Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Thomas J. Christl 301-796-2057.

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

January 2010
Procedural

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)

January 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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 contingency production plan that will ensure the highest possible quality MNP under the circumstances, 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 encourages drug product manufacturers to show this guidance to all suppliers and contractors

[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.

associated with the manufacture of MNPs and to discuss the guidance with them to stimulate planning to avoid or mitigate disruptions in supply.

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 an influenza pandemic. It is especially important for manufacturers of finished drug products to coordinate their suppliers' and contractors' responses to personnel shortages to ensure the availability of high quality materials and services that contribute to the manufacture of MNPs.

In addition to developing a written 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
- Ensuring that employees are immunized, as appropriate, if vaccine is available
- 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

A Plan should be developed, written, reviewed, and approved within the site's change control quality system in accordance with the requirements in 21 CFR 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). As appropriate, standard operating procedures should be reviewed and revised or supplementary procedures developed and approved to enable execution of the Plan.

A Plan should be specific enough to address unique considerations at each location where it is to be implemented. In the case of drug manufacturing, a company could consider developing a Plan for each individual manufacturing facility, as well as a broader Plan that addresses multiple sites within the organization. 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 a person or position title with the authority to activate the Plan, deactivate the Plan, and make decisions during the emergency that will provide the best chance to continue the manufacture of MNPs using CGMPs or with as little deviation from approved procedures as possible. In addition, each person or position identified in the Plan should have two designated alternates in the event the primary person is 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 take the following measures:

- 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 or manufacturing equipment)
- Make provisions for the use of alternative suppliers of goods and services, including distributors, based on the suppliers' projected absenteeism rates

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 and 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 risk assessment with the objective of meeting the demand for MNPs while continuing to provide a high level of assurance that manufacturers comply with CGMPs and 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, that the actions planned 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. Examples include:

- Not requiring second-person verification of activities for less critical steps (though we recommend a self-check of work when possible)
- Reducing the number of samples for labor-intensive laboratory testing
- Releasing components based upon review of a qualified supplier's certificate indicating conformance with specifications along with specific identification 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. In addition, it is an accepted principle in emergency management that the most appropriate time to begin preparations for a return to normal operations is the moment that the Plan is activated. 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 of 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 Emergency 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, 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 manage the creation and execution of the Plan through their quality system 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:

- Risk assessment, supporting documentation, and management approval for any change to an approved procedure or activity, including delaying, substituting, or reducing the frequency of an approved procedure or activity as part of the Emergency Plan.
- 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. TESTING THE EMERGENCY PLAN

The development of an emergency plan can be an iterative process that involves drafting, reviewing, testing, and revising the Plan, perhaps more than once. Testing an emergency plan can also be an iterative process if so desired, progressing from a simple discussion-based "table top" test, to a small test with limited scope, then to a full-scale test that includes manufacturing test batches using processes in 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.

An additional benefit of testing the Plan is the increased familiarity of personnel at all levels with the Plan and their responsibilities under the Plan. Each company should determine the most appropriate approach to maximize the likelihood of success in the execution of a Plan. CDER recommends that manufacturers consider the following activities to ensure preparedness for execution of the Plan:

- Practice activation and deactivation of the Plan, involving all levels and roles within the company
- Have fully trained employees observe cross-trained employees during an exercise and provide immediate constructive feedback
- Produce small test batches of products under the Plan procedures
- Analyze test batches for compliance with release specifications

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.