Draft Guidance: Risk Management Plans to Mitigate the Potential for Drug Shortage FDA-2022-D-0277, May 2022

Comments Submitted by: International Society for Pharmaceutical Engineering (ISPE)

GENERAL COMMENTS ON THE DOCUMENT
ISPE appreciates the opportunity to provide comments on the FDA draft guidance "Risk Management Plans to Mitigate the Potential for Drug Shortage" which provides details related to the implementation of the CARES Act requirements for a "redundancy risk management plan" (called a Risk Management Plans – RMP in the guideline). For nearly a decade, ISPE has been instrumental in facilitating communication between the different sectors of the pharmaceutical industry and global health authorities related to drug shortages. Ensuring availability of medically necessary drug products for patients in all end-markets is of paramount importance and ISPE believes that steps to address risks or offset supply disruptions with significant impact to patients should be rigorous. Applying similar rigor and formality for less significant supply disruptions could dilute limited resources and reduce focus on ensuring continuous supply of medically necessary products for the most vulnerable patient populations. Many of the following recommendations are intended to provide appropriate risk-based flexibility for the mitigation or prevention of drug shortages in alignment with ICHQ9(R1) to ensure a risk-balanced, resource-effective approach for both industry and the Agency.
Industry has historically maintained risk management plans as business documentation. Sharing of RMP content between stakeholders could be complicated by confidential and trade secret data. Applicants and manufacturers will need to evolve their business practices to provide a concise, adaptable, and portable set of data for sharing with stakeholders, regulators and business partners which could require a significant resource investment. Implementation of the RMPs could be very challenging for companies with large portfolios or complex supply chains. Additionally, manufacturers may need time to incorporate requirements for information sharing in their quality agreements with suppliers and CMOs. Consequently, the Agency should consider inclusion in the final guideline of an implementation period of at least 1 year from the publication of the final guidance prior to review of RMPs during inspections or by 704(a) information requests.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Lines 23-26	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.	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, ***e.g.,* reduced FDA inspections.**	Please consider elaborating on how regulatory oversight may be influenced by the RMPs. Inclusion of a clear example of how the level of direct regulatory oversight may change, such as reduced inspections, would present additional incentive for all stakeholders to develop RPMs.
Lines 136-149	**Secondary Stakeholders.** Secondary stakeholders are entities that are expected to have more detailed insight into specific segments of the supply chain for a drug product but may not have an understanding of its entirety. Secondary stakeholders include: – 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)	**Secondary Stakeholders.** Secondary stakeholders are entities that are expected to have more detailed insight into specific segments of the supply chain for a drug product but may not have an understanding of its entirety. Secondary stakeholders include: – 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)~~	Finished product manufacturers and API manufacturers should ensure any outsourced activity is covered by their RMP. The value of RMPs prepared by contract manufacturing organizations (CMOs) that only contribute to a portion of the process could be limited because: ➢ the CMO might not know sufficient details of the supply chain or the product to develop an effective RMP ➢ there could be redundancy of RMPs and related activities between the CMO and the contract-grantor. ➢ they may be little to no impact of the CMO's RMP if the primary stakeholder holds enough inventory to mitigate risk, or if the CMO's volumes are insignificant to the primary stakeholder

