Arcadia
BIOSCIENCES

Challenges to Biotech Innovation for Small Companies and the Public Sector

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Biosafety Symposium - February 2018

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
- Several commercialization approaches and examples:
  - Identity preserved products
    - Arcadia SONOVA GLA Safflower Oil
    - Arctic Apple – Okanagan Specialty Fruits Inc., Canada
    - Simplot potato, Seminis/Monsanto squash, USDA papaya, USDA plum
  - vs. Commodity products
    - Dicamba Soybean, Monsanto Company, St. Louis, Missouri, USA
  - vs. New plant breeding technologies – regulated or not?
- Strong stewardship programs are absolutely essential
  - Global approvals – which countries?
  - Control of products made from the biotech crop

GMO Labeling

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

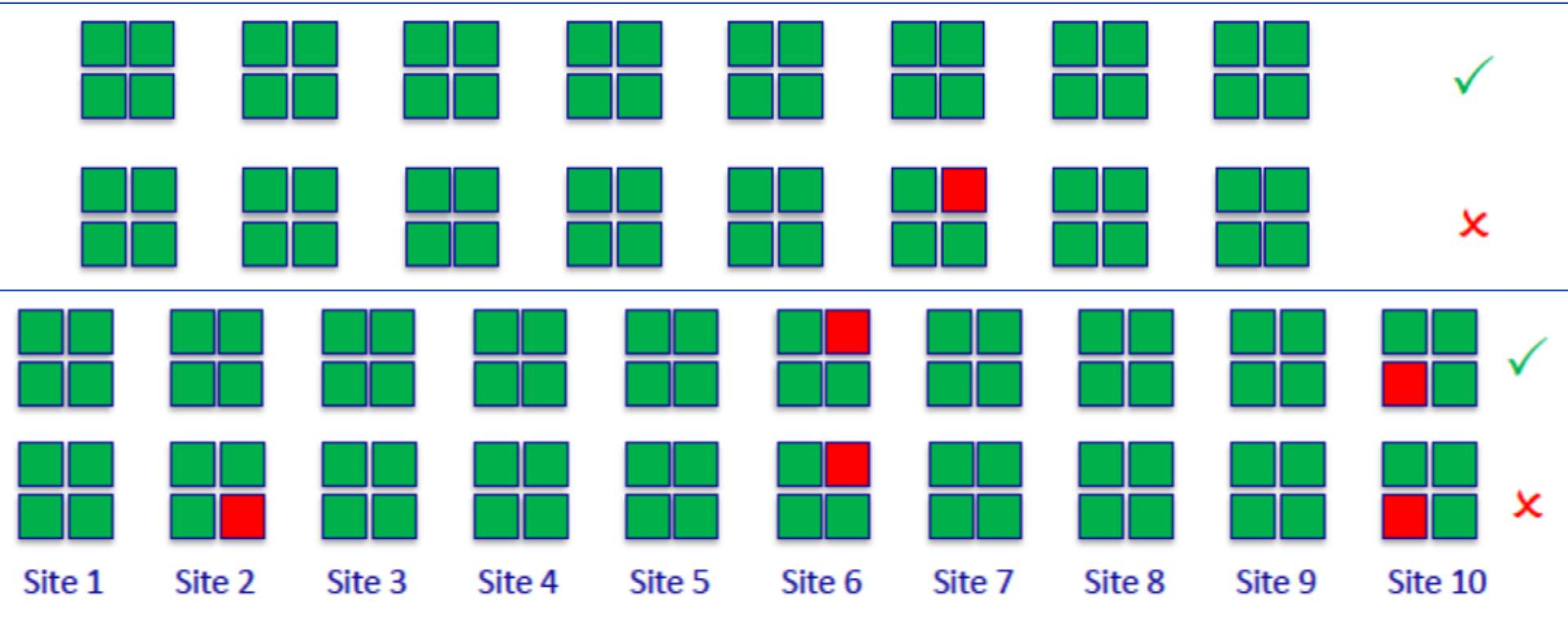
Additional safety data requirements – EU

- Field trials and composition data must be conducted under GLP
  - $1 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., November 20, 2017:
  - "This guidance is intended to assist applicants by indicating which scientific requirements of Annex II of Regulation (EU) No 503/2013 are considered necessary for the risk assessment of the presence at low levels of genetically modified plant material in food and feed."

