#234

Guidance for Industry

Question-Based Review for the Chemistry, Manufacturing, and Controls Technical Section Of Animal Drug Applications

Draft Guidance

This guidance is being distributed for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Julie Bailey, Center for Veterinary Medicine (HFV-145), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, (240) 402-0700, e-mail: julie.bailey@fda.hhs.gov.

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff, Center for Veterinary Medicine (HFV-6), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at http://www.fda.gov/AnimalVeterinary/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
March 2016

TABLE OF CONTENTS

Guidance for Industry

Question-Based Review for the Chemistry, Manufacturing, and Controls Technical Section Of Animal Drug Applications

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Applicants must submit information on chemistry, manufacturing, and controls (CMC) to support the approval of new animal drug applications (NADAs) and abbreviated new animal drug applications (ANADAs) or the conditional approval of applications for conditional approval (CNADAs).[1] The Center for Veterinary Medicine (CVM) reviews the CMC information for new animal drugs to ensure that applicants have methods and controls in place for manufacturing, processing, and packaging that are adequate for assuring and preserving the identity, strength, quality, and purity of the new animal drug and, in the case of a generic drug, to ensure that it is equivalent to the reference listed new animal drug (RLNAD). In order to improve the process for submission and review of CMC information for animal drugs, CVM has developed a series of questions that focus on the critical scientific and regulatory issues and pharmaceutical attributes essential for ensuring the quality of new animal drug substances and products. Termed Question-based Review (QbR), these questions provide a general framework for original CMC submissions to investigational new animal drug (INAD) files, generic investigational new animal drug (JINAD) files, NADAs, ANADAs, CNADAs, and veterinary master files (VMFs).

QbR is organized according to the Common Technical Document - Quality (CTD-Q).[i] Applicants who elect to use the QbR format for their CMC submissions should provide summary information to address the QbR questions in the CTD-Q Module 2 Quality Overall Summary (QOS), with supporting documentation and data in Module 3. QbR includes a number of high-level questions (**bolded and boxed**) applicants should address when preparing the QOS. Under each high-level question, there may be one or more detailed questions (**bolded**) focusing on specific information that applicants should provide as part of the response to the high-level question. In addition, this guidance document provides CVM's current thinking (*italicized*) on how applicants may best address the QbR questions and addresses some questions commonly asked by applicants (underlined). The schematic below illustrates the QbR formatting.

[1] 21 U.S.C. 360b(c)(2)(A)(i), 360b(d)(1)(C), and 360ccc(c)(1); 21 CFR 514.1(b)(4) and (5).

High-level question
CVM's current thinking

Detailed question
CVM's current thinking

Questions commonly asked by the applicant
CVM's current thinking

This guidance is divided into three sections. Section II of this guidance contains the QbR questions that address Section 2.3.S of the CTD-Q, drug substance. Section III of this guidance contains the QbR questions that address section 2.3.P of the CTD-Q, drug product. Sections IV through VII of this guidance contain the QbR questions that address sterile processing information for sterile drug substances and drug products. If you are a drug substance manufacturer, you should provide a response to each of the high-level questions included in Section II as part of your QOS. If you are an applicant seeking approval of a drug product, you should provide a response to each of the high-level questions in both Section II and Section III as part of your QOS.[2] If your drug substance or drug product is sterile, you should also provide a response to each of the high-level questions in Sections IV through VII that apply to your chosen method of sterilization (e.g., aseptic processing, gamma irradiation). All applicants seeking approval of sterile drug products should answer the questions regarding microbiological methods and stability considerations in Section VII. An applicant may reference a master file to respond to some of the high-level questions related to drug substance manufacturing and sterile process validation. When a master file reference may be appropriate, it is noted under the question.

CVM's eSubmitter templates for CMC technical section submissions ((J)INAD P) and original VMF submissions (Type II and V) also utilize the QbR format. The questions in the eSubmitter templates are derived from the high-level and detailed questions in this guidance but may be modified to better accommodate the electronic submission process. The applicant can find information equivalent to that provided in the QbR "questions commonly asked by the applicant," as well as CVM's current thinking about how applicants may best address the QbR questions, in the helpful hint (lightbulb icon) for each question in the eSubmitter template.

When an applicant submits a QOS that fully addresses the QbR, this helps to assure product quality and may reduce the number of CMC review cycles by enhancing the quality of submissions and reviews through the use of a standardized set of critical questions. **CVM reserves the right to request information or material or define conditions not specifically described in the QbR questions and this guidance document, in order to adequately assess the safety, effectiveness, and quality of the product.**

[2] The term "drug product" here refers to a pharmaceutical dosage form or Type A medicated article.

In general, FDA's guidance documents 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. DRUG SUBSTANCE (2.3.S) QUESTIONS

2.3.S.1 General Information

The drug product applicant should provide information for all questions in this section in the drug product submission.

What are the nomenclature, molecular structure, molecular formula, CAS number, and molecular weight?

Properties include but are not limited to:
Chemical Name:
CAS #:
USAN:
Molecular Structure (including relative and absolute stereochemistry):
Molecular Formula:
Molecular Weight:

What are the physicochemical properties?

Properties include but are not limited to:
Physical Description (appearance, color, physical state):
pKa:
Polymorphism (polymorph, solvate, hydrate, etc.):
Solubility Characteristics (as function of pH):
Hygroscopicity:
Melting/Boiling Point:
Partition Coefficient:
Optical Rotation:

Should all of these properties be reported, even if they are not critical?

Report ALL physicochemical properties listed in the question even if they are not critical. If a property is not quantified, explain why, for example:

- *"No pKa because there are no ionizable groups in the chemical structure";*
- *"No melting point because compound degrades on heating"; or*
- *"No other polymorph observed during polymorphism screening."*

Reference to a Master File (MF) is acceptable for non-critical physicochemical proprieties, but critical physicochemical properties should be provided in the application or (J)INAD file. Physicochemical information such as polymorphic form, pKa, solubility, or other properties critical to the successful development of a robust formulation and manufacturing process should be reported.

Should solubility data be provided?

The drug product applicant should include this information if the solubility is crucial to the successful development of a robust formulation and manufacturing process. Aqueous solubility should be reported as a function of pH in tabular form. Provide actual values for the solubility as well as descriptive phrases (such as "slightly soluble") as defined in the current United States Pharmacopoeia (USP).

Should pH-solubility profiles be provided for all known polymorphic forms?

No; it is essential that the pH-solubility profile be provided for the form present in the drug product. The relative solubility (at one pH) should be provided for any other more-stable form(s).

The CDER/CBER GFI *M4: The CTD-Quality Questions and Answers/Location Issues*[ii] states that only the polymorphic form used in the drug product should be described in S.1 and other known polymorphic forms should be described in S.3. Where does CVM want this information?

This information may be included in either S.1 or in S.3. Wherever presented, list all polymorphic forms reported in literature and provide brief discussion (i.e., which one is the most stable form) and indicate which form is used for this product.

Other polymorph information should be presented by the drug product applicant as follows:

- *2.3.S.3 Characterization: Studies performed (if any) and methods used to identify the potential polymorphic forms of the drug substance (e.g., X-ray, DSC, and literature)*
- *2.3.S.4 Specification: Justification of whether a polymorph specification is needed and the proposed analytical method*
- *2.3.P.2.1.1 Pharmaceutical Development – Drug Substance: Studies conducted to evaluate if polymorphic form affects drug product properties*

Why does CVM need to know the physicochemical properties? Why does the drug product applicant need to report these properties?

Physical and chemical properties may affect the development, manufacture, or performance of the drug product.

2.3.S.2 Manufacture

The drug product applicant may reference an MF to address some questions in this section. See individual questions for details.

Who manufactures the drug substance?

Reference to an MF is acceptable with a Letter of Authorization and identification of the US Agent (if applicable). Alternatively, provide the name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing. Identify the US Agent (if applicable).

What is the current FDA inspection status?

Provide any known information regarding the Good Manufacturing Practices (GMP) status of the facility, including FDA Establishment Identifier (FEI) number, last inspection date, and outcome.

What is the starting material(s)? Provide justification.

Reference to an MF is acceptable.

How does CVM define "starting material"?

CVM considers a regulatory starting material to be a well characterized, commercially available material that is also used outside the pharmaceutical industry, and that contributes to the final drug substance's structure. For more details, see CVM GFI #169: Drug Substance Chemistry, Manufacturing, and Controls Information;[iii] *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients;*[iv] *and ICH Guideline Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities).*[v]

What are the manufacturing processes and controls and how do they ensure consistent production of the drug substance?

Reference to an MF is acceptable. Include the source of the material (i.e., synthetic or natural) when both sources are available. The MF holder's Certificate of Analysis (COA) for the batch(es) used to manufacture the drug product should be provided in the body of data 3.2.S.4.4.

Alternatively, a complete and detailed description of the manufacturing process and controls used to produce the drug substance should be provided. This includes a flow diagram, the batch size, specifications for raw materials, the controls performed at critical steps of the manufacturing process, tests and acceptance criteria for isolated and final intermediates, and a description and justification of allowable reprocessing.

What should be included in the flow diagram?

A flow diagram of the manufacturing process should include reagents, reaction conditions, and solvents as well as chemical structures of starting materials, intermediates, and the final drug substance.

Where should specifications for raw materials be reported?

The quality control testing of raw materials such as solvents, reagents, etc. should be included in Module 3.

Can a different manufacturing process/facility be used for the pilot batches?

Yes; a comparison of the manufacturing processes and equipment should be provided. Where there are significant differences, provide data to support the changes.

Is the drug substance manufactured from, processed with, or does it otherwise contain material of animal origin?

Provide a risk assessment of possible adventitious agent contamination for the material in question and identify any steps adopted to mitigate the risk. For example, cattle derived material may be subject to prion contamination, among other things. To mitigate this risk you could source non-specified risk materials. A description or documentation Bovine Spongiform Encephalopathy / Transmissible Spongiform Encephalopathy (BSE/TSE certification) identifying the tissue source of the material, age of the animal, country of origin, etc. could be provided to substantiate that the sourced material is not a specified risk material and does not pose a significant risk to the recipient of the finished product.