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	– API manufacturers, as well as those manufacturers that physically process (e.g., milling, coating) or package the API.	– API manufacturers~~, as well as those manufacturers that physically process (e.g., milling, coating) or package the API~~.	
Lines 156-160	As described in the Background section of this guidance, the CARES Act added section 506C(j) to the FD&C Act, 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."[22,23]	As described in the Background section of this guidance, the CARES Act added section 506C(j) to the FD&C Act, 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."[22] **This guideline is applicable to products licensed under the PHS Act, such as proteins, blood related products, cell & gene therapy products, and vaccines filed in BLAs.** [23]	Please include in the main section of the guideline (rather than in Footnote #23) that the guideline is applicable to products filed under BLAs, such as proteins, blood related products, cell & gene therapy products, and vaccines. Additionally, it is recommended to use the more inclusive term of "drug substance" throughout the guideline rather than "active pharmaceutical ingredient (API)", since API is a term typically only used with small molecule products.
Line 162-164	Each manufacturer of the following drug products, APIs, and associated medical devices must develop, maintain, and implement, as appropriate, an RMP that identifies and evaluates risks to the supply of the drug product, as applicable	Each manufacturer of the following drug products, APIs, and associated medical devices must develop, maintain, and implement, as appropriate, an RMP that identifies and evaluates risks to ~~the~~ **significant disruptions in** supply of the drug product, as applicable	Brief logistical constraints and supply disruptions that do not impact patients occur frequently and should not require risk management activities as they will not improve continuous supply for patients.
Line 174-176	…any such drug that is critical to the public health during a public health emergency declared by the Secretary under section 319 of the Public Health Service Act	**Include information regarding how industry may identify or be notified of**: … any such drug that is critical to the public health during a public health emergency declared by the Secretary under section 319 of the Public Health Service Act	ISPE recommends that FDA develop communication channels to notify application holders when products are deemed to be critical to the public health during a public health emergency declared by the Secretary under section 247d of title 42 such that timely RMPs may be

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			developed. Currently, this information is not transparent to application holders.
Line 185	FDA considers the manufacturers that are subject to this requirement under section 506C(j) of the FD&C Act to include primary and secondary stakeholders as defined in section III.A. of this guidance.		Readers of the guidance may be unclear regarding the accountability expectations for each of the stakeholders. Refer to additional comments provided regarding Lines 265-269.
Lines 189-232: • Line 189 • Lines 199-203 • Lines 229-232	**Line 189: Products for Which RMPs Are Recommended** Lines 199-203: To the extent drug products or APIs incorporated in those products fall within a category described in the following list but are not drug products described in section 506C(a) of the FD&C Act or APIs included in such drug products, FDA nevertheless recommends that stakeholders develop, maintain, and implement RMPs for such products, as appropriate, to provide reliability of supply: Lines 229-232: Therefore, FDA recommends that stakeholders consider developing, maintaining, and implementing RMPs for their drug products or APIs that are not subject to the requirement in section 506C(j) of the FD&C Act, in addition to those that are	**Line 189: ~~Products for Which RMPs Are Recommended~~** **Additional Products to Consider for RMPs** Lines 199-203: To the extent drug products or APIs incorporated in those products fall within a category described in the following list but are not drug products described in section 506C(a) of the FD&C Act or APIs included in such drug products, ~~FDA nevertheless recommends that~~ stakeholders **may consider** develop**ing**, maintain**ing**, and implement**ing** RMPs for such products, as appropriate, to provide reliability of supply: Lines 229-232: Therefore, ~~FDA recommends that~~ stakeholders **may** consider developing, maintaining, and implementing RMPs for their drug products or APIs that are not subject to the requirement in section 506C(j) of the FD&C Act, in addition to those that are	The decision of manufacturers to expand RMPs beyond those required by the CARES Act should be a risk-based and business-driven decision, considering the factors included in Section III.C. It is likely that over time, manufacturers will appreciate the benefit to their business and to their patients of having effective RMPs and voluntarily adopt this practice beyond the required products, particularly for medically necessary products (definition available in CDER MAPP 4190.1, Rev 3, page 14) not covered by the CARES Act. Consequently, to ensure industry can prioritize any changes necessary to meet the RMP requirements as a first step in this journey of continual improvement, ISPE recommends that Section III.C be changed from "Products for Which RMPs are Recommended" to "Additional Products to Consider for RMPs" with appropriate changes to the subsequent text.

