CHAPTER 21 - FOOD COMPOSITION, STANDARDS, LABELING AND ECONOMICS

SUBJECT:	MEDICAL FOODS COMPLIANCE PROGRAM – IMPORT AND DOMESTIC
IMPLEMENTATION DATE:	8/24/2006 Correction Date: 10/01/2012 and 9/8/2025
DATA REPORTING	
PRODUCT CODES	INDUSTRY CODE: 41G
PRODUCT/ASSIGNMENT CODES	21002: MEDICAL FOODS – IMPORT AND DOMESTIC

NOTE: The work to be accomplished under this compliance program has been identified as high priority by HFP. 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. Districts are requested to complete 100% of the operations planned in the OII Field Workplan for this program.

FIELD REPORTING REQUIREMENTS:
New product codes have been established under Industry Code 41 for more specific coding of medical foods. Refer to Part III for complete coding instructions.

1. Inspectional
   All reports to headquarters are to be sent via email to the appropriate office identified below:

   a) Upload a copy of the complete EIR for each domestic and foreign inspection to eNSpect. If HFP has requested specific information be collected and documented during the inspection, that information should also be uploaded along with the EIR.

   b) Upload one (1) original of any product label, promotional pamphlet or brochure that is new or has been revised since the last inspection along with each domestic EIR. If HFP provided comments on any of the firm's product labels collected during the previous inspection, verify in the EIR that the firm was advised of the labeling deficiencies.

   c) As division learn of new medical food firms within their division, provide as many details as possible (FEI, name, address, products, and establishment type) in an e-mail to program monitor.

   NOTE: Due to the unique nature of medical foods and their compositional complexities, the

Human Foods Program (HFP) will continue to review inspection reports and analytical results for all medical food samples classified as laboratory class "2" or "3" that are uploaded in the Compliance Management System (CMS). When warning letters are warranted based on inspectional observations and/or analytical results, the Center will prepare these letters for issuance.

2. Analytical

a) Upload a copy of the complete analytical worksheet to CMS for all samples classified as lab class "2" or "3" for further evaluation by HFP.

b) Report results for all analysis into the Field Accomplishment and Compliance Tracking System using the following Problem Area Flags (PAF):

c) Nutrient Analysis = PAF "NIS"
d) Microbiological Analysis = PAF "MIC" (APC, Coliform, *B. cereus*, *Listeria, Salmonella*, *S. aureus*, Staphyloccoccal Toxin, *E. Coli*, ETEC & EHEC)

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"

HARD COPY REPORTING TO SOUTHEAST REGIONAL LABORATORY

Samples collected for routine surveillance purposes do not need to be accompanied by EIRs when forwarded to the laboratory. 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.

Contents

PART I – BACKGROUND

The nutritional management of the ill and infirm has dramatically evolved over the past 20 years. Today it is a very specialized science defined by technological advances in the preparation and administration of nutrients. The therapeutic importance of proper nutritional support (in terms of decreased hospital stay and lower incidence of complications and mortality) has been well documented in the literature.

During the past decade, several different terms have been used to describe those products used in the enteral (oral or tube fed) nutritional management of patients. The current term to describe these products is "medical foods".

The term "medical food" is defined in the Orphan Drug Act Amendments of 1988 [21 USC 360ee (b)(3)]. This definition was incorporated by reference into the Nutrition Labeling and Education Act (P.L. 101-535) in November 1990. It is incorporated into the agency's final rule on mandatory nutrition labeling published in January 1993. The definition of a medical food is a food which is formulated to be consumed or **administered enterally** under the **supervision of a physician** and which is intended for the **dietary management of a specific disease or condition** for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. (See 21 CFR 101.9(j)(8)).

Generally, to be considered a medical food, a product must, at a minimum, meet the following criteria:

a) The product is a food for oral or tube feeding.

b) The product is labeled for the dietary management of a medical disorder, disease, or condition; and

c) The product is labeled to be used under medical supervision, and is primarily obtained through hospitals, clinics, and other medical and long-term care facilities.

