#288

Chemistry, Manufacturing, and Controls in Support of Recombinant Protein Products for Veterinary Medicinal Use

Guidance for Industry

Draft Guidance

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For further information regarding this document, contact Lijuan He, Center for Veterinary Medicine (HFV-144), Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, 301-796-5122, email: Lijuan.He@fda.hhs.gov.

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This guidance for industry describes the Center for Veterinary Medicine's (CVM) recommendations for the information to be included in Chemistry, Manufacturing, and Controls (CMC) submissions to New Animal Drug Applications (NADAs), Conditional New Animal Drug Applications (CNADAs), Investigational New Animal Drug (INAD) files, and Veterinary Master Files (VMFs) specific to recombinant protein-based intermediates,[1] drug substances, and drug products.

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. Background

Recombinant proteins are produced with recombinant deoxyribonucleic acid (DNA) technology. They may be identical in amino acid sequence to endogenous proteins, or, alternatively, have modifications in the amino acid sequence. Some recombinant proteins may require post-translational modifications or chemical conjugations. Different host cell lines, including mammalian, yeast, bacteria, plant, or insect, and cell-free systems can be used for expressing recombinant proteins. The choice of host cells may be influenced by factors such as the type of protein, functional activity, and desired yield. For example, mammalian cells can facilitate desirable protein folding and glycosylation, as well as a broad spectrum of additional post-translational modifications for the target animal species. These characteristics have made cell lines such as Chinese Hamster Ovary (CHO) and Human Embryonic Kidney (HEK) 293 popular host cells for producing complex biologically active proteins for therapeutic use.

[1] For recombinant protein products, an intermediate is a material produced during a manufacturing process that is not the drug substance or the drug product but whose manufacture is critical to the successful production of the drug substance or the drug product. This includes material that may undergo further molecular modification or be held for an extended period before further processing.

The production of recombinant proteins has unique characteristics; therefore, the information related to manufacture, characterization, and stability may differ from published guidances specific to synthetic chemical substances. This recombinant protein guidance should benefit animal drug sponsors when used in context with already published guidances related to biotechnological or biological products, including:

- Guidance for Industry ICH Q5A (R2), "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin"[2]
- Guidance for Industry ICH Q5B, "Quality of Biotechnological Products: Analysis of the Expression Construct in Cells used for Production of r-DNA Derived Protein products"[3]
- Guidance for Industry ICH Q5D, "Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products"[4]
- Guidance for Industry #99 (VICH GL17), "Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products"[5]
- Guidance for Industry #177 (VICH GL40), "Specifications: Test Procedures and Acceptance Criteria for New Biotechnological/Biological Veterinary Medicinal Products"[6]
- Guidance for Industry, "For the Submission of Chemistry, Manufacturing, and Controls information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use."[7]

III. Scope

Recombinant protein-based animal drug products regulated by CVM are subject to the same statutory and regulatory requirements as other new animal drugs, including current good manufacturing practice (CGMP) and labeling requirements. This guidance focuses on recombinant proteins, including monoclonal antibodies (mAbs), bispecific antibodies, and fusion proteins, produced in mammalian cells. However, the general principles described in this document can be applicable to recombinant proteins produced in other types of host cells. This document does not cover proteins produced by animals containing intentional genomic

[2] https://www.fda.gov/media/163115/download (January 2024).

[3] https://www.fda.gov/media/71417/download (February 1996).

[4] https://www.fda.gov/media/71463/download (September 1998).

[5] https://www.fda.gov/media/70404/download (March 2001).

[6] https://www.fda.gov/media/69907/download (June 2006).

[7] https://www.fda.gov/media/77528/download (August 1996).

alterations or mAbs that are produced by hybridoma cell lines.[8] This document does not cover animal cells, tissues, and cell- and tissue-based products, bacteriophage products, competitive exclusion products, naturally derived or crude protein products, or DNA/RNA products that are produced by fermentation. Furthermore, this guidance does not address post-approval chemistry, manufacturing, and controls changes associated with recombinant protein-based products. For guidance on post-approval changes, refer to Guidance for Industry (GFI) #83, "Chemistry, Manufacturing, and Controls Changes to an Approved NADA or ANADA"[9] and GFI, "Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products."[10]

The information in this guidance generally follows the International Conference on Harmonisation (ICH) Common Technical Document (CTD)[11] and CVM's eSubmitter[12] templates for CMC technical section submissions. For brevity, this GFI has combined information for different sections in CTD and eSubmitter templates. However, CVM encourages sponsors to closely follow CTD and CVM's eSubmitter templates format when preparing the CMC technical section submission.

IV. General Information

A. Drug Substance

1. Nomenclature

The following information for the drug substance should be provided, if applicable:

- Recommended International Nonproprietary Name (INN)
- Compendial name
- Chemical name
- Company or laboratory code
- Other nonproprietary name(s), such as United States Adopted Name (USAN)
- Chemical Abstracts Service (CAS) Registry number

2. Structure

General structural information, such as a schematic representation of the recombinant

[8] The research and development process (e.g., to produce the candidate mAb molecules) of the mAb product covered by this guidance might use hybridomas.

[9] https://www.fda.gov/media/70323/download (May 2007).

[10] https://www.fda.gov/media/109615/download (June 2021).

[11] GFI ICH, "M4Q: The CTD – Quality" (August 2001).

[12] The CVM eSubmitter program is a free, question-based tool that allows animal drug sponsors to electronically and securely submit information to the center. See https://www.fda.gov/industry/fda-esubmitter/cvm-esubmitter-resource-center.

protein and the protein sequence indicating amino acids and post-translational modifications that are critical to the structure and function of the protein should be provided. Domains that play critical functional roles, such as binding, enzymatic, and transport, should be highlighted. Higher-order structures, including tertiary and quaternary (if applicable) structures, should be described with supporting data using appropriate characterization techniques.

