POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Drug Shortage Management

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PURPOSE

- This MAPP establishes the Center for Drug Evaluation and Research (CDER) procedures for notification, evaluation, and management of drug shortage situations for all CDER products (e.g., investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs), and critical products from any source).

- This MAPP also establishes the CDER Drug Shortage Program (DSP).

BACKGROUND

In recent years, the number, sources, and complexity of drug shortages have grown. The need to expand and enhance the management of shortage situations across the Center resulted in the formal establishment of the DSP. The DSP serves as the focal point for the evaluation and management of CDER drug shortage situations in support of the FDA's mission. Through communication, facilitation, and negotiation, the DSP works with internal and external stakeholders to prevent, alleviate, and resolve shortage situations

POLICY

- The Director of the Office of Antimicrobial Products (OAP) serves as the Drug Shortage Coordinator for the DSP. The primary DSP staff resides in the OAP immediate office.

- The DSP has a network of designated contacts within the FDA, including one in each division of the Office of New Drugs (OND), to comprehensively and proactively address drug availability issues.

  – For shortages involving compliance and regulatory actions, the OC Recall/Drug Shortage Manager supports the DSP by coordinating OC program actions for management of a shortage. This includes compliance actions such as deviations from current good manufacturing practices, misbranding, counterfeiting, new drug status, and adulteration.

  – For situations involving generic drug products, the DSP works with the designated Drug Shortage Coordinator within the Office of Generic Drugs (OGD). The OGD Drug Shortage Coordinator is designated by the OGD Director, and provides guidance and expertise on generic drugs involved in shortages.

  – Designated coordinators within the Division of Drug Information (DDI) work together with the DSP to handle shortage reports received by the DDI.

  – A lead chemist, designated by the Director of the Office of New Drug Quality Assessment (ONDQA), provides expertise on shortage management involving chemistry, manufacturing, and controls (CMC) issues.

  – Designated coordinators in the Office of Biotechnology Products (OBP) provide expertise on shortage management involving CMC issues for biologics and other protein products reviewed within this office.

  – The DSP interfaces with a designated contact in the Office of Counterterrorism and Emergency Coordination (OCTEC) on issues related to the SNS, and on emergency preparedness and response activities.

- The DSP monitors critical drugs and medical countermeasures, including those in the SNS, to ensure availability for emergency situations. The DSP serves as a liaison with other FDA centers, other government organizations including the CDC and the Department of Defense (DoD), and private industry.

- All potential or actual shortage situations and discontinuations of CDER drugs should be reported to the DSP as soon as they are known. Shortages and discontinuations also should be reported to the review division where the application resides. The time element is particularly important in the case of medically necessary, critical, and counterterrorism drugs. Shortages can be reported by phone to (301) 796-1300 or by e-mail to DrugShortages@CDER.fda.gov.

RESPONSIBILITIES AND PROCEDURES

(See the References section for the location of detailed process information.)

The DSP will:

When a drug shortage is reported:

- Receive reports from all sources (including industry, other FDA offices, American Society of Health-System Pharmacists and other external entities, health care professionals, and patients) related to drug shortages and discontinuations.

- Verify that an actual shortage or discontinuation exists through communications with manufacturers, other FDA offices, and external entities such as American Society of Health-System Pharmacists, and through use of market research data.

- Search drug shortage electronic databases for drug history, information on other drugs in the same class, related OC activity, any existing medical necessity determination, and status as a critical, emergency, or counterterrorism drug.

- Request a new or updated Medical Necessity Determination form from the division with the requisite expertise in that drug as needed.

- Work with the DSP network and involve other FDA offices, industry, and outside entities as needed to develop a shortage management plan.

- Monitor any significant shortage situation until resolution.

- If the drug is medically necessary, post shortage issues, as well as significant discontinuation information when it is provided by firms, on the Drug Shortage Web site (http://www.fda.gov/cder/drug/shortages).

- Communicate information to the appropriate divisions, offices, individuals, and non-HHS stakeholders from first report to resolution (e.g., OND office directors, division directors, project managers, the DSP network, the CDC, the DoD, American Society of Health-System Pharmacists).

When shortage of an emergency preparedness/counterterrorism (EP/CT) drug is reported:

- Notify OCTEC of all shortage and discontinuation situations related to drugs with known EP/CT-related uses or that involve the SNS. (Information on this group of drugs is not posted on the CDER Drug Shortage Web site because of national security considerations.)