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	subject to that requirement, as described earlier.	subject to that requirement, as described earlier.	
Lines 255-260	This approach is consistent with institutionalized quality management maturity that results in understanding the risk of supply disruptions that may lead to shortages across the supply chain, integrates redundancy into the supply chain, improves the forecasting of demand changes at all stages of production, maintains sustainable compliance, improves overall incentives between purchasers and manufacturers, and fosters collaboration with regulators.	This approach is consistent with institutionalized quality management maturity that results in understanding the risk of supply disruptions that may lead to shortages across the supply chain, **increases manufacturing reliability and operational agility,** integrates redundancy into the supply chain, **establishes appropriate stockpiling inventory,** improves the forecasting of demand changes at all stages of production, maintains sustainable compliance, improves overall incentives between purchasers and manufacturers, and fosters collaboration with regulators.	ISPE considers redundancy as one solution of many for reducing drug shortages. It is an expensive and resource-consuming option. ISPE has published an article (https://ispe.org/pharmaceutical-engineering/january-february-2021/business-continuity-planning-prevent-drug) which describes multiple options to help business continuity planning to prevent drug shortages. The key to supporting uninterrupted supply of a portfolio of products with varying significance to the patient is to blend the application of appropriate multiple sourcing, and stockpiling, with sustained manufacturing performance and improvement in many other areas important to drug shortage prevention.
Lines 260-261:	FDA recommends that the primary stakeholder RMP also include plans to repair the supply chain after a disruption, as appropriate	FDA recommends that the primary stakeholder RMP also include plans to repair the supply chain after a disruption, **which had meaningful impact to patients,** as appropriate	Brief logistical constraints and supply disruptions that do not impact patients occur frequently and should not always require risk management activities as they will not typically improve continuous supply for patients. Additionally, plans to repair the supply chain will depend on what is required and may be difficult to include in a RMP.
Lines 261-263	Further, FDA recommends that the primary stakeholder initiate RMP development as early as possible in the drug product's regulatory life cycle.	Further, FDA recommends that the primary stakeholder initiate RMP development as early as possible in the drug product's regulatory life cycle **and in**	A risk-based approach should be used to determine the appropriate time to implement an RMP, considering the factors included in the Appendix and the

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		alignment with the significance of product availability for patients.	significance of supply disruption to patients (e.g, availability of alternates, time to resupply based on manufacturing complexity).
Line 265-269	The Agency recommends that the primary stakeholder share as much of its RMP as possible with secondary and other stakeholders of the drug product to enable secondary and other stakeholders to incorporate the broad strategies of the primary stakeholder's RMP into their own plans and also contextualize the risks identified in the primary stakeholder's RMP, specifically for the manufacturing facility.	**Primary stakeholders are encouraged to notify secondary stakeholders and other stakeholders of their obligation to prepare an RMP, as appropriate.** The Agency recommends that the primary stakeholder **and the secondary stakeholder(s)** share as much of their ~~its~~ RMP **content** as possible ~~with secondary and other stakeholders of the drug product to enable secondary and other stakeholders to incorporate~~ **to coordinate on risk management strategies.** ~~of the primary stakeholder's RMP into their own plans and also contextualize the risks identified in the primary stakeholder's RMP, specifically for the manufacturing facility~~.	API manufacturers and other stakeholders will need information to understand their obligations to meet the criteria established in the CARES Act. Communication and information sharing between primary stakeholders and secondary stakeholders should be two-way. For example, drug product manufacturers will need information from their CMOs to prepare effective RMPs.
Line 288, Figure 1	Risk Identification – identify the risks with a potential to cause drug shortage.	~~Risk~~ **Hazard** Identification – identify the risks with a potential to cause drug shortage.	Please consider aligning the RPM steps with the ICH Q9(R1) Step 2 document, *e.g.,* hazard identification instead of risk identification.
Line 313	Risk Analysis — This involves estimating the risk associated with the identified hazards and effects considering the likelihood of occurrence, severity of harm, and detectability.	Risk Analysis — This involves estimating the risk associated with the identified hazards and effects considering the likelihood of occurrence, severity of harm **(i.e., to manufacturing operations, quality, or to patients),** and detectability.	Both the level of risk to quality and patient impact should be considered when determining the level of rigor for risk management plans to optimize use of limited resources for drug shortage prevention measures.