3. General properties

A list of physicochemical and relevant biological properties of the drug substance should be provided.

Physicochemical properties might include molecular weight (or size) and formula, isoelectric point (pI), charge variant isoform pattern, extinction coefficient, electrophoretic patterns, mass spectroscopy, circular dichroism, infrared spectroscopy, and liquid chromatographic patterns. Additional physicochemical properties may be needed for recombinant proteins with conjugation, such as the degree of conjugation of the modified product.

Relevant biological properties may include, but are not limited to, enzymatic reaction rates for enzymes, binding affinity between growth factors and their respective receptors, or immunochemical properties for antibodies.

B. Drug product

A description of the drug product including the dosage form, composition, reconstitution diluents (if applicable), and the type of container closure system (e.g., single dose versus multi-dose) should be provided. The description of composition should include a list of all components (including active pharmaceutical ingredient [API] and excipients) and their amounts (including overages if there are any), the function of each component, and a reference to their quality standards.

V. Identification of Manufacturing Facilities

All facilities should register with FDA prior to the submission of the CMC technical section to allow pre-approval inspections to be issued as needed. All manufacturers and facilities involved in manufacturing and testing of intermediates, drug substances, and drug products should be identified, including all contract facilities. The name, address, FDA Establishment Identification (FEI) number, Data Universal Numbering System (DUNS) number, and role of each facility (e.g., manufacturer, tester, packager, labeler, storer, etc.) along with the contact information for FDA correspondence should be provided in the Animal Drug and Manufacturing System (ADMS) in the FDA eSubmitter. Contact information for a U.S. agent must be provided if the facility is outside the United States.[13]

The following information about the drug substance and drug product manufacturing facilities,

[13] 21 CFR 514.1 *Applications*.

which may also be included in 3.2.A Appendices of the CTD, should be submitted:

- Description of the operations performed in each facility.

- A description of the equipment used, and its function should be provided. Information about the preparation, cleaning, sterilization (if applicable), and storage of specified equipment and materials.

- For single-use systems (SUSs), which are typically made of polymeric materials, an assessment should be provided to demonstrate that the SUS has no adverse effects on the product (e.g., extractables/leachables) during manufacture. Extractables/leachables (E/L) assessments can utilize risk assessment tools and an evaluation of extractables data during the selection phase and E/L data in the qualification phase. Additional information can be found in United States Pharmacopeia (USP) <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems[14] and USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems.[15]

- A floor diagram that indicates the general layout of the facility should be provided. This diagram should be sufficient for visualizing the manufacturing flow of the drug substance and the drug product. The information in the diagram of the facility might include floor plans for aseptic processing areas, air class designations, air/material/waste flow, HEPA filter maps, and personnel movement.

- For areas and equipment where cell bank preparation, cell amplification, and aseptic product manufacturing operations are performed, information should be included on procedures and design features of the facility that prevent contamination or cross-contamination.

- Information on any other approved or developmental products that are manufactured or manipulated in the manufacturing area should be provided. In addition, any other products that directly contact with the equipment used for the proposed drug substance and the drug product should be identified.

VI. Description of Manufacturing

A. Drug substance

1. Control of materials

i. Host cell/Parental cell

[14] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M7126_03_01.html (accessed March 11, 2024).

[15] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M7127_02_01.html (accessed March 11, 2024).

A detailed description of the host cell/parental cell including origin, source, and history should be provided. Information directly obtained from the source laboratory is preferred; literature references may be used if such information is not available. The host cell/parental cell should be adequately characterized for cell identity, purity, and stability, and those results should be included in the submission. Refer to ICH Q5D for more detailed guidelines on the characterization of the host cell/parental cell.

ii. Gene construct and expression vector

A description of the introduced gene construct(s), including their origin and source, and preparation method should be provided. The complete nucleotide sequence of the coding region with amino acid translation and the regulatory elements should be included. Summary reports of the data analysis should be included in the file and the actual sequence data may be submitted to CVM in FASTA/FASTQ format through the precisionFDA portal. Any modifications to the native sequences (e.g., mutations to increase stability, caninized, felinized) should be described.

A detailed description of the expression vector including its source, an annotated map, and the functions of its components should be provided. Examples of components include origin of replication, promoters, enhancers, antibiotic resistance genes, and genetic markers to be used for screening.

A step-by-step description of the procedure used to assemble the vector and gene inserts that make up the final construct should be included. A detailed component map and a complete annotated sequence of the plasmid (accompanied by the raw chromatogram of the sequencing) should be provided. Any non-coding sequences, such as introns, untranslated regions, and flanking sequences, included in the final plasmid should be minimized, justified, and adequately characterized if present.

iii. Cloning and establishment of recombinant cell lines

The transfer method of the expression construct into the host cell should be described. The copy number and the physical state of the construct in the host cell should also be described. In addition, the screening and selection procedures for isolation of the transformed host cell clone as well as methods for establishment of the seed should be described in detail. This includes the methods for confirming stable transformation of the host cell as well as establishing and maintaining clonality, if applicable.

For monoclonal antibody drug substance or intermediate, the sponsor should describe how monoclonality was achieved during the establishment process of the cell line. Results demonstrating the cell line clonality should be included in the CMC technical section.

iv. Cell bank system

The production and maintenance procedures of the Master Cell Bank (MCB) should be described in detail, including methods, reagents and media, date of creation, in-process controls, the container closure system, how many batches of product can be manufactured from the MCB, and storage conditions (e.g., temperature, humidity). The sponsor may want to consider redundant storage facilities to help ensure MCB survival in case of storage failure at any one site. After the initial MCB is established, new MCBs may be generated by separate transformation. In-process controls and acceptance criteria for new cell banks, and products derived from them, should also be described. Initial and newly produced MCBs should be characterized for identity, purity, and stability of both the host cell and the introduced genetic material during storage. This may include evaluation of the fidelity of the nucleotide coding sequence through DNA sequencing analysis and phenotypic evaluations for morphology, auxotrophy, and expression of the recombinant protein.

