Guidance for Industry

Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Xxxx 2010
Procedural

OMB Control No. 0910-xxxx

Expiration Date xx/xx/20xx
See additional PRA statement in section V of this guidance

Guidance for Industry

Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products

Additional copies are available from:

Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Xxxx 2010
Procedural

TABLE OF CONTENTS

Guidance for Industry[1]

Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to encourage manufacturers of medically necessary drug products (MNPs) and any components of those products to develop contingency production plans to use during emergencies that result in high absenteeism at production facilities. In CDER's Manual of Policies and Procedures (MAPP) 6003.1 "Drug Shortage Management,"[2] a *medically necessary drug product* is defined as:

> Any drug product that is 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.

The guidance provides considerations for the development and implementation of a plan for production of MNPs during a crisis, including specific elements that should be included in the plan. The guidance also discusses the Center for Drug Evaluation and Research's (CDER's) intended approach to helping to avoid drug product shortages that could have a negative impact on the national public health during such emergencies.

The guidance is intended for manufacturers of drug and therapeutic biological products regulated by CDER and manufacturers of raw materials and components used in those products. FDA strongly recommends that drug product manufacturers show this guidance to all suppliers and contractors associated with the manufacture of MNPs and discuss the guidance with them to stimulate planning to avoid or mitigate disruptions in supply.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] Information about the CDER Drug Shortages Program, including a link to CDER MAPP 6003.1 can be found at http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Medically necessary drug products and their components are manufactured all over the world. An emergency situation anywhere in the world thus might affect the availability of drug products in the United States and result in drug shortages. Emergency preparedness for situations that could result in high employee absenteeism is an important goal for manufacturers of drug products and their components. For example, in an influenza pandemic, widespread human outbreaks of illness would be expected in the United States and around the world, resulting in widespread high absenteeism that could hinder normal production activities and cause shortages in the supply of drug products, packaging materials, and drug components. It is therefore vital for industry to prepare before an emergency situation occurs and to develop plans to ensure continuity of operations during emergencies (including, for example, an influenza pandemic, natural disaster, or personnel issue) that would prevent a significant portion of the work force from reporting. It is especially important for manufacturers of finished drug products to be aware of their suppliers' and contractors' responses to personnel shortages and, when appropriate, work with them to ensure the availability of high quality materials and services that contribute to the manufacture of MNPs.

In addition to developing a written emergency plan, manufacturers can also benefit from preparing for emergencies (e.g., a pandemic) through prevention and risk mitigation. These preventative measures can include steps to prepare personnel such as:

- Educating employees on topics such as, in the case of a pandemic, personal hygiene (hand washing, coughing, and sneezing etiquette), social distancing, and appropriate use of sick leave
- Encouraging employees to get immunized as appropriate by providing information on local vaccination services or by offering on site vaccination services, if reasonable
- Providing information for and encouraging employees to develop family emergency preparedness plans
- Reviewing CGMP regulations regarding appropriate sanitation practices and restriction of ill or sick employees from production areas (see 21 CFR 211.28)

III. DEVELOPING AN EMERGENCY PLAN

When a crisis occurs, there might be insufficient time and management resources to develop an appropriate action plan. Therefore, CDER strongly recommends that manufacturers develop a plan in advance of an actual emergency to address an emerging personnel shortage that could affect the production of MNPs.

Despite activation of a manufacturer's emergency plan (Plan), an emergency might result in the manufacture of MNPs that do not meet all statutory and regulatory requirements. CDER is prepared to exercise enforcement discretion in such cases as appropriate to meet the national public health needs so long as the product remains safe and effective. Our goal is to ensure that medically necessary drug products are available throughout an emergency and that these products are safe and effective, and have adequate identity, strength, quality, and purity.

In the following sections, we recommend points to consider when developing a Plan for maintaining an adequate supply of MNPs during an emergency that results in high employee absenteeism.

A. General Considerations

Firms may already have plans in place to maintain business continuity during an emergency. CDER recognizes that the quality unit might not be designated to review or approve contingencies in the execution of a Plan having no potential to affect product quality. However, any planned changes having the potential to affect product quality should be reviewed and approved by the quality unit prior to implementation in accordance with the requirements in 21 CFR 211.22, 211.100(a) and 211.160(a); execution of the Plan should be documented in accordance with the requirements described in 21 CFR 211.100(b).

