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Dockets Management Staff
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2022-D-0277

Risk Management Plans To Mitigate the Potential for Drug Shortages; Draft Guidance for Industry; Availability; Agency Information Collection Activities; Proposed Collection; Comment Request

To Whom It May Concern,

Biotechnology Innovation Organization (BIO) welcomes the opportunity to comment on the Food and Drug Administration (FDA or Agency) draft guidance for industry entitled "Risk Management Plans to Mitigate the Potential for Drug Shortages". We recognize the importance and benefit that proactive actions to prevent human drug product and biological product shortages can bring to both industry and regulators alike, and ultimately, to our patients.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO is providing the comments below on the FDA draft guidance "Risk Management Plans to Mitigate the Potential for Drug Shortages". While in general, BIO agrees with the systematic approach for establishing risk management plans (RMPs) laid out in the draft guideline, we have serious concerns related to the scope and timing of the guideline, as discussed below.

(1) Definition of "manufacturer" in FD&C 506C

A critical concern is the guidance's introduction of the terms and definitions of "primary stakeholder", "secondary stakeholder" and "other stakeholder" to describe "manufacturer" in FD&C section 506C(a). These stakeholder definitions are very broad and could be interpreted that manufacturers of any step in the active pharmaceutical ingredient (API) or drug product manufacturing process need to prepare RMPs for the designated products. Such a requirement would be highly burdensome to manufacturers of API intermediates or drug product intermediates (e.g., milling operations, granulation operations) and could be non-value added since manufacturers of intermediates might not have knowledge of the information needed to provide a meaningful RMP.

BIO further notes that the definition of "manufacturer" established in this guideline is inconsistent with that established in the final guideline, "Notifying FDA of a Permanent Discontinuance or

Interruption in Manufacturing Under Section 506C of the FD&C Act" although they both refer to the same section of the Act. The definition of "manufacturer" in Section 506C(a) of the FD&C act previously established via the discontinuation guidance includes:

- Applicants with an approved new drug application (NDA) or approved abbreviated new drug application (ANDA) for a covered drug product
- Applicants with an approved biologics license application (BLA) for a covered biological product, other than blood or blood components
- Applicants with an approved BLA for blood or blood components for transfusion, if the applicant is a manufacturer of a significant percentage of the U.S. blood supply
- Manufacturers of a covered drug product marketed without an approved NDA or ANDA

BIO strongly recommends that the above previous established definition for "manufacturer" be used to describe requirements for drug product RMPs to provide consistency and minimize confusion. Likewise, we recommend that the requirement for API RMPs be limited to the manufacturer of the final API.

(2) Recommendations under Section III.C of the guideline

While BIO understands the potential benefits for RMPs in enhancing drug availability, we believe that the guideline's Section III.C: "Products for Which RMPs are Recommended" is more prescriptive than necessary as currently written. While the items listed in lines 205-225 are risk factors, they should be considered holistically using a risk-based approach. Additionally, RMPs are a new requirement for manufacturers and implementation for the required products will require a considerable time investment and have a substantial learning curve. Finally, BIO notes that while in general FDA guidelines are non-binding on the Agency or the public, the recommendations provided by guidance carry substantial weight. Consequently, BIO recommends that FDA change the wording in Section III.C from "recommendations" to "risk-based approach" with the considerations provided in lines 205-225.

(3) Timing of implementation

BIO emphasizes the importance of transparency and adequate time for companies developing internal processes in support of new programs or recommendations. Neither the draft guideline nor the Federal Register notice provides a timeline for implementation of the final guideline. While BIO notes that the requirement for "redundancy risk management plans" (called RMPs in the draft guideline) was effective September 23, 2020, up to this point, manufacturers had little direction on how to prepare such plans. BIO requests a period of at least two years from publication of a final guideline before FDA reviews RMPs during inspections or as part of a 704(a)(4) records request. Such an implementation timeline would ensure that manufacturers have adequate time to understand and properly implement practices to assist with the preparation of RMPs.

