CHAPTER 21 - FOOD COMPOSITION, STANDARDS, LABELING, AND ECONOMICS

SUBJECT:	INFANT FORMULA PROGRAM – INSPECTION, SAMPLE COLLECTION AND EXAMINATION
IMPLEMENTATION DATE:	Upon Receipt Pen and ink changes made: 8/5/2025
PRODUCT CODES:	See Table 1
PRODUCT/ASSIGNMENT CODES (PAC)	21006 Infant Formula Survey 21006N Domestic Infant Formula Environmental Samples

NOTE: Infant formula inspections are considered mission-critical activities. Any inspectional activity, for-cause and routine, for infant formula should continue to be prioritized in the event of a public health emergency or other unforeseen situations (e.g., government shutdown)[1].

FDA's Office of Inspections and Investigations, Office of Global and Specialty Human Food Inspectorate (OGSHFI) and Office of Import Operations (OIO) are required to complete 100% of the operations planned in the OII Field Workplan for this program.

[1]Mission-critical activities were prioritized by the FDA during COVID-19 pandemic (Resiliency Roadmap for FDA Inspection Oversight).

Table 1. Product Code Description

Industry Code: 40

Product Description	**Code**
Milk base formula product, powder formula)	40P[][]01
Milk base formula product, liquid concentrate)	40O[][]01
Milk base formula product, ready to feed)	40N[][]01
Soy base formula product, powder formula)	40P[][]02
Soy base formula product, liquid concentrate)	40O[][]02
Soy base formula product, ready to feed)	40N[][]02
Whey base formula product, powder formula)	40P[][]03
Whey base formula product, liquid concentrate)	40O[][]03
Whey base formula product, ready to feed)	40N[][]03
Other formula products, N.E.C., powder formula)	40P[][]99
Other formula products, N.E.C., liquid concentrate)	40O[][]99
Other formula products, N.E.C., ready to feed)	40N[][]99
Milk base human milk fortifier)	40S[][]01
Human milk base human milk fortifier)	40S[][]02
Goat milk base formula product, powder formula)	40P[][]05
Goat milk base formula product, liquid concentrate)	40O[][]05
Goat milk-base formula product, ready to feed)	40N[][]05

FIELD REPORTING REQUIREMENTS:

1. Inspection
   Report all inspections into eNSpect. Scan product labeling, promotional literature and brochures into eNSpect as an exhibit**.** Hard copy establishment inspection reports (EIRs) are not required.

2. Sample Collections and Import Field Examinations
   Report all domestic sample collections in the Field Accomplishment Compliance Tracking System (FACTS).

   Report all import sample collections and field/label examinations in the appropriate import system.

   Report sample collections and/or examinations utilizing the following Problem Area Flags (PAF):

PAF	PAF Description	Product Type
LBL	Labeling	Finished infant formula
MIC	Microbiological Analysis	Finished infant formula for microbiological analysis
NIS	Nutrition Sample Reporting	Finished infant formula for nutrients analysis

3. Analytical

   a) Per FMD-147, Office of Laboratory Operations and Applied Science (OLOAS) laboratories will communicate sample analytical findings to the appropriate compliance units and other FDA stakeholders identified in the compliance program. Preliminary and final results will be communicated using the CRO/Final Result SharePoint Notification tool

   b) All final results will be entered into the Field Accomplishment and Compliance Tracking System (FACTS) and completed analytical worksheet packets will be uploaded to Compliance Management System (CMS) as soon as possible following final result notification.

   c) Per FMD-147 and the Field Science - Laboratory Manual, completed original analytical findings will be submitted electronically to the responsible party named in the Collection Remarks on the Collection Report in an FDA 1551 Form.

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PART I – BACKGROUND

This compliance program provides instructions and tools for FDA investigators, laboratory analysts, and compliance officers. It is a comprehensive approach to covering inspection, sample collection, sample analysis, and compliance activities to accomplish FDA's mission to ensure infant formula products in the U.S. food supply are safe and wholesome.

The term "infant formula" is defined in the Federal Food, Drug, and Cosmetic Act (FD&C Act) in section 201(z) and in Title 21 section 106.3 of the Code of Federal Regulations (CFR) as "a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk." The term "infant" is defined as "a person not more than 12 months of age." (21 CFR 106.3). Furthermore, if a formula is labeled for an age where some of that range includes less than 12 months (e.g., 9 to 18 months), then the product is regulated as an infant formula.

The FD&C Act also provides special requirements for infant formula for infants with special medical and dietary needs. "Exempt infant formula" is a term used for any infant formula that is represented and labeled for use by an infant who has an inborn error of metabolism or low birth weight, or who otherwise has an unusual medical or dietary problem (see section 412(h)(1) of the FD&C Act). Exempt infant formulas are exempt, under section 412(h) of the FD&C Act, from certain aspects of the infant formula requirements. The following link provides a list of exempt infant formula manufacturers and products currently available in the U.S. marketplace: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm106456.htm.

There are three forms of infant formula:

- powder (must be reconstituted with water before feeding);
- ready-to-feed/ready-to-use liquid (do not add water before feed);
- concentrated liquid (must be mixed with water before feeding).

Typically, powder infant formula is manufactured by one of three manufacturing schemes: (1) wet mix/spray dry/powder fill, (2) wet mix/spray dry/dry blend/powder fill, or (3) dry blend/powder fill.

Liquid infant formulas typically undergo processing to make them commercially sterile, but powder infant formula is not sterile. Therefore, powder infant formula requires additional safety considerations and microbiological testing. The microbiological pathogens identified for testing of powdered infant formula are *Cronobacter* species (spp.) and *Salmonella* spp.

A. Pathogens

1. *Salmonella*

   Salmonella is the one of the main causes of foodborne illnesses in the United States. Incidence of salmonellosis in infants (i.e., a person not more than 12 months of age) is ~8 times higher than other age groups. In addition to infants, people with a weakened immune

system such as the elderly are more likely to have severe salmonellosis infections. Some *Salmonella* spp. can survive drying particularly well and are difficult to kill with heat when the *Salmonella* cells are dehydrated or are in low moisture products such as milk powder and powder infant formula. Symptoms of salmonellosis generally develop 12-72 hours following infection and usually lasts four to seven days and most people recover without treatment. Most people with salmonellosis develop diarrhea, fever, and abdominal cramps, and in some rare instances, bacteremia and/or meningitis in infants. More severe cases of salmonellosis may include a high fever, aches, headaches, lethargy, a rash, blood in the urine or stool, and in some cases may be fatal.

2. *Cronobacter*

Cronobacter spp. are gram-negative rod-shaped opportunistic pathogens within the family Enterobacteriaceae. They are naturally found in the environment although the specific reservoir is unknown. They are particularly good at surviving in dry environments and dry food such as milk powder, powder infant formula, starches, and herbal teas. The genus *Cronobacter* consists of seven species: *C. sakazakii*, *C. condimenti*, *C. dublinensis*, *C. malonaticus*, *C. muytjensii*, *C. turicensis*, and *C. universalis*. Although several of those species are capable of causing illness in humans, *C. sakazakii* is the most common species associated with illness. *Cronobacter* is harmless for most people. Typically, *Cronobacter* illnesses occur in infants younger than two months or those with underlying conditions, such as those who are premature, immunocompromised, and/or of low birthweight, although term infants without underlying conditions have experienced invasive *Cronobacter* spp. infections as well. Infections in infants can be deadly, with case-fatality rates ranging from 10% to 80%.

3. Environmental Pathogens

Salmonella spp. and *Cronobacter* spp. are pathogenic bacteria that are particularly well-adapted to survival through prolonged periods of dry/dehydration and other environmental conditions and are difficult to control. These organisms can survive drying particularly well and are difficult to kill with heat when they are dehydrated or in low moisture products. Both *Salmonella* and *Cronobacter* may enter a food facility several ways that can include, but are not limited to:

- Incoming raw ingredients
- Pallets (or skids)
- Personnel and traffic movement
- Equipment design and construction
- Pest vectors
- Facility integrity (roof leaks, etc.)
- Airflow, including dusts and/or aerosols

The growth of these organisms is favored in those areas of a manufacturing plant where water occasionally wets the area, either intentionally as part of periodic wet cleaning, or inadvertently as the result of leaking pipes or valves or a leaking roof. An ideal growth and survival environment is one which periodically gets wet (even if only once every few months) and then takes at least one day or more to fully dry. For example, when equipment is mounted

on the floor of the plant, water may seep under the structure of the equipment and then remain wet for many days. This type of area is considered to be a niche environment that enables the accumulation of residues (food debris, dust, and water). When environmental pathogens become established in a niche environment(s) it may be difficult to locate and eliminate them. These organisms may spread to other areas of the food processing plant from this niche environment(s) by various means such as dust, worker's feet, moving equipment such as forklifts and totes, strong air currents, and water used during wash down procedures, etc. Niche environments may be difficult to inspect or access and therefore can protect pathogens during routine cleaning and sanitizing.

It is important that food processing establishments that are vulnerable to *Cronobacter* spp. or *Salmonella* spp. contamination maintain a food manufacturing environment that is not colonized by these organisms.

Manufacturers or distributors who intend to distribute infant formula products in the United States must comply with applicable requirements in the FD&C Act and its implementing regulations. The implementing regulations are summarized below.

B. Section 412 of the FD&C Act

The FD&C Act has a specific provision that establishes parameters under which an infant formula would be deemed adulterated. Section 412 of the FD&C Act (21 U.S.C. § 350a) states that an infant formula shall be deemed to be adulterated if it (1) does not provide the required nutrients; (2) does not meet the quality factor requirements; or (3) the processing of such infant formula is not in compliance with the good manufacturing practices and the quality control procedures. The requirements for nutrient content are set out in section 412(i) of the FD&C Act and in 21 CFR Part 107. The quality factor requirements, current good manufacturing practice (CGMP), and quality control procedures are described in section 412(b) of the FD&C Act and 21 CFR Part 106.

C. 21 CFR Part 106

Title 21 CFR Part 106 includes requirements for current good manufacturing practice (CGMP), quality control procedures, audits and audit procedures, quality factors, records and reports, and registration, submission, and notification requirements specific to infant formulas.

- Subpart A provides the status and applicability of the regulations in Part 106 and definitions.
- Subpart B contains comprehensive CGMP requirements for infant formula that establish a framework in which specific processes and control decisions are assigned to the infant formula manufacturer. The regulations specify the result to be achieved but do not prescriptively mandate how the manufacturer must achieve the result.
- Subpart C includes quality control procedures that require each manufacturer to test in-process and finished infant formula to ensure that all nutrients required by 21 CFR 107.100 and any other added nutrients are present at appropriate levels. Manufacturers are also required to conduct comprehensive stability testing for new infant formulas and routine stability testing for product subsequently produced.

- Subpart D identifies requirements for audit plans and procedures for infant formula manufacturers.
- Subpart E establishes two quality factors (normal physical growth of infants and sufficient biological quality of protein) for infant formulas.
- Subpart F includes records and reports requirements, including those for CGMPs, quality control procedures such as nutrient testing, audits, complaints, and quality factor requirements.
- Subpart G includes infant formula registration, submission, and notification requirements.

In addition to the production requirements, the revision to Part 106 replaced the terms "batch" and "lot" with two new terms, "production aggregate" and "production unit." The rule defines "production aggregate" and "production unit" in a manner that clarifies the volume of formula and stage of production represented by each term as well as the relationship between the two volumes of formula. FDA used these new descriptors to clarify the quantity of formula associated with the master manufacturing order and with the requirements for microbiological and nutrient testing. *Production aggregate* means a quantity of product, or, in the case of an infant formula produced by continuous process, a specific identified amount produced in a unit of time, that is intended to have uniform composition, character, and quality, within specified limits, and is produced according to a master manufacturing order. *Production unit* means a specific quantity of an infant formula produced during a single cycle of manufacture that has uniform composition, character, and quality, within specified limits. A production aggregate may consist of one or more production units.

D. 21 CFR Part 107

Title 21 CFR Part 107 includes labeling requirements, terms and conditions for exempt infant formulas, nutrient requirements, and information and requirements for infant formula recalls. Subpart A includes the status and applicability of the regulations in Part 107 as well as definitions. Subpart B provides information about labeling of infant formulas including how nutrients are to be listed, specific requirements for directions for use, and exemptions. Subpart B also includes the requirement for inclusion of a "Use by" date on the infant formula product (21 CFR 107.20(c)).

Subpart C establishes the terms and conditions for Exempt Infant Formulas, which are specialty infant formulas intended for use by infants with special medical and/or dietary needs. Section 412(h) exempts these infant formula products from meeting the requirements of sections 412(a), (b), and (c). However, FDA has published guidance recommending manufacturers of exempt infant formulas follow, to the extent practicable, 21 CFR Part 106, Subparts A, B, C, D, and F. See FDA Guidance for Industry, Exempt Infant Formula Production: Current Good Manufacturing Practices (CGMPs), Quality Control Procedures, Conduct of Audits, and Records and Reports, available at: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm384451.htm.

Subpart D provides the nutrient requirements for infant formula, which includes identification of 30 required nutrients (minimum levels per 100 kilocalories for 30 nutrients and maximum levels for 10 nutrients). It also provides additional requirements for specific nutrients.

Subpart E establishes infant formula recall requirements that (1) specify mandatory recall procedures to be used by manufacturers in removing from the marketplace an adulterated or misbranded infant formula that the Agency has determined presents a risk to human health; (2) require a manufacturer recalling an infant formula that represents a risk to human health to request each retail establishment at which such infant formula is sold or available for sale to post a notice of such recall; and (3) establish requirements for retention of infant formula distribution records (54 FR 4006). The Food and Drug Omnibus Reform Act of 2022 included additional requirements related to infant formula recalls (see discussion below).

E. 21 CFR Parts 108, 113, and 114

In addition to complying with 21 CFR Parts 106 and 107, domestic and foreign manufacturers of low-acid and acidified liquid infant formulas must comply with the requirements specified in 21 CFR Part 108 Emergency Permit Control, 21 CFR Part 113 Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers, and 21 CFR Part 114 Acidified Foods as applicable. These regulations address manufacturing, processing, and packing of these products to control microorganisms including *Clostridium botulinum.* When conducting inspections of infant formula that are also subject to Parts 108, 113, and 114, the Acidified and Low-Acid Canned Foods Program – Domestic and Import compliance program should be used as reference.