A Plan should be specific enough to address unique considerations at each location where it is to be implemented. A broader Plan to address multiple sites within the organization could also be appropriate. This approach provides for the specific and unique considerations of individual facilities and the flexibility to shift operations, resources, or personnel from one manufacturing facility to another.

CDER recommends that the Plan identify people or position titles with the authority to activate the Plan, deactivate the Plan, and make decisions during the emergency. The Plan should allow for the possibility that one or more people or positions identified in the plan are unavailable.

B. Prioritizing Products Based on Medical Necessity

FDA encourages firms that anticipate high absenteeism to give highest priority to medically necessary products when scheduling manufacturing and making plans for reassigning or cross-training personnel. Special attention should be given to medically necessary products for which the company is sole source or supplies a significant share of the U.S. market, as well as products vulnerable to shortage because of low levels of finished product likely to be in the supply chain at any given time. Manufacturers should also consider whether particular emergency situations might affect whether certain products are considered medically necessary (e.g., antiviral drugs during an influenza pandemic). It is important to note that medical necessity during an emergency is not limited to products directly related to the specific emergency, but also encompasses products necessary for maintenance of dependent populations (i.e., for conditions such as diabetes, high blood pressure, congestive heart failure, asthma, and cancer). CDER is aware that during an emergency, it might not be feasible to consult with CDER to determine if a

product should be considered medically necessary. In such cases, each company should use its best judgment to determine the relative priority of a product within its manufacturing portfolio.

Companies might benefit from prioritizing their products (based on medical necessity) within a single manufacturing facility, as well as across groups of manufacturing facilities, or across their entire manufacturing operation, including approved contractors. This tiered approach could provide useful insight into how best to manage and shift resources to meet the public health need for the most critical products. If a company finds itself unable to maintain manufacturing of all of its products, suspension of the manufacturing of products that are not medically necessary may free resources used to manufacture MNPs.

C. Recommendations for Actions Prior to a Period of High Absenteeism

When it is possible to anticipate an emergency that could result in a high rate of absenteeism affecting production of MNPs, CDER recommends that manufacturers consider one or more of the following measures, as appropriate:

- Increase inventory of MNPs
- Increase inventory of components and other materials needed for the manufacture of MNPs
- Conduct cross-training exercises to ensure the competency of personnel that might be reassigned to the manufacture of MNPs or assigned to different roles in the manufacture of MNPs
- Perform maintenance, calibrations, and other activities that take place periodically so that these activities are not scheduled to occur while the Plan is active
- Make provisions for the use of competent resources that might be accessible at alternate sites, including contractors (e.g., qualified testing labs)
- Make provisions for the use of alternative suppliers of goods and services, including distributors, to reduce the potential for disruptions in the supply chain

D. Considerations for Plan Implementation During a Period of High Absenteeism

CDER acknowledges that the measures discussed in section III.C might not be possible or sufficient in all situations. Accordingly, CDER recommends that manufacturers develop a detailed Plan designed to maintain adequate supply of MNPs in a period of high absenteeism of manufacturing employees.

1. Developing Criteria for Activating the Plan

One critical element of any Plan is identifying criteria and the threshold for activation of the Plan. Knowledge acquired through the prioritization of medically necessary products will be helpful in developing these criteria by identifying the percentage of resources routinely dedicated to the manufacture of medically necessary products. It may be helpful to consider the following points when attempting to determine when to activate the Plan:

- Consider criteria based on factors directly relevant to the manufacture of MNPs (such as percent of employees in critical manufacture or laboratory positions absent at one time)

rather than external factors (such as the World Health Organization's Pandemic Influenza Phases).

- Identify criteria for each individual manufacturing site as well as for the company as a whole.
  - The criteria should be based on the relative amount of resources dedicated to production of MNPs. Activation of the Plan should be limited to periods when shortages of MNPs are anticipated as a result of increased absenteeism in critical manufacturing positions, including laboratory positions.
  - The criteria need to be based on data readily available to the responsible person.

