

SOPP 8407: Compliance Status Checks

Version: 5

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Table of Contents

I.	Purpose	1
II.	Scope	1
III.	Background	2
IV.	Definitions	3
V.	Policy	3
VI.	Responsibilities	6
VII.	Procedures	6
VIII.	Appendix	8
IX.	References	8
X.	History	9

I. Purpose

- A.** This Standard Operating Policy and Procedure (SOPP) serves as a guide for the Center for Biologics Evaluation and Research (CBER) staff for determining a manufacturer's compliance status before approval of an original application or supplement and is performed to ensure there are no ongoing or pending investigations or compliance actions. A compliance check must be performed prior to the issuance or reissuance of a license.
- B.** This SOPP also provides instructions for submitting a compliance check request to the Office of Compliance and Biologics Quality (OCBQ), Division of Case Management (DCM) in support of approval of a CBER submission.

II. Scope

- A.** This applies to all Biologics License Applications (BLAs), Premarket Approval Applications (PMAs), New Drug and Abbreviated New Drug Applications (NDAs, ANDAs), and Humanitarian Device Exemptions (HDEs).

- B.** It also applies to supplements of NDAs, ANDAs and BLAs, except minor labeling changes submitted under 21 CFR 601.12(f)(2), and standalone blood component labeling submitted under 21 CFR 601.12(f).
- C.** For PMA/HDE supplements, [Appendix A](#) lists those which require a compliance check and those which do not.
- D.** This SOPP **does not** apply to 510(k) submissions because under section 513(f)(5) of the Federal Food, Drug, and Cosmetic Act (the act), FDA may not withhold 510(k) clearance for failure to comply with any provision of the act unrelated to a substantial equivalence decision, including failure to comply with Good Manufacturing Practice (GMP)/Quality System Regulations (QSR), unless FDA finds that there is a substantial likelihood that failure to comply with the provision “will potentially present a serious risk to human health.”

III. Background

- A.** Section 351 of the Public Health Service Act (PHS Act) establishes FDA's regulatory authority for licensing biological products. Title 21 CFR 601.2(d) provides that approval of a BLA shall constitute a determination that the establishment(s) and product meet applicable requirements to ensure the continued safety, purity, and potency of such products. These requirements include the applicable good manufacturing practice (CGMP) regulations. The prerequisite of FDA's determination of compliance also applies to the approval of application supplements submitted under 21 CFR 601.12. In addition, 21 CFR 601.20 states that a BLA shall only be approved upon a determination that the product is produced in compliance with current CGMP and other applicable standards of the PHS Act, and the Federal Food, Drug, and Cosmetic Act (FD&C Act).
- B.** For medical devices, the FD&C Act states that a premarket approval application should be denied approval if “the methods used in, or the facilities or controls used for, the manufacture, processing, packing, or installation of such device do not conform to the requirements of section 520(f).” (Section 515(d)(2)(C)).
Note: As defined in 21 CFR 814.3(m), an HDE is a “premarket approval application” submitted to FDA pursuant to Subpart A, 21 CFR Part 814 “seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the FD&C Act as authorized by section 520(m)(2) of the FD&C Act.”
- C.** For drugs, the FD&C Act states that an NDA or ANDA should be approved unless the Agency finds the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity. (Sections 505(d)(3) and (j)(4)(A)).

- D. In determining whether appropriate manufacturing controls are in place, CBER's review of new applications includes a compliance status review of each manufacturing location(s) included in the application, or for supplements, each location affected by the changes in the supplement prior to approval.

IV. Definitions

- A. **Alternative Procedures** - an exception or alternative to any requirement in subchapter F of chapter I, 21 CFR (parts 600-680) regarding blood, blood components, or blood products. (21 CFR 640.120)
- B. **Equivalent methods and processes** – a modification of any particular test method or manufacturing process or the conditions under which it is conducted as required in 21 CFR parts 610 – 680. (21 CFR 610.9)
- C. **Establishment/Facility** - any facility in which the product is manufactured, processed, packed, or held and includes all such locations.
- D. **Location** - all buildings, appurtenances, equipment and animals used for the manufacture of a drug or device.
- E. **Manufacturer** - any legal person or entity engaged in or responsible for the manufacture of a drug or device, including biological products subject to the FD&C Act or license under the PHS Act. "Manufacturer" also includes any legal person or entity who is an applicant or named in an application, whereby the applicant assumes responsibility for compliance with the applicable product and establishment standards.

