POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Office of Biotechnology Products and Office of Process and Facilities, Interactions on BLA Assessments

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PURPOSE

This MAPP outlines policies and procedures in the Office of Biotechnology Products (OBP), and the Office of Process and Facilities (OPF), within the Office of Pharmaceutical Quality (OPQ) designed to:

- Ensure product quality as it relates to safety and efficacy of the product.
- Provide a team approach to product quality evaluation of biologics licensing applications.
- Define clear roles and responsibilities.
- Establish work processes that are effective.
- Develop a system that ensures problems are resolved in a timely and professional manner.

BACKGROUND

The Office of Biotechnology Products, and the Office of Process and Facilities, within OPQ, collaborate in the quality assessment of biologics license applications (BLAs). OBP and OPF have implemented a process improvement initiative to improve coordination in the evaluation of applications. This initiative includes development of the following:

- A timely and responsive system to ensure product quality throughout the product life cycle.
- A process that allows for efficiency, consistency, and innovation within the Agency and in industry.
- The use of science-based risk management and quality principles.
- An integrated (multi-disciplined) collaboration.
- As part of the process improvement initiative, this MAPP was created to outline OBP and OPF responsibilities and procedures.

POLICY

- The Office of Biotechnology Products and Office of Process and Facilities will work together to evaluate BLAs.

RESPONSIBILITIES

- **The joint responsibilities of OBP and OPF include the following:**
    - Quality assessment of BLAs in accordance with discipline specific areas of responsibilities.
    - Plan and conduct collaborative establishment inspections to ensure safety, purity, and potency of the product based on the firm's compliance history, the process control strategy, and facility information. Both offices will follow the current FDA compliance programs and the Investigations Operations Manual (IOM) for establishment inspections, including procedures for generating the FDA form 483.
- **The responsibilities of OPF include the following:**
    - Lead in assessing the manufacturing and control of **drug substance** and **drug product** as it relates to microbial control, sterility assurance, and microbiological product quality, including pertinent product labeling.

- Lead in assessing the conversion and use of facilities for multiproduct production as it relates to the assessment of contamination/cross contamination control.
- Lead in assessing the facilities and equipment.
- Participate, with OBP, in evaluating chemistry, manufacturing, and controls (CMC) process validation and robustness as it relates to microbial control and sterility assurance (see Attachment A).
- Provide IND assistance, as requested.
- Plan collaborative inspections.
- Lead on Pre-license inspections/Pre-approval Inspections (PLI/PAI) in accordance with FDA Compliance Programs.

- **The responsibilities of the Office of Biotechnology Products (OBP) include the following:**

  - Review product structure, relationship between structure and function, and impurities (including contaminants).

  - Review process controls throughout the biological product life cycle for impact on structure/function and impurities.

  - Participate in inspections throughout the biological product life cycle, with a focus on issues related to structure and function. This may include the following:
    - Evaluation of deviations, investigations, and process robustness/control.
    - Review batch record in relationship to process and product quality.
    - Analytical assays.

  - Assure appropriate OBP reviewer education in inspectional matters.

  - Evaluation of Biological Product Deviation Reports (BPDRs).

PROCEDURES

- The following are recommended communications between OBP and OPF:

  - Early supplement category risk assessment for applications.
  - Early identification of assigned team members.
  - Pre-inspection discussion specifying inspection focus (if appropriate).
  - Inspection assignment information.
  - Notification of important or cross-cutting issues/discussions.
  - Exchange of final review and recommendations.
  - Sharing of draft and finalized letters to ensure consistency.

- OBP and OPF are typically included in the following meetings:

- End of Phase 2 (EOP2) meetings and other Investigational New Drug (IND) meetings as appropriate
- Pre-BLA meeting.
- All original BLA meetings specified by Good Review Management Practices (GRMP) and 21st Century Review.
- Facilities-specific meetings.

- The following are procedures for shared BLA supplement[1] letters. Shared supplements include topics with OBP as the lead office and topics with OPF as the lead office (see Attachment B):

  - When OBP is the lead on a supplement, OBP signs off on the letter with OPF concurrence.

  - When OPF is the lead on a supplement, OPF signs off on the letter with OBP concurrence.

  - OBP has the lead on all shared supplements unless a different arrangement is agreed to.

  - Each component retains responsibility for comments (on the letter) in their lead areas.

  - The letter must circulate to all OPF/OBP staff involved in the supplement review and their responsible managers.

- The following are interest reconciliation procedures to resolve conflicts prior to formal dispute resolution:

  - OPF and OBP leadership will be trained in the process of "Interest Reconciliation." "Interest Reconciliation" specifies general steps to resolve conflict so agreements can be reached without formal dispute resolution.

