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# Manual of Standard Operating Procedures and Policies

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## Regulatory - License Applications

### Compliance Status Checks

**SOPP 8407**

**Version #4**

**Date: November 28, 2006**

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#### 1. Purpose

This document describes CBER's procedure for determining a manufacturer's compliance status before approving a manufacturer's submission that represents a moderate to significant change in manufacturing or intended use.

#### 2. Definitions

##### **Manufacturer**

Manufacturer means, for the purpose of this procedure, any legal person or entity engaged in or responsible for the manufacture of a drug or device, including biological products subject to the Food, Drug, and Cosmetic Act or license under the Public Health Service Act (PHSA). "Manufacturer" also includes any legal person or entity who is an applicant or named in an application for a biologics license or related application supplement or a premarket approval application or related supplement, whereby the applicant assumes responsibility for compliance with the applicable product and establishment standards.

##### **Location**

Location includes, for the purpose of this procedure, all buildings, appurtenances, equipment and animals used for manufacture of a drug or device.

##### **Establishment**

Establishment means, for the purpose of this procedure, any facility in which the product is manufactured, processed, packed, or held and includes all such locations.

##### **Days**

Days means calendar days.

#### 3. Background

Section 351 of the Public Health Service Act (PHSA) establishes FDA's regulatory authority for licensing biological products. Title 21, Code of Federal Regulations (CFR), Part 600, Section 601.2(d) provides that approval of a biologics license application (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 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 Good Manufacturing Practice (CGMP) and other applicable standards of the PHSA and the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Similar requirements exist for drugs and medical devices. 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)," the Quality System Regulation. [Section 515(d)(2)(C)]. For drugs, the FD&C Act states that a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) should be approved unless the Agency finds the methods used in, and 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)].

In determining whether appropriate manufacturing controls are in place, CBER's review of new applications and application supplements has included a review of the manufacturer's compliance status prior to approving the submission.

Many firms that manufacture biological products also manufacture drugs or devices handled by other Centers; thus enforcement actions may be initiated by the Centers responsible for those products or the Office of Regulatory Affairs (ORA). Each of the Centers should be aware of all compliance actions pertaining to a manufacturer prior to rendering a final decision regarding an application or application supplement that represents important changes.

#### 4. Policy

The compliance status of the manufacturer's applicable product(s) and establishments(s) shall be determined prior to rendering a final decision regarding applications and application supplements.

In general, CBER may approve a submission only when the compliance status of the product(s) and establishment(s) affected by the submission is acceptable. OCBQ will not recommend approval of a submission when the compliance status of the applicable product(s) and establishment(s) is unacceptable. An exception may be granted when an application supplement represents an improvement or change intended to help the manufacturer achieve compliance, or the specific product, manufacturing process, and relevant section of the facility used to manufacture the product are in compliance.

Submissions requiring a compliance status check before approval include:

- Original applications (BLA, PMA, NDA, and ANDA)
- Application supplements
- One-time exceptions to release products that were manufactured using equivalent methods and processes that represent modifications of any particular test method or manufacturing process or condition (21 CFR 610.9)
- One-time exceptions to release products that were manufactured using alternative procedures 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)
- Submissions other than those listed that an application division deems necessary

Submissions not requiring a compliance status check before approval include label changes submitted as changes being effected (CBE) to add or strengthen a contraindication, warning, precaution or adverse reaction (21 CFR 601.12(f)(2)(A)), to add or strengthen a statement about abuse, dependence, psychological effect, or overdose (21 CFR 601.12(f)(2)(B)), to add or strengthen an instruction about dosage and administration that is intended to increase the safety of the use of the product (21 CFR 601.12(f)(2)(C)), or to delete false, misleading, or unsupported indications for use or claims for effectiveness (21 CFR 601.12(f)(2)(D)).

#### 5. Responsibilities and Procedures

##### Responsibilities

- Division of Case Management (DCM)

- Maintain the compliance status check database.
- Request additional information from the requestor as soon as possible if a compliance status check request is unclear.
- Obtain appropriate information to determine the CGMP compliance status of the product and establishments that perform manufacturing steps that are pertinent to the submission.
- If the manufacturer is subject to a regulatory action (e.g. suspension, injunction, notice of intent to revoke), consult with the DCM Consumer Safety Officer (CSO) responsible for monitoring the case. The DCM CSO may issue the compliance status check response.
- If the compliance status appears to be unacceptable, notify supervisor.
- Inform the requestor as soon as possible if the compliance status appears to be unacceptable.
- Provide compliance status or interim response within 21 days of request.
- DCM, OCBQ: Branch and Division Supervisors
  - Evaluate all pertinent information when the compliance status appears to be unacceptable and make the final compliance status check determination.
- Applications Divisions: Division of Blood Applications (DBA), OBRR; Division of Vaccine and Related Products Applications (DVRPA), OVRP; Regulatory Management Staff, (RMS) OCTGT; and Division of Manufacturing and Product Quality (DMPQ), OCBQ
  - Request the compliance status check no less than 30 days prior to the submission's projected approval date. Requests should identify all manufacturing locations, including contract facilities, that perform manufacturing steps that are pertinent to the submission; for example, chemical and biological testing, drug substance manufacturing, formulation, sterile filling, lyophilization, and labeling.

Indicate on the compliance status check request if the change is intended to help the manufacturer achieve compliance, and why, if applicable.