Are any additives used? Provide justification.

What are the filling procedures for the primary container-closure system?

2.3.S.3 Characterization

The drug product applicant may reference a master file to address some questions in this section. See individual questions for details.

How was the drug substance structure elucidated and characterized?

Reference to an MF is acceptable.

Alternatively, a list of studies performed (e.g., IR, UV, NMR, MS, elemental analysis) and brief summary of the interpretation of evidence of structure should be provided. Include a discussion of the stereochemistry of the drug substance, if applicable.

What information should be provided for chiral drug substance?

When the drug substance contains one or more chiral centers, the applicant should indicate whether it is a racemate or a specific enantiomer. When the drug substance is a specific enantiomer, then tests to identify and/or to quantify the enantiomer should be included. Discussion of chirality should include the potential for interconversion between enantiomers (e.g., racemization/epimerization).

If polymorphic forms are present, how were they characterized?

There are a number of methods that can be used to characterize polymorphs of a drug substance. Demonstration of a nonequivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction can also be used to support the existence of polymorphs. Other methods, including microscopy, thermal analysis (e.g., differential scanning calorimetry and thermal gravimetric analysis), and spectroscopy, are helpful to further characterize polymorphic forms.

What attempts were made to identify and characterize potential impurities?

Reference to an MF is acceptable. The application or file for the drug product should include a list of potential impurities and their origins.

Alternatively, list impurities (e.g., starting materials, by-products, intermediates, chiral impurities, degradation products) observed or considered to be potentially present in the drug substance. Identify impurities by name or by other appropriate descriptor (e.g., RRT/HPLC). The structure, if known, should be provided. List analytical procedure used to detect or search for the impurity or the potential impurity. The origin of the impurities should be provided (e.g., process impurity or degradant). Indicate whether a potential impurity was actually detected in the drug substance and provide the limit of detection (LOD) or limit of qualification (LOQ) for the analytical method. A detailed accounting of the impurities found in various batches should be provided in S.4.4. The information can be provided in a tabular format such as below:

Example

ID	***Chemical Name***	***Structure***	***Origin***	***Detected and LOQ/LOD***	***Analytical Method***
	[specified impurity]				

Is identification of potential impurities needed if there is a USP related substances method?

Yes. The USP monograph provides the minimum requirements for a drug substance. Impurities not included in the monograph may arise from different manufacturing processes and should be explored.

2.3.S.4 Control of Drug Substance

The drug product applicant may reference a master file to address some questions in this section. See individual questions for details.

What are the drug substance specifications?

The drug product manufacturer should include the results for the batch(es) of drug substance used to produce the drug product. The specifications should consider all of the critical drug substance attributes. Test results and acceptance criteria should be provided as numerical values with proper units where applicable.

How should this information be formatted?

This information can be submitted in tabular format as shown below:

Example

Tests	***Acceptance criteria***	***Analytical procedure***	***Test results (lot#)***
Appearance			
Identification A B			
Assay			
Specified impurities Impurity # 1 Impurity # 2 Impurity # 3 Impurity # n, etc. Any unspecified impurity Total impurities			
Residual solvents			
[additional specifications]			

When is a drug substance particle size specification necessary?

A specification should be included when the particle size is critical to either drug product performance or drug product manufacturing.

How do the specifications compare to the USP?

If the specifications do not conform to current USP, justify the differences. If there is no USP monograph, all specifications should be justified.

What type of justification is needed for the specifications for impurities?

ICH/International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) limits and justification can be used for impurities. All residual solvents should be identified and limits should be established.

Applicants should develop impurity limits based on the MF holder's synthetic process. Provide levels of impurities found in drug substance batches used in safety, clinical and comparative studies.

Are the analytical methods suitable for their intended uses and validated or qualified?

If using a method from an MF, you may provide an MF reference and a transfer study report.

Provide a summary of each method and its validation/qualification. The method summary can be in tabular or descriptive format and include the critical parameters for the method and system suitability criteria. The validation summary can be in tabular or descriptive format and include results and acceptance criteria (including justification if necessary) for each parameter. For each analytical procedure, provide a page number to the location of the validation information in Module 3. Validation is required if the USP method is modified. If a drug substance has a USP monograph and the USP method is not used, then the method utilized should be demonstrated to be equivalent to or better than the USP method.

The analytical test method(s) for assay and impurities used in the stability program should be shown to be stability indicating.

What analyses were performed on the batches?

Reference to a master file is acceptable.

Alternately, provide batch analyses in this section in tabular format. Information may include batch identity (i.e., batch number), batch size, manufacture date, manufacturing site, manufacturing process (if different from process described in S.2), and batch purpose (e.g., bioavailability, stability). For quantitative data, the use of qualitative terms such as "conforms" or "meets specification" is generally not acceptable.

2.3.S.5 Reference Standards

The drug product applicant should provide information for all questions in this section. Reference to a master file is acceptable if the reference standard is supplied by the drug substance manufacturer. The answer should also discuss reference standards for impurities, if used.

Is the reference standard a USP standard?

Is there a working standard?

What is the expiry/retest of the standards?

How are the reference standards certified/qualified?

If the reference standard is obtained from the USP/NF (United States Pharmacopeia/National Formulary), then identify as such. A reference standard that is not obtained from USP should be of the highest purity and fully characterized. Include a COA

in Module 3, along with details of the reference standard's preparation, qualification, and characterization. This should be summarized in Module 2. Generally, the characterization information should include:

- *A brief description of the manufacture of the reference standard, if the process differs from the routine manufacturing procedure of the drug substance. Any additional purification procedures used in the preparation of the reference standard should be described. The purity of the reference standard should be stated.*

- *Information to substantiate the proof of structure should be provided. This may be performed utilizing a variety of analytical techniques, including UV, FTIR, NMR, MS, elemental analysis, specific optical rotation, DSC, TGA, and X-ray crystallography, as well as applicable functional group analysis. Relevant data/results obtained with these techniques should be submitted. For biotechnological/biological product reference standards, structure characterization may include, but not limited to, a determination of amino acid sequence, amino acid composition, peptide map, and carbohydrate structure. Adequate description of the test procedures should be submitted. Detailed interpretation of the test data in support of the claimed structure should be provided.*

An expiry/retest period should be proposed and supporting information submitted.

If a secondary (in-house) standard is used in addition to the primary reference standard that was characterized as described above, this secondary standard should be qualified against the primary reference standard.

2.3.S.6 Container Closure System

The drug product applicant may reference a master file to address all questions in this section.

What container closure system is used for packaging and storage of the drug substance?

The primary and secondary containers need to be clearly identified, as do their materials of construction and manufacturer/supplier. Reference master files as appropriate.

Does the primary container meet applicable CFR and/or USP requirements?

The primary packaging material should meet 21 CFR Parts 172– 186 as applicable. Documentation should be provided from the supplier of the packaging materials certifying this conformance. For other information related to packaging materials, reference to a Type III Drug Master File (DMF) or VMF is acceptable, with a Letter of Authorization from the DMF or VMF holder.

What information is included on the label?

The label should clearly indicate the storage conditions (with a numeric temperature range supported by long-term stability data), lot number, expiry/retest date, manufacturer's name, site of manufacture, and statements required by 21 CFR § 201.122. Labels or copies of the label should be provided in Module 3.

2.3.S.7 Stability

The drug product applicant may reference a master file to address all questions in this section.

What stability studies support the retest or expiry period and the storage conditions?

Information should include a summary of the stability data in tabular format (e.g., ranges of results), the conclusions reached regarding stability, and the retest or expiry period.

What are the conditions and tests for the stability program?

What is the proposed commercial packaging and how does it compare with the packaging chosen for the stability program?

What is the justification for the stability tests and specifications chosen?

If there are any differences between release and stability specifications, provide justification.

What are the stability protocol and post-approval stability commitment?

The stability protocol should describe the test specifications (methods, acceptance criteria, etc.), testing intervals, storage conditions, retest or expiry period, and packaging.

The post-approval stability commitment should include:

- *The first three production lots followed by 3-10% of the production lots (with a minimum of one lot per year);*
- *A commitment to report the stability data annually; and*
- *A commitment to withdraw from the market any production lot(s) found with out-of-specification results and investigate those lots immediately before and after the lot(s) in question.*

For more details, see CVM GFI #5: Drug Stability Guidelines.[vi]

III. DRUG PRODUCT (2.3.P) QUESTIONS

2.3.P.1 Description and Composition

What is the dosage form (provide description)? What are the components and composition of the final product? What is the function of each excipient?

What is the physical description of the drug product? What are the available strengths, route of administration, release mechanism, as well as any other distinguishable characteristics?

An example of an appropriate response would be - "The proposed drug product is available as an oval, round, immediate-release, aqueous film coated tablet in three strengths (5 mg, 10 mg, and 20 mg)."

What is the function of each component in the drug product?

List in tabular format (see example table below). Include all components used in the manufacture of the drug product (such as solvents and processing aids) even if removed during processing. Indicate which components are compendial. For each strength, list the quantitative composition of the finished dosage form. Excipient grade should be discussed in 2.3.P.4 (Control of Excipients). The total amount of material in pilot and production batches goes in 2.3.P.3 (Manufacture).

Example

Ingredient	***Function***	***Weight/Tablet***	***% (w/w)***
[Drug substance]	Active		
[Excipient]			
[Solvent]	Solvent*	N/A	N/A
Total weight			

*Removed during the manufacturing process.

Does this product contain multiple processing steps?

For example: tablet cores or beads

What is the composition of the significant intermediates?

Are there any overages in the formulation of the product? What is the justification for the overages?

Identify and justify any formulation overages that appear in the final product. Manufacturing overages should be discussed in 2.3.P.3.

