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

Re: Docket No. FDA–2011–N–0898: Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products; Proposed Rule; Request for Comments; 78 Fed. Reg. 65,904 (Nov. 22, 2013)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to provide comments in response to issuance by the Food and Drug Administration (FDA) of a proposed rule entitled "Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products."[1]

PhRMA is a voluntary, non-profit association that represents the country's leading pharmaceutical research and biotechnology companies, which are dedicated to developing medicines that allow patients to live longer, healthier, and more productive lives. In 2012, PhRMA members invested approximately $50 billion in discovering and developing new medicines, representing the vast majority of private investment in biopharmaceutical products in the United States.

PhRMA appreciates FDA's efforts to fulfill its commitments under the provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA) regarding drug shortages. We are committed to improving patient health and recognize the importance of avoiding unexpected disruptions in the supply of needed medicines to patients. While shortages affect less than 1 percent of all drugs on the market, and most shortages involve generic medicines, PhRMA and its member companies hope to continue working closely with FDA, supply chain partners, and providers to identify, avoid, and mitigate potential drug shortages.

PhRMA's comments address each of the changes to the current rule for drug shortages as identified in the proposed rule. In Part I, we outline our companies' strong desire that FDA's current collaborative, flexible approach to addressing drug shortages remains in practice under the proposed rule, building upon the open lines of communication that have emerged between FDA and manufacturers over the last few years. Such an approach takes into account the

[1] 78 Fed. Reg. 65,904.

unexpected nature of events that often leads to drug shortages and addresses potential supply chain issues while preventing hoarding. In Part II, we provide specific comments on the proposed changes to the proposed rule.

I. General Comments

PhRMA embraces the collaborative approach FDA has taken towards identifying and mitigating drug shortages, particularly the open communication and regulatory flexibility that the agency has exhibited since the signing of the President's Executive Order 13588 – Reducing Prescription Drug Shortages, in October 2011. We are proud that so many of our members have answered FDA's call and partnered with the agency to prevent potential drug shortages by keeping FDA apprised of inventory status, sharing commercial intelligence about market supplies, and providing prompt voluntary notifications about API sourcing issues, manufacturing challenges, and increases in demand. As Commissioner Hamburg has recognized, the tremendous progress recently made to address the drug shortage problem "demonstrates what government and industry can accomplish when we work together."[2]

PhRMA and its member companies hope to continue collaborating and openly communicating with FDA about potential drug shortages going forward. We strongly believe that retaining a flexible framework that allows FDA and manufacturers to interact and discuss potential drug shortages, combined with FDA's careful and appropriate public disclosure of that information in a manner that prevents hoarding and other negative consequences, is the best way to serve patients.

II. Specific Comments

A. Scope of Products Subject to Notification Requirements

1. *Products Subject to the Proposed Rule*

In Section III.B.1 of the proposed rule, FDA specifically notes concern over how the proposed definitions that relate to the scope of products subject to notification could "unintentionally broaden the scope of reporting to such an extent that the Agency is 'overnotified.'"[3] PhRMA believes that as the proposed rule is currently drafted, FDA could be overnotified—the definitions of the types of drugs covered by the proposed rule are broad in scope and could be construed to cover most drugs. We therefore respectfully request that FDA offer additional clarity in the final rule about the specific types of drugs that are within and without the scope of the proposed rule.

