
Risk Management Plans to Mitigate the Potential for Drug Shortages Guidance for Industry

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**May 2022
Pharmaceutical Quality/Manufacturing Standards (CGMP)**

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Risk Management Plans to Mitigate the Potential for Drug Shortages Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to help stakeholders² develop, maintain, and implement risk management plans (RMPs) to proactively assist in the prevention of human drug product and biological product shortages.³ RMPs can provide stakeholders with a framework to proactively identify, prioritize, and implement strategies to mitigate hazards that can cause a supply disruption. Such a supply disruption may lead to a drug shortage. 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

¹ This guidance has been prepared by the Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. In preparing this guidance, OPQ has also consulted with the Center for Devices and Radiological Health and the Office of Combination Products.

² For the purposes of this guidance, the term *stakeholder* includes each manufacturer of a drug described in section 506C(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356c(a)) or of any active pharmaceutical ingredient (API) included in such drugs. (See generally section 506C(j) of the FD&C Act.) The term *stakeholder* also broadly includes any person or entity who has oversight and control over the manufacture of drugs to ensure quality or owns or operates an establishment (as defined in 21 CFR 207.1 and 21 CFR 600.3) that manufactures a drug or biological product. Examples of stakeholders include: contract facilities as referenced in 21 CFR 200.10(b); applicants with an approved new drug application, abbreviated new drug application, or an approved biologics license application; manufacturers of drug products marketed without an approved application; manufacturers of components, including APIs, intended for use in the manufacture of drug products; and manufacturers of drug-led, drug-device or biologic-led, biologic-device combination products (as defined in 21 CFR 3.2(e)) regulated by CDER or CBER. This guidance references specific stakeholders individually where appropriate (e.g., if a specific section of the guidance is relevant to specific stakeholders only); otherwise, recommendations that refer to the manufacture of *drugs* are generally relevant to all stakeholders with the roles described above with respect to human drug and biological products.

³ *Drug shortage* or *shortage* means a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug (see section 506C(h)(2) of the FD&C Act). For the purposes of this guidance, *drug* or *drug product* refers to human drugs and biological products (see section 201(g)(1) of the FD&C Act).

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26 affect the extent and level of direct regulatory oversight.⁴ Based on recent publications and
27 reports, the majority of drug shortages are associated with quality issues.^{5,6,7,8} This guidance
28 describes a framework for stakeholders to consider when developing RMPs that aligns with
29 principles stated in the International Council for Harmonisation (ICH) guidance for industry
30 *Q9 Quality Risk Management* (June 2006). In addition, FDA also recommends risk factors to
31 consider when developing the content of the RMPs.

32
33 The contents of this document do not have the force and effect of law and are not meant to bind
34 the public in any way, unless specifically incorporated into a contract. This document is
35 intended only to provide clarity to the public regarding existing requirements under the law.
36 FDA guidance documents, including this guidance, should be viewed only as recommendations,
37 unless specific regulatory or statutory requirements are cited. The use of the word *should* in
38 Agency guidance means that something is suggested or recommended, but not required.

39
40

II. BACKGROUND

41
42
43 FDA recognizes that drug shortages pose a significant public health threat because they can
44 delay, and in some cases even deny, critically needed care for patients. Recent publications have
45 explained that proactively assessing risks to drug manufacturing processes and supply chains,
46 coupled with an understanding of market vulnerabilities, have enabled stakeholders to support
47 robust manufacturing operations that help to maintain the availability of a high-quality drug
48 through the drug's life cycle.⁹ The publications further explain that proactive risk assessment
49 has also enabled some stakeholders to predict and prevent supply disruptions that could
50 potentially lead to a drug shortage.¹⁰

⁴ See section VI., Integration of Quality Risk Management Into Industry and Regulatory Operations, in the ICH guidance for industry *Q9 Quality Risk Management* (June 2006). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. Note that appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements.

⁵ The term *quality* is defined in ICH Q9 as "The degree to which a set of inherent properties of a product, system, or process fulfills requirements."

⁶ The International Society for Pharmaceutical Engineering's (ISPE's) "Report on the ISPE Drug Shortages Survey" (June 2013) (<https://ispe.org/initiatives/drug-shortages/publications-tools>) shows that issues associated with the quality system, or the system that assures overall compliance with current good manufacturing practices and internal procedures and specifications, was the most common cause of drug shortages.

⁷ See the FDA report "Drug Shortages: Root Causes and Potential Solutions" (2019), p. 33 and Appendix F, at <https://www.fda.gov/media/131130/download>.

⁸ Chapman, S, G Dedet, and R Lopert, 2022, Shortages of Medicines in OECD Countries, OECD Health Working Papers, No. 137, OECD Publishing, Paris, <https://doi.org/10.1787/b5d9e15d-en>.

⁹ See the ISPE and The Pew Charitable Trusts report "Drug Shortages: An Exploration of the Relationship Between U.S. Market Forces and Sterile Injectable Pharmaceutical Drugs: Interviews With 10 Pharmaceutical Companies" (January 2017) at https://www.pewtrusts.org/-/media/assets/2017/01/drug_shortages.pdf. See also the final report by the inter-associations team with representatives from the European Federation of Pharmaceutical Industries and Associations, Medicines for Europe (formerly European Generics Association), Association of the European Self-Medication Industry, Plasma Protein Therapeutics Association, ISPE, and Parenteral Drug Association "Prevention of Drug Shortages Based on Quality and Manufacturing Issues" (December 2014) at <https://www.pda.org/docs/default-source/website-document-library/scientific-and-regulatory-affairs/drug-shortage/interrupted-supply-inter-association-summary-final-report-2014.pdf?sfvrsn=4>.

¹⁰ Ibid.

