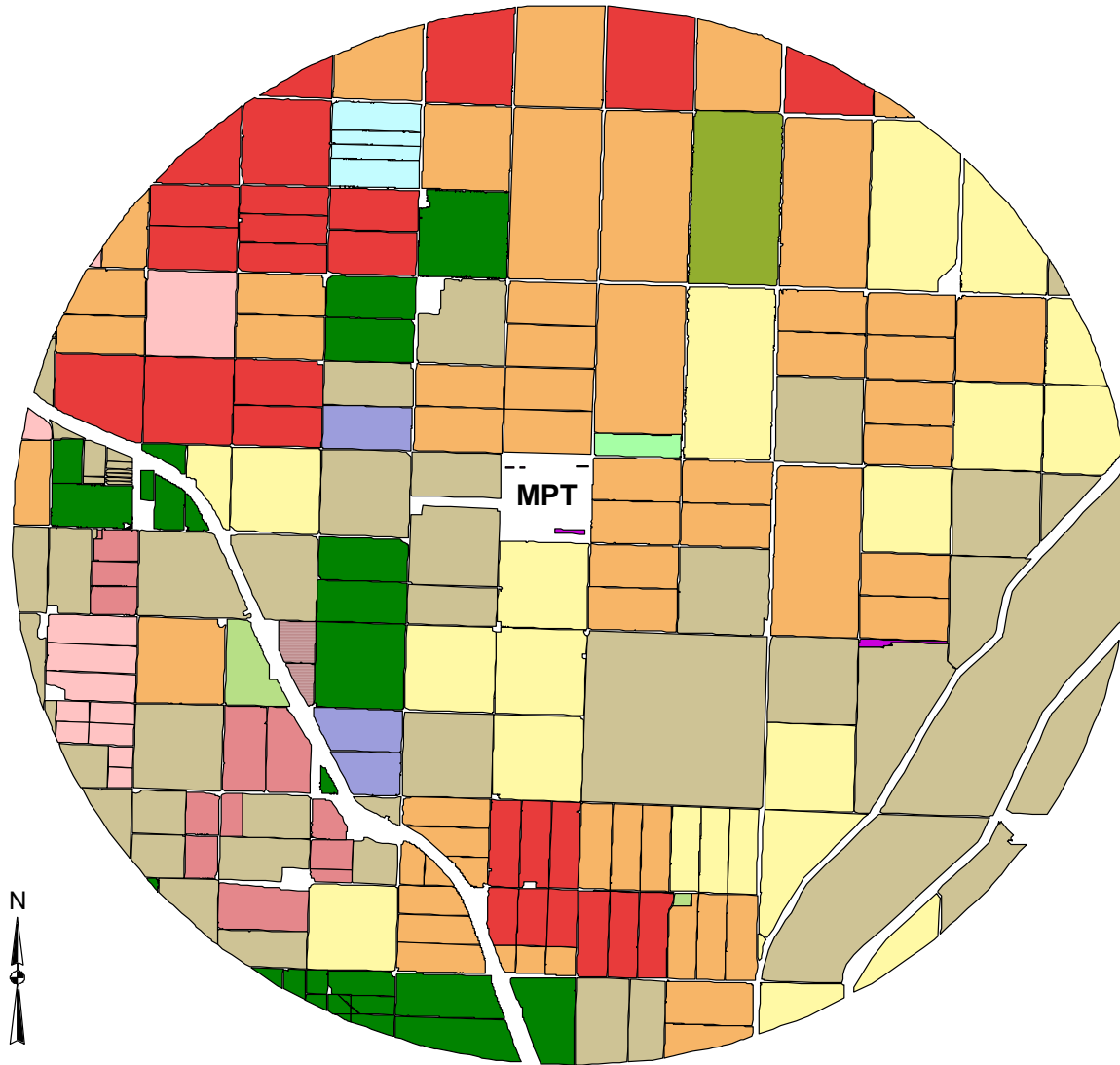
Field Operations

Containment Strategies - Field











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

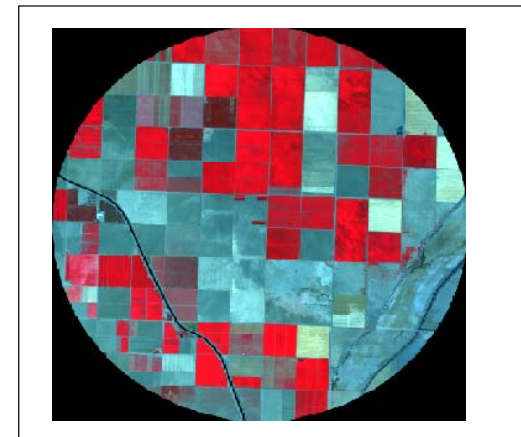
California Site

July 2002



Land Cover

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



0 1 2 3 Miles

Containment Strategies - Field

3. Large scale protein production plantings of corn can be conducted with male sterile (CMS) 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

