

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

SUBJECT: INFANT FORMULA PROGRAM – IMPORT AND DOMESTIC		IMPLEMENTATION DATE: 07/10/2018
DATA REPORTING		
PRODUCT CODES		PRODUCT/ASSIGNMENT CODES
40P[] []01 (milk base formula product, powder formula) 40O[] []01 (milk base formula product, liquid concentrate) 40N[] []01 (milk base formula product, ready to feed) 40P[] []02 (soy base formula product, powder formula) 40O[] []02 (soy base formula product, liquid concentrate) 40N[] []02 (soy base formula product, ready to feed) 40N[] []03 (whey base formula product, ready to feed) 40P[] []99 (other formula products, N.E.C., powder formula) 40O[] []99 (other formula products, N.E.C., liquid concentrate) 40N[] []99 (other formula products, N.E.C., ready to feed)		21006

NOTE: The work to be accomplished under this compliance program has been identified as high priority by CFSAN. The firms to be inspected and the products to be collected are considered high risk because of the susceptible population for which the products are intended. ORA Office of Human and Animal Food Operations (OHAFO) and Import Program divisions are required to complete 100% of the operations planned in the ORA Field Workplan for this program.

FIELD REPORTING REQUIREMENTS:1. Inspection

Report all inspections into eNSpect. Scan product labeling, promotional literature and brochures into eNSpect as an exhibit. Hard copy EIRs are not required.

2. Analytical

- a) Forward a copy of the complete analytical worksheet for all samples classified as lab class “2” or “3” to the Compliance Branch of the home OHAFO or Import Program division (and notify the collecting OHAFO or Import Program division if they are not identical) for regulatory follow-up immediately upon completion.
- b) Report results of all analyses into the Field Accomplishment and Compliance Tracking System (FACTS).

Contents

PART I – BACKGROUND	4
PART II - IMPLEMENTATION	8
1. Objective	8
2. Program Management Instructions	8
PART III - INSPECTIONAL	10
1. Operations	10
A. Inspections.....	10
B. Import Operations	26
C. Sample Collections	29
2. Hardcopy Reporting.....	33
PART IV - ANALYTICAL	35
1. Analyzing Laboratory	35
PART V - REGULATORY/ADMINISTRATIVE STRATEGY	41
PART VI- REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS	43
1. References	43
2. Attachments.....	43
A. Attachment A	46
B. Attachment B	49
C. Attachment C	52
D. Attachment D.....	53
3. Program Contacts	42
A. Compliance Program Monitor.....	42
B. Regulatory Contact.....	42
C. Policy Contact.....	42
PART VII - CENTER RESPONSIBILITY	45

PART I – BACKGROUND

The term “infant formula” is defined in the Federal Food, Drug, and Cosmetic Act (the 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.” While there is no statutory definition of “infant,” the definition in 21 CFR 106.3 of FDA regulations is “a person not more than 12 months of age.”

The 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 Act). Exempt infant formulas are exempt under section 412(h) of the Act from certain aspects of the infant formula requirements. The link to exempt infant formula manufacturers and products currently available in the U.S. marketplace is:

<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm106456.htm>.

To ensure the adequacy of the composition of infant formulas, section 412 of the Act and FDA regulations provide for, among other items:

- a) A definition of an “adulterated” infant formula product;
- b) Notification to the Secretary of Health and Human Services, of new infant formula products and changes in the formulation or processing procedures of infant formula products;
- c) Recall procedures (21 CFR 107.200);
- d) Minimum nutrient levels, and in some cases maximum nutrient levels, that infant formula products shall contain;
- e) NEW: Current good manufacturing practices (CGMPs) requirements specific to infant formula manufacture (21 CFR 106, Subpart B (106.5—106.90));
- f) NEW: Specific nutrient testing requirements to ensure appropriate levels of all nutrients required under 21 CFR 107.100 and any other nutrients added by the manufacturer in finished product and stability testing (21 CFR 106, Subpart C (106.91));
- g) NEW: Records and reports requirements for CGMPs and quality control procedures, including nutrient and microbiological testing (21 CFR 106, Subpart F (106.100(c), (e), (f), and (h)));
- h) Access to and the right to copy and verify records (21 CFR 106.100(l));
- i) Access to records assuring that regularly scheduled audits are being conducted, although the actual written report of such audit need not be made available (21 CFR 106.100(j));
- j) NEW: Access to quality factor records for growth monitoring studies and protein quality testing and records of exemption from testing by FDA (21 CFR 106.100(p), (q), and (l)).

- k) Access to complaints and complaint files (21 CFR 106.100(k) and (l)); and
- l) Certain exemptions from the nutrient requirements, CGMPs and quality control procedure requirements, and labeling requirements for infant formulas that are represented for use by infants who have an inborn error of metabolism or low birth weight or who otherwise have an unusual medical or dietary problem.

21 CFR Part 106

Title 21 CFR Part 106 sets forth regulations for the manufacture and quality evaluation of infant formulas. Because the 1986 Amendments to the Act mandated additional quality control and GMP regulations as well as quality factor requirements for infant formulas, FDA published a final rule to implement the 1986 Amendments on June 10, 2014 (FR Vol. 79, No. 111, pg. 33057). With one exception, the compliance date for the regulations was September 8, 2014. The compliance date for the exception (demonstration that eligible infant formulas meet quality factor requirements) in section 106.96(i) was November 12, 2015.

Title 21 CFR Part 106 includes new requirements for CGMPs, quality control procedures, audits and audit procedures, quality factors, and records and reports specific to infant formulas. 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 and do not prescriptively mandate how the manufacturer must achieve the result. Quality control procedures in Subpart C require each manufacturer to test in-process and final 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 subsequently produced product. Subpart D identifies requirements for audit plans and procedures for infant formula plants. Subpart E establishes two quality factors (normal physical growth of infants and sufficient biological quality of protein) for infant formulas.

Title 21 CFR Part 106, Subpart F, Records and Reports, was amended to include records and reports requirements for the new CGMPs, quality control procedures, and quality factor requirements. Together with previous requirements for records and reports in 21 CFR 106.100, these regulations establish requirements for records concerning:

- (1) food packaging materials;
- (2) nutrient premix testing;
- (3) current good manufacturing practices (CGMPs) for production and control of each production aggregate;
- (4) quality control procedures;
- (5) nutrient levels and testing results at the final product stage;
- (6) verification of nutrient levels present through the “use by” date on product;
- (7) microbiological and purity testing of raw materials and finished product;
- (8) distribution of infant formula;
- (9) manufacturer’s audits;
- (10) complaints; and
- (11) quality factors.

