

**Tools, Procedures and Policy
for
Plant-Made Pharmaceuticals**

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BIO Overview

- Over 1,100 members in all 50 U.S. states and in 33 countries
- Members include biotechnology companies, academic institutions, state biotechnology centers and related organizations
- Founded in 1993
- BIO's Food & Agriculture Section represents more than 12 companies working on plant-made pharmaceuticals and 5 companies working on animal-made pharmaceuticals

Field Operations

Regulatory

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

Field Operations

Regulatory

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**

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*

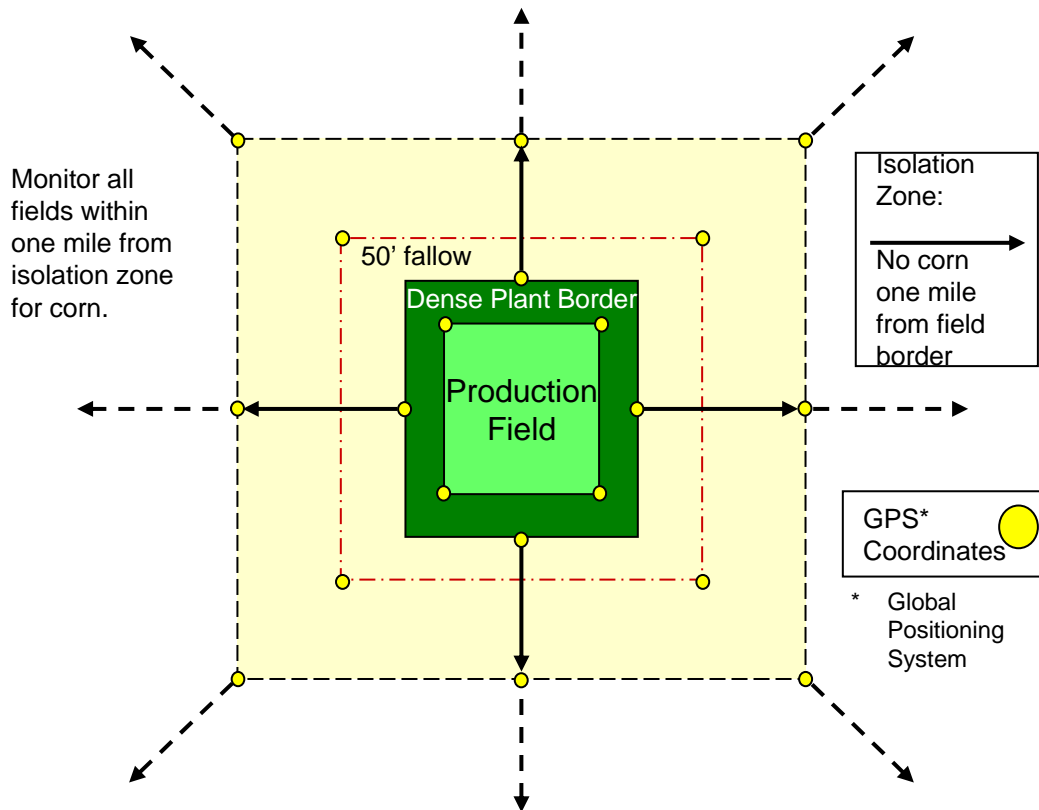


Diagram for illustration purposes only

*** 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

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**

Biotechnology PMP Committee

BIO PMP Industry Companies

- Monsanto
- Chlorogen
- Planet Biotech
- SemBioSys
- Syngenta
- Medicago
- Ventria BioScience
- Dow/Dow Agro Sciences
- Epicyte
- Meristem Therapeutics
- ProdiGene
- Biolex
- Dupont
- Bayer CropScience

Accomplishments to date:

- Industry reference document for confinement and development of PMP in the US (May, 02)
- Outreach to stakeholders (medical health, agri /food/feed/fiber chain, academics)
- Education: fact sheets, Q&As
- Pew Public Forum (July, 02)
- Industry reference document on contingency plans, e.g., sentinel testing, validated detection assays
- CACCP* approaches for PMPs