- Enter EP/CT drug shortage information in the Drug Shortage Critical Products database.

When conducting routine responsibilities:

- Manage the Drug Shortage Critical Products database, which contains supply and production information for drugs deemed critical for EP/CT-related uses as well as other medically necessary uses.

- Update information in the Drug Shortage Critical Products database biannually and whenever new information is provided by the manufacturers of these drugs.

- Maintain a public e-mail account accessed through the CDER Drug Shortage Web site and respond to drug shortage inquiries received through this account (DrugShortages@CDER.fda.gov).

- Write talk papers and briefings on shortage situations and handle interviews through the media office as needed.

The DSP Drug Shortage Coordinator will:

- Supervise DSP activities.

- Provide guidance on policy-level issues related to shortages.

- Provide guidance on shortage management as needed and when a shortage involves more than one OND office.

The Office of Compliance will:

- Screen and forward all reports of OC-related shortage situations to the DSP, including recalls and compliance actions that could lead to potential shortages.

- Request a medical necessity determination through the DSP regarding drugs with issues that could lead to a shortage.

- Support and coordinate with OC program units regarding the development of shortage management features in compliance corrective action plans to resolve shortages (e.g., additional testing, regulatory discretion, consultant oversight).

- Communicate drug medical necessity status and shortage information internally with all OC program units on recalled drugs or drugs involved in compliance actions.

- Initiate, facilitate, and monitor importation plans when deemed necessary and assist with importation procedures related to drug shortages.

- Request and process Health Hazard Evaluations (HHEs) from divisions as needed and project the effect of the evaluations on market supply.

- Facilitate expedited inspections or develop options related to inspections and re-inspections.

- Assist in identification of non-U.S. drug sources for drugs in shortage.

- Be involved in all compliance and regulatory discussions with industry where compliance actions, recall, or drug withdrawal are under discussion.

The Office of Generic Drugs will:

- Facilitate resolution of regulatory and scientific issues related to generic drugs in shortage.
- Serve as liaison with generic manufacturers for shortage resolution.
- Apprise the DSP of all ANDA approvals and discontinuations of drugs in shortage and EP/CT drugs.
- Notify the DSP of the need for medical necessity determination for generic drugs.

The Division of Drug Information will:

- Forward drug shortage inquiries received through the DDI e-mail and voicemail accounts to the DSP.
- Provide assistance to the DSP in responding to inquiries regarding known shortage issues.
- Assist with development and dissemination of information (e.g., talk papers, Dear Health Care Professional letters, notifications) regarding shortages.

The Office of New Drug Quality Assessment will:

- Serve as the DSP liaison to all ONDQA personnel involved in a shortage situation.
- Work with team members to facilitate resolution of shortages that involve CMC issues.

The Office of Biotechnology Products will:

- Serve as the DSP liaison to all OBP personnel involved in a shortage situation.
- Work with team members to facilitate resolution of shortages that involve CMC issues.

The Office of Counterterrorism and Emergency Coordination will:

- Serve as CDER's principal interface with the SNS.
- Assist with identifying drugs with EP/CT-known uses to be included in the Drug Shortage Critical Products database.
- Notify the DSP of issues relating to possible shortages or supply problems of any EP/CT drugs.

The Office of the CDER Center Director/Executive Operations Staff will:

- Report important drug shortage and discontinuation information to the Center Director and the Office of the Commissioner.
- Consult with DSP staff and obtain clearance on shortage press releases and talk papers as needed.

- Obtain signatures on correspondence relating to shortages that require Center-level sign-off.

The OND Office Directors will:

- Serve as points of contact for shortage situations involving drugs within their offices.
- Provide guidance to OND office staff on policy-level issues relating to shortages.
- Interact with other OND office directors regarding review issues if the shortage involves more than one OND office.
- Decide who takes the lead if the shortage involves two divisions within an office.
- Review and sign HHEs if OC requests this determination.

The OND Division Directors will:

- Serve as points of contact for shortage situations involving drugs within their divisions.
- Interface with other division directors when the shortage involves more than one division.
- Determine who (division staff, co-locates) should address the situation.
- Review and sign Medical Necessity Determination forms as needed.
- Review and sign HHEs if OC requests this determination.