The scope of drug and biological therapies subject to notification is defined through the interpretation of the term "product" that is offered in the preamble to the proposed rule: a

[2] Commissioner Margaret Hamburg, M.D., *Six Month Check-Up: FDA's Work on Drug Shortages*, FDA Voice blog (May 3, 2012).
[3] 78 Fed. Reg. at 65,909.

manufacturer must notify FDA if "a specific strength, dosage form, or route of administration of a drug or biological product" is subject to a permanent discontinuance or an interruption in manufacturing.[4] This is true even if other presentations of the same product are available.[5] Although PhRMA supports notification to FDA for monitoring purposes of disruptions that will affect the ability of patients to get the medical treatment they need, we are concerned about the unintended consequences of such a broad interpretation of the term "product," especially if such notifications result in public disclosure on the drug shortage list per Section 506E of the Federal Food, Drug and Cosmetic Act (FDCA). Specifically, Section 102 of the newly passed Drug Quality and Security Act[6] permits a compounder to begin manufacturing a drug once it is on the shortage list. Therefore, such a broad definition of the term product may allow drug compounders to begin manufacturing a specific drug before it is actually necessary, at the possible peril of public health.

PhRMA strongly believes widespread compounding is not a sensible public health approach to dealing with drug shortages, as the practice exposes patients to unapproved products made in facilities that have not been subject to a pre-approval inspection. As FDA has warned, because "compounded medications are not FDA-approved" and the agency "has not verified their quality, safety and effectiveness," such medications "pose special risks" to patients.[7] Given the grave public health concerns raised by copies of prescription drugs made without the benefit of FDA oversight, we suggest FDA affirmatively state in its preamble to the final rule that it will not list FDA-approved drugs on its drug shortage list under 505E if the public health benefit of doing so is outweighed by the possible public health consequences.

Given the possible public health consequences, PhRMA urges FDA to provide examples of such situations in which the agency will not list a drug or biological product, such as when a shortage of a certain strength, dosage form, or route of administration of a drug or biological product will not likely result a patient failing to receive appropriate treatment because other available strengths or dosage forms of the product or another FDA-approved product are available. Such a clarification would be fully consistent with the public health exception to the statutory requirement for FDA to publicly disclose, to the maximum extent possible, information on drug shortages. It is also consistent with the purpose of the proposed drug shortage list, which is not designed to be a monitoring tool to prevent shortages, as are notifications, but rather serves as a gatekeeper of information to advise patients and providers when alternative treatments should be sought and a mechanism for communicating to outsourcing facilities when the compounding of certain drugs is permissible.

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[4] *Id.* at 65,912.
[5] *Id.* ("For example, if Applicant X experiences an interruption in manufacturing of the 50-milligram (mg) strength of a drug product …but the 100 mg strength continues to be manufactured without delay, under the proposed rule, Applicant X must notify FDA of the interruption in manufacturing of the 50 mg strength if the interruption is likely to lead to a meaningful disruption in the applicant's supply of the 50 mg strength.")
[6] P.L. No. 113-54 (2013).
[7] FDA, Consumer Update: The Special Risks of Pharmacy Compounding (Dec. 3, 2012), *available at* http://www.fda.gov/forconsumers/consumerupdates/ucm107836.htm.

PhRMA also seeks confirmation from FDA that notification is not required when there is a shortage of a "count" of product but overall the quantity of that product is not in shortage (e.g., a manufacturer is in short supply of a 50-count bottle of 10 mg pills, but there are sufficient numbers of 25-count bottles of 10 mg pills to meet patient need). We have not found it to be FDA's practice to require notification in such circumstances, and not requiring reporting under these circumstances would be fully consistent with the language of the proposed rule.

2. *Biological Products*

Under Section 1001 of FDASIA, Congress gave FDA the option to apply Section 506C of the FDCA to biological products via regulation, and FDA has elected to do so under this proposed rule. PhRMA commends this decision, noting that application of these rules to biological products ensures that FDA has the tools and authority it needs to ensure the adequate supply of many lifesaving biological therapies that were previously excluded from the law, with a resulting benefit to public health.

3. *Dual Reporting Requirements*

In deciding which medicines were covered by the proposed regulations, PhRMA appreciates that FDA sought to avoid unnecessary dual reporting requirements. Also, because some of the quality issues subject to notification under the proposed rule also would be subject to reporting under Field Alert Reports for drugs and Biological Product Deviation Reports for biologic products, we suggest FDA attempt to coordinate these reports and the agency's follow-up thereon in order to minimize the burden on both FDA and applicants.

