

March 8, 2023

Dear Infant Formula Manufacturers, Packers, Distributors, Exporters, Importers, and Retailers:

This letter is directed to manufacturers, packers, distributors, exporters, importers, and retailers involved in the manufacturing and distribution of powdered infant formula. In late 2021 and early 2022, a series of *Cronobacter* spp. illnesses among infants in the U.S. was associated with feeding a certain brand of powdered infant formula. The U.S. Food and Drug Administration (FDA or “the Agency”) inspection of the associated manufacturing facility revealed the presence of *Cronobacter* spp. within the production environment, as well as other insanitary conditions, leading to a nationwide recall. This recall and the temporary shutdown of the plant was a major contributing factor to the infant formula shortage experienced across the U.S. in 2022.

In response, the FDA developed a strategy to prevent future *Cronobacter* spp. illnesses associated with powdered infant formula and is issuing this letter to share current information to assist industry in improving the microbiological safety of powdered infant formula.

### **Call to Action**

The FDA is calling on all members of the infant formula industry to help protect our most vulnerable population. Specifically, FDA asks that you:

- 1) Evaluate your established system of production and in-process controls (which must cover all stages of processing, from the receipt and acceptance of the raw materials, ingredients, and components through the storage and distribution of the finished product) and ensure that appropriate controls are implemented in accordance with [21 CFR 106.6\(c\)](#) at any point, step, or stage in the production process where control is necessary to prevent adulteration of infant formula;
- 2) Ensure full compliance with all relevant regulations – including the Infant Formula Requirements Pertaining to Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Records and Reports, and Notifications rule ([21 CFR part 106](#)) and the Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food rule ([21 CFR part 117](#));
- 3) Consider the concerns shared in this letter when evaluating your established system of production and in-process controls, including when taking corrective actions; and
- 4) Ensure adherence to the notification requirement of an adulterated or misbranded infant formula any time product has left the facility, in accordance with [21 CFR 106.150](#).

Lastly, FDA asks that firms voluntarily notify the Agency any time a product sample is found to be positive for *Cronobacter* spp. or *Salmonella*, even if the affected lot(s) have not been distributed.

## Areas of Concern at Powdered Infant Formula Manufacturing Facilities

The FDA has reviewed conditions during recent inspections of powdered infant formula manufacturers, including routine surveillance inspections, for-cause inspections to follow up on consumer complaints, and other interactions with manufacturers.<sup>1</sup> FDA has identified the following areas for improvement across the infant formula industry (summarized here and expanded in the letter below):

1. Controlling water in dry production areas
2. Verifying the effectiveness of controls through environmental monitoring
3. Implementing appropriate corrective actions following the isolation of a pathogen from an environmental sample or a product sample
4. Implementing effective supply-chain controls for biological hazards
5. Identifying all relevant biological hazards

FDA is sharing this information with you with the expectation that you will act to mitigate potential food safety risks in powdered infant formula in accordance with FDA regulations while further striving to improve operations, especially given the critical nature of these products.

### 1) Controlling water in dry production areas

The food industry acknowledges that reducing the presence of water in dry production environments for low moisture foods is essential to controlling environmental contamination, *e.g.*, from *Salmonella* and *Cronobacter* spp. In several inspections at powdered infant formula manufacturing facilities, FDA observed water present during production in areas that were intended to remain dry (at least during production). The sources of the water included leaks from roofs or other exterior facility features, leaks from equipment (during production and/or during sanitation), and condensation. Records of water observed by employees in the dry processing areas, and the identified sources can help a firm analyze trends or identify recurring problems. However, not all firms adequately record this information. *The incidence of water in dry production environments should receive prompt consideration by the industry.*

Poorly maintained equipment that leaked during clean-in-place (CIP) procedures was identified as one source of water in the dry production environment. However, sanitation activities, specifically CIP procedures used on certain equipment, introduce a large amount of water to equipment surfaces. Ensuring that equipment surfaces are fully dried following a CIP procedure and before starting production is also important for equipment used to process low moisture

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<sup>1</sup> Information relating to publicly disclosed inspectional findings is available on the FDA website. See, *e.g.*, [Infant Formula Information and Ongoing FDA Efforts to Increase Supply](#). Where appropriate, based on concerns from inspectional findings, FDA also conducted regulatory meetings with certain firms, during which the Agency engaged in detailed discussions with those firms concerning their corrective actions to cited deviations and reminded them of their obligations to comply with all applicable FDA regulations. In addition to gaining information through inspectional activities and exchanges about corrective actions, FDA gained information through the review of manufacturing and related processes related to FDA's issuance of its May 2022 guidance providing increased flexibilities regarding infant formula to help facilitate the availability of safe and nutritionally adequate infant formula products in the U.S. marketplace on a temporary basis to address the formula shortage.