(4) Clarity on applicability to biologics and proteins

BIO recognizes that Section 506C(i) of the FD&C Act permits application of Section 506C to biologic products under the PHS Act. However, the current draft guidance uses the term API (active pharmaceutical ingredient) which usually applies only to small molecule drugs rather than the more inclusive term “drug substance”. BIO recommends: (1) clarity on the scope of the guideline in the introduction to include biologics and vaccines, and (2) replacement of the term “active pharmaceutical ingredient (or API)” with “drug substance” wherever appropriate throughout the guideline.

(5) Clarity on products subject to RMPs

BIO notes that the definition of the covered products (i.e., life-supporting, life-sustaining, etc.) are subject to interpretation from individual manufacturers. API manufacturers may be unaware if their products are used for these purposes, especially if their products are used in multiple products or for multiple indications. Consequently, BIO recommends that FDA publish a list of the APIs that are covered under FD&C section 506C and for which RMPs are required.

(6) Information sharing

Section IV.A recommends that primary stakeholders share their RMPs with secondary and other stakeholders. BIO believes that two-way sharing of information should occur from contract manufacturing organizations (i.e., currently defined “secondary stakeholders” or “other stakeholders”) to the manufacturer of the final drug product or API would be more beneficial. The primary stakeholder is ultimately responsible for the availability of the drug and furthermore has leverage over their contractors through their contracts and quality agreements. BIO recommends that the Agency revise the sections on information sharing to recommend that CMOs (i.e., secondary stakeholders) additionally provide information on their manufacturing capabilities and resiliency to the primary drug manufacturers. Additionally, FDA should clarify whether the market application holder will have any responsibility or accountability for the RMP implementation of its external suppliers.

Please consider the following table outlining granular comments on specific language in the draft guidance.

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Line 24-26	*"Effective quality risk management can facilitate better, more informed decisions; can provide FDA with greater assurance that stakeholders understand and can manage the associated risks; and can potentially affect the extent and level of direct regulatory oversight".*	It would be helpful if FDA provides details around this previous statement, elaborating on how regulatory oversight may be influenced by the RMPs. If there is a tangible clear impact to oversight (e.g., such as reduced inspections), there would be benefits for both FDA and industry.
Line 28-30	*"This guidance describes a framework for stakeholders to consider when developing RMPs that aligns with principles stated in the International Council for Harmonization (ICH) guidance for industry Q9 Quality Risk Management (June 2006)."*	ICH Q9 Quality Risk Management is currently being revised. FDA should consider revising this new guidance when the updated ICH Q9 guidance becomes available for alignment.
II. BACKGROUND		
Line 70-76	*"In March 2020, with the enactment of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), Congress added section 506C(j) to the Federal Food, Drug, and Cosmetic Act (FD&C Act),16 which requires certain manufacturers to develop, maintain, and implement, as appropriate, a "redundancy risk management plan that identifies and evaluates risks to the supply of the drug, as applicable, for each establishment in which such drug or active pharmaceutical ingredient of such drug is manufactured." Section 506C(j) became effective on September 23, 2020 (see section III. in this guidance)."*	The Cares Act, the Quality Metrics (QM) and the Quality Management Maturity (QMM) programs are all designed to prevent drug shortages. It would be helpful to understand how the Agency plans to integrate the requirements to avoid redundancies among them.
III. RISK MANAGEMENT PLANS: STAKEHOLDERS AND PRODUCTS		
Line 128-134	Replace the definition of "Primary Stakeholder" to be consist with the definition of "manufacturer" in the final guideline *Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act.*	Replace lines 128-134 with: • Applicants with an approved new drug application (NDA) or approved abbreviated new drug application (ANDA) for a covered drug product • Applicants with an approved biologics license application (BLA) for a covered biological product, other than blood or blood components • Applicants with an approved BLA for blood or blood components for transfusion, if the applicant is a manufacturer of a significant