For animal generic drug products, note that, in general, the only acceptable justification for an overage in the final drug product formulation is the demonstration of a similar overage in the reference listed drug (RLD).

Does this product contain any materials with sizes in the nanometer ranges (<1 µm)?

For generic products, do the differences between this formulation and the reference listed new animal drug (RLNAD) present potential concerns with respect to therapeutic equivalence?

Describe any efforts taken to ensure the therapeutic equivalence to the RLD. If known, provide the formulation of the RLD.

2.3.P.2 Pharmaceutical Development

While the inclusion of a Pharmaceutical Development Report (PDR) is optional, a PDR provides a brief summary of the final drug product development. CVM considers the information in the PDR, such as a description of the research that led to the evolution and selection of components, formulation, specifications, etc. of the final product, very helpful in demonstrating process understanding. This may include information about alternative formulations that were tried and deemed not to be optimal. Important aspects of a useful PDR are described below. It is important to note that a PDR is most informative to CVM in describing why a component or a process was chosen.

The studies included in a PDR are distinct from the routine control tests conducted according to specifications, such as release or stability testing. Summary results from studies or references to relevant literature should be included in the PDR or as an attachment to the PDR.

2.3.P.2.1 Components of the Product

Applicants should explain the rationale behind the selection of the components of the drug product—the drug substance and the excipients used.

2.3.P.2.1.1 Drug Substance

Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

What are the key physicochemical characteristics of the drug substance selected, in particular those that can influence the performance or manufacture of the final drug product?

Physicochemical properties that may be of interest and concern include water content, solubility, particle size distribution, pH, pKa, or the existence of polymorphic forms. If the drug substance has been structurally modified from the active moiety, such as made into a salt, the applicant should discuss whether the modification will impact the manufacture and/or the quality of the drug product.

Are any of the key physicochemical properties determined to potentially influence the performance of the drug product? What studies were conducted to establish and to justify the drug substance specification?

What drug substance(s) (including grade) was selected?

Is there more than one drug substance in your product? What evidence supports the compatibility of the drug substances with each other?

If there is any incompatibility identified, justify the use of the drug substance with summary data, such as stability data or studies examining the impurities that arise from the interaction of the drug substance and the additional drug substance.

2.3.P.2.1.2 Excipients

What evidence supports compatibility between the excipients and the drug substance?

What compatibility screening was performed during the pre-formulation stage?

Discuss the issue of compatibility of the drug substance with the excipients in the drug product. The compatibility study should include a simulation of the most extreme conditions that the drug substance and excipients will be subjected to during the actual manufacturing process. The design and results of the screening should be provided and discussed.

Were any excipients found to be incompatible with the drug substance or with each other? Which excipients were found to be incompatible, and how was their selection justified?

Any excipients which were found to be incompatible with the drug substance should be identified. The selection of the excipients used in the final formulation should be justified using the results of the compatibility screening.

For generic products, were any attempts made to determine what excipients were used in the pioneer product?

If the excipients in the pioneer product being copied are not defined, describe attempts made to determine what they were. If identification was confirmed, and a decision was made to intentionally use different excipients, provide justification for using the ones ultimately chosen for use in the final formulation. If identification was not attempted or was not possible, provide rationale for the excipients chosen.

2.3.P.2.2 Drug Product

What attributes should the drug product possess?

Are there critical attributes that ensure product quality for the intended use and route of administration? Describe the critical attributes.

This section should identify and describe the formulation and process attributes (critical parameters) that may influence batch reproducibility, product performance and drug product quality.

Is the drug product an immediate release or controlled release? Describe the release mechanism.

The specific release mechanism should be described and the development studies leading to the final release mechanism should be summarized. The type of information may vary substantially since the development of release mechanisms will vary between different formulations, such as coated tablets versus in-situ forming gels.

How was the drug product designed to have these attributes?

For release profiles, how does the product achieve the desired profile?

For example, does it use an enteric coating or slow release matrix.

Are any overages used in the drug product? Why is an overage necessary?

The applicant should describe and justify the amount of the overage if needed to ensure dose delivery. This overage should also be included in the composition and batch formula.

Are there any special design features of the product?

A rationale should be given for these design features to support their appropriateness.

Were alternative formulations or mechanisms investigated?

What formulations were used to produce the clinical batches for safety and effectiveness studies?

Are there differences in formulation between the clinical or pilot batches and that proposed for commercial batches? Describe the different formulations.

Applicants should provide the complete list of formulations in the evolution of the final formulation. The rationale or justification should be given for differences in formulations between the commercial and clinical or stability batches. This information may include comparative in vitro *or* in vivo *studies to link the clinical formulation(s) with the proposed commercial formulation.*

How were the excipients and their grades selected?

What excipients were chosen for use in the final formulation and what are their roles in the drug product (e.g., anti-dusting agent, binding agent)?

The applicant should briefly explain and/or justify the selection of each excipient for its particular role in the drug product and provide evidence that the excipients can fulfill their intended role. Reference to 2.3.P.2.1.2, when applicable, is acceptable.

Are there multiple grades of an excipient available? What are the different grades and the properties that distinguish one grade from another (e.g., viscosity, particle size distribution)?

The applicant should provide justification for the use of one grade over another. If a USP monograph exists for the excipient, it can be used as a reference. If there is no USP monograph, the applicant should provide and justify specifications which ensure the quality of the excipient(s).

Does the excipient exert a critical function related to the product performance? What studies were executed to evaluate the appropriateness of multiple grades of that excipient for use with the drug substance and any other excipients?

The applicant should provide the results of any such studies. Reference to 2.3.P.2.1.2 is acceptable.

How was the final formulation optimized?

What studies were conducted that led to the final formulation?

Which formulations revealed the most useful information?

Indicate what the sponsor learned about what components are critical or non-critical to product performance.

Why was the formulation selected over other possible variations using the same components?

2.3.P.2.3 Manufacturing Process Development

Why was the manufacturing process described in 2.3.P.3 selected for this drug product?

The sponsor should first describe the choice of a manufacturing process at a high level. For example, for a solid oral dosage form the sponsor should explain the choice between direct compression versus wet granulation or other approaches.

What factors were considered in the selection of the manufacturing process - including the properties of the drug substance, the desired properties of the drug product, and the complexity and robustness of the process?

Once the process was selected, a sponsor should focus on describing particular steps for which there are alternatives available (for example rationale for the selection of high shear granulation versus fluid bed granulation) and explain the motivation for each choice.

How are the manufacturing steps (unit operations) related to the drug product quality?

What are the critical steps in the manufacturing process?

What studies established links between unit operations and the target product profile (through pilot scale studies or prior knowledge)?

A sponsor should demonstrate which unit operations are critical to which drug product properties. It may be useful to present this information in the form of a matrix between unit operations and quality attributes. Once a step is identified as being critical then the sponsor should design their process to ensure that this step succeeds or have tests in place to detect if the step fails.

How were the critical process parameters identified, monitored, and/or controlled?

A critical process parameter (CPP) is any measurable input (input material attribute or operating parameter) or output (process condition or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency. Scale independent CPPs, such as material attributes, are the most valuable, because they can be directly used for scale up. For example, a material attribute CPP, such as moisture content, should have the same target value in the pilot batch process and the commercial scale process. An operating parameter CPP, such as air flow rate, would be expected to change as the process scale changes.

What is the scale-up experience with the unit operations in this process?

Valuable experience includes experience with other products using the same unit operations, literature references/vendor scale-up factors, the lab scale to pilot batch process transfer for this product, pilot batch production, as well as modeling and dimensional analysis.

What resulting plan was developed to scale-up the process to commercial scale and how was this scale-up plan developed?

This should include identification of operating parameters that may be scale dependent and process monitoring (in excess of meeting regulatory specifications) that ensures the commercial scale process will be equivalent to the process that produced the pilot batch.

2.3.P.2.4 Container Closure System

What specific container closure attributes are necessary to ensure product performance?

How were materials for the container-closure system chosen (e.g., to provide light protection or minimize leachability)?

Standards for the selection and testing of glass and plastic containers to demonstrate their acceptability for use are provided in USP <660>[vii] and <661>,[viii] respectively.

What studies to determine the compatibility of materials with the drug product were performed?

For drug products that incorporate delivery devices (e.g., inhalation devices, spray pumps), pharmaceutical development studies conducted to select the device should be discussed in this section.

2.3.P.3 Manufacture

See CVM GFI #42: Animal Drug Manufacturing Guidelines[ix] for information intended to provide guidance for the submission of appropriate manufacturing data and information to support the approval of an original (A)NADA.

Who manufactures the drug product?

What are the names, addresses, and responsibilities of each manufacturer and each proposed production site or facility?

All manufacturers and contractors, such as contract sterilization, and all facilities involved in the manufacturing, testing, packaging, storage, and labeling should be identified. Building numbers or other specific identifying information should be provided for multi-facility campuses.

Is there a U.S. Agent for any of the manufacturers identified? If so, what is the contact information for each U.S. Agent?

US Agents for all foreign facilities should be identified.

Does any proposed production site or facility process sterile drug substances, drug products, or packaging components? If so, where are the sterile processing area(s)?

The sterile processing area may be described by room number, filling line, or other appropriate identifiers. Reference to a Type V VMF is acceptable with a Letter of Authorization (LOA) and identification of a US Agent (if applicable).

How do the manufacturing processes and controls ensure consistent production of drug product?

What manufacturing processes and controls are used for production of the finished drug product?

This may include flow chart(s), detailed description of the process, critical manufacturing processes and controls, specifications for raw materials, and acceptance criteria for in-process tests.

Is a flow chart(s) of the manufacturing process provided?

