Arcadia
BIOSCIENCES

Regulatory Challenges for Small Companies
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Key points - summary

- Basic safety data requirements from country-to-country are similar, but significantly greater data requirements are common – 2 examples:
  - European Union (EU)
  - China
- Commercial launch of a biotech crop is complicated and expensive
  - Renewal requirements increase complications
- Two approaches and examples:
  - Identity preserved product
    - Arctic Apple – Okanagan Specialty Fruits Inc., British Columbia, Canada
  - Commodity product
    - Dicamba Soybean, Monsanto Company, St. Louis, Missouri, USA
- Strong stewardship programs are absolutely essential
  - Global approvals – which countries?
  - Control of products made from the biotech crop
- Identity preserved crops – strategic choice for small companies
  - Also, partner with larger companies

Safety assessment of a biotech crop

Does the biotech crop have the equivalent chemical composition of the original crop, other than the intended effect of the genetic change?

- Approach used with the first biotech crop (FLAVR SAVR tomato in 1994) and each subsequent one
  - Substantial equivalency to parental crop, except for the intended effect of the genetic change
- Crop and gene source history and safety
- Identity and intended function of genetic modification
- Molecular analysis
- Compositional analysis
- Safety analysis on the specific, intended change

Safety assessment of a biotech crop

Are there any unintended consequences directly or indirectly resulting from the novel and intended change made in the biotech crop?

- Again, this is the approach used with the first biotech crop and each subsequent one
- Novel protein analysis and history of safety
  - Bioinformatics analysis
  - Allergenicity potential
  - Thermal and digestion degradation
- Nutritional assessment
- Cultivation and environmental impacts

Answers to these first and second sets of questions have generally been sufficient for USA and Canada approvals and for some other countries

Safety assessment of a biotech crop

- A number of countries require a focus on the precautionary principle:
  - One cannot predict all consequences that might happen with a biotech crop in regards to environmental release and use in food or feed
- The precautionary principle has resulted in:
  - A continuous increase in new testing guidance, often based on new scientific methodology
  - A significant increase in the regulatory costs and time requirements
  - Narrowing use of biotechnology to only a few, major commodity crops
  - Reduction in the number of new traits commercialized
  - Elimination of most small company, university, and government commercial efforts
  - Contributing to consolidation of the major agbiotech companies
- Two examples of the use of the precautionary principle
  - The European Union
  - China

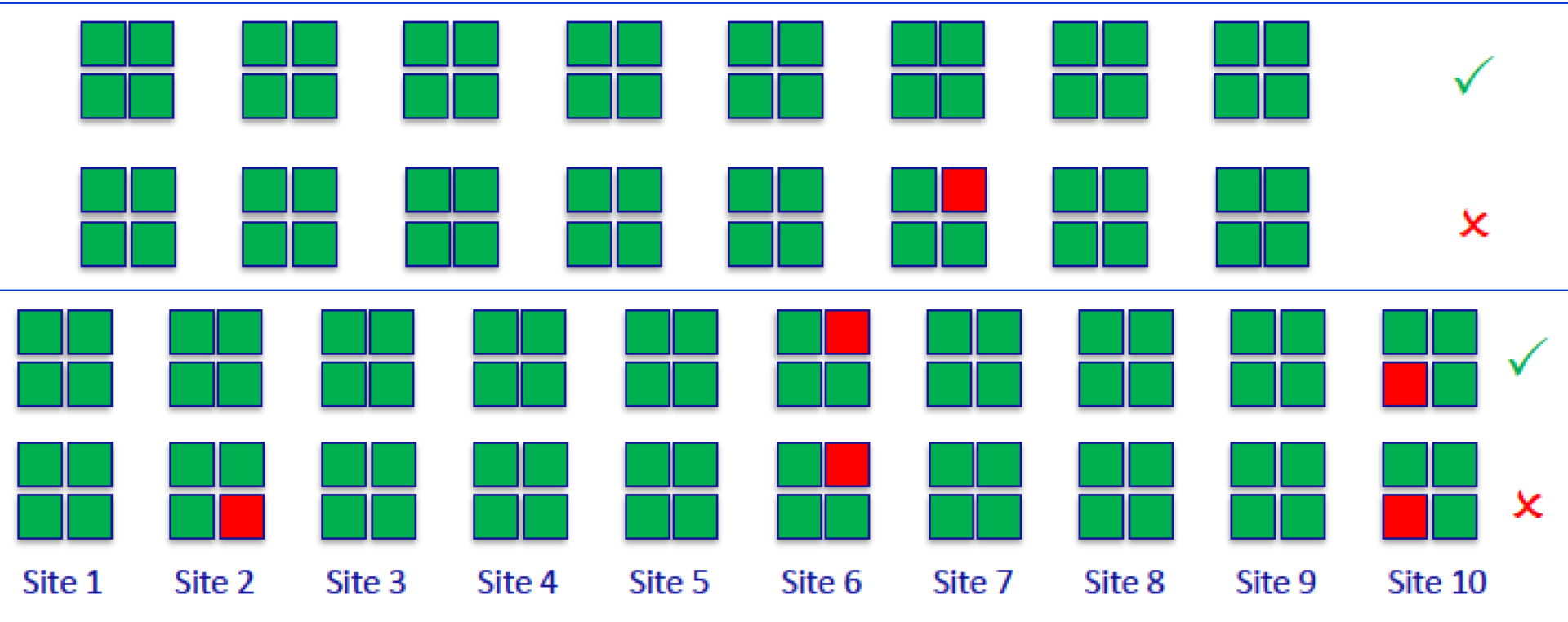
Additional safety data requirements – EU