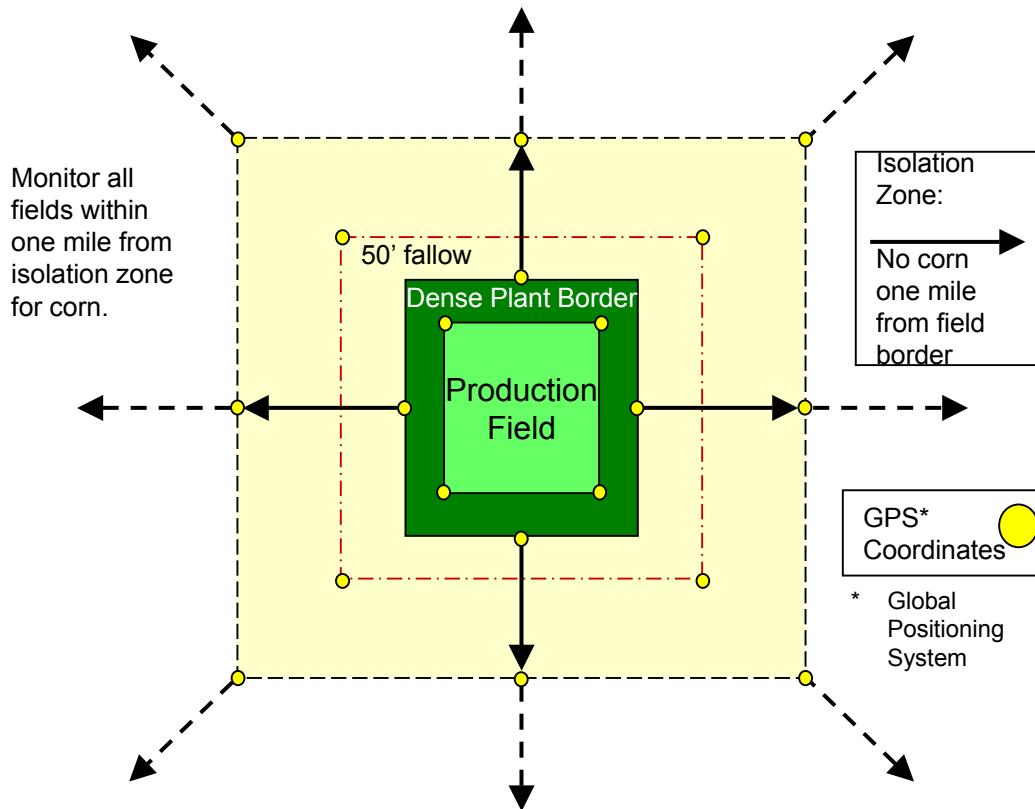
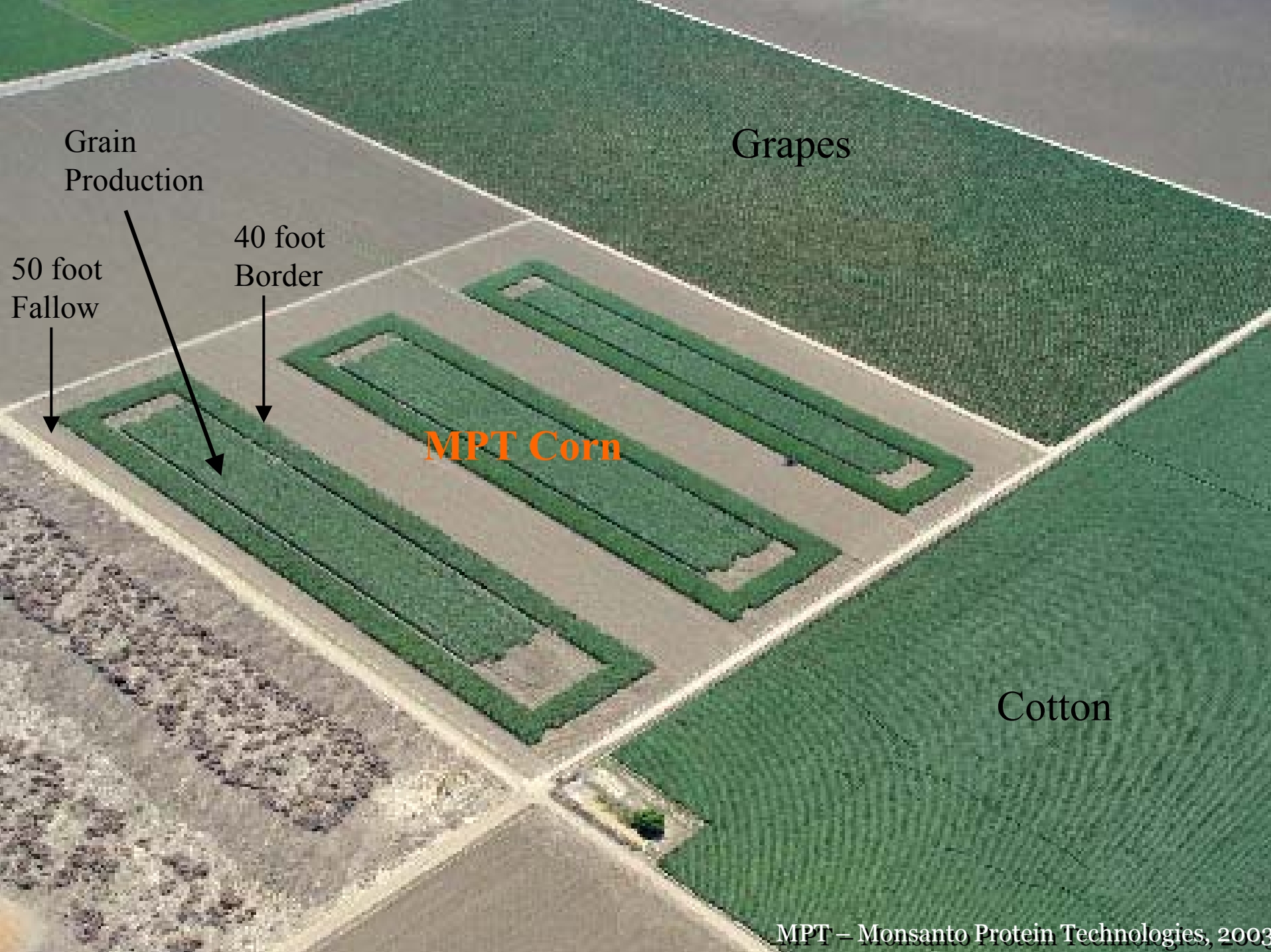