* **Confinement Analysis Critical Control Point**

Confinement Analysis and Critical Control Points (CACCP)

- An approach to confinement of PMP material modeled on the Hazard Analysis and Critical Control Points (HACCP) approach used in the food and pharmaceutical industries
- Some common elements with other risk assessment/management methodologies such as Zurich hazard analysis

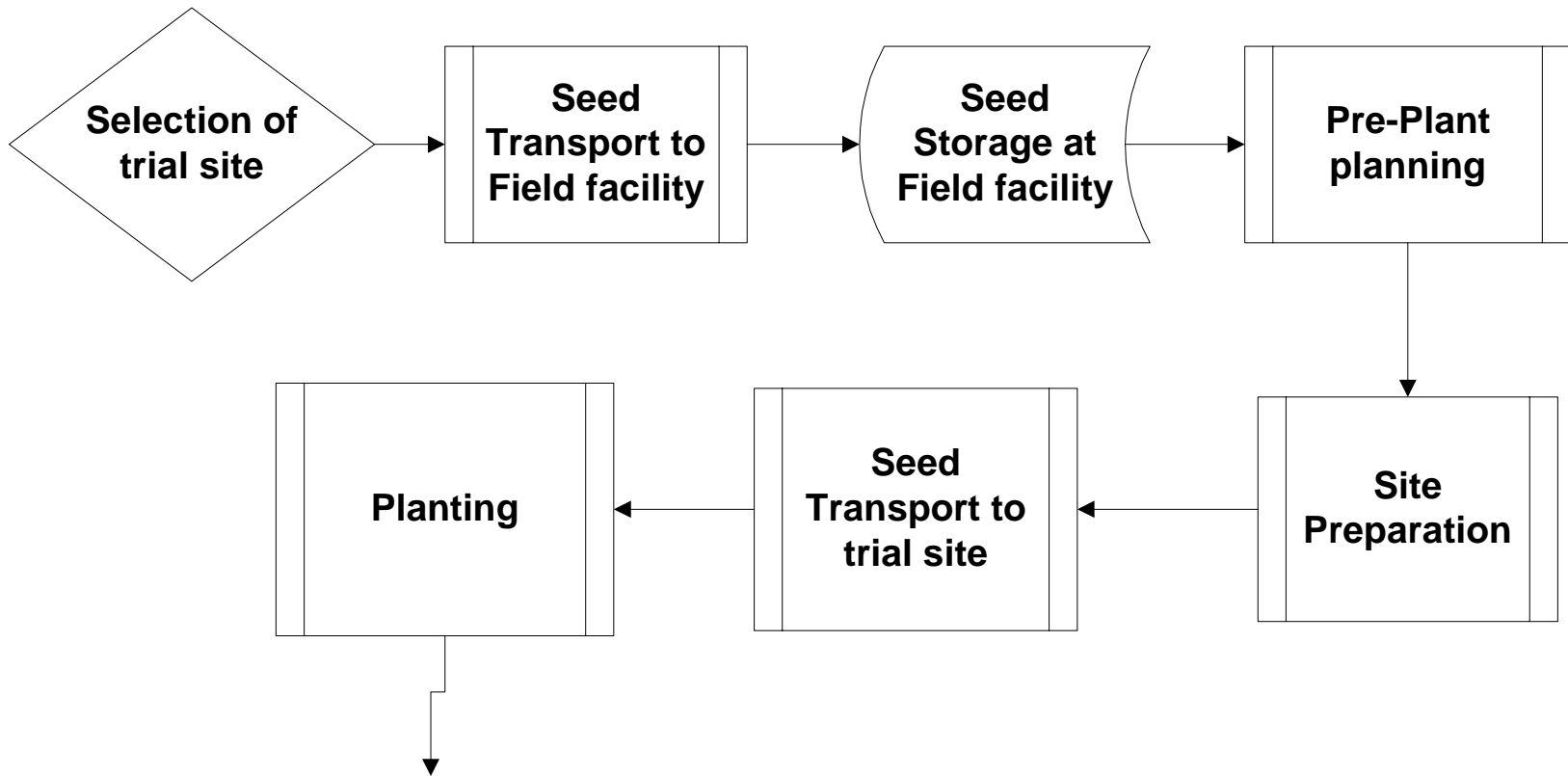
7 Principles

- Conduct loss of confinement analysis
- Determine critical control points
- Establish critical limits
- Establish monitoring procedures
- Establish corrective actions
- Establish verification procedures
- Establish record keeping and documentation

Overview of CACCP Process

- Assemble CACCP team
 - Multidisciplinary group with specific knowledge and expertise relevant to product/process
- Describe product, distribution, intended use
- Develop Process Flow Map and verify
- The CACCP team analyses each of step of the process flow map from the perspective of the 7 principles

Process Map



Confinement Analysis

- Identify loss of confinement scenarios/control measures for each step of process map
- Scenario evaluation-severity /likelihood
- Identification of process modifications/improvements
- Provides basis for identification of critical control points

Determine Critical Control Points

- A step at which control can be applied and is essential to prevent or reduce loss of confinement
- Example: flowering step and possible loss of containment via cross-pollination

Critical Process Parameters

- Critical process parameter is a process parameter that must be maintained within proscribed limits (critical limits) to achieve the desired quality outcome
- There may be more than one CPP for a process step
- Examples:
 - Isolation distance
 - bee netting

Critical Limits