*Note: the terms “batch” and “lot” were replaced in the infant formula rule 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 contemplated by each term as well as the relationship between the two volumes of formula. FDA did not intend to introduce new concepts or to make significant changes. Rather, the Agency is using 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.

Failure to comply with the requirements for records and reports renders the formula adulterated.

The regulations also define administrative requirements as to where, how, and for how long the records are to be maintained.

In particular, the section pertaining to consumer complaints provides the Agency the authority to review the complaints received by manufacturers in a comprehensive manner, and requires that manufacturers maintain procedures describing how all written and oral complaints will be handled. Refusal of access to or copy of records as required by section 412 is a prohibited act under section 301(e) of the Act.

In addition to the records and reports requirements in Subpart F, requirements to establish recordkeeping procedures and to make and retain records are part of the CGMP requirements in Subpart B.

21 CFR Part 107

The revised infant formula nutrient requirements (21 CFR 107, Subpart D) of the Act became effective January 14, 1986, for all affected products initially introduced or initially delivered for introduction into interstate commerce on or after that date (FR, Vol. 50, No. 210, Oct. 30, 1985, pgs. 45106-45108). On June 23, 2015, FDA added selenium to the list of nutrients required in infant formulas and set minimum and maximum levels for the mineral (FR, Vol. 80, No. 120, June 23, 2015, pgs. 35834–35841). The effective date for the mandatory addition of selenium was June 22, 2016.

The infant formula labeling requirements (21 CFR 107, Subpart B) became effective January 14, 1986, for all affected products (FR, Vol. 50, No. 9, Jan. 14, 1985, pgs. 1833-1841).

21 CFR 107, Subpart C, “Exempt Infant Formulas” became effective February 20, 1986, and established the terms and conditions under which those specialty infant formulas, intended for use by infants with special medical and dietary needs, will continue to be exempt from some requirements of the Infant Formula Act of 1980 (FR, Vol. 50, No. 226, Nov. 23, 1985, pgs. 48183-48188). Section 412(h) exempts these infant formula products from meeting the requirements of sections 412(a), (b), and (c). However, FDA has published guidance indicating that manufacturers of exempt infant formula products follow, to the extent practicable, 21 CFR 106 Subparts A, B, C, D, and F (FR, Vol. 81, No. 73, April 15, 2016, pg. 22174–22175). See

<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm384451.htm>.

21 CFR 107, Subpart E, “Infant Formula Recalls” became effective March 28, 1989, with 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 may present 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 (FR, Vol.54, No. 17, Jan. 27, 1989, pgs. 4006-4009).

PART II - IMPLEMENTATION

1. Objective

- a) To conduct an 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 section 412 of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA's implementing regulations under 21 CFR Parts 106 and 107.
- b) To collect samples of infant formulas during each domestic and foreign inspection for nutrient analysis (liquid and powder forms) and microbiological analysis (powdered products only).
- c) To collect new and revised labels and labeling of infant formulas (i.e., labels and labeling that are new or have been revised since last inspection).
- d) To ensure that imported infant formula manufactured by firms that have not filed the required notifications under the Act are monitored as instructed in Part III of this program.
- e) To ensure that infant formulas that are offered for import as U.S. Goods Returned are monitored as instructed in Part III of this program.

2. Program Management Instructions

The Act and FDA regulations apply equally to infant formulas produced in this country and infant formulas produced in other countries and imported into this country for distribution. Because of the susceptible population for which infant formulas are intended, the Agency is committed to assuring their continued safety and integrity through annual inspections of all infant formula manufacturers in the U.S. and those that export to the U.S.

Domestic

CFSAN/Office of Compliance/Division of Field Programs and Guidance will provide the inspection schedule that identifies the domestic firms to be inspected in a separate memorandum prior to the start of each fiscal year. **NOTE: The inspection schedule is also now located through links on the CFSAN/Office of Compliance intranet website.**

<http://inside.fda.gov:9003/CFSAN/OfficeofCompliance/default.htm>. Domestic inspections and sample collections are also entered into FACTS. In order for the Office Regulatory Science-Southeast Food and Feed Laboratory or any selected ORS lab to receive a steady flow of samples, it is imperative that this schedule be followed. **Contact the Infant Formula Program Manager at Kaniz.Shireen@fda.hhs.gov (240) 402-2775 if difficulties in implementation are encountered.**

When CFSAN is notified of a new infant formula manufacturer or a new or reformulated infant formula product, the appropriate OHAFO division may be contacted to conduct an unplanned inspection and/or collect samples. Attachment D is the current list of infant formulas manufactured in the U.S. that have undergone the required notification procedure.

Foreign Inspections

The CFSAN/Office of Nutrition and Food Labeling (ONFL) will contact all foreign firms to work on scheduling an inspection prior to each fiscal year. ONFL will provide OHAFO the list of firms and inspection dates and OHAFO will be contacting divisions during the fiscal year to arrange for an inspection to be conducted at each foreign firm listed on [Attachment C](#). The inspection will include collection of appropriate samples for nutrient and/or microbiological analysis and labels/labeling (only labels/labeling that are new or have been revised since the last inspection). Only products intended for export into the U.S. are to be sampled. Documentation of product exported to the U.S. must be collected and included as part of each EIR. If the firm is no longer manufacturing infant formulas, or no longer manufacturing infant formula that is distributed in the U.S. market, this information must be documented and reported in the EIR. The firm will be removed from the inventory and inspection schedule.

Import entries must be examined as described in Part III – Import Operations.

Note: Import Alert #40-04 “Detention without Physical Examination of Infant Formulas that have not Been Through the Required Notification Process” has been deactivated.

Import Alert #40-05 “Detention Without Physical Examination of Infant Formula Due to Failure to Meet Nutrient and Labeling Requirements” is active. The products listed on the Red List of this alert 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.

3. Program Interaction

During operations conducted under other FDA compliance programs, OHAFO and Import Program division personnel should be alert for products which may be represented as infant formulas, but that do not meet the requirements of section 412 of the FD&C Act. Such products have, in the past, been produced/promoted by firms that have not complied with the premarket registration and submission requirements of the Act. Report such surveillance coverage under this program (PAC 21006).