F. 21 CFR Part 117

Infant formula manufacturers are also subject to the applicable requirements in 21 CFR Part 117. The Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food final rule (CGMP & PCHF rule) includes requirements for current good manufacturing practices (primarily in Subpart B) and hazard analysis and risk-based preventive controls (primarily in subparts C and G). In general, the requirements for hazard analysis and risk-based preventive controls apply to domestic and foreign facilities that manufacture, process, pack, or hold food, including infant formula, for consumption in the United States and must register under section 415(a) of the FD&C Act.

Facilities that are subject to the requirements for hazard analysis and risk-based preventive controls must prepare and implement a written food safety plan under Subpart C. The food safety plan begins with conducting a hazard analysis to identify and evaluate known or reasonably foreseeable hazards for each type of food manufactured, processed, packed, or held at the facility to determine whether there are any hazards requiring a preventive control. The facility must also identify and implement written preventive controls, such as process controls, food allergen controls, sanitation controls, supply-chain controls, and a recall plan, as appropriate, to ensure that identified hazards are significantly minimized or prevented. Preventive controls are subject to preventive control management components including monitoring, corrective actions and corrections, and verification, as appropriate to ensure the effectiveness of the preventive controls.

Facilities are also required to document monitoring, corrective actions, and verification activities performed. Such records are subject to the requirements pertaining to records in Subpart F.

The requirements pertaining to the supply-chain program are in Subpart G. A manufacturer/processor (i.e., a receiving facility) that relies on a supplier to control hazards associated with raw materials or other ingredients must establish and implement a supply-chain program that includes using approved suppliers and determining, conducting, and documenting supplier verification activities. The supply-chain program must provide assurance that any hazards requiring a supply-chain-applied control have been significantly minimized or prevented.

In addition to preventive controls requirements, Part 117 also includes Current Good Manufacturing Practice requirements in Subpart B. Establishments subject to Subpart B, such as infant formula facilities, must ensure that all requirements are met pertaining to personnel, plants and grounds, sanitary operations, sanitary facilities and controls, equipment and utensils, processes and controls, warehousing and distribution, holding and distribution of human food by-products for use as animal food, and defect action levels. Infant formula facilities must meet the CGMP requirements in 21 CFR Parts 106 and 117.

21 CFR Part 117 also establishes in Subpart A requirements for all individuals engaged in manufacturing, processing, packing, and holding food to be qualified individuals and receive training in food safety and food hygiene. The training in food safety and food hygiene must be documented.

G. Food and Drug Omnibus Reform Act of 2022 (PL 117-238)

The Food and Drug Omnibus Reform Act of 2022 included several provisions related to infant formula. A few of the provisions are highlighted here.

The law added new requirements related to infant formula recalls. Section 3401(g) amended section 412 of the FD&C Act. Under new 412(k) of the FD&C Act, FDA is required to notify Congress within 24 hours after the initiation of an infant formula recall under section 412(e) of the FD&C Act. The recall notification must include a summary of specific information related to the recall and an estimate of the disruption in the marketplace. Section 3401(h) of the Food and Drug Omnibus Reform Act of 2022 requires that after initiation of a recall, manufacturers submit a plan to FDA of the actions the manufacturer will take, including to identify and address the root cause and restore operation of the impacted facilities. Section 3401(i) of the Food and Drug Omnibus Reform Act of 2022 requires communication with the manufacturer after an inspection of a facility impacted by a recall, including a substantive response to any corrective actions submitted by the manufacturer.

The law also added requirements related to inspections. Section 3401(i)(3) of the Food and Drug Omnibus Reform Act of 2022 requires an inspection of each domestic and foreign manufacturer every calendar year. Section 3401(i)(2) of the Food and Drug Omnibus Reform Act of 2022 requires timely communication with an infant formula manufacturer following an inspection and requires timely reinspection to ensure corrective actions were accomplished.

Infant formula firms are now also required to develop, maintain and implement, as appropriate, risk management plans to identify and evaluate risks to the supply of the critical food, such as infant formula, and ways to mitigate such risks. This is a new requirement mandated by Congress in the Food and Drug Omnibus Reform Act of 2022. Additional information is forthcoming.

PART II - IMPLEMENTATION

1. Objectives

a) To conduct an annual inspection at each domestic and foreign establishment manufacturing infant formulas for the U.S. market to ascertain the firm's compliance with the applicable requirements of the FD&C Act (e.g., sections 412 and 418) and FDA's regulations under 21 CFR Parts 106, 107, 108, 113, 114, and 117.

b) To collect samples of finished infant formula products at each domestic infant formula facility during annual inspection for nutrient analysis (liquid and powder forms) and microbiological analysis (powdered products only).

c) To perform environmental sampling once a year at each domestic powder infant formula manufacturing facility during annual or compliance follow up inspection for both *Cronobacter* and *Salmonella* analysis if there are no significant adverse supply-chain implications.

d) To collect new and revised labels and labeling of infant formulas (i.e., labels and labeling that are new or have been revised since the last inspection).

e) To increase the collection of samples of foreign manufactured finished infant formula products at the U.S. border, in import status for nutrient analysis (liquid and powdered products) and microbiological analysis (powdered products only) to ensure imported product is safe and comparable to domestically produced infant formula.

f) To ensure that imported infant formulas manufactured by firms that have not filed the required notifications under the Act are reviewed and examined as instructed in Part III of this compliance program.

g) To ensure that infant formulas offered for import as U.S. Goods Returned (USGR) are reviewed and examined as instructed in Part III of this compliance program.

h) To document significant inspectional and violative sample findings and initiate regulatory action(s), as warranted.

2. Program Management Instructions

FDA requirements apply to both domestic and imported products. FDA is committed to ensure the safety and integrity of infant formula through:

- annual inspections of all domestic and foreign facilities that manufacture infant formula for the U.S market,
- sample collections of domestic and imported infant formula for nutrient and microbiological analyses,
- appropriate compliance follow-up activities, and

- appropriate import activities (entry review of admissibility requirements, import examinations, & sample collections) for imported infant formula.

A. Inspection Priorities

FDA conducts annual inspections of all domestic and foreign facilities that manufacture infant formula for the U.S. market. HFP/Nutrition Center of Excellence (NCE)/Office of Critical Foods (OCF) Infant Formula Pre-Market Review Staff (IFPRS) will notify HFP Office of Compliance Operations and Implementation (OCOI) when they complete the review of a submission by a manufacturer or distributor relative to a new infant formula before marketing the products in U.S. commerce. The Office of Compliance Operations and Implementation (OCOI) along with the OII Critical Foods Coordination Team schedule inspections at these facilities and include them in the annual infant formula inspection schedule.

1. Domestic Inspections

HFP NCE OCF shares the name and address of domestic infant formula facilities with the infant formula compliance program monitor in OCOI to schedule inspections. The annual infant formula inspection and sample collection schedule has the current list of domestic infant formula manufacturers in the U.S. that have undergone the required notification procedure.

Division of Compliance Implementation (DCI) and OII Critical Foods Coordination Team prepares the annual inspection schedule that identifies and prioritizes the inspections of domestic infant formula firms based on:

- the facilities' previous inspection results
- number of consumer complaints since the last inspection
- number of violative samples collected by FDA in the last twelve months
- the previous environmental sampling results performed by FDA.

The inspection and sample collection schedule for infant formula is issued in a separate memorandum to OII Critical Foods Coordination Team and copy all Office of Human Food Inspectorates (OHFI) prior to the start of each fiscal year.

Email the Compliance Program Contacts in Part VI of this compliance program if difficulties in implementation are encountered.

When HFP is notified of a new infant formula manufacturer, the OII Critical Foods Coordination Team and the appropriate OHFI will be notified to conduct an unplanned inspection and/or sample collection at this facility.

2. Foreign Inspections

The HFP/NCE/OCF will provide OII Office of Global and Specialty Human Food Inspectorate (OGSHFI)/Division of Foreign Food Inspections and Global Operations

(DFFIGO) the list of foreign infant formula facilities and their addresses. DFFIGO will follow their established procedures to schedule inspections at the foreign facilities. The name and addresses of foreign infant formula facilities that have submitted the notification to HFP/NCE/OCF are listed in Attachment C of this compliance program.

Foreign inspections will not routinely include finished product sample collection for nutrient and/or microbiological analysis. Note: Please notify HFP Regulatory/Compliance Contacts immediately for further instructions if any of the foreign firm's testing results for finished product(s) yield positive results for the targeted pathogens. The investigator should obtain a list of finished product(s) intended to be offered for import into the U.S. If the firm is no longer manufacturing infant formula, or no longer manufacturing infant formula that is intended to be offered for import into the U.S. market, this information must be documented and reported in the EIR.

B. Planning Instructions

Before a new infant formula can be marketed in the United States, the infant formula manufacturer must provide FDA with a notification (i.e., new infant formula submission) about the proposed infant formula as required under section 412 of the FD&C Act. This premarket infant formula submission must contain detailed information about the formulation, an explanation of what has changed (if it is a reformulation), and nutritional and manufacturing assurances, and a demonstration that the formula meets the quality factor requirements.

This compliance program covers inspections of domestic and foreign infant formula manufacturing firms, as well as sample collection and analysis of domestic and foreign manufactured infant formula products for *Cronobacter* and *Salmonella* spp.

Environmental sample collections are planned at least once a year during annual, or compliance follow up inspections at each domestic powder infant formula facility for both *Salmonella* and *Cronobacter* analysis.

C. Interaction With Other Compliance Programs (CP)

The following inspections may be conducted concurrently during an infant formula inspection. Time expended under the following (or other) compliance programs should be reported under the specific Program/Assignment Code(s) for those programs:

a) Medical Foods - Import and Domestic Program, CP (7321.002)
Some infant formula manufacturers also manufacture medical foods. As a result, FDA may schedule an infant formula inspection and medical foods inspection to occur concurrently at such a manufacturing facility.

b) Acidified and Low-Acid Canned Foods Program – Domestic and Import, CP (7303.070)
In addition to 21 CFR Parts 106 and 107, manufacturers of liquid infant formulas are

also subject to the requirements of 21 CFR Parts 108, 113 and 114 as applicable. Therefore, the inspection of liquid infant formula manufacturers should include assessing for compliance with these regulations.

c) Preventive Controls and Sanitary Human Food Operations, CP, (7303.040)
Infant formula manufacturers are subject to the CGMP requirements and the preventive controls requirements in 21 CFR Part 117. Inspections of infant formula manufacturers should primarily focus on compliance with 21 CFR Part 106. However, there are certain requirements in Part 117 that are not addressed in Part 106, therefore, compliance with those requirements will need to be assessed in accordance with CP 7303.040. For specific information regarding requirements to be assessed under Part 117, please see the Infant Formula Resource Page for "Parts 106/117 Citations Table". In addition, inspections at the manufacturers supplying nutrients premix to infant formula manufacturers will be conducted in accordance with CP 7303.040. Further, for Foreign Supplier Verification Requirements (FSVP), see CP 7303.878.

D. Resource Instructions

Resources for inspections, sample collections, examinations, sample analyses, and any emerging issues for infant formula are provided in the OII field workplan. Resources are allocated through a prioritization process by HFP and OII.

E. Interactions with other Federal Agencies, State, and Local Counterparts, and Foreign Authorities

HFP, OII Office of Human Food Inspectorate (OHFI) and Office of Import Operations (OIO) regularly coordinate with other government agencies (OGAs) to take enforcement actions. Agencies retain regulatory authorities but use differing procedures to execute enforcement actions. Primary enforcement authority may be deferred to the agency best equipped to maximize enforcement outcomes and benefit public health.

For example, in the case of a U.S. Customs and Border Protection (CBP) seizure, any Customs officer may seize an imported article under U.S.C. Title 19, if there is reasonable cause to believe that any law or regulation enforced by CBP, Immigration and Customs Enforcement (ICE), or FDA has been violated. FDA may follow standard procedures in assisting CBP or Department of Homeland Security (DHS) in determining violations of the FD&C Act.

PART III – INSPECTIONAL

1. Operations

A. Inspections

General Information

As established in the Food and Drug Omnibus Reform Act of 2022, the FDA must conduct annual inspections at all domestic and foreign infant formula manufacturing facilities required to be registered. Additionally, FDA must reinspect infant formula manufacturers in a timely manner if reinspection is needed to ensure the manufacturer completed any remediation actions or addressed any deficiencies.

Inspections conducted under this compliance program should evaluate industry compliance with applicable regulations including 21 CFR Parts 106 and 107, and, as necessary, 108, 113, 114, and 117.

Refer to Infant Formula and Medical Food Inspection and Sample Collection Schedule for information on infant formula firms and their scheduled inspection dates.

Email the HFP and OII Compliance Program Contacts i) if an inspection cannot be completed as scheduled, ii) to obtain the plant report and to obtain information regarding ongoing activities pertaining to the facility.

See the Guide to Inspections of Manufacturers of Miscellaneous Food Products at http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074988.htm for guidance in conducting inspections. For background information and knowledge on infant formula regulations take the online training, "Infant Formula Regulation Update" at OII LearnED Training System.

When appropriate and as resources permit, HFP and laboratory personnel will accompany the investigator during an infant formula firm inspection.

When conducting inspections, investigations, recall effectiveness checks, or other operations directed by FDA compliance programs, be alert for products promoted as infant formulas but that may not meet the requirements of section 412 of the FD&C Act. Such products have, in the past, been found for sale in health food or natural food stores, in international food markets, or online. If products are found that are not on Attachment C and D of this compliance program, email the HFP Compliance Program Contacts with a copy of the label and labeling.

New Infant Formula or Significant Changes - Information for Attachment A

Attachment A must be completed and sent electronically to the HFP NCE OCF IFPRS, see Part VI of this compliance program upon completion of the inspection.
In advance of each inspection, HFP compliance program monitor will notify the OII Critical Foods Coordination Team with a "plant report" that contains information about infant formula submissions received since the last inspection as well as any special requests for the FDA investigator.

The regulation (21 CFR 106.120(a), (b) and (c)) requires manufacturers of infant formulas to submit notification when there are changes in formulation, processing, or packaging and for first production aggregate stability testing exemptions under 21 CFR 106.91(b)(1)(ii). **Do not** rely solely on HFP notification; the investigator must also ascertain this information from the firm. Specific questions for each of these items are included in Attachment A.

At the beginning of each inspection, obtain information regarding new infant formulas and infant formulas with changes in formulation, processing, or packaging and complete Attachment A.