- DVRPA, RMS, and DBA (for other than blood and blood components)
  - Initiate compliance status check requests if the submission has no DMPQ reviewer(s) on the committee.
- DMPQ
  - Initiate compliance status check requests if the submission has a DMPQ reviewer on the committee. When prelicense (PLI) or preapproval (PAI) inspection(s) have been performed in support of the submission, the compliance check request should include a dated copy of the memorandum closing the inspection(s). If an inspection was waived per CBER SOPP 8410, a copy of the dated waiver memorandum should be submitted.
- DBA (for blood and blood components)
  - Initiate all compliance status check requests for submissions regarding blood and blood components. When prelicense (PLI) or preapproval (PAI) inspection(s) have been performed in support of the submission, the compliance status check request should include a dated copy of the memorandum closing the inspection(s). If an inspection was waived per CBER SOPP 8410, a copy of the dated waiver memorandum should be submitted.

## Procedures

1. Requests may be made via hard copy using the **Establishment Evaluation Request Form (EER)** [Appendix 1] or electronically (e-mail) by providing the same information that is requested on the EER. E-mail requests should be addressed to "CBER Complicheck" ([complcheck@cber.fda.gov](mailto:complcheck@cber.fda.gov)). The requestor will enter the request into RMS-BLA as a communication.
  - The request should list all manufacturing locations that are pertinent to the pending submission, whether they are contract facilities or facilities owned by the applicant. (For original applications and all other application supplements, all pertinent manufacturing locations should be listed.)
  - For manufacturing supplements, the request should list all products (using for example, the RMS/BLA product description) and manufacturing locations that are affected by the changes described in the supplement. The request should indicate if the supplement represents an improvement or change intended to help the manufacturer achieve compliance, if applicable.

- For supplements submitted under 21 CFR 610.9, Equivalent Methods and Processes, 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 (if one-time use) or the circumstances that led to the need for an exception should be included with the compliance check request.
  - For supplements submitted under 21 CFR 640.120, Alternative Procedures, a complete description of the reason for an exception or alternate to any requirement in subchapter F of chapter I, 21 CFR parts 600-680, regarding blood, blood components, or blood products, or the circumstances that led to the need for an exception, should be included with the compliance check request.
  - All information referenced in the Establishment Evaluation Request form (Appendix 1) should be included in the request.
2. If the compliance status check request is unclear, the DCM compliance status check staff will contact the requestor as soon as possible for clarification. The requestor will respond as soon as possible.
  3. The DCM compliance status check staff will obtain the necessary information to make a determination of the manufacturer's compliance status. The information used to make the compliance status determination may include:
    - Inspection information
      - Classification of the most recent establishment inspection from the Division of Inspections and Surveillance (DIS) for Team Biologics inspections and the Division of Manufacturing and Product Quality for CBER-led inspections (pre-license and pre-approval).
      - Inspection and compliance information from the Field Accomplishment and Compliance Tracking System (FACTS), and FACTS Firms Profile databases. If the inspection information in the databases needs clarification, the DCM compliance check staff will contact the appropriate district by e-mail for additional information.
      - Current regulatory actions, including Warning Letters, administrative and legal actions, and any pending compliance actions.
  4. The DCM compliance status check staff will make an initial determination of the compliance status of the manufacturer's product(s) and establishment(s). Exception: If the manufacturer is under suspension, notice of intent to revoke or injunction, the DCM CSO responsible for monitoring the case may determine the compliance status.

If the information suggests an unacceptable compliance status, the compliance check staff will notify the Branch Chief, Biological Drug and Device Compliance Branch, DCM. The Branch Chief will make the final compliance status determination, consulting with the Division Director as needed.

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.

5. Within 21 days of receiving the request, DCM will forward a response (interim, acceptable, or unacceptable) via e-mail or hard copy to the requestor. If the final determination is that the compliance status is unacceptable, the requestor will be informed as soon as possible, but not more than 21 days after DCM receives the request.

If DCM cannot provide a determination of compliance status within 21 days, DCM will provide an interim response to the requestor, providing the status of the request and cause for delay. The interim response will instruct the requestor to resubmit the request. A recent inspection for which an EIR has not been submitted or classified will likely result in a delay in responding to a compliance status check request.

*Compliance status checks for recently inspected firms cannot be completed until the Division of Inspections and Surveillance, or the ORA Unit receives, reviews and classifies the EIR from the inspection.*

In addition, for PLIs and PAIs, compliance status checks cannot be completed until a close out memo is signed and dated. It is the responsibility of the DBA or DMPQ reviewer(s) to ensure that the memorandum closing the inspection is included with the compliance status check request.

When CBER receives a submission for a manufacturing location that has not been inspected, there will be

no inspectional history. In this case, DCM will state on the compliance status check response that the manufacturing location does not have an inspectional history with FDA and therefore OCBQ/DCM cannot determine the compliance status or recommend approval of the submission at this time.

6. The applications division will include a copy of the compliance status check response with the submission at the time that it is routed for final approval action.

#### 6. Appendices

[Appendix 1 - Establishment Evaluation Request \(PDF\)](#)

#### 7. Effective Date

November 28, 2006

#### 8. History

Written/Revised	Approved	Approval Date	Version Number	Comment
	Robert A. Yetter, PhD	November 26, 2006	4	This version is a technical correction to make the language consistent with 21 CFR 640.120.
OCBQ	Robert A. Yetter, PhD	December 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
		December 13, 1996	1	Original version

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