  - Interest reconciliation includes the following:

    - Team members involved in the conflict work with each other to find a resolution to ensure that their interests in the resolution of the conflict are satisfied.

    - If an agreement is not reached, the issue will be referred to their supervisors.

[1] Original BLA submissions are signed off by Office of New Drugs (OND).

- The appropriate next level supervisors of the individuals involved in the conflict will review the facts related to the conflict to determine whether they can resolve the issue at their level.

- If they cannot resolve the conflict, the issue will be referred to the appropriate next level of sub-office supervision The sub-office supervision will make sure to keep any intermediate levels of leadership aware of the referral and the process.

- When the conflict is resolved, an explanation of "how and why" the final decision was made is communicated to all involved in the process.

REFERENCES

1. Investigations Operations Manual (current year) http://www.fda.gov/ICECI/Inspections/IOM/default.htm
2. Guidance for industry on *Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070279.pdf
3. 21st Century Review
4. Code of Federal Regulations

DEFINITIONS

- BLA – Biologics License Application
- BPDR – Biological Product Deviation Reporting
- CMC – Chemistry, Manufacturing, and Controls
- cGMP – Current Good Manufacturing Practice
- IND – Investigational New Drug
- OBP – Office of Biotechnology Products
- OPF – Office of Process and Facilities
- OPQ– Office of Pharmaceutical Quality
- ORA – Office of Regulatory Affairs
- PAI – Pre-approval Inspection
- PLI – Pre-license Inspection
- CFR – Code of Federal Regulations

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
10/22/15		Updated format into the current template and transferred MAPP ownership to OPQ.
7/26/17	1	Updated to reflect that responsibilites previously performed by the Office of Compliance are now performed by the Office of Process and Facilities in OPQ and to reflect the current responsibilities of OPF and OBP in OPQ.

ATTACHMENT A

Roles and Responsibilities for Assessment of BLA Process Validation and Facility/Equipment Qualification

The assessments are grouped under the lead for review. When an advisor is involved, they assist the lead. In an integrated approach, all processes are subject to inspection. Typically, OPF leads PLI/PAI inspections. ORA typically leads surveillance inspections and OBP participates as specified on page 3 under OBP responsibilities.

OPF Assessment Lead:

- Microbial method qualification (CFR, or compendial methods for sterility, endotoxin, bioburden); equivalent methods for microbial qualification are shared with OBP (see Attachment B).
- Container-Closure Integrity, preservative effectiveness, shipment, and materials handling; OBP is lead on shipping stability.
- Finishing process design as it relates to drug product sterility (e.g., sterility assurance evaluation).
- Facility and equipment qualification and validation: contamination/cross contamination control.
- Drug Substance/Drug Product hold conditions at scale for contamination control; OBP is advisor.
- Validation for Cleaning/Sanitization of column chromatography and membrane systems during lifetime use.
- Product simulations for filling/finishing process and for fermentation/buffer tanks.
- Validation of sterilization processes used in drug product manufacturing.
- Validation of disposables for use in manufacturing; OBP is lead for leachables and extractables.
- Supplier (site) qualifications; OBP is lead for intermediates and synthesis process.

OBP Assessment Lead:

- Overall process design and flow for drug substance, non-sterility parameters of drug product: e.g., finishing process design as it relates to stability, extractables, leachables, and interaction with product; OPF is advisor.
- In-process controls for relevant operating and performance parameters; OPF is advisor.
- Hold time validation for product attributes; OPF is advisor for microbial control.
- Impurity and viral clearance validation.

- Lifetime use of chromatograph resins including impurity carryover. Shared with OPF.[2]
- Product quality assessment of in-process materials.
- Validation of consistency of submitted batches for commercial process; OPF is advisor.
- Method validation excluding compendial or CFR sterility, bioburden, and endotoxin method qualifications.
- Qualification of intermediates.
- Raw materials fitness for use.

[2] This is related to above OPF Assessment bullet regarding "Assessment of Validation for Cleaning/Sanitization of column chromatography and membrane systems during lifetime use."