V. Policy

- A. In general, CBER may approve a submission only when the compliance status of the product(s) and establishment(s) affected by the submission are acceptable. OCBQ\DCM will not recommend approval of a submission when the compliance status is unacceptable. Submissions requiring a compliance status check before approval include:
- Original applications (BLA, NDA, ANDA, PMA and HDE)
 - Supplements to the above application types deemed subject to a compliance check as described below.
- B. Compliance checks are performed for all applications and supplements (see exceptions under Scope, Section II B.) for critical manufacturing facilities regardless of whether they are the applicant's facility or a contract manufacturer; examples of critical manufacturers include:

- Drug substance manufacturing
 - Drug product manufacturing (includes fill/finish facilities, and filling for diluents and adjuvant filled separately)
 - Finished device manufacturing (includes terminal sterilizers)
 - Primary labeling/packaging
 - Final release testing
 - Terminal sterilization
 - Product for further manufacturing use (FFMU)
 - Blood components for transfusion
- C.** FDA recommends that at the time of registration, the owner or operator obtain a Field Establishment Identifier (FEI) number. The FEI number is needed by the Agency to proceed with the facility evaluation portion of the application/supplement review. **Note:** device manufacturers are not required to register before submitting their premarket submission. They are expected to wait until they have a cleared or approved product for distribution. See web link 'When to Register and List' under the References Section.
- D.** A compliance check request should be submitted 30 days *before* the projected approval or action due date. **Note:** Compliance checks need to be requested for each applicable submission, with the exception of bundled device submissions, Trans-BLAs, and Trans-NDAs; multiple submissions cannot use an existing compliance check as the compliance status of the location may have changed.
- E.** Typically, FDA inspections, including CBER pre-approval/pre-license inspections (PAIs/PLIs), must be completed and closed *before* the compliance status can be determined.
- F.** When a PAI or PLI inspection(s) has been performed in support of the submission, the compliance check request should include a dated copy of or link to the inspection endorsement memorandum. If the inspection was waived, a copy of the signed/dated waiver memorandum should be submitted.
- G.** If an inspection begins after a compliance check is issued, and compliance issues are identified (i.e. Official Action Indicated endorsement, on-going inspection, etc.), it renders the compliance check invalid. A new compliance check needs to be submitted after the compliance issue or inspection has closed.

- H. The compliance check determination is based on the outcome of any inspections, even if they are not performed by CBER for the subject submission, as well as any pre-existing compliance actions.
- I. Responsibilities for initiating a compliance check:
 - 1. **Product office (PO)** - Submits the compliance check request for product office chaired files when there is no PAI/PLI conducted.
 - 2. **OCBQ/DMPQ** – Initiates the compliance check request if submission has a DMPQ RPM assigned to the committee.
- J. Additional compliance checks may need to be submitted for the same submission in the following circumstances:
 - 1. One or more of the associated manufacturers was omitted from the original compliance check request;
 - 2. The original (or most recent) compliance check status was unacceptable and there is new information indicating that the compliance issues have been resolved;
 - 3. The applicant has responded to a Complete Response (CR) or deficiency letter and the submission is now ready for approval.
- K. For supplements submitted under 21 CFR 610.9 or 640.120 (Equivalent Methods, Processes or Alternative Procedures):
 - 1. Such supplements should be cleared by OCBQ/DCM *before* the review office files them.
 - 2. Note: 21 CFR 640.120 supplements dealing with blood components are cleared, filed (if appropriate) and reviewed in OBRR/DBCD.
 - 3. The review office should include a summary to DCM with a complete description of the reason for the modification of any particular test method or manufacturing process or the conditions under which it is conducted.
 - 4. The applicant is expected to provide evidence demonstrating that the modification will provide assurances of the safety, purity, potency, and effectiveness of the biological product at least equal to those assurances provided in the general standards or additional standards for the biological product. (21 CFR 610.09)

- L. For supplements, if the compliance status is unacceptable, yet the supplement represents an improvement or change intended to help the manufacturer achieve compliance, or the specific product, manufacturing process, and facility used to manufacture the product are in compliance, DCM may provide an acceptable compliance status check with an explanation of the circumstances.
- M. Within 21 days of receiving the request, DCM will provide a response (interim, acceptable, or unacceptable) to the requestor.

VI. Responsibilities

A. Product Office (PO) Regulatory Project Manager (RPM) (unless DMPQ RPM is assigned to the committee) - reviews the submission and determines whether a compliance status check is needed. Prepares and sends the compliance status request to DCM containing all pertinent information to conduct the check. Files DCM's response regarding the compliance decision in the application/ supplement.

B. Division of Manufacturing and Product Quality (DMPQ) RPM - initiates compliance status check request when the submission has a DMPQ RPM assigned to the committee.

C. OCBQ

1. DCM Compliance Staff

- a. Processes and maintains compliance status check requests via software/database.
- b. Requests additional information from the requestor as soon as possible, if a compliance status check request is unclear.

2. DCM Director and Chief of the Biological Drug and Device Compliance Branch (BDDCB)

- a. Evaluates all pertinent information when the compliance status appears to be unacceptable and makes the final compliance status check determination.