A description of the production and maintenance of Working Cell Banks (WCBs), including methods, reagents and media, date of creation, in-process controls, the container closure system, how many batches of product can be manufactured from the WCB, storage conditions (e.g., temperature, humidity), and maximum storage time should be provided. Furthermore, procedures, tests, and specifications for identity, purity, and stability for WCBs should be described. Data supporting the stability of the WCB, and fidelity of the gene insert throughout the proposed storage period should be provided.

A characterization of the cells at the limit of *in vitro* cell age used to produce the recombinant protein should be included. For example, the data supporting the stability of the cells throughout the growth period along with the proposed cell passage limit should be provided. Analyses to ensure fidelity of the gene insert throughout the course of production should be performed and provided.

Validation data or certification supporting the testing for endogenous and adventitious agents, such as mycoplasma, prions, viruses, or virus-like particles should be provided. The sponsor should follow the suggested tests for MCB, WCB, and cells at the limit of *in vitro* cell age used for production in ICH Q5A (R2).

v. Raw materials and reagents

The constituents of the media used at each step of the processing should be described. This includes cell culture media used for growth, passages, and maintenance, and any media used for induction of expression or metabolic selection. Details regarding the vendor qualification system for all purchased media and constituents should be described. This includes extent of initial testing, frequency of testing after qualification, and procedures for requalification. Representative certificates of analysis from the vendor and the sponsor's

confirmatory testing results should be provided. If the media composition is proprietary information of the vendor, the sponsor should discuss with the vendor on how to submit the information to the Agency. The vendor may establish a Veterinary Master File (VMF)[16] or a Drug Master File (DMF)[17] to provide the media composition information to the Agency, and the sponsor should then include a Letter of Authorization in the CMC technical section submission to reference the VMF or DMF.

A list of solvents, reagents, and auxiliary materials used in the production of recombinant proteins should be provided with descriptions of each material, including water, buffers, process gasses (e.g., carbon dioxide), antibiotics, sera, preservatives, antibodies, and enzymes. The descriptions of each material should include tests, specifications, and references to official compendia if applicable. Representative certificates of analysis and/or manufacturer's acceptance criteria should be provided in addition to details regarding the vendor qualification system for all purchased materials. For ancillary biological products, such as monoclonal antibodies used in purification or affinity chromatography, a detailed characterization of the auxiliary material should be provided.

For raw materials of human or animal origin that could harbor adventitious agents, such as mycoplasma, prions, viruses, and virus-like particles, risk mitigation strategies should be described, and data (e.g., viral clearance studies) and/or certification submitted demonstrating the absence of adventitious agents. CVM recommends that manufacturers not use materials derived from cattle that were born, raised, or slaughtered in countries where the risk for Bovine Spongiform Encephalopathy (BSE) is undetermined.[18] Furthermore, pursuant to 21 CFR 189.5 and 700.27, the use of certain cattle materials in human food, dietary supplements, and cosmetics is prohibited. The definitions for prohibited cattle materials in these regulations would be suitably applied to raw materials considerations in this guidance document.

2. Upstream and downstream processing

Flow chart(s) illustrating each step in the upstream (cell expansion and harvesting) and downstream (purification) processing should be provided, from the original inoculum through harvesting, isolating, and purifying the crude cell culture harvest (cell supernatant or cell pellet), to the final form of the recombinant protein drug substance. The intended maximum size of the commercial production batch should be stated and a list of the in-process controls and tests performed included, along with the sampling strategy, testing time intervals, and acceptance criteria. The indicated

[16] GFI #57, "Preparation and Submission of Veterinay Master Files," (January 1995).

[17] Draft GFI, "Drug Master Files," (November 2019). This guidance, when final, will represent the current thinking of the FDA on this topic.

[18] 9 CFR 92.5 *Determination of the BSE risk classification of a region*.

amount of each material should represent the maximum intended size of the production batch.

In addition to the flow chart(s), each step in the upstream and downstream processing should be described.

We recommend including the following information in the description of the upstream processing:

- The major equipment used in each step and the room or area where the operation is performed.
- The selection of inoculum, detailed description of the scale-up for expansion, cell culture conditions (e.g., temperature, CO2) and duration (i.e., total length of culture time) of each expansion step.
- Any feeds and other materials added during the cell culture process.
- The criteria for harvesting, for example, cell density and viability.
- The determination of yields for each critical step.
- Any induction performed to produce protein including induction conditions and controls.
- Any process used to inactivate cells prior to their release into the environment.
- All operating conditions and in-process controls should be described, and their associated numeric ranges, limits, or acceptance criteria should be established.
- The procedures used to transfer material between steps.
- The sterilization procedures for media (e.g., a batch sterilization process or continuous system).
- The mechanisms in place to prevent cross-contamination when manipulating more than one cell line in a single area or when one piece of equipment is used for more than one cell line.
- The procedures to minimize contamination by adventitious agents. The process controls to confirm inactivation or removal of adventitious agents. The procedures followed if contamination during cell culture occurs.
- The storage conditions (e.g., temperature, humidity) and time limits if the harvested cell supernatant or cell pellet is held prior to further processing.