A flow chart gives the steps of the process and shows where materials enter the process. The entire manufacturing process from the weighing of components through finished product release is generally pictured. The flow chart often includes the following:

a. Description of each manufacturing step
b. Identification of the material being processed
c. Identification of the critical process controls and point at which they are tested
d. Identification of the type of equipment used

The manufacturing process description represents the sequence of steps undertaken to produce a finished drug product. This description provides more detail than that provided in the flow chart and generally includes the following elements:

a. The complete manufacturing process for each drug product (e.g., strength, packaging configuration), including the scale of production
b. Identification of equipment by type (e.g., tumble blender, in line homogenizer) and working capacity where relevant. This is most relevant for tableting and sterile operations.
c. A detailed description of any novel processes or technologies and packaging operations that directly affect product quality
d. Identification of all process controls, including the critical process controls and the associated numeric ranges, limits, or acceptance criteria

Does the batch formula accurately reflect the drug product composition? If not, what are the differences and the justifications?

Is a batch formula provided for the drug product composition? What are the amounts of all the components, including overages, used in the manufacturing process?

Any explanatory notes (e.g., actual amount added based on purity) should be described for the batch formula. All ingredients should be included in the batch formula whether or not they remain in the finished product (e.g., processing agents such as water, ethanol, and nitrogen or other gases).

The batch formula included in the batch record should be the same as the batch formula included in the product composition section. Batch record information is provided in Module 3 under section 3.2.R.P.1 or 3.3.P.3.3. The batch record may include the following information:

a. *Batch identity (i.e., lot number), strength, and size*
b. *Use of batch (e.g., bioavailability, stability)*
c. *Date of manufacture*
d. *Site of manufacture*
e. *Batch number and manufacturer of the drug substance used in the drug product*
f. *Batch number and manufacturer of novel excipients or any excipients that are critical to product performance (e.g., excipients used to form liposomes)*
g. *The steps of the manufacturing process, including identification of the equipment, manufacturing time (start and end of operating), material handling*
h. *Identification of each in-process control, including the sampling technique, test specifications, and test results, as appropriate (The results of the testing should be expressed numerically or qualitatively, e.g., clear, colorless solution. Use of terms such as conforms or meets specification is discouraged)*
i. *Container closure system*
j. *Weight/Volume Checks – there are often two people initialing each step.*
k. *Yields (theoretical/actual yield, calculation)*
l. *Packaging and Labeling (packaging and labeling precautions to assure correct labeling, packaging)*
m. *Specifications for the release of the finished drug product*

What are the quality standards for each component used in the manufacturing process?

What are the in-process controls that ensure each step is successful?

"In-process controls" are tests and controls used during production to monitor and, if appropriate, adjust process parameters and/or to ensure an in-process material meets established acceptance criteria. Examples of process parameters and attributes that may be monitored are:

a. *Operating parameters -- parameters that can be adjusted to control the manufacturing process (e.g., temperature, pH, time, mixing speed)*
b. *Environmental conditions -- conditions associated with the manufacturing facility (e.g., temperature, humidity, clean room classification)*
c. *Quality attributes of in-process materials*

What in-process specifications were established?

Specifications should include the tests and acceptance criteria used to monitor and assess the performance of the process and the quality attributes of in-process materials.

Which in-process controls are used to monitor critical process parameters?

A critical process parameter is one whose variability impacts a quality attribute of the drug product, and therefore needs to be controlled to ensure that the process produces the desired quality.

Depending on the drug product and manufacturing process, a particular process parameter may or may not be critical as illustrated in the following examples:

- *Mixing speed range can be critical for forming an emulsion, but may not be critical for mixing a chemical solution.*
- *The humidity in the manufacturing facility can be critical for an effervescent tablet but may not be critical for an ointment.*
- *The clean room classification, while critical for a sterile product, may not be critical for a non-sterile product.*
- *The time frames for certain unit operations or overall drug product production can be critical for some products (e.g., blending time, hold times during sterile processing)*

Tests and acceptance criteria (with justifications for acceptance limits) performed at the critical steps of the manufacturing process should be provided to ensure that the process is controlled.

What is the reconciliation of the batch?

Reconciliation is a comparison of the actual yield to the theoretical yield of a batch. The reconciliation includes an account of materials (e.g., labels), a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

What is the difference in size between commercial scale and pilot batches and does the equipment use the same design and operating principles?

The equipment used for each scale should be briefly described and any differences in operating principles should be indicated.

Were developmental studies used to justify limits or identify critical parameters prior to execution of the pilot batch? What differences between equipment used in developmental studies and pilot batches are relevant to quality attributes of the material generated?

An illustrative example is included in the following table below:

Example

Unit Operation	***Equipment***	***Development Studies*** *[kg/batch] [units/batch]*	***(A)NADA Batch*** *[kg/batch] [units/batch]*	***Commercial Batch*** *[kg/batch] [units/batch]*	***Rationale for Change***
[Process step]	*[Equipment class]*	*[brand and size]*	*[brand and size]*	*[brand and size]*	
[Process step]	*[Equipment class]*	*[brand and size]*	*[brand and size]*	*[brand and size]*	

What is the rationale for differences in equipment, critical or quality related steps and controls?

For some changes, the rationale may be as simple as "due to larger batch size a larger bin blender was required," whereas, more complex changes (e.g., change in operating parameters) should be supported by data (reference to the Pharmaceutical Development Report is acceptable).

What evidence supports the plan to scale up the process to commercial scale? What operating parameters will be adjusted to ensure the product meets all in-process and final product specifications?

The plan to scale up the process to commercial scale may be supported by understanding of formulation, manufacturing process, and equipment or by information generated during the drug development phase.

Do you have prior experience with other products using the same unit operations, literature references/scale-up factors, or modeling and dimensional analysis to support scale up? Describe your prior experience.

If this or similar information is available, it may provide valuable information to support your process knowledge.

Are the process description and the in-process and release specifications fixed or likely to change prior to scale-up? How will scale-up affect these steps or specifications?

The sponsor has the flexibility to adjust the operating parameters (e.g., time, flow rate, temperature) to meet these constraints during scale-up. For commercial scale-up, a sponsor may either propose fixed ranges for these operating parameters in a proposed master batch record or indicate that an operating parameter will be adjusted to reach a desired end-point. An illustrative example is included in the following table below:

Example

Operating Parameter	***Pivotal Batch***	***Proposed Commercial Scale***	***Rationale***
Unit Operation #1			
Parameter 1	*Value or range*	*Value or range*	*Adjust to meet end-point*
Parameter 2	*Value or range*	*Value or range*	*Scale-independent variable*
Parameter 3	*Value or range*	*Value or range*	*Linear scale-up rule established in PD*
Unit Operation #2			
Parameter 1	*Value or range*	*Value or range*	

What additional rationale supports scale-up?

All rationale should be provided and should focus on critical steps in the manufacturing process. This rationale should build on the experience (including problems that were identified and resolved) obtained during development and/or the production of the pilot batch(es).

2.3.P.4 Control of Excipients

What are the specifications for the excipient ingredients and are they suitable for their intended function?

Provide COAs from supplier/vendor, and your qualification of results, for all excipients in Module 3.

USP Excipients
Are USP/NF excipients being utilized?

What are the USP/NF excipients utilized and their specifications?

Are there any differences between the provided specifications and USP/NF specifications?

What are the differences and justification for these differences?

What format should be used for presenting the excipient specifications?

For USP excipients a table indicating the grade is requested. Justify any differences from USP/NF tests.

Example

Ingredient	***Manufacturer***	***Grade***	***Lot Numbers****		***Complies with USP/NF***
			Supplier	*Applicant*	
[Excipient]					

*Lot numbers used in the production of the pilot batch.

Are there any excipients with additional specifications that are in excess of those included in the USP/NF?

What are these excipients and their specifications?

What is the justification for the additional specifications?

What format should the sponsor use for presenting specifications in excess of USP/NF specifications?

In this event, a sponsor should include a table for each excipient that has additional specifications. These additional specifications should be justified. Reference to 2.3.P.2.2 (Pharmaceutical Development Report) is acceptable.

Example

Tests	***Acceptance Criteria***	***Analytical Procedure***	***Batch Number***
[Extra Test]			*[Results from excipient batch]*

Non-USP Excipients
Are non-USP/NF excipients being utilized?

What are the non-USP/NF excipients utilized and their specifications?

What is the justification for the specifications utilized for non-USP/NF excipients?

What information is requested for non-USP excipients?

The specifications for the non-USP excipient should be included in the QOS in a tabular form. Provide justification for specifications (may be provided in Pharmaceutical Development Report). The grade used should also be indicated.

Excipients from Animal Origin
Are there excipients from animal origin?

What excipients are from animal origin and what information will allow CVM to assess the suitability of the supplier as it relates to TSE and other adventitious agents?

Reference the location of BSE/TSE certification, country of origin shall be provided, as applicable.

Novel Excipients

Are any novel excipients being utilized?

Novel excipients are those that have not been previously used in veterinary drug products. Novel excipients are generally not used in an ANADA product as safety and effectiveness information is not available.

What novel excipients are being utilized and what additional details are available to support their use?

These excipients may require additional details including manufacture, characterization, controls, or a DMF/VMF reference.

What information supports the suitability of the excipients for their intended functions?

How do I show that an excipient is suitable for its intended function?

The known functions of common excipients are sufficient to determine suitability. For example, magnesium stearate is used as a lubricant in the manufacture of immediate-release tablets. For novel excipients or novel uses of common excipients, describe studies that identified the critical attributes of that excipient (reference can be made to the pharmaceutical development report).

What is your vendor qualification program?

A description of your vendor qualification program should be provided. Initial qualification should include analysis of the first three lots received from a vendor to confirm their COA results, and the manufacturer should perform re-qualification testing for these excipients at least once per year.

Who manufactures the excipients?

Provide the name and address of each excipient manufacturer. Identify the U.S. Agent (if applicable).

2.3.P.5 Control of Drug Product

What is the drug product specification and does it include all the critical drug product attributes?

The drug product manufacturer should include the full release specifications. Acceptance criteria should be provided as numerical values with proper units where applicable. Dosage form specific tests should be included as appropriate (e.g., dissolution, uniformity of dosage units, water content, microbial limits, etc.) and their inclusion justified.