2. Performing Quality Risk Assessments

CDER recommends that each manufacturer, in developing a Plan to address high rates of absenteeism, conduct a prospective risk assessment and ensure that appropriate risk control measures are identified, approved by relevant decision makers, and used in development of the Plan, with the objective of meeting the demand for MNPs while continuing to provide a high level of assurance that manufacturers comply with CGMP and that products meet specifications. CDER recognizes that the primary measures recommended in the preceding sections might not be sufficient to address production of all MNPs when high absenteeism rates exist. CDER recommends that, as a secondary measure, manufacturers apply quality risk assessments to identify activities that might be reduced in frequency, delayed, or substituted by a suitable alternative. CDER recommends that before taking such measures, a manufacturer have a well-supported conclusion, based upon its process and product knowledge and quality risk assessments, that the anticipated actions to address absenteeism are not expected to unacceptably reduce assurance of product quality.

CDER recommends that manufacturers, when evaluating activities that might be reduced in frequency, delayed, or substituted by a suitable alternative, first identify and consider activities that are intended by the CGMP regulations to provide controls not connected with the manufacturing of any specific batch. Examples include:

- Production equipment routine maintenance
- Utility system performance checks and maintenance (e.g., air temperature, lighting, compressed air)
- Environmental monitoring of facilities such as cell culture, harvesting, and purification rooms during production
- Stability testing for certain drug products and components
- Periodic examinations of data and of reserve samples

If the demand for MNPs cannot be met by the measures described above, manufacturers can consider reducing activities that are more directly connected with batch manufacturing or a product accept/reject decision as long as they have a documented rationale or risk assessment to show the proposed changes will not unacceptably reduce assurance of product quality. Examples include:

- Not requiring second-person verification of activities for less critical steps (though we recommend a self-check of work)
- Reducing the number of samples for labor-intensive laboratory testing

- Forgoing an in-process test to assure adequacy of mix, particularly when making successive batches, where the risk is judged to be low in terms of drug safety and efficacy
- Delaying completion of deviation investigations of minor events

CDER recommends that in taking such measures, firms plan to carefully monitor indicators of product quality to note any unfavorable trends or shifts as a result of the implementation of the Plan. CDER also recommends that firms retain samples for testing at a later date in cases where testing is reduced or omitted because of lack of resources.

E. Returning to Normal Operations

A critical component of any emergency Plan is a procedure detailing when and how the transition back to pre-emergency, or normal, operations should occur. Once the Plan has been activated, it should remain active continuously until there is a reasonable expectation that normal operations will be maintainable for an extended period of time. The Plan should consider:

- What factors will indicate that it is time to return to normal operations or deactivate the Plan
- What resources will be necessary to complete postponed activities
- What activities will enable a successful transition back to normal operations

The following questions can stimulate some useful ideas for consideration and inclusion in the Plan:

- What information should be used to signal a return to normal operations (e.g., percentage of absenteeism in critical manufacturing and/or laboratory positions has remained below X percent for Y number of consecutive days)?
- How should efforts to resume processes suspended during the emergency be prioritized?
- What is the most efficient method to address delayed activities such as sample analysis and equipment calibrations?
- How should issues resulting from the execution of the Plan (e.g., out of specification test results, deviations, unusual complaints) be reported to CDER?
- What mechanism is most appropriate to review and summarize activities taken during Plan activation?

CDER encourages companies to maintain awareness of the emergency on the local, national, and global scale as much as possible. This awareness will help the company anticipate potential future concerns or imminent hazards that could affect their decision to resume normal operations or continue operating under their Plan. CDER also recommends that firms conduct a formal post-execution assessment of the execution outcomes and update their Plan as appropriate.