We recommend including the following information in the description of the downstream processing:

- The major equipment and materials employed, such as columns and membranes.
- The methods used in purification or separation of the cell culture harvest, such as precipitation, centrifugation, or filtration.
- The process parameters monitored.
- The precautions taken to ensure containment and prevention of contamination or cross-contamination, indicating any multi-use areas and equipment used during the isolation, purification, and downstream processing.
- The in-process controls and analytical tests used to demonstrate identity, purity, and concentration of the drug substance and to evaluate levels of impurities.
- Any steps where bioburden and endotoxin are evaluated including the acceptance criteria.
- Any reprocessing and the process used. Reprocessing should use a validated process.
- The conditions for reuse or the procedures for regeneration of columns, membranes, and adsorbents.
- The storage conditions (e.g., temperature, humidity) and time limits when the purified product is held prior to further processing.

3. Modification reactions

If recombinant proteins are further modified, we recommend that a flow diagram of the modification process and a description of the modification steps be included. Information detailing the reaction controls (e.g., pH, temperature, osmolarity, etc.) and the optimum range of operation to ensure that the modification reactions are consistent across batches should be included. Additionally, information about the biological source, preparation, and purity of any enzyme that is used for the modification reaction should be provided.

4. Batch and batch records

The sponsor should describe how each batch of drug substance is defined, the quantity of drug substance manufactured from each discrete quantity of starting material, and the typical quantity of each drug substance batch. The size of the pilot-scale or clinical batches should be provided along with the proposed commercial batch size(s).

It is recommended that the sponsor submits the commercial master batch record and a minimum of one executed batch record of the drug substance manufacture. The executed batch record should accurately follow the proposed master manufacturing record and should include complete information related to the production and control of each batch.

B. Drug product

1. Pharmaceutical development

Sponsors are encouraged to submit product development reports following GFI ICH Q8 (R2), "Pharmaceutical Development."[19] This information can provide background information to support and justify decisions that were made regarding critical aspects of the drug product. Data included in this section does not need to be validated, but rather should be used to demonstrate that the approach to the decisions made during drug product development was logical and reasonable. There are a few areas of pharmaceutical development that sponsors are recommended to discuss: critical quality attributes, formulation development, manufacturing process development, container closure system, microbiological control, and diluent compatibility (when applicable).

2. Batch formula

The size of the pilot-scale or clinical batches should be provided along with the proposed commercial batch size(s). All ingredients used in the manufacture of the drug product should be included in the batch formula even if they are not present in the finished product. An example of this would be nitrogen used as an overlay during the filling of the product.

3. Control of excipients

A list of all excipients used in the formulation of the final product should be provided. Compendial excipients should, at minimum, comply with specifications described in individual United States Pharmacopeia (USP)/National Formulary (NF) monographs. Deviation from the monograph specifications should be justified. Any test methods different than those in the monograph should be provided. Justification for proposed raw material specifications should be included for non-USP/NF materials. For excipients without USP/NF monographs, specifications in compliance with other compendial monographs, such as European Pharmacopeia, Japanese Pharmacopeia, etc., may be acceptable based on a case-by-case evaluation. Analytical method validation for excipient materials does not need to be submitted in the CMC technical section unless the excipient is a critical component for product safety or effectiveness.

Vendors of all excipients should be qualified, and the process of vendor qualification and re-qualification should be described. A minimum of one representative

[19] https://www.fda.gov/media/71535/download (November 2009).

certificate of analysis from the vendor should be provided for each excipient. Results from confirmatory testing of all the tests in vendor's certificate of analysis and any additional testing performed by the sponsor should also be provided.

The rationale for the use of any excipients that play a significant functional role in the formulation or novel excipients should be described and the details related to manufacture, characterization, and controls should be provided. Additionally, a statement should be provided identifying any excipients that are of human or animal origin along with information regarding adventitious agent testing and risk mitigation strategies.

4. Manufacture

A flow chart of the manufacturing process should be provided that indicates the production step, the equipment and materials used, the room or area where the operation is performed, and a listing of the in-process controls and tests at each step.

Accompanying this flow chart should be a complete description of the manufacturing process, including a description of any sterilization operations, aseptic processing procedures, lyophilization, and packaging procedures. The narrative should also include information on transfer of the product between steps, such as sterile and sanitary connections, or under laminar flow. Transfers should be described for movement of product between equipment, areas/rooms, buildings, and sites. Other sections of the CMC technical section can be cross-referenced for more detailed manufacturing process information.

5. Batch records

The master batch record for the commercial manufacture and executed batch records of representative drug product batches should be submitted. The master batch record should cover the entire manufacturing process, including compounding, filling, labeling, and packaging. The executed batch records should accurately follow the proposed master batch record and should include complete information related to the production and control of each batch.

C. Sterilization process

If the drug substance or drug product is sterile, the sterilization process and validation information should be provided in the CMC technical section or by referencing a Type V VMF or DMF. For details on information to be included and how to submit documentation related to sterilization processes, refer to GFI, "Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products,"[20] GFI, "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice,"[21] and GFI #234, "Question-Based

[20] https://www.fda.gov/media/71442/download (November 1994).

[21] https://www.fda.gov/media/71026/download (October 2004).

Review for the Chemistry, Manufacturing, and Controls Technical Section of Animal Drug Applications."[22]

D. Manufacturing scale-up for commercial batches

The maximum commercial batch size of the drug substance and drug product should not be more than 10 times the size of the pilot batches that are manufactured to support product approval.

Equipment used to produce commercial batches should use the same design and operating principles as used for pilot-scale batch manufacture, with allowances to account for the increased capacity. All these batches should be manufactured in compliance with CGMP using the same standard operating procedures, controls, formulations, and manufacturing procedures.

Process validation for the scale-up must be conducted prior to marketing of the product.[23] Stability data from the scale-up production batches should be generated in accordance with the post-approval stability commitment.

E. Reprocessing, reworking, recycling, regeneration, and salvaging

When appropriate, reprocessing, reworking, recycling, regeneration, and salvaging operations should be described. See GFI #169, "Drug Substance Chemistry, Manufacturing, and Controls Information,"[24] for general concepts that may be applicable to a recombinant protein drug substance or drug product manufacture.