foods, such as powdered infant formula. Several firms had either poor or no documentation that their dry-out procedures following a CIP procedure or other sanitation activity were capable of fully drying equipment surfaces, including food contact surfaces. FDA further noted that CIPs were being performed at greater frequencies than previously observed. Leaks in equipment, unverified dry-out procedures, and increased CIP frequency raise concerns with the management of water related to sanitation activities and represent potential areas for improvement.

## **2) Verifying the effectiveness of controls through environmental monitoring**

Environmental monitoring is an important verification measure to ensure that sanitation and hygiene controls are effectively preventing pathogens from entering or persisting in dry production areas. Inspections of powdered infant formula manufacturers revealed that, while facilities had implemented some form of environmental monitoring programs (EMPs), there were differences with regards to where in the facility sampling and testing was conducted specifically for pathogens, *e.g.*, *Cronobacter* spp.

Some firms have EMPs that limit the collection of environmental samples for *Cronobacter* spp. while relying heavily on monitoring for Enterobacteriaceae (EB) within the production area. Monitoring EB populations on environmental surfaces in dry production areas may serve as a useful indicator that unexpected water may have been introduced or some other breakdown of hygienic control may have occurred. However, FDA is not aware of sufficient data demonstrating a correlation between EB populations and the presence of *Cronobacter* spp. on environmental surfaces. Environmental samples collected by FDA investigators during these inspections recovered *Cronobacter* spp. from environmental surfaces where the firms were only conducting routine environmental testing for EB.

Manufacturers of powdered infant formula must establish a system of process controls covering all stages of processing that are designed to ensure that the product does not become adulterated due to the presence of microorganisms in the formula or in the processing environment. A well-designed and implemented EMP should provide information about the hygienic conditions at all stages of processing, while focusing the greatest amount of sampling on surfaces from which the risk of contamination to the product is greatest. While testing environmental surfaces for EB provides some information on the conditions within the facility, the presence or absence of EB on environmental surfaces is not a reliable indicator for the presence of *Cronobacter* spp.<sup>2</sup> Therefore, FDA encourages the direct testing for *Cronobacter* spp. at some frequency within the processing environment for powdered infant formula.

## **3) Implementing appropriate corrective actions following the isolation of a pathogen from an environmental sample or a product sample**

When verification testing detects a pathogen, *e.g.*, *Salmonella* or *Cronobacter* spp., in an environmental or product sample, firms must implement a corrective action plan as required under [21 CFR 106.6](#). The goals of a corrective action plan are to prevent affected product from entering the market and to determine the root cause of the problem to prevent recurrence.

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<sup>2</sup> See *e.g.*, [Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula, 79 Fed Reg 7934, 7983-7984](#) (Feb 10, 2014).

Effective corrective action plans often involve conducting a root cause investigation (RCI), (*i.e.*, performing an investigation to determine the source of the contamination) to inform appropriate containment and corrective action activities.

During our inspections, FDA investigators reviewed and/or observed corrective actions taken in response to detecting *Cronobacter* spp. in environmental and product samples. As part of their RCI, some facilities disassembled certain equipment, collected environmental samples from food contact surfaces, and tested those samples for indicator organism populations, *e.g.*, total aerobic plate counts, total coliforms, or total EB. The presence or absence of EB on environmental surfaces is not a reliable indicator for the presence of *Cronobacter* spp. In other instances, when responding to the detection of *Cronobacter* spp. in a product sample, some facilities immediately initiated sanitation activities on suspected environmental or equipment surfaces and then collected samples from these surfaces to verify sanitation effectiveness. This approach limited their ability to determine whether those surfaces contributed to the contamination event. FDA encourages firms conducting an RCI to thoroughly investigate the potential sources of contamination by collecting environmental samples **before** performing sanitation activities, in addition to other RCI activities such as evaluating incoming ingredients and reviewing production records.