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

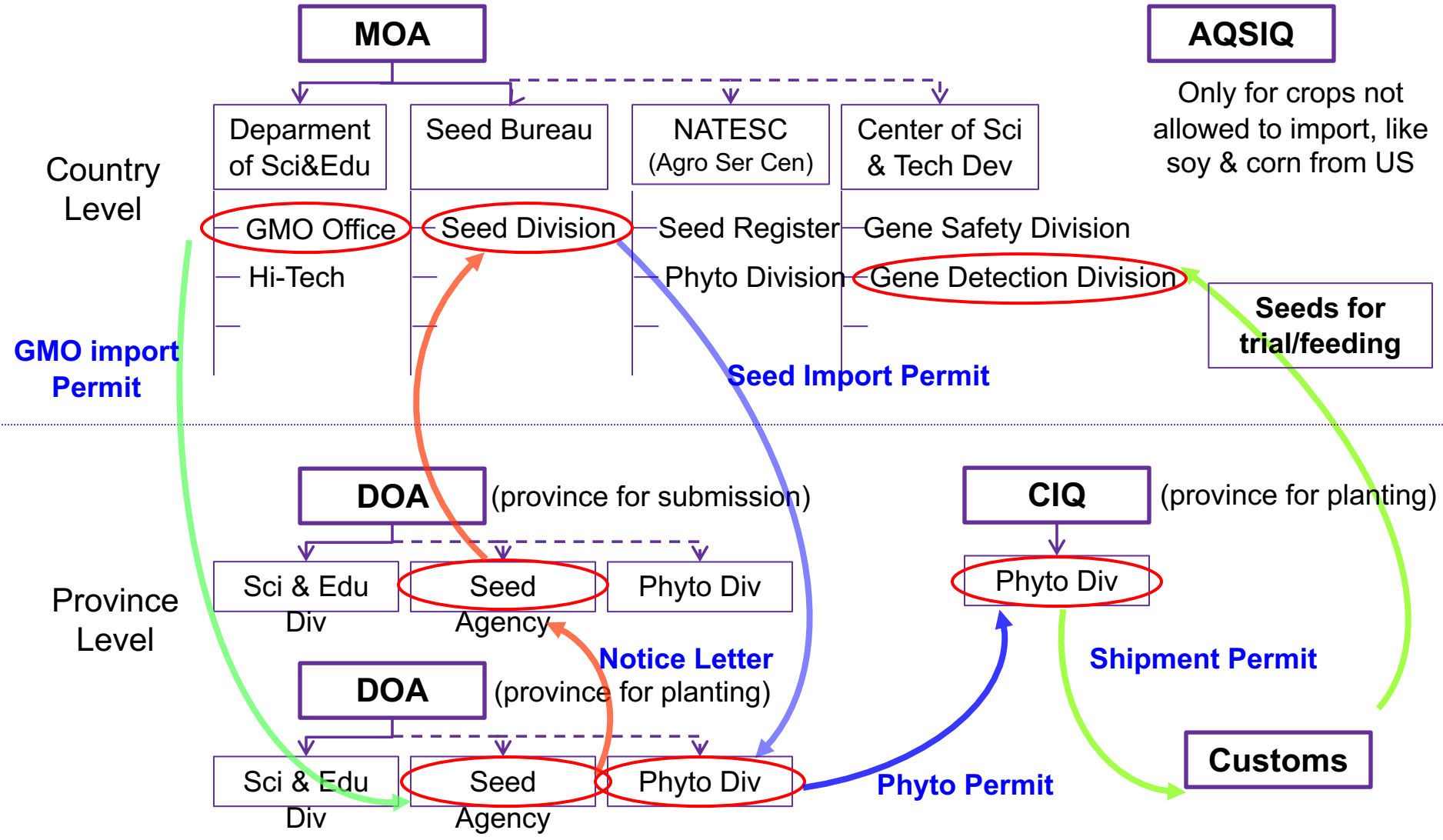


Additional safety data requirements – China

- 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 conducted in China are necessary
- Complicated import and approval processes
  - Seed import example…