VII. Procedures

A. Review the submission's documents as appropriate, e.g., FDA Form 356(h) or FDA Form 3514, (the CDRH Premarket Review Submission Coversheet). [PO RPM or DMPQ, as applicable]

- B.** Complete the compliance check request using T900.04: *Compliance Check Requests*. Note: JA 900.1: *Compliance Check Requests* includes the system data entry required for compliance checks. **[PO RPM or DMPQ RPM, as applicable]**
1. **Original Application:** identify the following:
 - a. List all manufacturing locations, including contract manufacturers and their respective FEI numbers. See Policy (section V), B., for examples of applicable manufacturers.
 2. **Supplement:** identify the following:
 - a. List only those manufacturing locations that are performing the manufacturing process(es) associated with the manufacturing change, including contract facilities and their respective FEI numbers.
 - b. Review the 356(h) or FDA Form 3514, submission cover letter, and CMC section if necessary. List only the locations associated with the supplemental change.
 - c. Indicate if the supplement represents an improvement or a change intended to help the applicant or facility achieve CGMP compliance (e.g., a response to a 483 observation or warning letter citation).
- C.** Include the FEI number for each location, otherwise the compliance check request may be returned. **[PO or DMPQ RPM, as applicable]**
- D.** Email the completed compliance check request using T900.04, and the signed and dated inspection endorsement memorandum, if applicable, **30 days before** the projected approval or action due date. **[PO or DMPQ RPM, as applicable]**
- E.** Enter the completed compliance check request email into the appropriate database as a communication and upload to the EDR. **[PO or DMPQ RPM, as applicable]**
- F.** Review the request and ensure it contains the necessary information. If information is missing or the request is unclear, contact the requestor. **[DCM Compliance Staff]**
1. If the requestor provided an incorrect FEI number, work with them to determine the correct FEI number. **Note:** the requestor (or applicable RPM) may need to contact the applicant to ensure the proper location(s) and FEI number(s) are used.

2. If a corrected FEI number was established, send a request to 'CBER RIMS' to correct the FEI number in the database.
- G.** Evaluate the incoming compliance check request and make a determination on the compliance status of the manufacturers' establishment(s). **[DCM Compliance Staff]**
1. Notify the DCM Branch Chief if the compliance status appears to be unacceptable. **[DCM Compliance Staff]**
 2. Make the final determination on the compliance status. **[DCM Compliance Staff Branch Chief]**
- H.** Respond to the requestor via the original email request with a response recommending approval or not recommending approval. **[DCM Compliance Staff]**
1. When the compliance status is unacceptable, notify the requestor as soon as possible, but not later than 21 days after DCM receives the request.
 2. Supply the requestor with the language to be included in the CR/deficiency or information request letter.
- I.** Enter DCM's compliance status response into the appropriate database as a communication. **[PO or DMPQ RPM, as applicable]**
- J.** Upload DCM's response to the EDR and send a notification to the Chair. **[PO or DMPQ RPM, as applicable]**

Note: If the compliance check is unacceptable, the RPM drafts a complete response or deficiency letter, as applicable, following established procedures.

VIII. Appendix

- A.** [PMA/HDE Supplement Compliance Check Requirements](#)

IX. References

- A.** References below are CBER internal:
1. JA 900.10: Compliance Check Requests
 2. T 900.04: Compliance Check Request Template
- B.** References below can be found on the Internet:

1. [SOPP 8410: Determining When Pre-License / Pre-Approval Inspections are Necessary](#)
2. [Device BLAs – When to Register and List](#)

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
C. Vincent	Chris Joneckis, PhD	March 17, 2019	5	Updated to reflect current policy and procedures.
L. Wilson	Robert A. Yetter, PhD	Nov 26, 2006	4	This version is a technical correction to make the language consistent with 21 CFR 640.120.
OCBQ	Robert A. Yetter, PhD	Dec 15, 2005	3	Incorporates changes from OCC and RMCC
		April 12, 2001	2	Incorporates changes resulting from eliminating the ELA and changes to 21 CFR 601.12
		Dec 13, 1996	1	Original version

SOPP 8407 Appendix A: PMA/HDE Supplement Compliance Check Requirements

Submission Type	CC Required	CC Not Required
PMA Panel-Track Supplements	X	
PMA 180 Day / HDE 75 Day Supplements with a design change	X	
Manufacturing Site Change Supplements	X	
Real-Time PMA Supplements with a design change	X	
PMA/HDE Special Supplements -Changes Being Effected		X
PMA/HDE 30-Day Notices / 135 Day Supplements		X
PMA/HDE Annual Reports		X
Special PMA Supplements - CBE		X

[Back to Appendix](#)