   Medical foods are distinguished from the broader category of foods for special dietary use and from foods that make health claims by the requirement that medical foods are to be used under medical supervision. The term "medical foods" does not pertain to all foods fed to sick patients. Medical foods are foods that are specially formulated and processed (as opposed to a naturally occurring foodstuff used in its natural state) for the patient who is seriously ill or who requires the product as a major treatment modality. Typical medical foods are enteral nutrition products, i.e., products provided through the gastrointestinal tract, taken by mouth, or provided through a tube or catheter that delivers nutrients beyond the oral cavity or directly to the stomach.

Medical Foods can be classified into the following categories:

a) Nutritionally complete formulas.

b) Nutritionally incomplete formulas, including individual "modular" type products that may be mixed with other products before use (e.g., protein, carbohydrate, or fat modulars).

c) Formulas for metabolic (genetic) disorders in patients over 12 months of age; or

d) Oral rehydration products.

Prior to 1972, medical foods were primarily formulas for managing patients with inherited metabolic diseases. They were mainly orphan products for limited populations. They were considered drugs and were so regulated to ensure their use under medical supervision. However, in 1972 the FDA reclassified these products from drugs to foods for special dietary use to enhance their development and availability. In the intervening years, a wide variety of products categorized as medical foods have been developed.

Currently, marketed medical foods with a wide variety of claims are used extensively as a life support modality in the management of the critically ill and elderly. They are required to conform only to those regulations dealing with general food safety and labeling to be distributed in the United States. Medical foods are foods as defined in the Act and are subject to the general food safety and labeling requirements of the Act. Refer to 101.9(j)(8) for exemption to NLEA labeling regulations for medical foods.

Formulas for managing infants under 12 months of age with inherited metabolic diseases are now regulated as exempt infant formulas (21 CFR 107, Subpart C). Attachment B is the current list of exempt infant formulas. These products must receive coverage under the Infant Formula Compliance Program (7321.006), not under this program.

Estimates of the current medical foods market are considered quite conservative. All indications are that the growth trend will continue, especially with increased usage of medical foods in nursing homes and the growing proportion of elderly in our society.

Adulterated and/or misbranded medical foods may constitute short- and long-term health hazards to persons who consume these products. Many extended care patients are nutritionally maintained solely with feedings of medical foods for prolonged periods of up to several years. Insufficient or excessive amounts of specific nutrients may not affect patients in short-term maintenance but can have a significant effect over time. Potential health hazards associated with medical foods include compositional errors and microbiological and/or environmental contamination. In 1986, four Peruvian infants died as a result of being fed oral rehydration solutions which, because of a manufacturing error in a New York firm, contained lethal concentrations of potassium. Potential problems may also be associated with labeling claims if clinical indications for use or compositional descriptions are not adequately supported by appropriate data.

Because of the susceptible population for which medical foods are intended, the agency is committed to assuring their continued safety and integrity through annual inspections of all medical foods manufacturers in the U.S. and foreign countries.

Prior to the start of each fiscal year, HFP/Office of Compliance and Enforcement (OCE)/Division of Compliance Implementation (DCI) will provide the Office of Inspections and Investigations (OII) a list of all foreign firms known to manufacture medical foods. OII will work with individual division to schedule an inspection at each of these firms.

PART II - IMPLEMENTATION

1. **Objective**

   a) To obtain information regarding the manufacturing/control processes and quality assurance programs employed by domestic and foreign manufacturers of medical foods through establishment inspections.

   b) To collect samples of medical foods during each domestic and foreign inspection for nutrient and/or microbiological analyses.

2. **Program Management Instructions**

   The inspection schedule that identifies the domestic firms to be inspected by division is no longer printed as part of this compliance program. HFP/OCE/DCI will issue the schedule to OII in a separate memorandum prior to the start of each fiscal year. The inspection schedule can be accessed on OCE Share Point Online (SPO) site under Active Assignments page. The inspections and sample collections are also entered into FACTS.

   In order for the HFP Laboratories to receive a steady flow of samples, it is imperative that the investigator follow Laboratory Servicing Table (LST) Dashboard before shipping samples. Contact the Medical Foods Program Manager if difficulties in implementation are encountered.

   If a division learns that a firm in their area manufactures, distributes, or re-packs medical foods (according to the definition in Part I), but is not included for coverage under the program, please provide the information to the Medical Foods Program Manager. Provide as much detail as possible in an e-mail to the compliance program contact. Include the FEI number, name, address, products, and establishment type.

