

SOPP 8410: Determining when Pre-License/Pre-Approval Inspections are Necessary

Version: 3

Effective Date: September 4, 2018

I. Purpose

- A.** This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff for determining whether pre-license or pre-approval inspections are necessary or can be waived.

II. Scope

- A.** This SOPP applies to Biologics License Applications (BLAs), New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Pre-Market Approvals (PMAs) and their respective supplements processed by CBER.

III. Background

- A.** Section 351 of the Public Health Service Act (PHS Act) and section 704 of the Federal Food, Drug and Cosmetic Act (FD&C Act) provide the regulatory authority to conduct inspections at any establishment where CBER regulated products are manufactured. Under 21 CFR 601.20, a biologics license shall not be issued except upon a determination that the product and establishment comply with the applicable regulations.
- B.** Some applications and supplements include manufacturing establishments that use production areas common to other licensed or approved products, so conducting a pre-license or pre-approval inspection before approval of every application or supplement may not be necessary; facilities that have demonstrated Current Good Manufacturing Practices (CGMP) compliance based on recent inspectional outcomes can and should be considered for inspectional waiver. Unnecessary inspections are a burden to both the industry and the agency.

IV. Definitions

- A. Pre-License Inspection** – Inspection of a facility (new or existing) that will be used to manufacture a new biological product (i.e., inspection for a new Biologics License Application). This includes inspections of

establishments that already manufacture other currently approved products.

- B. Pre-Approval Inspection (biologics)** – Inspection of an establishment used for manufacturing a licensed BLA product for which the applicant has submitted a supplement for a significant manufacturing change (including a new facility) or other change that ordinarily requires on-site review of the change.
- C. Pre-Approval Inspection (drugs and devices that are not biologics)** – Inspection of a facility (new or existing) that will be used to manufacture a new drug or new device (i.e., inspection for a New Drug Application or Pre-Market Approval Application), or inspection of a facility (new or existing) performing a significant manufacturing step(s) in new (unapproved) areas, including use of different equipment (representing a process change), i.e. a PAS, or a PMA supplement.
- D. Inspection waiver** – Approval to waive an inspection, granted by DMPQ/OCBQ or DBCD/OBRR (for BPB products), based on risk and resource management.
- E. License** – Authority granted by CBER to an applicant to manufacture a biologic product(s) at a specified location. New applications for new products may be submitted under the same license, provided the products are manufactured within a five-mile geographic radius of one another. The license number is a unique four-digit number and is not to be confused with the biologics license application (BLA) number, a unique six-digit number assigned to each product.

V. Policy

- A.** CBER's policy is to ensure that manufacturing establishments and processes meet the appropriate requirements and comply with the applicable regulations through inspections and other mechanisms.
- B.** CBER is committed to making the best use of available resources. CBER will determine if a pre-license or pre-approval inspection is necessary based on an assessment of the potential benefits vs risks to the public health, associated with conducting or not conducting an inspection. The Director of the division with product responsibility and the Director, Division of Manufacturing and Product Quality (DMPQ), Office of Compliance and Biologics Quality (OCBQ) or, for Blood and Plasma Branch (BPB) products, the Director, Division of Blood Components and Devices (DBCD), Office of Blood Research and Review (OBRR) must both concur if an inspection is to be waived in the event that no additional public health benefit will be provided.

- C.** A pre-license or pre-approval inspection will generally be necessary for an original application or supplement if any of the following criteria are met:
- 1.** FDA has not recently inspected the establishment.
 - 2.** The facility is new (applicant or contract manufacturer), and/or;
 - 3.** There is a new production suite within an existing facility. For blood establishments, this could include adding a communicable disease donor testing lab, an immunohematology lab or a new room for performing the pathogen reduction technology procedures to an approved blood establishment manufacturing facility, and/Or;
 - 4.** The supplement involves significant manufacturing changes to include new methodology or scale-up and/or;
 - 5.** The facility does not have a compliance history.
- D.** If all the following criteria are met, the facility typically qualifies for an inspection waiver:
- 1.** The facility in question has already been reviewed and/or inspected as part of a current product approval.
 - 2.** The FDA has recently inspected the establishment.
 - 3.** The previous inspection was not classified as Official Action Indicated (OAI), and thus did not reveal significant CGMP deficiencies in areas similar or related to the processes in the submission, and/or did not indicate systemic problems, such as Quality Control (QC)/Quality Assurance (QA) oversight. No Action Indicated (NAI) or Voluntary Action Indicated (VAI) would both yield an acceptable compliance status.
 - 4.** The establishment is not performing a significant manufacturing step(s) in new (unlicensed or unapproved) areas using different equipment (representing a process change).
- E.** Neither an inspection nor a waiver memorandum may be necessary for the following:
- If the manufacturing process, equipment, and facilities are not significantly different from those of other approved products produced by the establishment, a waiver might not even be required. Some examples of changes that do not constitute significantly different processes, equipment or facilities include the following (not all-inclusive lists):

