SOPP 8506: Management of Shortages of CBER-Regulated Products

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for the Center for Biologics Evaluation and Research (CBER) staff for the receipt, evaluation, and follow up to notifications of actual or potential shortages of CBER-regulated products and the additional steps to be taken in the event of actual shortages of medically necessary CBER-regulated products that can have significant public health consequences.

II. Scope

This SOPP applies to all products regulated by CBER.

III. Background

A. Product shortages can arise for a variety of reasons. Quality problems at the manufacturing facility are the most common causes of shortages of CBER-regulated products. Other causes of product shortages include increased demand, corporate delays in manufacturing or shipping, distribution disruptions, production changes, unavailability of component materials, new

indications, business decisions to discontinue the product, or natural disasters.

B. The Food and Drug Administration Safety and Innovation Act (FDASIA) amended section 506C of the Federal Food Drug and Cosmetic Act (FD&C) Act (21 U.S.C. 356c) to require all manufacturers of certain drugs to notify the Food and Drug Administration (FDA) six months in advance, or as soon as practicable, of a permanent discontinuance or an interruption in manufacturing.

C. FDASIA also permitted the FDA to apply section 506C to biological products by regulation and required the FDA to issue a final rule implementing certain drug shortages provisions in FDASIA. The final rule was issued on July 8, 2015, and became effective September 8, 2015 (80 FR 38915, July 8, 2015).

1. The rulemaking created new sections for drugs, including 21 CFR 314.81 and 21 CFR 600.82, "Notification of a permanent discontinuance or an interruption in manufacturing," that requires an applicant of a biological product, other than blood or blood components for transfusion, which is licensed under section 351 of the Public Health Service Act (PHS Act), and which may be dispensed only under prescription under section 503(b)(1) of the FD&C Act (21 U.S.C. 353(b)(1)), to notify the FDA in writing of a permanent discontinuance of manufacture or an interruption in manufacturing that is likely to lead to a meaningful disruption in supply in the United States (21 CFR 600.82(a)(1)) if:

- The biological product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such biological product used in emergency medical care or during surgery; and
- The biological product is not a radiopharmaceutical biological product.

2. An applicant of blood or blood components for transfusion must notify the FDA in writing of a permanent discontinuance of manufacture of any product listed in its license or an interruption in the manufacturing of any such product that is likely to lead to a significant disruption in the supply of that product in the United States (21 CFR 600.82(a)(2)) if:

- The product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such product used in emergency medical care or during surgery; and
- The applicant is a manufacturer of a significant percentage of the U.S. blood supply.

3. The regulations at 21 CFR 314.81 and 600.82 do not apply to biological products that also meet the definition of a device per section 201(h) of the

Federal Food, Drug and Cosmetic Act (FFDCA), CBER-regulated devices approved or cleared under FFDCA section 515 and 510(k), or HCT/Ps regulated solely under section 361 of the PHS Act.

D. The Coronavirus Aid, Relief, and Economic Security Act (CARES Act) was signed into law on March 27, 2020, to aid response efforts and ease the economic impact of COVID-19. In addition to the COVID-19 response efforts, the CARES Act included authorities intended to enhance FDA's ability to identify, prevent, and mitigate possible drug shortages by, among other things, enhancing FDA's visibility into drug supply chains. Drug shortages can occur for many reasons, including manufacturing and quality problems, delays, and discontinuations. Drug manufacturers provide FDA with most of the drug shortage information the agency receives, and the agency works closely with them to prevent or reduce the impact of shortages. Section 3111 of the CARES Act amended subsection 506C(g) (Expedited Inspections and Reviews) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as follows:

> If, based on notifications described in subsection (a) or any other relevant information, the Secretary concludes that there is, or is likely to be, a drug shortage of a drug described in 506C(a).[1,2] the Secretary shall, as appropriate -
>
> - prioritize and expedite the review of a supplement to a new drug application submitted under section 355(b) of this title, an abbreviated new drug application submitted under section 355(j) of this title, or a supplement to such an application submitted under section 355(j) of this title, that could help mitigate or prevent such shortage; or
>
> - prioritize and expedite an inspection or reinspection of an establishment that could help mitigate or prevent such drug shortage.

[1] A drug described in FD&C Act s. 506C(a) is a prescription drug that is life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery or any such drug critical to the public health during a public health emergency declared by the Secretary under section 319 of the Public Health Service Act (42 U.S.C. 247d) and that is not a radio pharmaceutical drug product or a product otherwise designated by FDA. *See* FD&C Act s. 506C(a); *see also* FD&C Act s. 506C(h)(1).

