



January 3, 2014

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2011-N-0898 Proposed Rule: Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the “Proposed Rule: Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products.”

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

Drug shortages can create significant concerns for patients seeking to maintain a treatment regime for their disease or condition and can even delay or halt clinical trials necessary to bring new therapies to market. The biotechnology industry is committed to the discovery and development of new, novel treatments for serious and life-threatening diseases, and drug shortages that prevent patient access to needed treatments stands counter to our driving mission to extend and enhance the lives of patients.

BIO supports FDA efforts to implement sections 506C and 506E of the Federal Food Drug and Cosmetic Act (FFDCA) as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), including the general application of the drug shortage notification provision to biological products, taking into account the unique considerations around the manufacture and distribution of therapeutic biologics and vaccines.

BIO supports advance notification, which allows FDA to work with all stakeholders and exercise regulatory flexibility to prevent and minimize the impact of drug shortages. BIO appreciates and acknowledges the dedicated, hard-working individuals at the FDA who have partnered collaboratively with industry to prevent and mitigate drug shortages. Actions taken by FDA in the years 2011 through 2013 clearly support the value of advance reporting and coordination between industry and FDA in the prevention and



mitigation of drug shortages. While shortages of biotechnology products represent only a small minority of overall drug shortages, BIO recognizes there have been shortages of a handful of biological products in recent years due in part to the challenges associated with the manufacturing these products. In the experience of many biotechnology companies, FDA staff work constructively and collaboratively with the manufacturer in the event of a shortage to help resolve the problem and restore patient access to needed FDA-approved therapies as soon as possible.

Furthermore, BIO strongly believes that permitting widespread compounding of drug products deemed in shortage is not an appropriate solution to any one drug shortage. The public health consequences of increased availability of drug products that are not FDA approved, thus calling into question their quality, safety, and effectiveness, solely replaces one patient risk with another. Compounding exposes patients to unapproved products made in facilities not subject to FDA pre-approval inspection or governed by FDA Good Manufacturing Practices (GMPs).

We ask the Agency to consider our specific comments below, and BIO looks forward to continuing to work with the Agency, manufacturers, and other key public health stakeholders to further prevent and mitigate drug shortages.

SPECIFIC COMMENTS:

A. Scope of Products Subject to Notification

The proposed rule would apply to all prescription drug products approved under a New Drug Application (NDA) or Abbreviated Drug Application (ANDA), all marketed unapproved prescription drug products, and all prescription biological products approved under a Biologics License Application (BLA) that are: life supporting; life sustaining; or intended for use in the prevention or treatment of a debilitating disease or condition, including any such product used in emergency medical care or during surgery; and not radiopharmaceutical products. The Agency proposes to define a "life supporting or life sustaining" drug product as one that is "essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life." The phrase "intended for use in the prevention or treatment of a debilitating disease or condition" would refer to "a drug product intended for use in the prevention or treatment of a disease or condition associated with mortality or morbidity that has a substantial impact on day-to-day functioning".

BIO appreciates that the proposed rule clarifies that the proposed definitions of "life supporting or life sustaining" and "intended for use in the prevention or treatment of a debilitating disease or condition" are different than FDA's definition of "medically necessary" as used in the context of the existing Center for Drug Evaluation and Research (CDER) Manual of Policies and Procedures (MAPP) on drug shortages (CDER MAPP 6003.1 or the MAPP). It is BIO's understanding that FDA considers a product to be medically necessary under the MAPP if "there is no other adequately available drug product that is judged by medical staff to be an appropriate substitute". Under the proposed rule, the applicant would be required to notify FDA of a permanent discontinuance or an interruption in manufacturing of a drug or biological product that is



life supporting, life sustaining, or intended for use in the prevention or treatment of debilitating disease or condition, whether or not the product is considered medically necessary under the MAPP. Under the MAPP, FDA uses the definition of medically necessary to prioritize the Agency's response to specific shortages or potential shortages and to allocate internal Agency resources appropriately. BIO believes that understanding the intended use of these definitions is critical to ensure correct and consistent interpretation and application of the proposed rule by both applicants and the Agency. Therefore, we request that the Agency further clarify that the MAPP definition of "medically necessary" solely relates to the allocation of internal Agency staffing and resources, and that it has no bearing on the scope of products subject to notification under the proposed rule or FDA's determination of an actual shortage, and public notification of a shortage.