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Line 333-336	This can include building redundancy into manufacturing operations, establishing adequate controls on the supply chain, strengthening relationships with suppliers (e.g., contract manufacturers, ingredient suppliers), and/or identifying alternative suppliers.	This can include **increasing manufacturing reliability and operational agility**, building redundancy into manufacturing operations, **stockpiling inventory,** establishing adequate controls on the supply chain, strengthening relationships with suppliers (e.g., contract manufacturers, ingredient suppliers), and/or identifying alternative suppliers.	ISPE considers redundancy as one solution of many for reducing drug shortages. It is an expensive and resource-consuming option. ISPE has published an article (https://ispe.org/pharmaceutical-engineering/january-february-2021/business-continuity-planning-prevent-drug) which describes multiple options to help business continuity planning to prevent drug shortages. The key to supporting uninterrupted supply of a portfolio of products with varying significance to the patient is to blend the application of appropriate multiple sourcing and stockpiling, with sustained manufacturing performance and improvement in many other areas important to drug shortage prevention.
Line 344-345	At the end of the Risk Control step, a report should be developed to document the risk assessment and risk control strategies.	At the end of the Risk Control step, a report should be developed to document the risk assessment and risk control strategies. **The level of detail and formality of this report should be commensurate with potential level of patient impact of a supply disruption.**	Patient impact should be considered when determining the level of rigor in documenting risk management plans to optimize use of limited resources for drug shortage prevention measures.
Lines 349-350	The Agency recommends *at least* an annual, internal review and revision of an RMP throughout the life cycle of a drug.	The Agency recommends ~~at least an annual~~, **periodic** internal review and revision of an RMP throughout the life cycle of a drug. **Appropriate periodicity should be established by considering the significance of a supply disruption of the product to the patient and product specific risk considerations (see Appendix).**	The frequency of Risk Review for RMPs should not have a minimum period of at least once per year. Rather, the frequency should use a risk-based approach considering the factors included in the Appendix and the significance of supply disruption to patients (e.g, availability of

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			alternates, time to resupply based on manufacturing complexity).
Line 353-354	This review also can include an assessment of communication with regulators and whether the communication should be improved.	This review also can include an assessment of communication with regulators and whether the communication should be improved **or expanded to include proactive review of RMP regulatory plans with the FDA Drug Shortage Staff.**	The Agency should consider a collaborative mechanism to voluntarily advise on regulatory discretion proposals in advance of potential, substantial disruptive events. This collaborative mechanism could minimize product unavailability for patients. For example, for products that require a RMP and would present meaningful impact to patients if unavailable, the applicant holder could, as appropriate, proactively share their RMP regulatory plans with the Drug Shortage Staff for comments and suggestions.
Line 401-402	Determine which drugs, including components, manufactured at the facility are vulnerable to a supply disruption	Determine which drugs, including components, manufactured at the facility are vulnerable to a supply disruption **that would have meaningful impact to patients.**	Brief logistical constraints and supply disruptions that do not impact patients occur frequently and should not always require risk management activities as they will not typically improve continuous supply for patients. Additionally, quality and supply resiliency risks are different to the risk to the patient from an absence of drug product supply. Not all supply disruptions have the same patient impact from a clinical perspective. Accordingly, there should be flexibility available for stakeholders to reduce risk management activities for products that are not deemed to be medically necessary (definition available in CDER MAPP 4190.1, Rev 3, page 14). Providing for this

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			flexibility should further ensure continuous supply of products for the most vulnerable patient populations when prioritization of risk management in**ve**stments is necessary.
After Line 483	-	**Insert additional bullet:** • **Time required to implement a post approval change, including data collection, submission activities and approval (with potential for global complexity).**	ISPE applauds the recognition and ongoing efforts by many health authorities in addressing global regulatory challenges and support their continuing efforts to harmonize. In ISPE's view, reference to the time for post approval changes and approved global regulatory requirements should be included in the draft RMP guidance because ensuring continuous supply of drug product can be a globally interdependent issue.