[2] In issuing regulations implementing s. 506C of the FD&C Act as required by s. 506C(i), FDA applied the term "drug" as defined in s. 506C to biological products licensed under section 351 of the Public Health Services Act (42 U.S.C. 262), with the exception of biological products that also meet the definition of a device at FD&C Act s. 201(h) and of source plasma. *See also* FD&C Act s. 506C(h).

E. CBER may be notified of actual or potential shortages by manufacturers, medical professionals, consumers/patients, other government offices, patient advocacy groups, media sources, and others.

F. Shortage notifications may come to the CBER Product Shortage Coordinator through:

- The CBER Shortage email account at CBERshortage@fda.hhs.gov
- The CBER Biological Product Shortages dedicated phone line at (240) 402-8380
- Any of CBER's offices
- FDA's Office of Inspections and Investigations (OII)
- Media reports or inquiries from FDA's Press Office
- Patients/consumers individually or through associations
- Healthcare provider reports filed in the:
  - MedWatch
  - Vaccine Adverse Event Reporting System (VAERS)
- CBER's Biological Product Deviation Reporting System

IV. Definitions

A. CBER-regulated product shortage or shortage – The period of time when the demand or projected demand for the biological product within the United States exceeds the supply of the product (21 CFR 600.82(f)).

B. Intended for use in the prevention or treatment of a debilitating disease or condition - A biological product intended for use in the prevention or treatment of a disease or condition associated with mortality or morbidity that has a substantial impact on day-to- day functioning (21 CFR 600.82(f)).

C. Life supporting or life sustaining - A biological product that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life (21 CFR 600.82(f)).

D. Meaningful disruption - A change in production that is reasonably likely to lead to a reduction in the supply of a biological product by a manufacturer that is more than negligible and affects the ability of the manufacturer to fill orders

or meet expected demand for its product, and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time (21 CFR 600.82(f)).

E. Medical necessity determination – A formal, written assessment made by a CBER medical officer or officers with requisite expertise on the CBER-Regulated Product, stating whether the product meets the definition of medically necessary. Multiple CBER offices and/or divisions may be asked to make this determination.

F. Medically Necessary Product - A product is considered medically necessary when it is used to treat, cure, mitigate, prevent, or diagnose a serious disease or medical condition and there is no adequate alternative product available for that use. Note: Patient inconvenience alone is an insufficient basis to classify a product as a medically necessary.

G. Significant disruption - A change in production that is reasonably likely to lead to a reduction in the supply of blood or blood components by a manufacturer that substantially affects the ability of the manufacturer to fill orders or meet expected demand for its product, and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time (21 CFR 600.82(f)).

V. Policy

A. For drugs, including biological products, regulated by CBER, 21 CFR 314.81(b) and 600.82(b) require notification electronically in a format that the FDA can process, review, and archive.

1. Applicants must email notifications to CBERshortage@fda.hhs.gov (for products regulated by CBER):

- At least six months prior to the date of the permanent discontinuance or interruption in manufacturing; or
- If six months advance notice is not possible because the permanent discontinuance or interruption in manufacturing was not reasonably anticipated six months in advance, as soon as practicable thereafter, but in no case later than five business days after such a permanent discontinuance or interruption in manufacturing occurs.

2. Notifications required under 21 CFR 314.81(b) and 600.82(b) must include the following information (21 CFR 314.81(c) and 600.82(c)):

- Name of the CBER-regulated product subject to the notification

- Name of the applicant
- Whether the notification relates to a permanent discontinuance or an interruption in manufacturing.
- Description of the reason for the discontinuance or interruption
- Estimated duration of the interruption in manufacturing

3. Under 21 CFR 314.81(e) and 600.82(e) CBER may issue a noncompliance letter to an applicant who fails to submit a notification as required under the regulations.

B. For all other CBER-regulated products, CBER encourages voluntary notification of a permanent discontinuance or an interruption in manufacturing that is likely to lead to a meaningful disruption in supply of that product in the United States in the same manner as for CBER-regulated drugs (including biological products). Early notification concerning a permanent discontinuance or an interruption in manufacturing, enables CBER to work with a manufacturer, and may help to prevent or mitigate a product shortage. The most important way to prevent or mitigate a product shortage is for CBER to learn about a permanent discontinuance or an interruption in manufacturing as soon as possible. The sooner CBER is notified of a discontinuance or interruption in manufacturing, the more time CBER has between the disruption and the potential shortage to assist, where possible, in the best interest of public health.