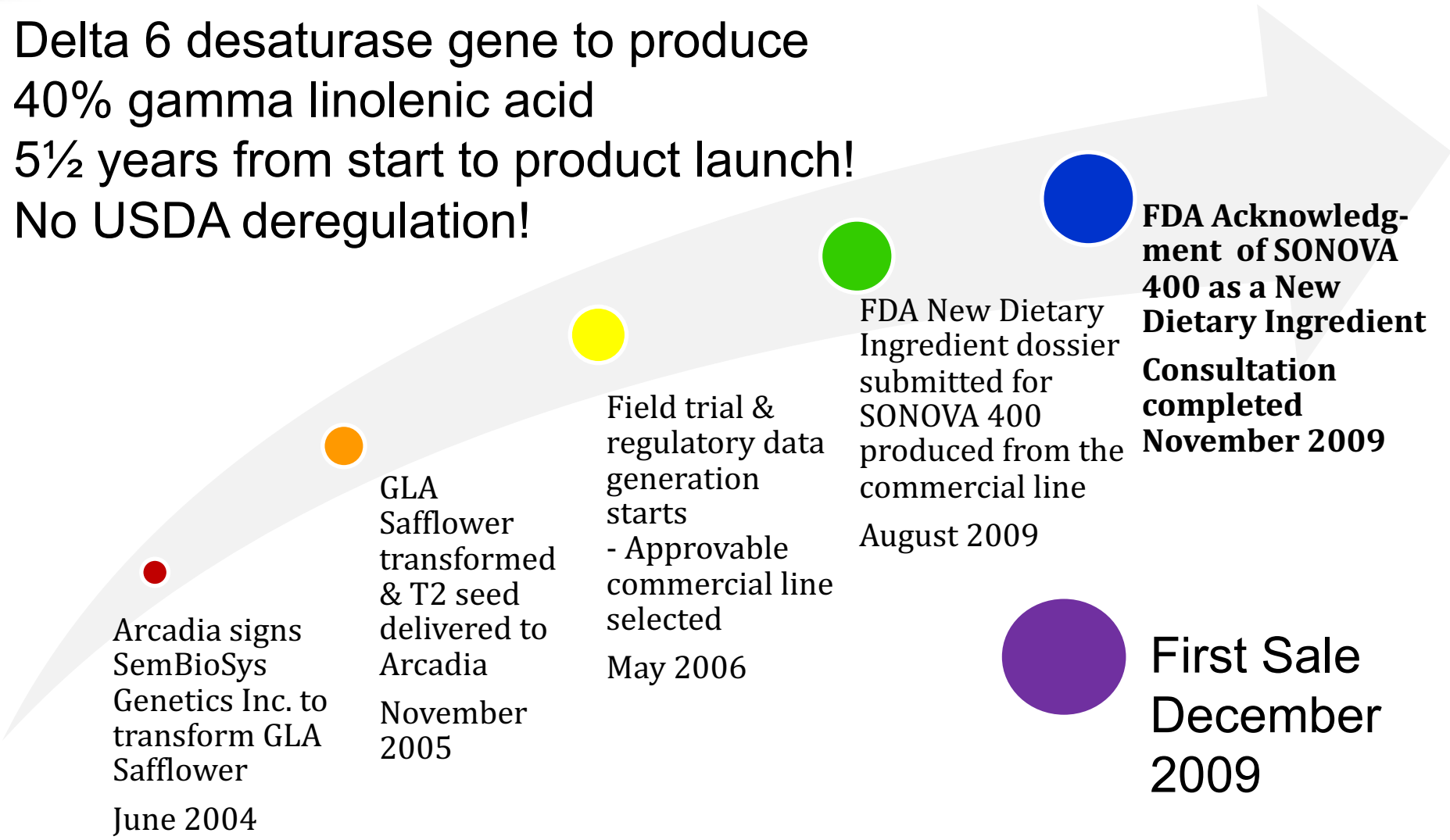
Plus, grain importation renewals every 3-5 years