The proposed rule would apply to all "products" and defines product as "[a] specific strength, dosage, form, or route of administration of a drug or biological product." BIO appreciates that the "permanent discontinuance or interruption in manufacturing of a specific strength, dosage form, or route of administration of a drug or biological product can have a significant impact on the targeted needs of particular patients" and may "exacerbate patient difficulties in acquiring the product." While the rationale for the proposed broad definition of product may be understood for a dosage form that cannot be readily substituted, BIO believes the rationale should not apply equally across all products. As written, the proposed rule would apply individually to all strengths, dosage forms, or routes of administration for a given product regardless of the supply status for other presentations and dosages of the same product. For example, in some circumstances it may be possible to rectify the unavailability of a particular dosage or presentation by using other dosages or an alternate presentation. The proposed rule should allow greater flexibility to permit applicants to take into account known and reasonable interchangeabilities.

The proposed rule includes "marketed unapproved prescription drugs". BIO requests FDA clarify that off-label indications are not included within the scope of "marketed unapproved prescription drugs." BIO also requests FDA to clarify that all references to and requirements of applicants equally apply to manufacturers of a covered drug marketed without an approved application.

The proposed rule does not discuss the effect of the notification framework on product allocation systems. Products with inherently limited supply have been historically put on allocation systems by manufacturers to prioritize the allocation based on developed factors, and to prevent the hoarding of products. Such allocation systems help manage and track product supplies, curb gray market distribution, and prevent price hikes. Since section 506(D)(d) of the FFDCRA directs FDA to establish a mechanism by which health care providers and other third party organizations may report to the Agency evidence of a drug shortage, we ask that the Agency confirm a shortage-evidence notification does not extend to situations where a receiving entity (e.g. hospital) reaches its allocation limits. In other words, the notification regulations apply only to applicants of products and address the manufacturing of products rather than individual entities' ability to receive products.



B. Notification Triggers

The proposed rule would require applicants to notify the FDA of an interruption in manufacturing that is likely to lead to a “meaningful disruption” in supply. The statute defines meaningful disruption as a “...change in production...reasonably likely to lead to a reduction in...supply...that is more than negligible and affects the ability of the applicant 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 applicant expects to resume operations in a short period of time.” BIO believes the subjective nature of the proposed definition may not support mutually agreeable and consistent identification of shortages on the part of both regulators and industry. Terms within the definition such as “reasonably likely”, “more than negligible”, and “short period” contribute to the definition’s subjectivity and are insufficiently precise to ensure consistent conclusions on the part of applicants and FDA.

The proposed definition would also require applicants to notify FDA if any of their existing products are under allocation or the demand for the product exceeds supply. FDA should consider additional language clarifying that an adverse impact to supply is unable to be remediated or minimized through allocation or other means of prioritization.

Many factors could potentially affect the ability of applicants to fill orders, including some that are not within an applicant’s control. Applicants do not ultimately determine, nor can they in all cases accurately predict, volumes of orders/product demand. BIO is concerned that under the proposed rule, the product of an applicant that successfully executes their target production plan, developed based on factors including expected demand, could be deemed in shortage. We ask FDA to consider language that better clarifies that the definition of “meaningful disruption” is intended to reflect situations in which the availability of a product to patients would be impacted. Accordingly, BIO suggests the proposed rule should clarify to whom the applicant should have to fill an order to, in order to distinguish between the temporary inability to fulfill an order to a wholesaler as opposed to the inability of a patient to obtain their prescription or experience a delay or an interruption in therapy.

C. Over Reporting: Examples of Reportable Discontinuances or Interruptions

While the proposed rule provides a number of examples of “reportable discontinuances or interruptions in manufacturing of a covered drug or biological product”, not all of these examples would result in a shortage of product to patients and may result in industry ‘over-reporting’ events to the Agency, for example:

- A delay in acquiring active pharmaceutical ingredients (API) or inactive ingredients that is likely to lead to a meaningful disruption in the applicant’s supply of a covered drug or biological product while alternative API suppliers are located.
- Equipment failure or contamination affecting the quality of a covered drug or biological product that necessitates an interruption in manufacturing while the equipment is repaired or the contamination issue is addressed



and that is likely to lead to a meaningful disruption in the applicant's supply of the product.

- Manufacturing shutdowns for maintenance or other routine matters, if the shutdown extends for longer than anticipated.

BIO requests the Agency further clarify the requisite link between examples such those above and an actual "meaningful disruption" in supply.

D. FDA Shortage Determination Criteria

Under the proposed rule, the Agency makes the ultimate determination as to whether a shortage exists. The proposed rule states that "FDA would maintain publically available lists of drugs and biological products that are determined by FDA to be in shortage, whether or not FDA has received a notification under this proposed rule concerning the product in shortage." BIO requests the Agency clarify its processes and procedures for determining an actual shortage and making such determination publically available, including but not limited to continued applicability of the current MAPP.