- 1.** For products reviewed by DMPQ:
 - a.** Transition from dedicated to multi-product use.
 - b.** Different types of columns and/or new purification methods.
 - c.** Different production cell lines.
 - d.** Different analytical test methods that require a determination of accuracy and sensitivity.
 - e.** Transition from traditional aseptic processing to use of an isolator or closed system technology at an already approved building.
 - f.** New lab area in an already approved building, for introduction of final release testing or other testing.

 - 2.** For products reviewed by Blood and Plasma Branch (BPB)/DBCD:
 - a.** Switching from automated collection instruments from one device manufacturer to automated collection instruments from a different device manufacturer
 - b.** Relocation of an approved blood establishment manufacturing facility with no change in core personnel
 - c.** Implementation of a 510(k)-cleared blood establishment computer software system in an approved blood establishment facility
 - d.** Addition of new Whole Blood collection centers if the applicant is already approved to manufacture Whole Blood
- F.** If the particulars of the submission (either an original application or a supplement) are not adequately addressed by the criteria above, or if the review committee agrees that an inspection is not appropriate, but the situation does not meet the criteria above, a meeting should be held with the appropriate office representatives, including the product office and the OCBQ, to discuss and recommend a course of action for the Director, CBER.
- G.** If an inspection is waived, documentation of the decision to waive the inspection and the basis for waiving the inspection will be included in the administrative file. If more than one waiver (e.g., for additional facilities pertinent to the submission) is required for a particular submission, one memorandum consolidating all information can be generated.
- H.** The decision should be made as soon as possible, preferably by the filing date and within 30 days for a supplement; documentation should be uploaded to the appropriate regulatory database/system as soon as possible after the decision is finalized, preferably no later than mid-cycle. This policy may not apply to certain blood and blood component applications as outlined in OBRR SOPPs.
- I.** If the application is deficient in some material sense such that the firm would have to put forth significant effort to address the deficiency, e.g., an additional clinical study or substantial manufacturing changes or the firm would need at least a year or more to correct deficiencies, the review

committee may decide that the inspection should be postponed until the applicant has submitted information to address the deficiency. The Director, DMPQ, or Director, DBCD (for BPB products), and the Director, product division, should concur in the decision to postpone the inspection. In this case, a complete response letter may be issued without an inspection having been performed. The complete response letter should inform the applicant that because of the length of time anticipated to correct the deficiencies, CBER will not perform an inspection until the applicant submits information that appears to address the deficiencies.

- J.** If CBER is informed by the applicant or the Office of Regulatory Affairs, FDA, that the establishment(s) is not ready for inspection, and all other portions of the review have been completed by CBER, a complete response letter may be issued without performing an inspection. The complete response letter should include the lack of availability of the establishment(s) for inspection as a deficiency.

- K.** For biological products regulated under PDUFA, all original applications and supplements are expected to include a comprehensive and readily located list of all manufacturing facilities included or referenced in the application or supplement. This list provides FDA with information needed to schedule inspections of manufacturing facilities that may be necessary before approval of the original application or supplement.
 - 1.** If, during FDA's review of an original application or supplement, the Agency identifies a manufacturing facility that was not included in the comprehensive and readily located list, the goal date may be extended.
 - a.** If FDA identifies the need to inspect a manufacturing facility that is not included as part of the comprehensive and readily located list in an original application or efficacy supplement, the goal date may be extended by three months. (Note: Only one extension for any reason can occur within the review cycle. Therefore, if an extension is given for a major amendment, an extension cannot be given for a missing facility and vice versa.)
 - b.** If FDA identifies the need to inspect a manufacturing facility that is not included as part of the comprehensive and readily located list in a manufacturing supplement, the goal date may be extended by two months.