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) Preventive Controls in Human Foods Inspections, DFIG Assignment #18-03;
- b) Import Acidified and Low-Acid Canned Foods Program, C.P. 7303.003;
- c) Medical Foods - Import and Domestic Program, C.P. 7321.002; and
- d) Domestic Acidified and Low-Acid Canned Foods Program, C.P. 7303.803A;

PART III – INSPECTIONAL

1. Operations

A. Inspections

General Information

If problems are encountered with the inspection schedule discussed in Part II, Page 1, notify the Infant Formula Program Manager at Kaniz.Shireen@fda.hhs.gov (240-402-2775). The inspection schedule lists the week of inspection and sample collection. This scheduling is necessary to ensure an even sample flow to the laboratory.

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. To gain background information and knowledge on infant formula regulations take the online training, “Infant Formula Regulation Update” at <https://orauportal.fda.gov/stc/ora/psciis.dll?COURSE=ora&CODE=FD9000W>. When appropriate, chemists and/or microbiologists should accompany the investigator. A subject matter expert (SME) from CFSAN/ONFL will accompany the OHAFO division investigator on inspections of foreign firms when available.

When conducting inspections, investigations, recall effectiveness checks, or other operations directed by FDA compliance programs or assignments, 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, or in ethnic markets. Now such products may also be found for sale online.

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

New infant formula means (1) an infant formula manufactured by a person 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. Examples of the types of changes to be reported on Attachment A include the following:

- 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 Federal Food, Drug, and Cosmetic 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).

Attachment A must be completed and sent electronically to the Infant Formula and Medical Foods Staff Team Leader at carrie.assar@fda.hhs.gov upon completion of the inspection. In advance of each inspection, CFSAN will notify the OHAFO divisions of new infant formulas; changes in formulation, processing, or packaging; requests for quality factor information; and first production aggregate stability testing exemptions under 21 CFR 106.91(b)(1)(ii) that the firm has filed under the submission requirements of the Act. **Do not** rely solely on CFSAN notification; the investigator must also ascertain this information from the firm. Specific questions for each of these items are included in Attachment A.

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 the 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 CFSAN 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 3. 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. 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 or not 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 preclude microbial contamination.

Review consumer complaint files, according to the following procedures, at those firms identified in the inspection schedule with “(COMPLAINTS)” after the firm name. This information review should cover the time period since the last infant formula inspection.

- 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) Determine 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.

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.

This 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).

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 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 includes:

- establishment of specifications and corrective action plans,
- documented reviews and material disposition decisions for articles not meeting a specification, and
- the quarantine of any article that fails to meet a specification pending completion of a documented review and material disposition decision.

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 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 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 G, I, J, and K of Subpart B in the Assessment of Compliance with Individual CGMP Requirements below for information on review for compliance with these requirements.

Evaluate compliance with the requirements of 21 CFR 106.80 (coding information). See section K of Subpart B in the Assessment of Compliance with Individual CGMP Requirements below for information on review for compliance with these requirements. (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.

Controls are also required to prevent adulteration of infant formula from microorganisms (106.55). 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 H 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 L of Subpart B in the Assessment of Compliance with Individual CGMP Requirements below for additional information on CGMP audit requirements.

Notes on Inspections of Exempt Infant Formula Manufacturers, Premix Manufacturers, and Foreign Manufacturers

Exempt: Review CGMPs, 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 CGMPs, quality control procedures, conduct of audits, and records and reports requirements required for manufacturers of nonexempt products. See <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm384451.htm>.

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

Premix: Infant formula premix manufacturers are covered under this program and will be inspected on an annual basis. However, firms that produce premixes are not subject to comprehensive infant formula inspections as outlined below. Section 412(b)(4)(A)(iii) of the Act and 21 CFR 106.100(d) require that premix manufacturers retain all records necessary to confirm the accuracy of all premix certifications and guarantees of analysis. Those records include the following: the results of tests

conducted to determine the purity of each ingredient; the weight of each ingredient added; and the results of any quantitative tests conducted to identify the nutrient levels present when the premix reaches its expiration or shelf life date. Inspections of premix manufacturers should be focused on these requirements and the general Good Manufacturing Practice (GMP) regulations described in 21 CFR Part 110 or 117 and any other relevant regulations.

Foreign: The following information must be obtained during foreign inspections in order to facilitate detention of future entries, should inspectional or analytical results warrant such 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.

Assessment of Compliance with Individual CGMP Requirements

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.

Subpart B Current Good Manufacturing Practice

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

Note: 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 CGMP requirements of this subpart are met.

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.
- b. The manufacturer has a corrective plan for when a specification is not met that includes a documented review to be conducted by a qualified individual to make a material disposition decision to reject, reprocess, recondition, or release the article for use or distribution.
- 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.
- d. Investigators should review 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. Records to be reviewed [106.100(e)(3)] 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 in the following areas:
 - i. Manufacture of infant formula
 - ii. Processing of infant formula
 - iii. Packing of infant formula
 - iv. Holding of infant formula
 - v. Supervision of all operations to ensure correctly and fully performed
 - vi. Recordkeeping
- b. Personnel working directly with infant formula practice good personal hygiene while on duty to protect against the contamination of raw materials, packaging, or equipment or utensil contact surfaces, including:
 - i. Wearing clean outer garments and, as necessary, protective apparel such as head, face, hand, and arm coverings.
 - 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 work station, and at other times when the hands may become soiled or contaminated.
- 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 the production area until the condition is corrected or resolved.

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.
- 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.
- 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:
 - 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.
- e. The lighting permits for the easy reading of instruments and controls necessary in processing, packaging, and laboratory analysis.
- 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.
- 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.
- 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.
- 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).
 - 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 waste water 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.
- 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 in good repair and sanitary 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.

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 and
 - ii. Are constructed so that contact surfaces are made of nontoxic materials and are not reactive or absorptive.
- 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.
- c. The manufacturer has procedures to ensure equipment and utensils used in the manufacture of infant formula are cleaned, sanitized, and maintained at regular intervals.
- 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.
- e. Review the records [106.100(f)(4)] for equipment cleaning, sanitizing, and maintenance to determine and document compliance with 106.100(f)(4) including:
 - i. The date and time of such cleaning, sanitizing, and maintenance;
 - 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 21 U.S.C. 346(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.
- 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.
- 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.
 - 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.
 - 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. 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.
 - k. Cold storage compartments and thermal processing equipment have easily readable temperature-indicating devices.
 - l. The manufacturer utilizes one of the following methods to ensure that the temperature of each cold storage compartment is maintained. 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.
 - n. If compressed gas is used to replace air removed from the headspace of containers, the manufacturer has in place a filter 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.