- Field trials and composition data must be conducted under GLP
  - $2 million+ for GLP regulatory field trials alone
- Nutritional and toxicity studies
  - 90-day rodent study – mandatory
  - 42-day chicken broiler study – maybe
  - 28-day toxicity study – maybe
- Detection method for event
  - Quantitative real-time PCR detection
  - Method requires an external laboratory for GLP validation
- Constant changes: new regulations, new guidance, new data
  e.g., July 26, 2016:
  - EFSA proposals on “non-IgE-mediated immune adverse reactions to foods, *in vitro* protein digestibility tests and endogenous allergenicity. New scientific and regulatory developments on these three topics are described in this document and the necessity for their implementation in the risk assessment of genetically modified plants is discussed and recommended…”

Plus, renewal every 10 years

GLP regulatory field trial requirements – EU

- *Guidance on the agronomic and phenotypic characterisation of genetically modified plants*, EFSA Journal 2015;13(6):4128
- *Guidance on selection of comparators for the risk assessment of genetically modified plants and derived food and feed*, EFSA Journal 2011; 9(5):2149
- *Statistical considerations for the safety evaluation of GMOs*, EFSA Journal 2010; 8(1):1250

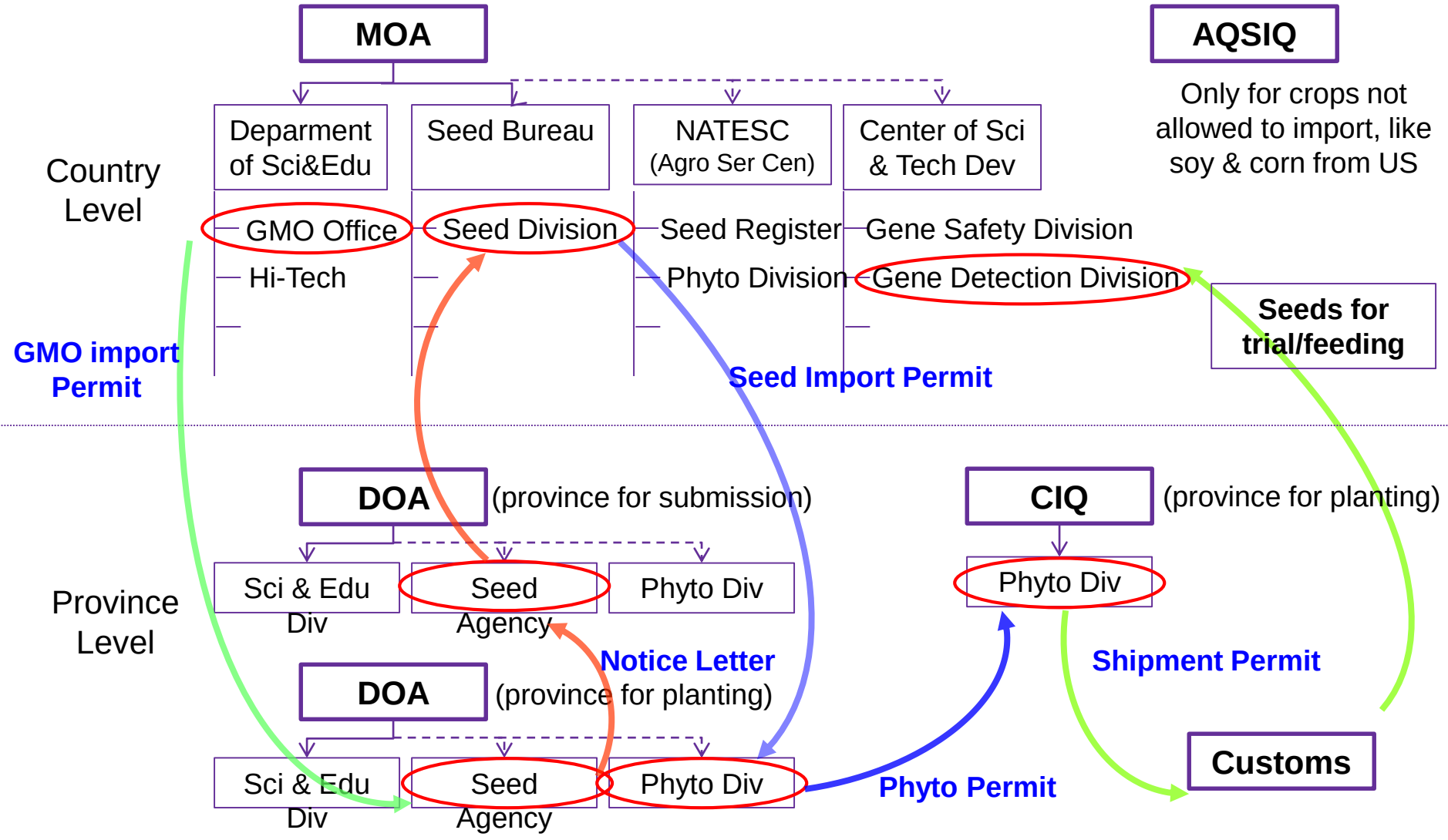


Additional safety data requirements – China

- Safety dossier not acceptable until biotech crop is first approved in another country
- Nutritional & toxicity studies
  - 14-day toxicity study of protein at 5,000 mg/kg BW – mandatory
    - Recalcitrant proteins?
  - 90-day rodent study provided by company – may be mandatory
- Detection method for event
  - Qualitative and quantitative PCR detection methods required
- A Chinese conducted field trial and 90-day rodent study is necessary
- Complicated import and approval processes
  - Seed import example…

Plus, grain importation renewals every 3-5 years

China: seed import process for field trial



Arctic Apple – identity preserved

- RNAi gene silencing to reduce polyphenol oxidase (PPO), which is a key enzyme causing browning.
- ~10 years development, field trials & regulatory
- Commercial approvals in US and Canada ~3-4 year process
- No additional country approvals needed, if…
- Control apple orchards
- Control apple sales
- Robust stewardship required
- Estimated Regulatory Costs:
  - ~$2 million US & Canada
- Labeled? Arctic Advantage™

Okanagan Specialty Fruits photo

Dicamba Soybeans (MON 87708)