See CVM GFI #176/VICH GL39: Specifications: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances.[x] *It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new medicinal products.*

Does the drug product conform to a USP monograph?

How do the specifications compare to the USP? If the specifications do not conform to current USP, justify the differences.

If the drug product has a USP monograph, is there a difference between the USP monograph and the limits proposed?

What is the justification?

Are the analytical methods suitable for their intended uses and validated or qualified? What is the justification of the validation acceptance criteria?

Provide a summary of each method and its validation/qualification.

The method summary should include the critical operational parameters. The validation summary should include results and acceptance criteria for each parameter. For each analytical procedure, provide a page number to the location of the validation information in Module 3. Validation is required if the USP method is modified or if there is no USP method (see CVM GFI #64: Validation of Analytical Procedures: Methodology[xi]*). If a USP method exists and is not used, then the proposed method should be demonstrated to be equivalent to or better than the USP method.*

For each analytical test method for assay used in the stability program, what information demonstrates it is a stability indicating method?

Are impurities quantified using impurity reference standards? What are the relative response factors for impurities?

What is the batch control numbering system for the finished product?

Is the batch analysis data included?

What are the batch analysis results for all pilot and clinical batches, including those used for stability studies?

Batch analyses should at least include release testing results. The batch analysis reports and collated batch analyses data should also include the following information:

- *Batch identity (i.e., batch number), strength, and size*
- *Date of manufacture*
- *Site of manufacture*

- *Manufacturing process, where applicable*
- *Container closure system*
- *Use of batch*
- *Batch number and manufacturer of the drug substance used in the drug product*
- *Batch number and manufacturer of novel excipients or any excipients that are critical to product performance*

Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Quantitative results should not be reported in general terms such as "complies," "conforms," or "meets limit." Results below the LOD or LOQ for validated methods should not be reported as "0," but rather as less than the value of the LOD or LOQ.

What are the impurities of the drug product?

What are the potential drug product impurities?

Information on the drug product impurities (see CVM GFI #93/VICH GL11(R): Impurities in New Veterinary Medicinal Products (Revised)[xii]) should be provided. All potential drug product impurities should be listed in this section of the application whether or not the impurities are included in the drug product specification.

Which potential impurities are included in the drug product specification?

Provide justification for any potential impurities not included in the drug product specification.

What characterization studies (i.e., structural characterization) were performed for the impurities?

2.3.P.6 Reference Standards and Materials

Provide information about reference standards used to test the finished product and raw materials. Information for the drug substance can be referenced back to section 2.3.S.5.

Is the reference standard a USP standard?

Is there a working standard?

How are the reference standards certified/qualified?

If the reference standard is obtained from the USP/NF, then identify as such.

A reference standard that is not obtained from USP should be of the highest purity and fully characterized. Include a COA as a supporting document in Module 3, along with details of the reference standard's preparation, qualification, and characterization. This information should be summarized in Module 2. Generally, the characterization information should include:

- *A brief description of the manufacture of the reference standard, if the process differs from the routine manufacturing procedure of the drug substance. Any additional purification procedures used in the preparation of the reference standard should be described. The purity of the reference standard should be stated.*
- *Information to substantiate the proof of structure should be provided. This may be performed utilizing a variety of analytical techniques, including UV, FTIR, NMR, MS, elemental analysis, specific optical rotation, DSC, TGA, and X-ray crystallography, as well as applicable functional group analysis. Relevant data/results obtained with these techniques should be submitted. For biotechnological/biological product reference standards, structure characterization may include, but is not limited to, a determination of amino acid sequence, amino acid composition, peptide map, and carbohydrate structure. Adequate description of the test procedures should be submitted. Detailed interpretation of the test data in support of the claimed structure should be provided.*
- *An expiry/retest period should be proposed and supporting data submitted.*

If a secondary (working) standard is used in addition to the primary reference standard that was characterized as described above, this secondary standard should be qualified against the primary reference standard.

The answer should also discuss reference standards for impurities, if used.

2.3.P.7 Container Closure System

What container closure system(s) is proposed for packaging and storage of the drug product?

How should the information for the container closure system be presented?

In tabular form, provide a summary of the container closure systems used. Include the different packaging configurations, size of container closure for each configuration, units per packaging configuration, and the manufacturer/supplier and DMF or VMF numbers. If a DMF or VMF is referenced, a letter of authorization to reference the file should be provided.

Example

Type *[Component]*	***Description (Packaging Configuration)*** *[Description] (Packaging that uses this)*	***Supplier***	***DMF or VMF***
Bottle	60 mL white square HDPE (60,100 tablets)		

Has the container closure system been qualified for use with this drug product?

Do the packaging materials meet FDA and USP requirements?

What testing or certification supports the safety of the packaging with the drug product?

Examples include those tests described in the USP (e.g., USP<661>[xiii]). Reference to the supplier's DMF or VMF may be appropriate.

Provide any other testing or certification such as 21 CFR references (Federal Regulations under 21 CFR sections 174-186 provide a list of materials that are safe for use in direct or indirect food contact).

A statement may be provided referencing products that have been approved using the same packaging system. However, a copy of the test results that qualify the container closure system as safe should be provided in the referenced body of data.

Are copies of the label provided?

If the label is not final, provide the language used in the draft label to indicate CMC relevant information, such as storage conditions (e.g., numeric temperature range), active ingredients, how supplied, space for expiration date and lot number, and any special instructions (e.g., "The stopper may only be punctured 35 times.").

2.3.P.8 Stability

What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?

The description of stability specifications should include the test methods, acceptance criteria, etc. If there are any differences between release and stability specifications, provide justification.

What stability studies support the proposed shelf life and storage conditions?

Information should include a summary of the stability data in tabular format (e.g., ranges of results), the conclusions reached regarding stability, and the expiry period. Include results of accelerated stability studies, if the accelerated data is needed to support proposed expiry or label stated storage conditions.

What are the post-approval stability protocol and commitment?

What are the post-approval stability specifications (methods, acceptance criteria, etc.)?

What are the stability storage conditions and testing intervals?

What packaging is used for stability samples?

What is the proposed post-approval stability commitment?

The post-approval stability commitment should include:

- *A commitment to place the first three production lots followed by 3-10 % of the production lots on stability (with a minimum of one lot per year);*
- *A commitment to report the stability data to CVM in a Minor Changes and Stability Report annually; and*
- *A commitment to withdraw from the market any production lot(s) found with out-of-specification results and to investigate those lots immediately before and after the lot(s) in question.*

For more details, see CVM GFI #5: Drug Stability Guidelines.[xiv]

IV. STERILE PROCESS VALIDATION QUESTIONS: ASEPTIC PROCESSING

Buildings and Facilities

Is this information for your sterilization process referenced in a Type V master file?

Provide letter of authorizations to master files, if necessary.

What are the critical areas and supporting clean areas used in the manufacturing operations of the product?

Provide floor plans for these critical areas and supporting clean areas, including aseptic processing area, air class designations, material/component flow, and personnel movement.

Process

What are the unit operations in the aseptic process?

For example: lyophilization, filtration

What filling line was used for production?

Identify the filling line(s) that will be used during production by line number and / or room number.

What types of sterile equipment were used during production?

For example: tanks, filter housings, barriers, isolaters, etc. The process simulation should incorporate the equipment listed here.

What are the normal sterile production parameters for this product?

These should include all vial sizes used, volume filled into each unit, the number of units filled per production run, line speed, and the duration of fill times. Proposed hold times should also be included. Validation of these parameters is addressed in the section that describes process simulations.

How are aseptic connections made during production?

Describe the environmental monitoring that occurs while the aseptic connections are being made. The SOP describing how aseptic connections are made should be referenced in the batch record.

Is the product directly filled into vials or filtered into a surge tank?

If a surge tank is used, identify the size, its location and how it is sterilized.

If you intend to use campaigns in normal production of this product, what is the proposed duration of those campaigns?

CVM considers campaigns to be the number of batches produced without cleaning in between.

Is lyophilization of the finished drug product or sterile API proposed?

If so, provide a description or schematic of the lyophilizer, load diagram(s), and a floor plan showing flow of product from the filling area to the lyophilizer.

Provide a narrative explaining the transportation of containers from the filling area to the lyophilizer and procedures taken to protect the containers from contamination.

Specify the lyophilization steps and cycle parameters including but not limited to the loading of the trays, preparation phase, e.g., pre-lyophilization shelf temperature, and the primary and secondary phases. Provide the duration, temperature and chamber pressure of each phase.

Document the procedures used for sterilizing the chamber and provide the supporting validation data (biological data, cycle data, where applicable). See the Steam in Place section of the Sterilization of Equipment section for information that should be included in this section.

Are thermocouples used to monitor the temperature in the lyophilization chamber during routine production?

Filtration

How is the product filtered?

Describe the filtration process. Information provided here should include whether the production filters are sterilizing or clarifying, the number of filters used, the pore size of the filters, the filter manufacturer, and the composition of the filters used.

How is filter integrity examined during production?

Describe the method used to measure filter integrity. Specify whether integrity testing was performed before and after product filtration.

How do the filters used during filter validation compare to the filters used during production?

Information provided here should include the composition of the filters used.

What parameters were used during filter validation?

Were "worst case" parameters used in the validation? Describe the parameters used. For example: how many times the filter was autoclaved, product exposure time, temperature, pressure.

What method was used to determine filter compatibility during filter validation?

Provide a summary of the results of these tests. Describe the studies performed and parameters used to determine compatibility.

What method was used to determine filter extractables during filter validation?

Provide a summary of the results of these tests. If applicable, justification for the presence of these extractable materials should be provided.

What method was used to determine drug adsorption to the filter during filter validation?

Provide a summary of the results of these tests. If applicable, describe the steps performed to eliminate this adsorption.

What method was used to determine bacterial retention during filter validation?

This information should include whether the tests were performed in one or two parts, the organism used, and if simulated or actual product was used as the challenge solution. If a simulated product was used, provide a description of the simulated product. Also, the time the product was recirculated through the filter and the pressure used should be included.