Per 21 CFR 106.3, new infant formula means (1) an infant formula manufactured by a person (see also the definition of manufacturer in 21 CFR 106.3), that has not previously manufactured an infant formula, and 2) an infant formula manufactured by a person that has previously manufactured infant formula and in which there is a major change in processing or formulation from a current or any previous formulation produced by such manufacturer, or which has not previously been the subject of a submission under **section 412(c) of the Federal Food, Drug, and Cosmetic Act for the U.S. market. For further information, see Regulations and Information on the Manufacture and Distribution of Infant Formula.**

Examples of the types of changes to be reported on Attachment A include the following (see the definition for "major change" in 21 CFR 106.3):

a) Any infant formula produced by a manufacturer who is entering the U.S. market;
b) Any infant formula powder processed and distributed by a manufacturer who previously only produced liquids (or vice versa);
c) Any infant formula having a significant revision, addition, or substitution of a macronutrient (i.e., protein, fat, or carbohydrate), with which the manufacturer has not had previous experience;
d) Any infant formula manufactured on a new processing line or in a new plant;
e) Any infant formula manufactured containing a new constituent not listed in section 412(i) of the FD&C Act (21 U.S.C. § 350a(i)), such as taurine or L-carnitine;
f) Any infant formula processed by a manufacturer on new equipment that utilizes a new technology or principle (e.g., from terminal sterilization to aseptic processing); or
g) An infant formula for which there has been a fundamental change in the type of packaging used (e.g., changing from metal cans to plastic pouches).

The following items pertain specifically to the above submissions and should be submitted with the EIR to determine the significance of the change. The following is relevant, whether or

not the firm has previously reported the change to the Agency, to verify that firms have reported the required data.

a) Results of analyses demonstrating compliance with 21 CFR 106.91(b) (shelf-life stability) must be obtained from the comprehensive stability testing required for new infant formulas and the routine stability testing required for subsequently produced formulas; (note: see section below on 106.91 requirements)

b) Information on homogeneity must be collected when changes in processing occur that could affect the homogeneity of the formula, e.g., change in blending operations, change in point where nutrient is added, etc.;

c) Compare the list of processing changes that HFP has provided with the list of processing changes the firm provides or that are observed during the inspection. Any differences or deviations must be documented in the EIR; and

d) Refer to C. Sample Collection later in this Part for instructions on collecting samples.

Collection of labels and labeling

Collect one original of product labels and labeling (e.g., promotional literature, brochures, physician letters, or web pages) **that are new or revised since the last inspection**. Note that labeling does not include coupons, samples, internal presentations, or promotional materials that are not intended to accompany the product at the point of sale; see the definition of labeling in 21 CFR 1.3(a). Be aware that each product may be produced at different caloric levels; each of these labels should be considered a different product for the purpose of this program. Submit them along with the EIR.

Determine if the firm has any related plants that spray dry, manufacture, or package infant formula.

For manufacturers of finished product infant formulas, determine whether nutrient premixes are supplied by outside firms. Report the names and physical locations of all related plants and firms in the EIR. When inspecting firms that pasteurize, condense or spray dry infant formula ingredients, or dry blend infant formula ingredients, ensure that manufacturing procedures prevent microbial contamination.

Review of Consumer Complaints Files During Inspection

Review consumer complaint files for the time-period since the last infant formula inspection, according to the following procedures. The below information should be included in the EIR. Additional information about manufacturers' responsibilities concerning handling of complaints can be found in 21 CFR 106.100(k).

a) Review the complaint histories for all new or reformulated products. For reformulated products or products that have undergone a processing or packaging change, compare

the complaint history for product before versus after the reformulation, process, or packaging change.

b) For each formula and type (ready to feed, concentrate, powder), determine the number of complaints and the total number classified as possibly involving a health hazard.

c) Report the basis used to determine whether or not a potential health hazard existed.

d) For those complaints found to involve a potential health hazard, report how the firm followed up.

e) Determine which three production aggregates of infant formula had the largest number of complaints involving a health hazard potential. Obtain a listing of those complaints with sufficient information to assess for trends.

Records of Positive Results

Investigators should immediately notify HFP Regulatory/Compliance contact (see Part VI of this compliance program) if they encounter positive finished product sample results or positive environmental sample results during record review.

Inspection for Compliance with Infant Formula CGMP Requirements

The investigator should cover the entire production and in-process control system established by the firm to ensure compliance with 21 CFR 106.5 through 106.90 (Subpart B).

Under 21 CFR 106.6, manufacturers are required to implement a system of production and in-process controls that covers all stages of processing. The system must be set out in a written plan or set of procedures that is designed to ensure that the infant formula is manufactured in a manner that will prevent adulteration and includes:

- establishment of specifications and corrective action plan for when a specification is not met;
- monitoring of the production and in-process control point, step, or stage;
- documented reviews and material disposition decisions for articles not meeting a specification;
- the quarantine of any article that fails to meet a specification pending completion of a documented review and material disposition decision; and
- establishment of recordkeeping procedures that ensure compliance with the requirements in 21 CFR 106.6.

Specific controls are required to prevent adulteration by

- workers (106.10),
- facilities (106.20),
- equipment or utensils (106.30),

- automatic (mechanical or electronic) equipment (106.35), and
- ingredients, containers, and closures (106.40).

Under 21 CFR 106.50, manufacturers are required to prepare and follow a written master manufacturing order that establishes controls and procedures for the production of an infant formula. In 21 CFR 106.55, manufacturers are required to implement controls that will prevent infant formula from adulteration with microorganisms. In addition, controls are specified to prevent adulteration during packaging and labeling (106.60) and on the release of finished infant formula (106.70). Infant formula must be coded with a sequential number that permits identification of the product, including the location where it was packed, and tracing of all stages of manufacture (106.80). See sections 7, 9, 10, and 11 of Subpart B in the Assessment of Compliance with Individual CGMP Requirements below.

Note to investigators: The production aggregate number does not have to match the number on the package so long as the manufacturer is able to link them for traceability.
Ascertain if coding information is used by the firm to control the finished product in the marketplace, and how the firm has outdated product removed from the marketing channels (manufacturing representative visit, retail store management, etc.). Determine disposition of outdated product and amount disposed of in the last year.

Manufacturers of liquid products are required to comply with the procedures specified in 21 CFR Part 113 for thermally processed low-acid canned foods packaged in hermetically sealed containers and 21 CFR Part 114 for acidified foods. Because powdered infant formulas are not sterile products, testing is required for powdered infant formula at the final product stage, before distribution, for two microorganisms, *Cronobacter* spp. and *Salmonella* spp. See section 8 of Subpart B in the Assessment of Compliance with Individual CGMP Requirements below for information on review for compliance with the controls to prevent adulteration from microorganisms.

Review approximately 7 days of production records for one infant formula. The record review should include all records related to CGMPs and quality control procedures required under Subpart F (106.100) and the provisions of Subpart B and Subpart C.

Under 21 CFR 106.90, manufacturers are required to conduct regularly scheduled audits to determine whether their production of infant formula has complied with the CGMPs required under 21 CFR 106.5 -106.80. Manufacturers must provide investigators with access to records assuring that the audits are being conducted but are not required to provide the actual written reports of the audits. See 21 CFR 106.100(j) and section 12 of Subpart B in the Assessment of Compliance with Individual CGMP Requirements below for additional information on CGMP audit requirements.

Inspection for Compliance with CGMP and Preventive Controls for Human Food Requirements in 21 CFR Part 117:
In addition to the Part 106 requirements, investigators should also assess compliance with certain requirements in Part 117, as applicable. These include:

CGMP requirements in 21 CFR Part 117 (Subparts A, B)

- Requirements in 21 CFR 117.4(b)(2) and 117.4(d) pertaining to training in food hygiene and food safety and documentation of that training
- Requirements in 21 CFR 117.10 pertaining to unsecured jewelry; maintenance of gloves; storage of personnel belongings, eating food, chewing gum, drinking beverages, or using tobacco; hand sanitizing; and protection against contamination with perspiration, hair, cosmetics, tobacco, chemicals, and medicines applied to the skin
- Requirements in 21 CFR 117.20(a) pertaining to harborage, roads, yards, parking lots, drainage areas and waste treatment
- Requirements in 21 CFR 117.35(c) pertaining to pest control
- Requirements in 21 CFR 117.95 pertaining to human food by-products for use as animal food
- Requirements in 21 CFR 117.20(b) pertaining to plant construction and design, particularly outdoor bulk vessel storage and adequate screening against pests

Hazard Analysis and Preventive Controls requirements (Subparts C, F, and G)

- Requirements in 21 CFR 117.130 of Subpart C pertaining to conducting and having a written hazard analysis
- Requirements in 21 CFR Part 117, Subpart G pertaining to supply-chain preventive controls
- Requirements in 21 CFR Part 117, Subpart F pertaining to hazard analysis and supply-chain program records

The inspection team should cover supply-chain program requirements, when applicable, under 21 CFR Part 117. Infant formula facilities must establish and implement a written supply-chain program if they receive raw materials or other ingredients where significant hazards are controlled by the supplier. The basic required components include: having a written supply-chain program; using approved suppliers; and determining, conducting, and documenting supplier verification activities to provide assurance that hazards requiring a supply-chain-applied control have been significantly minimized or prevented.

"Parts 106/117 Citations Table" on the Infant Formula Resource Page provides information in the Notes column on when to cite under 21 CFR Part 117.

Assessment of Compliance with Individual CGMP Requirements
Subpart B – Current Good Manufacturing Practice

Specific determinations needed to assess whether manufacturers have complied with each requirement of the CGMP regulations in Subpart B (21 CFR 106.6-106.90) are listed below.

1. Production and in-process controls system (106.6)

   A manufacturer is required to implement a system of production and in-process controls. The system shall 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 shall be designed to ensure that all the requirements of 21 CFR 106, Subpart B are met (21 CFR 106.6(a)).
   Investigators should determine and document whether:

   a. The manufacturer has a production and in-process control system set out in a written plan or set of procedures designed to ensure that an infant formula is manufactured in a manner that will prevent adulteration of the infant formula (21 CFR 106.6(b)).

   b. The manufacturer has established specifications; monitors the production and in-process control point, step, or stage; has established a corrective action plan for use when a specification is not met; reviews the results of monitoring and when a specification is not met, a documented review shall be conducted by a qualified individual to make a material disposition decision to reject, reprocess, recondition, or release the article for use or distribution (21 CFR 106.6(c)).

   c. There is a quarantine system in place designed to prevent the use of an article that fails to meet a specification pending completion of the documented review and material disposition decision (21 CFR 106.6(c)).

   d. The manufacturer has the documentation and records of the monitoring at any point, step, or stage in the manufacturer's production process where control is deemed necessary to prevent adulteration (106.100(e)(3)). Records to be reviewed include:

      i. A list of the specifications established at each point, step, or stage in the production process where control is deemed necessary to prevent adulteration including documentation of the scientific basis for each specification
      ii. The actual values obtained during the monitoring operation, any deviations from established specifications, and any corrective actions taken; and
      iii. Identification of the person monitoring each point, step, or stage in the production process where control is deemed necessary to prevent adulteration).

2. Controls to prevent adulteration by workers (106.10)

   Investigators should determine and document whether:

   a. The manufacturer employs sufficient personnel (qualified by education, training, or experience) to perform all operations, including all required record keeping, in the manufacture, processing, packing, and holding of each infant formula and to supervise such operations to ensure that the operations are correctly and fully performed (21 CFR 106.10(a)).

   b. Personnel working directly with infant formula, infant formula raw materials, infant formula packaging, or infant formula equipment or utensil contact surfaces practice good personal hygiene while on duty to protect infant formula against contamination (106.10(b)). Good personal hygiene, includes:

      i. Wearing clean outer garments and, as necessary, protective apparel such as head, face, hand, and arm coverings (106.10(b)(1)).
      ii. Washing hands in a hand washing facility with soap and running water at a suitable temperature before starting work, after each absence from the workstation, and at other times when the hands may become soiled or contaminated (106.10(b)(2)).

   c. The manufacturer has a process in place to prevent any person with an apparent illness or open lesions that may adversely affect the safety of infant formula from entering the production area until the condition is corrected or resolved. (106.10(c)).

3. Controls to prevent adulteration caused by facilities (106.20)

   Investigators should determine and document whether:

   a. Buildings used in the manufacture, processing, packing, or holding of infant formula are in a clean and sanitary condition (106.20(a)).

   b. The manufacturer has adequate space for the separation of incompatible operations including handling of raw materials, the manufacture of the product, and packaging and labeling operations (106.20(a)).

   c. The manufacturer has separate areas or a system of separation (e.g., computerized inventory control, written card system, automated system of segregation) for holding raw materials, in-process materials, and final infant formula product at the following times (106.20(b)):
      i. Pending release for use in infant formula production or pending release of the final product;
      ii. After rejection for use in, or as, infant formula; and
      iii. After release for use in infant formula production or after release of the final product.

d. There is adequate lighting that allows for the easy identification of raw materials, packaging, labeling, in-process materials, and finished products that have been released for use in infant formula product (106.20(c)).

e. The lighting permits for the easy reading of instruments and controls necessary in processing, packaging, and laboratory analysis (106.20(c)).

f. Lighting fixtures directly over or adjacent to exposed raw materials, in-process materials, or bulk (unpackaged) finished product have protection to prevent broken glass from contaminating the product in the event of breakage (106.20(c)).

g. The manufacturer has adequate ventilation or control equipment, which may include the use of air filtration, to minimize odors and vapors in areas where they may contaminate raw materials, in-process materials, final product infant formula, packing materials, and infant formula-contact surfaces (106.20(d)).

h. Rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents are stored and used in a manner that protects against contamination of infant formula (106.20(e)).

i. The potable water used in the manufacture of infant formula meets the standards prescribed in the Environmental Protection Agency's (EPA's) Primary Drinking Water regulations in 40 CFR 141 (except that the water must not be fluoridated or must be defluoridated to a level as low as possible prior to use) (106.20(f)).

    i. The water supplied is under continuous positive pressure in a plumbing system that is free of defects, and there is no backflow from, or cross-connection between, piping systems that discharge wastewater or sewage and piping systems that carry water for infant formula manufacturing.
    ii. The manufacturer tests representative samples of the potable water drawn at a point in the system in which the water is in the same condition as when used in infant formula manufacturing.
    iii. Review records (106.100(f)(1)) of the frequency and results of the potable water testing. The tests must be conducted no less than annually for chemical contaminants, every 4 years for radiological contaminants, and weekly for bacteriological contaminants.

j. The manufacturer uses only culinary steam at direct infant formula product contact points and the culinary steam is in compliance with the 3-A Sanitary Standards, No. 60903. The boiler water additives in the steam are used in accordance with 21 CFR 173.310 (106.20(h)).

k. The manufacturing site has readily accessible toilet and hand washing facilities that include hot and cold water, soap or detergent, single-service towels, or air dryers; the facilities are sanitary, in good repair and allow for proper disposal of sewage; and the doors to the toilet facility do not open into areas where infant formula, ingredients, containers, or closures are processed, handled, or stored unless alternate means have

been taken to protect against contamination (106.20(i)).