During the production of powdered infant formula where the product is in a dry powder form, manufacturing activities may operate for extended periods of time between complete sanitation activities. Although limited dry cleaning may be conducted between some production lots (*e.g.*, vacuuming, brushing, tapping, sweeping, or flushing equipment surfaces), FDA has observed during inspections that many production lots may be processed on such equipment without an intervening sanitation break that would involve the application of a sanitizing treatment to all food contact surfaces (hereafter referred to as sanitation break). The best current available science demonstrates that the only adequate remediation for food contact surfaces contaminated by a bacterial pathogen is the application of a sanitizing treatment (*e.g.*, a thermal treatment or a chemical treatment). To date, other remediation procedures, such as physical dry-cleaning techniques, have not proven effective against eliminating pathogens from equipment surfaces.

Additionally, the widespread availability of whole genome sequencing (WGS) has offered an unprecedented opportunity for conducting RCIs following the detection of a pathogen in an environmental or product sample. In reviewing product testing plans and EMPs, FDA investigators noted that some facilities do not use technologies such as WGS to investigate pathogen isolates to help determine the root cause. Samples collected during some of our investigations identified more than one strain of *Cronobacter* spp. within the same facility. FDA strongly recommends using WGS (and the public database of genomes available at the National Center for Biotechnology Information) to analyze and investigate any pathogen isolated from a production environment or product. The data from this analysis can provide the most complete information available to identify and implement appropriate and effective corrective actions.

#### **4) Implementing effective supply-chain controls for biological hazards**

Some facilities involved in the manufacturing of powdered infant formula have processes or process steps that use raw materials or other ingredients in a manner that does not apply a treatment to these raw materials or other ingredients that would be lethal to bacterial pathogens, such as *Salmonella* or *Cronobacter* spp. An example of this process would be the dry blending of an ingredient into an infant formula base to produce a finished powdered infant formula product. The powdered infant formula manufacturer must evaluate any known or reasonably foreseeable hazards associated with these raw materials or other ingredients, determine if they require control at the supplier, and if they do, establish a supply chain program for those raw materials or other ingredients (see [21 CFR 117.405\(a\)\(1\)](#)).

In addition to inspections of powdered infant formula manufacturers, the FDA has also conducted inspections of domestic and foreign suppliers of raw materials and ingredients used in the manufacturing of powdered infant formula. FDA observed that the supply-chain program at the powdered infant formula manufacturer did not always fully characterize the risk associated with bacterial pathogens, such as *Cronobacter* spp., at the supplier's facility. Suppliers of raw materials or other ingredients that will not receive a lethal treatment at the powdered infant formula manufacturing facility are an extension of the infant formula manufacturing process, particularly when it comes to sanitation controls for production and maintaining a production environment in conditions suitable for producing infant formula. Verifying these conditions at the supplier, as well as informing the suppliers of the intended use of their raw materials or other ingredients, are the responsibility of the powdered infant formula manufacturer.

#### **5) Identifying all relevant biological hazards**

Although much of the recent focus has been on *Cronobacter* spp., FDA reminds the industry that there are other known or reasonably foreseeable biological hazards associated with powdered infant formula. FDA has conducted follow up investigations in response to complaints related to *Cronobacter* spp. infections, *Salmonella* infections, and infant botulism cases among infants who consumed powdered infant formula from a variety of manufacturers.

Historical associations between powdered infant formula and pathogens such as *Cronobacter* spp., *Salmonella*, and *Clostridium botulinum* should be considered when designing and implementing controls for the safe manufacture of all foods for infants and young children. Our regulations define an infant as a person not more than 12 months of age ([21 CFR 106.3](#)). However, many infant formula manufacturers also produce powdered drinks intended for other young children, such as toddler drinks intended for persons aged 12 to 36 months. Although the risk of certain pathogens, such as *Cronobacter* spp., may be lower for persons in this age range than for infants, there is still a risk for some who may have certain medical conditions or reduced immune function. Accordingly, FDA encourages industry to evaluate its practices to mitigate the potential risk of *Cronobacter* spp. and other biological hazard contamination in all foods for infants and young children.

## In Closing

This letter is intended to assist industry in improving the microbiological safety of powdered infant formula. The information shared includes certain observations from recent FDA inspections at facilities involved in the manufacturing of powdered infant formula and subsequent dialogue with those firms. While this letter focuses on certain observations FDA found concerning, the Agency also observed many procedures and practices that were performed in compliance with the applicable regulations.

As stated above, FDA calls on all members of the infant formula industry to use the information in this letter to take prompt action to improve processes and programs for the protection of our most vulnerable population. FDA will continue conducting inspections and working with industry to ensure the safety of all infant formula in the U.S. market. In closing, FDA thanks industry members for improvements made thus far and everyone's continued efforts to ensure the safety of infant formula products in the United States.

Sincerely,



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