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Guidance for Industry

Chemistry, Manufacturing, and Controls (CMC) Information — Fermentation-Derived Intermediates, Drug Substances, and Related Drug Products for Veterinary Medicinal Use

Comments and suggestions regarding this guidance should be sent to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Comments can be submitted electronically on the Internet at http://www.regulations.gov. All written comments should be identified with the Docket No. FDA-2011-D-0112.

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Additional copies of this guidance document can be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm.

U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance provides recommendations on what documentation to submit to support the chemistry, manufacturing, and controls (CMC) information for fermentation-derived intermediates, drug substances, and related drug products for veterinary medicinal use. This information is filed to the Center for Veterinary Medicine (CVM) in a new animal drug application (NADA), conditional new animal drug application (CNADA), investigational new animal drug file (INAD), abbreviated new animal drug application (ANADA), generic investigational new animal drug file (JINAD), drug master file (DMF), or veterinary master file (VMF).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Fermentation processes are frequently used to manufacture intermediates, drug substances, and related drug products for veterinary medicinal use. Traditionally, most manufactured fermentation products were extracted from the media or cell mass and either further purified or molecularly modified to create another entity. Today, a variety of products are manufactured from fermentation processes, including:

- Biomass products (i.e., drug and cell mass constitute the product)
- Competitive exclusion products (i.e., the product consists of one or more microorganisms intended to exclude harmful bacteria, such as *Salmonella*, from colonizing)
- Biotech products

- Bacteriophage products

Microbial systems can introduce manufacturing variability that can affect the purity and quality, and ultimately, the safety and effectiveness of a product, if not controlled. Even though fermentation is a common manufacturing practice, CVM currently provides no CMC guidance to pharmaceutical sponsors about fermentation-derived intermediates, drug substances, or related drug products.

III. SCOPE

Filing information for the CMC of a new animal drug application is described in 21 CFR 514. The first specific mention of CMC requirements for fermentation products occurs in 21 CFR 514.1(b)(4)(iii)(a-e) in the Component and Composition section. Most other required CMC information is described in 21 CFR 514.1(b)(5). This guidance provides recommendations for CMC information to support fermentation-derived intermediates, drug substances, and related drug products intended for veterinary use.

The information in this guidance loosely follows the International Conference on Harmonisation (ICH) Common Technical Document (CTD). Due to the redundancy of information between fermentation-derived intermediates, drug substances, and drug products, sections were combined and are not specifically labeled in the CTD format (e.g. Description of Manufacturing Process and Process Controls (S.2.2)). In addition, some CTD sections may have been omitted as they are common to all intermediates, drug substances, and drug products (e.g. General Information), whether or not they relate to fermentation. CVM will accept quality related documents in CTD format.

This guidance does not address postapproval changes associated with fermentation-derived products. Although the guidance addresses fermentation issues associated with semi-synthetic drug substances, it only provides limited information for some semi-synthetic steps post-fermentation. More detailed post-fermentation recommendations can be found in the CVM guidance for industry *169: Drug Substance Chemistry, Manufacturing, and Controls Information*. Additionally, this guidance does not address special characterization and control requirements for biomass, competitive exclusion, phage, and other fermentation-related products produced by microorganisms genetically engineered using recombinant DNA (rDNA) technology. Even though these products are not specifically covered, the underlying fermentation principles described in this document would be applicable to these products as well.

IV. INTERMEDIATES, DRUG SUBSTANCES, DRUG PRODUCTS

CMC information for fermentation-derived intermediates, drug substances, and related drug products can be provided directly in a NADA, CNADA, INAD, ANADA, or JINAD. Typically, the information for intermediates and drug substances are provided by reference to a DMF or a VMF.

Master files provide an avenue for manufacturers to submit proprietary information to the Agency without submitting that information to the applicant. Master files can also be used by a drug sponsor as an organizational tool for different processes (e.g., to separate the process for drug substance manufacturing from the finished dosage form process). For the Agency to review a

DMF or VMF, a letter of authorization (LOA) from the DMF or VMF holder should be submitted as part of the referencing submission provided by the applicant.

The following describes information that should be provided in either a master file(s) or an application, depending on which is used.

A. Identification of Manufacturing Facilities

Facilities involved in the manufacture and/or testing (including contract manufacturers and testing laboratories) of fermentation-derived intermediates, drug substances, and related drug products should be identified. The name, address, and manufacturing responsibility operations/processes performed should be provided for each firm.