4. Controls to prevent adulteration caused by equipment or utensils (106.30)

   Investigators should determine and document whether:

   a. Equipment and utensils used in the manufacture, processing, packing, and holding of infant formula are:
      i. Of appropriate design and installed to facilitate their intended function, cleaning, and maintenance (106.30(a)) and
      ii. Are constructed so that contact surfaces are made of nontoxic materials and are not reactive or absorptive (106.30(b)).

   b. The manufacturer uses equipment and utensils that are easily cleanable, are able to withstand the environment of their intended use and maintained to protect against contamination of infant formula (106.30(b)).

   c. The manufacturer ensures equipment and utensils used in the manufacture of infant formula are cleaned, sanitized, and maintained at regular intervals (106.30(f)).

   d. The manufacturer has an individual (qualified by education, training, or experience) who conducts reviews of all cleaning, sanitizing, and maintenance to ensure that it has been satisfactorily completed (106.30(f)(1)).

   e. The manufacturer maintains the records for equipment cleaning, sanitizing, and maintenance to document compliance with 106.100(f)(4) (106.30(f)(2)) including:

      i. The date and time of such cleaning, sanitizing, and maintenance; and
      ii. The production aggregate number of each infant formula processed between equipment startup and shutdown for cleaning, sanitizing, and maintenance; and
      iii. The date and signature or initials of the person performing and checking the cleaning, sanitizing, and maintenance indicating that the work was done.

   f. The sanitizing agents used on the equipment and utensils that are regulated as pesticide chemicals under FD&C Act Section 408(a) comply with the Environmental Protection Agency's regulations and if all other such sanitizers comply with applicable Food and Drug Administration laws and regulations (106.30(b)).

   g. The manufacturer has procedures, controls, or a system in place to ensure that any substance required for the operation of infant formula manufacturing equipment (e.g., lubricant or coolant) does not come in contact with formula ingredients, containers, closures, in-process materials, or with infant formula product during the manufacture of an infant formula (106.30(c)).

   h. The manufacturer has procedures, controls, or a system in place to ensure that each instrument used for measuring, regulating, or controlling mixing time and speed,

temperature, pressure, moisture, water activity, or other parameter at any point, step, or stage where control is necessary to prevent adulteration during processing is accurate, easily read, properly maintained, and present in sufficient number for its intended use (106.30(d)).

i. Determine and document if the instruments and controls have been calibrated against a known reference standard at the time of or before first use and at routine intervals as specified by the manufacturer of the instrument or control.
ii. Review the records (106.100(f)(2)) of accuracy checks of instruments and controls. At a minimum, the records must specify the instrument or control being checked, the date of the accuracy check, the standard used, the calibration method used, the results found, any actions taken if the instrument is found to be out of calibration, and the initials or name of the individual performing the test.
iii. Determine if the manufacturer has procedures for actions to take if calibration of an instrument shows failure to meet a specification. If so, determine and document if those procedures include a written evaluation of all affected product and any actions that need to be taken with respect to that product.

i. The manufacturer conducts thermal processing of infant formula packed in hermetically sealed containers. If so, determine whether the equipment and procedures conform to 21 CFR Parts 108 and 113 (106.30(e)(1)).

i. Determine if the manufacturer monitors the temperature in thermal processing equipment at points where temperature control is necessary to prevent adulteration.
ii. Determine if the monitoring is conducted at the frequency required by regulation or necessary to ensure temperature control is maintained.

j. The manufacturer maintains all areas of cold storage at 40 °F (4.4 °C) or below (106.30(e)(2)(i)). If not, determine if the manufacturer maintains cold storage areas at a temperature no more than 45 °F (7.2 °C) and obtain documentation that shows the manufacturer has the scientific data or other information to demonstrate that the time and temperature conditions are sufficient to ensure that there is no significant growth of microorganisms of public health significance (106.30(e)(2)(ii)).

k. Cold storage compartments and thermal processing equipment have easily readable, accurate temperature-indicating devices (106.30(e)(3)(i)).

l. The manufacturer utilizes one of the following methods to ensure that the temperature of each cold storage compartment is maintained (106.30(e)(3)(ii). Review the associated temperature records (106.100(f)(3)).

i. Monitoring the temperature on a temperature-indicating device and recording with such frequency as is necessary to ensure temperature control is maintained;
ii. Equipping with one or more temperature-recording devices that reflects, on a continuing basis, the true temperature within the compartment;

iii. Equipping with a high temperature alarm that has been validated to function properly and records the temperature with such frequency as is necessary to ensure temperature control is maintained; or
iv. Equipping with a maximum-indicating thermometer that has been validated to function properly and records the temperature with such frequency as is necessary to ensure temperature control is maintained.

m. The manufacturer has procedures, controls, or a system in place to ensure that compressed air or other gases that are mechanically introduced into infant formula, that are used to clean equipment, or that come into contact with a surface that contacts ingredients, in-process materials, or infant formula product do not contaminate the infant formula (106.30(g)).

n. The manufacturer has a filter in place capable of retaining particles 0.5 micrometer or smaller, installed as close as possible to the end of the gas line that feeds gas into the space (106.30(g)).

5. Controls to prevent adulteration due to automatic (mechanical or electronic) equipment (106.35)

Investigators should determine and document whether:

a. The manufacturer has written procedures to ensure (that at any point, step, or stage where control is necessary to prevent adulteration of infant formula) all hardware is routinely inspected and checked and that hardware that is capable of being calibrated is routinely calibrated (106.35(b)(1)).

b. The manufacturer checks and documents the accuracy of input into and output generated by any system used in the production or quality control of infant formula (106.35(b)(2)).

c. The manufacturer validates each system prior to the release for distribution of any infant formula manufactured using the system (106.35(b)(3)).

d. The manufacturer revalidates following the modification and prior to the release for distribution of any infant formula manufactured using the modified system, when the system is modified (106.35(b)(4)).

e. There is an individual who is designated to modify software and whether the manufacturer checks the modified software to ensure that infant formula that is produced or analyzed using the modified software is in compliance with CGMP and quality control procedures requirements (106.35(b)(4)).

f. The manufacturer has records for mechanical and electronic equipment used in the production or quality control of infant formula that documents compliance with 106.100(f)(5) (106.35(c)), including:

i. A list of all systems used with a description of the computer files and the defined capabilities and inherent limitations of each system;
ii. A copy of all software used;
iii. Records that demonstrate installation, calibration, testing or validation, and maintenance of the systems used;
iv. A list of all persons authorized to create or modify software;
v. Records that document modifications to software, including the identity of the person who modified the software;
vi. Records that document retesting or revalidation of modified systems; and
vii. A backup file of data entered into a computer or related system. The backup file shall consist of a hard copy or alternative system, such as duplicate electronic records, tapes, or microfilm, designed to ensure that backup data are exact and complete, and that they are secure from alteration, inadvertent erasures, or loss.

6. Controls to prevent adulteration caused by ingredients, containers, and closures (106.40)

Investigators should determine and document whether:

a. The manufacturer has written specifications for ingredients, containers, and closures used in manufacturing infant formula and follows written procedures to determine whether all ingredients, containers, and closures meet these specifications (106.40(d)).

b. An individual (qualified by education, training, or experience) conducted and documented a review and made and documented a material disposition decision to reject, reprocess or recondition, or approve and release the ingredient, container, or closure or the affected infant formula if any specification is not met (106.40 (d)).

c. The manufacturer stores ingredients, containers, and closures in separate areas or with a system of segregation (e.g., computerized inventory control, written card system, or automated system of segregation) clearly designated for materials pending release for use, released for use, or rejected for use in infant formula production (106.40(e)).

d. The manufacturer has a quarantine system in place designed to prevent the use of any ingredient, container, or closure that has been exposed to heat, air, or other condition that may adversely affect it until a documented review and documented material disposition decision can be made (106.40(e)(1)).

i. Determine if the system specifies that any rejected ingredient, container, or closure be clearly identified as having been rejected and controlled under quarantine to prevent its use.
ii. Determine if the system specifies that any ingredient, container, or closure that has not been manufactured, packaged, labeled, or held under conditions to prevent adulteration under section 402(a)(1) through (a)(4) of the Federal Food, Drug, and Cosmetic Act must not be approved and released for use.

e. The manufacturer has records for ingredients, containers, and closures used in the manufacture of infant formula to document compliance with 106.100(f)(6) (106.40(g)), including:

   i. The identity and quantity of each lot of ingredients, containers, and closures;
   ii. The name of the supplier;
   iii. The supplier's lot numbers;
   iv. The name and location of the manufacturer of the ingredient, container, or closure, if different from the supplier;
   v. The date of receipt;
   vi. The receiving code as specified; and
   vii. The results of any test or examination (including retesting and reexamination) performed on the ingredients, containers, or closures; and the conclusions derived therefrom; and the disposition of all ingredients, containers, or closures.

7. Controls to prevent adulteration during manufacturing (106.50)

Investigators should determine and document whether:

a. The manufacturer has a written master manufacturing order that establishes controls and procedures for the production of an infant formula (106.50(a)).

b. The manufacturer has established controls to ensure that each raw or in-process ingredient required by the master manufacturing order is examined by one person and checked by a second person, or system, to ensure that the correct ingredients and weights or measures are added (106.50(b)).

c. The manufacturer has an established system of identification for the contents of all compounding and storage containers, processing lines, and major equipment used during the manufacture of a production aggregate of an infant formula (106.50(c)).

d. The manufacturer has established controls to ensure that the nutrient levels required by 21 CFR 107.100 are maintained in the formula, and that the formula is not contaminated with microorganisms (106.50(d)). Determine and document that the controls include the following:

   i. The mixing time, speed, temperature, and flow rate of product and other critical parameters to ensure the addition of required ingredients to, and the homogeneity of the formula (106.50(d)(1));
   ii. The spray-drying process for powdered infant formula, including the filtering of the intake air before heating, to prevent microbial contamination (106.50(d)(2);
   iii. The removal of air from the finished product to ensure that nutrient deterioration does not occur (106.50(d)(3)); and
   iv. Each container of finished product is properly sealed (106.50(d)(4)).

e. The manufacturer has established controls that ensure equipment used at points where control is deemed necessary to prevent alteration is monitored, so that personnel will be alerted to malfunctions (106.50(e)).
f. The manufacturer has established controls for in-process material(106.50(f)) as follows:

    i. For any specification established in accordance with §106.6(c)(1) that a manufacturer fails to meet for in-process material, an individual qualified by education, training, or experience shall conduct a documented review and shall make a material disposition decision to reject the affected in-process material, to reprocess or otherwise recondition the affected in-process material, or to approve and release the affected in-process material for use or distribution;
    ii. Pending a documented review and material disposition decision, any in-process material that fails to meet any specification established in accordance with §106.6(c)(1) shall be clearly identified as such and shall be controlled under a quarantine system designed to prevent its use in manufacturing or processing operations until completion of the documented review and material disposition decision (106.50(f)(2));
    iii. Any in-process material that has been reprocessed or otherwise reconditioned shall be the subject of a documented review and material disposition decision by an individual qualified by education, training, or experience to determine whether it may be released for use (106.50(f)(3)); and
    iv. Any rejected in-process material shall be clearly identified as having been rejected for use in infant formula and shall be controlled under a quarantine system designed to prevent its use in infant formula manufacturing or processing operations (106.50(f)(4)).

8. Controls to prevent adulteration from microorganisms (106.55)

Investigators should determine and document whether:

a. The manufacturer has an established system of process controls covering all stages of processing that is designed to ensure that infant formula does not become adulterated due to the presence of microorganisms in the processing environment (106.55(a)).

b. The manufacturer of liquid infant formula complies with the procedures specified in 21 CFR Part 113 for thermally processed low-acid foods packaged in hermetically sealed containers and 21 CFR Part 114 for acidified foods (106.55(b)).

c. The manufacturer tests representative samples of each production aggregate of powdered infant formula at the final product stage (before distribution) to ensure each production aggregate meets the microbiological quality standards. Determine and document whether the manufacturer is following the sampling requirements for *Cronobacter* spp. and *Salmonella* spp. (106.55(c)).

d. The manufacturer has the records for the testing of powdered infant formulas for microorganisms to determine and document compliance with 106.100(e)(5)(ii) and (f)(7) (106.55(d)), including:
    i. The results of any testing conducted to verify compliance with the microbiological quality standards in 106.55(e). Any powdered infant formula with a test result of greater than zero for *Cronobacter* spp. or *Salmonella* spp. must be deemed adulterated.
    ii. A full description of the methodology used to test powdered infant formula to verify compliance with the microbiological quality standards.

9. Controls to prevent adulteration during packaging and labeling of infant formula (106.60)

   Determine and document that the manufacturer has procedures, controls, or a system in place to examine packaged and labeled infant formula during finishing operations to ensure that all containers and packages in the production aggregate have the correct label, the correct use-by date, and the correct traceability code.

10. Controls on the release of finished infant formula (106.70)

    Determine and document that the manufacturer has a quarantine system designed to prevent the distribution of each production aggregate of infant formula until it determines that the production aggregate meets all of the manufacturer's specifications.

11. Traceability (106.80)

    Determine and document that the manufacturer codes each production aggregate with a sequential number that identifies the product and the establishment where the product was packed and that also permits tracing of all stages of manufacture.

12. Audits of current good manufacturing practice (106.90)

    Investigators should determine and document whether:

    a. The manufacturer conducts regularly scheduled audits to determine compliance with CGMP regulations.

    b. The individual or team conducting the audits has any direct responsibility for the matters that the individual or team is auditing or have any direct interest in the outcome of the audit. The audit must be unbiased.