VII. Process Controls

Process controls should be established to monitor and adjust the manufacturing process and to ensure intermediates, drug substances, and drug products conform to their respective specifications. Process controls for recombinant protein manufacture may include:

- Operating or manufacturing parameters that control the manufacturing process. For example, temperature, mixing speed, pH, time, and pressure.

- Environmental controls that are associated with the manufacturing facility. For example, temperature, humidity, and clean room classification.

- Process tests that are used to monitor and assess the on-going operation performance. For example, density, purity, and viability of cells in upstream processing; concentration of protein after purification or polishing steps in downstream processing.

[22] https://www.fda.gov/media/96718/download (December 2016).

[23] 21 CFR part 211 *Current Good Manufacturing Practice for Finished Pharmaceuticals*.

[24] https://www.fda.gov/media/69923/download (August 2010).

- In-process tests used to assess the quality attributes of in-process materials that ultimately lead to a decision to accept or reject the material or drug product. For example, impurity and bioburden testing.

A. Critical in-process controls

The critical steps or critical control points and the in-process control specifications during the manufacturing process of intermediates, drug substances, and drug products should be identified. Any supporting data and justifications for the proposed acceptance criteria should also be included. The procedures to conduct critical in-process controls, including any in-process sampling plans, should be in the master batch records. For further details about in-process sampling, see GFI, "Process Validation: General Principles and Practices."[25]

B. Non-critical in-process controls

Non-critical in-process controls are controls that do not impact the quality of the finished product. CVM encourages the identification and description of non-critical in-process controls to demonstrate understanding of the manufacturing process.

C. Validation or evaluation of manufacturing procedures

For recommendations on process validation of recombinant protein intermediate, drug substance, or drug product see the principles outlined in GFI #216, "Chemistry, Manufacturing, and Controls (CMC) Information – Fermentation-Derived Intermediates, Drug Substances, and Related Drug Products for Veterinary Medicinal Use."[26]

A description and results from studies that demonstrate the suitability and adequacy of critical manufacturing steps should be provided in the CMC technical section. Below are a few examples of these studies:

- Cell growth and harvesting processes to ensure the reproducibility of routine batches.

- Purification process demonstrating that contaminants, leachables, reagents used for purification, endotoxin, antibiotics, residual host proteins, and residual host DNA are adequately removed, where appropriate.

- Viral clearance processes demonstrating appropriate viral load reduction.

VIII. Characterization of Drug Substance

The sponsor should adequately characterize the recombinant protein drug substance. All test methods for the characterization should be described and should provide results that are reliable

[25] https://www.fda.gov/media/71021/download (January 2011).

[26] https://www.fda.gov/media/79873/download (March 2012).

and reproducible. Raw data for the drug substance characterization, including legible copies of chromatograms and spectra and photographs of gel electrophoresis, should be provided in the CMC technical section. New analytical technologies are continually being developed and their use is encouraged when and where appropriate. Examples of drug substance properties that should be characterized are described below.

A. Elucidation of structure and other characteristics

1. Physicochemical characterization

The following physicochemical properties should be characterized:

- The amino acid sequence should be confirmed using appropriate techniques such as amino acid compositional analysis, full amino acid sequencing, and peptide mapping. The determination of disulfide linkages, where applicable, should be provided.

- Molecular weight or size determined using size exclusion chromatography, mass spectrometry, or other appropriate techniques.

- Extinction coefficient determined by UV absorption.

- Electrophoretic patterns for identity, purity, and heterogeneity determined by isoelectric focusing, capillary electrophoresis, or other appropriate techniques.

- Liquid chromatographic patterns determined using size exclusion chromatography, reverse phase chromatography, ion exchange chromatography, or other appropriate techniques.

- Spectroscopic profiles for higher order structure characterization examined using circular dichroism, Fourier-transform infrared spectroscopy, differential scanning calorimetry, or other appropriate techniques.

- Glycosylation profiles of glycoproteins determined by peptide mapping, glycan analysis, Z-number (for sialic acid content), or other appropriate techniques.

- Characterization of other types of post-translational modifications (e.g., oxidation, deamidation, ubiquitination, etc.) that are important for the structure, function, and safety of the recombinant protein.

- The heavy chain and light chain of monoclonal antibodies should be characterized using reducing sodium dodecyl sulphate–polyacrylamide gel electrophoresis or other appropriate techniques.

- For products derivatized with other agents such as other proteins, toxins, or chemicals: the degree of derivatization or conjugation should be characterized.

The amount of free recombinant protein and free components for conjugation should be determined.

Due to inherent biosynthetic processes implemented by mammalian cells to produce proteins, structural heterogeneity often occurs in recombinant protein drug substances. The sponsor should define and control the pattern of product heterogeneity. The recombinant protein structure observed in the batches used in clinical studies and the proposed commercial manufacturing process should be demonstrated to be consistent across batches. If a consistent pattern of product heterogeneity is not demonstrated, an additional evaluation of the activity, effectiveness, and safety (including immunogenicity) of individual forms may be warranted.

2. Biological activity (Potency assay)

The sponsor should establish validated biological assays to measure the specific ability or capacity of the recombinant protein to achieve a defined biological effect. The correlation between the expected clinical response and the activity in the biological assay should be established in pharmacodynamic or clinical studies. Information about the batches used along with the results that support the clinical relevance of the biological activity should be provided.

CVM recommends that batches used in target animal safety (TAS) and effectiveness studies be characterized using adequately developed biological assay(s). The sponsor is encouraged to contact CVM regarding the proposed biological assay(s) in early product development.