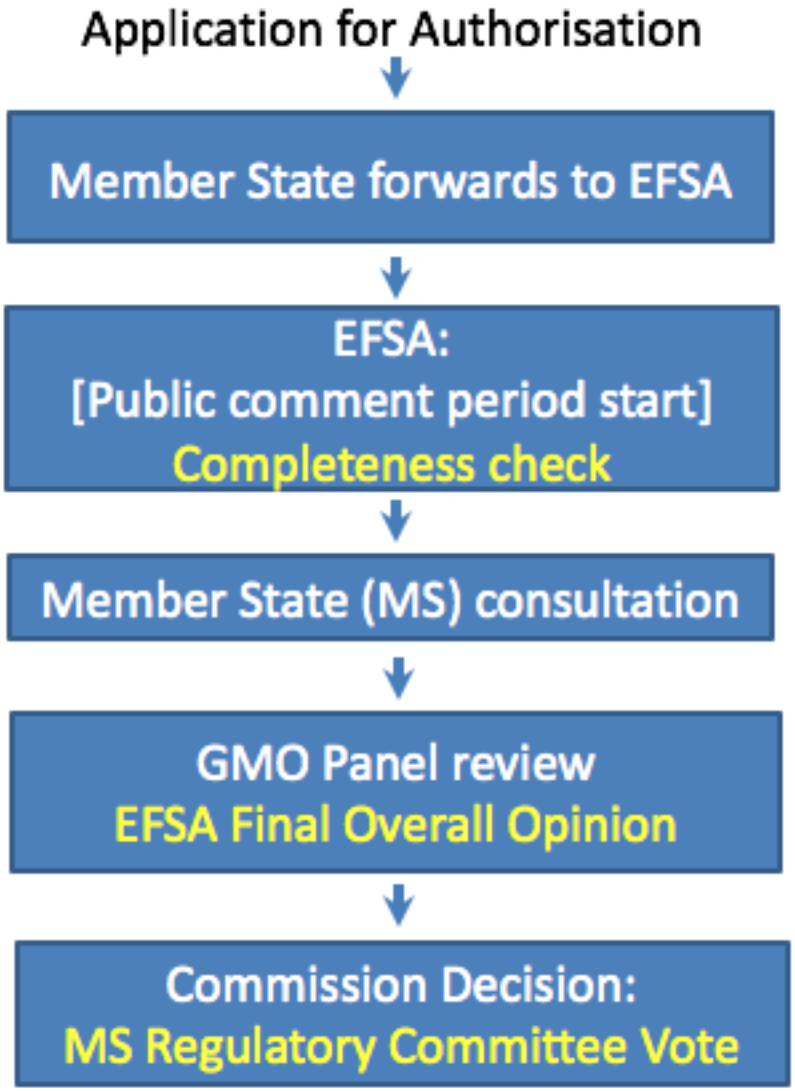
- Dicamba mono-oxygenase (DMO), which confers resistance to the herbicide dicamba
- ~7-10 years for regulatory approvals
  - Food and feed approvals for importing countries – next slides
- Still requires EPA registration of dicamba use on soybeans
- Estimated regulatory costs:
  - ~$30 million+
  - Not including EPA chemical registration
- Some stewardship required
- Labeled? Yes in some countries, but not others.

Monsanto graphic

Dicamba Soybeans EU Approval

EU Approval Procedure Reg. 1829/2003 (1/2)

QMV = Qualified Majority Vote



Theoretical Time elapsed (cumulative)

1 month

3 months + stoppages

7 months

13 months + stoppages

19 months

Actual Time MON 87708 Dicamba Soy Submitted 2/2011

MON 87708 Dicamba took 32 months

No QMV for/against

Dicamba Soybeans EU Approval

EU Approval Procedure Reg. 1829/2003 (1/2)

Application for Authorisation Continued

↓

No QMV for/against

Time elapsed (cumulative)

↓

Decision referred to Council of Agriculture Ministers — 22 months

↓

Agriculture Council (of ministers) vote — 25 months

Decision 1999/468/EC Art 5.6

↙ ↓ ↘

QMV - rejected | No QMV for/against | QMV - authorised

↓

Council Decision 1999/468/EC, Article 5(6)

"...the proposed implementing act shall be adopted by the Commission"

