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Connecting People, Science and Regulation®

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Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Reference: Draft Guidance for Industry on Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products; Docket No. FDA-2009-D-0568

Dear Sir/Madam,

PDA is pleased to offer comments on the draft Guidance for Industry "*Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products*". PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts, including members of our Regulatory Affairs and Quality Committee. PDA appreciates the opportunity to offer comments on this proposed rule and wishes to thank FDA for the opportunity to do so.

We have provided detailed comments identified by section of the draft and have included a supporting rationale in the accompanying table.

In addition to the specific comments on the draft guidance, PDA has some general concerns regarding particular aspects of the guidance.

- While PDA understands and is supportive of FDA's responsibility to address and alleviate shortages of medically necessary products, we believe that this issue is already managed by companies outside GMP systems. Typically pharmaceutical companies have "business continuity plans" which take into account potential high absenteeism as well as additional factors that could impact production such as natural disasters, equipment/facility failures, and raw material shortages.

These plans are developed, reviewed, and implemented as a business process outside of GMP systems though they clearly support operations consistent with GMP principles. They also include plans for areas which are not governed by GMPs. PDA does not believe that the plan should be incorporated and governed by the GMP quality system as stated in the draft guidance. PDA considers that the intent and legal basis of the GMPs (21 CFR § 210, 211 and 600's) is to ensure control and consistency of the manufactured products rather than assuring continuity of manufacturing operations. Assuring the availability of medically necessary products (MNP) is critical for public health, but in PDA's view, is outside the scope of GMPs.

Furthermore, the draft guidance as presently written is open to misinterpretation which could have unanticipated negative impact on GMP compliance of manufacturers if they are required to actually test the implementation of the plan. Each event which could trigger a business interruption plan would be different and unique, and testing each would be impractical. Tying up a plant with small test batches could interrupt the normal production cycles and result in product shortages, an unintended consequence which would clearly be undesirable.

We suggest that FDA consider providing guidance on business continuity plans in the form of a white paper that would include other Centers dealing with MNP issues (e.g. CBER) where said Centers also carry responsibility for MNPs.

- As outlined in our specific comments, PDA suggests that FDA notify a firm if they are a producer of a MNP as it would be difficult if not impossible for a firm to know when they would become or no longer are, a MNP supplier.

PDA would be pleased to offer our assistance in a public discussion and/or meeting with FDA to provide clarification of our recommendations and comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson
President, PDA

CC: Robert Dana, PDA
Rich Levy, PhD, PDA

**PDA Comments; Draft Guidance for Industry *Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products*; January 2010**

| Line No. | Current Text | Proposed Change | Rationale |
|---|---|---|---|
| Through out document | "The Plan" / Emergency Plan / Contingency Plan | Replace with existing industry terminology "business continuity plan" | The current terms are non-uniform and not commonly used in the industry. A Business Continuity Plan usually extends beyond absenteeism alone. |
| 22 | …and any components of those products | Delete | It should be the responsibility of the MNP manufacturer to ensure continuity of supply chain. It may not be feasible for manufacturers to be aware of specific component issues. Lines 40 – 42 support this approach. |
| 27-29 | Definition of MNP: 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 | Add:<br>FDA will identify and notify manufacturers if they are (or become as a result of a disaster) producers of MNP | It may not be possible for a manufacturer to know if they are a producer of MNP, therefore FDA notification would ensure they are aware they fall in the scope of the guidance |
| 32 | … will ensure the highest possible quality MNP under the circumstances | Reword to read:<br>Will ensure appropriate quality of the MNP despite the circumstances | As presently written the sentence could be misinterpreted as permitting release of substandard product |
| 61 | Including an influenza pandemic | Delete | Example already used (line 56). Reuse suggests undue concern for pandemics at the expense of an overall approach to business continuity e.g. hurricanes, earthquakes etc. |
| 62 - 64 | It is especially important for manufacturers of finished drug products to coordinate their suppliers' and contractors' responses….. | Change from<br>…to coordinate…<br>to read:<br>…to be aware of …. | It is not feasible for a company to "coordinate" suppliers'/contractors' responses. |

| Line No. | Current Text | Proposed Change | Rationale |
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| 67 | emergencies (e.g., a pandemic) through prevention and risk mitigation | Delete "e.g. a pandemic" | Same as line 61 –undue importance ascribed to one issue |
| 68 | These preventative measures can include steps to prepare personnel such as: | Delete this section | The type of preventive measures mentioned are managed by CDC and are not appropriate in this document. In addition, firms cannot ensure employees are immunized as medical records are confidential personal information and protected under other government regulations. |
| 84-85 | 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 | Change to:<br>It is recognized than an emergency might result in the manufacture of MNPs that do not meet all statutory and regulatory requirements or commitments. | It may not be possible to meet certain specific commitments made in regulatory applications in addition to statutory and regulatory requirements |
| 97-98 | 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); | Reword as follows:<br>**"**Companies should develop business continuity plans that may impact manufacture, testing and distribution of medically necessary products. These plans should be developed and implemented in a way that supports conformance to the principles of GMP during their period of implementation." | As mentioned earlier, most companies have a business continuity plan. The plan is a business process outside GMP systems although consistent with GMP principles. It also includes areas not governed by GMPs. The requirement to manage the plan within the GMP Quality System is burdensome without providing extra protection of public health |