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- Notify agency 7 days prior to planting and 21 days before harvest/crop destruct
- Detailed plot maps, acreage, isolation monitoring data, etc., to be submitted
- 50 foot fallow ground surrounding the test site
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- Volunteer monitoring for one years after crop destruction
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APHIS confinement standards for a PMP field release



Grain
Production

Grapes

50 foot
Fallow

40 foot
Border

MPT Corn

Cotton

Field Operations

Containment Strategies

Containment Strategies

**Seed conditioning
and storage facilities**



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.**

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**



6-13-2003

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**

Field Operations

Containment Strategies

Containment Strategies

Volunteer Monitoring



Field Operations

Containment Strategies - Volunteer

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

Field Operations

Containment Strategies - Volunteer

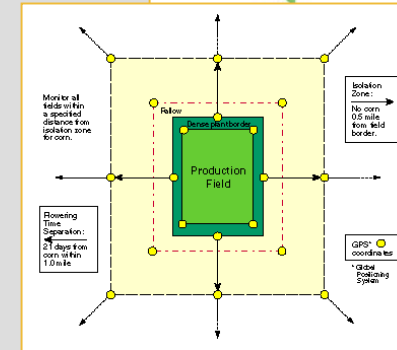
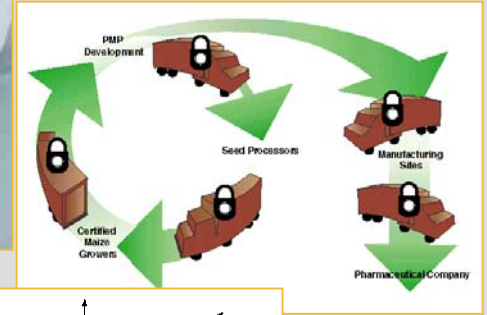
- 2. A minimum of 12 months of monitoring in rotational crops is required**

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

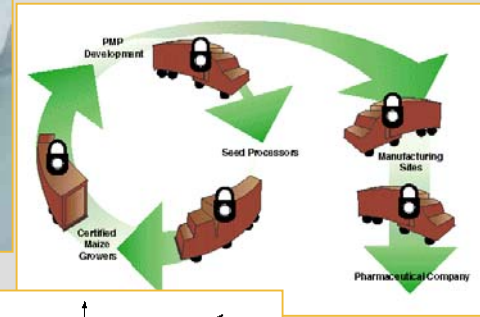


The goal of the containment strategy is to insure that no PMP plant material will enter the food chain

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Maize transformation	■		■	■		■
Trait development	■	■	■	■		■
Seed breeding	■		■	■		■
Field production	■	■	■	■	■	■
Harvest	■	■	■	■	■	■
Grind	■	■	■	■	■	■



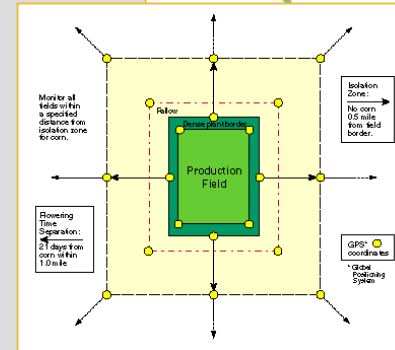
Field Operations



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



	USDA	USDA APHIS PERMIT	FDA	GLPs	cGMPs	SOPs
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Maize transformation	■		■	■		■
Trait development	■	■	■	■		■
Seed breeding	■		■	■		■
Field production	■	■	■	■	■	■
Harvest	■	■	■	■	■	■
Grind	■	■	■	■	■	■



Conclusions

Plant-made pharmaceutical production:

Is like any other pharmaceutical production system:

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