
Manual of Standard Operating Procedures and Policies

Regulatory - Review

Review Responsibilities for the CMC Section of Biologic License Applications and Supplements

SOPP 8401.4

Version #1

Apr. 8, 2005

1. Purpose

The purpose of this document is to provide guidance to all CBER reviewers for the areas of responsibility when reviewing the Chemistry, Manufacturing and Controls (CMC) section of a Biologics License Application (BLA) and BLA supplements. Since it follows the CMC format for BLAs, it does not address review responsibilities for NDAs, PMAs, or blood and plasma products.

2. Definitions

The following designations are defined for the purposes of this SOPP. Each section is associated with a designation to clarify review responsibilities. Areas of review responsibilities are listed as general categories: Primary, Shared, FYI, and Inspection. Where necessary, the responsibilities as they pertain to the Product Offices or DMPQ will be noted.

Primary (1°)

A primary responsibility for either the Product Office (PO) or the Division of Manufacturing and Product Quality (DMPQ) means that they have the primary review responsibility for this particular section, and the review must be documented in a review memo.

Shared

Product office and DMPQ share the review responsibilities. Assessment must be documented in a review memo. Product office and DMPQ will perform a complete review of these sections.

FYI

When a particular review group has primary review responsibility, other review team members should review for background information to aid in review of the submission. Documentation of review is not usually required.

Insp

The product offices and DMPQ should review in preparation for the pre-approval/license inspection. These items may be noted as separate issues in a review memo, however the primary means of review will be through documentation in the Establishment Inspection Report.

3. Background

This SOPP covers the review responsibilities for the CMC section of Biologics License Applications and supplements. It follows the general sequence of the relevant CMC guidance documents (see references). The sections for review are noted, and where necessary, the depth of review is discussed. This SOPP does not preclude reviewers from looking at the entire CMC section; the function of this SOPP is to clarify specific areas of responsibility for review team members. The CMC sections may vary between product classes. Please note that guidance for the review of unique CMC sections for the other product classes or *in vitro* diagnostic products will be noted in the appropriate section. This SOPP is not intended to provide all the detailed information expected in a submission and should be used in conjunction with the appropriate CMC guidances and regulations.

This SOPP does not address the adequacy of information submitted or the format for the reviewer's comments. This SOPP covers the following products: therapeutic recombinant DNA-derived products; monoclonal antibodies; vaccines or related products; human plasma-derived products; and biological in-vitro diagnostic products (see appropriate CMC guidance documents in the reference section) and therefore each sub-section may not be applicable for every review.

4. Policy

It is CBER policy that the CMC section of a BLA application or supplement will be reviewed by staff assigned as described below.

5. Responsibilities and Procedures

DRUG Substance or *In vitro* Diagnostic Substance

A. Description and Characterization Section

1. Description (PO 1°, DMPQ FYI)

Description of the drug or *in vitro* substance (e.g., chemical structure, molecular weight, USAN name, etc.)

2. Characterization/Proof of Structure (PO 1°, DMPQ FYI)

a. Physiochemical Characterization of Reference Standard and Qualifying Lots

- Physiochemical characterization of the reference standard and qualifying lots including the results of all analytical testing (data and legible copies of chromatograms, photographs, etc.) to support the identity, purity, stability of the drug or *in vitro* substance and consistency of manufacture.
- Description and validation of the assays, including the methods and standards used, the inter- and intra-assay variability, analytical sensitivity and specificity, linearity (for quantitative tests) and the acceptance criteria (upper and lower limits)

b. Biological Activity/Activity of the *in vitro* substance

- Description and results of *in vivo* and *in vitro* biological testing performed on the reference standard and qualifying lots to show the potency and activity(ies) of the drug or *in vitro* substance
- Description and validation of the bioassays including the methods and standards used, the inter- and intra-assay variability, analytical sensitivity and specificity, linearity (for quantitative tests), the limits of detection of the assay, and the acceptance criteria (upper and lower limits)

c. Statistical analysis/data validating methods ensuring accurate results

Procedures, data, and results of statistical analysis should be provided, and are normally the responsibility of the Office of Biostatistics and Epidemiology.