Authorisation published in Official Journal — 26 months

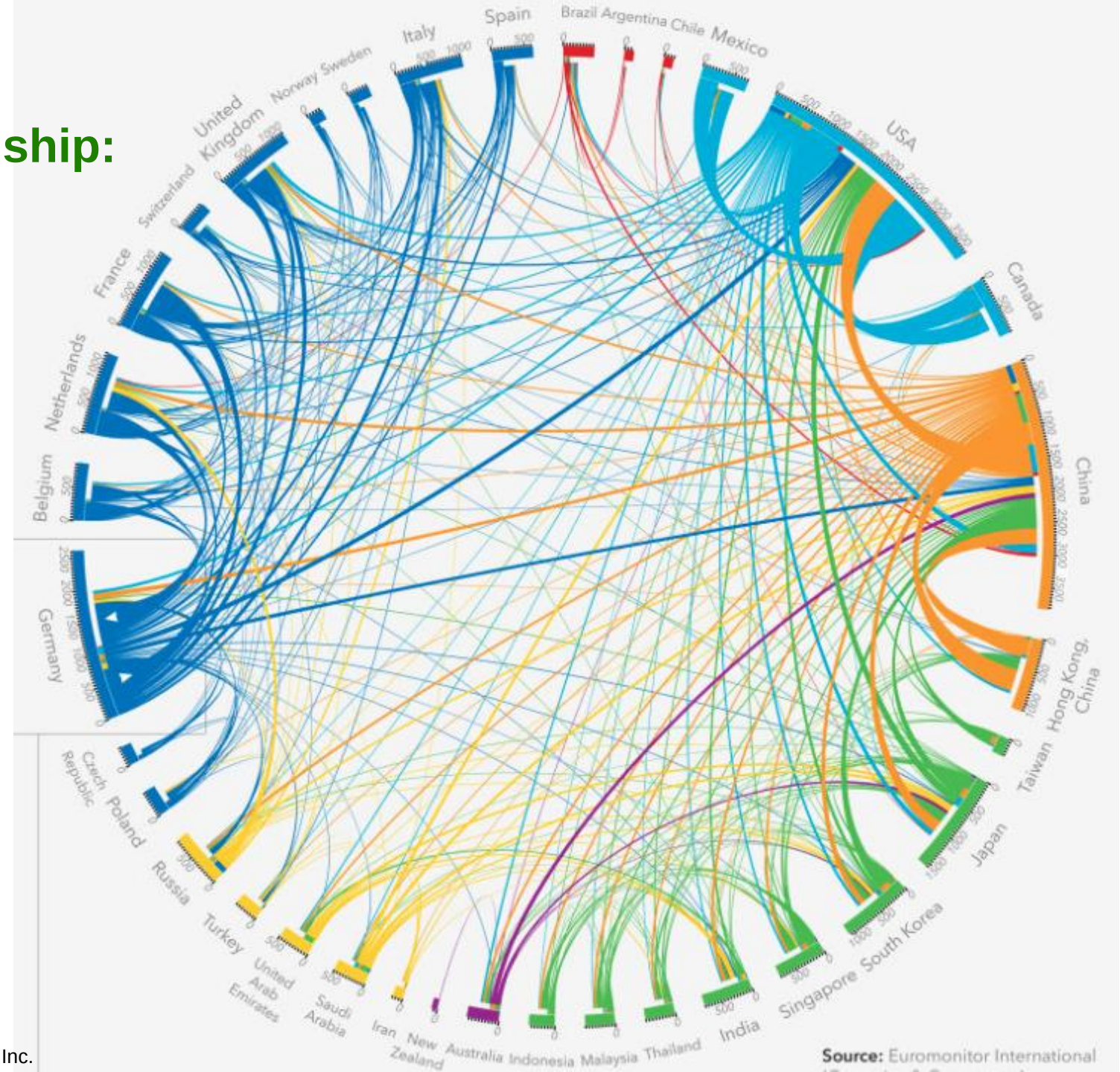
MON 87708 Dicamba approval 50 months ←

Dicamba Soybeans country approvals

Country	Food	Feed	Cultivation
Australia	2012		
Canada	2012	2012	2012
European Union	2015	2015	
Indonesia	2015		
Japan	2013	2013	
Mexico	2012		
New Zealand	2012		
Philippines	2014	2014	
South Korea	2013	2012	
Taiwan	2013		
Vietnam	2015	2015	
United States	2011	2011	2015

- Other soy importing countries to consider for import approvals: China, Egypt, India, Iran, Malaysia, Morocco, Pakistan, Russia, Saudi Arabia, Thailand, Turkey, and Venezuela