C. The appropriate CBER product office - Office of Blood Research and Review (OBRR), and/or the Office of Therapeutic Products (OTP), and/or the Office of Vaccines Research and Review (OVRR) - will assist in identifying and gathering all necessary information about products for which there is a notification of an actual or potential shortage and determine if the product is medically necessary, as appropriate.

D. In consultation with the appropriate CBER product office, the Office of Compliance and Biologics Quality (OCBQ) will determine whether any of the following mitigation strategies are appropriate to address the potential or actual drug shortage:

1. Prioritize and expedite the review of an application or application supplement that could help mitigate or prevent such shortage;

2. Prioritize and expedite an inspection (including pre-license or pre-approval inspection) of an establishment that could help mitigate or prevent such drug shortage;

3. Prioritize and expedite official CBER release of lots of licensed biological products;

4. Work with the affected manufacturer(s) to ensure adequate investigation into the root cause of the shortage and corrective actions;

5. Review application supplement requests for extensions of expiration dating;

6. Exercise temporary regulatory flexibility for new sources of medically necessary drugs.

E. OCBQ processes regulatory action recommendations. One of the many considerations in deciding on the appropriate action to take is the overall effect of the action on the availability of the products that are manufactured by the company that is the subject of the potential action. In matters of enforcement that could potentially result in shortages of CBER-regulated product(s), OCBQ will consult with CBER product offices and the Office of Inspections and Investigations (OII) prior to concurring with any recommended action(s).

F. A decision on whether or not to take enforcement action is based on careful consideration of the impact of the violations on the quality of the product, the medical risks associated with the violations, and any other factor(s) that CBER may deem relevant.

1. Where agency actions may impact the supply of CBER-regulated products, CBER carefully considers the alternatives. In an event where agency action may impact the supply of products, CBER carefully considers whether to exercise enforcement discretion in taking action.

2. If CBER determines that the shortage of a CBER-regulated product is not compliance related, (e.g., manufacturing facility destroyed by fire, facility closed for renovations), special actions may be taken by CBER to help mitigate the shortage. Special actions may range from discussions with industry to the acceleration of review activities or lot release as described in section D, above.

3. If CBER determines that the shortage of a CBER-regulated product is compliance-related (e.g., approved product does not meet any or all of the specification(s) in the license):

    a. CBER may consider whether or not to modify enforcement actions to address the impact on the availability of products. (In some circumstances, the agency may exercise enforcement discretion or

prioritize and expedite a review, or prioritize and expedite an inspection.)

b. CBER may decide to modify enforcement actions based on careful consideration of the impact of the violation(s) on the quality of the product, the risks to the public that would result from use of the product versus inability of the public to use the product, and other factors CBER may deem relevant.

c. CBER may consult with CBER product offices, Office of the Chief Counsel (OCC), and Office of CBER Director (OD).

d. CBER may also consider taking special actions deemed relevant to the individual situation to help alleviate the shortage.

VI. Responsibilities

A. CBER Product Shortage Coordinator (PSC) - Office of Compliance and Biologics Quality (OCBQ), Immediate Office of the Director (IOD)

1. Receives all notifications, reports or inquiries of potential or actual product shortages including notifications of discontinuations that are likely to lead to a meaningful disruption in supply in the United States.

2. Evaluates each potential or actual product shortage notification, report or inquiry.

3. Verifies that an actual product shortage exists through communications with manufacturers and other stakeholders.

4. Determines if the notification of shortage was received at least six months prior to the date of the permanent discontinuance or interruption in manufacturing or, if six months advance notice is not possible, notification was received as soon as practicable but no later than five business days after a permanent discontinuance or interruption in manufacturing was discovered.

5. Verifies that the notification of shortage includes:

a. Name of the CBER-regulated product subject to the notification

b. Name of the applicant or manufacturer

c. Whether the notification relates to a permanent discontinuance or an interruption in manufacturing.

d. Description of the reason for the discontinuance or interruption

e. Estimated duration of the interruption in manufacturing

6. Communicates each potential or actual CBER-regulated product shortage notification to CBER product offices so that the product offices can evaluate the status of each new shortage notification and, when necessary, make a medical necessity determination of the product in shortage.

7. Ensures that product shortage information posted on the CBER-Regulated Products: Shortages and Discontinuations Web page is accurate and current.

8. Ensures that updated public information is posted on the CBER-Regulated Products: Shortages and Discontinuations Web page as soon as possible.

9. Communicates information to the appropriate stakeholders both within and outside of the Agency from first notification to resolution.

10. Monitors each product shortage situation until resolution.

11. Provides CBER's Office of Communication, Outreach, and Development (OCOD) with information/materials, as appropriate.