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51
52 In July 2012, with the enactment of the Food and Drug Administration Safety and Innovation
53 Act (FDASIA), Congress empowered FDA with tools to work in collaboration with industry to
54 help prevent or mitigate drug supply disruptions and drug shortages, and clarified current good
55 manufacturing practice requirements relevant to the oversight and controls over the manufacture
56 of drugs to ensure quality.¹¹ In 2011 and 2012, FDA assisted in mitigating 368 new drug
57 shortages and preventing 473 drug shortages. In contrast, in the 6-year span after FDASIA was
58 enacted, FDA assisted in mitigating 222 new drug shortages and preventing 806 drug
59 shortages.¹² Although the number of new drug shortages has declined significantly since the
60 peak in 2011, reaching a low in 2015 and 2016, this downward trend did not continue in
61 subsequent years. Drug shortages continue to occur and at roughly the same levels since 2018.
62 Further, drug shortages have grown more persistent (i.e., increased length of active drug
63 shortages).¹³ Many of the reasons for drug shortages are, for example, issues related to drug
64 quality, disruptions to supply chain manufacturing operations (e.g., caused by natural disaster or
65 discontinuation of components by suppliers), limitations in forecasting future demand, and
66 market withdrawals of drug products.¹⁴ Additionally, in recent years, FDA has observed a rise in
67 number of cyberattacks on drug manufacturers and is increasingly concerned about the effect of
68 such attacks on the drug supply chain.¹⁵

69
70 In March 2020, with the enactment of the Coronavirus Aid, Relief, and Economic Security Act
71 (CARES Act), Congress added section 506C(j) to the Federal Food, Drug, and Cosmetic Act
72 (FD&C Act),¹⁶ which requires certain manufacturers to develop, maintain, and implement, as
73 appropriate, a “redundancy risk management plan that identifies and evaluates risks to the supply
74 of the drug, as applicable, for each establishment in which such drug or active pharmaceutical
75 ingredient of such drug is manufactured.” Section 506C(j) became effective on September 23,
76 2020 (see section III. in this guidance).

77

¹¹ Generally, section 506C(a) of the FD&C Act, as amended by FDASIA (Public Law 112-144) and the Coronavirus Aid, Relief, and Economic Security Act (Public Law 116-136), requires certain applicants and manufacturers to notify the Agency of: (1) a permanent discontinuance in the manufacture of certain drug products; (2) an interruption in manufacturing of certain drug products that is likely to lead to a meaningful disruption in the supply of such products in the United States; (3) a permanent discontinuance in the manufacture of the API of certain drug products; and (4) an interruption in the manufacture of the API of certain drug products that is likely to lead to a meaningful disruption in the supply of the API of those products. Notifications under section 506C(a) must include disclosure of the reasons for such discontinuance or interruption. Section 506E of the FD&C Act (21 U.S.C. 356e) requires FDA to maintain an up-to-date list of drugs that are determined by FDA to be in shortage in the United States. Section 711 of FDASIA amended section 501 of the FD&C Act (21 U.S.C. 351) to clarify that, for purposes of section 501(a)(2)(B), the term *current good manufacturing practice* includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

¹² See the Drug Shortages Infographic web page (<https://www.fda.gov/drugs/drug-shortages/drug-shortages-infographic>). These statistics refer to shortages tracked by CDER.

¹³ See Slides 35 and 36 from the November 28, 2018, conference “Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions” at Duke University’s Margolis Center for Health Policy (accessed July 21, 2020, https://healthpolicy.duke.edu/sites/default/files/2020-02/presentation_slides__0.pdf).

¹⁴ See footnote 7.

¹⁵ Millar, A, 2021, Five Pharma Cybersecurity Breaches to Know and Learn From, Pharmaceutical Technology, accessed October 15, 2021, <https://www.pharmaceutical-technology.com/features/pharma-cyber-attacks/>.

¹⁶ See Public Law 116-136.

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78 FDA believes that its efforts in navigating drug shortage issues through the statutory and
79 regulatory framework and its partnership with stakeholders have contributed to the reduction in
80 the number of new drug shortages as well as a reduction in the time to resolve existing drug
81 shortages. However, the Agency acknowledges that shortages and shortage mitigation efforts
82 pose a significant financial and resource burden on stakeholders and FDA. FDA views RMPs as
83 an important mechanism that stakeholders can use to proactively identify, assess, and mitigate
84 the risks that might lead to a disruption in the supply of drug products, and thus preemptively
85 reduce the financial and resource burden associated with resolving a shortage and problems that
86 may lead to a shortage.

87
88 RMPs involve the systematic application of quality management policies, procedures, and
89 practices to the tasks of assessing, controlling, communicating, and reviewing risk. These
90 approaches and techniques are commonly used by multiple industries to manage a broad range of
91 risks that have the potential to adversely affect their businesses. For the pharmaceutical industry,
92 drug manufacturers use quality risk management, a systematic process for the assessment,
93 control, communication, and review of risks to drug product quality, across the drug's life cycle.
94 Quality risk management is based on two principles:¹⁷

95
96 (1) The assessment of the risk to quality should be based on scientific knowledge and
97 ultimately link to the protection of the patient

98
99 (2) The level of effort, formality, and documentation of the quality risk management process
100 should be commensurate with the level of risk

101
102 The pharmaceutical industry has taken incremental steps to implement quality risk management
103 principles since the publication of ICH Q9 in 2006. As a result, the Agency believes that many
104 stakeholders have already established processes and procedures to proactively identify, assess,
105 and mitigate the effect of a broad spectrum of risks to their business processes using these risk
106 management principles. The Agency encourages the use of these approaches to proactively
107 manage the risk of supply disruptions that may lead to drug shortages.

108
109

III. RISK MANAGEMENT PLANS: STAKEHOLDERS AND PRODUCTS

110
111

112 This section defines stakeholders in the manufacturing supply chain for drugs and describes
113 those products for which an RMP is required under section 506C(j) of the FD&C Act, as well as
114 those products for which an RMP is recommended.