B. Description of Manufacturing Process and Controls

A detailed description of the manufacturing process and process controls should be provided for intermediates, drug substances, and related drug products:

- Describe the entire process (including original inoculum, propagation, harvest, isolation/purification, and any modification reactions)
- Identify all process controls

For drug products, a master batch record covering the entire process including original inoculum, propagation, harvest, isolation/purification, and any modification reactions should be provided.

Recommendations for executed (completed) batch records are provided in CVM guidance for industry *42: Animal Drug Manufacturing Guidelines-Series of Four Guidelines* (1994). CVM encourages the submission of executed batch records for lots of drug substance and drug product used in support of the application as they provide valuable detail and insight into the manufacturing process and proposed controls.

1. Pharmaceutical Development Reports

Sponsors are encouraged to provide pharmaceutical development reports (PDRs) that describe the scientific rationale for the chosen manufacturing process(es) and controls for fermentation-derived intermediates, drug substances, and related drug products. A sponsor's ability to demonstrate process understanding can be factored into CVM's risk-based decision making (e.g., Pre-Approval Inspection Decision Support System (PAIDSS)). Suggestions for PDRs can be found in ICH *Q8: Pharmaceutical Development.*

2. Cell Growth (Propagation) and Harvest

A description should be provided that includes a flow diagram illustrating each step in propagation from the original inoculum (e.g., cells from one or more vials of the working cell bank) through the last harvesting operation.

- All steps should be included along with the relevant information, such as the growth conditions and in-process tests performed (e.g., cell concentrations, volumes, pH, cultivation times, temperatures).
- Critical steps and intermediates for which specifications are established should be identified, along with sampling plans and testing time points.

- The flow diagram can be supplemented with information presented in tabular form, if appropriate.

A narrative describing each manufacturing step in the process should accompany the flow diagram:

- Identify all process controls and the associated numeric ranges, limits, or acceptance criteria
- Highlight any process controls that are considered critical
- Identify the intended scale of the process. The amounts indicated should be representative of a maximum-sized production batch.

We recommend the following be included in the narrative:

- A description of the major equipment involved in each step
- A description of inoculation and each step in propagation with growth conditions specified
- The composition of the media used at each step, including water quality and additives used
- The sterilization procedures for media (e.g. a batch sterilization process or continuous system)
- The equipment (e.g. fermentation vessel), feeds, and other materials added during the fermentation process
- Process parameters monitored and controls for critical steps and intermediates
- Procedures used to transfer material between steps
- Procedures used to minimize contamination by adventitious agents
- Process controls to confirm the effectiveness of the specific manufacturing steps used to inactivate and or remove adventitious agents
- Criteria for harvesting
- Criteria for rejecting/accepting a fermentation batch if contamination occurs
- The determination of yields
- Criteria for pooling more than one harvest, if applicable
- Storage conditions and time limits if the harvested crude fermentation product is held prior to further processing

3. Purification and Downstream Processing

The description should include a flow diagram that illustrates and a narrative that describes all the steps involved in isolating and purifying the crude fermentation product to its final form, along with any relevant information (e.g., volumes, pH, temperatures, holding times). Critical steps and intermediates for which specifications are established should be identified, along with testing time points.

The narrative describing each manufacturing step should accompany the flow diagram and should identify all process controls and the associated numeric ranges, limits, or acceptance criteria and include the following:

- Methods used in purification or separation of the crude fermentation product (e.g. precipitation, centrifugation, filtration) including major equipment (e.g. columns, membranes

- Process parameters monitored
- The in-process controls and analytical tests used to show identity, purity, and concentration and to evaluate levels of process- and product-related impurities
- The determination of yields
- Precautions taken to prevent or control microbial contamination during purification
- Conditions for reuse and/or procedures for regeneration of columns, membranes, and adsorbents
- Storage conditions and time limits, if the purified fermentation product is held prior to further processing

4. Modification Reactions (If Applicable)

a. Chemical Modifications

When a product of fermentation is to be subjected to further molecular change through chemical means, a description of the synthetic steps should be included in the procedural narrative. Additionally, a flow diagram of the synthetic process should be provided. For more details, see CVM guidance for industry *169: Drug Substance: Chemistry, Manufacturing, and Controls Information*.

b. Enzymatic Modifications

When the fermentation product is further modified using enzyme catalysts, the steps should be included in the flow diagram and detailed in the procedural narrative. Enzymatic reactions are considered chemical reactions since the conversion of substrate product involves breaking and forming chemical bonds. Thus, much of the information submitted in the manufacturing description should be the same as that submitted for chemical processes (drug substance). However, because enzymatic functionality requires carefully controlled conditions (e.g., pH, temperature, osmolarity), the description should contain detailed information on reaction controls and the optimum range of operation. Furthermore, the biological source of the enzyme should be provided along with a description of the enzyme's preparation and information about its purity.

