REGULATORY CHALLENGES FOR FOOD INGREDIENTS PRODUCED THROUGH NOVEL TECHNOLOGIES: AN INTERNATIONAL PERSPECTIVE

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As a consultant I work for the industry at large filing international regulatory submissions. I received no direct support for today's presentation.
• **Novel Technologies Related to Food Ingredients**
  • Potential benefits

• **International Regulatory Perspectives**
  • Similarities
  • Differences (recent examples: nanotechnology and cultured meat)

• **Case Study**
  • Steviol glycosides produced *via* glucosylation, bioconversion and fermentation
  • A comparison of the safety evaluation approach and outcomes by different regulatory authorities
  • Future Proposed streamline regulatory methodology

• **Conclusions**
NOVEL TECHNOLOGIES RELATED TO FOOD INGREDIENTS
NOVEL TECHNOLOGIES RELATED TO FOOD INGREDIENTS

• Novel Technologies are developed for many reasons both from a technical and economic perspective.

• GM Technology
  – Crops (pesticide resistant (crop protection), nutritional value)
  – Fermentation (production of food ingredients *e.g.*, *via* GM yeast)
  – Bioconversion (enzymes)

• Nanotechnology
  – Taste health and diet
  – Packaging
  – Delivery and absorption

• Plant Protein Substitution
• Cultured Meat (clean meat)
  – Reduction in natural resources
  – Environmentally and economically sustainable
NOVEL TECHNOLOGY DEVELOPMENT

• Over the last several years, innovation in food and food ingredient production through novel technologies has been developing at a rapid rate in many different novel technical areas.

• The challenge has been for the regulatory authorities to keep pace with such innovation in terms of setting regulatory guidelines and policy for determining the safety of such products.

• Today I will focus on those major regulatory authorities including the EU (EFSA/Commission), U.S. (FDA), Australia/NZ (FSANZ), Canada (Health Canada) and WHO/FAO JECFA.
INTERNATIONAL REGULATORY PERSPECTIVES
The goal of all of the major regulatory authorities is to ensure the safety of the food supply for the consumer. As a result, all ingredients produced via new technologies are required to undergo a thorough safety evaluation. Nature identical ingredients produced through novel technologies are required to be substantially equivalent:

- Meet current specifications

- No introduction of potential harmful impurities
  - Proteins/allergenicity

Following review and evaluation of the novel technology applications, regulatory authorities publish scientific opinions and update legislation accordingly.
REGULATORY DIFFERENCES REGARDING FOOD INGREDIENT ASSESSMENT FROM NOVEL TECHNOLOGIES

• SAFETY
  • Current international regulatory guidelines regarding safety study requirements are not harmonized
  • Require different data requirements and potentially different safety studies
  • In the EU, EFSA has introduced an evidence based approach to food ingredient safety
  • This has led to the need for additional studies not required by the JECFA or other regulatory authorities

• POLICY
  • EFSA (independent academic scientists) undertake the safety evaluation/risk assessments, while the EU Commission sets regulatory policy/legislation
  • In contrast, the FDA, FSANZ and Health Canada personnel are government employees who are involved in both the development of regulatory policy/legislation (termed the food code in AU/NZ) as well as the evaluation of food ingredient safety
  • However, in AU/NZ the state or territory government agencies are responsible for enforcing the code
REGULATORY DIFFERENCES REGARDING INTERPRETATION OF TOXICOLOGICAL DATA

• NANOTECHNOLOGY

• Recent concerns have surfaced within France regarding the use of titanium dioxide (TiO2) as a food colour as it is purported to contain particles partially in nanometric form

• TiO2 has been used for many decades as a food ingredient

• The French Authorities have passed an amendment banning the use, import and marketing of any food product containing TiO2 as a food additive as a component based upon a French scientific study highlighting potential carcinogenic risks of TiO2 nanoparticles

• However, EFSA stated in 2016 that TiO2 poses no health concerns and this was confirmed in June 2018 following the evaluation of 4 additional safety studies