The OND Team Leaders and Medical Officers will:

- Provide guidance to the team or participants in the area of expertise to develop and carry out a management plan for the shortage situation.
- Complete an HHE, if OC requests it, obtain division- and office-level signatures, and send the form to OC and the DSP.
- Complete the Medical Necessity Determination form, if requested by the DSP, obtain the necessary signatures, and return the form to the DSP.

The OND Project Managers will:

- Communicate all shortage information to the appropriate team members, OND office directors, and division directors.
- Update the DSP on team activities related to the shortage.
- Set up internal and external meetings as necessary, provide meeting minutes, and enter the minutes into the document archive for INDs, NDAs, or BLAs.

- Monitor the completion of the Medical Necessity Determination form and the HHE if used, provide copies to the requestor (the DSP and/or OC), and file the completed forms in the document archive if an IND, NDA, or BLA.

Manage the documentation for IND, NDA, and BLA regulatory actions associated with shortage activities of the team.

REFERENCES

- Detailed facts on the DSP process: http://www.fda.gov/cder/drug/shortages
- Federal Food, Drug, and Cosmetic Act, section 506C (drug product discontinuation)

DEFINITIONS

- **ANDA —** Abbreviated new drug application
- **BLA —** Biologics license application
- **CDC —** Centers for Disease Control and Prevention
- **DDI —** Division of Drug Information
- **DoD —** Department of Defense
- **Drug —** Refers to all drug and biological products regulated by CDER.
- **Drug discontinuation —** A situation in which a drug is no longer being commercially distributed by an FDA-regulated manufacturer whether or not a formal withdrawal request is made to the FDA. Formal notice to the FDA of the discontinuation of sole-source, medically necessary products is required under section 506C of the Federal Food, Drug, and Cosmetic Act.
- **Drug shortage —** A situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the user level. In general, the DSP focuses on shortages of medically necessary products that have a significant effect on public health.
- **Drug Shortage Program (DSP) —** The program designated by the CDER Center Director to oversee and facilitate the resolution of all shortage situations involving CDER drug products. The DSP also monitors the production and availability of emergency and counterterrorism drug products.
- **EP/CT —** Emergency preparedness/counterterrorism

- **Health Hazard Evaluation (HHE) —** A formal determination of patient safety (risk-benefit) related to the drug product in question. This determination is requested by the Office of Compliance (OC), completed by the division or divisions with requisite expertise in the drug product, provided to OC and the DSP, and filed in the document archive. (See Attachment A.)

- **IND —** Investigational new drug application

- **Medically necessary product —** Any drug product used to treat or prevent a serious disease or medical condition for which there is no other adequately available drug product that is judged by medical staff to be an appropriate substitute. Off-label uses and IND drug products can be considered medically necessary. Patient inconvenience alone is an insufficient reason to classify a drug product as medically necessary.

- **Medical necessity determination —** A formal, written assessment made by the CDER medical officer or officers with requisite expertise on the drug, stating whether the drug meets the definition of a medically necessary product. Multiple CDER divisions may be asked to make this determination when there are approved indications and/or off-label uses requiring the expertise of more than one division. This determination is provided to the DSP on the Medical Necessity Determination form (see Attachment B).

- **NDA —** New drug application

- **OAP —** Office of Antimicrobial Products

- **OC —** Office of Compliance

- **OCTEC —** Office of Counterterrorism and Emergency Coordination

- **OGD —** Office of Generic Drugs

- **OND —** Office of New Drugs

- **ONDQA —** Office of New Drug Quality Assessment

- **Strategic National Stockpile (SNS) —** A federal asset of medical supplies, including drugs, to be used in response to national emergencies (both natural and man-made). The SNS is maintained by the Centers for Disease Control and Prevention (CDC) (see http://www.bt.cdc.gov/stockpile).