5. Reprocessing, Reworking, Recycling, Regeneration, and Salvaging

When appropriate, reprocessing, reworking, recycling, regeneration, and salvaging operations should be described. For more detail, see CVM guidance for industry *169: Drug Substance: Chemistry, Manufacturing, and Controls Information*.

C. Control of Materials

A list of materials used in the manufacture of fermentation-derived intermediates, drug substances, and drug products should be provided (i.e., the microorganism, cell bank system, media components, solvents, reagents, auxiliary materials). Information pertaining to the quality and control of these materials should also be provided.

1. Microorganism

Information about the microorganism used for production (i.e., genus, species, and type strain) and known genotypic and phenotypic characteristics should be provided. Additionally, the origin of the source material (or isolate) should be identified or described.

2. Cell Bank System

a. Master Cell Bank

A brief description of the procedures used to generate the master cell bank (MCB) and the criteria used for qualification should be provided. The information should include:

- Method, reagents, and media used in preparation
- Date of preparation
- Process controls
- Storage conditions
- Procedures used in testing for relevant phenotypic and genotypic markers and determining culture purity
- Procedures used to ensure the absence of contamination from adventitious agents (e.g., microbial contamination and cross–contamination by other cell types) with tests and acceptance criteria specified

b. Working Cell Bank

Preservation of the microbial purity of the MCB is an important factor in maintaining the production strain. Often a working cell bank (WCB) is created so that the MCB will be less likely to be compromised. Creation of a WCB occurs via the propagation of the MCB through defined culture conditions, and then aliquots of the resultant homogenous culture suspension are partitioned into individual storage containers of appropriate size for routine production purposes.

A brief description of the procedures used to derive a WCB from the MCB and the criteria used for qualification should be provided. Information similar to that submitted for the MCB should also be submitted for the WCB.

3. Media Components

A list of the media components used at each stage of the fermentation process should be included in the submission. Specifications should be provided for each component for verification that the material is of suitable quality for its intended purpose.

- If ruminant-based media components are used in the fermentation process, they should comply with the proposed BSE Medical Products Rule, issued on January 12, 2007 (72 FR 1582).
- All animal-derived components should be identified and appropriate mitigation steps taken to prevent the transmission of adventitious agents.

4. Solvents, Reagents, Auxiliary Materials

A list of solvents, reagents, and other auxiliary materials used in the fermentation process should be provided. Specifications for each material should be included for verification that the material

is of suitable quality for its intended purpose. When water is used in the process, it should be of an appropriate quality for its intended use.

D. Control of Critical Steps and Intermediates

All critical process controls and their associated numeric ranges, limits, or acceptance criteria should be identified and justified and a brief description of the test provided. Furthermore, any experimental data to support the justification should be included.

- Good controls are essential during fermentation to ensure product consistency.
- End product testing alone is not adequate for demonstrating a fermentation process is under control.
- Manufacturing processes, including fermentation, should be controlled to ensure that the product meets previously identified quality attributes.

All controls used in determining an isolated intermediate's acceptability for downstream processing should be identified. When the intermediate represents the end of the fermentation process and the beginning of a synthetic scheme, the controls warranted are generally more extensive than those used for other types of intermediates. For more detail, see CVM guidance for industry *169: Drug Substance: Chemistry, Manufacturing, and Controls Information*.

E. Non-Critical In-Process Controls

CVM encourages sponsors to identify and describe non-critical in-process controls conducted on a routine basis (e.g., carbohydrate burn rate, may affect yield, but won't necessarily affect product quality). Although these controls may not directly demonstrate that a process produces a quality product, a description of the tests being conducted and why they are not critical, aid in demonstrating process understanding.

F. Process Validation and/or Evaluation

When a fermentation-derived intermediate, drug substance, or drug product is sterilized, the process validation information and data in support of the sterilization process(es) should be provided. Refer to CVM guidance for industry *48: For the Submission of Documentation for Sterilization Process Validation In Applications For Human And Veterinary Drug Products*.