- Critical limits are upper and/or lower boundaries within which the CPP must be maintained
- Example: 200m minimum isolation distance

Monitoring Procedures

- Critical control points must be monitored to ensure that process parameters are within the appropriate range.

Corrective Action

- Predetermined response to deviation of Critical Process Parameter outside the acceptable range or lack of adequate control at a Critical Control Point

Verification

- Initial validation of plan to determine that it is scientifically and technically sound
- Periodic auditing to ensure plan is being followed
- Review of plan, CCP monitoring records and corrective action records

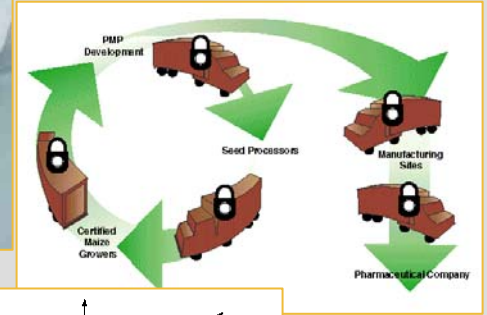
Record Keeping and Documentation

- Documentation should include:
 - Summary of the CACCP analysis
 - The CACCP plan
 - All records generated during operation
 - Eg. Monitoring record, corrective actions, etc.

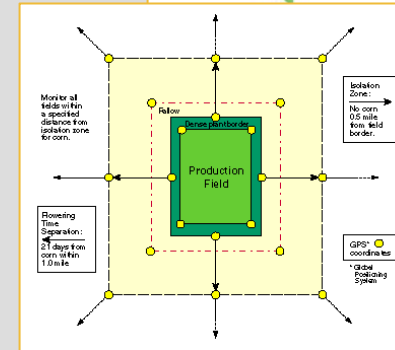
Factors for Success

- Commitment from management to the CACCP process
- Pre-requisite programs/ practices, examples
 - cGMP or other QA systems
 - Facilities standards
 - Supplier control
 - Cleaning and sanitation practices
- Education and training

Field Operations



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



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



Conclusions

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

Useful References

- “Hazard Analysis and Critical Control Points Principles and Application Guidelines”, National Advisory Committee on Microbiological Criteria for Foods, Food and Drug Administration, U.S. Government
- “HACCP: A Process Validation Tool for Ensuring Quality of Biotech and Pharmaceutical products”
Vega-Mercado et al, BioProcess International May 2003 pages 50-57
- WWW.BIO.ORG