Inspection for Compliance with Infant Formula Quality Control Procedures Requirements Subpart C – Quality Control Procedures

The investigator should cover the quality control procedures established by the firm to ensure compliance with 21 CFR 106.91.

1. At times, records of analyses required by the Infant Formula Quality Control Procedures are not available at the plant being inspected but are located in a centralized facility doing the quality control analyses. If analytical records are not available at the plant being inspected, request that the firm obtain the records from the centralized facility for inclusion with the inspection report. If the firm is uncooperative in making this request, report this in the EIR, and submit a request for these records to the OII Inspectional Contact(s), see Part VI of this compliance program, so they can facilitate the collection of records from the centralized facility location.

2. Verify that testing for each nutrient required by 21 CFR 107.100 and any other nutrients added by the manufacturer in every production aggregate occurs prior to product entering interstate commerce. **Document the firm's nutrient testing procedures for the product(s) covered during the inspection on Attachment B**. Obtain any data the firm has on stability testing of their infant formulas as described below for Subpart C.

3. Review manufacturers quality control and audit procedures, and records of exempt infant formulas. For exempt infant formulas, FDA has posted guidance that recommends that manufacturers of exempt infant formulas follow, to the extent practicable, Subparts A, B, C, D, and F of 21 CFR Part 106.

Assessment of Compliance with Individual Requirements for Quality Control Procedures

Specific determinations that are needed to assess whether manufacturers have complied with each requirement of the Quality Control Procedures regulations in Subpart C (21 CFR 106.91 and 106.92) are listed below.

1. <u>General quality control (106.91)</u>

   Per 106.3, the term ***nutrient*** means any vitamin, mineral, or other substance or ingredient that is required in accordance with the "Nutrients" table set out in section 412(i)(1) of the Federal Food, Drug, and Cosmetic Act or by regulations issued under section 412(i)(2) or that is identified as essential for infants by the Food and Nutrition Board of the Institute of Medicine through its development of a Dietary Reference Intake, or that has been identified as essential for infants by the Food and Drug Administration through a Federal Register publication. Investigators should determine and document whether:

   a. The manufacturer tests **each** production aggregate, during manufacture, for nutrients as follows (106.91(a)):

      i. Each nutrient in each nutrient premix used in the manufacture of infant formula that the manufacturer is relying on the premix to provide.
      ii. During the manufacturing process, after the addition of the premix, or at the final product stage (but before distribution), at least one indicator nutrient for each of the nutrient premixes.
      iii. At the final product stage (but before distribution), vitamins A, C, E, and thiamin.

iv. During the manufacturing process or at the final product stage (but before distribution), all nutrients required to be included under 107.100 and any nutrient added by the manufacturer for which testing has not already been conducted under 106.91(a)(1) or (a)(3).

b. The manufacturer tests **each** production aggregate of finished product for nutrients as follows (106.91(b)):

i. For a new infant formula, the manufacturer tests a representative sample of the **first production aggregate** of each physical form for the levels of all nutrients required under 107.100 and all other nutrients added by the manufacturer. The testing required by 106.91(a) can serve as this initial final product testing requirement.
   - Determine if the manufacturer has procedures in place to repeat the testing every 4 months throughout the shelf life of the product. (Note: testing for minerals is not required here.)
   - If not, determine if the manufacturer has an exemption under 106.91(b)(1)(ii) from FDA that exempts them from the requirement of conducting nutrient testing every 4 months for the first production aggregate of a new infant formula.

ii. The manufacturer tests a representative sample of **each** production aggregate of finished product of infant formula in each physical form for the levels of all nutrients required under 107.100 and all other nutrients added by the manufacturer. The testing required by 106.91(a) can serve as this initial final product testing requirement.

iii. The manufacturer repeats such nutrient testing at the **end of the shelf life** of the product.

Note: Infant formula manufacturers may individually request enforcement discretion from the end-of-shelf-life nutrient testing requirement for **each** production aggregate. If granted, the manufacturer must be able to provide evidence of enforcement discretion to the investigator.

c. The manufacturer has procedures to follow if the nutrient testing results show that any required nutrient is not present in the production aggregate at the level required by 107.100 or that any nutrient added by the manufacturer is not present at the level declared on the label. Determine if these procedures require the manufacturer to do the following (106.91(b)(4)):

i. Investigate the cause of the variance in the nutrient level);
ii. Evaluate the significance of the results for other production aggregates of the same formula that have been released for distribution);
iii. Address all production aggregates released and pending release for distribution that are implicated by the test results); and
iv. Determine whether it is necessary to conduct additional testing.

d. The manufacturer conducts all quality control testing using appropriate, scientifically valid test methods (106.91(c)).
e. The records of all nutrient testing performed on the production aggregate of infant formula, including testing performed in-process, at the final product stage, on the finished product, and throughout the shelf life documents compliance with 106.100(e)(5)(i) (106.91(d)). These records must include:

    i. The results of all testing to verify that each nutrient required by 107.100 is present in each production aggregate of infant formula at the level required and that all other nutrients added by the manufacturer are present at the appropriate level;
    ii. A summary document identifying the stages of the manufacturing process at which the nutrient analysis for each required nutrient is conducted; and
    iii. A summary document on the stability testing program conducted including the nutrients tested and the frequency of nutrient testing throughout the shelf life of the product.

2. Audits of quality control procedures (106.92):

Investigators should determine and document whether:

a. The manufacturer conducts regularly scheduled audits to determine compliance with requirements for quality control procedures necessary to ensure that an infant formula provides the required nutrients.

b. The individual or team conducting the audits has any direct responsibility for the matters that the individual or team is auditing or have any direct interest in the outcome of the audit. The audit must be unbiased.

Inspection for Compliance with Infant Formula Quality Factors Requirements
Subpart E — Quality Factors

Eligible Infant Formulas

Determine and document if the manufacturer has made and is retaining records required under 21 CFR 106.96(i)(5) to demonstrate that each of its "eligible" infant formulas (an infant formula that could have been or was lawfully distributed in the United States on December 8, 2014 (106.3)) supports normal physical growth in infants when fed as the sole source of nutrition and that the protein is of sufficient biological quality. The records demonstrating normal physical growth and protein quality required under 106.96(i)(5) are to be made and retained in accordance with 106.100(p)(2) and 106.100(q)(2), respectively.

Copy (as authorized under 106.100(l)) the manufacturer's records required under 21 CFR 106.96(i)(5) and send to the Infant Formula Pre-Market Review Staff (IFPRS) for review to evaluate whether the records comply with the requirements of 106.96(i). If these records have already been provided to the IFPRS from a previous inspection, they do not need to be sent again.

New Infant Formulas that are not Eligible Infant Formulas

Determine and document that the manufacturer has made and is retaining records required under 21 CFR 106.96(d) demonstrating that each of its new infant formulas that is not an eligible infant formula meets the quality factor of normal physical growth. These records are to be made and retained in accordance with 106.100(p)(1) and must include records of a growth monitoring study conducted in compliance with the requirements of 106.96(b) or records demonstrating satisfaction of an applicable exemption under 106.96(c).

Determine and document that the manufacturer has made and is retaining records required under 21 CFR 106.96(h) demonstrating that each of its new infant formulas that is not an eligible infant formula meets the quality factor of sufficient biological quality of the protein. These records are to be made and retained in accordance with 106.100(q)(1) and must include records of an appropriate modification of the Protein Efficiency Ratio (PER) rat bioassay in compliance with the requirements of 106.96(f) or records demonstrating satisfaction of an applicable exemption under 106.96(g).

Note: Infant formula manufacturers are required to submit, as part of a new infant formula submission, the scientific evidence to demonstrate that the formula meets the quality factor requirements or request an applicable exemption and submit the required information for the exemption. This information is reviewed by the IFPRS in HFP.

Inspection for Compliance with Infant Formula Records and Reporting Requirements Subpart F — Records and Reports

See "Infant Formula Records and Reports Inspection Aid" document for a list of all the records requirements.

See above sections on inspections for CGMP, Quality Control Procedures, Audit Procedures, and Quality Factors for specific information on reviews of records during audits.

Inspections of Foreign Manufacturers

The following information must be obtained during foreign inspections in order to assist in identifying future shipments offered for import into the U.S., should inspectional or analytical results warrant additional action:

a) The exact products/brands being exported to the U.S;
b) The means of shipment (e.g., air, sea, truck);
c) The size and frequency of the shipments;
d) The importer(s) of record for the shipments;
e) The U.S. ports where the products are offered for entry; and
f) A list of the U.S. distributors, if available.

The infant formula manufacturer is required to have records for distribution under 106.100(g). Verify the U.S. exporter by reviewing the manufacturer's records.

Inspections of Exempt Infant Formula Manufacturers

Review CGMPs, quality control (QC) and audit procedures, and manufacturer's records. FDA has issued guidance recommending that manufacturers of exempt infant formulas follow, to the extent practicable, the General Provisions (Subpart A), CGMPs (Subpart B), Quality Control Procedures (Subpart C), Conduct of Audits (Subpart D), and Records and Reports (Subpart F) of 21 CFR Part 106 as amended by the final rule published on June 10, 2014, in the production of their formula products. See **Guidance for Industry: Exempt Infant Formula Production (APRIL 2016).** However, because exempt infant formula is not required to meet the processing requirements in Part 106, exempt infant formula manufacturers must not be cited under part 106, except if the manufacturer failed to provide notice of adulteration or misbranding as required under 21 CFR 106.150. Observations at facilities that only manufacture exempt infant formulas must be cited under 21 CFR Part 117.

Follow up and document any observations that indicate that the formula may contain nutrient(s) that it is specifically formulated not to contain.

B. Import Operations

Import activities may include examination, sample collection, or both to verify imported formula meets FDA regulatory requirements.

In the absence of specific instructions outlined in an assignment or other directive, use the information below.

1. Summary of Admissibility Requirements

The FDA will verify compliance with the following requirements at the time of import, as applicable:

a) Manufacturers are registered in accordance with section 412(c)(1)(A) of the FD&C Act.

b) Manufacturer(s) and distributor(s) have submitted information as required by section 412(d)(1) of the FD&C Act (The firms that have met the requirements in (a) and (b) are listed on Attachment C of this compliance program).

c) Infant formula manufacturers that do not meet the above requirements (and are not on Attachment C) or are not on the FDA enforcement discretion list may be subject to Detention Without Physical Examination (DWPE) to prevent the importation of products from non-notified facilities.

d) Product must be labeled in accordance with 21 CFR Parts 101, 107 and 403(w) of the FD&C Act.

e) Exemptions and Special Considerations
   i. Specialty infant formulas, intended for use by infants with special medical and dietary needs, see 21 CFR Part 107 Subpart C - These products should be reviewed according to requirements for conventional foods.
   ii. Infant formula for personal use - FDA typically does not object to the personal importation of infant formula that meet the criteria outlined in the Regulatory Procedures Manual (RPM) Chapter 9, Subchapter 9-2: Coverage of Personal Importations.
   iii. USGR must meet all applicable regulatory requirements. Typically, reasons for returning U.S. manufactured infant formula include quality issues, overstock, product recalls, or packaging and/or labeling issues.
      - USGR must be returning to the original manufacturer.
      - Manufacturers who produce infant formula product for export only must meet requirements as outlined in 21 CFR 106.120(c) including affirmation that the product will not be sold or offered for sale in domestic commerce.

f) Infant formula offered for import does not appear on the list of products in Import Alert #40-05 "Detention Without Physical Examination of Infant Formula Due to Failure to Meet Nutrient and Labeling Requirements". The products listed have either been analyzed by FDA and fail to meet the nutrient requirements applicable to infant formula as specified in 21 CFR 107.100 or were found to be misbranded due to labeling violations.

2. Import Entry Review

Entry review should be performed in accordance with the Investigations Operations Manual (IOM) Entry Review and the Import Summary of Admissibility Requirements section above.

a) Verify infant formula products (finished or base powder) meet or are exempt from associated admissibility requirements.

b) Assign a label examination (LEX/LBL) when:

   i. USGR are not consigned to the original manufacturer which must be listed on Attachment D.
   ii. entry/line is flagged for label examination within the import system.

c) Assign a sample collection when entry/line is part of a sample collection assignment.

3. Import Examinations

a) Examinations should be conducted in accordance with the IOM 6.4, Field Examination.

b) When conducting label examinations verify:

i. that the imported product and manufacturer matches the product and manufacturer listed on Attachment C or Attachment D.
ii. the product is labeled in accordance with 21 CFR 101.2, 101.3,101.4, 101.5, 101.7, 101.15, and 107.20, and 403(w) of the FD&C Act.
iii. If the label does not reveal any apparent violations, a sample may be collected during the examination (see Import Sample Collection below).

c) Special Considerations for all USGR, including export only formula:

i. Determine the intended disposition of the shipment once in domestic commerce (for example, commercial distribution, charitable donation, return for testing, etc.);
ii. Collect evidence to document any violation and the reason the product is being returned to the U.S.

4. Import Sample Collection

Imported infant formula surveillance samples will be collected while in import status, as warranted. Contact the HFP compliance program monitor(s) to determine if there are any supply chain concerns prior to any sampling.

a) Samples of infant formula should only be collected when:

i. requested by HFP compliance program monitor
ii. instructed by an assignment,
iii. identified by import system screening, or
iv. adverse finding(s) is observed during an examination. Adverse conditions that warrant laboratory analysis may include in-transit or storage damage, concerns regarding inadequate storage temperature conditions, strange odors, and/or evidence of over-labeling.

b) Samples should be collected in accordance with the IOM Section 6.4.9-Special Domestic Import Samples.

c) Method of Collection - Samples should be collected and labeled in accordance with IOM Chapter 4: Sampling.

d) Sample Size - See Section D "Sample Size" of this compliance program. Sample Size - See Section C "Sample Size" of this compliance program.

e) Possible sample collections are outlined in "FIELD REPORTING REQUIREMENTS"

C. Sample Collection (During Domestic Inspection)

The samples collected under this compliance program are collected in accordance with the separate inspection and sample collection schedule issued annually by HFP Office of Compliance and Enforcement. However, additional compliance samples should be collected as warranted by inspectional findings.

