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Key Legal and Regulatory Considerations Related to Microbiological Risks

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The U.S. Food and Drug Administration (FDA) and other regulators continue to focus on microbiological risks associated with drug products. Product recalls and serious adverse events associated with ineffective microbiological controls has shifted regulatory scrutiny from not only sterile injectables but to other non-sterile products as well. Manufacturers need to be thoughtful in dealing with increased scrutiny and be prepared to address the increasing legal and regulatory risks in this area.

Multiple companies over the last several years have initiated recalls because of known or potential microbiological contamination. FDA recently reported that between 2014 and 2017, it identified over 50 voluntary recall actions associated with objectionable microbiologically contaminated non-sterile drugs.[1] In that same timeframe, it received 197 adverse event reports related to microbiological or fungal contamination for these products, including 32 reports of serious adverse events. Of particular concern to FDA are recalls involving potential contamination with *Burkholderia cepacia* (*B. cepacia*), an opportunistic human pathogen that can survive and proliferate in non-sterile products despite the presence of an otherwise adequate preservative system. These events present important legal and regulatory risks.

FDA has recently issued guidance about the need to implement robust cGMP controls to address the risk of microbiological contaminants, including *B. cepacia*[2] and its related genomovars. Many of these controls focus on liquid or aqueous products given the higher potential for contamination in these dosage forms. *B. cepacia*-related recalls have frequently involved product types such as topical gels, creams, oral solutions, and foams. For these product types, FDA recommends careful, risk-based review of the manufacturing process to identify materials and activities known to support microbial proliferation. Companies should emphasize greater process controls for these materials and activities, including microbiological monitoring methods and acceptance criteria, validation of in-process holding periods, equipment cleaning and drying, well-controlled water systems, and management of raw material bioburden.

In its recent guidance, FDA noted that the level and type of microorganisms even in non-sterile drugs must be limited during manufacturing and shelf life, and it expects manufacturers to establish or maintain a monitoring and control program to prevent objectionable microorganisms in their products. While the U.S. Pharmacopeia (USP) does not identify all objectionable microorganisms, FDA recommends that manufacturers of appropriate non-sterile products use the USP compendial test for *B. cepacia* (USP 60 – Microbiological Examination of Nonsterile Products—Tests for Burkholderia Cepacia Complex). FDA does not expect application holders of approved drug products to amend their

specifications where it is inconsistent with the recommendations in the draft guidance document, but FDA noted that when manufacturers submit supplemental applications requesting changes that may impact the risk of microbiological growth, its reviewers might request updates to the microbiological testing information in the product specifications before approving the application. Thus, reviewing and updating these specifications in advance may expedite future application changes.

Not all assessed risks require more stringent specifications or the addition of microbiological controls. Where appropriate, risk assessments can result in the reduction or elimination of microbiological release testing for solid oral dosage forms. For example, where controls and results provide appropriate support, there may be cases where the finished drug product presents minimal microbiological risk. Microbiological testing may also be reduced or eliminated in stability programs as appropriate. Even non-solid dosage forms, though typically presenting higher risk, may present the opportunity for reduced testing if supported with appropriate data.

It is important to recognize that the legal and regulatory risks extend beyond microbial contamination to the generation and control of the microbiological data. Regulators continue to scrutinize manufacturers' data management controls, and the data supporting the contamination controls must be reliable for the program to be effective.

Microbiological sample collection and testing pose different risks from those in other areas of the Quality Control laboratory or manufacturing. Many of the microbiological activities rely on trained personnel performing their testing and documenting their results manually. Some automated controls are becoming more common, including rapid technology, digital image capture, and automated plate readers. Limitations exist, however, even for these technologies, and there is likely a continuing need for analyst judgment in interpreting and confirming results. The most recent PIC/S guidance on data management suggests a secondary review of data, even in real time, when critical test interpretations are made by a single individual and in accordance with risk management principles.[3] It is not uncommon for a single analyst to interpret plates and other microbiological data, and appropriate oversight by Quality Assurance is key.

Without the appropriate controls, quality culture and QA oversight, it becomes much easier to challenge data and undermine the company's broader microbiological controls.

Accordingly, companies should consider taking a number of steps to reduce these legal and regulatory risks in light of FDA's focus on microbiological quality in the aftermath of recent contaminations and recalls:

- Evaluate existing microbiological risk assessments, in particular for non-sterile products, to confirm their thoroughness based on the factors identified by FDA and their consideration of particular risks such as *B. cepacia* and its related genomovars
- Review related specifications to ensure they correlate appropriately to identified risks;
- Assess manufacturing controls and acceptance criteria related to contamination control in light of FDA's recent draft guidance;
- Review data management controls, including third-party assessments, for activities within the microbiological laboratory and related sample collection and testing.

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If you have any questions concerning these developing issues, please do not hesitate to contact any of the following Paul Hastings lawyers:

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[1] FDA Draft Guidance for Industry: Microbiological Considerations in Non-Sterile Drug Manufacturing (Sept. 2021) ("Draft Guidance on Microbiological Considerations").

[2] Draft Guidance on Microbiological Considerations. FDA is requesting comments on the draft guidance by December 29, 2021.

[3] PIC/S Guidance: Good Practice for Data Management and Integrity in Regulated GMP/GDP Environments 8.8 (1 July 2021).