115

A. Stakeholders in the Manufacturing Supply Chain

116
117

118 The content of an RMP, including the steps needed to reduce risks of a disruption in drug supply,
119 may vary among the different stakeholders in the supply chain for a given drug product. For the
120 purposes of this guidance, stakeholders in the drug supply chain are categorized as follows.

121

¹⁷ See ICH Q9.

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- 122 • **Primary Stakeholder.**¹⁸ The primary stakeholder is generally the entity that determines
123 which materials and services are necessary to produce a drug product. This knowledge
124 results in greater understanding of the entire supply chain for a drug product, and
125 therefore, makes the primary stakeholder best positioned to manage many of the risks of
126 supply chain disruption. Primary stakeholders include:
127
- 128 – For drug products with approved applications, the holder of the new drug application,
129 abbreviated new drug application, or biologics license application
130
 - 131 – For drug products without an application, the entity with understanding of and
132 capability to make changes to the supply chain (e.g., add a redundant active
133 pharmaceutical ingredient (API) source or mitigate a disruption in the supply of drug
134 product containers) for the finished drug product
135
- 136 • **Secondary Stakeholders.**¹⁹ Secondary stakeholders are entities that are expected to
137 have more detailed insight into specific segments of the supply chain for a drug product
138 but may not have an understanding of its entirety. Secondary stakeholders include:
139
- 140 – Finished product manufacturers that are not primary stakeholders, including any such
141 manufacturers that operate establishments involved in physically manipulating the
142 drug product (e.g., blending, tableting) and any such manufacturers of a drug-led,
143 drug-device combination product or biologic-led, biologic-device combination
144 product regulated by the Center for Drug Evaluation and Research (CDER) or the
145 Center for Biologics Evaluation and Research (CBER).^{20,21}
146
 - 147 – API manufacturers, as well as those manufacturers that physically process (e.g.,
148 milling, coating) or package the API.
149
- 150 • **Other stakeholders.** Other stakeholders in the supply chain for drugs that are not
151 primary or secondary stakeholders, such as inactive ingredient manufacturers, packagers,
152 and distributors.
153

B. Products for Which RMPs Are Required

154
155
156 As described in the Background section of this guidance, the CARES Act added section 506C(j)
157 to the FD&C Act, which requires certain manufacturers to develop, maintain, and implement, as
158 appropriate, a “redundancy risk management plan that identifies and evaluates risks to the supply

¹⁸ See the Appendix for risk factors for primary and secondary stakeholders to consider when developing an RMP.

¹⁹ Ibid.

²⁰ This does not include establishments that only perform testing, relabeling, or repackaging operations.

²¹ This category includes persons that operate establishments that manufacture drug-led, drug-device or biologic-led, biologic-device combination products (i.e., single entity, co-packaged, and cross-labeled combination products, as defined in 21 CFR 3.2(e)) but does not include persons that operate establishments that only manufacture the device constituent part of such a combination product (e.g., an establishment that only manufactures the device constituent part of a cross-labeled combination product).

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159 of the drug, as applicable, for each establishment in which such drug or active pharmaceutical
160 ingredient of such drug is manufactured.”^{22,23}

161
162 Each manufacturer of the following drug products, APIs, and associated medical devices must
163 develop, maintain, and implement, as appropriate, an RMP that identifies and evaluates risks to
164 the supply of the drug product, as applicable, for each establishment in which such drug product
165 or API of such drug product is manufactured.²⁴

- 166
- 167 • Prescription drug products that are:²⁵
 - 168 – Life-supporting²⁶
 - 169 – Life-sustaining²⁷
 - 170 – Intended for use in the prevention or treatment of a debilitating disease or condition,²⁸
171 including any such drug used in emergency medical care or during surgery²⁹ or any
172 such drug that is critical to the public health during a public health emergency declared
173 by the Secretary under section 319 of the Public Health Service Act³⁰
 - 174
 - 175
 - 176
 - 177
 - 178 • Any API included in the prescription drug products described above
 - 179
 - 180 • Any associated medical device used for preparation or administration included with the
181 prescription drug products described above, namely, any device constituent part of drug-

²² The identification and evaluation of risk specified in section 506C(j) are elements of the risk assessment step of an RMP (this concept is further illustrated in Figure 1, Recommended Risk Management Plan Steps Using the ICH Q9 Framework). Redundancy (e.g., more than one supplier) is an example of a risk control strategy that may help reduce risk identified during the risk assessment step but is not the only possible approach to risk control. For the purposes of this guidance *risk management plan* is the same as *redundancy risk management plan*.

²³ Through rulemaking, FDA applied section 506C of the FD&C Act to all biological products, including recombinant therapeutic proteins, monoclonal antibody products, vaccines, allergenic products, plasma-derived products and their recombinant analogs, blood or blood components, and cellular and gene therapy products (see 80 FR 38918, July 8, 2015; 21 CFR 600.82; and section 506C(h)(1), (i)(3) of the FD&C Act). Therefore, section 506C(j) is applicable to all biological products. Section 506C(a) applies only to applicants of blood or blood components for transfusion that manufacture a significant percentage of the U.S. blood supply (see 21 CFR 600.82; 80 FR 38926).

²⁴ See section 506C(j) of the FD&C Act.

²⁵ Excluding radiopharmaceutical drug products and any other product as designated by the Secretary (see section 506C(a)(2) of the FD&C Act).

²⁶ See 21 CFR 314.81(b)(3)(iii)(f) and 21 CFR 600.82(f).

²⁷ *Ibid.*

²⁸ *Ibid.*

²⁹ See section 506C(a)(1) of the FD&C Act.