B. Manufacturers

1. Identification (Shared)

- Names, addresses, FDA registration number for each manufacturer or manufacturing location
- Operations performed by each party
- Responsibilities delegated to each manufacturer by the applicant

2. Floor Diagram(s) (DMPQ 1° PO FYI)

- General layout of the facilities (simple diagram depicting the relationships of the manufacturing areas)
- Diagram of the facility which traces the drug or *in vitro* substance through the manufacturing process
- Description of adjacent areas not used in the manufacture of the product
- Room numbers or unique identifiers should be present

3. Other Products (Shared)

- Additional products manufactured or manipulated in the same areas
- Description of the type and developmental stages of each
- Indication whether multiple products will be produced on a campaign or concurrent basis
- Indication whether equipment is shared or dedicated; if equipment is shared, discussion on cleaning should be included. Data for cleaning should be evaluated on inspection. See establishment description section when required for respective product classes with respect to cleaning validation.

4. Contamination Precautions (Shared unless noted)

- Air quality classification of room or area in which an operation is performed, as validated and measured during production (DMPQ 1°)
- Narrative description of the procedures or facility/equipment design for the control of contamination, cross contamination and containment
- A general description of the equipment with respect to processes (for example, open vs. closed, sterile vs. non-sterile processing or manufacturing steps). (DMPQ 1°)
- A description of the in-process controls performed to prevent or identify contamination or cross-contamination
- When more than one cell line or product is manipulated in a single area - Discussion of measures to prevent cross contamination, including segregation of pre-and post- viral inactivation/clearance steps, or use of dedicated equipment. For cell banks, the locations of cell line storage, identification and segregation of cell lines, and validation of integrity of storage vials or ampoules should also be evaluated.

C. Methods of Manufacture

1. Raw Materials and Reagents (PO 1°, DMPQ INSP)

Issues associated with raw materials used in the manufacture of a product are addressed either by the Product Offices or DMPQ depending on the nature of the issue. For example, GMP issues such as sampling plans and suitability of storage should be reviewed by DMPQ on inspection. Issues such as setting specifications or test methodologies are generally the responsibility of the product office reviewers.

Details of the vendor qualification programs, raw material handling, and compendial equivalence if applicable should be reviewed and evaluated on inspection. Process gases and water are also considered raw materials and should be reviewed, along with their companion systems, during the inspection. Determinations of country of origin must be made for all animal source raw materials and reagents and should be verified during the inspection. All raw materials and reagents should be carefully evaluated as to their source materials. For example, trypsin is usually derived from porcine sources, but may also be a recombinant product. The source of all human blood and blood components must be determined, i.e., U.S. licensed facility, U.S. registered facility, or foreign facility.

- Review tests and specifications of all special reagents and raw materials used in the manufacture of the drug or *in vitro* substance (e.g., culture media, buffers, sera, antibiotics, preservatives, etc.)
- Review ancillary products (e.g., monoclonal antibodies used in affinity chromatography)
- Review the description of the tests and specifications for materials of human or animal origin that have the potential to be contaminated with adventitious agents. Validation data or certification supporting the freedom from adventitious agents should be reviewed.

2. Flow Charts (PO 1°, DMPQ Insp)

A complete visual representation of the manufacturing process should include:

- Steps in the production
- Equipment and materials used
- Room or area where the operation is performed
- A complete list of in-process controls
- In-process holding steps, including time and temperature limits
- Methods used in product transfer between steps or between equipment, areas, or buildings
- Computer-controlled steps should be identified

3. Detailed Description

a. Animal Sources (PO 1°, DMPQ FYI)

- Species, age, and health status
- Country of origin
- Source and type
- Genetic stability for transgenic animals
- Adventitious agent screening and quarantine section

- Animal husbandry procedures and veterinary oversight
- Immunogens used
- Substance harvested
- Animal facility GMP issues should be evaluated during inspection (DMPQ INSP)

b. Cellular Sources (Shared unless noted)

i. Cell Substrate/Host Cell/Expression Vector System (PO 1°, DMPQ FYI)

A. Recombinant DNA Products

- Host cells (source, phenotype and genotype, markers for cell stability, purity, and selection)
- Gene construct (detailed description of inserted genetic material)
- Vector
- Final gene construct
- Cloning and establishment of the recombinant cell line

B. Monoclonal antibodies

- Detailed description of the development and immortalization procedures

C. Animal Cells

- Species and age of animals and the source tissue
- Health status of the animals, including veterinary and laboratory monitoring
- Description of the primary cell substrates
- Explanation of concurrent testing done to demonstrate absence of adventitious agents