Non-sterile process validation is conducted prior to commercial marketing. CVM may request that process validation protocols and data be submitted in support of manufacturing processes. Scale-up issues encountered during process validation and any modifications to the process to accommodate these issues must be reported through the appropriate postapproval submission process (see 21 CFR 514.8(b)).

G. Characterization

1. Elucidation of Structure and other Characteristics

Confirmation of the structure and characterization data for a fermentation-derived intermediate, drug substance, or drug product should be provided. When the fermentation product is a mixture of active components, isolation and purification of individual components for structural analysis and characterization may be appropriate.

a. Structural Elucidation

Structural confirmation using physical and chemical techniques (e.g., elemental analysis, mass spectrometry, infrared spectroscopy) should be provided for the intermediate or drug substance. Additionally, the data and details of its interpretation should be included. The amount of data warranted to support the elucidation of structure can vary depending on the complexity of the molecule. For USP labeled drug substances, structural confirmation can be accomplished by demonstrating conformance to a USP reference standard.

b. Physicochemical Characterization

The kind and extent of the physicochemical characterization information that should be provided depends on (1) the type of drug substance (e.g., semi-synthetic molecule, protein), (2) the type of dosage form in which the drug substance will be used, (3) the ability or tendency of the drug substance to occur in one or more solid state forms, and (4) the importance of the differences in physical characteristics of the different forms to the stability, dissolution, or bioavailability of the drug product. For more details on the type of information that should be submitted, see CVM guidance for industry *169: Drug Substance: Chemistry, Manufacturing, and Controls Information, Draft Guidance*.

c. Biological Activity

When a biological assay (e.g., antimicrobial activity for antibiotics) is used to assess potency/strength of the intermediate or drug substance, biological activity data should be provided to complete the characterization profile. Data should be provided on the reference standard lot or other relevant lots to demonstrate the potency/strength of the intermediate, drug substance, or drug product.

In some cases, the product of fermentation is a complex mixture of major and minor components that together make up a product's biological activity. In evaluating the impurity profile for these fermentation products, efforts should be made to identify and characterize the active components (major and minor) that contribute to the product's overall potency and distinguish them from impurities. This may not be practical or feasible in all cases. We recommend an applicant with related questions consult the appropriate review team for additional guidance.

2. Impurities

Information concerning impurities in the fermentation-derived intermediate, drug substance, or drug product should be provided (e.g., organic impurities, inorganic impurities, and residual solvents).

- Impurities may derive from the manufacturing process (e.g., residual media components, residual protein and nucleic acid derived from microbial cells, processing reagents, inorganic salts, filter aids, solvents), or they may be structurally related to the desired fermentation product, but not share the same properties with respect to biological activity, efficacy, and safety (e.g., other microbial metabolites, precursors, by-products).
- Process related impurities derived from the fermentation and downstream processing should be minimized as much as possible through the use of a well-controlled and reproducible manufacturing process.

- Structurally related impurities should be identified, tracked, and controlled throughout the fermentation, isolation, and purification processes.

A summary should be provided of the impurities most likely to arise during the fermentation, isolation, purification, and storage (e.g., holding time) of the intermediate, drug substance, or drug product. The summary should include impurity profiles (i.e., chromatograms), test results from representative batches, and results from forced degradation studies used to identify the potential impurities that may arise during storage. The impurities reported can be of known structure, partially characterized, or unidentified. Studies done in characterizing the structure of impurities should be summarized. Documentation should also be provided demonstrating that the analytical procedures used in quantifying impurities are properly validated or qualified.

The specifications for fermentation-derived intermediate, drug substance, or drug products should include limits for impurities (i.e., organic impurities, inorganic impurities, and residual solvents). Additionally, a rationale for the inclusion or exclusion of impurities in the specifications should be presented. As appropriate, this rationale should include a discussion of the impurity profiles observed in batches used for clinical, safety, and stability testing, as well as batches representative of the proposed commercial process.

Although relevant guidances (*92: Impurities in New Veterinary Drug Substances, VICH GL10 (R) and 93: Impurities in New Veterinary Medical Products, VICH GL11(R)*) on impurities did not address fermentation products, the principles described in these guidances are still applicable. Furthermore, levels for reporting, identifying, and qualifying organic impurities as described in these guidances are applicable to non-complex, well-characterized fermentation products.

For complex fermentation products that are not well-characterized in terms of structure, physicochemical properties, biological activity, and purity, it is recommended that the levels for organic impurities be determined on a case-by-case basis.