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		percentage of the U.S. blood supply • Manufacturers of a covered drug product marketed without an approved NDA or ANDA
Line 140-145	The definition of "secondary stakeholder" is very broad and can be interpreted collectively to mean that manufacturers of <u>any</u> step in the active pharmaceutical ingredient (API) or drug product manufacturing process need to prepare RMPs for the designated products. Such a requirement would be highly burdensome to manufacturers of API intermediates or drug product intermediates (e.g., milling operations, granulation operations) and could be non-value added since these manufacturers might not have knowledge of the information needed to provide a meaningful RMP.	Delete lines 140-145: ~~Finished product manufacturers that are not primary stakeholders, including any such manufacturers that operate establishments involved in physically manipulating the drug product (e.g., blending, tableting) and any such manufacturers of a drug-led, drug-device combination product or biologic-led, biologic-device combination product regulated by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER).~~
Line 151	Manufacturers of drug product or API intermediates should be considered "other stakeholders" for which RMPs are not required	Other stakeholders in the supply chain for drugs that are not primary or secondary stakeholders, such as manufacturers of API intermediate or drug product intermediates, inactive ingredient manufacturers, packagers, and distributors.
Line 167	Products for which RMPs are required	FDA should be encouraged to publish and maintain a list of medically necessary products (by generic name) or a list of diseases for which RMPs are expected. FDA should assist industry by publishing and maintaining this information. FDA should publish this list for this expectation to meet the aspiration of mitigating drug shortages. Supply chains are opaque, and industry does not have visibility of redundancy/risks in supply chains of competitor companies.
Footnote 23	This footnote is critically important as it clarifies that the scope of the guideline is applicable to proteins, vaccines, biologic etc.	Include the content of Footnote 23 in the main text of the document, in a section clearly marked as "Scope"

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Line 189	Recommendations for additional RMPs are too broad	Change to: "Products for Which RMPs ~~Are Recommended~~ Should be Considering using a Risk Based Approach"
Line 202	Recommendations for additional RMPs should consider both the medical necessity of the product as well as manufacturing risks.	Change to: "….FDA nevertheless recommends that stakeholders use a risk based approach to determine when to develop, maintain, and implement RMPs ~~for such products~~, as appropriate to provide reliability of supply:" Additionally, we suggest that the guidance include wording to reflect that companies are empowered and have accountability for deciding which additional products need RMP and which do not based on their own internal preliminary assessment or criteria. For example, products with no or low history of OSS notifications, HA notifications, etc., can be omitted from recommendations based on historical strong supply performance. Or, a product in late life cycle with a low market share and a high number of competitors would lower priority for RMP. Finally, this section is for recommended RMPs, but would be the area that could end up in disagreement between FDA and industry. If there is a decision not to have a RMP for the Recommended category, it is unclear what would need to be provided as justification.
IV. RMP FRAMEWORK AND DEVELOPMENT STRATEGY		
Line 260-261	It is not feasible to plan how to repair every potential supply disruption	Change to: "FDA recommends that the primary stakeholder RMP also include ~~plans~~ potential approaches to repair the supply chain after a disruption, as appropriate."
Line 261-263	Unclear if the statement "Further, FDA recommends that the primary stakeholder initiate RMP	During the initial commercial launch phase of a new product, demand

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	development as early as possible in the drug product's regulatory life cycle." is inclusive of clinical phase or for approved products. RMPs would only be necessary for certain products in the clinical phase, based on patient need.	projection has significant uncertainty. Starting RMP development at this stage may have a limited value. Change to: "Further, FDA recommends that the primary stakeholder use a risk-based approach to determine if and when to initiate RMP development ~~as early as possible~~ in the drug product's regulatory life cycle."
Line 265-267	Information sharing should be two-way amongst stakeholders	The Agency recommends that ~~the primary~~ stakeholders share as much of ~~its~~ their RMPs as possible with each other ~~with secondary and other stakeholders of the drug product~~ to enable ~~secondary and other stakeholders to incorporate the~~ broad and coordinated strategies of the primary, secondary and other stakeholders. ~~stakeholder's RMP into their own plans and also contextualize the risks identified in the primary stakeholder's RMP, specifically for the manufacturing facility.~~
Line 278-280	*"The stakeholders that are involved in the supply chain for a particular drug product should work together to address RMP development and implementation. The Appendix of this guidance provides risk factors for stakeholders to consider when developing an RMP strategy."*	This statement indicates that the guidance requires collaboration across the supply chain between legal entities and companies for which there may be competitive intelligence, business risk, or legal concerns which prohibit sharing of information. This circumstance needs to be taken into account in this document.
Line 288	Figure 1: Recommended Risk Management Plan Steps Using the ICH Q9 Framework We note confusion with the definitions as written.	Please consider aligning the RPM steps with the revised ICH Q9, e.g., hazard identification instead of risk identification.
Line 295	*"Cross-cutting coordination and collaboration is critical to development, implementation, and maintenance of an effective RMP."*	Please provide details on what cross-cutting coordination and collaboration entails. It is unclear whether this is referring to coordination and collaboration across companies.
Line 301-302	The text should be less prescriptive since there are multiple ways to evaluate risks	The risk assessment involves identifying the associated hazards, evaluating the risk of each hazard,