F. Notifying CDER

It is probable that despite every effort to avoid shortages, the very nature of an emergency makes shortages of products possible or even likely. To foster communication between companies and CDER and protect the national public health, we encourage manufacturers to include a procedure in their Plan for notifying CDER when the Plan is activated and when returning to normal

operations. These communications are intended to help CDER maintain awareness of any potential shortage situations and act accordingly to avoid or mitigate them. During periods when manufacturers are experiencing high rates of absenteeism, it is possible that CDER will also experience staff shortages. In such circumstances, CDER's ability to confirm receipt or subsequent activities could be delayed. We suggest that notifications of this nature include the following information, and be sent to CDERStaffingNotice@FDA.HHS.GOV:

- Within 1 day of Plan activation:
  - Manufacturing facilities affected
  - Date the Plan is implemented at each affected facility
  - Contact information for site-responsible person
  - Company-identified criteria that have triggered activation of the Plan
  - Products to be manufactured under the altered procedures of the Plan (include NDA, ANDA, and BLA numbers)
  - Products to have manufacturing temporarily delayed (include NDA, ANDA, BLA numbers)
  - Any anticipated or potential shortages
  - Quantity of finished product on hand for any product with an anticipated or potential shortage
- Within 1 day of the Plan deactivation:
  - Manufacturing facilities affected
  - Date the Plan was implemented at each affected facility
  - Date each affected facility returned to normal operations
  - Contact information for site-responsible person

If, after releasing a MNP under the Plan, a firm obtains information leading to suspicion that the product might be defective, the firm should contact CDER immediately in adherence to existing recall reporting regulations (21 CFR 7.40) or defect reporting requirements for drug application products (21 CFR 314.81(b)) and therapeutic biological products regulated by CDER (21 CFR 600.14).

G. Documenting Emergency Activities

CDER recommends that manufacturers evaluate changes to be made in accordance with the execution of the Plan and manage those changes having the potential to affect product quality in accordance with the CGMP requirements. Records that support decisions to carry out changes to approved procedures for manufacturing and release of products under the Plan should be retained at the site in accordance with the CGMP requirements (see, e.g., 21 CFR 211.180). Records FDA expects to be available include but are not limited to the following:

- Any supporting documentation for the Plan, including risk assessments and management approval for any change to an approved procedure or activity (e.g., delaying, substituting, or reducing the frequency of an approved procedure or activity)
- Lot numbers and application numbers of each product manufactured under the Plan

- Analytical data and relevant records for all products manufactured under an unapproved or nonstandard process, including the outcomes of delayed activities that are part of approved procedures or requirements for batch release (e.g., results from delayed specification tests)
- Timeline for completion of delayed or substituted activities that are part of the approved application or standard operating procedures, such as sample analysis and equipment calibrations and outcomes

If these records were to be reviewed during an inspection, FDA will consider the prevailing circumstances and the rationale used by a manufacturer to justify any observed discrepancies or deviations from a manufacturer's standard operating procedures and approved application(s).

IV. OPTIMIZATION AND DEMONSTRATION OF PREPAREDNESS

The optimization of an emergency plan can be an iterative process that involves drafting, reviewing, testing, and revising the Plan, perhaps more than once. Optimization can involve progressing from a simple discussion-based "table top" event toward a more elaborate simulation demonstrating the capability of the Plan. To derive the most benefit from this process, any tests should strive to simulate anticipated emergency conditions as closely as possible and should be conducted in a no-fault environment with the goal to improve the plan and not place blame for mistakes or oversights.

Each company should determine the most appropriate approach to ensure preparedness for execution of the Plan. CDER recommends that manufacturers conduct practice drills before an emergency appears imminent to increase familiarity of personnel at all levels with the Plan and their responsibilities under the Plan. CDER recommends considering the following activities, if feasible and practical:

- Practicing activation and deactivation of the Plan, involving all levels and roles within the company
- Having fully trained employees observe cross-trained employees during an exercise and provide immediate constructive feedback
- Carrying out contingency analytical procedures in conjunction with standard procedures

Any observations or outcomes resulting from these activities should be used to optimize the Plan and minimize any potential safety or product quality concerns. These corrections are typically best addressed through a formal meeting process following the exercise.

V. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average xx hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Office of Counter-Terrorism and Emergency Coordination, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 3341, Silver Spring, MD 20993-0002.

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR 7.40 have been approved under OMB Control No. 0910-0249; the collections of information in 21 CFR part 211 have been approved under OMB Control No. 0910-0139; the collections of information in 21 CFR 314.81(b)(1) have been approved under OMB Control No. 0910-0001; the collections of information in 21 CFR 600.14 have been approved under OMB Control No. 0910-0458.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-xxxx (expires xx/xx/20xx).