Technical Utility Manufacturing Chemistry: Methods & Controls

Dennis McCurdy, Ph.D., DABT

AAFCO Mid-Year Meeting
Presentation Ft. Worth TX

January 18, 2004

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

Manufacturing Process (cont.)

- **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
Repeatability
(within labs)
Reproducibility
(between labs)

Bias
(systematic error)
Imprecision
(random error)

Practicality *(efficiency)*

Speed
Limit of detection
Limit of quantification

Standard range
Cost
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:

Temperature	Min. duration
37°C	3.0 months
45°C	1.5 months
60°C	1.5 weeks

Manufacturing Methods and Controls

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