D. Cell lines

- Source of the cell line
- History of the cell line
- Adventitious agent testing of the cell line

ii. Cell Seed Lot System (PO 1°, DMPQ INSP)

A. Master Cell Bank

- Detailed description including methods, reagents, and media
- Methods of identification
- Test methods for characterization, genetic sequence, or detection of contamination

- Storage location and conditions
- Quantity of vials

B. Working Cell Bank

- Method of production including reagents, media, date of creation, quantity of the cell bank, number of cell doublings from the master cell bank
- Storage location and conditions
- Quantity of vials and expected yield

C. End of Production Cells

- Detailed description of characterization

DMPQ: This section should be reviewed to become familiar with the cell banking system used by the manufacturer. All aspects of cell banking, including storage and records should be reviewed during the inspection.

iii. Cell Growth and Harvesting (Shared)

Propagation

- Detailed description of the process of inoculation, cell growth, and harvesting
- Description of equipment used
- Composition of media used
- Operating control parameters
- In-process testing
- Stages of cell growth
- Inactivation procedures

Harvesting

- Description of methods used for separation of the crude drug/*in vitro* substance from the propagation system including:
 1. parameters monitored
 2. definition of a batch
 3. precautions taken to prevent contamination, equipment sterilization, and for aseptic processing
 4. description of the procedures to monitor bioburden
 5. storage conditions
- Propagation information related to prevention of contamination
- How transfers between vessels are made and whether they are closed or open

- Precautions taken to prevent contamination, including sterilization of equipment

iv. Purification and Downstream Processing (Shared)

- Rationale for methods used
- Description of the methods used
- Bioburden and endotoxin limits
- Reprocessing (if any) should be discussed
- Methods to prevent cross-contamination

Product office reviews should focus on product characterization and specifications as well as life-time and regeneration (reuse) of columns, including column effectiveness data such as flow rates, pressures, storage, re-packing, etc.

1. Description of the methods and materials by which intermediate forms and the final bulk of the drug or *in vitro* substance are separated and concentrated from cell, media, solvents or solutions used in the production process;
2. Inactivation methods, including agents used and parameters monitored;
3. Purification including methods used and equipment used.

DMPQ reviews should focus primarily on cleaning, endotoxin and bioburden monitoring and limits, prevention of cross-contamination and other GMP issues as they relate to these steps in manufacturing.

v. Detoxification (for toxoid or toxoid-containing vaccines)

- Methods and agents used for the detoxification
- Stage in production where detoxification is performed
- Parameters that are monitored

vi. Synthetic drug substance (PO 1°)

- Details of synthesis for synthetic peptides
- Conjugates or modified drug substances derived from another drug substance or intermediate through chemical or enzymatic modification
- A detailed description of the specification and acceptance criteria for the native drug or *in vitro* substance starting materials
- The conditions of all reactions and /or syntheses used to produce a semi-synthetic conjugated molecule, derivatized molecule, or subunit.

c. Human Sources (PO 1°, DMPQ FYI)

- Donor suitability/acceptance criteria
- Collection method, volume, and receptacle
- Anticoagulants used

- Description of component of interest
- Testing performed (especially viral marker testing)
- Purification and inactivation procedures
- Storage conditions
- Viral inactivation procedures
- Immunization dose and schedule
- Other unique characteristics

d. Virus sources (PO 1°, DMPQ FYI)

- Original Source of the virus
- Passage history of the virus
- Details of the seed lot system
- The culture techniques for virus seed maintenance

e. Synthetic sources (*In vitro* diagnostic products only) (PO 1°, DMPQ FYI)

- Detail of the peptide synthesis including purification

4. Batch Records (Shared)

Review complete batch records (of at least one executed batch)

D. Process Controls Section

- In-Process controls (Shared)

This section should be reviewed to gain familiarity with sampling procedures, test methods, and criteria for accepting or rejecting a batch or in-process batch.

The description of the methods used for in-process controls, e.g., fermentation, harvesting, and downstream processing, should be reviewed. The rationale for reprocessing steps that describes the circumstances under which reprocessing would be allowed, and validation data to indicate the effect on the product, should be evaluated.