3. Immunochemical properties for monoclonal antibodies

The mAb drug substance should be fully characterized for its immunological properties. Affinity and on- and off-rates, avidity, and antigen specificity should be determined using appropriate binding assays. The target molecule bearing the relevant epitope should be biochemically defined. For immunoconjugates that contain toxins or drugs, immunoreactivity before and after conjugation should be assessed.

B. Impurities

The sponsor should provide an assessment of impurities that may be present in the drug substance. The impurities should be adequately characterized with biological activities evaluated where appropriate and when adequate quantities can be generated. Impurities may be either product- or process-related.

1. Product-related impurities including degradation products

Product-related impurities are molecular variants of the drug substance that possess different properties from those of the desired product. Specific product-related

impurities will vary from product to product. The sponsor should assess and characterize any applicable product-related impurities in the recombinant protein drug substance, such as fragmentation, oxidization, deamidation, dimerization, disulfide bridge scrambling (mis-folding), and aggregation of the recombinant protein, which may occur during the manufacturing process or storage.

2. Process-related impurities

Process-related impurities that arise during the manufacture of the recombinant protein can be classified into three major categories: cell substrate-derived; cell culture-derived; and downstream-derived.

- Cell substrate-derived impurities include host cell proteins (HCP) and host cell DNA (HCD) from the cell substrate. A wide range of HCP may be detected by immunoassays. The sponsor is encouraged to establish platform or process-specific HCP assay(s) following the recommendations in USP <1132> Residual Host Cell Protein Measurement in Biopharmaceuticals.[27] It should be noted that the phased clinical studies referenced in USP <1132> are not applicable to veterinary drug product development. The manufacturers for veterinary drug products should consider developing platform- or process-specific HCP assay(s) during the TAS and effectiveness studies. Individual problematic HCPs, which can cause aggregation or fragmentation of the drug, or degradation of excipients, may be detected and quantified by chromatographic and proteomic techniques. The quantity of DNA from the host cells can be determined by quantitative PCR or other appropriate techniques.

- Cell culture-derived impurities may include inducers, antibiotics, or other media components.

- Downstream-derived impurities may include enzymes, chemical and biochemical processing reagents, solvents, carriers, ligands (e.g., monoclonal antibodies, protein A ligands), inorganic salts, heavy metals, and other leachables.

Process-related impurities should be minimized by appropriately controlling the manufacturing process. Any process-related impurities that could not be adequately removed during the manufacturing process should be characterized.

C. Microbiological attributes

The recombinant protein drug substance should be controlled for bioburden based on product attributes, target animal species, as well as dosage form and route of

[27] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M8647_01_01.html (accessed March 11, 2024).

administration of the drug product, as appropriate. Sterile recombinant protein drug substance may need additional sterility and endotoxin testing.

IX. Control of Drug Substance and Drug Product

A. Specifications

The proposed specifications should include the tests that will be performed on each batch of drug substance and drug product, references to the analytical procedures that will be used to perform the testing, and appropriate acceptance criteria for each test. Certain tests as described in this section, are applicable to all drug substances and drug products. Certain dosage forms, drug substances, or drug products could be subject to additional pharmacopoeial testing requirements[28] beyond what is specified in this guidance.

1. Appearance and description

Specifications for the appearance and description of the drug substance and drug product should contain statements describing its color and physical state. For example, "A clear, colorless solution free of particulates" or "A fine, white powder."

2. Identity

The tests for identity should be based on properties specific to the recombinant protein. The use of multiple tests investigating structure, physicochemical, or immunological properties of the drug substance, as described in section VIII.A. *Elucidation of structure and other characteristics*, may be needed to establish the identity of the recombinant protein.

Examples of potential identity tests include those that evaluate heterogeneity patterns resulting from post-translational modifications during biosynthesis such as glycoforms and charge variants. Variants having activity, effectiveness, and safety properties comparable to those of the desired protein product are considered as product-related substances.

3. Purity and impurities

The purity of the drug substance and drug product should be determined after thorough characterization of process- or product-related impurities through properly validated methods, as described in section VIII.B. *Impurities*. For impurities that are generated and controlled during the manufacturing process of the drug substance, such as HCP and HCD, it might not be necessary to evaluate them during the manufacture of the drug product.

[28] Section 501(b) of the Federal Food, Drug, and Cosmetic Act.

For additional information relevant to the characterization of impurities, the sponsor may refer to the following GFIs and USP General Chapters:

- Draft GFI #100 (VICH GL18 (R2)), "Impurities: Residual Solvents in New Veterinary Medical Products, Active Substances, and Excipients (Revision 2),"[29] GFI #211, "Residual Solvents in Animal Drug Products Questions and Answers,"[30] GFI ICH Q3C (R8), "Impurities: Guidance for Residual Solvents,"[31] and USP <467> Residual Solvents[32] should be consulted when setting limits for residual solvents.

- GFI #255, "Elemental Impurities in Animal Drug Products Questions and Answers."[33]

- The sponsor may refer to USP <1132> Residual Host Cell Protein Measurement in Biopharmaceuticals and USP <1130> Nucleic Acid-Based Techniques – Approaches for Detecting Trace Nucleic Acids (Residual DNA Testing)[34] for the recommendation on the quantitation of HCP and HCD, respectively.

- Although GFI #92 (VICH GL10(R)), "Impurities in New Veterinary Drug Substances (Revision),"[35] does not address recombinant protein products, the levels for reporting, identifying, and qualifying organic and in-organic process-related impurities as described in this guidance are applicable to well-characterized recombinant protein products.

4. Biological activity (Potency)

Assays for biological activity or potency of the recombinant protein should be validated for the drug substance and drug product. The potency assays should be measurable, quantitative, and clinically relevant. The capability of the potency assays to differentiate manufacturing changes and to indicate stability of the drug substance and drug product should be demonstrated. More information about potency assays can be found in GFI #177 (VICH GL40) and in the following USP General Chapters:

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[29] https://www.fda.gov/media/70410/download (July 2022). This draft guidance, when finalized, will represent the current thinking of the FDA on this topic.

