(Petition for) Determination of Non-Regulated Status

USDA-APHIS Case Study: SpuntaG2 Bt Potato

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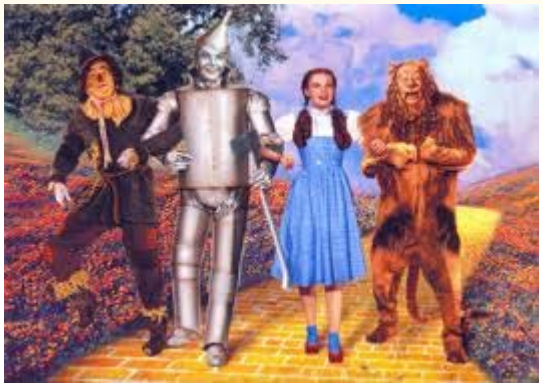
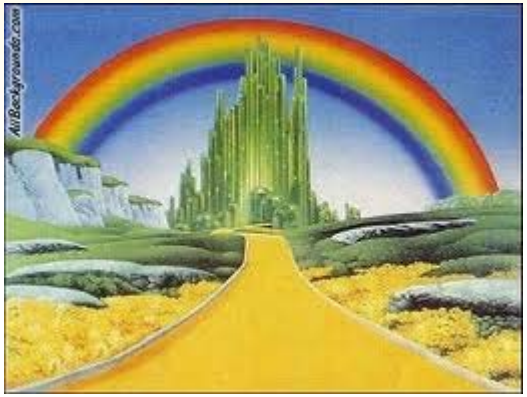
Follow the Yellow Brick Road!





SpuntaG2 Potato

- **SpuntaG2 potato was developed for South Africa.**
  - **Contains *Cry1Ia1* Bt gene for insect resistance.**
  - **Contains *nptII* as a selectable marker.**
- **There are currently no plans to submit a petition to USDA-APHIS for a determination of non-regulated status.**
- **Confined (regulated) field trials were conducted in the US from 1994-2006 (agronomic) and from 2004-2006 (efficacy).**

APHIS Regulatory Authority

- **APHIS regulatory authority is based on plant pest risk.**
  - **Whether regulated articles pose plant pest risks to plants or plant products.**

- **SpuntaG2 potato is a regulated article because:**
  - **The genes were delivered by *Agrobacterium tumefaciens*, a plant pest.**
  - **Some of the gene donors are also plant pests: Cauliflower mosaic virus and *A. tumefaciens*.**

International Differences in Regulatory Structure

- **US Coordinated Framework:**
  - **USDA – Environmental Safety**
  - **FDA – Food and Feed Safety**
  - **EPA – Safety of Plant-Incorporated Protectants (PIPs).**
- **Result:**
  - **From 1 to 3 distinct regulatory dossiers in the US system, depending on product type.**
  - **Three distinct and separate regulatory reviews.**
- **Most developing countries:**
  - **A single regulatory body conducts both the environmental and food safety reviews.**
  - **Applicant submits a single regulatory dossier.**

Interface with APHIS

- **Since the product is not intended for the US market, there were no pre-submission meetings with APHIS.**
  - **Several regulated field trials were conducted in the US as part of the overall product development plan.**
  - **US regulatory approvals are often beneficial when seeking regulatory approvals in other countries**

- **Public sector and small company developers are encouraged to interface with APHIS as early as possible in the process.**
  - **Important to understand what kinds of data need to be generated for the petition.**

Petition Review
Two Step Review Process

Plant Pest Risk (PPR): A Regulatory Requirement

- **7 CFR 340.6, Petition for determination of non-regulated status**

- **Transgenic Potato:**
  - **Do the introduced genes or their products present a plant pest risk?**
  - **Will the product become a weed?**
  - **Will the genes confer weedy or invasive properties to wild relatives?**
  - **Will the introduced traits impact non-target organisms?**
  - **Will the product damage agricultural commodities?**

Environmental Assessment (EA): A Federal Obligation

- **NEPA 7 CFR 372, and ESA 16 U.S.C. §1531 et seq.**

- **Transgenic Potato:**
  - **Will there be any impact on a broad range of environmental factors including soil, air, water, biological resources, and human health?**
  - **Will the product result in changes to agricultural practices?**
  - **Will there be any socio-economic impacts?**
  - **Will the product have any impact on listed endangered or threatened species?**

Types of Petition Data I

- **Plant Pest Properties**
  - **Data on reaction to insect and disease pests from field trials.**
    - **Consider entering GE lines in public / regional disease nurseries.**
    - **Consider conducting some field trials without pesticides to allow insect and disease pressure to develop; or consider including unsprayed controls.**
    - **These are both suggestions, not data requirements.**
- **Weediness / Invasiveness**
  - **Crop Biology Data**
    - **Life cycle, growth habit, vigor, ability to overwinter, etc.**
    - **Reproductive biology: timing and duration of flowering, pollen fertility, self compatibility, etc.**
  - **Persistence Data**
    - **seed dispersal, dormancy, and germination; dispersal and persistence of vegetative propagules.**