Global Stewardship: Who Trades With Whom



Identity preserved crops – strategic choice for small companies

- Based on significant regulatory and stewardship costs and hurdles, the best biotech strategy for small companies is identity preserved crops
  - Partnering with a larger company is another option
- Identity preserved crops with specific and limited cultivation and consumption markets can still be achieved; e.g.:
  - Seminis® virus resistant squash and zucchini – 1995 (Asgrow/Monsanto)
    - US grown, US and Canadian food approvals
  - Rainbow and SunUp virus resistant papaya – 1998 (USDA)
    - US grown, US, Canada and Japan (2011) food approvals
  - HoneySweet plum pox resistant plum trees – 2011 (USDA)
    - Ralph Scorza presenting this later today
  - SONOVA® 400 GLA safflower oil – 2009 (Arcadia Biosciences)
    - US grown, US and Canadian approvals for dietary supplements
  - Innate™ bruise-resistant potato – 2016 (Simplot)
    - US and Canadian grown and food approval
- A strong and robust stewardship program is required to prevent exports

Conclusions

- All biotech crops have gone through very rigorous safety assessments – they have been tested far more extensively than non-biotech crops
- The increasing use of excessive safety testing have not provided increased safety – not one health or environmental problem has occurred
- Unfortunately, the use of use of excessive safety testing required by stringent regulations has resulted in stifling the use of genetic engineering in improving a safe and sufficient global food supply
  - Increased costs and time for approvals
  - Fewer crops using genetic engineering
  - Fewer traits commercialized
  - Consolidation of the agbiotech industry
- For small companies, universities and government research laboratories, a focus on developing identity preserved biotech crops with limited cultivation and consumption markets has been shown to have the best chance for successful product commercialization