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENT 1

CDER Health Hazard Evaluation Request and Consult Form

EVALUATION REQUESTED BY: _____, RECALL OFFICER

Division of Manufacturing
and Product Quality, HFD-320
Office of Compliance

Evaluation Requested of:

Date of Request:

Date Completed Evaluation Needed:

****Note:** **You are being asked to complete a health hazard evaluation for a specific drug or biologic product defect. Please complete sections 4 through 13 of this form. The clinical significance of the product defect should be described in detail. This consult will be used to develop a regulatory plan/recall strategy by the Office of Compliance Recall Unit.**

If you have questions about completing this form, please contact:

_____

CDER HEALTH HAZARD EVALUATION

1. PRODUCT INFORMATION

a) Product name:

b) Product description:

c) [ ] See attached copy of label distributed with product

[ ] Copy of label distributed with product to be forwarded

d) Identification number (e.g., unit, lot, serial number, catalog number, order number, application number):

2. FIRM INFORMATION

Name and location:

3. NATURE OF PROBLEM (specify and describe estimated extent of defect)

[ ] Product mix-up

_____

_____

[ ] Counterfeit

_____

_____

[ ] FDA lab analysis of counterfeit product or other relevant documentation attached

[ ] Other

4. a) Have any adverse events or other indication of injuries or diseases been reported relating to **this particular product**?

[ ] No
[ ] Yes – Attach copies of relevant reports or explain

_____

_____

b) Have any adverse events or other indication of injuries or diseases been reported for **products of the same class or products used for the same indication**?

[ ] No
[ ] Yes – Attach copies of relevant reports or explain

_____

_____

c) Is the defective product easily identified by the user?

[ ] No
[ ] Yes

d) Would there be a significant number of new users of the product who might not be familiar with the product and therefore unable to easily identify the defect such as in a mix-up situation?

[ ] No
[ ] Yes

If "yes," please explain and provide an estimate of the number of such new users.

_____

_____

5. Use indications for the product

   a) Approved uses:

   _____

   _____

   _____

   b) Known off-label uses:

   _____

   _____

   _____

   c) Is the extent of product use greatest for approved use indications or for known off-label uses?

   [ ] approved use indications

   [ ] known off-label uses

6. Patient population **most likely to use** the product:

   (Check all that apply. If more than one choice is selected, please provide an estimate of the percentage of use by each population.)

   ____ Infants

   ____ Children

   ____ Women of childbearing age

   ____ Pregnant women

   ____ Nursing mothers

____ Surgical patients

____ Immune-suppressed individuals

____ Special clinical situations (describe: _____)

____ Other (please describe)

_____

_____

_____

7. Patient population **most at risk from use** of the product and why:

(Check all that apply. If more than one choice is selected, please provide an estimate of the percentage of use by each population.)

Note: The patient population most likely to use the product and that most at risk from use of the product may be different.

____ Infants

____ Children

____ Women of childbearing age

____ Pregnant women

____ Nursing mothers

____ Surgical patients

____ Immune-suppressed individuals

____ Special clinical situations (describe: _____)

____ Other (please describe)

_____

_____

a) Within the population most at risk, could individuals suffering from any particular conditions or diseases (e.g., immune system debilities, diabetes, cardiac problems, use of concomitant medications) be at more or less risk and, if so, why?

_____

_____

8. Product consumption: What is the recommended dose, dosing regimen, and maximum total daily dosage of the product:

(*If these doses and dosing regimens are different for different use indications, please describe.)

a) For the population **most at risk**:

i) Recommended dose:

_____

ii) Recommended dosing regimen:

_____

iii) Maximum total daily dose:

_____

b) For the population **most likely to use** the product:

i) Recommended dose:

_____

ii) Recommended dosing regimen:

_____

iii) Maximum total daily dose:

_____

Note: For product mix-ups, please also provide this information for the product with which the mix-up could occur as noted in items 1-3 of this form:

Dose, dosing regimen, and maximum total daily dose for _____ as noted in items 1-3:

c) For the population **most at risk**:

i) Recommended dose:

_____

ii) Recommended dosing regimen:

_____

iii) Maximum total daily dose:

_____

d) For the population **most likely to use** the product:

i) Recommended dose:

_____

ii) Recommended dosing regimen:

_____

iii) Maximum total daily dose:

_____

9. Clinical significance or health implications of the product defect (i.e., adverse health consequences that could occur with use of the product):

_____

_____

_____

10. What is the likelihood of an adverse event occurring if the defective product is used by the population **most likely to use** the product?

____ Highly likely to occur (every time the product is used)

____ Likely to occur (reasonable probability of occurrence)

____ Might occur (remote probability of occurrence)

____ Unlikely to occur

____ Unknown (please explain) _____

11. What is the likelihood of an adverse event occurring if the defective product is used by the population **most at risk**?