³⁰ *Ibid.*

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182 led, drug-device combination product or biologic-led, biologic-device combination
183 product manufactured by the establishment and regulated by CDER or CBER.^{31,32}
184

185 FDA considers the manufacturers that are subject to this requirement under section 506C(j) of
186 the FD&C Act to include primary and secondary stakeholders as defined in section III.A. of this
187 guidance.
188

C. Products for Which RMPs Are Recommended

191 Certain types of drug products³³ and APIs not included in the requirement under section 506C(j)
192 of the FD&C Act,³⁴ if subject to a supply disruption and shortage, would be of particular concern
193 to the Agency because of the potential effect on patient care. In addition, FDA has found that
194 certain drug products, such as those with less redundancy in their supply chains, are at higher
195 risk of shortage. The products listed in this section may or may not be products for which
196 manufacturers must develop, maintain, and implement RMPs under section 506C(j). For
197 example, drug products intended to treat rare diseases or conditions may or may not also be drug
198 products for which RMPs must be developed, maintained, and implemented under section
199 506C(j). To the extent drug products or APIs incorporated in those products fall within a
200 category described in the following list but are *not* drug products described in section 506C(a) of
201 the FD&C Act or APIs included in such drug products, FDA nevertheless recommends that
202 stakeholders develop, maintain, and implement RMPs for such products, as appropriate, to
203 provide reliability of supply:
204

- 205 • Drug products intended to treat rare diseases or conditions³⁵
- 206
- 207 • Drug products that lack appropriate alternatives
- 208
- 209 • Medical countermeasures used in the event of a potential public health emergency
- 210 stemming from a terrorist attack with a biological, chemical, or radiological/nuclear

³¹ Manufacturers of an associated medical device used for preparation or administration included in the prescription drug products described above include persons that operate establishments that manufacture drug-led, drug-device or biologic-led, biologic-device combination products (i.e., single entity, co-packaged, and cross-labeled combination products, as defined in 21 CFR 3.2(e)) but does not include persons that operate establishments that only manufacture the device constituent part of such a combination product (e.g., an establishment that only manufactures the device constituent part of a cross-labeled combination product).

³² An RMP developed by such a manufacturer should address the risks associated with sourcing of the device constituent part.

³³ These considerations also apply to drug-led, drug-device and biologic-led, biologic-device combination products regulated by CDER or CBER subject to the requirement in section 506C(a) of the FD&C Act but for which availability of the device constituent parts could be a reason for, or a risk factor in, the supply disruption or shortage of the combination product.

³⁴ See section III.B. of this guidance.

³⁵ See section 526(a)(2) of the FD&C Act.

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211 material, or a naturally occurring emerging disease³⁶ and other threat agents (i.e.,
212 essential to national security)³⁷

- 213
- 214 • Sole source products³⁸
 - 215
 - 216 • Drug products with only one API manufacturer in the product’s supply chain that has
217 been appropriately qualified by the quality unit of the finished dosage form (FDF)
218 establishment^{39,40}
 - 219
 - 220 • Drug products with only one FDF manufacturer in the product’s supply chain⁴¹
 - 221
 - 222 • Drug products that are manufactured in a facility (including packaging facilities and
223 laboratories) with an inspection in the last 5 years that was classified as official action
224 indicated (OAI)⁴² and there is no other manufacturing facility that is qualified in the
225 product’s supply chain to conduct that operation⁴³
 - 226

227 RMPs are a useful tool to facilitate compliance with a firm’s regulatory requirements.⁴⁴ As a
228 general matter, the Agency believes that RMPs are a good practice to help ensure reliability of
229 supply of drug products and APIs. Therefore, FDA recommends that stakeholders consider
230 developing, maintaining, and implementing RMPs for their drug products or APIs that are not
231 subject to the requirement in section 506C(j) of the FD&C Act, in addition to those that are
232 subject to that requirement, as described earlier.

233
234

³⁶ The term *medical countermeasures* means items that meet the definition of “qualified countermeasure” in 42 U.S.C. 247d–6a(a)(2)(A); “qualified pandemic or epidemic product” in 42 U.S.C. 247d–6d(i)(7); “security countermeasure” in 42 U.S.C. 247d–6b(c)(1)(B); or personal protective equipment described in 29 CFR part 1910.

³⁷ See Section 7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security: Strategic Plan for Regulatory Science at <https://www.fda.gov/science-research/advancing-regulatory-science/section-7-facilitate-development-medical-countermeasures-protect-against-threats-us-and-global>.

³⁸ For the purposes of this guidance, a *sole source product* is a drug product of a specific strength, dosage form, or route of administration manufactured by only one entity for sale in the United States. MAPP 5240.3 Rev. 5 *Prioritization of the Review of Original ANDAs, Amendments, and Supplements* describes criteria to help manufacturers evaluate whether a product is a sole source product. MAPPs can be found on the Manual of Policies and Procedures web page at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp>.

³⁹ See 21 CFR 211.84.

⁴⁰ Additionally, for application products, the API establishment(s) are named in the approved application.

⁴¹ Additionally, for application products, the FDF establishment(s) are named in the approved application.

⁴² The term *official action indicated (OAI)* generally refers to a classification made following an inspection when a facility is observed to be in an unacceptable state of compliance and regulatory action may be warranted.

⁴³ For application products, it is also expected that any other manufacturing facility is named in the approved application.

⁴⁴ See generally the recommendations in ICH Q9, which describes the scope of the guidance on risk management principles for processes throughout the life cycle of drug substances, drug products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug products, and biological and biotechnological products).

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235 **IV. RMP FRAMEWORK AND DEVELOPMENT STRATEGY**

236
237 FDA recommends using the quality risk management process and principles described in ICH
238 Q9 as the framework to develop an effective RMP. This guidance is intended to add to the
239 elements of the framework described in ICH Q9, to describe considerations for stakeholder
240 oversight for RMPs, and to assist with the interpretation of the quality risk management process
241 within the context of developing RMPs.⁴⁵ Further, stakeholders may benefit by integrating the
242 RMP with other aspects of their operations.