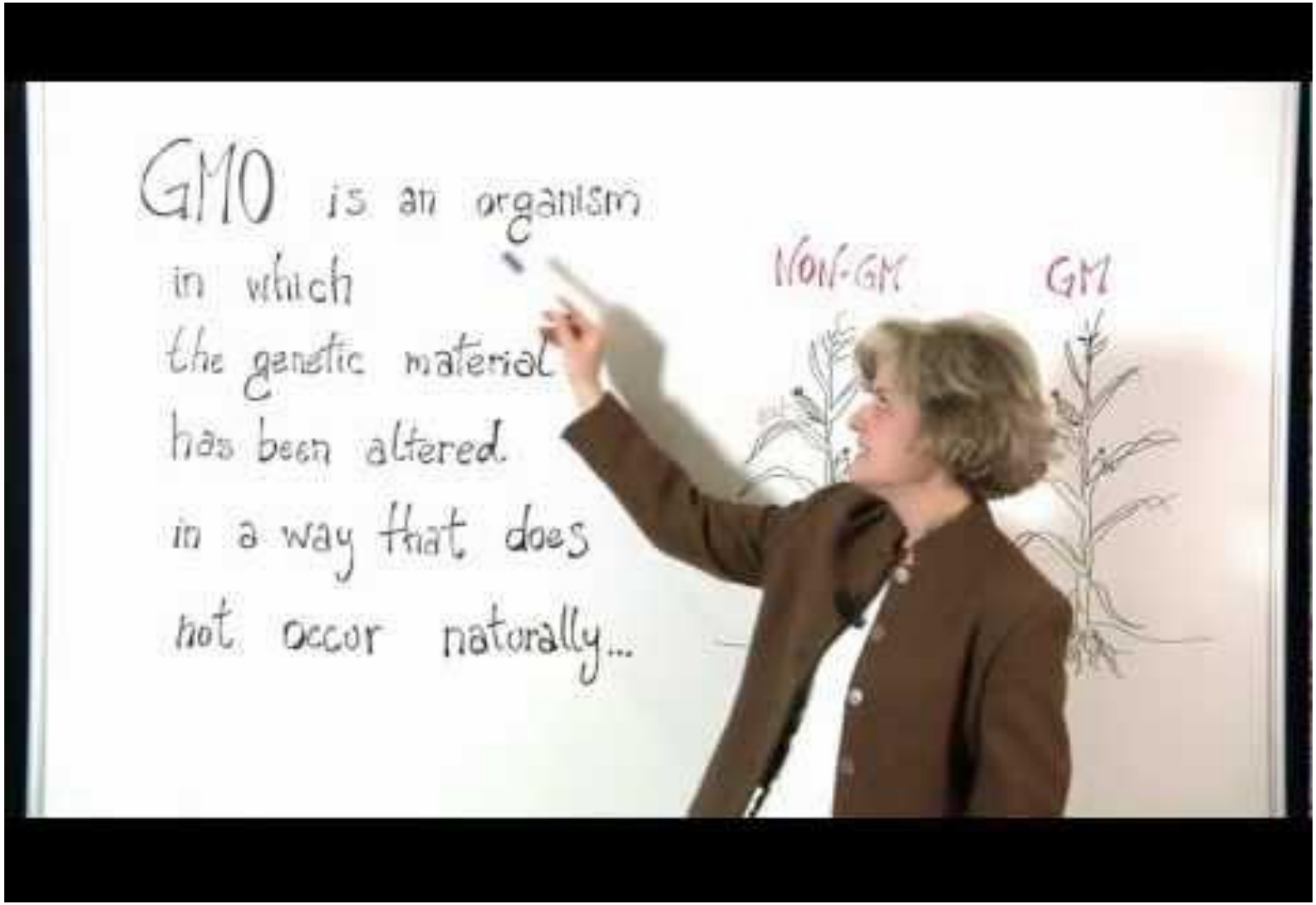
Back-up Slides

Abstract

- Since the launch in 1994 of the first, commercial, genetically engineered crop (Calgene's FLAVR SAVR tomato), the agricultural biotechnology industry has consolidated from dozens of companies to six large ones (BASF Plant Science, Bayer CropScience, Dow AgroSciences, Dupont Pioneer, Monsanto and Syngenta), with further consolidation likely resulting in just four. Although small companies played major roles early in the development of agbiotech and the commercial launch of some of the first products, very few small companies are able to do this today. Two of the most significant hurdles are the high cost of obtaining global approvals and meeting the necessary stewardship requirements. This talk will focus on small companies and strategies for dealing with these hurdles. Examples will include a global crop and an identity-preserved crop.

GMO Labeling

Precautionary Principle



EFSA Photograph

Key EU Regulations

- REGULATION (EC) No 1829/2003 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2003 on genetically modified food and feed
- DIRECTIVE 2001/18/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC
- COMMISSION IMPLEMENTING REGULATION (EU) No 503/2013 of 3 April 2013 on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and amending Commission Regulations (EC) No 641/2004 and (EC) No 1981/2006
  - General requirement checklist itself is over 70 pages long!

EFSA Guidance Documents

- Risk assessment of food and feed from GM plants (2011)
- Environmental risk assessment of GM plants (2010)
- Guidance on the submission of applications for authorisation of GM food and feed and GM plants for food and feed (2011)