The acceptable levels for organic impurities will also depend on how the fermentation product is to be used. The levels will likely be less stringent for a drug substance or an intermediate that will be subjected to further modification and/or purification compared to that of a drug product that does not undergo further processing.

For inorganic impurities and residual solvents, limits should generally be based on pharmacopeial standards (e.g., USP General Chapter <467> Residual Solvents) or known safety data. Additionally, the ICH guidance *Q3C Impurities: Residual Solvents* or the CVM guidance *100: Impurities: Residual Solvents in New Veterinary Medical Products, Active Substances, and Excipients, VICH GL18(R)* should be consulted, as appropriate.

For most fermentation products (e.g., antibiotics), it is expected that purification and downstream processing effectively remove process-related impurities, such as residual media components, residual protein and nucleic acid-derived from microbial cells, and other processing reagents. Thus, in most cases, limits need not be included in the specification for these impurities. However, when studies suggest that process-related impurities are not effectively removed from the purification process, these impurities should be controlled with limits in the specifications, as appropriate.

Microbial impurities tests (e.g., for endotoxins) for drug products may be required based on the intended route of administration of the drug product in accordance with 21 CFR 514.1(5)(xi). In some instances when there is a safety concern, drug substances (e.g., gentamicin sulfate) may

contain an endotoxin requirement. Consult the appropriate USP monograph or consult the appropriate review team as needed.

3. Degradation Products

Degradation products observed during stability studies of the drug substance or drug product should be summarized, including:

- Product-related impurities arising from degradation of the drug substance and reaction products of the drug substance with an excipient and/or a component of the container/closure system
- Test results from representative batches and results from forced degradation studies on the drug substance or product

Studies done in characterizing the structure of the degradation products should be provided. Documentation that analytical procedures used in quantifying degradation products are properly validated or qualified should also be provided.

Specifications for the drug substance or drug product should include limits for degradation products expected to occur under recommended storage conditions. A rationale for the exclusion of a degradation product in the specification should be provided.

H. Control of Intermediates, Drug Substances, and Drug Products

1. Specifications

The proposed specifications for the fermentation-derived intermediate, drug substance, or drug products should be provided and include the tests that will be performed on each batch, a reference to the analytical procedure used in performing the test, and the acceptance criteria for each test. The specifications should focus on those characteristics found to be useful in ensuring the safety and efficacy of the intermediate or drug substance. With regard to intermediates, the above recommendations are more specific to those intermediates marketed for resale. Justification for the proposed specifications for the intermediate, drug substance, and drug product should be provided.

For some fermentation-derived drug substances, a nonspecific bioassay (e.g., microbiological type assays for antibiotics) is proposed for use in determining the content of the drug substance. In these cases, the development of a specific, stability-indicating assay (e.g., High Performance Liquid Chromatography (HPLC)) is encouraged as it offers considerable advantages in terms of separation of components, accuracy, and precision. Nevertheless, a nonspecific assay may be used when justified (e.g., the USP monograph prescribes a nonspecific assay method). However, when an adequately justified nonspecific assay is employed it should be accompanied by other supporting analytical procedures to achieve overall accuracy and specificity. For example, where antimicrobial activity or an iodometric titration is used to assay the drug substance, it should be combined with a suitable test for impurities.

2. Analytical Procedures

Copies of the analytical procedures used in testing the fermentation-derived intermediate, drug substance, or drug product should be provided. However, specific citations may be used when

the analytical procedure is from an official compendium or other FDA-recognized standard reference and the analytical procedure is not modified in any way.

3. Validation of Analytical Procedures

Validation data for the analytical procedures used in testing the fermentation-derived intermediate, drug substance, or drug product should be provided. For analytical procedures defined in the USP, qualification data demonstrating the user's capability to successfully perform the analytical method is suitable.

4. Reference Standards or Materials

Information pertaining to reference standards or reference materials used for testing should be provided. Relevant information includes, for example, characterization, storage conditions, working solutions, and stability of the reference standard.

5. Batch Analyses

Batch analysis data using the proposed analytical procedures and specifications for all relevant batches of the intermediate, drug substance, or drug product from safety batches (pharmacology and/or toxicology), clinical batches for safety and efficacy, bioavailability/bioequivalence batches, stability batches, and batches representative of the proposed commercial process should be provided.

