"Research and Development of Non-Food Biotechnology Applications and the Associated Regulatory Aspects"

RDEAB-APEC Workshop
Santiago, Chile

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Products in the pipeline in Safflower Seeds

- Human insulin
- Apo AI -- a cardiovascular therapy which reduces and stabilizes plaque associated with acute coronary syndrome (heart attacks and angina) and stroke.
- Docosahexaenoic acid (DHA), an omega-3 fatty acid. DHA has proven cardiovascular and neurological health benefits
- Omega-6 fatty acid gamma linolenic acid (GLA) used as an ingredient in the topical, food and nutrition markets

Products in The Pipeline

- Lactoferrin is a glycoprotein and is a multifunctional protein. It has following properties:
  - Anti-bacterial, anti-viral, anti-fungal, antioxidant, and immunomodulatory
- Lysozyme: Lysozyme is a protein found in human breast milk as well as in most epithelial surface secretions. It has also the similar properties as lactoferrin - Anti-bacterial, anti-viral, anti-fungal, antioxidant, and works with lysozyme to potentiate the activity of both the proteins

Products in The Pipeline in Chloroplasts

- Chlorogen, a biotech company, has invented and patented genetic sequences or regulatory signals, which tell foreign genes to function within the chloroplasts and only the chloroplasts.
- Two important advantages:
  - chloroplasts are inherited maternally – no transfer of genes via pollen to conventional crops or other sexually compatible plants
  - Enhanced protein production because of 10,000 copies of the introduced gene in a plant as opposed to only one or two via nuclear expression

Challenges

- Protecting food and feed supply from adulterating compounds originating from GE plants which are not yet approved or intended to be used as food.
- Performing scientifically sound assessments of a new generation of products which may have novel traits. Assessments must be scientifically credible and legally defensible.
- Increasing emphasis on environmental effects in assessments.

Challenges — Contd.

- Ensuring that regulations for plants are adequate for the new generation of products.
- Ensuring regulations build confidence in public as well as in states/provinces.
- Supplying sufficient appropriate information to the public and other interested stakeholders.
- Listening to stakeholders concerns, addressing as appropriate.

Release of Plants Genetically Engineered to Produce Pharmaceutical and Industrial Compounds

Plants engineered to produce Pharmaceutical and industrial compounds those plants that meet the following three criteria:

1) The plants are engineered to produce compounds that are new to the plant;

2) The new compound has not been commonly used in food or feed; and

3) The new compound is being expressed not for food and feed purposes but for pharmaceutical and industrial uses.

Pharmaceutical Plants

REGULATED BY:

- Two programs within USDA-APHIS
  BRS and - Center for Veterinary Biologics (CVB)
- OR
- Two programs: USDA-APHIS-BRS and Food Drug Administration (FDA)

Regulating Genetic Engineered Organisms (GEOs)

- GEOs have been regulated on a case-by-case basis since 1987.
- Assessments are science-based and commensurate with the level of potential risks.
- Regulations are flexible so that changes were made as we gained experience with genetically engineered organisms.
- Rules have been either streamlined or strengthened based on potential risks of new products
- Pharmaceutical-producing plants biosafety rules have been enhanced or strengthened.

Comparison of isolation distances in traditional GEOs and Pharmaceutical producing plants

Plants	Traditional	PMPs
Corn	660 ft	0.5 to 1.0 mile
Rice	10 ft	200 ft
Safflower	1320	2.0 mile

- Many other conditions are/can be levied based on the perceived risks of genetic modifications.

Release of plants producing Pharmaceuticals and Industrials Requires an USDA Permit

Information required for the permit is described on our Website:
www.aphis.usda.gov/brs

Non-regulated Status

- - Not expected for most of such plants
- - No Food or Feed Use - without devitalization

Guidance to Industry:
Confinement Measures for Commercial Production of PMPs

- Should have procedures or genetic mechanisms to prevent PMP plants/seeds/products from entering the food/feed supply
- Tests should be developed to detect target gene and product
- Identity Preservation (IP) system should be in place to track seeds from shipping to planting, and from harvest to extraction
- Harvesting procedures, including equipment identification and cleaning
- Appropriate disposal of wastes
- Federal government auditing of the system

Current Supplemental Permit Conditions and Agency Actions for PMPs/PMIs

- Confinement measures and their implementation
  - Equipment use and cleaning
  - Storage facilities
  - Standard Operating Procedures (SOPs)
  - Fallow zones, land use restrictions, reproductive isolation,
  - Training programs
- APHIS will consider variances, case-by-case
- APHIS has increased inspections and has begun auditing to ensure compliance

Information needed for an APHIS Permit for Field Release of PMP/PMIs

- Final and intermediate destinations
- Environment and conditions of the release
- Measures for physical and reproductive isolation from planting to harvest
- Site security, monitoring, and inspection
- Plans for termination, devitalization, disposal, and post-harvest monitoring and land use

Planters and Harvesters

- Dedicated to use in the permitted test site(s) for the duration of the test
- Notify APHIS-USDA if moved between test site(s)
- APHIS-approved cleaning procedures
- APHIS inspection before use other than permit use