VI. Responsibilities

- A. **BPB/ DBCD CMC Reviewer or DMPQ CMC Reviewer, if on the Review Committee or Product Office Chair, if DMPQ CMC Reviewer is not on committee-** determines which facilities associated with the application or supplement require an inspection or waiver, writes the waiver memo accordingly, and obtains applicable input, concurrence and signatures.
- B. **Product Office Chair and Product Office CMC reviewer(s) or BPB/DBCD Branch Chief** – provides input into the waiver determination and signs for concurrence.
- C. **Product Office Division Director** – concurs on inspection waivers (for submissions reviewed by DMPQ).
- D. **DMPQ Branch Chief** - concurs on inspection waivers.
- E. **Division Director DMPQ or DBCD (for BPB products)** – concurs on inspection waivers.

VII. Procedures

- A. For non-blood and blood component product submissions (i.e., those reviewed by DMPQ) :
 - 1. Assess each facility against the criteria listed in the policy section no later than the filing meeting for original applications and within 30 days for supplements. **[DMPQ CMC Reviewer, Product Office Chair]**
 - 2. If eligible for a waiver:
 - a. Generate draft inspection waiver memorandum using reviewer template *T870.01: CBER Inspection Waiver Memorandum* with input from Chair, prior to mid-cycle. **[DMPQ CMC Reviewer]**
 - b. Sign the waiver memo. **[DMPQ CMC Reviewer(s), Product Office CMC Reviewer(s) Product Office Chair, DMPQ Branch Chief, DMPQ division director, Product Office Division Director]**
 - c. Finalize waiver memorandum and enter/upload as an inspection related communication into the appropriate regulatory database/system. **[DMPQ CMC Reviewer]**
 - 3. If inspection(s) are deemed necessary, refer to the inspection procedures in *SOPP 8401: Administrative Processing of Original Biologics Applications (BLA) and New Drug Applications (NDA)* or *SOPP 8401.2: Administrative Processing of BLA and NDA*

Supplements for Supplements, as applicable. **[DMPQ CMC Reviewer]**

- B.** For blood and blood component product submissions (i.e., reviewed by BPB/ DBCD):
- 1.** Assess each facility or manufacturing process against the criteria listed in the policy section no later than filing period for applications and within 30 days after receipt of the PAS submission **[BPB/DBCD CMC Reviewer, BPB/DBCD Branch Chief]**
 - 2.** If eligible for a waiver:
 - a.** Generate draft inspection waiver memorandum using reviewer template *T870.01: CBER Inspection Waiver Memorandum* with input from BPB/DBCD Branch Chief prior to mid-cycle. **[BPB/DBCD CMC Reviewer]**
 - b.** Sign the waiver memo. **[BPB/DBCD CMC Reviewer, BPB/DBCD Branch Chief, DBCD Division Director]**
 - c.** Finalize waiver memorandum and enter/upload as an inspection related communication into the appropriate regulatory database/system. **[BPB/DBCD CMC Reviewer]**
 - 3.** If inspection(s) are deemed necessary, refer to the inspection procedures in *SOPP 8401: Administrative Processing of Original Biologics Applications (BLA) and New Drug Applications (NDA)* or *New Drug Applications (NDA)* as applicable **[BPB/DBCD CMC Reviewer]**

VIII. Appendix

N/A

IX. References

- A.** References below are CBER internal:
- 1.** T870.01: CBER Inspection Waiver Memorandum
- B.** References below are found on the Internet:
- 1.** [SOPP 8401: Administrative Processing of Original Biologics Applications \(BLA\) and New Drug Applications \(NDA\)](#)

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Nicole Trudel (DMPQ), Judy Ciaraldi (OBRR)	Christopher Joneckis, PhD	August 27, 2018	3	Major revision throughout, update to new SOPP format and FDA's Visual Identity
Jennifer Thomas	Robert Yetter, PhD	December 4, 2001	2	Changes to Streamline the Document
RMCC	Rebecca Devine	November 10, 1998	1	Original