OUTLINE

US Regulatory process for food ingredients
  – Supporting safety through manufacturing control and knowledge

• A practical approach
  – Solve for how to demonstrate safety of a novel ingredient
DOSE MAKES THE POISON

This statement still holds true for food additives and ingredients
  • All chemicals can cause toxic effects in large enough amounts

There exists:
  • Beneficial and harmful chemicals and ingredients

The goal and responsibility of toxicology studies is to ensure the safety of products for human use.
US REGULATORY CLASSIFICATION

Food:
Consumed for taste, aroma, and nutritive value

GRAS:
Intended to become a component of or affect characteristics of food

Dietary Supplement:
Intended to supplement the diet

YOUR PRODUCT

Food Additive:
Intended to become a component of or affect characteristics of food

Drug:
Intended to diagnose, cure, mitigate or treat disease
DIFFERENT REGULATORY PATHS

Proposed Ingredient or Supplement
  ↓
Phase I: Feasibility and Data Gaps Review
  ↓
Phase II: Safety Dossier Preparation
  ↓
Physical and Chemical Characterization
  ↓
Safety Characterization (Mechanism, ADME, Toxicology, Clinical Studies)

Food Additive Petition to FDA
  ↓
FDA Review
  ↓
Years
Food Additive Regulation (21 CFR)
  ↓
GRAS Determination (Expert Panel)
  ↓
Self-Determination
  ↓
GRAS Notification to FDA
  ↓
NDI Notification to FDA
  ↓
Market Dietary Supplement

Market Food Product Containing Ingredient
## DIFFERENT REGULATORY PATHS – DIFFERENT REQUIREMENTS

<table>
<thead>
<tr>
<th>FOOD ADDITIVE</th>
<th>GRAS</th>
<th>Dietary Supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information and data may be unpublished</td>
<td>Pivotal Information and data must be published</td>
<td>Information and data may be unpublished</td>
</tr>
<tr>
<td>Assumes lifetime exposure</td>
<td>Assumes lifetime exposure</td>
<td>Duration and frequency of exposure dictated on label</td>
</tr>
<tr>
<td>Can not exclude sub-populations</td>
<td>Can not exclude sub-populations</td>
<td>Can target and exclude sub-populations on the label</td>
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GENERALLY RECOGNIZED AS SAFE - GRAS

Definition

General recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food.

Basis may be through scientific procedure or by common use in food prior to January 1, 1958.
SELF GRAS VS GRAS NOTIFICATION

• Self GRAS
  - The data package is assembled and reviewed solely by a convened expert panel

GRAS Notification

• The data packaged is assembled and reviewed by a convened expert panel – the data package is then submitted to the FDA for review.
• GRAS Notifications are NEVER approved
  - Only receipt of a “No questions” letter from the agency
SECTIONS OF THE GRAS DOSSIER

1. Description of GRAS substance
2. Historical Use and Consumer Exposure
3. Intended Effect
4. Analytical Methodology
5. Safety Data
DESCRIPTION OF THE GRAS SUBSTANCE

Physical and chemical characteristics
  – Chemical Name, CAS registry number, chemical structure

• Detailed description of the manufacturing process
  – Stepwise process which details all of the equipment and processing aides used in production of the ingredient

• Established food grade specifications
  – Company must determine and indicate specifications for the ingredient – if the ingredient is off these specs it is no longer GRAS

• Batch analysis results
  – Data on 3-5 non-consecutive lots which demonstrate the suppliers ability to meet the specifications

• Contaminants identified
  – Any potential contaminant, residual, impurity etc. must be disclosed

• Documented stability data for the supplied ingredient
HISTORICAL USE AND CONSUMER EXPOSURE

History of use of the ingredient in the food supply and or natural occurrence of the ingredient in the standard variable diet.

The intended uses and use levels must be detailed

– Product category (food type and class adult, pediatric, infant, etc) – Exposure potential
– The level which will be in each product category – potential dose

• A calculation of the estimated daily intake is then calculated for the mean exposure as well as the 90th percentile.

• Analytical Characterization
ANALYTICAL METHODOLOGY

• Validated analytical methods are needed for each of the different specifications
  • Method must be either publically available and standardized, and used as published or must be provided to confirm it is validated for the intended ingredient.

• Unpublished or non-standard methods must be provided for review

• Data using these methods must also be provided for 3-5 non consecutive lots which demonstrate the validity of the method for confirming each specification
PRODUCT STEWARDSHIP IS KEY TO SAFETY

The entire supply chain must be controlled
SAFETY DATA

• GRAS evaluates the ingredient – not the product that the ingredient will be present in (clinical studies are with product).