I. Container Closure System

A description of the container closure system for fermentation-derived intermediates, drug substances, and drug products should be provided. In addition, a description of the storage containers for the MCB and WCB should be provided.

The supplier of each component (excludes MCB and WCB containers) should be identified and letters of authorization to master files for raw material component manufacturing should be provided.

- Schematics and raw material specification sheets for the components should also be included.
- If components are irradiated, pre-sterilized by other means, or pre-washed, information should be submitted in support of these processes. This information is often provided through a reference to a VMF or DMF.
- Container closure systems for drug substances and finished dosage forms should also meet USP monograph specifications and should be tested as appropriate to USP General Chapter <661> Containers and if applicable, USP General Chapter <671> Containers-Permeation.

J. Labeling

Copies of primary and secondary packaging labels for fermentation-derived intermediates (for resale), drug substances, and drug products should be provided. For intermediates and drug substances, the following should be included on the label:

- Name of the chemical entity
- Number of units or micrograms of activity per milligram when activity is expressed in biological terms
- Number of grams or kilograms in the immediate container
- Batch or lot number
- Statement "Sterile" or "Non-sterile"
- Expiration or retest date, as supported by appropriate stability studies
- Storage conditions [1]

For fermentation-derived drug products, the usual labeling procedures for non-fermentation-derived drug products should be followed.

K. Stability Summary and Conclusions

Information relating to the stability of the fermentation-derived intermediate, drug substance, or drug product should be provided.

For general stability guidance, please refer to the following guidances: CVM *5: Stability Guidelines* and *73: Stability Testing Of New Veterinary Drug Substances And Medicinal Products,* VICH GL3(R).

With regard to intermediates, the recommendations for stability are more applicable to intermediates intended for re-sale but not generally otherwise. A summary of the types of studies conducted, protocols used, and the results from the studies should be provided for fermentation-derived intermediates, drug substances, and drug products. For intermediates and drug substances, conclusions regarding appropriate storage conditions and an ***appropriate retest or expiration date*** should be provided. For drug products, conclusions regarding the storage conditions and an ***appropriate expiration date*** should also be provided.

1. Batch Selection for Stability Studies

For fermentation-derived intermediates, drug substances, and drug products, studies should be conducted on three separate batches, at least two of which are generated from different WCB vials. These batches can be pilot scale. However, the manufacturing process for the pilot-scale batches should fully represent and simulate the proposed full-scale production process.

2. Expiration Date versus Retest Date

For fermentation-derived intermediates and drug substances, a retest period/date may be appropriate in cases where the fermentation-derived intermediate or drug substance shows little change in terms of potency loss and or/degradant increase throughout the proposed shelf life.

[1] Storage conditions should be defined in accordance with the standard definitions for *Freezer*, *Cold*, or *Controlled Room Temperature*, provided in the USP. When critical for maintaining the quality of the intermediate or drug substance, more specific numerical storage conditions should be used, rather than general terms (see USP General Chapter <1079>, Statements/Labeling of the Immediate Containers or Package Insert).

In situations where there is a marked change or trend in the potency and/or degradation profile, such that there is a concern that an out-of-specification test result could occur during stability studies, an expiration date should be used. When an expiration date is assigned to a fermentation-derived intermediate or drug substance, it means the material must not be used beyond that date and is to be discarded. On the other hand, a retest date allows for use of a material beyond the retest date.

A retest date is that date prior to which the material meets all applicable specifications. Beyond that date, the material may be retested and, if acceptable, used within a reasonable amount of time (i.e., within 30 days). The retest date should include those test attributes critical to the fermentation-derived intermediate or drug substance (e.g., potency, moisture content). Expiration dates and retest dates should both be established based on supportive stability data.

For fermentation-derived drug products, an expiration date should be established based on supportive stability data. Retest dates are not appropriate for fermentation-derived drug products.

3. Postapproval Stability Protocol and Commitment

For fermentation-derived intermediates, drug substances, and drug products, a postapproval stability protocol (on-going) and commitment should be provided. The sponsor should commit to place the first three full-scale production batches into the long-term stability program postapproval. In addition, a commitment to place a percentage of the total number of manufactured batches per year, with a minimum commitment to place at least one lot annually, should be provided.

4. Stability Data

Appropriate stability data for the support of a retest or expiration date at the proposed storage conditions should be provided. For the minimal filing requirements, consult CVM *73: Stability Testing Of New Veterinary Drug Substances And Medicinal Products,* VICH GL3(R).