- Process Validation (Shared)

In general the product office will have the primary responsibility for reviewing most aspects for establishing limits, ranges, and specifications; DMPQ will have shared responsibility for the consistency of manufacture and the reproducibility of the quality of the lots produced.

The description and documentation of the validation studies should be reviewed, including:

1. Validation studies for the cell growth and harvesting process (Shared)
2. Validation studies for the purification process (Shared)
3. Microbiology (Shared)
 - media sterilization

- effectiveness of preservatives
- decontamination
- inactivation of cells prior to release into the environment (PO 1°)
- for sterile bulks see below

4. Reprocessing/rework (Shared)
5. Inactivating or removing infectious pathogens (PO 1°)
6. Others, as appropriate

E. Reference Standard(s) (PO 1°)

1. Primary Reference Standard (PO 1°)

- Citation for the standard (WHO, NIBSC, FDA)
- Certificate of analysis
- In-house primary standards should be reviewed including characterization, specifications, and the results of testing

2. Working Reference Standard (PO 1°)

- Description of the preparation, characterization, specifications, testing, storage and shelf life

F. Specifications/Analytical Methods (PO 1°, DMPQ FYI)

1. Drug Substance / *In Vitro* Substance Specifications and Tests (PO 1°, DMPQ FYI)

- a. Description of the specifications and analytical methods for release and shelf life (specifications and tests for the drug or *in vitro* substance to describe the identity, purity, strength/potency, and lot-to-lot consistency)
- b. Certificates of analysis and analytical results for three consecutive qualification lots should be submitted

2. Impurities Profile (PO 1°)

A discussion of the impurities profile with supporting analytical data should be reviewed.

G. Container/Closure System(s) (DMPQ 1°, PO FYI)

Note that this may be submitted in a companion Master File.

- Description of container closure system
- Compatibility, toxicity, and biological test data
- Information regarding supplier of the container/closures

DMPQ should review container/closure integrity testing and biocompatibility studies.

H. Drug or *In vitro* Substance Stability (PO 1°, DMPQ as noted)

- Description of the storage conditions, study protocols, and results

- Data to measure biological activity and degradation products
- Data to support storage of intermediates (DMPQ 1°)

DMPQ should evaluate the stability program and the number of samples kept for stability and retests.

DRUG Product / *In Vitro* Diagnostic PRODUCT

A. Composition, including components (PO 1°, DMPQ FYI)

- All components and batch quantities for the drug or *in vitro* diagnostic product.
- The composition of all ancillary products that might be included in the final product should be reviewed.

B. Specifications & Methods for Drug or *In Vitro* Diagnostic Product Ingredients and Ancillary Components (PO 1°, DMPQ FYI)

1. Drug or *In vitro*

Diagnostic Substance Including All Active Ingredients and Ancillary Components (PO 1°, DMPQ FYI)

This section should be reviewed to gain familiarity with the tests and specifications for all active ingredients, if not specified in the drug or *in vitro* diagnostic substance section.

2. Excipient(s): (PO1°, DMPQ FYI)

- a. Compendial Excipient(s)
- b. Non-Compendial Excipient(s)

3. Adjuvants (PO1°, DMPQ FYI)

- List of the chemical formula and precise quantity used per unit dose
- Method used to determine quantity (assay or calculation)

4. Preservatives (PO1°, DMPQ as noted)

- Each preservative identified by chemical and trade name
- Rationale when used with single-dose products
- Preservative effectiveness studies (Shared)

This section should be reviewed to gain familiarity with the tests and specifications for excipients.

C. Manufacturer(s) (Shared)

This section should be reviewed to determine all manufacturers involved in the manufacturing and testing of the drug product including contractors and responsibilities of each.

D. Methods of Manufacture and Packaging (DMPQ 1°)(PO as noted)

- Sterilization operations, aseptic processing procedures, lyophilization (PO for product stability as noted in section "I" below), and packaging procedures.

E. Specification & Test Methods for Drug or *In Vitro* Diagnostic Product (Shared)

- Sampling Procedures (Shared)

This section should be reviewed to determine sampling procedures for monitoring a batch of finished drug or *in vitro* diagnostic product.

- Specifications & Methods (Shared)

This section should be reviewed to gain familiarity with test methods selected to assure identity, purity, strength and/or potency, as well as lot-to-lot consistency.