All Other Field Equipment

- Cleaned according to APHIS approved protocols

Storage Facilities

- Dedicated facilities for the storage of equipment and regulated articles
  - locked or secure buildings, bins, or areas, posted as restricted to authorized personnel
- Cleaning per APHIS-approved protocols, and inspection prior to general use

Seed Cleaning and Drying

APHIS-approved protocols to minimize seed loss/spillage

Regulatory Compliance Mechanisms: Reporting Requirements

- **Planting and harvesting notice**
- **Notice of equipment movement/cleaning**
- **4-week post-planting report**
- **Field test reports are due 6 months after field test**
- **Termination and interim reports may be required**
- **Post-season report on destruction of volunteers**

Fallow Zones and Land Use Restrictions

- Increased perimeter fallow zone to 50 ft. - allows movement of equipment without entering or commingling with adjacent food/feed crops
- Restricted production of food/feed crops for the following growing/volunteer monitoring season in cases where volunteer plants could be harvested with the following crop
- Does NOT exclude cover crops

Pharm Plant Confinement

Crops: Corn, Tobacco, Rice, & Safflower

Corn Confinement Options

50 ft fallow zone with no food or feed crop

If Open Pollinated PMP Corn

1 mile (= 1.6 km) No Corn

If Controlled Pollination of PMP Corn

½ mile (= 0.8 km) No Corn

½ - 1 mile 28 Day Temporal Isolation

Transgenic Tobacco Containing 4 Genes for Antibody against Tooth Decay Bacteria

Pharmaceutical Field Trial Requirements

Permit Conditions

No Flowering

Raised No New Issues

No New Env. Assessment for Small Field Trial

Transgenic TMV with Aprotinin gene inoculated onto Tobacco

Pharmaceutical Field Trial Requirements

Permit Conditions

Raised No New Issues

No New Environmental Assessment for Small Scale Field Trial

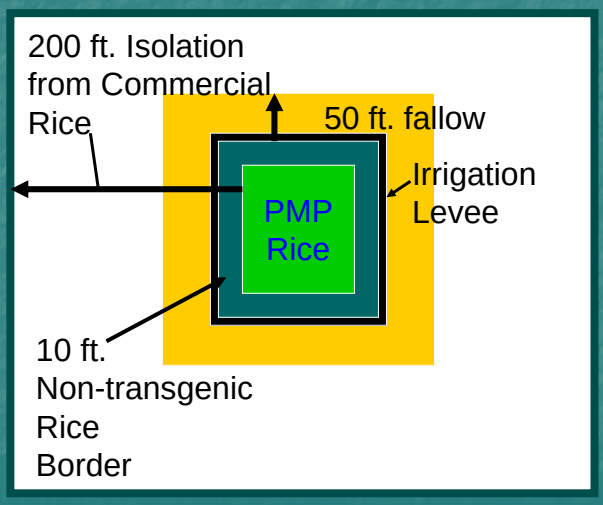
Aprotinin

- Found in many bovine tissues (lung and pancreas)
- Lack of DNA sequence similarity to allergens and toxins
- Not toxic to honey bees at levels found in transgenic plants
- Not absorbed into the bloodstream when taken orally by mammals and birds
- Approved for use by the Food and Drug Administration since 1991
- No impact to TES if seeds are not left for foraging

Rice
Confinement Considerations

- **Highly Self–pollinated**
  - **Only ~ 3.9% natural cross-pollination by wind, most within 2 meters (Virmani, 1994)**
  - **AOSCA, CCIA, foundation seed isolation is 10 ft.**
  - **International Rice Research Institute (IRRI) uses 10 meter isolation – has seen no gene flow at 10 & 20 meters (Clegg et al., 1993)**
  - **Gene flow study in California - no gene flow at even shorter distances**
- **Pollen loses viability in 5 minutes**
- **Transplanted or drill-seeded into flooded fields**
- **No seed dormancy**
- **Rice is not weedy, no weedy relatives at site**

Rice
Confinement Measures



Safflower
Confinement Measures

- **50 ft. fallow border around the test**
- **2 mile isolation from other safflower**
  - **Mostly self-pollinating- 4 wk. bloom stage**
  - **<10% out-crossing – pollinator mediated**
  - **No known sexually related species in the USA**
- **2 year monitoring for volunteers within test area and fallow zone**
  - **safflower not recognized as having seed dormancy, but related species do**
- **No harvest of food/feed crops from monitoring area without USDA permission.**

Pharmaceutical Plants

- First pharmaceutical permit issued in 1991
- Steady increase in number of permits since 1991
- Plants used for this purpose are: Tobacco, Rice, Corn, Safflower, Sugarcane
- Area:
  - 2002 – 134 Acres (34 sites)
  - 2003 – 25 Acres
  - 2004 – 45 Acres
  - 2005 – 79 Acres

In Conclusion

- USDA has made and continues to make changes in its regulations as new developments in agricultural biotechnology take place.
- In the last three years, new regulations have been proposed and implemented for pharmaceuticals and industrials producing plants.
- The environmental and food safety issues are considered seriously for maintaining public confidence in the US regulatory system.

USDA-APHIS

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