China: seed import process for field trial



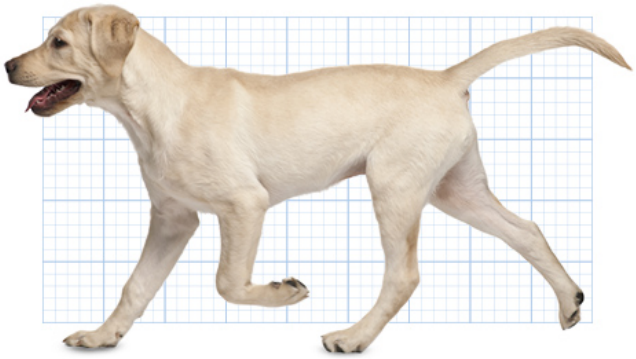
Arcadia Biosciences, Inc.
SONOVA® GLA Safflower Oil – Identity Preserved

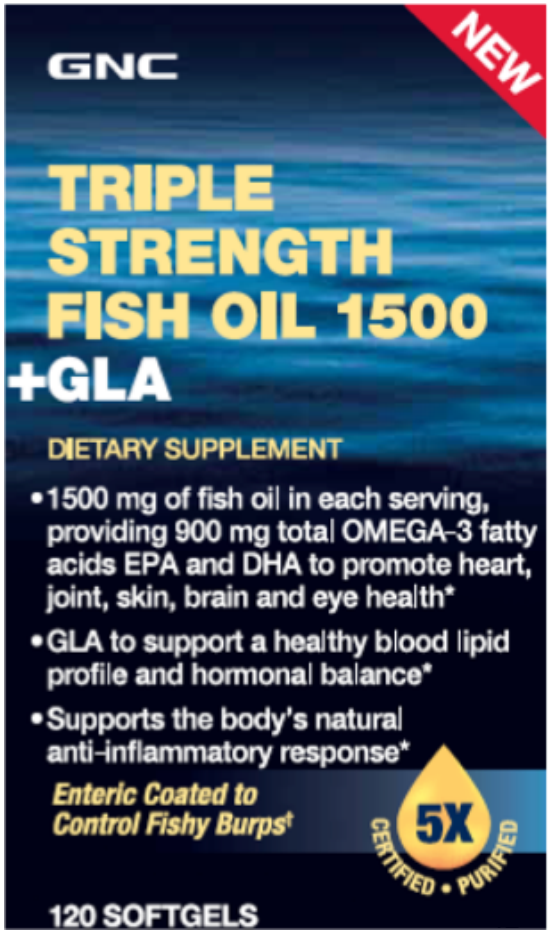
Delta 6 desaturase gene to produce
40% gamma linolenic acid
5½ years from start to product launch!
No USDA deregulation!



Arcadia Biosciences, Inc.
SONOVA® GLA Safflower Oil – Identity Preserved

- Safflower (*Carthamus tinctorius* L.)
- Commercialized as dietary supplement in 2009
  - Canada Natural Health Products approved 2012
  - GRAS status as nutritional and medical foods 2016
  - Food Additive Regulation for Dog food ingredient US 2017 (cat food ~2018)
- No additional country approvals required, if…
  - Control GLA Safflower seeds & oil
  - Sales of oil only in the US and Canada
- Labeled? FDA-established common or usual name: **GLA Safflower oil**





Okanagan Specialty Fruits
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
  - Arctic Golden & Arctic Granny in 2015
  - Arctic Fuji 1/30/2018 (Canada)
- No additional country approvals
  - Control apple orchards
  - Control apple sales
  - Robust stewardship required
- Estimated Regulatory Costs:
  - ~$2 million US & Canada
- Labeled? Arctic® Apples