12. Provides guidance on policy-level issues related to product shortages, as requested.

13. In conjunction with the Center for Drug Evaluation and Research (CDER) submits to Congress an annual report on drug shortages and FDA's efforts to address them.

14. Issues a noncompliance letter to an applicant who fails to submit a notification as required under 21 CFR 600.82(a) and (b) as appropriate.

B. CBER product offices (with product review responsibilities) - OBRR, OTP, and OVRR

1. Evaluates the nature and status of each new shortage notification and, when necessary, makes a medical necessity determination of the CBER-regulated product in shortage.

2. Regulatory Project Management (RPM) Branch Chief within the CBER product offices:

a. Serves as the office representative for the purposes of triaging the notification.

b. Forwards the notification to the appropriate review personnel within the office.

C. CBER Office of Communication, Outreach, and Development (OCOD)

1. Forwards all notifications, reports, and inquiries concerning CBER-regulated product availability to the PSC.

2. Posts the information concerning product shortages, as appropriate, on the CBER-Regulated Products: Shortages and Discontinuations Web page.

3. Posts the information concerning product discontinuations that will lead to a meaningful disruption in supply in the United States on the CBER-Regulated Products: Shortages and Discontinuations Web page.

4. Posts the information concerning the resolution of product shortages on the CBER-Regulated Products: Shortages and Discontinuations Web page.

D. CBER Office of Biostatistics and Pharmacovigilance (OBPV)

1. Forwards all MedWatch and VAERS reports concerning actual or potential CBER-regulated product shortages to the PSC at CBERshortage@fda.hhs.gov.

2. Assists the product offices and the PSC as necessary in assessing such reports.

E. FDA Office of Inspections and Investigations (OII)

Program Divisions will:

1. Forward all information concerning CBER-regulated product shortage situations that do not involve compliance issues directly to the PSC via the product shortage email account at CBERshortage@fda.hhs.gov or via phone call at (240) 402-8380.

2. Alerts the PSC to all CBER-regulated product shortage situations involving compliance issues at CBERshortage@fda.hhs.gov or at (240) 402-8380.

3. Works with CBER, as necessary, in determining the nature and scope of all CBER-regulated product shortage situations.

VII. Procedures

A. Forward all notifications, reports, or inquiries, including any related MedWatch and VAERS reports, concerning actual or potential product shortages to the CBER Product Shortage Coordinator (PSC) in OCBQ. **[CBER Product Office(s) (OBRR, OCBQ, OTP, OVRR), OBPV, OCOD, OII and/or RPMs from Product Offices]**

1. If there is an emergency that requires immediate attention, the CBER staff member receiving the notification, report, or inquiry will attempt to contact the PSC by phone at (240) 402-8380.

2. If the situation is not urgent, the person receiving the notification, report, or inquiry will promptly send it to CBERshortage@fda.hhs.gov.

B. Forward each notification of new shortage to the appropriate CBER product office RPM and/or contact person. **[PSC]**

C. Forward to appropriate review personnel within CBER product office. **[RPM]**

D. Evaluate the actual or potential product shortage. **[CBER Product Office(s) and PSC]**

The evaluation may include:

1. Data identifying manufacturers of similar versions of the product in shortage as well as data showing total units of product distribution in the United States (U.S.).

2. Inventory data of product available at the manufacturer(s) and major wholesalers throughout the U.S.

3. Reports of the 30-day back order status of the manufacturer.

4. Reports from health care personnel, consumers, trade, or patient groups regarding current and projected product availability and demand.

5. A determination if the CBER-regulated product in shortage is medically necessary. This may include a formal request of medical necessity determination from the CBER product office with expertise on that CBER-regulated product.

    a. Typically, if an alternative product compliant with the FDA's current Good Manufacturing Practice requirements (CGMPs) exists, is in adequate supply, and could be used to treat the same serious disease or medical condition as the shortage product then the product may not be considered to be medically necessary.

    b. If there is not an alternative product available, then the product may be considered to be medically necessary.

    c. In certain instances when the decision about whether or not the product is medically necessary is particularly complex, the CBER product office representative will consult with CBER management, as appropriate.

6. A determination if the medically necessary product shortage is related to manufacturing and quality issues.

   a. If CBER determines that the shortage of a medically necessary CBER-regulated product is not related to manufacturing and quality issues (e.g., manufacturing facility destroyed by fire, facility closed for renovations, natural disaster), special actions may be taken by CBER to help mitigate the shortage.