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.
- 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.
- c. The manufacturer validates each system prior to the release for distribution of any infant formula manufactured using the system.
- d. When any system is modified, the manufacturer revalidates following the modification and prior to the release for distribution of any infant formula manufactured using the modified system.
- 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.
- f. Investigators should review the records for mechanical and electronic equipment used in the production or quality control of infant formula to determine and document compliance with [106.100(f)(5)], 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.

- b. If any specification is not met, 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.
 - 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.
 - 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.
 - 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. Investigators should review the records for ingredients, containers, and closures used in the manufacture of infant formula to determine and document compliance with 106.100(f)(6), 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.
- 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.
- 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.
- 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. Determine and document that the controls include the following:
 - i. The mixing time; the 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;
 - ii. The spray-drying process for powdered infant formula, including the filtering of the intake air before heating, to prevent microbial contamination;
 - iii. The removal of air from the finished product to ensure that nutrient deterioration does not occur; and
 - iv. Each container of finished product is properly sealed.
 - 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.
 - f. A manufacturer shall establish controls for in-process material 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;
 - 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; 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.
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.
- b. The manufacturer of liquid infant formula complies with the procedures specified in 21 CFR 113

for thermally processed low-acid foods packaged in hermetically sealed containers and 21 CFR 114 for acidified foods.

- 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.
- d. Investigators should review 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), 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

The investigator should cover the Quality Control Procedures established by the firm to ensure compliance with 21 CFR 106.91 (Subpart C).

1. Frequently, 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 OHAFO division where the centralized facility is located.
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 in Section A of Subpart C in Assessment of Compliance with Individual Requirements for Quality Control Procedures.
3. Review quality control and audit procedures, and records of manufacturers 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 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) are listed below.

*Subpart C — Quality Control Procedures*1. General quality control (106.91)

Note: 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:
 - 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:
 - 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 have individually requested 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 include the following:
 - i. Investigates the cause of the variance in the nutrient level;
 - ii. Evaluates the significance of the results for other production aggregates of the same formula that have been released for distribution;
 - iii. Addresses all production aggregates released and pending release for distribution that are implicated by the test results; and
 - iv. Determines whether it is necessary to conduct additional testing.
- d. The manufacturer conducts all quality control testing using appropriate, scientifically valid test methods.
- e. Review 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 to determine and document compliance with [106.100(e)(5)(i)]. 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.

Assessment of Compliance with Individual Requirements for Quality Factors

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 and Medical Foods Staff (IFMFS) for review to evaluate whether the records comply with the requirements of 106.96(i). If these records have already been provided to the IFMFS 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 IFMFS in CFSAN.

Subpart F — Records and Reports

See “Infant Formula Records and Reports Inspection Aid” document for a list of all the records requirements:

<http://inside.fda.gov:9003/downloads/ProgramsInitiatives/Food/FieldPrograms/UCM512568.pdf>

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

B. Import Operations

This section is related to Part V – Regulatory/Administrative Strategy section. Below you will find informational components as well as instructions for conducting import operations/investigations.

During operations conducted under other FDA compliance programs, OHAFO and Import Program division personnel should be alert for products which may be represented as infant formulas, but that do not meet the requirements of section 412 of the FD&C Act. Such products have, in the past, been produced/promoted by firms that have not complied with the premarket registration and submission requirements of the Act. Report such surveillance coverage under this program (PAC 21006).

Refer to Attachments C and D for firms who have complied with the premarket registration and submission requirements. When in doubt as to whether an infant formula has complied with the premarket registration and submission requirements, contact CFSAN/OC/DE for guidance (see contact information in Part VI).

Infant Formula Import Entries, or shipments of infant formula offered for entry by a firm, may be classified into four different categories:

- i. From one of the manufacturer/product combinations listed in Attachments C or D, other than those products falling under iii. or iv below.
- ii. From one of the manufacturer/product combinations NOT listed in Attachments C or D. These products are considered new infant formulas and therefore may not be permitted for the U.S. market in accordance with section 412 of the Act. Refer to instructions for entry review of infant formula products below, and the corresponding action item in Part V – Regulatory/Administrative Strategy, as necessary.
- iii. From one of the manufacturer/product combinations listed in Attachment D which has been exported and is being offered for re-import into the U.S., to a destination that is not the original manufacturer. Refer to the section on U.S. Goods Returned below for operational instructions, and the corresponding regulatory action item in Part V – Regulatory/Administrative Strategy, as necessary.
- iv. Products manufactured in the U.S. labeled for “Export Only” which are being offered for re-import into the U.S. These products may not meet the U.S. nutrient requirements because they were designed for the country to which they were originally exported. Refer to the section on U.S. Goods Returned & “Export Only” Formula below for operational instructions, and the corresponding regulatory action item in Part V – Regulatory/Administrative Strategy, as necessary.

Infant Formula Entry Review

All entries containing infant formula product codes are flagged for manual review within Entry Review (ER).

- a) Refer to Attachments C and D for manufacturer/product combinations that have complied with the premarket registration and submission requirements. These line(s) of infant formula from the indicated manufacturers are eligible for release without additional

follow-up, unless other compliance concerns exist or the articles are considered U.S. goods returned as outlined below.

- b) If the manufacturer/product combination is not on Attachment C or D, contact CFSAN/OC/DE (see Part VI) to determine if additional follow-up is warranted. CFSAN/OC/DE will review recall, outbreak or related information to help determine next steps, and subsequently respond back to the Import division with a recommendation for examination and/or sample collection, as warranted. Follow-up may include, but is not limited to, the following activities:
 - 1. Label examination (LEX/LBL)
 - 2. Sample collection for microbiological analysis (generally for *Cronobacter* spp. and/or *Salmonella* spp.)
 - 3. Sample collection for nutrition analysis (CFSAN will indicate the nutrient analyses to request)

U.S. Goods Returned

Shipments that fall into categories “iii” and “iv” above are considered “U.S. Goods Returned”. Import divisions shall examine the entry documentation, attempt to determine why the product is being returned to the U.S., and determine intended disposition.