• Overall, the EFSA considered that there was no merit in opening their existing opinion related to the safety of TiO2

• As a result, there is a difference in opinion between the EFSA and ANSES regarding the safety of TiO2 based upon the potential nanoparticle content
Cultured Meat (2 years ago)

- U.S.
  - The FDA and USDA has now only just proposed a joint regulatory framework for cell based meat
  - We still do not understand if pre-market approval will be required and the process (food additive/GRAS)
- EU
  - These products would be covered under the novel food regulations since “food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, micro-organisms, fungi or algae” are captured under the novel food definition
- Australia/NZ
  - The novel food provisions in the Code may be applicable for products that are non-traditional, or are produced through non-traditional processes. The Code also includes definitions of ‘meat’, which may present some issues with regard to identifying products such as “clean meat”

Summary

- Industry is therefore challenged with determining the regulatory approach and the adequacy of the safety database for future novel technology applications based upon differences in regulatory requirements
Steviol Glycoside Case Study
STEVIO GLYCOSIDES – WHAT ARE THEY?

• A sweetener having up to 350 times the sweetness of sucrose that originally was solely extracted from the leaves of the plant *Stevia rebaudiana*

• The plant extract has gained widespread international approval as a high intensity sweetener and is approved for use in more than 150 countries and has approvals from all the major international regulatory authorities

• The major glycosides present in the *S. rebaudiana* leaves include stevioside and Rebaudioside A

• Stevioside and Rebaudioside A however do not have the best taste and sensory qualities
Some of the minor glycosides present only at very low levels within the *S. rebaudiana* leaf extract such as rebaudioside D and M have been shown to have preferable sensory and sweetness qualities.

Not possible to extract enough of these glycosides from the leaf in a commercial, economical and sustainable manner.

The industry has therefore developed a number of novel technologies to produce these materials on a commercial scale.
NOVEL STEVIOL GLYCOSIDE PRODUCTION TECHNOLOGIES

• **Glucosylated Steviol Glycosides**
  - Manufactured using purified *S. rebaudiana* plant extracts (>95%) and an enzyme system (from a GM or non GM microbial source) to transfer sugar/glucose units to the steviol glycosides – glucoxylation

• **Bioconversion**
  - Involves the enzymic conversion of steviol glycosides extracted from the plant (e.g. Reb A) to different steviol glycosides such as *rebaudiana* D and M by adding one or more glucose units from a sugar source, using enzymes obtained through genetically modified (GM) technology
  - The various enzymes produced through the GM technology are isolated and then reacted with the plant extract
  - The resulting end products are identical to those steviol glycosides found in the stevia leaf but are not directly extracted from the stevia plant
• **Stevia Glycosides from Genetically Modified Organisms Via Fermentation**

  • Steviol glycosides are produced directly from GMM such as *Saccharomyces cerevisiae* and *Yarrowia lipolytica*, via fermentation

  • The GM organisms are modified to produce rebaudiosides D and M

  • Produced through fermentation procedures

  • No involvement of the plant extract
A Comparison of the Safety Evaluation Approach and Outcomes
REGULATORY STATUS OF THESE NEW TECHNOLOGIES IN THE U.S.

Glucosylated Steviol Glycosides
- Generally Recognized as Safe (GRAS) in the United States (U.S.) (GRN# 337,375,448,452,607,662)

Bioconversion
- Several products have gained GRAS status in the U.S. (GRN #667, 715, 745, 764, 780, 799)

Steviol Glycosides from GMO
- Four products currently have GRAS status in the U.S. (GRN#626, 632, 744, 759)
- Regulatory status of each of the new technologies based primarily upon the safety of the steviol glycoside products which meet the JECFA specification
- The FDA found no specific safety concerns regarding the novel methods of production
The EFSA Food Additive Panel concluded that the information provided to support the safety of glucosylated steviol glycosides was insufficient.

Based upon their recent “evidence based approach” published data showing that glucosylated steviol glycosides are metabolized in a similar manner to those from the leaf (read across), was not considered appropriate.