243 244 **A. Stakeholder RMP Development Strategy**

245
246 RMPs help to ensure that risks with the potential to disrupt the drug manufacturing process and
247 the drug supply chain have been identified, assessed, and mitigated. An individual stakeholder's
248 role in developing and implementing an RMP varies with that stakeholder's level of involvement
249 with the drug manufacturing process or supply chain. Nonetheless, FDA believes that risk
250 management principles should be applied throughout the drug supply chain to help mitigate the
251 risk of drug shortages.

252
253 A primary stakeholder RMP should contain a broader strategy that establishes overarching
254 approaches to consistently identify, assess, and mitigate risk across the organization or a
255 subsector of the organization. This approach is consistent with institutionalized quality
256 management maturity⁴⁶ that results in understanding the risk of supply disruptions that may lead
257 to shortages across the supply chain, integrates redundancy into the supply chain, improves the
258 forecasting of demand changes at all stages of production, maintains sustainable compliance,
259 improves overall incentives between purchasers and manufacturers, and fosters collaboration
260 with regulators. FDA recommends that the primary stakeholder RMP also include plans to
261 repair the supply chain after a disruption, as appropriate. Further, FDA recommends that the
262 primary stakeholder initiate RMP development as early as possible in the drug product's
263 regulatory life cycle.

264
265 The Agency recommends that the primary stakeholder share as much of its RMP as possible with
266 secondary and other stakeholders of the drug product to enable secondary and other stakeholders
267 to incorporate the broad strategies of the primary stakeholder's RMP into their own plans and
268 also contextualize the risks identified in the primary stakeholder's RMP, specifically for the
269 manufacturing facility. Sharing the primary stakeholder's RMPs with secondary and other

⁴⁵ Similarly, for combination products, this guidance would also serve to augment a risk management program based on ISO 14971 *Application of risk management to medical devices* (2019). With regard to combination products, either ICH Q9 or ISO 14971/ISO TR 24971 *Guidance on the application of ISO 14971* (2020) could serve as a basis for developing a suitable framework for risk management, and reference to both can be helpful in developing such a framework. For combination products that include a device constituent part, use of an ISO 14971/24971-based framework, incorporating relevant considerations from ICH Q9, is recommended to ensure a sufficiently robust risk management process consistent with current best practices and global regulatory trends and norms. See, for example, AAMI TIR 105 2020, *Risk Management for Combination Products*.

⁴⁶ See the FDA report "Drug Shortages: Root Causes and Potential Solutions" (2019) (available at <https://www.fda.gov/media/131130/download>). More advanced levels of quality management maturity aim to robustly detect vulnerabilities and address them to prevent the occurrence of problems as well as establishing a culture that rewards process and system improvements.

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270 stakeholders may also further refine the mitigation and avoidance strategies specific to the
271 individual drug, or its unique manufacturing process. For example, if a primary stakeholder's
272 RMP already addresses availability of raw materials, it may be appropriate for this risk factor not
273 to be addressed in a contract manufacturer's RMP. However, in such a situation, FDA
274 recommends that the contract manufacturer's RMP still address general and product-specific
275 facility risks, such as maintaining process control, manufacturing equipment robustness, and
276 product-specific utility requirements.

277
278 The stakeholders that are involved in the supply chain for a particular drug product should work
279 together to address RMP development and implementation. The Appendix of this guidance
280 provides risk factors for stakeholders to consider when developing an RMP strategy.

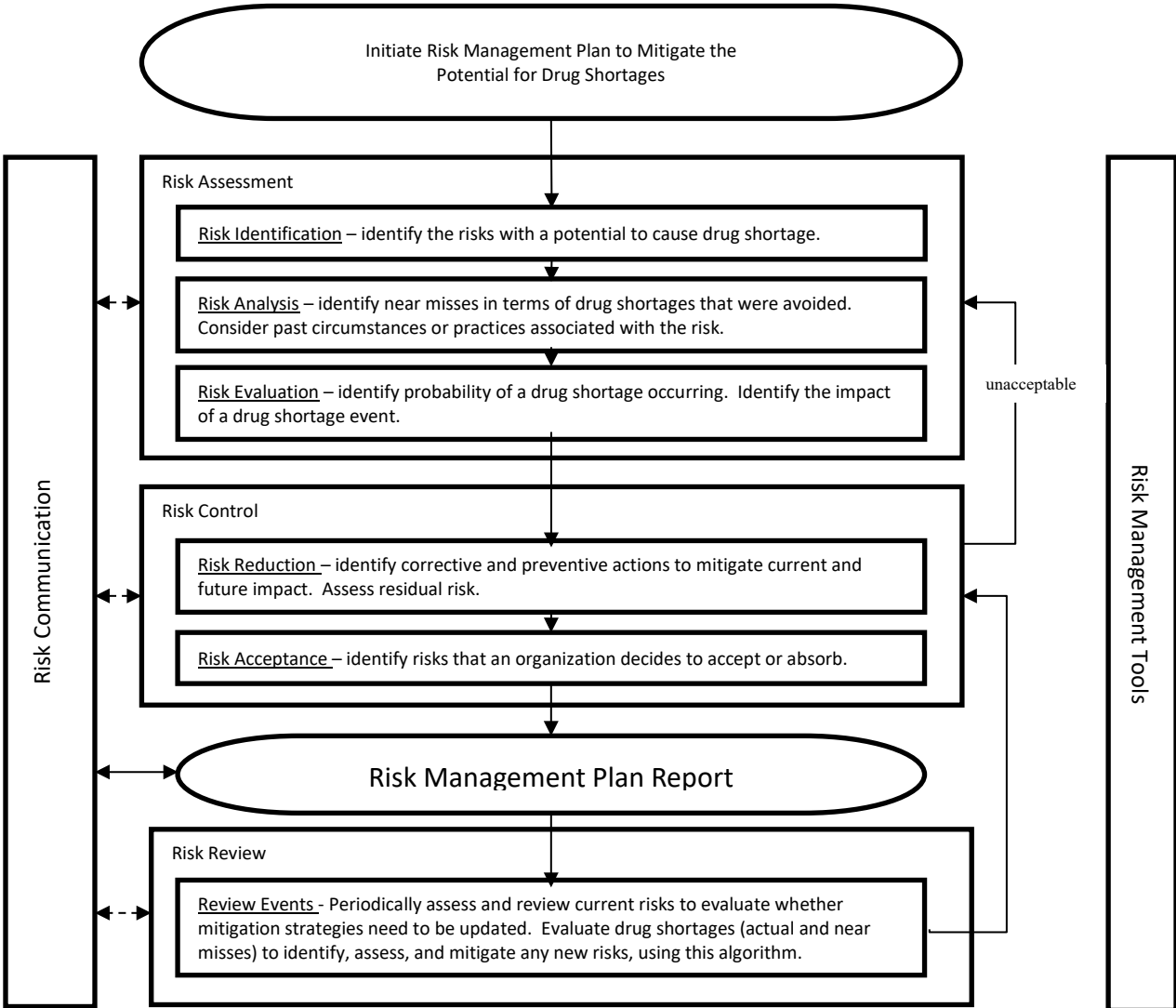
281
282 **B. Quality Risk Management Process Framework**