- a) Obtain any documents accompanying the entry, which may help identify whether the product was originally manufactured, distributed, or packed by one of the U.S. or foreign manufacturers listed in Attachment C or D. Such information includes package codes, lot numbers, and product labels;
- b) Determine the intended disposition of the shipment once in domestic commerce (for example, commercial distribution, charitable donation, return for testing, etc.); and
- c) Obtain additional distribution information from the importer of record or consignee, if possible.

When it is determined that the entry is considered “U.S. Goods Returned”:

- a) If the shipment is not being returned to the original manufacturer, the Import division shall contact CFSAN/OC/DE and provide the indicated information above. CFSAN/OC/DE will review recall, outbreak or related information to help determine next steps, and subsequently respond back to the Import division with a recommendation for examination and/or sample collection, as warranted.
- b) If the shipment is consigned to the original U.S. manufacturer, the Import division shall:
 - contact CFSAN/OC/DE and provide the indicated information above. CFSAN/OC/DE will review recall, outbreak or related information to help determine next steps, and subsequently respond back to the Import division with a recommendation for examination and/or sample collection, as warranted.; and,
 - notify the home OHAFO division responsible for the manufacturer so that they may verify the disposition and manufacturer’s records for the returned product(s) during the next inspection;
- c) The shipment should be examined and sampled for laboratory analysis if there is other reason to believe that an appearance of a violation may exist. Goods should be detained with the appropriate charge when they are or appear violative, based on examination of samples or otherwise.

“Export Only Formula”

When infant formula is labeled for “Export Only” and being re-imported into the U.S, the Import division shall notify the home OHAFO division of the U.S. manufacturer so that they can follow-up on the firm’s intention for disposition of the product.

Refer to section on U.S. Goods Returned above for additional operational guidance.

The home OHAFO division should also be referred to the requirements of “Export Only” manufacturers in regards to these products:

- a. Infant formula manufacturers who produce an infant formula product for export only must make a submission to FDA that complies with 21 CFR 106.120(c):
 - Manufacturers may submit, in lieu of the information required under paragraphs 21 CFR 106.120(b)(5) and (b)(6), a statement certifying that the infant formula meets the specifications of the foreign purchaser, the infant formula does not conflict with the laws of the country to which it is intended for export, the infant formula is labeled on the outside of the shipping package to indicate that it is intended for export only, and the infant formula will not be sold or offered for sale in domestic commerce. Such manufacturer shall also submit a statement certifying that it has adequate controls in place to ensure that such formula is actually exported out of U.S. commerce. The components of that statement are consistent with the requirements of 801(e).
- b. Manufacturers are required by 21 CFR 106.100(g) to keep records showing that the product is actually exported. Such records shall include all information and data necessary to effect and monitor recalls of the manufacturer's infant formula products in accordance with subpart E of part 107.

C. Sample Collection**General Guidance**

In general, the samples collected under this program are surveillance samples collected in accordance with the separate schedule issued by the Infant Formula Compliance Program Contact, CFSAN/OC/HFS-615. However, additional compliance samples should be collected as warranted by violative 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 first 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 OHAFO division 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 CFSAN.

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 Contact at 240-402-2775 or, CFSAN/ONFL at 240-402-2373 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.

Do not commingle production aggregates.

Domestic Inspection Samples

Because samples collected under this program are collected at the owner named on the label or his agent, a 702(b) portion will not be collected (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.

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 OHAFO division office prior to sampling.

The inspection schedule provided in a separate memorandum (and also available on CFSAN/Office of Compliance intranet website) has additional guidance for sample collection. The link is <http://inside.fda.gov:9003/ProgramsInitiatives/Food/FieldPrograms/ucm015774.htm>

Foreign Inspection Samples

Infant formulas produced by foreign manufacturers that have filed the appropriate notifications under the Act are listed on Attachment C. These infant formulas will be sampled during the annual inspection conducted at each foreign manufacturer. **The general guidance provided for above applies equally to foreign inspection samples.** Sample only those formulas and production aggregates intended for export to the United States. The infant formula manufacturer is required to have records for distribution under 106.100(g). Verify the U.S. export by reviewing the manufacturer's records. Obtain the additional information on product export listed under "**Note Regarding Foreign Inspections.**"

To lessen the burden on investigators conducting foreign inspections and sample collections, the following method is to be used for sampling these products: 1) investigator selects the formula to be sampled, using the criteria above; 2) investigator seals the number of units required for analysis as discussed below; 3) investigator provides a pre-addressed international mailing label(s) for the firm to use to mail the sample to the OHAFO division investigator's U.S. address.

The investigator must mark the mailing label(s) as follows: **“U.S. FOOD AND DRUG ADMINISTRATION OFFICIAL SAMPLE—DO NOT REMOVE OR OTHERWISE TAMPER WITH THIS LABEL OR SHIPPING CONTAINER. U.S. CUSTOMS AND BORDER PROTECTION CONTACT INSERT INVESTIGATOR’S SUPERVISOR NAME AND PHONE NUMBER UPON RECEIPT OF THIS SHIPMENT.”**

The sampling OHAFO division should notify ORA/OHAFO/Office of the Director if any product sampled in the foreign firm is not received in the division within a reasonable time. Upon the investigator’s return to the U.S., a collection report must be prepared and the sample immediately forwarded to the analyzing laboratory upon its receipt.

Shipping Instructions for FDA samples collected during a foreign establishment inspection to the US:

The Division of Food Defense Targeting (DFDT) and the Division of Import Operations (DIO) will help coordinate the entry of these shipments.

After the sample has been collected and is ready, but before they are delivered to the carrier:

Email DIO (ORA OEIO DIO Directors) and DFDT (ORA Prior Notice Watch Commanders (see addresses below)) with the following information:

- Name of carrier (UPS, FedEx, etc)
- Date to be shipped
- Tracking number(s)
- Number of packages
- Declared contents (we recommend "FDA Food Sample for analysis")
- Product(s): Description of product(s), sample size including individual retail package size (if collected),
- FDA Lab and address to be shipped to
- Name and office address for the contact point (Person shipping the sample)
- Manufacturer: Name and full address of the facility who manufactured the product(s)

The DFDT is available to file and provide Prior Notice (PN) confirmation numbers 24 hours a day, 7 days a week. Once the PNs are filed, the DFDT will provide the PN confirmation numbers by return e-mail so that they can be provided to the carrier at the time they are delivered for shipment. If necessary, the shipper can call or email the DFDT at any time and ask for the Watch Commander on duty. If contacting the DFDT by phone, please call direct @ 571-468-1488 or, if able to call toll free, use 866-521-2297.