Additional studies required.

Industry repeated the metabolism studies producing the predicted metabolic results.

EFSA are currently considering applications for both the bioconversion and fermentation technologies.

Questions have been raised regarding both applications with respect to:
- Information relating to the production and characterization of the genetically modified microorganisms
- Impurity analyses arising from the use of GM microorganisms in the manufacturing process.
REGULATORY STATUS OF THESE NEW TECHNOLOGIES IN CANADA

• To date, two bioconversion applications have been filed
• Health Canada has indicated that both of these products (reb D & M) are subsumed under the permitted uses of steviol glycosides from *Stevia rebaudiana* Bertoni provided that they meet the steviol glycosides specifications set out in the Food Chemicals Codex or the Combined Compendium of Food Additive Specifications (*i.e.*, the specifications established by the Joint FAO/WHO Expert Committee on Food Additives, or “JECFA”)
• Health Canada is currently reviewing a steviol glycoside application produced *via* a GM modified yeast
• The fermentation product does not appear to have been captured under the simplified process for the bioconversion products even though they likewise meet FCC specifications
REGULATORY STATUS OF THESE NEW TECHNOLOGIES IN AUSTRALIA/NZ

• To date, two bioconversion dossiers and one fermentation dossier have been filed

Bioconversion

• According to the Draft Variation to The Australia New Zealand Food Standards Code (The Code) published in July 2018 for Reb M produced by bioconversion:
  • Enzymes that are used in the bioconversion process are considered ‘Processing Aids’ and will be added to Schedule 18 (Processing Aids) of The Code
  • The current specification for ‘Steviol Glycosides from Stevia rebaudiana Bertoni ’ (S3-35) will be amended to include the bioconversion manufacturing process

Fermentation

• One fermentation application is currently under review by FSANZ
• Initial guidance from FSANZ indicated that the GM production organism would likewise be considered a processing aid
• More recent discussions with FSANZ suggest that according to The Code, classification as a processing aid is possibly not appropriate
• How fermentation materials will be captured in The Code is presently undefined
SUMMARY OF STEVIOL GLYCOSIDE INTERNATIONAL APPLICATIONS

• Steviol glycoside applications to the 4 major regulatory authorities for the novel technologies have resulted in totally divergent outcomes
• The outcomes ranged from not requiring a full application in Canada to the need for additional safety testing in the EU
• Details required on the GMMs and enzymes varied greatly between jurisdictions
• Even within individual jurisdictions (e.g., Australia/NZ and Canada) even though the final products meet the current steviol glycoside purity specifications, it appears that the different technologies will not be evaluated and regulated in the same manner
The industry working through the International Steviol Council (ISC) has developed a comprehensive research paradigm beyond standard toxicity testing to support the safety of each of the new technologies and future GM developments.

This approach was recently submitted to JECFA for evaluation in June.

The Research Paradigm covers safety through evidence of substantial equivalence to the leaf as well as showing in detail the lack of protein and rDNA in the final product corroborated by a lack of allergenicity and toxicogenicity.

The hope is that future GM developments may lead to either a future abbreviated application or none at all.
CONCLUSIONS

• Industry continues to strive to develop new technologies for the generation of new and existing food and food ingredients

• Industry is committed to ensuring the safety of these products through the development of sound science to enable marketing world wide

• Regulatory requirements are for such new technologies are not always clear and can differ considerably between jurisdictions

• As a consequence different regulatory outcomes are obtained for the same dataset, which also may require additional research or clarification

• In the case of steviol glycosides the industry has come together to work with JECFA to align on the safety requirements for the new technologies which hopefully will streamline the review process in the future and limit the need for future applications as long as certain criteria have been met
KEY TAKEAWAYS

• Regulatory challenges will continue for Industry for such novel technologies on the basis of a lack of sufficient harmonisation between different regulatory authorities.

• Industry is therefore challenged with determining the regulatory approach and the adequacy of the safety database for future novel technology applications based upon differences in regulatory requirements.
Thank You!

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