Under the statute a drug shortage is defined as "a period of time when the demand or projected demand for the drug within the US exceeds the supply of the drug." The MAPP defines a drug shortage as "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." And under the MAPP, if a drug is deemed medically necessary, the Drug Shortage Program (DSP) will then post shortage issues on the Drug Shortage Website, as well as significant discontinuation information when it is provided by firms. Given the different definitions and understandings among the statute, the proposed rule, and the current MAPP, there may be situations where the Agency and the applicant, each operating in good faith, reach dissimilar conclusions regarding a product's supply status. Yet there is no mechanism for resolving such differing conclusions and mitigating an applicant's exposure to a non-compliant assessment.

Moreover, while the proposed rule specifies that FDA will publish information about "actual drug shortages", the proposed rule does not specify the Agency's position on potential drug shortages. MAPP 6003.1 directs "[a]ll potential or actual shortage situations and discontinuations of CDER drugs should be reported to the DSP as soon as they are known." BIO requests that the Agency clarify that the proposed rule is limited to actual drug shortage determinations due to the unintended consequences that may result if information about potential drug shortages is made publically available. The reporting of potential shortages may lead to hoarding by distributors, pharmacies, hospitals and other purchasers and may cause or exacerbate an otherwise manageable situation. Also, under such conditions, patients may not take their medication as prescribed, for example, by decreasing the dosage to make the prescription last longer, leading potentially to an ineffective course of treatment. The public release of information about an impending shortage may also facilitate the introduction of counterfeit drugs or drugs from questionable sources into the legitimate supply chain.



E. Notification Timing Requirements and Non-compliance

The proposed rule requires “notification to FDA at least 6 months prior to interruption in manufacturing or if not possible, as soon as practicable but in no case later than 5 days after the interruption in manufacturing occurs for situations involving both permanent discontinuance of a product as well as manufacturing interruptions”.

Concerning a permanent discontinuance, six months may be in most cases represent a reasonable timeframe for advanced notice. However, there may be situations where an applicant may not be able to accurately predict changes that may affect business strategy for a given product sufficiently in advance to meet the proposed standard (for example, an applicant may elect to add, eliminate, or modify supply plans for a given product following abrupt and significant changes in market conditions, operating costs, etc.). Although the “as soon as practicable” standard could presumably be invoked in such situations, the “but in no case later than 5 days after interruption” standard cannot be consistently upheld in situations where a supply impact of a single event is not evident at the time the event occurs. Concerning “meaningful disruptions”, it may take applicants longer than 5 days to assess inventory position in the distribution channel due to the complexity of supply chains, especially since most supply chains are global and expand all time zones. Additional time may also be needed to allow for the proper preparation of the shortage notification.

It is also unclear as to when the timing clock would begin. Since the timeframe will be used to determine non-compliance, it is imperative that the timing be clarified in order to be interpreted and enforced in a fair and consistent manner. For example, it is unclear as to whether the clock begins on the date of the event causing the interruption, or on the date the applicant becomes aware that an interruption could cause a shortage. If the latter, it may be difficult to determine the exact point in time. For example, if a mechanic is called in to look at a broken piece of equipment, then the potential for a shortage would not be considered until the applicant realizes that it could take a long time to source a part required to repair the equipment.

Per the proposed rule it ultimately becomes FDA’s judgment as to whether an applicant complied with the reporting requirements. BIO believes FDA should consider eliminating the 5 day reference and leave the “as soon as practicable” language. If a timeframe is deemed necessary, BIO strongly suggests extending the notification timeframe to 15 days, and inserting qualifying language such as “once it can conclusively be determined that a manufacturing issue will adversely impact supply”.

In addition, it is questionable as to whether the Agency would in all cases be in a position to fairly and accurately assess, particularly in retrospect, whether or not an applicant was able to anticipate a permanent discontinuance or supply interruption and/or whether an applicant did or did not notify FDA “as soon as practicable”. BIO requests FDA outline a process by which they work with applicants in order to determine compliance. Also, while the proposed rule makes it clear that non-compliance letters will be made publically available, the proposed rule does not put forth a process to adjudicate the non-compliance letters nor identify a process to ensure that no confidential or proprietary information is publically disclosed. BIO requests the final rule include both an adjudication process and confidentiality protection measures.



F. Drug Shortage List – Content and Confidentiality

Under the proposed rule the Agency "...would consider the reason for the shortage supplied by the applicant in its notification...in determining how to categorize the reason for the shortage", but the "...the Agency, not the applicant, would be responsible for determining which categorical reason best fits a particular situation". In addition, to the statutorily provided categorical reasons, the Agency has proposed adding an additional category of "other" and also providing a brief summary of the reason for the shortage submitted by the applicant. Companies have always considered supply information to be proprietary since it provides a window into capacity and other sensitive areas. Industry also acknowledges that problems experienced by an individual applicant may have a great impact on public health and that this information needs to be communicated and shared as early as possible. BIO requests the Agency develop and identify a process by where the Agency shares with the applicant its intended public communication, prior to posting on the Internet, and provide applicants the opportunity to make corrections, including those related to the unintentional disclosure of confidential or proprietary information.