If sending an email, it should be addressed to ORAPriorNoticeWatchCommanders@fda.hhs.gov, and ORAHQOEIODIRECTORS@FDA.HHS.GOV

DIO will handle any issues that may arise with the entry of this shipment.

Imports

Infant formulas may be sampled and analyzed for the following nutrients: vitamins A, D, C, and E, thiamine/thiamin (vitamin B₁), total metals (calcium, phosphorus, magnesium, iron, zinc, manganese, copper, sodium, selenium, and potassium) and chloride. CFSAN/OC will specify the nutrient analyses

indicated from their review of the product. The analytes indicated by the Center must be specified in the collection report.

In addition, infant formulas may be sampled and analyzed for microbiological contamination (and reviewed for labeling compliance) in accordance with guidance contained in this program to determine compliance with the Act. CFSAN/OC will specify the microbiological analyses (and any necessary sampling parameters outside of those indicated below under 'Samples for Microbiological analysis') indicated from their review of the product. The analytes indicated by the Center must be specified in the collection report.

Samples for Nutrient analysis

For domestic samples, follow the schedule issued by CFSAN to determine the number and types of formulas to be sampled.

Do not collect nutrient premixes during inspections of premix manufacturers. 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 four (2 or 3) oz. units, such as Nursettes, collect two **(2) subs** from each of twelve (12) randomly selected shipping cases.
- 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.

Samples for Microbiological analysis

All **finished dried product** infant formula samples (domestic or import) designated for microbiological analysis, collect 1 sample from each production aggregate.

Microorganism	Number of samples	Number of sub samples	Sample size/sub	Total amount/sample
<i>Salmonella</i>	1	60	25 g (grams)	1,500 (grams)
<i>Cronobacter</i>	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 sample from bulk containers of raw material ingredient using aseptic technique in accordance with [IOM Section 4.3.6](#). For more guidance on aseptic technique, investigators may consult the course [Food Microbiological Control 10: Aseptic Sampling](#), which is available to FDA employees through the ORAU intranet site. Examples of ingredients to be collected include soy powder, nonfat dry milk, dried whey, delactosed whey, demineralized whey, whey protein concentrate, caseinates.

NOTE: Since sample requirements are different for the nutritional analysis and microbiological analysis of infant formula samples, separate samples should be obtained for each referencing the parameters which follow.

D. Sample Shipment

Samples for nutrient analysis and/or microbiological analysis

Send samples to:

Food and Drug Administration
Southeast Food and Feed Laboratory (SFFL)
60 Eight Street, NE
Atlanta, Georgia 30309

Note on the C/R and FDA-525 whether the sample is to be analyzed by the Nutrient Analysis Branch (NAB), HFR-SE680, (404-253-1181) or the Microbiology Branch HFR-SE670, (404-253-1179).

Contact the appropriate SFFL unit in advance of shipment to provide the shipping details.

Samples collected for routine surveillance purposes do not need to be accompanied by EIRs when forwarded to SFFL/NAB (HFR-SE680) or SFFL/Microbiology Branch (HFR-SE670). However, compliance samples should have a copy of the EIR submitted to the laboratory as soon after sample submission as possible to assist the laboratory in analyzing the sample.

2. Hardcopy Reporting

- a) Report EIR for both domestic and foreign inspections into eNSpect. **No need to mail hardcopy EIR to the Center.**
- 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 CFSAN/ONFL/Food Labeling and Standards Staff (HFS-820).

- c) Attachment A must be completed and sent electronically to Infant Formula Program at carrie.assar@fda.hhs.gov upon completion of the inspection when information obtained during the inspection indicates changes in processing or formulation have occurred.

PART IV - ANALYTICAL

NOTE: NAB MUST USE THE METHODS LISTED BELOW FOR ALL NUTRIENT ANALYSES. HOWEVER, IF NEW NUTRIENT ANALYSIS METHODS ARE DEVELOPED AND VALIDATED, THEY MUST BE AGREED UPON IN ADVANCE BY THE OFFICE OF REGULATORY AFFAIRS-OFFICE OF FOOD AND FEED LABORATORY OPERATIONS AND THE CFSAN METHODS CONTACTS. FOR OTHER ANALYSES, ANY NEW METHODS USED MUST BE VALIDATED AND MEET OR EXCEED THE PERFORMANCE CHARACTERISTICS OF THE CITED METHODS PRIOR TO THEIR USE.

1. Analyzing Laboratory

For nutrient analysis and label review:

SFFL/Nutrient Analysis Branch(NAB), HFR-SE680

For microbiological analysis:

SFFL/Microbiology Branch, HFR-SE670

Samples collected from the manufacturers that failed to meet pre-market 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 indicator nutrients analysis are negative.

2. Label Reviews

SFFL (NAB and/or Microbiology Branch) will review the labels of all samples using 21 CFR Part 101 and 107.

3. 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 107 Subpart D except for choline, iodine, and inositol.

Use factor 6.25 to convert nitrogen content to protein if 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 Dr. Gregory Noonan (HFS-715) at (240-402-2250).

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. Sampling	Method 985.30
2. Proximates	Method 986. 25 or AOAC 990.03 (PROTEIN)
3. Vitamin C	Method 985. 33 or AOAC 2012.22
4. Thiamin (Vitamin B ₁)	Method 986. 27 or AOAC 2015.14
5. Riboflavin (Vitamin B ₂)	Method 985. 31 or AOAC 2015.14
6. Vitamin B ₆	Method 2004.07 or AOAC 2015.14
7. Vitamin B ₁₂	Method 2011. 10 or AOAC 2014.02
8. Niacin (Vitamin B ₃)	Method 985. 34 or NAB Level II validated LCMS method
9. Chloride	Method 986. 26 or 2016.03
10. Phosphorus	Method 986.24 or 984. 27 or 2011.14
11. Vitamin A	Method 2012.10
12. Vitamin D	Method 992.26 or 995. 05 or AOAC 2016.05
13. Vitamin E	Method 2012.10
14. Vitamin K	Method 999.15 with modifications as needed for specific matrices* or LIB 4557
15. Folic Acid	Method 2004.05 or AOAC 2011.06
16. Pantothenic Acid	Method 2012. 16 or NAB Level II validated LCMS method
17. Calcium, Copper, Iron, Magnesium, Manganese, Potassium, Sodium, and Zinc	Method 985.35 or 984. 27 or AOAC 2011.14 or AOAC 2015.06 or EAM 4.7
18. Fat	Method 2012.13
19. EFA (Linoleic acid)	Method 2012.13
20. Selenium	Method 2011. 19 or 2015.06 or EAM 4.7