Okanagan Specialty Fruits photo

Simplot Plant Sciences
Innate® Potato – Identity Preserved

- RNAi gene silencing to regulate four potato genes, including polyphenol oxidase (PPO), which is a key enzyme causing browning
- Russet Burbank, Ranger Russet, Atlantic and Snowden
- Reduced acrylamide by 50-80% for baked and fried potatoes
- Commercial approvals in US, Canada, Australia/NZ, Mexico, Japan
- Targeted for fresh market and regional chippers in US & Canada but not frozen or dehydrated potatoes
- No additional country approvals, if…
  - Control potato production
  - Control potato sales
  - Control export market
- Labeled? Innate® Potato

Craig Richael Simplot photo

Other Identity Preserved Crops

- **Squash** – virus resistant. Asgrow/Seminis/Monsanto 1995 & 2000.
  - Approved in US and Canada. Not labeled.
  - Both events still being sold by Monsanto
- **Rainbow Papaya** – virus resistant. USDA & Univ. Hawaii 1999.
  - Approved in US, Canada and Japan (2012). Labeled.
- **HoneySweet Plum** – resistant to plum pox virus. USDA 2009.
  - Approved in US.
  - Never commercialized because the plum pox virus was contained by conventional methods.

HoneySweet Plum- Transgenic resistance Plum Pox Virus

Ralph Scorza –USDA-ARS Kearnysville

Failed Identity Preserved Biotech Product: Calgene FLAVR SAVR Tomato

- First commercial ag/biotech product in 1994
  - US approvals in 1992/4 – FDA stated it was “as safe as tomatoes bred by conventional means”
  - Mexico approval 1996
  - Canada and UK approvals 1996
  - Seed not sold, tomato labeled as GE
- Antisense polygalacturonase acid gene
- Sold out at grocery stores with very strong repeat purchases
  - Outstanding consumer acceptance
  - But not profitable
- Monsanto cancelled product after acquiring Calgene in 1997

Failed Identity Preserved Biotech Product: Petoseed/Zeneca Thicker Tomato Paste

- Improved tomato paste – commercialized in 1996 in the UK
  - US approvals in 1994/5
  - UK MAFF approval 1995
  - Canada approval 1996
  - Seed not sold, labeled
- Was top selling tomato paste in the United Kingdom in 1996
- Lower cost, or
  - Larger can size
- Zeneca cancelled product because of EU moratorium on cultivation approvals – too costly to grow in and ship from California fields

(This was not a FLAVR SAVR tomato)

Commodity Crop Example: Monsanto's Dicamba Soybeans (MON 87708)