Describe the method used to determine filter integrity during filter validation. State whether testing was done before and after the bacterial challenge or only after the challenge.

Provide a summary of the results of these tests.

Process Simulations (also known as media fills)

What are the parameters evaluated during the process simulations to ensure the efficacy and consistency of the process?

Describe the simulated product formulation and characteristics. If not media, provide a justification for the use of a simulated product.

What filling line was used for the process simulation?

This should be the same filling line used during production.

What types of sterile equipment were used during the process simulation?

This should be the same equipment used during production. If there are similar equipment types, these should be rotated during process simulation re-qualifications so that they are periodically used during a process simulation.

What is the number of units filled versus the number of units incubated?

How many process simulations were performed and when were they conducted?

Provide a justification for the number of process simulations performed if less than three.

What incubation conditions are used for units from the process simulation?

How does the process simulation simulate the production parameters?

Specify line speed, fill volume, number of containers filled, duration of fill, etc. Specify any down time during duration of fill. If a campaign is used, specify whether the process simulation simulates the duration of the campaign or is performed at the end of a production campaign to simulate worst-case conditions.

What are the hold times validated by the process simulation?

These should be the same as those proposed for use during production.

Is a matrix or bracketing approach proposed?

Provide the justification for the proposed approach.

What method is used to perform growth promotion testing?

The acceptable organisms are described in USP <71> "Sterility Tests."[xv] *If you are performing growth promotion concurrently with the process simulation incubation, describe how you are confirming the identity of the positive controls and how you are ensuring that the growth is not from an organism introduced during the process simulation process.*

Were there any positive units during the process simulation?

Provide the acceptance criteria for process simulations and actions that will be taken in the event of one or more positive units.

What is the requalification schedule for process simulations in the filling room?

Is any reprocessing of components or product proposed?

Additional questions addressing this topic are found in the section that describes stability considerations.

Is lyophilization of the finished drug product or sterile API proposed?

If so, include a comparison of the lyophilization process and how it is simulated during the process simulation.

If a bracketing approach is proposed, provide a description of and justification for the proposed approach.

Describe how the containers were exposed to the vacuum (e.g., whether unsealed and frozen or unfrozen containers were used, partial vacuum was pulled, and whether an aerobic environment was maintained, etc.)

Steam-In-Place

Is steam-in-place used for sterilization of equipment?

What are the characteristics of the process that demonstrate the thermal qualification of the cycle? How were the critical process parameters selected, validated, and monitored?

What cycle parameters were used for validation and production runs? For example: cycle time and temperature setpoint(s)

What equipment is sterilized?

What are the acceptance criteria for the qualification of the cycle? How were these developed?

For example: F_0

How were locations of thermocouples selected?

Describe how the cold spots were determined. Provide a rationale for the locations of the thermocouples.

What were the results of the heat penetration studies?

What is the requalification schedule?

Component Preparation

Are containers / closures depyrogenated in-house or depyrogenated by the supplier of the component?

If depyrogenated in-house, was depyrogenation performed by dry heat or washing?

If dry heat, was a tunnel or dry heat oven used?

If depyrogenation is not done in house, then provide a reference to the master files associated with the depyrogenation of the component(s) if applicable. If you utilize a process that does not allow for endotoxin contamination (i.e., blow-fill-seal), provide an explanation. If you purchase a component which is not depyrogenated prior to use, provide a justification for the use of these components as well as data or a reference to a master file to demonstrate that the component is naturally low or free of pyrogens.

What are the characteristics of the process that demonstrate the qualification of the endotoxin removal process? How were the critical process parameters selected, validated, and monitored?

What cycle parameters were used for validation and production runs? For example: temperature setpoint(s), belt speed. What are the acceptance criteria for the qualification of the cycle? How were these developed? For example: 3-log reduction in endotoxin. What loading patterns were used? Were diagrams of the various loading patterns provided? Written descriptions and / or diagram showing locations of thermocouples and endotoxin-spiked components are useful. Diagrams of loading patterns may be submitted in Module 3. What is the source of the endotoxin used? Was the concentration of endotoxin verified? Was a representative COA for the control standard endotoxin provided to Module 3? How was the endotoxin inoculated onto the component? How was recovery performed? What is the requalification schedule? Provide a justification for a bracketing approach, if applicable.

For dry heat depyrogenation:

Heat distribution studies:

How were locations of thermocouples selected for heat distribution studies, if performed?

Describe how the cold spots of the load were determined.

What were the results of any heat distribution studies performed?

Heat penetration studies:

How were locations of thermocouples and endotoxin-spiked components selected for heat penetration studies?

What is the source of the endotoxin used? Was the concentration of endotoxin verified? Was a representative COA for the control standard endotoxin provided to Module 3?

How was the endotoxin inoculated onto the component, as appropriate? How was recovery performed?

What are the acceptance criteria for the qualification of the cycle? How were these developed? For example: minimum 3 log reduction in endotoxin
How were locations for endotoxin-spiked components selected?
What were the results of the heat penetration studies?

For depyrogenation by washing, the following information should be included.
What loads were used? Written descriptions of the placement of thermocouples and endotoxin-spiked components are useful.
What cycle parameters were used for validation and production runs? For example: washing time
What type of water is used? For example: Water for Injection (WFI) is used for the final rinses
What is the source of the endotoxin used? Was the concentration of endotoxin verified? Was a representative COA for the control standard endotoxin provided to Module 3?
How was the endotoxin inoculated onto the component or into the product, as appropriate? How was recovery performed?
What are the acceptance criteria for the qualification of the cycle? How were these developed? For example: minimum 3 log reduction in endotoxin
What is the requalification schedule?
Provide a justification for a bracketing approach, if applicable.
Provide a justification for the worst-case vial size selected, if applicable.

Are containers / closures sterilized before filling?

Provide a summary of the thermal qualification and microbiological efficacy of the cycle. In addition, provide the validation reports in Module 3. The qualification information typically summarizes cycle parameters, acceptance criteria, loading patterns, monitoring locations, sources of biological indicators, results of the studies, and the requalification schedules.

Microbiological Monitoring of the Environment

What are the microbiological monitoring programs used in the production areas to ensure the quality attributes of the product?

What types of monitoring were performed (for example: non-viable particulate, contact plates, anaerobic organisms)? Were diagrams showing environmental monitoring locations provided in Module 3, including room classifications? What are the alert / action limits for each monitoring type and location being monitored? Describe steps to be taken if alert / action limits are exceeded. What was the frequency of each type of monitoring in each room classification? What media and incubation conditions were used for each type of monitoring?

Describe the level of identification of organisms performed for each room classification. Indicate when isolates are identified.

For example: to the genus and species level for Class 100 areas

How is bioburden monitoring performed? Is the method suitable for its intended use and validated? What are the specifications used?

Provide a summary here and a copy of the validation report to Module 3. Provide a copy of the method used for bioburden testing if it is not included as a part of the report. Identify the volume tested and any dilutions performed. Describe the number of rinses performed and the rinsing agent used if a membrane filtration method is utilized.

Is there a program in place to control bioburden / endotoxin of raw materials used in the manufacture of the product?

If so, provide a description and validation to Module 3, if appropriate.

Process Control Documentation

What documentation ensures process control?

What documentation was provided in support of the sterilization process?

For example: evidence of formal written procedures, list of SOPs, copies of the relevant SOPs.

Have the sterilization process controls been documented in the batch record?

The Batch Record should be submitted to the Regional Information Appendix. Sterilization process batch records may include the following information:

a. *Filling line or filling room.*
b. *The major pieces of sterile production equipment used.*
c. *Holding times.*
d. *If instruction or references to SOPs for sterilization/depyrogenation of components are present (or CIP if justified).*
e. *If instructions or references to SOPs for sterilization of the finished product are present.*
f. *If instructions for collection of sterility and endotoxin samples are present (how many units and how collected).*
g. *If instructions for collecting the bioburden sample and the bioburden limit are specified (a SOP may be specified).*
h. *The number of vials or volume of product that is discarded due to filter extractable or adsorption (if applicable).*

Aseptic processing batch records may include the following additional information:

i. *Identification of filter (manufacturer and number).*
j. *Maximum pressure for filtration.*
k. *Final filter integrity specifications (e.g., bubble point, wetting agent).*

V. STERILE PROCESS VALIDATION QUESTIONS: TERMINAL MOIST STEAM STERILIZATION

Description of the Process and Product

Is this information referenced in a Master File?

Is a letter of authorization for the Master File provided, if necessary?

Provide letter of authorization to master files, if necessary.

What is the sterilization process? How was it developed?

For example: saturated steam

Identify the autoclave within the facility.

Provide the location of the autoclave(s) and identify what autoclave is used for the process.

Is this an overkill or bioburden-based cycle?

Describe any studies that were performed to support the use of the proposed cycle. This may be further explained in the section that describes the quality attributes of the product.

What container / closure system was used during cycle development?

This should be the container / closure system that is intended for marketing of the product.

Are containers / closures depyrogenated before filling?

Is depyrogenation done by dry heat or washing? If depyrogenation is not performed, a justification for eliminating this process should be provided.

For dry heat depyrogenation, is an oven or tunnel used?

What cycle parameters were used for validation and production runs? For example: temperature setpoint(s), belt speed.

What are the acceptance criteria for the qualification of the cycle? How were these developed? For example: 3-log reduction in endotoxin.

What loading patterns were used? Were diagrams of the various loading patterns provided? Written descriptions and / or diagram showing locations of thermocouples and endotoxin-spiked components are useful. Diagrams of loading patterns may be submitted in Module 3.

Heat distribution studies:

How were locations of thermocouples selected for heat distribution studies, if performed?

Describe how the cold spots of the load were determined.

What were the results of any heat distribution studies performed?

Heat penetration studies:

How were locations of thermocouples and endotoxin-spiked components selected for heat penetration studies?