FDA-IFC Collaborative Study Methods

20. Biotin Proc. Soc, Explt, Biol. Med. 56:95, 1944 c (modified) - Extraction - IN H₂SO₄

***Note 1:** AOAC Official Method 992.27 was the only method available for analysis of vitamin K prior to approval of Official Method 999.15. AOAC Official 992.27 is no longer used. 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 JAOAC Internatl. 93 (2): 650-652 and Delmonte et al., 2013, JAOAC Internatl. 96 (1): 91-101] should be consulted and appropriate adjustments made.

Note 2: AOAC Official Method 996.01 is applicable to cereal products. AOAC Official Method 996.06 is more appropriate and should be used.

Note 3: AOAC Official Method 996.01 cannot be used to measure cis- or trans- fatty acids. Consult CFSAN (Dr. Gregory Noonan, above) for recommendations on appropriate methods.

Calculate levels detected as follows:

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

4. Microbiological Analyses

SFFL must refer to the guidance contained in the ORA-LAB.002, Standard Operating Procedure: routine subtyping of *Salmonella* spp. Do not delay the sample classification or pursuit of additional regulatory action and/or follow-up pending the results of these additional tests.

Refer to the Bacteriological Analytical Manual (BAM) Current Edition, which can be accessed online at <http://www.fda.gov/food/foodscienceresearch/laboratorymethods/ucm2006949.htm> (referred to as e-BAM). For any question regarding analytical method, contact Thomas Hammack (thomas.hammack@fda.hhs.gov).

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.

Salmonella

1. Methodology

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)

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 C₁. 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*.

2. 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 3375 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 $35 \pm 2^\circ \text{C}$ for 24 ± 2 h.

3. 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 $42 \pm 0.2^\circ \text{C}$ and incubate TT broth 24 ± 2 h at $35 \pm 2^\circ \text{C}$. 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 18-24 h at $41\text{-}42^\circ \text{C}$. 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 $41\text{-}42^\circ \text{C}$ for 6-8 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 $41\text{-}42^\circ \text{C}$. Continue as described in the kits instructions (AOAC 2011.03).
- d) 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) and PFGE ASAP - upon confirmation of *Salmonella*.

All *Cronobacter* isolates should also be sequenced (treated the same as *Salmonella*).

Speciation - prepare slants, and provide hardcopy information requested under BAM, Chapter 5, Section E.11., for shipment to:

Food and Drug Administration
Arkansas Laboratory (HFR-SW500)
3900 NCTR Road, Building 26
Jefferson, AR 72079-9502
Attn: Stephanie Horton 870-543-4608 or
Cindy Jeffrey 870-543-4636

Contact the laboratory in advance of shipment to provide the shipping details.

Cronobacter spp. see [BAM Chapter 29](#). Sample preparation requires 3 – 10 sub composites.

5. Reporting of Results to CFSAN and the Home OHAFO Division

NAB should use the following criteria to determine when analytical results should be forwarded to the Compliance Branch of the home OHAFO division for further evaluation:

- The actual caloric content, total fat, or sodium exceeds the value declared on the label by 20% or more;
- Total amounts of each vitamin, mineral, protein, or linoleic acid, are not at least equal to the value declared on the label; or
- Any of the following nutrients are present in the infant formula at less than 80% of the value declared on the label:

Vitamins, total carbohydrate
Minerals, protein

- The amount of any nutrient in the product is less than or greater than the nutrient specifications for infant formulas in section 412(i) of the Act and 21 CFR 107.100.
- An exempt infant formula that is found to contain a nutrient(s) which it is specifically formulated to not contain.

The Southeast Food and Feed Laboratory will inform ORS leadership to immediately contact CFSAN Regulatory/Compliance Contact, the CFSAN Premarket Notification and Infant Formula Regulations Policy Contact, and the CFSAN Regulatory/Policy Contact as well as the home OHAFO division when:

- Nutrient levels are found below the minimum or above the maximum permitted by the Infant Formula Act and 21 CFR 107.100.

- Sample results with the following microbiological values are found:

Salmonella spp.: presence

Cronobacter spp.: presence

6. Hardcopy Reporting

For any sample given a lab class of “2” or “3,” express mail a copy of the complete analytical worksheet immediately upon completion to the Compliance Branch of the home OHAFO division (and notify the collecting OHAFO division if not identical) for regulatory consideration.

7. Data Reporting

Report results of all analyses into the Field Accomplishment and Compliance Tracking System (FACTS) using the following Problem Area Flags (PAF):

Nutrient Analysis PAF: NIF

Microbiological Analysis PAF: MIC (*Cronobacter* spp., *Salmonella* spp.)

If appropriate

PAF: SAL (*Salmonella* serotyping)

PAF: ABR (*Salmonella* antibiotic resistance)

PAF: GSA (PFGE *Salmonella*)

PAF: GEC (PFGE; *E. coli* 0157:H7)

Label Reviews

PAF: FDF Results Flag FDL

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

This section is related, in part, to Part III Inspectional 2 - Import Operations.

OHAFO and Import Program divisions may consider the following regulatory actions for infant formulas permitted for the U.S. market and new infant formulas not permitted for the U.S. market:

1. Situations Presenting a Health Hazard

If a situation poses a health hazard, whether it pertains to conditions at a firm or analytical findings, the OHAFO or Import Program division should contact CFSAN immediately. If inspectional or analytical findings are particularly egregious, CFSAN may support proceeding directly to seizure, injunction, or import regulatory action. In either case, OHAFO or Import program divisions should contact the CFSAN Regulatory/Contacts listed in Part VI to discuss the facts involved on a case-by-case basis.