In general, attempt to collect different products from those collected in recent inspections. Collection of products designed for healthy, full-term infants (i.e., non-exempt infant formula) should be given priority. However, products indicated for treatment of infant health conditions, such as inborn errors of metabolism and low birth weight (exempt infant formulas), can also be collected. If inspectional evidence indicates that an exempt infant formula may contain a nutrient(s) that it is specifically formulated to **not** contain, document the evidence and collect an official sample for laboratory confirmation.

If only bulk product is manufactured by the firm being inspected, submit a request for sample collection to the OII Critical Foods Coordination Team where the finished product is packaged.

Attempt collection from the most recent production date of a production aggregate released by the firm's quality control unit. Note the production date on Collection Reports.

If surveillance activities disclose products which are promoted as infant formulas and which do not appear to meet the requirements of section 412 of the FD&C Act, collect one sample for nutrient analysis as described under the section titled: "Samples for Nutrient Analysis" below.

If a new or reformulated infant formula product is encountered or the firm has introduced changes in its processing, determine if a premarket notification for this product was submitted to HFP IFPRS.

Collect a sample of each new or reformulated product, or product manufactured with revised processing procedures. If more than 1 or 2 new or reformulated products are encountered, contact the Infant Formula Program Contacts (see Part VI) for assistance in prioritizing the sample collections. Follow the sampling guidance below and sample each new or reformulated infant formula for nutrient analysis and, in the case of powders, microbiological analysis. When collecting samples of new or reformulated infant formula or products manufactured with revised processing procedures, make certain to flag the collection report as such.

When samples are collected under this program at the owner named on the label or his agent, a 702(b) portion will not be required (see IOM 4.3.3.2). Firms should be encouraged to collect their own portion for analysis. If necessary, consult with your supervisor and/or the program monitor for further instructions.

Prior to sample collection, email HFP Compliance Program Contacts to check any supply chain issues that may warrant modifying the sampling plan.
After the inspection has been initiated, but prior to collecting samples, determine the firm's policy with respect to FDA standard sampling procedures and solicit the firm's cooperation. If firms do not permit backfilling, determine sample cost and obtain approval of the OII CFC Team prior to sampling.

For domestic samples, follow the infant formula inspection and sample collection schedule issued by HFP to determine the number and types of formulas to be sampled.

Sample Collection During Foreign Inspection

Finished product samples of infant formula produced by foreign manufacturers are not expected to be collected during foreign inspections. Foreign manufactured finished product samples are expected to be collected at the time of import. However, if warranted, additional sampling will be considered during a foreign facility inspection on a case-by-case basis following discussion with HFP. See Import Sample Collection under Import Operations above.

Environmental Sample Collection

Environmental sampling will be conducted at each domestic powder infant formula facility at least once annually and may be collected during annual or compliance follow up inspection to (1) evaluate the firm's processes and procedures to control *Cronobacte*r and *Salmonella* in the processing environment; and (2) conduct environmental sampling to determine whether or not these bacteria are present in the food processing environment of these plants and thus present a risk of product contamination.

During the inspection, collect environmental samples in accordance with SOP-001052 d IOM subchapters 4.3.6.6, 4.3.6.6.1, 4.3.6.6.2 and C.P. 7303.050, Sampling for Foodborne Biological Hazards and Filth, Domestic and Import, while focusing on dry production areas after the final "kill step".

Environmental sampling should focus on zone two sites near potential product exposure points in the process (i.e., transfer points, fluid bed, sifters, rotary valves, man doors into drying system, filling lines, blending equipment, raw material handling equipment, etc.) including any areas indicating water accumulation. Additional sampling should also be done from zone three sites, which may suggest a route of contamination (i.e., doorways, traffic routes, etc.) to dry production areas, finished product or food contact surfaces. Zone one sites should not be swabbed as these zones can be hard to reach and may introduce contamination during swabbing of a closed system. Unless conditions observed indicate a possible route of contamination, we would not recommend swabbing zone four areas at a high frequency.

General Swabbing Areas for Consideration:

- Ceilings, walls, floors, or other surfaces where moisture, leaks, or condensation is observed or where it appears there was moisture or a leak that had dried up
- Inspection doors, hatches, or other entryways used by the firm to gain access to the inside of enclosed production equipment
- Support equipment (e.g., auto-samplers, ladders, lifts, fans, hoists, scales, removable steps, stools, forklifts, pallet jacks, supply cabinets, tools, air intake vents and filters, air supply vents, etc.)
- Cracked and/or exposed pipe insulation, if any
- Sanitation tools and equipment used in post-kill step powder production areas (e.g., brushes, squeegees, mops, vacuums, floor scrubbing machines, water hoses, compressed air hoses, retractable hose reels, etc.)

Collect between 100-300 environmental swabs for *Cronobacter* spp. and collect 100-300 environmental swabs for *Salmonella* spp. at each firm, depending upon the size of the facility.

Use the "Remarks" section of the collection report to identify the zone from which the subsamples (subs) were collected.

D. Sample Size

1. Nutrient analysis

Samples of the finished product will be collected at the manufacturing plant.

Each sample (domestic or import) designated for nutrient analysis by Nutrient Analysis Branch (NAB) is to consist of the following:

a) For one (1) pound powders and eight (8) oz. liquids, collect one **(1) sub** from each of twelve (12) randomly selected shipping cases.

b) For 2 or 3 oz ready-to-feed units, such as Nursettes, collect eight (8) units from each of twelve (12) randomly selected shipping cases. The units from each shipping case may or may not be banded together into 4 packs for distribution.

c) For larger (2.5/5 lbs.) powders and thirty-two (32) oz. liquids, collect one **(1) sub** from each of twelve (12) randomly selected shipping cases.

d) When more than one sub is collected per case, add a letter designation to the sub number (i.e., a, b, c, or d). This will ensure that the portion of the sample analyzed includes product from each case sampled.

2. Microbiological analysis

All **finished dried product** infant formula samples (domestic or import) designated for microbiological analysis, collect one sample from each production aggregate.

Microorganism	Number of samples	Number of sub samples	Sample size/sub	Total amount/sample
Salmonella	**1**	**60**	**25 g (grams)**	**1,500 (grams)**
Cronobacter	**1**	**30**	**10 g (grams)**	**300 (grams)**

a) For *Salmonella* analysis, each sample should consist of a total of 60 cans (for 60 subs) and each sub sample should consist of **twenty-five grams (25 g) or larger**.

b) For *Cronobacter* analysis, each sample should consist of a total of 30 cans (for 30 subs) and each sub sample should consist of **ten grams (10 g) or larger.**

NOTE: i) If the sample is collected for both *Salmonella* and *Cronobacter* analyses, then the sample amount (60 cans/25 g each) collected for *Salmonella* analysis can also be used to perform *Cronobacter* analysis.

ii) Do not submit commercially sterilized products, such as low acid canned foods, for microbiological analysis unless processing records or the appearance of the product containers indicate the product may be microbiologically contaminated.

c) For dry blended products, collect 1 sample (60 subs) of **finished product** and 1 sample (60 subs) of a principal **raw material ingredient** from each production aggregate used in that finished product. When possible, collect an ingredient from the same production aggregate used in the manufacture of the sampled finished product. Collect samples from bulk containers of raw material ingredient using aseptic technique in accordance with IOM Section 4.3.6. Examples of ingredients to be collected include soy powder, nonfat dry milk, dried whey, delactosed whey, demineralized whey, whey protein concentrate, and caseinates. Before collecting carbohydrate or starch-, investigators should consult with the Office of Lab Operations and Applied Science (OLOAS) Contacts /Microbiological Analysis (see Part VI of this compliance program).

NOTE: Since sample requirements are different for the nutritional analysis and microbiological analysis of infant formula samples, separate samples shall be obtained for each.

E. Sample Shipment

Finished products and environmental samples for microbiological analysis may be shipped to any of the following servicing laboratories. Samples for nutrient analysis

may only be shipped to the ATLHAF laboratory. Please refer to the LST dashboard for assistance in selecting a servicing lab.

Send samples to:

Food and Drug Administration
Atlanta Human and Animal Food Laboratory (ATLHAF)
60 8th Street, NE
Atlanta, Georgia 30309

Food and Drug Administration
Arkansas Human and Animal Food Laboratory (ARLHAF)
3900 NCTR Rd. Bldg 26
Jefferson, AR 72079

Food and Drug Administration
Denver Human and Animal Food Laboratory (DENLHAF)
6th Ave and Kipling St.
Building 20, Entrance W-10
Denver, CO 80225

Food and Drug Administration
New York Human and Animal Food Laboratory (NYLHAF)
158-15 Liberty Ave.
Jamaica, NY 11433

Food and Drug Administration
Seattle Human and Animal Food Laboratory (SEAHAF)
22201 23rd Dr. SE
Bothell, WA 98021-4421

Food and Drug Administration
San Francisco Human and Animal Food Laboratory (SANLHAF)
1201 Harbor Bay Pkwy.
Alameda, CA 94502

Food and Drug Administration
Irvine Human and Animal Food Laboratory (IRVLHAF)
19701 Fairchild Rd.
Irvine, CA 92612

Shipping of Environmental Samples:

Divisions must provide advanced notice to laboratory management (>2 days) of the upcoming swab collection to ensure the laboratories have sufficient supplies available for analysis. Field inspection staff must notify the analyzing laboratory via e-mail prior to shipping samples. The

e-mail must contain the sample number(s), the name of this compliance program, storage conditions required, the FACTS number, and sample tracking information. Contact the analyzing lab directly if there are any questions related to the analysis.
Samples should be shipped by UPS "Next Day Air Early A.M." to ensure arrival at the servicing laboratory within 24 hours. Samples may be shipped Monday through Thursday. **Do not** ship samples on Friday. Samples should be stored refrigerated prior to shipment. Ship samples in an insulated transport container with frozen gel packs to keep the samples cold, but not frozen. Field inspection staff may choose to separate samples from the frozen gel packs using cardboard or other material to prevent direct contact and freezing of sample broth.

2. Reporting

a) Report EIR for both domestic and foreign inspections into eNSpect.

b) Collect product labels and labeling (e.g., promotional literature and brochures) **that are new or revised since the last inspection, scan them into eNSpect as an exhibit.** This information will be reviewed by HFP/ONFL/Food Labeling and Standards Staff.

c) Attachment A must be completed and sent electronically to the HFP Infant Formula Premarket Review Staff Contact (see Part VI) upon completion of the inspection when information obtained during the inspection indicates changes in processing or formulation have occurred.

Report all domestic sample collections in the Field Accomplishment and Compliance Tracking System (FACTS).

Report all import sample collections and field/label examinations in the appropriate import system. (See the Field Reporting Requirements section on page 2).

Report domestic sample collections utilizing the following PAC/PAF Combinations:

PAC	PAC Description	PAF	PAF Description
21006	Infant Formula Survey	NIF MIC	Infant formula Survey Reporting Microbiological Analysis
21006N	Domestic Infant Formula Environmental Samples	MIC	Microbiological Analysis
03040U	Focused PCHF	N/A	N/A

PART IV – ANALYTICAL

1. Analyzing Laboratories

For nutrient analysis:

ATLHAF Nutrient Analysis Branch (NAB)

For microbiological analysis:

ATLHAFL/Microbiology Branch
ARLHAFL/Microbiology Branch
DENLHAFL/Microbiology Branch
NYLHAFL/Microbiology Branch
SEAHAFL/Microbiology Branch
IRVLHAFL/Microbiology Branch

Samples collected from the manufacturers that failed to meet premarket notification requirements are to be analyzed for microbiological analysis (*Cronobacter* spp. and *Salmonella* spp.) and abbreviated nutrition analysis testing (4 indicator nutrients). The lab should conduct comprehensive nutrient analysis if the results from the indictor nutrients analysis are negative.

2. Analyses to be Conducted

Nutrients and microbiological analyses

3. Methodology

Sample composites shall be analyzed using a method from the FDA foods program compendium of analytical methods or an AOAC official method, as available and appropriate for infant formula, as shown below. These sources shall take precedence over single lab validated method. All methods must be validated for infant formula, and any method extensions must follow the FDA foods program guidelines for the validation of chemical methods and be completed prior to the submission of regulatory sample results. Any new nutrient analysis methods that are developed and validated must be agreed upon in advance by the HFP Office of Laboratory Operations and Applied Science (OLOAS) and the HFP methods contacts (listed below).

(a) Nutrient Analyses

- Prepare a composite using the AOAC, Current Edition, Method 985.30.
- Assay finished product infant formulas for all nutrients listed in 21 CFR Part 107, Subpart D except for choline, iodine, and inositol.
- Use factor 6.25 to convert nitrogen content to protein for meat/poultry, 5.71 for soy, or 6.38 for milk, as appropriate.

NOTE: The protein content can be calculated from the nitrogen present by applying a factor considered suitable for a particular food. Many commonly occurring proteins contain approximately 16% nitrogen and 6.25 is the factor often used for general purposes. Other more specific factors are available and must be used when appropriate. For example, the factor of 6.38 is appropriate for milk and the factor 5.71 is appropriate for soy protein. If there are any questions, contact HFP OLOAS Method Contacts (see Part VI).

Calculate carbohydrate by difference and kilocalories per unit weight or volume as appropriate. Use the determined kilocalories to calculate nutrient content per 100 kilocalories.

Exempt infant formulas and other specially formulated formulas must be analyzed for all nutrients listed as absent for medical reasons (e.g., "lactose free", analyze for lactose). Analyze the composite by the following methods or validated, equivalent techniques:

Official Methods of Analyses (AOAC) International Current Edition

1. Biotin (Vitamin B_7)	AOAC 2016.02 or LIB 4523
2. Chloride	AOAC 986. 26 or AOAC 2016.03
3. Cobalamin (Vitamin B_{12})	AOAC 2011. 10 or AOAC 2014.02
4. Calcium, Copper, Iron, Magnesium, Manganese, Phosphorous, Potassium, Sodium, and Zinc	AOAC 2011.14 or AOAC 2015.06 or EAM4.4 or 4.7**
5. EFA (Linoleic Acid)	Method AOAC 2012.13 or AOAC 996.01
6. Fat	Method AOAC 2012.13 or AOAC 996.01
7. Folic Acid (Vitamin B_9)	AOAC 2004.05 or AOAC 2011.06
8. Niacin (Vitamin B_3)	AOAC 985. 34 or AOAC 2015.14 or WSV method
9. Pantothenic Acid (Vitamin B_5)	AOAC 2012. 16 or WSV method
10. Proximates (Protein, Ash,	Method 986. 25 or AOAC 990.03
11. Pyridoxine (Vitamin B_6)	AOAC 2004.07 or AOAC 2015.14 or WSV method
12. Riboflavin (Vitamin B_2)	AOAC 985. 31 or AOAC 2015.14 or WSV method
13. Sampling	AOAC 985.30
14. Selenium	Method 2011. 19 or 2015.06 **
15. Thiamin (Vitamin B_1)	AOAC 986. 27 or AOAC 2015.14 or WSV method
16. Vitamin A	AOAC 992.06 or AOAC 2012.10 99992.032016.13
17. Vitamin C	AOAC 985. 33 or AOAC 2012.22
18. Vitamin D	AOAC 2016.05
19. Vitamin E	AOAC 992.03 or AOAC 2012.10
20. Vitamin K	AOAC 999.15 with modifications as needed for specific matrices*

***Note 1:** AOAC Official Method 999.15 is not adequate to extract vitamin K from nutritional products formulated with free amino acids and partially hydrolyzed proteins. For such cases, the publication "Modifications of AOAC Official Method 999.15 to improve the quantitation of vitamin K1 in complex formulated nutritional products" [Schimpf et al., 2010 J. AOAC Int.