F. Container/Closure System (DMPQ 1°, PO FYI)

- This section should be reviewed to determine the container closure compatibility with the drug product.
- Review results of biocompatibility, toxicity and biological tests.
- Evidence of container closure integrity testing.

G. Microbiology (DMPQ 1°)

H. Lyophilization (DMPQ 1°, PO FYI)

- Narrative description of the validation and validation summary
- Explanation of excursions or failures
- Deviation reports and results of investigations
- Certification that IQ and OQ have been completed
- Note that product quality issues are a primary review function of the product offices and are addressed in other sections

DMPQ review should focus on the information provided by the firm as required in "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products." (November 1994)

I. Drug / *In Vitro* Product Stability (PO 1°, DMPQ FYI)

- Study protocols and
- Results supporting the stability of the Drug or *In Vitro* Diagnostic Product.
- Plans for post approval stability testing

J. Investigational Product/Formulation (PO 1°, DMPQ FYI)

This section should be reviewed to gain familiarity with differences in formulation, manufacturing process, or site between the clinical trials materials and commercial production batches of drug substance and drug product.

K. Environmental Assessment (DMPQ 1°)

An environmental assessment (EA) as outlined in 21 CFR Part 25, or a request for a categorical exclusion with the basis for the exclusion, as outlined in 21 CR Part 25.31(a), (b) or (c) should be submitted. If an EA is appropriate, it should include a description of the action that is being considered and should address all components involved in the manufacture and disposal of the product.

L. Methods Validation (Shared)

- the analytical methods used to evaluate the drug or *in vitro* substance and the drug or *in vitro* diagnostic product with the product office as the primary reviewer.
- DMPQ review should focus on method validation and qualification of the microbiological assays such as sterility, endotoxin, bioburden, and preservative effectiveness studies.
- Refer to the Guideline for Submitting Samples and Analytical Data for Methods Validation (February 1987)

M. Establishment Description Section (DMPQ 1°)(unless noted) -

1. General information to be submitted should include:

- Product, personnel, equipment, waste, and air flow
- Indication of areas served by each air handling unit
- Air pressure differentials between adjacent areas

2. Water systems

- Review should evaluate the production and maintenance of water systems used in manufacturing and rinsing of product contact equipment and containers/closures. Information submitted should include at least a general description of the water system, specifications and monitoring frequency.

3. Heating, Ventilation and Air Conditioning Systems (HVAC)

- Information should include the number and segregation of the air handling units
- Whether air is single-pass or recirculated
- Any containment features and air changes per hour
- Review the HVAC systems to ensure adequate control over the manufacturing areas, and information to be considered would be the qualification process, action and alert limits, routine monitoring program, and corrective actions when limits are exceeded

4. Contamination/Cross-contamination issues

This section includes information that should be reviewed to determine the potential impact on product quality from environmental sources or carryover from other products.

- Cleaning procedures and methods should be submitted, including information on the validation procedures for the removal of product and cleaning agents, as well as the sampling methods and analytical methods.
- Shared equipment: a list of the dedicated and shared equipment should be provided, and the changeover procedures/cleaning procedures for shared equipment.
- Containment features such as air pressure differentials, airlocks, and segregation of air handling units.

5. Lyophilization (DMPQ 1°, PO 1° for product-related issues such as stability)

- Information would include a validation summary for lyophilization of the intermediate or final product, equipment qualification, and data derived from process validation and conformance

lots.

6. Computer systems

- Submission should contain information on computer systems that control critical manufacturing processes. Information should include:
 - Developer of the system
 - List of computer-controlled manufacturing steps
 - Description of the validation process and validation summary
 - Deviation reports and explanation of failures, including investigations

Note that there is no Establishment Description section for therapeutic recombinant-derived products.

- See CMC Guidance Documents

6. **Appendix**

Appendix 1 - [Table of Assignments](#)

7. **Effective Date**

April 8, 2005

8. **References**

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 (August 1996)

Guidance for Industry, Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (January 1999)

Guidance for Industry, Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological *In Vitro* Diagnostic Product (March 1999)

Guidance for Industry, For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma, or Serum-Derived Products (February 1999)

9. **History**

Comment / Revision	Approved By	Approval Date	Version Number	Comment
Leonard Wilson, RMCC	Robert Yetter, PhD	6/11/2002	1	Original Prepared to implement PDUFA commitments.

Updated: April 18, 2005