   OII will be contacting individual division during the fiscal year to arrange for an inspection to be conducted at each firm listed on Attachment A. The inspection will include collection of appropriate samples for nutrient and/or microbiological analysis. Only products intended for exportation to the U.S. are to be sampled. Documentation indicating that the product has recently been exported to the U.S. must be collected and included as part of each EIR. If the firm is no longer manufacturing medical foods, or no longer distributes medical foods in the U.S. market, this information must be documented and reported in the EIR so that the firm can be removed from the inventory and annual inspection schedule.

3. Program Interaction

The following inspections may be conducted during a medical foods inspection, if appropriate. 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 and Sanitary Human Food Operations (7303.040)
b) Acidified and Low-Acid Canned Foods Program - Import & Domestic (7303.070)
c) Infant Formula Program - Inspection, Sample Collection and Examination (7321.006)

PART III – INSPECTIONAL

1. **Operations**
   A. Inspections
   Note Regarding Foreign Inspections: To assure that future shipments of foreign-manufactured medical foods are not permitted entry should inspectional or analytical results warrant, the following information must be obtained during these foreign inspections:

   a) The exact products/brands being exported to the U.S.;
   b) The size and frequency of the shipments;
   c) How the products are shipped;
   d) The importer of record for the shipments;
   e) The U.S. ports where the products are offered for entry; and if possible,
   f) A list of the U.S. distributors.

   Most of the instructions below on inspections is intended for facilities that manufacture medical foods. If it is found that a firm does not manufacture medical foods, determine if the firm distributes, imports, repacks, or promotes medical foods. If they do, obtain a listing of all medical foods, labeling, and names and addresses of the manufacturers of the products. Include this information in the EIR.

   Unless product problems have been identified through complaints or unless directed by HFP, inspect and sample up to two products not covered during the previous inspection. If the firm being inspected subcontracts with other firms or utilizes multiple in-house locations for all or part of the manufacturing process, report all details in the EIR.

   Inspections should cover all aspects of the manufacturing and quality assurance procedures employed by the firm. Refer to Parts 113 and 114 for coverage of medical foods that are low acid canned foods (LACF) or acidified foods (AF). If a form FDA-483 is issued, only food CGMP deviations should be included, but the significance of all observations concerning weaknesses in production/control should be explained to management.

   Inspections should document specific conditions, which can be considered insanitation that may have rendered medical foods wither contaminated with filth or injurious to health, during the preparing, packaging or holding of the medical foods.

Inspectional coverage should include:

a) suitability of buildings and facilities, including sanitation

b) receipt, storage, and testing of raw materials, including packaging

c) warehousing and distribution procedures

d) production and processing procedures and controls, including the production and processing procedures used to control potential microbiological contamination

e) Laboratory quality control specifications and procedures for raw material, in-process, and finished product testing. Obtain the firms' criteria for acceptance/rejection of test results.

Specifically identify testing conducted to:

a) ensure nutrient uniformity and stability;

b) ensure nutrient content and quantity represented on the labeling;

c) identify potential microbiological and environmental contaminants;

d) ensure packaging and seal integrity;

e) production master and batch records; and

f) records/procedures relating to equipment cleaning, laboratory controls, complaints, and returned products.

If a firm is found to be only a distributor of domestic and/or imported medical foods, report details in the EIR, including supplier names/address/products, any quality assurance procedures employed by the distributor, and copies of available labeling/literature.

Collect four (4) originals of medical food product labels, promotional literature, brochures or physician letter that are new or revised since the last inspection. 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. **In addition, if HFP has provided the division with written comments on particular product labels collected during prior inspections, document in the EIR that the firm was informed of the Center's comments.**

Special Note Concerning Ross Labs: At the request of Ross Laboratories corporate office, promotional literature and brochures for all Ross medical foods will be collected when necessary during the inspection conducted at the Columbus, Ohio location. Labels for Ross medical foods will still be collected when necessary at the manufacturing plants.

B. Import Investigations

Shipments of medical foods listed on Import Alert (IA) # 41-03 should be handled in accordance with the instructions outlined in that IA.

Attachment A is a list of known foreign medical food manufacturers and their products. The inspection of these firms will include collection of medical food products intended for exportation to the U.S. and they do not need to be ***routinely*** sampled under this compliance program when offered for import (see note below). However, districts may sample the products listed on Attachment A under other compliance programs if appropriate, i.e., obvious label errors, obvious product contamination, suspicion of tampering/terrorism issues.