    ____ Highly likely to occur (every time the product is used)

    ____ Likely to occur (reasonable probability of occurrence)

    ____ Might occur (remote probability of occurrence)

    ____ Unlikely to occur

    ____ Unknown (please explain) _____

12. Describe the degree of the health hazard associated with use of the defective product by the population **most likely to use it**:

**Please cite literature references when applicable.

**If more than one choice is selected, please explain.

____ Life-threatening (death has or could occur).

____ Could result in permanent impairment of a body function or permanent damage to a body structure.

____ Necessitates medical or surgical intervention to preclude or reverse permanent damage to a body structure or permanent impairment of a body function.

____ Could cause temporary or reversible (without medical intervention) adverse health consequences.

____ Could cause limited adverse health consequences (transient, minor impairment, or complaints).

____ Not likely to cause adverse health consequences.

____ Hazard cannot be assessed with the data currently available (please explain).

Explanation:

_____

13. Describe the degree of the health hazard associated with use of the defective product by the population **most at risk**:

**Please cite literature references when applicable.

**If more than one choice is selected, please explain.

____ Life-threatening (death has or could occur).

____ Could result in permanent impairment of a body function or permanent damage to a body structure.

____ Necessitates medical or surgical intervention to preclude or reverse permanent damage to a body structure or permanent impairment of a body function.

____ Could cause temporary or reversible (without medical intervention) adverse health consequences.

____ Could cause limited adverse health consequences (transient, minor impairment, or complaints)

____ Not likely to cause adverse health consequences

____ Hazard cannot be assessed with the data currently available (please explain)

Explanation:

_____

_____

Signature, MD _____ Date:_____

Signature, Division Director _____Date:_____

Signature, Office Director _____Date: _____

ATTACHMENT B

Medical Necessity Determination Form

Document Information Page

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	
Communication Type:	Forms
Communication Group:	ADMINISTRATIVE
Communication Name:	Medical Necessity Determination For Drug_____
Communication ID:	FRM-ADMIN-13
Drafted by:	
Clearance History:	
Finalized:	
Filename:	
Use Statement:	
Notes:	

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

CENTER FOR DRUG EVALUATION AND RESEARCH
MEDICAL NECESSITY DETERMINATION

INSTRUCTIONS

Please evaluate the medical need for this product by answering the questions below. Keep in mind that a medically necessary drug product is a product that is used to treat or prevent a serious disease or medical condition for which there is no drug or alternative drug, available in adequate quantity, that is judged by medical staff to be an acceptable substitute. Patient *inconvenience* alone is an insufficient reason to classify a product as medically necessary.

NAME OF DIVISION _____
Name of person(s) making determination_____
Date of Medical Necessity Request_____

PRODUCT(S) NDA, BLA number(s):

Trade name
Established, proper, or generic name
Formulation(s)

MANUFACTURING FIRM

Name of firm
Address of firm
Phone number

Single-source product or multiple-source product?

BACKGROUND

1. Is the product used to treat a serious disease or medical condition?

[ ] No
[ ] Yes – Explain

2. What are the labeled indications for this product?

3. Are there important "off-label" uses such as those for a serious medical condition? ***(Please note that off-label uses can be considered medically necessary.)***

4. Are there generic forms of this product?

[ ] No
[ ] Yes – Are there any special benefits/risks associated with the generic product(s)?

5. Are there alternative products available?

[ ] No
[ ] Yes – Please explain the risk(s) and benefit(s) of the alternative product(s). Please cite the NDA number(s), trade name(s), and generic name(s).

6. From the above assessment, is this product medically necessary? (Please note that this question refers only to the overall medical necessity of the product(s), not whether the specific (manufacturer's) product in question is appropriate for continued administration to patients. If the product is determined to be medically necessary, an assessment will then be made as to whether the product in question may be used (for instance with additional testing) to alleviate shortage situations. If it is not appropriate to administer the product to patients then alternative approaches will be examined. When necessary, a separate Health Hazard Evaluation (HHE) will be requested to address newly identified defects, impurities, and/or risks associated with this drug.)

[ ] No
[ ] Yes (Please state if this is only for specific indications.)

7. Additional comments:

8. Signature of person performing this medical necessity determination.

{See appended electronic signature page}

Medical Officer Date

{See appended electronic signature page}

Medical Officer, Team Leader Date

{See appended electronic signature page}

Division Director Date