93 (2): 650-662 and Delmonte et al., 2013, J. AOAC Int. 96 (1): 91-101] should be consulted and appropriate adjustments made.

****Note 2:** If using an AOAC method for elemental analysis, the inclusion of quality assurance measures included in Elemental Analysis Manual Methods (e.g., digestion blank, sample duplicate, reference material) is required.
Calculate levels detected as follows:

- Convert amount of nutrient found by analysis to units per 100 kcal as listed in section 412 of the Act (i.e., calculate to respective nutrient units)

- Convert amount of nutrient found by analysis to the respective nutrient units declared on the label

(b) Microbiological Analyses

Salmonella

Refer to the BAM Chapter 5: Salmonella | FDA Current Edition.

Perform the following analyses on each sample of soy or milk based finished products and soy or milk-based ingredients.

NOTE: Before proceeding with the following microbiological analyses, prepare **four** composites from the 60 subsamples for *Salmonella* analysis.

Each composite must be prepared as follows:

a) Using subs 1-15 remove 25 ml or g from each of 15 subsamples for a total of 375 ml or g for composite 1; then

b) Using subs 16-30 remove 25 ml or g from each of 15 subsamples for a total of 375 ml or g for composite 2; then

c) Using subs 31-45 remove 25 ml or g from each of 15 subsamples for a total of 375 ml or g for composite 3; then

d) Using subs 46-60 remove 25 ml or g from each of 15 subsamples for a total of 375 ml or g for composite 4; then

e) Analyze each of the four 375 mL or g composites using the instructions below.

NOTE: The VIDAS *Salmonella* SLM as a screening method has been used by FDA field labs in recent years for analysis of samples.

(a) VIDAS *Salmonella* SLM (AOAC OMA method 2004.03)

(b) VIDAS *Salmonella* SLM Easy (AOAC OMA method 2011.03)

NOTE: FDA *Salmonella* qPCR assay as a screening method has been posted on the Foods Program Compendium of Analytical Laboratory Methods | FDA and validated for PIF. Any of the HFP field labs that correctly performed the FDA *Salmonella* qPCR MLV can use the qPCR method for the analysis of PIF.

Isolation and Confirmatory Tests - BAM, Chapter 5

NOTE: The serovar of *Salmonella* that has been identified in the contamination of some dried infant formula samples is *S.* Tennessee*,* a member of *Salmonella* Group C_1. Recent isolates of this serovar from dried products have been **lactose-positive, so please be aware that infant formula can be contaminated with lactose-positive *Salmonella***.

Sample Preparation

Combine 25 g (ml) from each of 15 individual sub-samples into a sterile flask (375 g (ml) composite), or other appropriate container. Add 3,375 ml lactose broth and mix thoroughly to a smooth suspension. Loosely cap the flask. Let stand for 60 ± 5 min. Adjust pH to 6.8 ± 0.2, if necessary. Four composites are prepared. Incubate composite at 35 ± 2º C for 24 ± 2 h.

Testing

After pre-enrichment, samples are to be selectively enriched as described below.

a) For the *Salmonella* culture method, transfer **0.1** ml pre-enriched broth to 10 ml RV medium and 1 ml pre-enriched broth to 10 ml TT. Vortex. Incubate RV medium for 24 ± 2 h at 42 ± 0.2°C and incubate TT broth 24 ± 2 h at 35 ± 2°C. Incubate both RV and TT in a circulating thermostatically controlled water bath. After incubation, follow the BAM Online, *Salmonella,* Chapter 5, section D, *Isolation of Salmonella*.

b) For the **VIDAS SLM Assay for *Salmonella*** (AOAC OMA method 2004.03), transfer 0.1 ml pre-enriched broth to 10 ml RV medium and transfer 1 ml pre-enriched broth to 10 ml TT broth and incubate in a circulating, thermostatically controlled water bath for 6-8 h at 41-42°C. Subculture 1ml aliquots from the incubated TT and RV broths to separate tubes containing 10 ml portions of M- broth (post enrichment) and incubate at 41-42°C for 18-24 h. Continue as described in the kits (AOAC OMA method 2004.03) instructions.

c) For the **VIDAS® Easy** Method (OMA First Action Method 2011.03), transfer 0.1 ml pre-enriched broth to 10 ml SX2 broth and incubate in a circulating, thermostatically controlled water bath for 18-24 h at 41-42°C. Continue as described in the kits instructions (AOAC 2011.03).

d) For the FDA *Salmonella* qPCR method, follow the protocol (https://www.fda.gov/media/168834/download) for sample collection from pre-

enrichment culture (Section D), DNA extraction (Section E) and qPCR analysis (Section F-H). Modified boiling DNA extraction method (E 2) and automatic DNA extraction methods (E 3) are recommended to use for infant formula.

e) Presumptive positive samples must be confirmed culturally by streaking selective enrichments to selective agars as described in the BAM Online, *Salmonella*, Chapter 5, section D-3 and section D-4. Continue as described in the BAM.

Positive Isolates:

Laboratories must perform whole genome sequencing (WGS) upon confirmation of *Salmonella.*

Cronobacter

Refer to BAM Chapter 29 for analysis of finished product and raw ingredients. A draft method to analyze environmental samples for *Cronobacter* is available on Infant Formula Resource Page.

For finished product and raw ingredients that need alternative sample preparation and enrichment procedures, contact HFP OLOAS Method Contacts for specific instructions.

For finished product and raw ingredients, each composite must be prepared as follows:

A) Using subs 1-10, remove 10 ml or grams from each of 10 subsamples for a total of 100 ml or g for composite 1, then;

B) Using subs 11-20, remove 10 ml or grams from each of 10 subsamples for a total of 100 ml or g for composite 2, then;

C) Using subs 21-30, remove 10 ml or grams from each of 10 subsamples for a total of 100 ml or g for composite 3

Analyze each of the 3 composites following BAM Chapter 29: Cronobacter.

HFP laboratories will perform WGS on all *Cronobacter spp*. isolates recovered.

4. Reporting

HFP and OII contact information are provided in Part VI of this compliance program. HFP laboratories will inform ORTS Scientific Program Coordinators (SPCs) to immediately contact HFP Regulatory/Compliance Contacts, the HFP Premarket Notification and Infant Formula Regulations Policy Contact, HFP Compliance Program Contacts, HFP Critical Foods Coordination Team as well as the home HFP OII division when:

- Sample results with the following microbiological values are found:

Salmonella spp.: presence
Cronobacter spp.: presence

- Nutrient levels are found below the minimum or above the maximum permitted in section 412(I) of the Act and 21 CFR 107.100.

Reporting of Results to HFP and OII CFC Team

ATLHAF/NAB should use the following criteria to determine when analytical results should be forwarded to the HFP Regulatory/Compliance Contacts and HFP Compliance Program Contacts for further evaluation:

- The amount of any nutrient in the product is less than the minimum level or greater than the maximum level specified for each 100 kilocalories of infant formula as defined in section 412(i) of the Act and 21 CFR 107.100.

- The calorie, total fat, or sodium content exceeds the value declared on the label by 20% or more.

- For any added vitamin, mineral, protein, or linoleic acid, the nutrient content is not at least equal to the value declared on the label for that nutrient.

- An exempt infant formula that is found to contain a nutrient(s) which it is specifically formulated to not contain.

Per FMD-147, HFP laboratories will communicate sample analytical findings to the appropriate compliance units and other FDA stakeholders identified in Part VI of the compliance program.

- Preliminary and Final results will be communicated using the CRO/Final Result SharePoint Notification tool.

- All final results will be entered into the Field Accomplishment and Compliance Tracking System (FACTS) and completed analytical worksheet packets will be uploaded to CMS as soon as possible following final result notification.

- Per FMD-147 and the HFP Laboratory Manual, completed original analytical findings will be submitted electronically to the responsible party named in the Collection Remarks on the Collection Report in an FDA 1551 Form.

Data Reporting:
Reporting PAC/PAF Combinations

PAC	PAC Description	PAF	PAF Description
21006	Infant Formula Survey	NIF MIC	Infant Formula Survey Reporting Microbiological Analysis
21006N	Domestic Infant Formula Environmental Samples	MIC	Microbiological Analysis

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

The overarching program goal is to ensure that infant formula is safe and meets manufacturing, nutrient, and labeling requirements. The goal of this regulatory strategy is to obtain high rates of industry compliance with requirements applicable to infant formula. As part of FDA's enhanced oversight of infant formula, FDA's regulatory strategy is focusing on taking appropriate, timely action to achieve compliance in an expeditious manner. These actions are intended to drive safety forward and advance the building of a more resilient, safe, and nutritious infant formula supply.

OHAFO and OIO divisions may consider the following when considering an appropriate regulatory response related to infant formula:

1. Situations Presenting a Health Hazard

If a situation poses a possible health hazard, whether it pertains to conditions at a firm or analytical findings, the initial focus will be on the safety of the product and taking action to remove impacted product from the marketplace. If such conditions are identified, the OII CFC Team should contact the HFP Regulatory Contacts immediately. HFP may support proceeding directly to a compliance action such as recall, seizure, injunction, or import regulatory action.

If a review of records during an inspection of the firm's microbiological testing of finished product and/or in-process product has detected *Salmonella* and/or *Cronobacter* that has not been notified to FDA, please notify HFP Regulatory Contacts immediately of these findings. To further assess the firm's evaluation of impacted products and subsequent corrective actions, we would recommend obtaining information surrounding this incident to include:

- name of product(s)
- product type (i.e.: liquid or powder)
- volume of product produced
- routine formula or exempt formula?
- the organism detected
- identification of the manufacturing scheme
  For example: 1) wet-mix/spray-dry or
  2) wet-mix/spray-dry/dry-blend or
  3) dry blend only
- identification of the firm's cleaning and sanitization activity that occurred before and after the lot with the positive finding(s) was produced
- identification of the firm's cleaning and sanitization activity which may have occurred during the production campaign
- corrective actions the firm took in response to the product positive(s)
- copy of the firm's root cause analysis/investigation
- information on how the firm assessed other potentially impacted product within that campaign

- distribution information and/or current disposition of product(s)
  For example: is the product still within the firm's control? If not, what volume of the product was distributed?

Further evaluation of impacted products and subsequent corrective actions may result in the consideration of prompt compliance action, including recall.

2. Domestic and Foreign Inspections

Compliance follow-up inspections: HFP requests communication with OII CFC Team prior to the initiation of a non-routine inspection to discuss strategy and requests updates during the inspection. These updates should include significant findings regarding the firm's microbiological or nutrient testing of finished product and in-process product; significant findings regarding the firm's environmental monitoring program; developing observations of concern to include routes of contamination; and/or findings related to consumer complaint follow up. HFP requests that these inspectional updates be sent to HFP Regulatory Contacts and Compliance Program Contacts listed in Part VI.

Factors to Consider

The following factors should be considered when contemplating a compliance action:

- Is the deficiency indicative of a problem which may lead to a route of contamination?
  Observations associated with potential routes of contamination are significant and would generally warrant a compliance response.

- Is the deficiency an isolated (one-time) situation or a systemic issue?
  An isolated issue (e.g., a piece of equipment dedicated to a low hygiene zone is used in a medium hygiene zone) may be of lesser concern, whereas a pattern of deviations (e.g., equipment is not dedicated to a specific hygiene zone, moves all over the facility without proper cleaning and sanitizing between zones) may be of greater significance.

- Is the finding a first-time observation or repeat over multiple inspections?
  Repeat observations may be more significant because they may be indicative of a general lack of control and inability to make lasting corrections.

- Has the facility been forthcoming with information regarding product positives, and taken appropriate corrective action?

- If the facility had a recent recall related to food safety, is the observation associated with the root cause of the recall?
  Observations associated with the root cause of a recall may be more significant because they may indicate a lack of process controls or may show the firm's inability to fully address product safety issues

Observations of significant public health importance

Observations of significant public health importance are those that have contributed to or have a high likelihood of contributing to product contamination or a failure of the infant formula to provide the necessary nutrients if not corrected. These observations are significant and should be included on a Form FDA 483, Inspectional Observations. An inspection of an infant formula facility that identifies these types of observation(s) will generally be classified as "Official Action Indicated" (OAI) and may require immediate action to address violative product and /or issuance of an advisory action.

Based on review of conditions during recent inspections of infant formula manufacturers, critical findings resulting from evidence collected include:

- Violative results from microbiological testing in finished product or in-processed product samples

- Violative results from nutrient testing:
  - The amount of any nutrient in the product is outside of the specifications in section 412(i) of the Act and 21 CFR 107.100.
  - The analyzed caloric content, total fat, or sodium exceeds the value declared on the label by 20% or more.
  - For any added vitamin, mineral, protein, or linoleic acid, the nutrient content is not at least equal to the value declared on the label for that nutrient.
  - An exempt infant formula is determined by analysis to contain a nutrient(s) that it is specifically formulated to not contain.

- Violative environmental findings for target pathogens (*Salmonella* and/or *Cronobacter*) with no appropriate corrective action.

- Inspectional observations which could contribute to routes of contamination including, but not limited to:
  - Lack of water control in dry production areas
  - Lack of appropriate corrective actions and conducting a root cause analysis/investigation following the isolation of a pathogen from an environmental sample or a product sample
  - Lack of appropriate hygienic zoning controls
  - Facility and/or equipment disrepair

- Failure to conduct an appropriate investigation when information signals a potential problem, such as a consumer complaint.