NOTE: Investigators must check IA #41-03 first when making entry admissibility decisions on imported medical foods.

All shipments of medical foods determined to be American Goods Returned and all shipments of medical foods not listed on Attachment A must be sampled and held as instructed below. In addition to sampling, notify the Medical Foods Program Manager so that the firm can be investigated for possible addition to the inventory for annual inspection and sample collection.

C. Sample Collections

General Instructions

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

Unless product problems have been identified through complaints or unless directed by HFP, attempt to collect products not covered during the previous inspection. If new products are available or manufacturing procedures have changed for certain products, these should be prioritized for sample collection. Otherwise, the following medical food categories are listed in order of priority for collection for NUTRIENT analyses:

a) Oral Rehydration Products;
b) Formulas nutritionally complete for their intended use;
c) Formulas for metabolic disorders in patients over 12 months of age;
d) Nutritionally incomplete formulas (e.g., "modulars")

Do not collect single ingredient nutrient products that are promoted for the treatment of specific disease states, or any injectable nutrient formulations under this program. However, these products may be candidates for sampling under CDER programs.

DO NOT COMMINGLE CODES.

NOTE: Notify the appropriate SRL segment by phone when compliance samples are collected and provide all shipping information so that arrangements can be made to expedite sample analysis.

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 Chapter 4.3.2.2). Firms should be encouraged to collect their own portion for analysis. If necessary, consult with your supervisor and/or the Program Manager for further instructions.

Domestic Samples

Unless inspectional findings warrant more intensified sampling, collect the designated number of surveillance samples from each firm as listed on the inspection schedule referenced in Part II under Program Management Instructions.

The inspection schedule designates certain firms for collection of samples for microbiological analysis. Collect for microbiological analysis any powdered product with an ingredient such as soy powder, nonfat dried milk, dried whey, demineralized whey, whey protein concentrate, or caseinates. DO NOT collect oils, oral rehydration salts, or LACF products for microbiological analysis unless a specific problem is observed.

Sample Collection During Foreign Inspection

Finished product samples of medical foods produced by foreign manufacturers are not expected to be collected during foreign inspections. Foreign manufactured finished product samples are expected to be collected at the time of import. However, if warranted, additional sampling will be considered during a foreign facility inspection on a case-by-case basis following discussion with HFP.

Import Samples

All shipments of medical foods determined to be "American Goods Returned" and all shipments of medical foods which are not listed on Attachment A should be sampled and analyzed for nutrients, microbiological contamination, and labeling in accordance with the instructions contained in this program to determine compliance with the Act. The lots from which samples are collected must be held pending laboratory analyses. If the lot size does not permit collection of sufficient number of sub-samples noted below, contact the Program Manager for guidance.

Samples for Nutrient Analysis

Collect 12 labeled finished product containers of the same code, one container from each of 12 randomly selected shipping cases. The sample must be collected from a lot of 12 or more cases. If the individual finished product containers being collected each contain less than 8 ounces of product, then collect twice the number of specified units (2 containers from each of 12 cases).

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

For products that are dried, collect 1 sample of finished product. **NOTE:** 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.

For dry blended products, collect one sample of finished product and one sample of a principal raw material ingredient used in that finished product. When possible, collect an ingredient from the same lot used in the manufacturing of the sampled finished product. Examples of ingredients to be collected include soy powder, nonfat dry milk, dried whey, delactosed whey, demineralized whey, whey protein concentrate, caseinates, etc.

All finished product and raw material medical food samples designated for microbiological analysis should be collected according to the Salmonella Sampling Plan (see IOM Chapter 4, Sample Schedule, Chart 1). **However, each sample should consist of thirty (30) subsamples of eight ounces each (or larger).** Number subsamples 1-30 to facilitate analysis.

For potentially violative samples and all follow up compliance samples, flag C/Rs with "COMPLIANCE SAMPLE - ANALYZE UPON RECEIPT". Compliance samples should be shipped via the district's express mail carrier with all accompanying records (C/R, labeling, complaint report, etc.).