283
284 FDA recommends the following process for developing RMPs based on the quality risk
285 management framework in ICH Q9, as shown in Figure 1. Each process step is detailed in the
286 following subsections.

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288 **Figure 1: Recommended Risk Management Plan Steps Using the ICH Q9 Framework**
289
290



291
292 *1. Initiating an RMP*
293

294 The purpose of initiating an RMP is to allow a stakeholder to proactively assess the risks of a
295 drug supply disruption, rather than wait for an actual disruption to occur. Cross-cutting
296 coordination and collaboration is critical to development, implementation, and maintenance of an
297 effective RMP.

298
299 *2. Risk Assessment*
300

301 The risk assessment involves identifying the associated hazards, evaluating the risk of each
302 hazard, and evaluating the risk of a drug supply disruption based on: (1) what might go wrong;
303 (2) what is the likelihood (probability) it will go wrong; and (3) what are the consequences
304 (severity).

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306 • **Risk Identification** — This involves identifying the hazards, including critical
307 operations or processes, that have the potential to cause a drug supply disruption.
308 Potential hazards can be identified through: historical data analysis; theoretical analysis;
309 informed opinions; relationships with suppliers, vendors, and contractors; audits; market
310 forces that may affect the availability or reliability of raw materials; and overall
311 manufacturing process stability and reliability.^{47,48,49}

312

313 • **Risk Analysis** — This involves estimating the risk associated with the identified hazards
314 and effects⁵⁰ considering the likelihood of occurrence, severity of harm, and detectability.
315 That is, is there an increased potential for supply disruption of the finished drug product
316 based on the hazards (e.g., location of manufacturing, source of components)? This
317 analysis may include historical information, such as if there were one or more *near-miss*
318 situations where a shortage was narrowly avoided.

319

320 • **Risk Evaluation** — Based on the risk analysis, the probability of each risk resulting in
321 patient impact or a supply disruption should be systematically evaluated.

322

323 At the end of the Risk Assessment step, the hazards should have been identified, analyzed, and
324 evaluated, and a determination should have been made as to which hazards are considered a
325 higher risk to drug supply disruption than others.

326

327 3. *Risk Control*

328

329 The Risk Control step is intended to reduce risks of a disruption in supply to an acceptable level
330 and/or accept these risks.

331

332 • **Risk Reduction** — This involves identifying strategies that can be used to potentially
333 mitigate or avoid the identified risks. This can include building redundancy into
334 manufacturing operations, establishing adequate controls on the supply chain,
335 strengthening relationships with suppliers (e.g., contract manufacturers, ingredient
336 suppliers), and/or identifying alternative suppliers.⁵¹ Once the applicable strategies are
337 implemented, the risk assessment should be periodically re-evaluated to determine if

⁴⁷ With regard to market disruption for combination products, this would include appropriate engagement of personnel with requisite expertise and responsibility to understand risks associated with sourcing of device constituent parts, which include components of device constituent parts, that might cause disruption to manufacture of the combination product including development and management of associated purchasing controls (see 21 CFR part 4, 21 CFR 820.50).

⁴⁸ Since 2013, FDA has been encouraging manufacturers to implement and improve quality metrics and quality culture programs in support of overall manufacturing process stability and reliability. The Quality Metrics Program is also part of the long-term strategy to mitigate drug shortages by addressing the robustness of quality oversight, given that quality issues have been found to be the most common underlying cause of shortages.

⁴⁹ See also the Appendix: Risk Considerations for Specific RMPs.

⁵⁰ See the ISPE/Pew Report mentioned in footnote 9 at p. 11, which identifies potential patient effects of stakeholder decisions to remain in the market or invest in new facilities or equipment to mitigate the risk of creating a drug shortage.

⁵¹ See the requirements for making changes to the conditions established in an approved application under 21 CFR 314.70 and 21 CFR 601.12.

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338 additional hazards are present. Risk control strategies also can account for residual risk
339 arising after a mitigation strategy is implemented.

340

- 341 • **Risk Acceptance** — This involves identifying if the remaining risk is acceptable⁵² or if
342 the risk should be further reduced through additional risk reduction strategies.

343

344 At the end of the Risk Control step, a report should be developed to document the risk
345 assessment and risk control strategies.

