

August 18, 2022

Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

**Re: Risk Management Plans to Mitigate the Potential for Drug Shortages (FDA-2022-D-0277)**

*Submitted electronically*

Dear Sir/Madam:

Biocom California appreciates the opportunity to offer comments on the Food & Drug Administration's (FDA) draft guidance on [Risk Management Plans to Mitigate the Potential for Drug Shortages](#)<sup>1</sup>.

Biocom California is the largest, most experienced leader and advocate for California's life science sector, which includes biotechnology, pharmaceutical, medical device, genomics, and diagnostics companies of all sizes, as well as research universities and institutes, clinical research organizations, investors and service providers. With more than 1,600 members dedicated to improving health and quality of life, Biocom California drives public policy initiatives to positively influence the state's life science community in the research, development, and delivery of innovative products. California's life sciences industry generates over \$400 billion in annual economic activity, supports almost 1.4 million jobs, and increases labor income by \$131 billion per year<sup>2</sup>.

As the Agency noted in the draft guidance, drug shortages can pose a significant health risk to patients, especially those in critical need of care. Per the recent FDA report to Congress, [Drug Shortages for Calendar Year 2021](#), the Agency prevented 317 drug shortages in 2021<sup>3</sup>. We applaud the Agency for this record number and its diligent efforts. While many drug shortages have been mitigated and resolved through regulatory and statutory frameworks, shortage mitigation endeavors continue to pose a resource burden to many stakeholders. In 2021, 41 new drug shortages were counted by the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER)<sup>3</sup>. As highlighted in the 2019 FDA report, [Drug Shortages: Root Causes and Potential Solutions](#), drug shortages can worsen patients' health outcomes due to delays in treatment or changes to treatment regimens requiring the use of less effective treatment options<sup>4</sup>.

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<sup>1</sup> Federal Register, 87 FR 30963, pp. 30963-30966, May 20, 2022.

<sup>2</sup> Biocom California 2021 Economic Impact Report Databook. <https://www.biocom.org/eir/>

<sup>3</sup> U.S. Food and Drug Administration, Report to Congress Drug Shortages for Calendar Year 2021. <https://www.fda.gov/media/159302/download>

<sup>4</sup> U.S. Food and Drug Administration, Drug Shortages: Root Causes and Potential Solutions 2019. <https://www.fda.gov/media/131130/download>



Risk Management Plans (RMPs) can be proactive mechanisms to assess and mitigate potential drug shortage risks. We appreciate the Agency providing their current thinking on the topic in this draft guidance and aligning their proposed framework with principles found in the International Council for Harmonisation (ICH) guidance for industry [Q9 Quality Risk Management](#) (June 2006)<sup>5</sup>. We thank the FDA for its commitment to working with stakeholders on this issue and we respectfully provide the following comments and recommendations below:

### **Stakeholders and RMP Information Exchange**

On lines 265-269, the draft guidance states “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.” A primary concern of this guidance is that it sets an unprecedented information exchange between various stakeholders, such as applicant holders, contract manufacturers, and Active Pharmaceutical Ingredient (API) manufacturers.

**It is unclear if the Agency expects primary stakeholders to share their RMP with all possible stakeholders and whether the primary stakeholder is responsible for ensuring that subsequent stakeholders have required RMPs in place.** If this is the intention, this may cause issues for primary stakeholders since secondary and other stakeholders do not always consider supplier tiers and the number of suppliers can be extensive in situations of complex manufacturing assembly or sterilization of finished drug products (i.e., for combination products). **We recommend including additional language which clarifies each stakeholder’s RMP responsibilities in accordance with FDA’s Least Burdensome Principles.**

Furthermore, many RMPs include confidential information, strategy, and business risk decisions that cannot be shared externally. We expect transitioning internal documents for external use will require a significant resource investment. **To accommodate for this administrative burden, we recommend that the FDA allows for a target implementation date to be set for at least one year forward.**

### **RMP Review Burden**

On line 349 of the draft guidance, “the Agency recommends at least an annual, internal review and revision of an RMP throughout the life cycle of a drug.” We believe an annual review of the RMP is resource-intensive and burdensome, especially for companies with large drug product portfolios. If no drug adverse effects have been identified during postmarketing surveillance and/or the manufacturer maintains a mature Quality Management System (QMS), we believe an annual review of the RMP is unnecessary.

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<sup>5</sup> <https://www.fda.gov/media/71543/download>

**We provide the following three recommendations for revising the frequency of RMP review:**

- 1) RMPs are reviewed once every three years, or**
- 2) RMPs are reviewed on an “as needed” basis for newly identified risks, or**
- 3) The frequency of review is determined by a risk-based approach that considers the risk factors and the impact a potential drug shortage could have on patients.**

### **Risk Control Strategies in RMPs**

This draft guidance frequently mentions ‘redundancy’ i.e. using alternate suppliers, as a risk control strategy and it is a common theme for RMP development throughout the document (Footnote 22, lines 255-260, 265-269, 333-336, 341). As described in footnote 22, we acknowledge that redundancy can be a risk control strategy option to prevent or mitigate drug shortages. However, we do not believe that it should be the primary solution since this method can be expensive, difficult to maintain, and not always practical, especially in the case of sole source API suppliers. **It is unclear if the FDA would deem it unacceptable for any/all components of a product to only have one source supplier; especially in the case where the drug is indicated to treat critical conditions. We request that the Agency explain its thinking on this topic by including additional clarifying language in the guidance.**