What is the source of the endotoxin used? Was the concentration of endotoxin verified? Was a representative Certificate of Analysis for the control standard endotoxin provided to Module 3?

How was the endotoxin inoculated onto the component? How was recovery performed?

What are the acceptance criteria for the qualification of the cycle? How were these developed? For example: minimum 3 log reduction in endotoxin

How were locations for endotoxin-spiked components selected?

What were the results of the heat penetration studies?

What is the requalification schedule?

Provide a justification for a bracketing approach, if applicable.

Provide a justification for the worst-case vial size selected, if applicable.

For depyrogenation by washing, the following information should be included.

What loads were used? Written descriptions of the placement of thermocouples and endotoxin-spiked components are useful.

What cycle parameters were used for validation and production runs? For example: washing time

What type of water is used? For example: WFI is used for the final rinses

What is the source of the endotoxin used? Was the concentration of endotoxin verified? Was a representative COA for the control standard endotoxin provided to Module 3?

How was the endotoxin inoculated onto the component or into the product, as appropriate? How was recovery performed?

What are the acceptance criteria for the qualification of the cycle? How were these developed? For example: minimum 3 log reduction in endotoxin

What is the revalidation schedule?

Provide a justification for a bracketing approach, if applicable.

Are containers / closures sterilized before filling?

Provide a summary of the thermal qualification and microbiological efficacy of the cycle. In addition, provide the validation reports in Module 3. The qualification information typically summarizes cycle parameters, acceptance criteria, loading patterns, monitoring locations, sources of biological indicators, results of the studies, and the requalification schedules.

Was the cycle validation performed using a simulated product?

Describe the simulated product formulation and characteristics as well as a justification for the use of a simulated product.

Is a matrix or bracketing approach proposed?

Provide the justification for the proposed approach.

Is a filtration step used? What is the purpose of this filtration step in your process?

Is the purpose to clarify the solution or as bioburden reduction?

Do you intend to pursue parametric release for this product? If so, what are the critical parameters to ensure the success of your sterilization process? Is there a risk assessment plan in place (e.g., control strategies of the cycle, risk of product failure, prior manufacturing experience and knowledge)?

Refer to CDER/CVM/CBER GFI: Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes.[xvi]

What are the quality attributes of the components or product that are impacted by the sterilization process?

For example: heat labile

Are there attributes of the product that may influence the terminal sterilization process?

For example: viscosity, density

Thermal Qualification of the Cycle

What are the characteristics of the process that demonstrate the thermal qualification of the cycle? How were the critical process parameters selected, validated, and monitored?

What cycle parameters were used for validation and production runs?

For example: cycle time and temperature setpoint(s)

What are the acceptance criteria for the qualification of the cycle? How were these developed?

For example: F_0

What loading patterns were used? Were diagrams of the various loading patterns provided?

Written descriptions and / or photographs showing items in the load as well as locations of thermocouples and biological indicators are useful. This information will aid in the review of the information provided in the Microbiological Efficacy of the Cycle section below. Diagrams of loading patterns, including locations of thermocouples and biological indicators, may be submitted in Module 3.

How were locations of thermocouples selected for heat distribution studies?

Describe how the cold spots of the load were determined.

What were the results of the heat distribution studies?

Provide a rationale for locations of thermocouples for heat penetration studies.

What were the results of the heat penetration studies? If this is a new autoclave, was representative raw thermocouple data provided in Module 3 for verification of the F_0 calculation?

What is the requalification schedule?

How often is requalification performed? Which loads are requalified?

Microbiological Efficacy of the Cycle

What are the process controls to ensure the microbiological efficacy and consistency of the cycle? How were the critical process parameters selected, validated, and monitored?

What biological indicators were used?

For example: species of organism, spore strip or spore suspension

What is the source of the biological indicator? How are biological indicators qualified (i.e., D-value, spore concentration)? Was a representative Certificate of Analysis for the biological indicator provided in Module 3?

What are the acceptance criteria for the qualification of the cycle? How were these developed?

For example: sterility assurance level (SAL) of 10^{-6}

Provide a rationale for the locations of the biological indicators for the heat penetration studies.

How was the biological indicator inoculated onto the component or into the product, as appropriate?

If direct inoculation is not used, provide justification for use of an alternate method (e.g., for biological indicator vials).

What incubation conditions were used for biological indicators?

What were the results of the lethality studies?

What is the requalification schedule?

Microbiological Monitoring of the Environment

What are the microbiological monitoring programs used in the production areas to ensure the quality attributes of the product?

What types of monitoring were performed? For example: non-viable particulate, contact plates, anaerobic organisms. Were diagrams showing environmental monitoring locations provided in Module 3, including room classifications? What are the alert / action limits for each monitoring type and location being monitored? Describe steps to be taken if alert / action limits are exceeded. What was the frequency of each type of monitoring in each room classification? What media and incubation conditions were used for each type of monitoring?

Describe the level of identification of organisms performed for each room classification. Indicate when isolates are identified.

For example: to the genus and species level for Class 100 areas

How is bioburden monitoring performed? Is the method suitable for its intended use and validated? What are the specifications used?

Provide a copy of the validation report to Module 3. Provide a copy of the method used for bioburden testing if it is not included as a part of the report. Identify the volume tested and any dilutions performed. Describe the number of rinses performed and the rinsing agent used if a membrane filtration method is utilized.

Is there a program in place to control bioburden / endotoxin of raw materials used in the manufacture of the product?

If so, provide a description and validation to Module 3, if appropriate.

Process Control Documentation

What documentation ensures process control?

What documentation was provided in support of the sterilization process?

For example: evidence of formal written procedures, list of SOPs, copies of the relevant SOPs

Have the sterilization process controls been documented in the batch record?

The Batch Record should be submitted to the Regional Information Appendix. Sterilization process batch records may include the following information:

a. *Filling line or filling room.*
b. *The major pieces of sterile production equipment used*
c. *Holding times.*
d. *If instruction or references to SOPs for sterilization/depyrogenation of components are present (or CIP if justified).*
e. *If instructions or references to SOPs for sterilization of the finished product are present.*
f. *If instructions for collection of sterility and endotoxin samples are present (how many units and how collected).*
g. *If instructions for collecting the bioburden sample and the bioburden limit are specified (a SOP may be specified).*
h. *The number of vials or volume of product that is discarded due to filter extractable or adsorption (if applicable).*

VI. STERILE PROCESS VALIDATION QUESTIONS: RADIATION STERILIZATION

Description of the Process and Product

Is this information referenced in a master file?

Is a letter of authorization for the master file provided, if necessary?

Provide letter of authorization to master files, if necessary.

What is the sterilization process? How was it developed?

Is this an overkill or bioburden-based cycle?

Describe any studies that were performed to support the use of the proposed cycle and the desired sterility assurance level. This may be further explained in the section that describes the quality attributes of the product.

What container / closure system was used during cycle development?

This should be the container / closure system that is intended for marketing of the product.

Are containers / closures depyrogenated before filling?

Is depyrogenation done by dry heat or washing?

For dry heat depyrogenation, is an oven or tunnel used?

What cycle parameters were used for validation and production runs? For example: temperature setpoint(s), belt speed

What loading patterns were used? Were diagrams of the various loading patterns provided? Written descriptions and / or diagram showing locations of thermocouples and endotoxin-spiked components are useful. Diagrams of loading patterns may be submitted in Module 3.

Heat distribution studies:

How were locations of thermocouples selected for heat distribution studies, if performed?
Describe how the cold spots of the load were determined.
What were the results of any heat distribution studies performed?

Heat penetration studies:

How were locations of thermocouples and endotoxin-spiked components selected for heat penetration studies?
What is the source of the endotoxin used? Was the concentration of endotoxin verified? Was a representative Certificate of Analysis for the control standard endotoxin provided to Module 3?
How was the endotoxin inoculated onto the component? How was recovery performed?
What are the acceptance criteria for the qualification of the cycle? How were these developed? For example: minimum 3 log reduction in endotoxin
How were locations for endotoxin-spiked components selected?
What were the results of the heat penetration studies?

What is the requalification schedule?

Provide a justification for a bracketing approach, if applicable.

Provide a justification for the worst-case vial size selected, if applicable.
For depyrogenation by washing, the following information should be included.

What loads were used? Written descriptions of the placement of thermocouples and endotoxin-spiked components are useful.

What cycle parameters were used for validation and production runs? For example: washing time

What type of water is used? For example: WFI is used for the final rinses

Are containers / closures sterilized before filling?

Provide a summary of the thermal qualification and microbiological efficacy of the cycle. In addition, provide the validation reports in Module 3. The qualification information typically summarizes cycle parameters, acceptance criteria, loading patterns, monitoring locations, sources of biological indicators, results of the studies, and the requalification schedules.

Was validation performed using a simulated product?

Describe the simulated product formulation and characteristics as well as a justification for the use of a simulated product.

Is a matrix or bracketing approach proposed?

Provide the justification for the proposed approach.

Is a filtration step used? What is the purpose of this filtration step in your process?

Is the purpose to clarify the solution or as bioburden reduction?

Do you intend to pursue parametric release for this product? If so, what are the critical parameters to ensure the success of your sterilization process? Is there a risk assessment plan in place (e.g., control strategies of the cycle, risk of product failure, prior manufacturing experience and knowledge)?

What are the quality attributes of the components or product that are impacted by the sterilization process?

For example: degradation products, excipient loss, container damage. Any controls used to ensure packaging is adequate following the radiation treatment should be included here.

Are there attributes of the components or product that may influence the radiation sterilization process?

For example: viscosity, density, polymer type

Dose Mapping and Validation Studies

What are the characteristics of the process that demonstrate the radiation qualification of the cycle? How were the critical process parameters selected, validated, and monitored?

How was an acceptable radiation dose for the load demonstrated?

What radiation dose was used for validation and production runs?

What are the acceptance criteria for the qualification of the cycle? How were these developed?

What loading patterns were used? Were diagrams of the various loading patterns provided?