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		and evaluating the risk of a drug supply disruption, for example, based on: (1) what might go wrong; (2) what is the likelihood (probability) it will go wrong; and (3) what are the consequences (severity). Additionally, we recommend changing "evaluating" to "analyzing" to align with the three steps of risk assessment.
Line 313-314	The language should be less prescriptive since there are multiple ways to analyze risks.	This involves estimating the risk associated with the identified hazards ~~and effects considering the likelihood of occurrence, severity of harm, and detectability~~.
Line 320	Definition of risk evaluation not aligned with ICH Q9 and ISO 3100	Risk Evaluation consists of comparing the results of the risk analysis with the established risk criteria (risk significance, risk appetite), to determine whether the risk is acceptable or additional action is required. Risk evaluation is the prioritization (decision making) based on the significance of the risk (high, medium, low).
Line 338	We note confusion with the language as written.	Consider the following wording: "RA should be periodically re-evaluated to determine if additional hazards are present and/or if control strategies are still adequate and effective."
Line 349-350	Risk review periodicity be on a risk-basis, which could be less than annual, using similar considerations to those in Section III.C. If an upper time limit is deemed necessary, it should be greater than 1 year (e.g., 3 years).	The Agency recommends periodic risk review at a frequency established on a risk basis ~~*at least* an annual~~, internal review and revision of an RMP throughout the life cycle of a drug. Frequency of review should be risk based and up to the company to decide.
Line 352-353	*"In some instances, it may be useful to quickly integrate the additional identified risks and mitigation strategies into the RMP rather than waiting for the next annual review cycle. This review also can include an assessment of communication with regulators and whether the communication should be improved."*	Please explain "communication with regulators" in the context of risk review. For example, it is unclear whether this includes drug shortage notifications or whether there are other kinds of communications that should be considered here.

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	Event-based frequency review will bring more value as will ensure timely incorporation of new knowledge into the existing plan. It is also in line with the current ICH Q9 expectation. As highlighted before, it will be more frequent early in the product life-cycle, or upon introduction of a new CMO/supplier, but will subside once the product is in advanced stages and the supply chain is established.	
V. APPENDIX: RISK CONSIDERATIONS FOR SPECIFIC RMPS		
Line 358-360	*"FDA encourages stakeholders to engage in proactive communication of their RMPs with organizations within their drug supply chains, and where appropriate, with external stakeholders and regulators throughout the process."* It is unclear how this would be implemented and which part of FDA would be responsible for this, e.g., Drug Shortage staff, other Offices, etc. It is also unclear when FDA would expect stakeholders to provide this information outside of site inspections.	Further guidance on what scenarios would require risk communications with regulators would be helpful. For example, the Agency could clarify the appropriate point of contact in FDA for RMP. FDA could consider that stakeholders should only provide RMP in the event of a shortage, if warranted, or if the company is unable to meet the expectations of the guidance.

Conclusion

BIO appreciates this opportunity to submit comments regarding FDA's draft guidance for industry entitled "Risk Management Plans to Mitigate the Potential for Drug Shortages". As FDA continues to consider this program, we would welcome future opportunities to discuss these points.

Sincerely,

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Biotechnology Innovation Organization