[30] https://www.fda.gov/media/79782/download (April 2015).

[31] https://www.fda.gov/media/138334/download (December 2021).

[32] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M99226_08_01.html (accessed March 11, 2024).

[33] https://www.fda.gov/media/111953/download (November 2020).

[34] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M2744_01_01.html (accessed March 11, 2024).

[35] https://www.fda.gov/media/70365/download (November 2007).

USP <111> *Design and Analysis of Biological Assays*,[36] USP <1030> *Biological Assay Chapters – Overview and Glossary,*[37] USP <1032> *Design and Development of Biological Assays,*[38] USP <1033> *Biological Assay Validation*,[39] and USP <1034> *Analysis of Biological Assays*.[40]

5. Quantity

The total amount of recombinant protein present should be determined using appropriate assay methods and provided as part of the drug substance and drug product specifications.

6. Microbiological attributes

Microbial testing is generally recommended for non-sterile products. Refer to the principles as outlined in Draft GFI, "Microbiological Quality Considerations in Non-sterile Drug manufacturing."[41]

For sterile formulations, refer to USP <71> *Sterility Tests*[42] for appropriate assessment of the product sterility. Endotoxin should be assessed following USP <85> *Bacterial Endotoxins Test*.[43]

7. Additional testing

Special considerations should be given to the product dosage form, route of administration, and target animal species to determine if any additional tests are warranted. Any additional testing, such as particulate matter, pH, osmolality, particle

[36] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M98860_02_01.html (accessed March 11, 2024).

[37] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M5877_01_01.html (accessed March 11, 2024).

[38] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M1354_01_01.html (accessed March 11, 2024).

[39] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M912_01_01.html (accessed March 11, 2024).

[40] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M5677_01_01.html?msclkid=5f037abecfa911ec84ff300e282f58cc (accessed March 11, 2024).

[41] https://www.fda.gov/media/152527/download (September 2021). This draft guidance, when finalized, will represent the current thinking of the FDA on this topic.

[42] A preview of this USP chapter can be found at https://www.usp.org/harmonization-standards/pdg/general-methods/sterility-test (accessed March 11, 2024).

[43] A preview of this USP chapter can be found at https://www.usp.org/harmonization-standards/pdg/general-methods/bacterial-endotoxins (accessed October 23, 2023).

size distribution of powder, and the respective proposed acceptance criteria, should follow the appropriate pharmacopeial guidelines.

For example, for recombinant protein product formulated in liquid dosage forms, the sponsor should characterize the visible particulate matter. Additionally, for liquid injectable products, compliance with USP General Chapters <787> *Subvisible Particulate Matter in Therapeutic Protein Injections*,[44] <789> *Particulate Matter in Ophthalmic Solutions*,[45] and <790> *Visible Particulates in Injections*[46] are recommended as appropriate. Information on appropriate test methods for injectable products may be found in USP General Chapters <1787> *Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections*,[47] <1788> *Methods for the Determination of Subvisible Particulate Matter*,[48] and <1790> *Visual Inspection of Injections*.[49]

B. Analytical procedures

Analytical procedures should be provided if they are not from the USP compendium or other FDA-recognized standard references or are procedures that are modified from those sources. Such analytical procedures should be described in sufficient detail to allow a competent analyst to reproduce the necessary conditions and obtain results within the proposed acceptance criteria.[50]

C. Validation of analytical procedures

For the validation of analytical procedures, refer to GFI #63 (VICH GL1), "Validation of Analytical Procedures: Definition and Terminology,"[51] GFI #64 (VICH GL2), "Validation of Analytical Procedures: Methodology,"[52] USP <1225> *Validation of*

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[44] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M6497_02_01.html (accessed March 11, 2024).

[45] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M99587_01_01.html (accessed March 11, 2024).

[46] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M7197_01_01.html (accessed March 11, 2024).

[47] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M7866_03_01.html (accessed March 11, 2024).

[48] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M3023_02_01.html (accessed March 11, 2024).

[49] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M7198_06_01.html (accessed March 11, 2024).

[50] GFI, "Analytical Procedures and Methods Validation for Drugs and Biologics," (July 2015).

[51] https://www.fda.gov/media/70168/download (July 1999).

[52] https://www.fda.gov/media/70189/download (July 1999).

Compendial Procedures,[53] and USP <1226> *Verification of Compendial Procedures*[54] for more information. Furthermore, the recommendations in USP <1033> *Biological Assay Validation* should be followed for biological activity or potency assays.

D. Batch analysis

The primary batches[55] of drug product reported in the CMC technical section should be used in TAS and effectiveness studies. Drug product sponsors should contact CVM to discuss situations in which the CMC primary batches may be different than those used in TAS or effectiveness studies.

Analysis data should be provided for batches used for TAS and effectiveness studies, stability batches, as well as batches produced in relevant process development and process validation. Analysis should be performed using validated analytical procedures. A description of each batch (e.g., batch size, manufacturing date, purpose of the batch) should also be provided. For a drug product having multiple strengths, at least one batch of each strength should be included in the batch analysis.

E. Justification of specification

To justify the proposed specifications, the sponsor should follow the principles in GFI #177 (VICH GL40).

X. Reference Standards or Materials

The establishment of reference materials should follow principles described in CVM GFI #177 (VICH GL40). The clinical relevance of the reference standard used in biological activity or potency assays should be established.