B. What Triggers Notification

Title X of FDASIA requires that a manufacturer of a covered drug report any "permanent discontinuance in the manufacture of the drug or an interruption of the manufacture of the drug that is likely to lead to a meaningful disruption in the supply of that drug in the United States, and the reasons for such discontinuance or interruption."[8] Meaningful disruption is defined in FDASIA as "a change in production that is reasonably likely to lead to a reduction in the supply of a drug 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."[9]

PhRMA and its member companies are concerned that some of the terms used in the statutorily provided definitions are ambiguous and might be interpreted differently by manufacturers without further clarification by FDA. For example, it is unclear at what point an issue becomes "likely" to lead to a meaningful disruption. Manufacturers often have several

[8] Food and Drug Administration Safety and Innovation Act, P.L. No. 112-144, 126 Stat. 993 (2012).
[9] *Id.*

alternate plans to implement when an issue arises that might lead to an interruption, and if one plan does not work the manufacturer will change course and adopt a different plan. At the outset of the issue, an interruption might not appear "likely" but may become "likely" to lead to a disruption as the events progress. FDA may later re-characterize the trigger event causing the interruption when notification "should" have been submitted as the initial problem when, in fact, there was no indication to the manufacturer at that time that a disruption would be "likely." Therefore, it is important for FDA to provide additional clarity on how the Agency will determine at what point a shortage or interruption was triggered. We suggest that the appropriate trigger to start the notification "clock" is the date on which information becomes available to the applicant from which it could be reasonably determined that a meaningful disruption is likely to occur. Because the manufacturer may not know that a given issue is likely to lead to a drug shortage on the date that the issue arises, the date that the applicant becomes aware or reasonably should have become aware that the issue will lead to a meaningful disruption is a more appropriate standard.

C. When to Notify FDA

Section III.C.2 of the proposed rule requires applicants "to notify the FDA of a permanent discontinuance or an interruption in manufacturing at least 6 months in advance of the date of the permanent discontinuance or interruption in manufacturing; or, if 6 months' advance notice is not possible, as soon as practicable thereafter, but in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs."[10] PhRMA appreciates the importance of prompt notification to FDA concerning conditions that could potentially lead to drug shortages of important, life-saving drugs. The "in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs" language, however, does not provide manufacturers sufficient time to investigate and confirm that actions taken in response to the interruption will not affect the ability of the manufacturer to fill orders or meet expected demand. Therefore, as previously mentioned, the "clock" for an interruption in manufacturing that is likely to lead to a meaningful disruption in the supply of that drug in the United States should begin on the date that the information becomes available to the applicant from which it could be reasonably determined that a meaningful disruption is likely to occur. And, because the 5 business day limit is not required by statute, PhRMA believes it is sufficient to require notification "as soon as practicable" after such information becomes available to the application. However, if FDA requires a specific time period for reporting, it should be no shorter than 15 business days, which is a more reasonable timeframe for manufacturers to investigate and confirm how the actions taken in response to the interruption will affect the ability of the manufacturer to fill orders or meet expected demand.

D. How to Notify FDA

The proposed rule requires "an applicant to notify FDA of a permanent discontinuance or

[10] 78 Fed. Reg. at 65,914.

an interruption in manufacturing electronically in a format FDA can process, review, and archive."[11] As applicants are currently submitting information in a non-specified format via e-mail, PhRMA recommends FDA provide greater clarity on whether this practice is intended to continue under the proposed rule, and if not, whether FDA will be specifying a uniform process for applicants to follow when submitting notifications.

E. What to Include in the Notification

The proposed rule requires "all applicants of covered approved drugs or biological products–including certain applicants of blood or blood components for transfusion and all manufacturers of covered drugs marketed without an approved application–to notify the FDA."[12] Section III.C of the proposed rule identifies the "contents of notification" for an applicant but fails to identify the "contents of notification" for a manufacturer of a covered drug marketed without an approved application. Therefore, we respectfully request that FDA provide a list of the "contents of notification" for manufacturers of drugs marketed without an approved applicant.