      Medical Necessity Determination:

      Upon request of OCBQ, provide within five (5) working days of receipt of the shortage notification by the product office, a completed medical necessity determination via email to the CBER PSC at CBERshortage@fda.hhs.gov. **[CBER Product Office POC]**

E. Submit public product shortage information to OCOD for posting in the CBER-Regulated Products: Current Shortages section of the CBER-Regulated Products: Shortages and Discontinuations Web page and ensure that the posted information remains current. **[CBER PSC]**

The information to be supplied to OCOD for posting will include:

1. Product Name;
2. Proprietary Name (Trade Name);
3. Manufacturer and Manufacturer Contact Information;
4. Product Availability and Estimated Shortage Duration (when known);
5. Shortage Reason (per FDASIA);
6. Manufacturer recommendation(s) or additional information (if provided by the manufacturer) intended for public use (e.g. weblinks, phone numbers, etc.);
7. Date shortage began and any dates when updates occurred.

F. Submit information concerning CBER-regulated products which have been determined to no longer be in shortage status to OCOD. Request for OCOD to remove posting from the CBER-Regulated Products: Current Shortages section of the CBER-Regulated Products: Shortages and Discontinuations Web page and place new information (posting) in the CBER-Regulated Products: Resolved Shortages section of the CBER-Regulated Products: Shortages and Discontinuations Web page when the shortage has been determined to be resolved based on drug supply information provided from sponsor(s) or manufacturer(s). Generally, a shortage is considered to be

resolved when all backorders have been filled and the supply is once again meeting or exceeding demand. **[CBER PSC]**

The information to be supplied to OCOD for posting will include:

1. Product Name;
2. Proprietary Name (Trade Name);
3. Manufacturer;
4. Manufacturer Contact Information;
5. Additional Information – which consists of a short summary of the reason for the shortage and any other helpful information;
6. Resolved Date.

G. Submit information concerning CBER-regulated products which the manufacturer has permanently discontinued and, as a result, CBER has determined may likely lead to a meaningful disruption in the supply of that product in the United States to OCOD for posting in the CBER-Regulated Products: Discontinuations section of the CBER-Regulated Products: Shortages and Discontinuations Web site and ensure that the posted information remains current. **[CBER PSC]**

The information to be supplied to OCOD for posting will include:

1. Product Name;
2. Proprietary Name (Trade Name);
3. Manufacturer;
4. Manufacturer Contact Information;
5. Additional Information – which consists of a short summary concerning the reason for discontinuation and any new recommendations, instructions, etc.;
6. Discontinued Date.

H. Document all meetings, telecons, etc. and include in the OCBQ record system and/or CBER's Electronic Repository (CER) as appropriate. **[CBER PSC, RPM, Product Reviewer]**

VIII. Appendix

Not Applicable

IX. References

A. References below may be found on the Internet:

1. Executive Order 13588, Reducing Prescription Drug Shortages (October 31, 2011)
2. Food and Drug Administration Safety and Innovation Act (FDASIA), (July 9, 2012)
3. Federal Food, Drug, and Cosmetic Act, (FD&C Act), Sec. 506 C
4. Strategic Plan for Preventing and Mitigating Drug Shortages (October 2013)
5. Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products (80 FR 38915, July 8, 2015)
6. Coronavirus Aid, Relief, and Economic Security Act (CARES Act) (March 27, 2020)
7. FDA, Office of Regulatory Affairs (ORA), Field Management Directive (FMD) 15 – Product Shortage Communication
8. CBER-Regulated Products: Current Shortages
9. CBER-Regulated Products: Discontinuations

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Joseph P. Manik	Martha Monser, Regulatory Review Document Lead Coordinator, RABOB/DROP/ORO	October 07, 2025	9	Updated ORA to OII, removed outdated references.
M. Monser	N/A	February 27, 2023	8	Technical update for 2023 CBER reorganization
M. Monser	N/A	February 27, 2022	7	Technical update for 2022 CBER reorganization

Written/ Revised	Approved By	Approval Date	Version Number	Comment
J. Manik, A. Richardson, OCBQ	Christopher Joneckis, PhD	July 30, 2021	6	Revised to include CARES Act, Section 3111 provisions, corrected typos.
M. Monser	N/A	December 11, 2020	5	Technical Update for retirement of EDR and replacement with CER
M. Monser	N/A (Reviewed by JA Coordinator)	January 14, 2020	4	Technical Revision to Current Font/Format
J. Manik, A. Richardson, OCBQ	Christopher Joneckis, PhD	August 27, 2018	3	Revised to include new procedures as a result of new regulations
J. Manik, A. Richardson, OCBQ	Robert Yetter, PhD	March 29, 2012	2	Revised to include new procedures
M. Knippen, J. Davis, OCBQ	Robert Yetter, Ph.D.	January 2, 2004	1	Original