- Risk assessment of GM microorganisms and their products intended for food and feed use (2011)
- Risk assessment of GM plants used for non-food or non-feed purposes (2009)
- Renewal of authorisations of existing GMO products (2006)
- Risk assessment of food and feed from GM animals and on animal health and welfare aspects (2012)
- Technical Guidance - Tolerance and efficacy studies in target animals (2011)

EFSA Guidance Documents (continued)

- Guidance on the selection of comparators (2011)
- Opinion on statistical considerations including field trials (2010)
- Opinion on the assessment of allergenicity of GM plants and microorganisms (2010)
- Opinion on potential impacts on non-target organisms (2010)
- Report on animal feeding trials (2008)
- Guidance on the Post-Market Environmental Monitoring (PMEM) of GM plants (2011)
- EFSA guidance on the submission of applications for authorisation of genetically modified plants under Regulation (EC) No 1829/2003 (2013)
- Statement of EFSA on the consolidated presentation of opinions on the use of antibiotic resistance genes as marker genes in genetically modified plants (2009)

EFSA Guidance Documents (continued)

- Guidance for renewal applications of genetically modified food and feed authorised under Regulation (EC) No 1829/2003 (2015)
- Draft guidance on allergenicity assessment of genetically modified plants (2016)
- Report of the EFSA GMO Panel Working Group on Animal Feeding Trials (2007)
- OECD GUIDELINE FOR THE TESTING OF CHEMICALS Repeated Dose 90-day Oral Toxicity Study in Rodents 408 (1998)
- OECD GUIDELINES FOR THE TESTING OF CHEMICALS Repeated Dose 28-Day Oral Toxicity Study in Rodents 407 (2008)
- ISO 24276 FOODSTUFFS – METHODS OF ANALYSIS FOR THE DETECTION OF GENETICALLY MODIFIED ORGANISMS AND DERIVED PRODUCTS (2006)