2. Imported infant formulas which are or appear to be violative

- a) Import divisions should submit a detention recommendation case to CFSAN/OC/DE/LDSCT for infant formula when:
- samples are positive for one or more microbiological analyte(s) (generally *Salmonella* and/or *Cronobacter*, however other analytes may be found which support subsequent regulatory action); and/or
 - samples are violative for an abbreviated or comprehensive nutrient analysis; and/or
 - the product is misbranded (based on a labeling review).

Recommendations for detention must be accompanied by all analytical worksheets and other appropriate documentation (entry paperwork, collection report, labeling, etc.) CFSAN will review the detention recommendation case concurrently for possible addition to detention without physical examination, as circumstances warrant.

- b) If not already completed as part of the detention recommendation case review, Import divisions may consider submitting a recommendation to DIO to add the firm/product to detention without physical examination under Import Alert 40-05 “Detention Without Physical Examination of Infant Formula Due to Failure to Meet Nutrient and Labeling Requirements” (see import alert for applicable adulteration and misbranding charges) or other applicable Import Alert(s).

Foreign Inspections

CFSAN will review establishment inspection reports and analytical worksheets resulting from foreign inspections for compliance with the Federal Food, Drug, and Cosmetic Act (the Act). Warning Letters or import actions will be prepared by CFSAN when conditions observed during the inspection warrant regulatory follow-up.

Domestic Inspections

The OHAFO division should contact the CFSAN Regulatory/Compliance Contact prior to submitting Warning Letter recommendations to the Center for the following:

- a) All domestic inspections classified as Official Action Indicated (OAI) on a case-by-case basis, including those during which no samples were collected; and
- b) Firms whose sample(s) yield the following analytical results.
- The actual caloric content, total fat, or sodium exceeds the value declared on the label by 20% or more;
 - Total amounts of each vitamin, mineral, protein, linoleic acid or potassium are not at least equal to the value declared on the label; or
 - Any of the following nutrients are present in the infant formula at less than 80% of the value declared on the label:

vitamins	total carbohydrate
minerals	protein
- The amount of any nutrient in the product is less than or greater than the nutrient specifications for infant formulas in section 412(i) of the Act and 21 CFR 107.100; or
 - An exempt infant formula determined by analysis to contain a nutrient(s) that it is specifically formulated to not contain.

Until such time as guidance for interpreting analytical results and label declarations is developed, the OHAFO division Compliance Branches should contact the CFSAN Regulatory/Compliance Contacts listed in Part VI of this program prior to preparing recommendations for regulatory follow-up.

PART VI - REFERENCES, ATTACHMENTS, AND 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>)

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”
<http://www.ecfr.gov/cgi-bin/text-idx?SID=af995814549945e54e6ee7208f021b5e&mc=true&node=pt21.2.106&rgn=div5>

Code of Federal Regulations, Title 21, Part 107, “INFANT FORMULA” (including Subpart E - Infant Formula Recalls).
<http://www.ecfr.gov/cgi-bin/text-idx?SID=da1daea2bb8310761e07e40be023745e&mc=true&node=pt21.2.107&rgn=div5>

Link to Exempt Infant Formulas Marketed in the United States
<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm106456.htm>

Link to **Infant Formula Regulation Update** training course
<https://orausportal.fda.gov/stc/ora/psciis.dll?COURSE=ora&CODE=FD9000W>

2. Attachments

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

3. Contacts

General Program Guidance Contact

Kaniz Shireen, CFSAN/OC/DFPG/PAMB 240-402-2775, HFS-615

Regulatory/Compliance Contact

Marjorie Davis, CFSAN/OC/DE/Labeling and Dietary Supplement Compliance Team (LDSCT), 240-402-6672

Premarket Notification and Infant Formula Regulations Policy Contact

Carrie Assar, CFSAN/ONFL/Infant Formula and Medical Foods Staff (IFMFS), 240-402-1453, HFS-850

Regulatory/Policy Domestic and Import Contact

Rene Miguel Amaguana, CFSAN/ONFL/Food Labeling and Standards Staff, 240-402-1760, HFS-820

WGS and PFGE Inquiries

David Melka, Division of Microbiology, ORS-CFSAN, 240-402-2293, HFS-712,
david.melka@fda.hhs.gov

Inspectional Inquiries

Elizabeth Mayer, ORA/OHAFO at 612-834-4830, HFR-CEB850

Martha Myrick, ORA/DHAFO/DHAFOB at 616-304-6283 (Blackberry), 240-402-5840 (Office),
HFR-CE7555.

Import Operations

Robert Hatch ORA/DIO 240-402-6081, robert.hatch@fda.hhs.gov, HFR-SE2570, HFS-100

For methodology other than metals/minerals - Dr. Gregory Noonan, 240-402-2250, HFS-715

For methodology involving metals/minerals - Primary contact - Dr. Shaun MacMahon,
240-402-1998, HFS-706

ORA/OFFLO Methods Contacts

Peggy Carter, (Microbiology), ORA/Office of Food and Feed Laboratory Operations, HFC-141, 301-
796-6239, peggy.carter@fda.hhs.gov

Mike Farrow, (Chemistry), ORA/Office of Food and Feed Laboratory Operations, 404-253-2246,
james.farrow@fda.hhs.gov

PART VII - CENTER RESPONSIBILITIES

The Director, Office of Nutrition and Food Labeling (ONFL) will evaluate the effectiveness of the program and provide further guidance to the Director, Office of Compliance as appropriate. Working in conjunction with the Program Office, the Program Evaluation Branch (PEB) of the Division of Field Programs and Guidance (DFPG) will prepare a yearly summary report for this compliance program. The summary will outline the Program Office's current objectives, highlight their accomplishment data for the year, and list recommendations for the upcoming year. The report will be made available on the Inside.FDA intranet site under the Programs and Initiatives page:

<http://inside.fda.gov:9003/ProgramsInitiatives/Food/FieldPrograms/ucm013763.htm>

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:

- Page 47 of 53

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 CFSAN and OHAFO.

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 been posted on OC Intranet site. Please click on the following link for updated list of foreign infant formula manufacturers.

<http://inside.fda.gov:9003/downloads/ProgramsInitiatives/Food/FieldPrograms/UCM533293.pdf>

ATTACHMENT D

Attachment D has been posted on OC Intranet site. Please click on the following link for updated list of domestic infant formula manufacturers.

<http://inside.fda.gov:9003/downloads/ProgramsInitiatives/Food/FieldPrograms/UCM533293.pdf>