Precision Fermentation in Food Innovation: Regulatory and Safety Challenges
Disclosures

• Full-time employee at Cargill – US.
• The content, remarks, opinions presented here today are mine and do not necessarily reflect those of Cargill.
Cargill by the Numbers

155,000 Employees

70 Countries

155 Years of experience

Purpose: 
*Nourishing the world in a safe and sustainable manner*
Overview

- Precision Fermentation in the Food Industry
- Complexity of Food Regulations
- Case Study – Next Gen Stevia Sweetener
  - *US FDA GRAS*
  - *EU Novel Foods*
- Looking Forward – Innovation and Regulatory Challenges
Fermentation & Food Innovation

Terminology not harmonized. Currently no regulatory definitions in the US

Conventional

- Vitamins (B2, B12, C, D2)
- Citric Acid
- Enzymes (Chymosin)
- Vanillin
- Erythritol

Biomass/Single Cell

Precision Fermentation

- Vitamins (B2, B12, C, D2)
- Citric Acid
- Enzymes (Chymosin)
- Vanillin
- Erythritol

EverSweet® Stevia Sweetener
Standards of Safety in Regulated Industries

Pharma

- >30 years since inception
- Global alignment on Quality, Safety, and Efficacy – Guidelines
- Accepted standards for global pharmaceutical development
- VICH – Veterinary equivalent >25 years
- Model for Regulatory Harmonization

Food

Little to no alignment!
What Factors Can Impact Safety?

- **Specifications**
  - Contaminants
  - Composition
  - Impurities

- **Process**
  - Manufacturing process steps
  - Inputs and processing aids
  - Food contacts

- **Intended Uses**
  - Technical function(s)
  - Allowable food categories
  - Use levels

So many variables could impact the safety of a single ingredient!
Next Generation Stevia Sweetener

FERMENTATION
To make this new sweetener, we use the age-old process of fermentation—*with a modern twist.*

- Commercially viable quantities
- Affordability
- The ability to scale rapidly
- Less land use
- Less by-product/waste
- Lower risks related to crop—weather, disease, supply chain, etc.

- Great sweet taste
- No bitter or chemical aftertaste
- Enables greater sugar reduction
US FDA GRAS Path

• OFAS – CFSAN – Consultation/Pre-Notification
• Dozens of GRAS Notices – FDA Inventory
• Ability to bridge published safety data on SGs
• Same product and intended uses
• Microorganism, genetic changes and process
• Evaluate “worst-case” scenario of exposure

Fermentation Reb M & D = From Leaf Reb M & D
**FDA GRAS Submission – GRN626**

- **In vitro** metabolism:

  ![Steviol formation](image)


- Common metabolic pathway for all steviol glycosides – bridges to published safety data

- Challenge – *Provide sufficient detail on organism to evaluate safety without disclosing CBI*

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**List of studies taken from FDA Redbook 2000 Guidance**

<table>
<thead>
<tr>
<th>Study Type</th>
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<tbody>
<tr>
<td>Genetic Toxicity Tests</td>
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<tr>
<td>Short-term rodent study</td>
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<tr>
<td>Sub-Chronic rodent</td>
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<tr>
<td>Sub-Chronic non-rodent</td>
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<tr>
<td>One-Year non-rodent</td>
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<tr>
<td>Two-Year rodent chronic toxicity/carcinogenicity</td>
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<tr>
<td>Reproduction study</td>
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<tr>
<td>Developmental Toxicity</td>
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<tr>
<td>Metabolism and Pharmacokinetic studies</td>
</tr>
<tr>
<td>Human Clinical Trials (safety only)</td>
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</tbody>
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- Food and Chemical Toxicology – Volume 46 (2008) – Rebaudioside A: An Assessment of Safety
EFSA Submission (EU)

• Consultation?
• Guidance documents

GM Foods or foods produced from GM organisms – Regulation (EC) No. 1829/2003

Food additives – Regulation (EC) No. 1333/2008
GMM Categories

Category 1
Chemically defined purified compounds and their mixtures in which both GMMs and newly introduced genes have been removed

Category 2
Complex products in which both GMMs and newly introduced genes are no longer present

Category 3
Products derived from GMMs in which GMMs capable of multiplication or of transferring genes are not present, but in which newly introduced genes are still present

Category 4
Products consisting of or containing GMMs capable of multiplication or of transferring genes

EFSA Guidance

TIER 1
- Absorption
- Genotoxicity
  - In vitro testing
- Toxicity
  - Extended 90-day toxicity study

Triggers for considering Tier 2
- Systemic availability
- Toxicity in the 90-day study
- Genotoxicity in vitro

TIER 2
- ADME
  - Single dose
- Genotoxicity
  - In vivo testing
- Toxicity (stand-alone or combined)
  - Chronic toxicity
  - Carcinogenicity
- Reproductive & Developmental toxicity
  - EOGRTS
  - Prenatal developmental toxicity

Triggers for considering Tier 3
- Bioaccumulation
- Positive in vivo genotoxicity
- Chronic toxicity/carcinogenicity
- Reproductive & Developmental toxicity

TIER 3
- ADME
  - Repeated dose, volunteer studies
- Carcinogenicity
  - Mode of action
- Reproductive & Developmental toxicity
- Specialised studies
  - Immunotoxicity
  - Neurotoxicity
  - Endocrine activity
  - Mode of action

Toxicology Testing
EFSA Submission (EU)

- Microorganism and processing data:
  - Safe strain lineage
  - Inserted genes, source, sequence, construct, integration site and methods used
  - Confirmation of organism removal and inactivation in processing steps
  - Microscopy to show intact cells after separation
  - Lack of residual DNA and protein in finished product
  - BLAST-P Alignment search – allergen/toxin

- Toxicology and ADME:
  - 90-day rodent study (OECD 408)
  - Ames test (OECD 471), *in vitro* chromosomal aberration test (OECD 473)
  - *In vitro* metabolism
FDA-EFSA Comparison

• GRAS process encourages pre-consultation with FDA
• FDA focus on final product & specifications, EFSA focus on process
• GRAS process focuses on safety endpoints
• EFSA emphasis on GM aspects not related to safety
• US – labeling focuses on chemical identity (Reb D & Reb M)
• EU – labeling distinguishes process (ex. Reb D & Reb M from fermentation by a GM yeast...)
• JECFA framework for steviol glycosides
• Varying Review Periods
What About Strain Changes?

FDA Guidance Document

Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives

JUNE 2014

• FDA Guidance Document
• Strain improvements evaluated on a case-by-case basis
• Most do not impact the specifications of the final product
• Changes in micro-organism and genes used would be a new regulatory filing
Going Forward

• The FDA GRAS process is designed to support innovation like precision fermentation. Focus on safety of the product is important.
• The overall process in the EU is more complex, with significant data requirements and timeline for approval.
• EU is not the only region that puts significant emphasis on the organism safety and genetic changes.
• Novel technologies like cultivated meat may be challenging in some geographies. Biodiversity regulations?
• Advocating for a global regulatory approval framework (i.e. – ICH for the pharmaceutical industry) would be beneficial for the food industry and the government agencies that oversee it.
Questions?

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