Additionally, we do not believe that the draft guidance sufficiently balances redundancy with other opportunities to prevent or mitigate shortages and the guidance lacks examples of additional mitigation recommendations. Innovation could be considered a risk control strategy through methods such as digitization of manufacturing facilities and primary containers that enable unit-level identification (recorded detailed pedigree of drug lots down to the individual container level). Digitization and unit-level identification allow the industry to fully integrate its supply chains and improve operational processes, making them more adaptive and responsive. **We ask the Agency to consider innovative risk reduction methods and provide examples in the guidance of additional risk controls which may also be effective.**

**Furthermore, while the draft guidance describes the type of information within a RMP, the Agency does not specify what is an acceptable level of risk. We find this especially concerning for sole sourced components since it is not always possible or practical for manufacturers to have redundant suppliers or eliminate all supply risks.** For example, a manufacturer may have considered a redundant supplier but deemed them insufficient due to quality or business reasons. Thus, the manufacturer may choose to only have one source to ensure their ability to deliver a safe and economical product to patients. Under these circumstances, using a single source supplier may present a risk, but it has been accepted to ensure that a safe and effective product remains available to patients. Considering this situation, **we recommend updating the text for lines 255-260, line 336, and lines 407-408 to explain that, while manufacturers are encouraged to identify redundant suppliers, this may not always be feasible or possible. Please see the following proposed text edits (in red) and rationales:**

**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 (~~where applicable/possible~~), ~~may~~ improves the forecasting of demand changes at all stages of production, maintains sustainable compliance, ~~may improve overall incentives between purchasers and manufacturers~~, and fosters collaboration with regulators.”

**In line 336, we recommend changing “and/or identifying alternative suppliers” to “identifying alternative supplier(s) sites, and/or digitization of manufacturing and primary containers (e.g., unit-level identification).”** As we mentioned, identifying an alternative supplier (i.e., redundancy) is not always possible or applicable and, in some instances, selecting a new supplier may not be effective since the cause of component disruption could be site-specific rather than supplier specific. For example, a single source component supplier with multiple global sites may be more resistant to supply chain disruptions than a single site supplier. **Therefore, we also recommend revising lines 407-408 to state “...sole source single manufacturing site provider”** so that ‘supplier(s) sites’ and ‘manufacturing sites’ are emphasized rather than ‘suppliers’ or ‘providers’ themselves.

### **Risk-based approach for RMP Development**

We believe patient centricity can play a larger role as a risk consideration when developing a RMP. On lines 96-99, the draft guidance states that “Quality Risk Management is based on two principles: (1) The assessment of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient. (2) The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.” **While we acknowledge these two principles, we believe the potential impact on patients should be evaluated and emphasized during risk assessment; especially for drugs where a shortage would have the greatest impact on patients (i.e., those common in the standard of care, those without alternatives or generics, or those with manufacturing complexity). We also believe the rigor of the risk-based approach for RMP development should be commensurate to the drug shortage’s potential impact on patients.** For example, if there is an increased potential for patient impact, then we recommend that these drugs should have a more rigorous risk-based approach to RMP development activities. **Lastly, we suggest that the FDA considers adding an “at-risk critical drugs” category to its FDA Drug Shortages monitoring list in addition to “current, resolved and discontinuations”<sup>6</sup> for drugs at risk of facing a shortage that would have a great negative impact on patients.**

Additionally, there may be situations where frequent, yet minor supply chain disruptions occur but do not pose an impact on patients nor cause an interruption of the supply to the patient. **We recommend the draft guidance include language explaining that minor disruptions posing no impact on patients should not be included in the scope of RMP activities and RMPs should be used to identify and evaluate risks related to substantial supply disruptions.** We do not believe that RMPs for minor disruptions, which are generally logistical in nature, will improve the overall supply.

### **General Comments**

**We recommend that the draft guidance include more information regarding the content needed in a RMP for a combination product; specifically in the case where the drug is the primary mode of action and the product has a medical device component for drug delivery.**

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<sup>6</sup> <https://www.accessdata.fda.gov/scripts/drugshortages/>

On line 167, the draft guidance specifies which prescription drug products require a RMP. However, in Section C “Products for which RMPs are Recommended,” the guidance does not indicate whether the “drug products” referenced in lines 205, 207, 216, 220, 222 are referring to prescription drugs only or if over the counter (OTC) drug products are applicable as well. Some OTC drugs, such as topical antiseptics, can be used in the prevention of, and/or treatment of debilitating diseases and/or conditions when used during emergency medical care or surgery. **We recommend the Agency include language clarifying whether this guidance or sections of this guidance apply to OTC drug products.**

On lines 201-207 the guidance recommends that stakeholders develop, maintain, and implement RMPs for “drug products that lack appropriate alternatives.” It is unclear what the FDA believes is an “appropriate” alternative for a drug product and we believe the current language in the draft guidance is highly subjective. **We recommend the draft guidance either 1) include specific examples of drug products that lack appropriate alternatives or 2) revise the bullet point on line 207 to state “drug products that do not have alternatives.”**

Lastly, in Appendix: Risk Considerations for RMPs, the draft guidance does not highlight outdated manufacturing or primary container technologies as risk factors. However, in FDA’s 2019 Drug Shortage report, 62% of shortages were attributed to ‘manufacturing or product quality problems’<sup>4</sup>. **Thus, we recommend adding the following bullet point after line 426 as a potential risk factor consideration:** “Assess whether manufacturing processes and/or primary containers are out of date or obsolete with industry standards. Consider whether the facility, processes, or primary container components promote superior performance.”

We appreciate the opportunity to provide feedback on behalf of our members and thank you for your time and diligence in examining our comments. Please contact Biocom California’s Associate Manager of Regulatory Policy, Zoe Bilis, at [zbilis@biocom.org](mailto:zbilis@biocom.org) for additional information or questions. We look forward to continuing working with you on this important matter.

Sincerely,



Joe Panetta  
President and CEO  
Biocom California