• In preclinical animal testing the ingredient is fed in a relevant diet for the animal to evaluate safety compared to control

• Must review pivotal published and unpublished data including
  • *In vitro* and *in vivo* toxicology studies
  • ADME data
  • Clinical studies

• The studies are testing not only the safety of the ingredient but also any potential residuals or impurities from the manufacturing of the ingredient.
SAFETY STUDIES MAY ADDRESS THESE ENDPOINTS

Once data gaps are assessed – Justification/data to be provided to address the topics below or a rationale to conduct or not conduct studies

ADME/Pharmacokinetics

Acute Toxicity

Subchronic and Chronic Toxicity

Carcinogenicity

Reproductive Toxicity/ Teratology

Neurotoxicity

Immunotoxicity/ Allergenicity
DRAFT FDA GUIDANCE ON PRECLINICAL TESTING

Genotoxicity Battery
  – Ames assay, *in vitro* cytogenetics, *in vivo* mammalian test

• ADME

• Repeat dose toxicity
  – 14-day range finding study
  – 90-day subchronic study

• Chronic Carcinogenicity

• Reproductive
  – One generation
  – Multi-generation

• Developmental / Teratology

• Decision to conduct studies based on gaps, intended population, dose, frequency...
TOXICOLOGY TESTING DECISION TREE

- No existing documentation of historical use in the United states or Use in Food in Other Regulated Countries (EU, Codex, Canada)
  - Compositional analysis of the ingredient allows bridging to existing database of toxicology studies – there is adequate data to assess safety
    - No new testing is needed
  - Compositional analysis of the ingredient does not allow bridging to existing toxicology data – there is inadequate data to assess safety
    - New testing is needed
- Amount, frequency and/or duration of use proposed are greater than the documented US historical use
- Amount, frequency and/or duration of use proposed are less than the documented US historical use
  - No new testing is needed
WHEN TOXICOLOGY STUDIES ARE NEEDED?

When we can’t bridge the safety of the ingredient for its intended use to documentation of historical use or because of changes in:

– Chemical composition
– Indication for use
– Target population
– Delivery matrix or formulation change
– Dose or amount ingested
– Duration of administration
– Frequency of administration
INFORMATION IN THE LITERATURE & GAP ASSESSMENT

Gap assessment has demonstrated:

- The source of the substance, potential for anti-nutrient factors, well tolerated in livestock

- Gaps – based on population to be fed (infant, pediatric, adult, and medically compromised)
  - No analytical characterization
  - No allergy/immunology data
  - No genetox studies or animal studies in the peer reviewed literature.
  - No clinical studies
**PRECLINICAL ANIMAL DATA**

- Classic rodent studies evaluate toxicity

- Beyond the rodent study - animal model must be chosen to appropriately to extrapolate to humans and considering the intended population:
  - Bioavailability when taken orally
  - Nutritional requirements and limitations of model animal
  - Differences in metabolic parameters
  - Developmental stage – modeling human life stage

- Must consider and prevent differences in dietary requirements to prevent confounding – diet must provide the correct nutrient requirements for the species which is being evaluated!
DOSE RANGE SELECTION

This can be difficult –

• Unlike pharmaceutical ingredients safety margin is dependent on the type of ingredient.

• Nutritive Ingredients (protein, fat, carbohydrate) –
  – We cannot feed large margins over the dietary requirements of the specific species and the life stage
  – Physiological versus Toxicological endpoints

• Functional Ingredients (added for a specific efficacy purpose – amino acids, etc)
  – We can use larger safety margins – depending on the type of ingredient
  – Depending on the ingredient, results may be interpreted closer to those of a drug, if there is a direct intended effect.
Nutritional ingredients are not pharmaceuticals
- There is no discussion of risk vs benefit!

- Ingredients that are taken orally can potentially have many different effects
  - Local, short-term, immediate effects
  - Distal, irreversible, delayed effects

- Food ingredients that are not absorbed and have local effects have the ability to disturb the gastrointestinal tract – diarrhea, vomiting, gas, bloating, etc.
  - If the effect is in fact local and the substance is having a direct effect on the GI tract, these effects would be seen as tolerance issues – they may be adverse but are likely not toxicity

- Food ingredients which are absorbed and have an unexpected and negative effect

- If the effect is due to the ingredient that is fed this effect would be seen as adverse and related to systemic toxicity of the ingredient or residuals
SUMMARY

Nutritional studies are not the same as pharmaceutical studies.

Studies are designed to evaluate oral dietary exposure of a specific ingredient with likely chronic exposure –

- daily use = lifetime exposure

Similar to pharma – the appropriate model is chosen based on physiological similarities between the model and the relevant human population.

Doses are limited based on physiological relevance and limitations.

Results are interpreted based on the ingredient, its intended effect and the type of outcome.

Study data is used to support GRAS or other safety dossiers.
THANK YOU!!