ATTACHMENT B

Additional Clarification in CTD Format

Manufacturing and Product Quality Assessment Responsibilities Between OBP and OPF: BLA or Submission Content From CDT Format Module 3: Format of Quality Section; 3.2 Body of Data

Table 1: Drug Substance Quality Assessments

3.2.S. Drug Substance		OBP	OPF
S.1 General Information	1. Nomenclature	X[3]	Background information for microbial[4] control – no assessment
	2. Structure	X	
	3. General Properties	X	
S.2 Manufacture	1. Manufacturers	Provide support for inspection planning and participation	X Conduct facilities assessment. Identify sites for PLI /PAI inspection; plan inspection and identify and lead team
	2. Description of Manufacturing Process and Process Controls	X	Background for inspection and assess microbial control strategy
	3. Control of Materials	X Including microbial, prion and viral evaluation of cell bank and other biological materials as per 3.2.A.2	Background for inspection and assess microbial control strategy
	4. Controls of Critical Steps and Intermediates	X	Background for inspection and assess microbial control strategy
	5. Process Validation and /or Evaluation	X	Background for inspection and assess validation at scale of the microbial control strategy
	6. Manufacturing Process Development	X	Background for inspection
S.3 Characterization	1. Elucidation of Structure and other Characteristics	X	

[3] X denotes the lead office except where otherwise noted in the columns.
[4] In this MAPP, microbial refers to bacteria and fungi, not viruses or prions.

3.2.S. Drug Substance		OBP	OPF
	2. Impurities	X	
S.4 Control of Drug Substance	1. Specification	X Equivalent microbial specifications are shared[5]	CFR, compendial, or equivalent microbial specifications only
	2. Analytical Procedures	X Equivalent microbial methods are shared[6]	CFR, compendial, or equivalent microbial analytical procedures only
	3. Validation of Analytical Procedures	X Equivalent microbial methods are shared[6]	Validation of CFR, compendial, or equivalent microbial analytical procedures only
	4. Batch Analyses	X	Microbial Attributes only
	5. Justification of Specification	X Equivalent microbial specifications are shared[6]	CFR, compendial, or equivalent microbial specifications only
S.5 Reference Standards or Materials		X	
S.6 Container Closure System		X	
3.2.S.7 Stability	1. Stability Summary and Conclusions	X	Microbial attributes only
	2. Post-approval Stability Protocol and Stability Commitment	X	Microbial attributes only
	3. Stability Data	X	

[5] For equivalent microbial methods, review will be shared and there will be communication between the offices to enable an overall assessment and recommendation on the assay. In general, for extracellular organisms OPF will lead. For intracellular organisms or for equivalent endotoxin methods OBP will lead.

Table 2: Drug Product Quality Assessments

3.2.P DRUG PRODUCT		OBP	OPF
P.1 Description and Composition of the Drug Product		X	Background information for sterility assurance review
P.2 Pharmaceutical Development	1. Components of the Drug Product	X	
	2. Drug Product	X	X
	3. Manufacturing Process Development	X	Background for inspection
	4. Container Closure System	X	X
	5. Microbiological Attributes		X Container Closure integrity: microbial ingress/dye ingress, etc. Preservative effectiveness
	6. Compatibility	X	
P.3 Manufacture	1. Manufacturers	Provide support for inspection planning and participation	X Identify sites for PLI/PAI inspection; plan inspection and identify and lead team
	2. Batch Formula	X	
	3. Description of Manufacturing Process and Process Controls	X	Background information for inspection and for sterility assurance review
	4. Controls of Critical Steps and Intermediates	X	Background information for sterility assurance review
	5. Process Validation and/or Evaluation	X	Review sterilization process/aseptic process validation data for sterility assurance
P.4 Control of Excipients	1. Specifications	X	
	2. Analytical Procedures	X	
	3. Validation of Analytical Procedures	X	
	4. Justification of Specifications	X	
	5. Excipients of Human or Animal Origin	X	

3.2.P DRUG PRODUCT		OBP	OPF
	6. Novel Excipients	X	
P. 5 Control of Drug Product	1. Specifications	X Equivalent microbial specifications are shared[6]	CFR, compendial, or equivalent microbial specifications only
	2. Analytical Procedures	X Equivalent microbial methods are shared[6]	CFR, compendial, or equivalent microbial analytical procedures only
	3. Validation of Analytical Procedures	X Equivalent microbial methods are shared[6]	Validation of CFR, compendial, or equivalent microbial Analytical Procedures
	4. Batch Analyses	X	CFR, compendial, or equivalent microbial specifications only
	5. Characterization of Impurities	X	
	6. Justification of Specifications	X Equivalent microbial specifications are shared[6]	CFR, compendial, or equivalent microbial specifications only
P.7 Container Closure System		X	
P.8 Stability	1. Stability Summary and Conclusion	X	Microbial attributes only
	2. Post-approval Stability Protocol and Stability Commitment	X	Microbial attributes only
	3. Stability Data	X	Microbial attributes only
A APPENDICES	1. Facilities and Equipment	X	X
	2. Adventitious Agents Safety Evaluation	X	
	3. Novel Excipients	X	
R REGIONAL INFORMATION		X	X
3.3 LITERATURE REFERENCES		X	When necessary