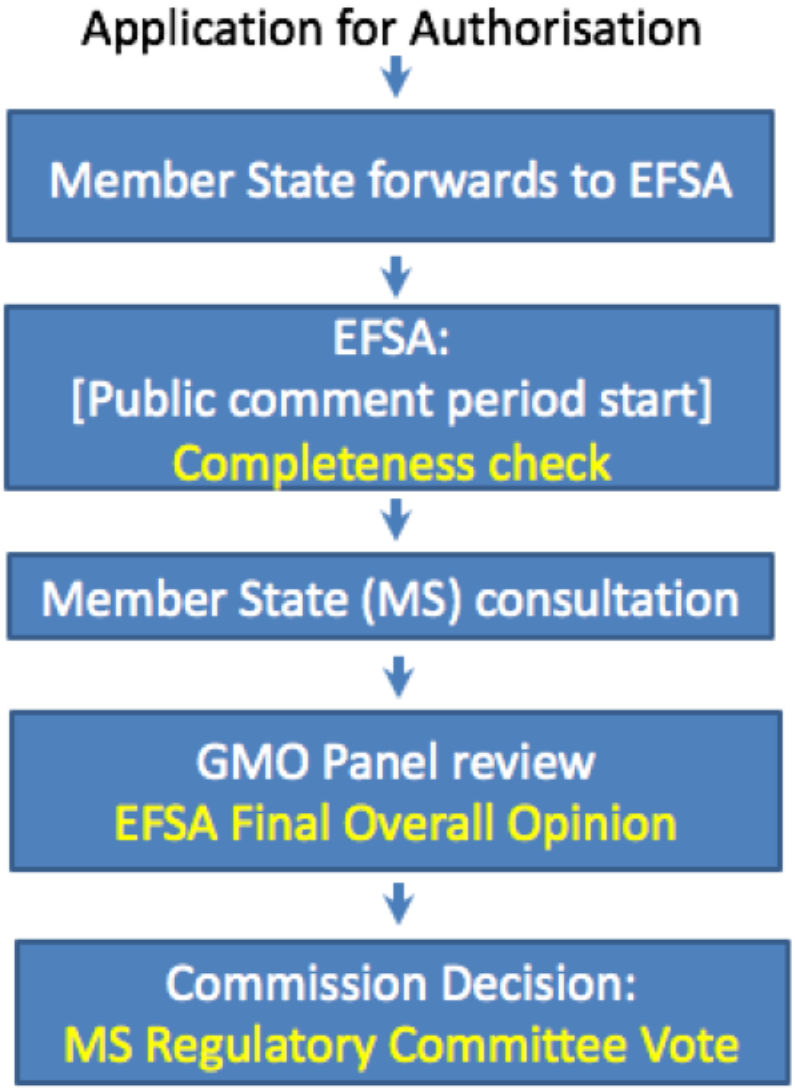
- Dicamba mono-oxygenase (DMO), which confers resistance to the herbicide dicamba
- ~7-10 years for regulatory approvals
  - Food and feed approvals for importing countries – next slides
- Estimated regulatory costs:
  - ~$30 million+
  - Not including EPA chemical registration in the United States
- Stewardship required
  - NY Times Nov. 1, 2017: "Crops in 25 States Damaged by Unintended Drift of Weed Killer"
  - EPA response to crisis
- 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
China	2016	2016	
European Union	2015	2015	
Indonesia	2015		
Japan	2013	2013	
Mexico	2012		
New Zealand	2012		
Philippines	2014	2014	
South Korea	2013	2012	
Taiwan	2013		
Turkey		2017	
Vietnam	2015	2015	
United States	2011	2011	2015

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

Government Regulation of New Plant Breeding Technologies (NPBTs) in Agriculture

- **No global consensus on NPBTs – industry hopeful, regulators uncertain, opponents determined**
  - **Some countries making decisions**
- **Key issue for many countries is the type of site directed nuclease (SDN) and how their regulations define GMOs**
  - SDN-1 – point mutation
  - SDN-2 – deletion with repair
  - SDN-3 – sequence insertion
    - Cisgenetic – could go either way on being considered GMO
    - Transgenetic – likely to be considered GMO
- **Regulatory approach: SDN-1 and SDN-2 targets**
  - This is what Dupont Pioneer is doing with its waxy corn SDN-1

Nature Biotechnology photo

United States Regulation of NPBTs in Agriculture

US FDA – likely consultation process for gene editing

- Scott Gottlieb (Commissioner) May 31, 2017: "Similarly, gene editing of plants for human food provides new opportunities for innovation. But we also need to consider the most appropriate regulatory framework for these new commodities."
- 1/18/17 Request for Comments on FDA's regulatory approach for food produced using genome editing. Comments due 6/19/17.
- Proposal to regulate through existing consultation process.
- 1/18/18 – FDA has not completed a gene editing consultation.
- FDA decision likely in 2018.

USDA – "Am I Regulated?"

- If no plant pest used, the gene edited plant is not regulated as a GE organism (e.g., Pioneer waxy corn, Penn State crispr mushroom).
- As of 11/2017, USDA responded on 16 edited products as **not regulated**

US EPA – regulated if PIP or herbicide tolerant

EU Regulation of NPBTs in Agriculture

- 1/18/2018 – The European Court of Justice Advocate General, Michal Bobek, said New Plant Breeding Technologies (NPBTs) should be exempt from European GMO rules, except, for example, where gene editing was used to insert foreign DNA in a precise location
  - "*Mutagenesis techniques are exempt from the obligations of the GMO Directive provided that they do not involve the use of recombinant nucleic acid molecules or GMOs other than those produced by one or more of the methods listed in Annex I B.*"
  - Most NPBTs do not fall within scope of Annex 1 A Part 1, are not GMOs, and are in the category of point mutations
- An ECJ Advocate General's legal opinion is non-binding and advisory for the panel of judges who will decide the case, with a decision expected this summer
- However, many opponents of NPBTs insist they be regulated as GMOs

