Technical Utility
Manufacturing
Chemistry: Methods & Controls

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Manufacturing Chemistry: Purpose

- To adequately identify the feed ingredient (composition, purity, specifications) so that its safety and utility can be evaluated and relied upon.
- To identify possible contaminants or breakdown products derived from starting materials, manufacturing process, and storage that may affect the ingredient’s safety and utility.
- To ensure that label claims of utility and stability are based on sound science, and can be relied upon by consumers.
Manufacturing Chemistry: Topics

- Chemical Identity
- Utility--Technical Effect in Feed
- Manufacturing Process
  - Bio-technological processes
  - Incorporation into pre-mixes and feeds
- Specifications
- Manufacturing & Analytical Controls
  - Purity, identity, quality
  - Stability
  - Analytical methods
Chemical Identity

- Define
  - How achieved
Utility

- Feed ingredients must demonstrate utility:
  - Technical effect in the feed
  - Examples: Pelleting aids, anti-caking agents, preservatives, antioxidants
  - Established through information available in the scientific literature or through experimentation or studies conducted by the sponsor
Manufacturing Process

- A description should be provided, with sufficient detail to permit an independent evaluation of whether the manufacturing process can produce a feed ingredient that:
  - Is consistent from batch to batch
  - Meets the claimed strength (concentration and/or potency), purity and quality
Manufacturing Process (cont.)

- The description of the manufacturing process should include
  - A list of all starting materials, including substances used in the
    - Synthesis
    - Extraction
    - Purification
    - Other steps
Manufacturing Process (cont.)

- The description of the manufacturing process should include (cont.)
  - **Specifications and quantities** for all solvents, catalysts and other reactive chemicals used in the manufacture and purification of the ingredient
  - **Order in which the chemicals are added** to the batch during the process
  - **Times, temperatures and pH conditions** for each step in the process
The description of the manufacturing process should include (cont.):

- Statistical control procedures and all critical control points in the manufacturing process
- Methods used to monitor the process, including details of the analytical methods, their validation, and the acceptable analytical variation
- Flow charts or diagrams
- A complete material balance for the final product, including impurities
**Bio-technological Manufacturing Processes**

- Are manufacturing processes that include fermentors and bio-reactors
- Additional information provided should include:
  - **Source and type of organism** used to produce the ingredient, including genus and species
  - **Changes made to the organism**, and how the genetic integrity of the altered organism is maintained, including genetic drift
Bio-technological Manufacturing Processes (cont.)

- Additional Information provided should include (cont.):
  - **Description of the media** used to cultivate the microorganism
  - **Chemicals added to the fermentation broth**, identified by analytical tests and specifications
  - **Temperatures, times, pH conditions** and other controls used to maintain the integrity of the organism and the broth
Bio-technological Manufacturing Processes

- Additional information provided should include (cont.):
  - **Critical control points** used to monitor the fermentation process
  - **A complete description of the extraction and purification process** and quantities and specifications for all chemicals used in these processes
  - **Specifications for the final ingredient**
Preparation of Pre-mixes and Supplements

If the ingredient will be further processed into a premix or supplement with other ingredients or carriers, the following should be provided:

- A complete description of the packaging process, including information about the container and its labeling.
- Comparison of the theoretical vs. actual weight of the packaged product.
Specifications

- Specifications are used to establish an ingredient’s identity
  - They can be chemical, physical, and/or biological
  - Ideally, specifications and their ranges should be based on the results of 3 to 5 production batches
  - Specifications can also be based on pilot production batches; the number of such batches should be sufficient to ensure that the estimated specification ranges for the finished product are statistically valid
Specifications (cont.)

- Specifications should include:
  - **Raw data and their statistical analyses**
  - **Analytical tests** used to establish finished product specifications should be validated by the sponsor or should be commonly accepted methods (e.g., Association of Official Analytical Chemists, Food Chemical Codex)
Manufacturing & Analytical Controls

- Establish and control the purity, quality, strength, and stability of an ingredient
- Confirm that an ingredient can
  - meet its label guarantees
  - achieve its claimed (intended) technical effect
  - be adequately mixed in feed & extracted
Analytical Controls

- **Analytical methods and data should be provided for the ingredient**
  - As the raw material (e.g. in pure form),
  - As the marketed product (e.g., in a premix or in feed), and
  - In feed
Analytical Controls (cont.)

- **Analytical methods should:**
  - **Provide information on the**
    - composition of the ingredient
    - the identity of its components
    - their concentrations in the ingredient
  - **Be validated**
Performance Characteristics

- Analytical data should include information about the performance characteristics of the methods used to make these determinations, including their
  - Applicability
  - Reliability/Error
  - Practicability
Performance Characteristics (cont.)

Applicability (usefulness)
   Specificity (identity, selectivity)

Reliability (correctness)
   Accuracy
   Bias (systematic error)
   Repeatability (within labs)
   Imprecision (random error)
   Reproducibility (between labs)

Practicality (efficiency)
   Speed
   Standard range
   Limit of detection
   Cost
   Limit of quantification
   Reagents
Stability Testing

- **Adequate stability** is usually defined as +/- 10% of the initial amount added after a period of storage, using an analytical method of relatively low error.
- **Stability data** are used to determine label guarantee.
- **Stability can**
  - Vary with the amount added to the premix or feed
  - Depend on interactions of the ingredient with other components of these matrices
**Stability Testing** *(cont.)*

- **Example:** To establish that an ingredient is stable in a matrix for one year:
  - Stability should be determined after *3, 6, 9 and 12 months* (the end of the study) of storage.
  - **Data at room temperature** should be provided (usually 20 to 25°C).
  - **Data at elevated temperatures** should be provided if it is expected that the ingredient will be stored at elevated temperatures during all or part of its shelf life.
Stability Testing (cont.)

- Analysis of stability data from one-year study at room temperature
  - Stability data should be fitted to a least squares regression, with the upper and lower 95% confidence limits shown; all graphs and calculations used to determine room temperature stability should be provided
  - An alternative, less-preferred analytical method is Analysis of Variance
Stability Testing (cont.)

- **Analysis of stability data from an elevated temperature study (accelerated stability study):**
  - Shorter durations at elevated temperatures can substitute for one year at ambient temperature
  - Data should be presented as *Arrhenius (kinetic) plots*
  - Testing protocols should be submitted to CVM for concurrence prior to initiating studies
Stability Testing (cont.)

Minimum Durations of Stability Data at Higher Temperatures (Accelerated Studies)-- Examples:

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Min. duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>37°C</td>
<td>3.0 months</td>
</tr>
<tr>
<td>45°C</td>
<td>1.5 months</td>
</tr>
<tr>
<td>60°C</td>
<td>1.5 weeks</td>
</tr>
</tbody>
</table>
Manufacturing Methods and Controls

- **Summary**: Data on the manufacturing chemistry of a feed ingredient establishes its
  - Chemical Identity, Purity and Quality
  - Specifications
  - Stability
  - Utility