F. Dissemination of Information to the Public

Section III.C.4 of the proposed rule states the "Agency, not the applicant, would be responsible for determining which categorical reason [for the shortage] best fits a particular situation" when posting this information on the public webpage.[13] PhRMA and its member companies appreciate FDA's commitment to "generally choos[ing] the categorical reason that best fits the applicant's supplied description."[14] Building off our earlier comments regarding the importance of collaboration between FDA and applicants, we feel it is important that the process of reviewing a potential drug shortage includes discussing FDA's concerns with the applicant before any information is made public. This has been FDA's general practice to date, and though we appreciate that this type of process requires additional resources, we also believe it helps to ensure that the appropriate information is made public at the point in time when it is most useful and when it will not result in hoarding and other unintended consequences.

G. Confidentiality

Section III.C.5 of the proposed rule requires FDA to "publicly disclose, to the maximum extent possible, information on drug shortages, including information provided by applicants in a notification of a permanent discontinuance or an interruption in manufacturing."[15] PhRMA and its member companies appreciate the cautious approach that FDA has adopted to avoid releasing proprietary and confidential information. PhRMA respectfully asks that FDA confirm that the language in the proposed rules does not intend to broaden FDA's current practices and that FDA

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[11] *Id.* at 65,915.
[12] *Id.* at 65,904.
[13] *Id.* at 65,916.
[14] *Id*.
[15] *Id.* at 65,916.

will continue to work with applicants to avoid the disclosure of proprietary information or any information that could lead to hoarding and other unwanted consequences.

H. Noncompliance

Section III.C.6 of the proposed rule requires FDA to issue a letter of noncompliance to an applicant (or for a covered, unapproved drug to a manufacturer) who fails to notify FDA of a permanent discontinuance or interruption in manufacturing within the required timeframe. The applicant has 30 days to respond to a noncompliance letter and justify its failure to notify FDA of a permanent discontinuance in manufacturing or an interruption in manufacturing. Then within 45 days of issuing the noncompliance letter, FDA can either publicly disclose both the noncompliance letter and applicant's response letter public or decide not to publicly disclose either letter.[16]

PhRMA and its member companies are concerned that the proposed framework for issuing and responding to a noncompliance letter does not provide sufficient opportunity for applicants to work with FDA to resolve any concerns about the timing and circumstances surrounding a notification to the agency or the issuance and contents of a noncompliance letter. In particular, we believe that noncompliance letters should only be issued after a discussion has occurred between the applicant and FDA, and applicants should be given sufficient opportunity to appeal FDA's determination of noncompliance. There are many situations in which an applicant or manufacturer may only become aware of an interruption in manufacturing after alternate plans for dealing with disruptions in manufacturing have also failed. Given the current 5-day notification rule and the ambiguity around what constitutes the "trigger" for notification purposes, this dialogue will be very important if FDA is to avoid over-issuing non-compliance letters to preserve their impact. Because the proposed rule only provides vague guidance about how FDA would handle and adjudicate letters of noncompliance, we recommend FDA specify in the preamble to the final rule: how the Agency anticipates issuing these letters in practice; a process through which manufacturers can appeal any decisions to issue noncompliance letters; and that the Agency will retract and remove any non-compliance letter from the public website if the appeal is successful. Additionally, PhRMA respectfully asks for FDA to confirm that failure to notify would be addressed through this noncompliance letter process alone, and not via GMP inspections.

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Thank you for the opportunity to comment on the proposed rule. PhRMA commends FDA's efforts to obtain feedback from a variety of stakeholders on the issues and challenges associated with potential drug shortages.

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[16] *Id.* at 65,917.

Respectfully submitted,

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