XI. Container Closure System

The container closure should be evaluated and selected for its capability to maintain drug product quality through expiry under the labeled storage and use conditions. If an intermediate or drug substance is to be stored after manufacture, but before final manufacturing into drug substance or drug product, the container closure for the intermediate or drug substance should also be evaluated. Additional information for container closure system can be found in applicable USP General Chapters, including USP <660> *Containers – Glass*,[56] USP <661> *Plastic Packaging*

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[53] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M99945_04_01.html (accessed March 11, 2024).

[54] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M870_03_01.html (accessed March 11, 2024).

[55] For the purpose of this guidance, primary batches are defined as drug product batches manufactured and used for the registration of the drug product with the FDA.

[56] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M1757_02_01.html (accessed March 11, 2024).

Systems and Their Materials of Construction,[57] USP <670> *Auxiliary Packaging Components*,[58] and USP <671> *Containers – Performance Testing.*[59]

Furthermore, additional factors should be considered during the selection of packaging materials for recombinant protein products. For products packaged in prefilled syringes, the following issues should be considered:

- Residual tungsten particles originating from the manufacturing process of glass prefilled syringes may induce protein aggregation.
- Silicone oil, commonly used to lubricate the inside of glass prefilled syringes, can interfere with proteins and lead to protein aggregates.
- Syringeability may be an issue for viscous, highly concentrated drug products (e.g., those with protein concentrations above 50 mg/mL) and should be evaluated.
- Filling of syringes (homogeneity) could be an issue for viscous, highly concentrated drug products, especially if the filling line stops during the filling process.

For multi-dose container closures for injectable drug products, it should be demonstrated that quality is maintained through expiry or depletion of the filled contents. Further guidance on how multi-dose container closures should be evaluated and whether an associated statement should be placed on the labeling (including package insert) is discussed in GFI #242, "In-Use Stability Studies and Associated Labeling Statements for Multiple-Dose Injectable Animal Drug Products."[60]

XII. Stability

A. Pre-approval stability data

The pre-approval stability testing for recombinant protein products should follow the principles in GFI #99 (VICH GL17). CVM recommends that the stability batches to support the product expiry are manufactured in the same facility proposed for the commercial manufacture.

Protein drug product stability depends on complex (and sometimes unpredictable) interactions between the intrinsic properties of the specific protein, protein concentration in the formulation, and other extrinsic factors, such as formulation composition, container closure, and environmental conditions. Therefore, bracketing and matrixing stability

[57] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M99420_05_01.html (accessed March 11, 2024).

[58] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M2316_03_01.html (accessed March 11, 2024).

[59] A preview of this USP chapter can be found at https://doi.usp.org/USPNF/USPNF_M99430_03_01.html (accessed March 11, 2024).

[60] https://www.fda.gov/media/102469/download (November 2020).

study designs are generally inappropriate for recombinant protein products, and every variation of the drug product (e.g., drug strength, excipient concentration, container closure) should be placed into the stability program.

Other stability tests that may need to be performed include:

- Photostability. Refer to GFI #75 (VICH GL5), "Stability Testing: Photostability Testing of New Veterinary Drug Substances and Medicinal Products."[61]

- Freeze-thaw study of intermediates, drug substances, or drug products in liquid and semi-solid dosage forms.

- For drug products that are lyophilized and intended for reconstitution prior to administration, a study should be conducted to demonstrate drug product stability after reconstitution to support the storage conditions and maximum use period as specified on the drug product label.

- For drug products in liquid dosage forms, the stability study may be performed at different orientations of the container, such as upright, inverted, or horizontal, to support the labeling language on the orientation of the container during storage.

- For combination product, testing of the fully assembled delivery device prefilled with the protein product should be performed. Both the functionality of the device and the stability of the product within the device should be tested. In-use studies, when applicable, should simulate patient use per the instructions (including the duration of time and the temperature) on the labeling.

B. Post-approval stability protocol and stability commitment

A post-approval stability protocol and stability commitment should be provided. The sponsor should follow the general format in GFI #5, "Drug Stability Guidelines,"[62] when submitting the stability study commitment for drug substance and finished drug product. For example, the sponsor should commit to placing the first three full-scale production batches into the long-term stability program post-approval, if such stability data are not included in the CMC technical section, followed by a percentage of annual production batches (with a minimum of one batch per year).

XIII. Labeling

If an intermediate or drug substance is to be stored after manufacture, but before final manufacturing into drug substance or drug product, the label on the container closure for the intermediate or drug substance should be provided. The following should be included on the label of intermediates and drug substances:

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[61] https://www.fda.gov/media/70262/download (September 1999).

[62] https://www.fda.gov/media/69957/download (December 2008).

- Name
- Units of activity (e.g., micrograms per milligram, microgram per microliter, units per gram)
- Amount in the primary container
- Batch number
- Statement regarding sterility if applicable
- Expiry or re-test date
- Storage conditions expressed as a numerical value or range (e.g., 5° ± 3°C)
- Statement regarding number of permitted freeze-thaw cycles, if applicable

The following CMC information should be included on the label of drug products:

- The proprietary and established name
- Units of activity (e.g., micrograms per milligram, microgram per microliter, units per gram)
- Amount in the primary container
- Batch number
- Statement regarding sterility if applicable
- Expiration date
- Storage conditions expressed as a numerical value or range (e.g., 5° ± 3°C)
- For prescription parenteral drugs, all components, both active and inactive, and their quantities or proportions should be listed
- Statement regarding number of permitted freeze-thaw cycles, if applicable

Specific storage conditions should be stated (e.g., for drug products that cannot tolerate freezing or that need to be protected against light or humidity). For freeze-dried products intended for reconstitution, labeling should include the maximum storage period after reconstitution as supported by stability studies. For multi-dose vials, labeling should include any limitations of use after the first dose is withdrawn. For specific labeling statements for multi-dose injectable products, refer to GFI #242. CVM recommends that draft text of the label be submitted in the CMC technical section.