| Line No. | Current Text | Proposed Change | Rationale |
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| 97 - 101 | A Plan should be developed, written, reviewed, and approved within the site's change control quality system in accordance with ... 21 CFR 211.100(a) and 211.160(a); execution … should be documented in accordance with …. 21 100 CFR 211.100(b). | Delete the section | Requiring the Plan to be in accordance with specified sections of 21 CFR is overly prescriptive regarding how a company should comply with the guidance. |
| 114 | In addition, each person or position identified in the Plan should have two designated alternates in the event the primary person is unavailable. | Delete text | Overly prescriptive and would be handled by internal continuity procedures. |
| 143 - 147 | When it is possible to anticipate an emergency… CDER recommends…<br>• Increase inventory of MNPs<br>• Increase inventory of components and other materials needed for the manufacture of MNPs | Delete first two bullet points regarding inventory and Change to read:<br>When it is possible to anticipate an emergency, companies should operate in accordance with their business continuity plan. Points to consider may include:…<br>Continue with additional bullet points | The revision allows for appropriate risk management of inventory and execution of the firm's business continuity plan. |
| 194 - 197 | CDER recommends that before taking such measures, a manufacturer have a well-supported conclusion, based upon its process and product knowledge, that the actions… not expected to unacceptably reduce assurance of product quality | Revise as follows:<br>CDER recommends that in developing a Plan, a manufacturer perform a risk assessment, based upon process and product knowledge to minimize the likelihood of adverse impact on product quality. | Adoption of risk assessment principles |
| 233 - 235 | 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. | Delete | Revised text allows for professional discretion on the part of the person activating and deactivating the plan on a case-by-case and risk related basis. Lines 236 – 242 make that point. |

| Line No. | Current Text | Proposed Change | Rationale |
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| 246 - 251 | What information should be used to signal a return to normal operations … | Delete | This should also be handled on a case-by-case basis. GMPs have adequate provisions for handling deviations, temporary changes etc. |
| 277 | Within 1 day of Plan activation: | Delete: "within 1 day of plan activation"<br>Replace by:<br>Notification to CDER is required where, as part of the plan, production or processes differ from product regulatory filings or deviate from cGMPs. Where feasible notification to CDER should occur within 3 business days or as soon as the situation allows. | Notification within one day is too short a time frame considering the acuteness of the situation and scarce resources. Where a business continuity plan does not involve deviations from GMPs or from regulatory filings it is overly burdensome for industry to notify CDER of activation/deactivation. |
| 289 | Within 1 day of Plan deactivation | Reword to read:<br>"If exceptions to product regulatory filings or cGMPs are part of the Plan, CDER should be notified of Deactivation within 7 business days. | Deactivation is also likely to require rapid redeployment of resources. PDA believes companies should be able to meet a seven day timeframe for notification of deactivation once the worst of the crisis is over. |
| 303 -307 | CDER recommends that manufacturers manage the creation and execution of the Plan through their quality system in accordance with the CGMP requirements. Records ….. should be retained at the site in accordance with the CGMP requirements (see, e.g., 21 CFR 211.180). | Reword entire paragraph to read:<br><br>CDER recommends that the Plan should be developed and implemented in a way that supports conformance to the principles of GMP throughout its implementation. | Most pharmaceutical companies have developed business continuity plans. As mentioned earlier, this is a business process outside GMP systems although supporting operations consistent with GMP principles. Specific references to CFR are overly prescriptive and burdensome for industry. |

| Line No. | Current Text | Proposed Change | Rationale |
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| 308 | 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 | Delete "Risk assessment"<br>Sentence reads:<br>Supporting documentation, and management approval for any change…" | Execution and documentation of risk assessments is useful to ensure informed management decision making regarding production / supply in emergency situations. Singling out risk assessments as a specific record is unnecessary and covered by "supporting documentation" |
| 334 - 345 | An additional benefit of testing the Plan …<br>• Analyze test batches for compliance with release specifications | Delete this entire section. | Test implementation of these plans to include actual manufacture and testing of product is of questionable value, could be unnecessarily burdensome and expensive and raises GMP compliance concerns. These concerns include the introduction of new products into a facility which will have impact on both cleaning and process validation. In addition, this type of test implementation may itself result in product shortages which would be undesirable from the perspective of the company, FDA and the patient population. Each event which may require activation of the plan could be unique and it would not be practical to test all possible scenarios.<br><br>We suggest that each company choose how to test their plan, but that actual manufacture not be specified in the Guidance. Testing of this type of plan is not comparable to testing of a company recall process. |