346

347 4. *Risk Review: Review Events*

348

349 The Agency recommends *at least* an annual, internal review and revision of an RMP throughout
350 the life cycle of a drug. RMP review and revision should include lessons learned, including the
351 root cause of new and near-miss supply disruptions. In some instances, it may be useful to
352 quickly integrate the additional identified risks and mitigation strategies into the RMP rather than
353 waiting for the next annual review cycle. This review also can include an assessment of
354 communication with regulators and whether the communication should be improved.

355

356 5. *Risk Communication*

357

358 FDA encourages stakeholders to engage in proactive communication of their RMPs with
359 organizations within their drug supply chains, and where appropriate, with external stakeholders
360 and regulators throughout the process.

361

362 Certain stakeholders are required to submit notifications to the Agency about drug product and
363 API permanent discontinuances and certain manufacturing interruptions under section 506C of
364 the FD&C Act.^{53,54} For the notifications received, FDA works with the stakeholder to assess the
365 situation and prevent or mitigate any shortage that may result, when possible. Stakeholders that
366 are covered by the notification requirement under section 506C must submit certain information
367 to FDA as part of the notification.⁵⁵ Along with the information that is required to be submitted,
368 the Agency recommends that manufacturers provide additional information that may assist the
369 Agency in addressing the situation. FDA has published a list of questions for manufacturers to
370 consider as they evaluate the situation and prepare to notify FDA, including whether the
371 manufacturer has a proposal for FDA to review to expedite availability of a product.⁵⁶ This
372 information would likely be contained in an RMP. A stakeholder can leverage an RMP to

⁵² See ICH Q9.

⁵³ For more information, see section 506C(a) of the FD&C Act and FDA's implementing regulations at 21 CFR 310.306, 21 CFR 314.81(b)(3)(iii), and 21 CFR 600.82, which address, among other things, which persons and drug and biological products are covered by the notification requirement, what information must be submitted in a notification, and when notifications must be submitted.

⁵⁴ Under section 506J of the FD&C Act, certain medical device manufacturers are required to notify the Agency about permanent discontinuances or interruptions in manufacturing likely to lead to a meaningful disruption of the supply of the device in the United States. Such notifications are outside the scope of this guidance. For more information about device notifications, see section 506J of the FD&C Act.

⁵⁵ See footnote 53.

⁵⁶ See the guidance for industry *Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act* (March 2020); see also 80 FR 38915 at 38922 (July 8, 2015).

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373 communicate and quickly share information with the Agency to prevent or mitigate a shortage.
374 Additionally, an established RMP can serve to support stakeholders during these times when
375 their resources are typically strained with numerous internal and external requests.

376
377 RMPs that are developed, maintained, and implemented by stakeholders pursuant to the
378 requirement in section 506C(j) of the FD&C Act are subject to inspection and copying pursuant
379 to an FDA inspection or a request under section 704(a)(4) of the FD&C Act (21 U.S.C. 374).⁵⁷
380 RMPs, or elements of an RMP, need not be submitted as part of a biologics license application,
381 new drug application, abbreviated new drug application, or drug master file.

382
383 *6. Risk Management Tools*

384
385 There are a variety of off-the-shelf and customizable risk management tools that may be helpful
386 when developing and maintaining an RMP. The Agency believes the recommendations in this
387 guidance can be applied regardless of the format or tool used.

388

⁵⁷ See section 506C(j) of the FD&C Act.

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**APPENDIX:
RISK CONSIDERATIONS FOR SPECIFIC RMPS**

The following risk factors should be considered when developing specific risk management plans (RMPs) to mitigate the potential for drug shortages.

All RMPs — Each drug has product-specific characteristics (e.g., dosage form, active pharmaceutical ingredient source, manufacturing and test methods) that may be used to help determine instances when the product’s supply may fluctuate. At a high level, the following list identifies some risk factors that may be considered together with a drug’s product-specific characteristics to help manufacturers uncover weaknesses that may impact product supply:

- Determine which drugs, including components, manufactured at the facility are vulnerable to a supply disruption
- Identify weaknesses in manufacturing process specific to individual drugs¹
- Determine whether any of the suppliers of drug product container-closure systems or device constituent parts, which include components of device constituent parts, are a sole source provider
- Identify weaknesses in inventory management at the manufacturing facility, including understanding market forecast for a drug, to ensure that supply is able to meet anticipated demand
- Ascertain whether the drug manufacturing relies on incapable or unreliable equipment, such as older equipment or equipment that breaks down frequently where maintenance is difficult or parts are not easily replaced or available (incapable equipment may also include equipment that relies on software or other technologies that are not able to be updated (i.e., patched), which increases such equipment’s susceptibility to cybersecurity threats)
- Identify the normal capacity and surge capacity of the manufacturing facility to manufacture a drug or its components that are vulnerable to shortage
- Evaluate the drug’s stability data, including finished product and components, to determine whether the data demonstrate safety and efficacy beyond the labeled expiry date or retest date and, if needed, reassess the drug’s stability program
- Be aware of and implement changes and alterations to requirements for relevant articles in the United States Pharmacopeia or National Formulary

¹ A Quality Metrics Program, as referenced in footnote 48 of the guidance, is intended to measure different key performance indicators to assist in identifying which manufacturing processes are weaker than others, in order to identify improvement projects and certain products that could be targeted for improvement.