The proposed rule states that "FDA may choose not to make information... available to the public...if the Agency determines that disclosure of such information would adversely affect the public health (such as by increasing the possibility of hoarding or other disruption)". This proposed provision presumes that FDA is uniquely qualified to determine the relative value and/or risk associated with public dissemination of information related to product supply and product shortages. The proposed provision potentially disregards the extensive experience and influence on the part of applicants in terms of balancing supply and demand in the market, as well as managing relationships with customers; factors that are critical in terms of responsible management of products in limited supply. Therefore, BIO suggests, at a minimum, that the input of applicants should be incorporated into the decision making regarding public dissemination of information related to supply constraints.

BIO also requests that the Agency specify the criterion that needs to be met and the corresponding FDA process and procedures to remove a product from the shortages list.

Finally, we request that FDA clarify that there will be one public shortage list for all products covered under the proposed rule, including both drugs and biologics. As currently drafted, the rule could be interpreted that there would be separate shortage lists for drugs and biologics. A single, comprehensive shortage list would be preferable so that patients and the public have access to consolidated information on all medicines in shortage.

G. Specific Concerns Related to Vaccines

The vaccine enterprise in the United States is a remarkable success story that has resulted in freedom from disease for millions of Americans. As a result, the vaccine industry supports the Agency's initiative to work with manufacturers to lessen the public health burden realized when a critical drug or vaccine product is not readily available. We would like to highlight that vaccine manufacturing has a number of distinctive



variables that are not found in conventional pharmaceutical manufacturing and consequently, oversight of vaccine supply shortages should be managed accordingly. In terms of production, vaccine manufacturing requires utilization of biological organisms which do not always grow or respond on demand. In addition, production lead times are long, the quality control process is strict and each vaccine lot must pass purity and potency testing performed by both the manufacturer and the FDA prior to distribution. The vaccine marketplace is also distinctive in nature since vaccine manufacturers' deal with tens of thousands of providers each year, both public and private.

In response to the unique nature of vaccines, the Centers for Disease Control and Prevention (CDC) has successfully partnered with vaccine applicants to reduce, if not eliminate completely, impacts to public health that may arise due to a supply shortage. As a result, the CDC continues to be in the best position to monitor and manage vaccine supply. In addition, for over a decade now, the vaccine industry has voluntarily strived to provide the FDA with the requested minimum 6 month notice when making a determination to discontinue production of a particular vaccine where such a decision was foreseeable. Although the variability of biologics presents its share of challenges, the vaccine industry currently meets the objectives specified in the proposed rule. The existing system fundamentally works and, therefore, BIO believes no additional FDA regulation is necessary. However, if FDA still determines that the Agency should include vaccines under this regulation, then BIO requests the Agency consider the following changes.

i. Scope of Products Subject to Notification

As discussed above in relation to all qualifying drug products, the term "meaningful disruption" should not be applied to a vaccine product if an alternate presentation of the same vaccine is available.

BIO also notes that some vaccines, such as those for influenza, are seasonal products by design and consequently are unavailable for a significant portion of the year. Therefore, BIO requests FDA clarify that the proposed rule does not apply to vaccines that have such intentionally restricted availability.

ii. Notification Triggers

BIO requests FDA consider providing distinctions between specific types of vaccine products and limit the scope of the proposed rule to non-Vaccines For Children (VFC) vaccines since there already are effective notification and distribution systems in place under the VFC program.

The CDC maintains a stockpile of VFC vaccines as part of its vaccine shortage notification program. Due to the CDC's regular collaboration with vaccine manufacturers, this program has proven highly successful in mitigating or completely eliminating supply disruptions. Since the FDA does not have the authority to maintain comparable stockpiles, broader application of this successful approach would require expanding the stockpiles held by CDC, or for the FDA to encourage creation and funding of other government stockpiling programs for non-VFC vaccines and other life-saving products.



BIO also requests FDA permit applicants to take into consideration the existence of a CDC stockpile in assessing whether an interruption in manufacturing is reasonably likely to disrupt supply chains.

iii. Drug Shortage List – Content and Confidentiality

BIO suggests that the CDC continue to act as a confidential facilitator of critical supply information that is provided by applicants, to maintain these data as proprietary and confidential, and to allow them to use the information so that other applicants can fill the gap in the event of an imminent shortage.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Proposed Rule: Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
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Biotechnology Industry Organization (BIO)