EU Regulation of NPBTs in Agriculture

- EU Member States likely to make their own decisions after the European Court of Justice issues its ruling
- ^Decisions by competent authorities of Sweden, Finland, Germany and Spain for targeted mutagenesis: “Not under the scope of directive 2001/18”
- Sweden concluded crispr is not regulated but will follow EU regulations
- Germany said Cibus gene-edited oilseed rape is not regulated, but this decision is now tied up in court case
- ^Draft Dutch proposal for amendment of Annex I B of Directive 2001/18 (exclusion criteria) – proposal to exclude outcomes for plants where no DNA from non-crossable species remains in the final product

^Ana Atanassova, Bayer Crop Science

Government Regulation of NPBTs in Agriculture

- **Canada – gene editing falls under novel crops/food**
- **Argentina – gene editing likely not regulated**
  - If no new combination of genetic material or no transgenes
  - Submit data with decision in 60 days
- **Chile – gene editing not regulated as GMO**
  - If outside scope of Resolution Nº 1523 of 2001
  - If no transgene present: submit data with decision in 20 working days
- **Brazil – anticipated to be aligned with Argentina and Chile**
- **South Africa – ???**

Government Regulation of NPBTs in Agriculture

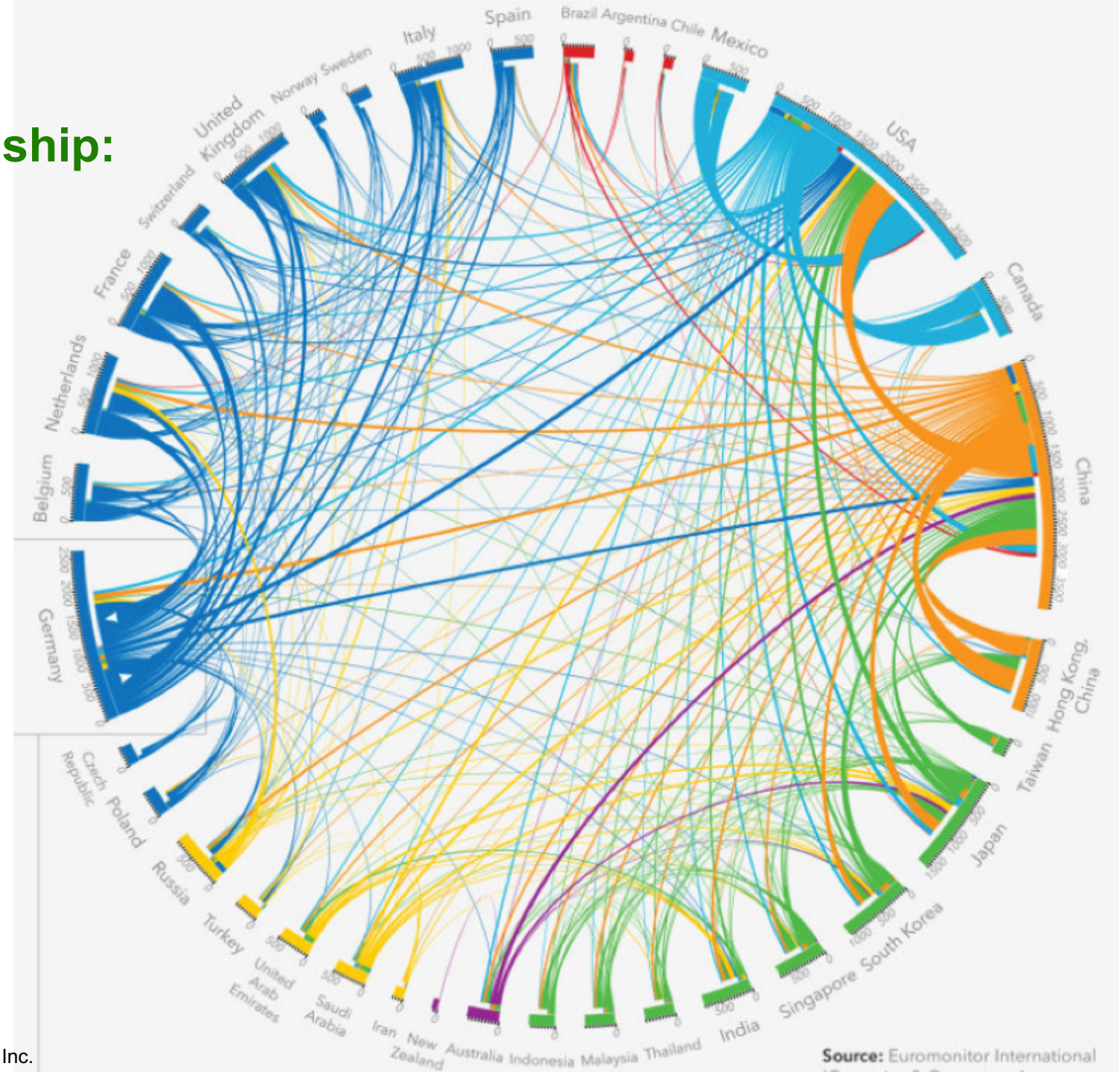
- **China – Ian Jepson 11/2017 (Syngenta, now owned by the Chinese government) said the the government has an undefined "Green Track" for edited plants, but has not defined what this will be other than it will be streamlined**
  - Chinese government is testing crispr in humans
- **Japan – considering regulating gene editing, but it is not GE**
- **India – gene editing regulated at state level like other new varieties. But…**
  - India was positive about gene editing but has now turned away but may still exempt SDN-1 (Ray Dolbert, Monsanto and Ana Atanassova, Bayer Crop Science, November 2017)
- **Israel – gene editing is not transgenic & not under 2005 Seed Act**
  - 2013 & 2017 National Committee for Transgenic Plants "Product not transgenic if result of targeted mutagenesis, and no insertion/incorporation of foreign DNA in final product"