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431 **Primary Stakeholder’s RMP** — The following list provides risk factors for a primary
432 stakeholder to consider when developing an RMP to ensure that it provides an overarching
433 strategy to consistently identify, assess, and mitigate risk across multiple manufacturing facilities
434 and drugs from an oversight perspective. This RMP often can include product-specific concerns,
435 which in turn should result in further extrapolation at the facility level. The risk factors (not an
436 exhaustive list) for a primary stakeholder to consider when developing an RMP include:

- 437
- 438 • Geographic risk factors, including potential for natural disasters, as well as political
439 instability and regulatory uncertainty, that can affect the overall ability to consistently
440 manufacture a drug.
- 441
- 442 • Supply chain vulnerabilities, such as sole source manufacturers of critical components in
443 a drug product, including active pharmaceutical ingredient, and sole source
444 manufacturers of a drug product.
- 445
- 446 • Manufacturing vulnerabilities, including lack of manufacturing capacity to meet an
447 unexpected surge in demand, inadequate backup manufacturing capability, lack of
448 availability of contract manufacturers or other alternate sources, lack of availability of
449 laboratory services to support manufacturing, and inadequacy of management oversight.
- 450
- 451 • Distribution vulnerabilities, including the complexity of distribution or transportation of
452 components, drug product containers and closures, and drug products.
- 453
- 454 • Whether the equipment or systems used in manufacturing or distribution could be
455 susceptible to cybersecurity threats
- 456
- 457 • Emergency situations that reduce staff or facility availability to continue manufacturing.
- 458
- 459 • Whether the drug is life-supporting, life-sustaining, intended for use in the prevention or
460 treatment of a debilitating disease or condition, including any such drug used in
461 emergency medical care or during surgery or any such drug that is critical to the public
462 health during a public health emergency declared by the Secretary under section 319 of
463 the Public Health Service Act, intended to treat rare diseases or conditions, a drug that
464 lacks appropriate alternatives, used as a medical countermeasure in the event of potential
465 public health emergency, or critical in response to specific targeted threat agents
466 (essential to national security).
- 467
- 468 • The capability and historical record of the facilities in the supply chain, including
469 whether there is a history of sustained current good manufacturing practice (CGMP)
470 compliance. This should include inspectional findings at the headquarters unit that
471 provides global quality oversight and all facilities in the supply chain that might affect the
472 availability of the drug, and details relating to the presence or recurrence of quality
473 issues, CGMP violations, recalls, and lapses in quality management oversight.
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- Compliance with applicable regulatory reporting requirements, including: notifications under section 506C or section 506I of the Federal Food, Drug, and Cosmetic Act (FD&C Act),² postmarketing safety reports,³ and field alert reports.⁴
 - Communication vulnerabilities with secondary and other stakeholders within the supply chain that might hinder timely distribution or receipt of quality-related information (e.g., agreements with contract manufacturers that prohibit disclosure of information at other contract facilities).

483

484 **RMPs for Secondary Stakeholders and Other Stakeholders** — When a stakeholder that is not

485 the primary stakeholder (i.e., a secondary or other stakeholder) develops its RMP, it typically

486 should interpret the broader risks identified in the primary stakeholder’s RMP within the context

487 of a specific manufacturing facility, and address unique risks at a manufacturing facility that are

488 unlikely to be identified by the primary stakeholder. Furthermore, many of the risks might have

489 specific implications to the drugs manufactured at a facility (e.g., environmental controls might

490 affect a sterile, parenteral drug more than a solid, oral dosage drug). The RMP for stakeholders

491 that are not the primary stakeholder should consider the effect of identified risks on the

492 manufacturing facility as well as on the drugs manufactured at that facility. The following non-

493 exhaustive list provides risk factors for such stakeholders to consider as part of developing an

494 RMP. Some of these risk factors may also be useful to the primary stakeholder, depending on

495 the responsibilities of the primary stakeholder.

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- Identify vulnerabilities in the supply chain for each drug product vulnerable to supply disruptions. Consider limitations in supply for raw materials, intermediates, components, and drug product containers and closures.
 - Ensure that appropriate communication with contract manufacturing facilities and component suppliers is established to proactively address risks that might lead to meaningful drug supply disruptions.⁵
 - Identify weaknesses in the infrastructure and utilities; water systems; heating, ventilation, air conditioning, and environmental control; and the proximity of support services such as laboratory testing.

² See section 506C(a) of the FD&C Act.

³ See generally the requirements contained in 21 CFR 310.305 (marketed prescription drug products without approved new drug applications (NDAs) or abbreviated new drug applications (ANDAs)), 21 CFR 314.80 (drug products with approved NDAs), 21 CFR 314.98 (drug products with approved ANDAs), 21 CFR 600.80 (biological products with approved biologics license applications), section 760 of the FD&C Act (marketed nonprescription drug products without approved NDAs or ANDAs), and 21 CFR part 4, subpart B (combination products and constituent parts).

⁴ See 21 CFR 314.81 (drug products with approved NDAs and ANDAs) and 21 CFR part 4, subpart B (combination products and constituent parts).

⁵ See the guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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- 509 • Ascertain whether the manufacturing facility has incapable or unreliable equipment, such
510 as equipment that is unsuitable for its intended use, legacy equipment that breaks down
511 frequently, or equipment with parts that are not easily replaced or available.
512
- 513 • Identify challenges and weaknesses in monitoring vulnerable equipment.
514
- 515 • Identify equipment that operates with limited down time, which could be prone to
516 accelerated wear and tear.
517
- 518 • Identify the normal capacity and surge capacity of the facility to manufacture a drug that
519 is vulnerable to shortage.
520
- 521 • Ascertain whether the equipment or systems used in manufacturing or distribution could
522 be susceptible to cybersecurity threats.
523
- 524 • Assess the suitability and competence of potential contractors before outsourcing
525 operations or selecting material suppliers.
526
- 527 • Assess the reliability of potential contractors to deliver operations or materials on time
528 and of good quality to meet manufacturer deadlines and to avoid interruptions in
529 processing.
530
- 531 • Assess the record of CGMP performance, including the presence or recurrence of quality
532 issues, CGMP violations, potential for major defects and recalls, inspectional findings at
533 the facilities in the supply chain, and adequacy of quality management oversight, that
534 might affect the availability of the drug.
535