Types of Petition Data II

- **Wild Relatives (often a literature review)**
  - **Distribution, life cycle and reproductive biology.**
  - **Does the crop form natural hybrids with the wild relatives?**
  - **Are they weeds or endangered species?**
- **Non-Target Organisms**
  - **Species abundance data from field trials.**
    - **Beneficial organisms: pollinators. Predators, parasites, etc.**
  - **Compositional data**
    - **APHIS primary focus is on levels of anti-nutrients and toxins**

Product Development Considerations

- **Comparators**
  - **Appropriate comparators are required for each study.**
    - **These are typically isogenic lines in self-pollinated species.**
      - **Null segregants are often the source of the most appropriate comparator.**
    - **For hybrid crops, some studies are conducted with the GE inbred and some with the GE hybrid; different comparators are used in each case.**
  - **OECD Consensus Documents**
    - **When available, an essential resource of compositional considerations.**
    - **Advise that the regulated article and comparator are treated identically.**
- **Reference Varieties**
  - **When differences are detected between the regulated article and the comparator, the reference varieties often becomes the basis for concluding that the data for the regulated article is within normal ranges for this specific crop.**

Very Nice to Do!

- **Two commendable actions by the developers of SpuntaG2 potato:**
  - **Publication of their regulatory data in the peer reviewed Journal of the American Society of Horticultural Science (Volume 35, Issue 4).**
    - **Insertion and characterization.**
    - **Protein safety evaluations for the Cry1Ia1 protein.**
    - **Field and storage evaluations.**
  - **Developed a product development roadmap to commercialization.**
    - **A roadmap is an excellent planning tool to ensure that all of the required data is generated in the desired time frames.**
    - **<u>Roadmaps are not required</u>, the next 2 slides are only meant to be food for thought.**

Product Development Roadmaps – I

- **Product Development Activities**
  - **Transformation; Screening for high quality events.**
  - **Introgression of lead events into elite germplasm.**
  - **Bulking up planting material may take several years.**
- **Regulatory Activities**
  - **Environmental Characterization Studies**
    - **Field studies – agronomy, fertility, pest reaction, etc.**
    - **Impacts on Non-Target Organisms.**
  - **Food Safety Studies**
    - **Production of purified protein product.**
  - **Regulatory submissions in other countries**
    - **Will the product be exported as a commodity or in processed products?**

Product Development Roadmaps – II

- **Licensing**
  - **Do you have "freedom to operate?"**
  - **Research licenses rarely allow for commercialization or sub-licensing.**
- **Communication and Outreach**
  - **Public acceptance is part of the project!**
  - **Stewardship considerations:**
    - **grower agreements**
    - **detection methods**
    - **identity preservation systems**

Nice to Submit

- **Since the SpuntaG2 data package was developed for regulatory approval in South Africa, there are some differences relative to what is required by APHIS.**
  - **Published paper #1 says that sequencing the insert is required.**
    - **Often the integrity of the insert is demonstrated by hybridizations to a series of overlapping probes.**
  - **Published paper #2 includes data from an animal feeding study.**
    - **Feeding studies are not required for APHIS review.**
    - **Compositional analysis is adequate for environmental safety review.**
  - **Published paper #3 includes data from field trials covering 2 site years over 5 cropping seasons.**
    - **Most petitions include data from 2 cropping seasons.**
    - **Socio-economic impacts are not a component of the PPRA.**

Need to Submit

- **Information on donor organisms:**
  - **Are any of the gene donors plants pests?**
    - **This question may not be asked in other countries.**
- **Information on sexually-compatible wild relatives:**
  - **While not present in South Africa, there are diploid tuber-bearing *Solanum* species in North America.**
  - **APHIS needs to consider these wild relatives:**
    - **Do they grow in proximity to potato production?**
    - **Do they flower at the same time as cultivated potatoes?**
    - **Will hybridization result in viable seeds?**
    - **If the introduced genes introgressed from the crop to the wild species, would they enhance the fitness of the wild species?**
      - **Would the wild species become more weedy or invasive?**

A Few Closing Thoughts

- **Start with a comprehensive project plan.**
  - **Develop a Road Map!**
  - **Revisit the road map on a regular basis – things change!**
- **Consult with regulators early and often.**
  - **We are here to facilitate the process!**
- **Network with colleagues who have gone through the process.**
  - **Expertise is widely available!**
- **If possible, build your product with components that have already been evaluated for environment risk.**
  - **Example: *nptII* has been through numerous risk assessments.**
- **Can you confer your trait without expressing protein?**
  - **Lack of protein in RNAi traits alleviates several concerns.**
- **If gene flow is a concern, consider sterile products.**