Government Regulation of NPBTs in Agriculture

- **New Zealand – "All techniques not in use before 29 July 1998 are considered to create organisms that are GMOs" EPA 10/2017**
- **Australia/New Zealand – likely to be regulated, but under debate.**
  - "In 2012 and 2013, FSANZ convened workshops that concluded that food derived from gene edited crops with small changes – such as those produced using CRISPR techniques – need not be considered GM because such mutations are indistinguishable from mutations that might occur naturally or through traditional mutagenic techniques."
  - "However, it was concluded that foods from edited crops with inserted genes should be categorised as GM."
  - "Gene Technology Regulator is undertaking a technical review of the Gene Technology Regulations 2001 to provide clarity about whether organisms developed using a range of new technologies, including CRISPR techniques to make small changes, are subject to regulation as GMOs." May exempt SDN-1 (Ana Atanassova, Bayer Crop Science).

R. Dronov and W. Howard. September 2017. Gene editing and crispr. Office of the Chief Scientist, issue 14. Australian Government.

Global Stewardship: Who Trades With Whom

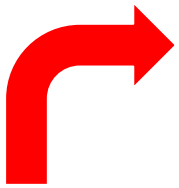


Identity preserved crops & NPBTs – strategic choices for small companies & government agencies

- Based on significant regulatory and stewardship costs and hurdles, the best biotech strategy for small companies is identity preserved crops and new plant breeding technologies
  - Partnering with a larger company for commodity crops is another option
- Identity preserved crops with specific and limited cultivation and consumption markets can still be achieved; e.g.:
  - Arcadia SONOVA® 400 GLA safflower oil
  - Okanagan Arctic Apples – non-browning
  - Simplot Innate™ bruise-resistant potato
  - Seminis/Monsanto virus resistant squash and zucchini
  - USDA Rainbow and SunUp virus resistant papaya
  - USDA HoneySweet Plum – virus resistance
- A strong and robust stewardship program is required for IP crops to prevent exports to non-approved countries
- NPBT crops are rapidly moving toward commercialization

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



New Plant Breeding Technologies

- 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