If the inspectional observations encompass any of the above-mentioned areas of concern, prior to closing out an inspection please schedule a meeting with the HFP Regulatory Contacts to

further discuss. If inspectional or analytical findings warrant regulatory consideration, HFP would consider pursuing an action which may include, warning letter, seizure, or injunction.

Other Observations

Observations that do not fall within the examples above but that could impact the safety of the product or nutrient content if not corrected would normally be included on the Form FDA 483. This would also include observations that could develop into a larger issue if the firm fails to address the problem or fails to monitor the adequacy of their corrective actions. Inspections with these types of observations may be classified as OAI and may result in a regulatory action, especially if the issues are repeated from previous inspections or are indicative of a systemic problem.

Observations that are not likely to have an impact on the safety or nutrient content of the product will generally not be included on the Form FDA 483, unless they are repeat observations. Inspections with these types of observations will usually be classified as "No Action Indicated" (NAI) and the observations will be discussed with facility management. Although these observations are generally not considered significant from a public health perspective, facilities should be encouraged to address these observations during the inspection closeout.

3. Imported Infant Formula

Import divisions should submit a detention recommendation case within CMS to HFP/OCE/OE/Regulatory Contacts (prior to issuing Notice of FDA Action) for infant formula when:

- samples are positive (LC 2 or LC 3) for one or more microbiological analyte(s) of public health significance
    - The most common analytes are *Salmonella* and *Cronobacter;* however, other analytes may be found which support subsequent regulatory action.
    - The HFP Regulatory Contact should be alerted as soon as possible when positive microbiological sample results are identified.

- samples are violative for an abbreviated or comprehensive nutrient analysis (LC 2 or LC 3):
    - The amount of any nutrient in the product is outside of the specifications in section 412(i) of the Act and 21 CFR 107.100.
    - The analyzed calorie, total fat, or sodium content exceeds the value declared on the label by 20% or more.
    - For any added vitamin, mineral, protein, or linoleic acid, the nutrient content is not at least equal to the value declared on the label for that nutrient.
    - An exempt infant formula is determined by analysis to contain a nutrient(s) that it is specifically formulated to not contain.
- the product is misbranded in a significant way

- Examples include: failure to declare an allergen; failure to bear required nutrient information; unauthorized nutrient content or health claims; failure to bear required information in English; failure to bear directions for use.

Detention recommendations must be accompanied by all analytical worksheets and other appropriate documentation (entry paperwork, collection report, labeling, etc.). Division recommendation should include a request for evaluation for the placement of the firm and product on the applicable Import Alert. HFP will review the detention recommendation case concurrently for possible addition to detention without physical examination, as circumstances warrant.

If concurrence for addition of a firm/product to DWPE has been provided by HFP within the detention recommendation case, import divisions should submit a recommendation to OIO/DIO to add the firm/product to DWPE under Import Alert #40-05, "Detention Without Physical Examination of Adulterated and Misbranded Infant Formula," (see import alert for applicable adulteration and misbranding charges) or other applicable Import Alert(s).

Further, screening criteria is a formal request to flag a specific firm and/or product combination to ensure coverage of future shipments to develop additional evidence to support an FDA action. Prior to requesting screening criteria, import divisions should consult with the HFP Regulatory/Compliance Contacts to ensure that holds, investigations, and sampling are appropriate for the specific firm/product combination.

4. Charges

Charges that may be applicable to this program include:

- The product is adulterated within the meaning of section 412 of the Act [21 U.S.C. § 350a] in that (1) such infant formula does not provide nutrients as required by subsection 412(i); (2) such infant formula does not meet the quality factor requirements prescribed by the Secretary under subsection 412(b)(1); or (3) the processing of such infant formula is not in compliance with the good manufacturing practices and the quality control procedures prescribed by the Secretary under subsection 412(b)(2).

- An article of food is adulterated under section 402(a)(4) of the Act [21 U.S.C. § 342(a)(4)] in that it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health.

- An article is misbranded within the meaning of section 403(a)(1)/201(z) of the Act [21 U.S.C. §§ 343(a)(1)/321(z)] in that the label is false or misleading because the product purports to be an infant formula intended to be used as the sole source of nutrition by infants less than 12 months old; however, the product is not labeled as required by 21 CFR Part 107.

- The failure to provide the notice required by section 412(c) [21 U.S.C. § 350a(c)] or 412(e) [21 U.S.C. § 350a(e)], the failure to make the reports required by section 412(f)(1)(B) [21 U.S.C. § 350a(f)(1)(B)], the failure to retain the records required by section 412(b)(4) [21 U.S.C. § 350a(b)(4)], or to fail to meet the requirements prescribed under section 412(f)(3) [21 U.S.C. § 350a(f)(3)] are prohibited under section 301(s) of the FD&C Act [21 U.S.C. § 331(s)].

- The failure of the owner, operator, or agent in charge of a covered facility to comply with the preventive control provisions of the Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food regulation (CGMP & PC rule), Title 21, Code of Federal Regulations, Part 117 is prohibited by section 301(uu) of the FD&C Act [21 U.S.C. § 331(uu)].
  Examples of situations where a preventive controls citation might be used include issues with conducting and having a written hazard analysis (21 CFR 117.130) or establishing and implementing an adequate supply-chain program (21 CFR Part 117, Subpart G).

5. Requirements Related to Recalls

- Under new 412(k) of the FD&C Act, FDA is required to notify Congress within 24 hours after the initiation of an infant formula recall. The recall notification must include specific information related to the recall and an estimate of the disruption in the marketplace.

- Section 3401(h) of the Food and Drug Omnibus Reform Act of 2022 requires that after initiation of a recall, manufacturers submit a plan to FDA of the actions the manufacturer will take, including to identify and address the root cause and restore operation of the impacted facilities (this section sunsets September 30, 2026).

- Section 3401(i) of the Food and Drug Omnibus Reform Act of 2022 requires certain types of communication with the manufacturer after an inspection of a facility impacted by a recall. When conducting an inspection under circumstances covered under this section of the Food and Drug Omnibus Reform Act of 2022, consult with the HFP Regulatory Contact before initiation and close out of the inspection.

PART VI REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

1. References

Guide to Inspections of Manufacturers of Miscellaneous Food Products, Volume II, Section 4. (http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074988.htm)

Federal Food Drug & Cosmetic Action, Section 412 (21 U.S.C 350a)

Code of Federal Regulations, Title 21, Part 106, "INFANT FORMULA REQUIREMENTS PERTAINING TO CURRENT GOOD MANUFACTURING PRACTICE, QUALITY CONTROL PROCEDURES, QUALITY FACTORS, RECORDS AND REPORTS, AND NOTIFICATIONS"
eCFR :: 21 CFR Part 106 -- Infant Formula Requirements Pertaining to Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Records and Reports, and Notifications

Code of Federal Regulations, Title 21, Part 107, "INFANT FORMULA" (including Subpart E - Infant Formula Recalls).
eCFR :: 21 CFR Part 107 -- Infant Formula

Code of Federal Regulations, Title 21, Part 108, "EMERGENCY PERMIT CONTROL"
eCFR :: 21 CFR Part 108 -- Emergency Permit Control

Code of Federal Regulations, Title 21, Part 113, "THERMALLY PROCESSED LOW-ACID FOODS PACKAGED IN HERMETICALLY SEALED CONTAINERS"
eCFR :: 21 CFR Part 113 -- Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers

Code of Federal Regulations, Title 21, Part 114, "ACIDIFIED FOODS"
eCFR :: 21 CFR Part 114 -- Acidified Foods

Code of Federal Regulations, Title 21, Part 117, "GOOD MANUFACTURING PRACTICE, HAZARD ANALYSIS, AND RISK-BASED PREVENTIVE CONTROLS FOR HUMAN FOOD"
eCFR :: 21 CFR Part 117 -- Current Good Manufacturing Practice, Hazard Analysis, and Risk–Based Preventive Controls for Human Food

Link to Exempt Infant Formulas Marketed in the United States By Manufacturer and Category
http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm106456.htm

Link to **Infant Formula Regulation Update** training course LearnED Training System

2. Attachments

(See Infant Formula Resource Page)

A. Reporting Changes in Processing and Reformulation for Infant Formulas
B. Infant Formula Nutrient Information Reporting Form
C. Foreign Infant Formula Manufacturers and Products
D. Domestic Infant Formula Manufacturers and Products

3. Program Contacts

(See "Infant Formula Program Contacts Information" in the Infant Formula Resource Page).

Compliance Program Contacts

Kaniz Shireen, HFP/OCE/DCI/Compliance Program and Assignment Branch,
Email: Kaniz.Shireen@fda.hhs.gov, Phone: (240)-402-2775

Janice King, HFP/OCE/DCI/Compliance Program and Assignment Branch,
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HFP Regulatory/Compliance Contacts

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Darren Morgan, HFP/OCE/OE/DCFDSE/Critical Foods and Labeling Enforcement Branch,
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Daniel Arrecis, HFP/OCE/OE/DCFDSE/Critical Foods and Labeling Enforcement Branch,
Email: Daniel.Arrecis@fda.hhs.gov, Phone: 312-596-4263

HFP Infant Formula Premarket Review Staff Contact

Carrie Assar, HFP/NCE/OCF/IFPMRS
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HFP Office of Lab Operations and Applied Science Contacts

Microbiological Analysis

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Nutrients, Metals Analysis

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OII CFC Team Inspectional Inquiries

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Andrea Charles-Julien, OII/OHFI/OGSHFI/DCSF/CFIB,
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HFP Import Contact

Bobby Hatch, HFP/OCE/OE/DPIE/IEB,
Email: Robert.Hatch@fda.hhs.gov, Phone: (240) 402-6081

OII Office of Import Operations (OIO) Contacts

Allison Scott, OII/OIO/DIO/IOB
Email: Allison.Scott@fda.hhs.gov, Phone: (301) 796-4526

PART VII - CENTER RESPONSIBILITIES

The Office of Critical Foods (OCF) will provide subject matter expertise in the maintenance and evaluation of the compliance program and provide guidance to the Office of Compliance and Enforcement (OCE) with regard to program priorities, relevant evaluation questions, and recommended program changes. The OCE will lead the effort and work in conjunction with OCF to prepare routine compliance program evaluations. Evaluation will be conducted on a periodic basis and outline the program office's current objectives, general and specific program evaluation questions, list recommendations for process improvement, and highlight data patterns and trends for better targeting and resource allocation. The OCE will make these evaluations available internally to FDA. In addition, the OCE will prepare an annual summary report of this compliance program which will be available for internal use only at Compliance Program Summaries.

ATTACHMENT A

Reporting Changes in Processing and Formulation for Infant Formulas

Complete this form and send electronically to carrie.assar@fda.hhs.gov upon completion of the inspection. The information should be submitted whether or not the firm has previously reported the change to the Agency because many firms report insufficient data for the Agency to determine the significance of the change.

FIRM NAME _____

FIRM ADDRESS _____

1. Nature of the change: Processing_____ Formulation_____ Packaging_____

2. Has the company reported the change to FDA in accordance with 21 CFR 106.120(a), (b) and (c)?
   Yes____ No ____. If yes, report the date the company reported the change:

3. Name of the infant formula and forms (i.e. liquid, powder, concentrate) involved in the change:

4. Describe the change in detail:

5. Describe purpose(s) or reason(s) for the change:

6. List nutrients changed (if any) and the target levels in the final product before and after reformulation:

7. Describe equipment, processing, and packaging changes (if any) and their purpose:

8. Describe all testing completed or underway (chemical and biological) to assure compliance with nutrient requirements of section 412(i) of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR 107.100 or any other nutrient added by the manufacturer.

9. Describe all testing completed or underway to assess nutrient bioavailability in the final product to assure compliance with section 412(a)(2) (specific testing required by 21 CFR 106.96(b) and (f) or exemptions as provided for under sections 106.96(c) and (g) for non-eligible infant formulas and the records required under 106.96(i) for eligible infant formulas):

10. Has the firm submitted the verification notification required under 106.130?

11. Attach new labels if change resulted in any label changes. (attach additional sheet(s) if necessary)

ATTACHMENT B

Infant Formula Nutrient Information Reporting Form

This form is to be completed during each inspection of a finished product manufacturing process. It is intended to show the source of nutrients, at what stage of the manufacturing process they are analyzed, and the analytical methods used. Indicate the source of the nutrient using the abbreviations at the end of the form, on page 2, of this Attachment. Indicate the stage of the process by placing an "X" in the appropriate box. Indicate the method reference by giving specific number (e.g., AOAC #), or by general description (ICP, GC, etc.). Send the completed form along with the Summary of Findings to HFP Contacts.

PRODUCT:_____

FIRM NAME:_____

FIRM ADDRESS:_____

FEI:_____

FORM OF PRODUCT (READY TO USE, POWDER, CONCENTRATE):_____

DATE:_____

Nutrient	Source*	Raw Material	In Process	Finished Product	Method Reference
Protein					
Linoleic Acid					
Fat					
Carbohydrate					
Vitamin A					

Nutrient	Source*	Raw Material	In Process	Finished Product	Method Reference
Thiamine (Vitamin B_1)					
Riboflavin (Vitamin B_2)					
Niacin (Vitamin B_3)					
Vitamin B_6					
Vitamin B_{12}					
Folic Acid					
Pantothenic Acid					
Biotin					
Vitamin C					
Vitamin D					
Vitamin E					
Vitamin K					
Choline					
Inositol					
Calcium					

Nutrient	Source*	Raw Material	In Process	Finished Product	Method Reference
Phosphorus					
Magnesium					
Iron					
Iodine					
Zinc					
Copper					
Manganese					
Sodium					
Potassium					
Chloride					
Selenium					
Other					

*FSPM - Fat Soluble Premix, WSPM - Water Soluble Premix

MPM - Mineral Premix IA - Independent Addition, FB - Formula Base

ATTACHMENT C

Infant Formula Products Manufactured by Foreign Manufacturers

Attachment C has updated list of foreign infant formula manufacturers, posted on Office of Compliance SharePoint site.

ATTACHMENT D

Infant Formula Products Manufactured by Domestic Manufacturers

Attachment D has updated list of domestic infant formula manufacturers, posted on Office of Compliance SharePoint site.