Written descriptions and / or photographs showing items in the load as well as locations of radiation dosimeters and/or biological indicators are useful. This information will aid in the review of the information provided in the Microbiological Efficacy of the Cycle section below. Diagrams of loading patterns, including dosimeter placement, may be submitted in Module 3.

How were locations of dosimeters selected for dose mapping studies?

*Provide a rationale for locations of dosimeters for dose mapping studies***.**

What were the results of the dose mapping studies?

If bioburden approach was used, what are results of dose confirmation studies?

What is the requalification schedule?

How often is requalification performed? Which loads are requalified? For bioburden approaches, what is the frequency of bioburden audit?

Microbiological Efficacy of the Cycle

What are the process controls to ensure the microbiological efficacy and consistency of the radiation treatment? How were the critical process parameters selected, validated, and monitored?

What biological indicators (if any) were used?

For example: species of organism, spore strip or spore suspension. If none, provide a rationale.

What is the source of the biological indicator? How are biological indicators qualified (i.e., D-value, spore concentration)? Was a representative Certificate of Analysis for the biological indicator provided in Module 3?

What are the acceptance criteria for the qualification of the cycle? How were these developed?

For example: sterility assurance level (SAL) of 10^{-6}

What incubation conditions were used for biological indicators, as appropriate?

What were the results of the lethality studies?

What is the requalification schedule?

Microbiological Monitoring of the Environment

What are the microbiological monitoring programs used in the production areas to ensure the quality attributes of the product?

What types of monitoring were performed? For example: non-viable particulate, contact plates, anaerobic organisms. Were diagrams showing environmental monitoring locations provided in Module 3, including room classifications? What are the alert / action limits for each monitoring type and location being monitored? Describe steps to be taken if alert / action limits are exceeded. What was the frequency of each type of monitoring in each room classification? What media and incubation conditions were used for each type of monitoring?

Describe the level of identification of organisms performed for each room classification. Indicate when isolates are identified.

For example: to the genus and species level for Class 100 areas

How is bioburden monitoring performed? Is the method suitable for its intended use and validated? What are the specifications used?

Provide a copy of the validation report to Module 3. Provide a copy of the method used for bioburden testing if it is not included as a part of the report. Identify the volume tested and any dilutions performed. Describe the number of rinses performed and the rinsing agent used if a membrane filtration method is utilized.

Is there a program in place to control bioburden / endotoxin of raw materials used in the manufacture of the product?

If so, provide a description and validation to Module 3, if appropriate.

Process Control Documentation

What documentation ensures process control?

What documentation was provided in support of the sterilization process?

For example: evidence of formal written procedures, list of SOPs, copies of the relevant SOPs

Have the sterilization process controls been documented in the batch record?

The Batch Record should be submitted to Module 3. Sterilization process batch records may include the following information:

a. *Filling line or filling room;*
b. *The major pieces of sterile production equipment used;*
c. *Holding times;*

d. *If instruction or references to SOPs for sterilization/depyrogenation of components are present (or CIP if justified);*
e. *If instructions or references to SOPs for sterilization of the finished product are present;*
f. *If instructions for collection of sterility and endotoxin samples are present (how many units and how collected);*
g. *If instructions for collecting the bioburden sample and the bioburden limit are specified (a SOP may be specified); or*
h. *The number of vials or volume of product that is discarded due to filter extractable or adsorption (if applicable).*

VII. STERILE PROCESS VALIDATION QUESTIONS: MICROBIOLOGICAL TESTING CONTROLS AND STABILITY CONSIDERATIONS

The questions in this section are applicable to all sterile products, regardless of the method used to sterilize the product.

What test methods are included in the product release and stability testing to support the quality attributes (sterility) of the product?

Is endotoxin, sterility, or preservative effectiveness (for multi-use products that don't contain a preservative) included in the product release and/or stability testing of the product? What is the schedule for any tests performed as a part of the proposed stability commitment?

Are there product or component characteristics that are impacted by the sterilization method that should be monitored (e.g., excipients that are sensitive to the sterilization process used)?

Is reprocessing of product or components proposed?

Provide data to support multiple sterilization cycles of components and/ or product. This should include stability studies for lots manufactured using components and/or product that has undergone the maximum number of sterilization cycles. For aseptically processed products, routine reprocessing is generally not acceptable.

Container-Closure Integrity

What method was selected to perform container-closure integrity testing?

For example: Dye ingress

How was the method demonstrated to be suitable for its intended use and validated?

Is a copy of the validation report provided to the submission?

Provide a copy of the method used to determine container-closure integrity if it is not included as a part of the report.
How many containers were tested?
How were the positive and negative controls prepared?
What were the results of the challenge to the container/closure system?
If a quantitative method (e.g., Dye Ingress) is used, what is the detection limit?

Preservative Effectiveness

Is testing performed according to USP General Chapter <51> Antimicrobial Preservative Effectiveness?[xvii]

Is a copy of the validation report provided to the submission?
What concentration(s) of preservative were tested for preservative effectiveness?

The minimum concentration of preservative shown to be effective will be taken into consideration when setting the specifications for shelf life. For example, if the proposed stability specification for the preservative is 90-110%, a batch formulated at 90% of the label claim should be demonstrated to maintain preservative effectiveness.

What were the results of the preservative effectiveness testing?

Pyrogen or Endotoxin Testing

Is testing performed according to USP General Chapter <85> Bacterial Endotoxins?[xviii]

Is a copy of the validation report provided to the submission?

What method was selected to perform endotoxin testing?

For example: gel clot

How was the method demonstrated to be suitable for its intended use and validated?

What vendor was selected to provide the lysate? Was the sensitivity of the lysate confirmed?

Is a copy of a representative Certificate of Analysis for the control standard endotoxin and the lysate provided to the file?

What calculations were performed to determine MVD, NIC, and routine dilution as appropriate?

An explanation of how the routine dilution was selected may be helpful.

Is a commitment to perform inhibition/enhancement testing on the first three production lots provided in the submission?

This commitment only applies if the stability batches were manufactured at the pilot scale.

If a photometric method is utilized, is the standard curve utilized to perform the validation provided in the validation report?

Sterility Testing

Is testing performed according to USP General Chapter <71> Sterility Test?[xix]

Was a membrane filter or direct inoculation method selected?

How was the method demonstrated to be suitable for its intended use and validated?

Is a copy of the validation report provided to the submission?

Provide a copy of the method used to determine sterility testing if it is not included as a part of the report.
Identify if the appropriate number of containers and volume tested from each container has been selected based on the batch size and container size as indicated in USP General Chapter <51>.[xx]

Has a description of the bacteriostasis/fungistasis testing been provided to the file?

The description should include the number of rinses performed and the rinsing agent used if a membrane filtration method is utilized.

Microbiological Release and Stability Testing

What tests are included in the product release and stability specifications to support the biological/microbiological quality attributes of the product?

Provide a description of the tests performed at each stability test station which support the biological/microbiological quality attributes of the product.

USP General Chapter <1> "Injections"[xxi] *and CVM GFI #176/VICH GL 39: Specifications: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances*[xxii] *provide additional information regarding the setting of specifications.*

ENDNOTES

[i] CDER GFI: M4Q: The CTD – Quality (ICH) (August 2001) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073280.pdf

[ii] CDER/CBER GFI: M4: The CTD – Quality Questions and Answers/Location Issues (ICH) (June 2004) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073285.pdf

[iii] CVM GFI #169: Drug Substance Chemistry, Manufacturing, and Controls Information (August 2010) http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052498.pdf

[iv] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (November 2000) http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf

[v] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) (May 2012) http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.pdf

[vi] CVM GFI #5: Drug Stability Guidelines (December 2008). http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM051556.pdf

[vii] United States Pharmacopoeia Chapter <660> *Containers-Glass.* The United States Pharmacopeial Convention, Rockville, MD. http://www.usp.org/

[viii] United States Pharmacopoeia Chapter <661> *Containers-Plastics.* The United States Pharmacopeial Convention, Rockville, MD http://www.usp.org/

[ix] CVM GFI #42: Animal Drug Manufacturing Guidelines (Revised 1994) http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm053405.htm

[x] CVM GFI #176/VICH GL39: Specifications: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances (June 2006).
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052487.pdf

[xi] CVM GFI #64: Validation of Analytical Procedures: Methodology (July 1999).
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052379.pdf

[xii] CVM GFI #93/VICH GL11(R): Impurities in New Veterinary Medicinal Products (Revised) (November 2007).
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052432.pdf

[xiii] United States Pharmacopoeia Chapter <661> *Containers-Plastics*. The United States Pharmacopeial Convention, Rockville, MD
http://www.usp.org/

[xiv] CVM GFI #5: Drug Stability Guidelines (December 2008).
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM051556.pdf

[xv] United States Pharmacopoeia Chapter <71> *Sterility Tests*. The United States Pharmacopeial Convention, Rockville, MD.
http://www.usp.org/

[xvi] CDER/CVM/CBER GFI: Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes (February 2010).
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072180.pdf

[xvii] United States Pharmacopoeia Chapter <51> *Antimicrobial Preservative Effectiveness*. The United States Pharmacopeial Convention, Rockville, MD.
http://www.usp.org/

[xviii] United States Pharmacopoeia Chapter <85> *Bacterial Endotoxins*. The United States Pharmacopeial Convention, Rockville, MD.
http://www.usp.org/

[xix] United States Pharmacopoeia Chapter <71> *Sterility Tests*. The United States Pharmacopeial Convention, Rockville, MD.
http://www.usp.org/

[xx] United States Pharmacopoeia Chapter <51> *Antimicrobial Preservative Effectiveness*. The United States Pharmacopeial Convention, Rockville, MD.
http://www.usp.org/

[xxi] United States Pharmacopoeia Chapter <1> *Injections*. The United States Pharmacopeial Convention, Rockville, MD.
http://www.usp.org/

[xxii] CVM GFI #176/VICH GL39: Specifications: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances (June 2006).
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052487.pdf