4. Sample Shipment

Finished product samples for microbiological analysis may be shipped to any of the servicing laboratories. Samples for nutrient analysis may only be shipped to the ATLHAF **laboratory. Please refer to the LST dashboard for assistance in selecting a servicing lab.**

Note on the C/R and FDA-525 whether the sample is to be analyzed for nutrients or micro.

Notify labs in advance when shipping compliance samples. Provide all shipping information so that arrangements can be made to expedite sample analysis.

Compliance samples should have a copy of the EIR submitted to the lab as soon after sample submission as possible to assist the laboratory in nutrient analyses. Surveillance samples **do not** need to be accompanied by EIRs when forwarded to the lab.

D. Reporting

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

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

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

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

The following new product codes have been established and are currently in effect for coding medical foods.

Industry 41—Dietary Conventional Foods and Meal Replacements

41G Medical Foods (foods that are specially formulated and processed for the patient who is seriously ill or requires the product as a major treatment modality)

Product ID's

01 Nutritionally Complete Formulations
02 Nutritionally Incomplete Formulations (modulars—may be protein, carbohydrate, or fat modulars intended to be mixed with other products prior to use)
03 Oral Rehydration Products
99 Medical Foods Not Elsewhere Classified (N.E.C.)

NOTE: The description for 41E Meal Replacement (Metracal, Sego, Instant Breakfast, etc.) has been further defined as 41E Meal Replacement (i.e., no disease, conditions, or treatments on or in the labeling); and 41F Geriatric Foods is no longer in use.

Report sample collections utilizing the following PAC/PAF Combinations:

PAC	PAC Description	PAF	PAF Description
21002	Medical Foods	NIF MIC	Infant formula Survey Reporting Microbiological Analysis

PART IV - ANALYTICAL

1. **Analyzing Laboratories**

   For nutrient analysis:

   ATLHAF Nutrient Analysis Branch (NAB)

   For microbiological analysis:

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

2. **Analyses to be Conducted**
   Nutrient Analysis

   Do not perform nutrient analyses on samples containing more than one manufacturing lot code. Notify the collecting division to resample if this occurs.

   ACNA should use the following criteria in determining the nutrient analysis to be performed: 1) analyze for those nutrients listed on the label as absent for medical reasons; 2) analyze for each nutrient forming the basis for any health claim made on the product label; 3) analyze for up to 4 nutrients per product including those already identified above in 1) and 2). NOTE: If the product is labeled as the sole source of nutrition, perform a complete nutrient analysis for the nutrients/amino acids listed on the label.

   Products that have a source of selenium (i.e., sodium selenite) in the ingredient statement should be assayed for selenium using the method referenced in the Total Diet Study Compliance Program (7304.839).

   Use factor 6.25 to convert nitrogen content to protein.

   Calculate carbohydrate by difference and kilocalories per unit weight or volume as appropriate.

3. **Methodology**

   Perform analyses for nutrients as follows:
   NOTE: ACNA MUST USE THE METHODS LISTED BELOW OR METHODS AGREED TO IN ADVANCE BY THE HFP METHODS CONTACTS FOR ALL NUTRIENT ANALYSES.

   Composite 12 subsamples (24 for containers of less than 8 ounces of product) (see AOAC, Current Edition Method 985.30).

NOTE: Analyze all samples of Oral Re-hydration Products on an individual product container basis. **DO NOT** composite sub-samples. Weigh the individual containers, and if the weights are consistent, randomly select one container for analysis. If weights are not consistent, select the heaviest unit for analysis. Procedures for quality assurance and analysis should be consistent with the Official Monograph for Oral Rehydration Salts, USP Current Version. Additional information and/or methodology can be found in WHO/CDD/SER 85.8 entitled Oral Rehydration Salts available from Director, Diarrhoeal Control Programme, WHO, 1211 Geneva 27, Switzerland.

CAUTION: Vitamins A, Thiamin, C, and E potency deteriorates with time and when improperly handled. Begin all analyses as soon after compositing as possible.

Analyze the composite by the following methods:

Official Methods of Analyses (AOAC) International Current Edition

1. Sampling	Method 985.30
2. Proximates	Method 986.25
3. Vitamin C	Method 985.33
4. Thiamin	Method 986.27
5. Riboflavin	Method 970.65
6. Vitamin B_6	Method 985.32
7. Vitamin B_{12}	Method 986.23
8. Niacin	Method 985.34
9. Chloride	Method 986.26
10. Phosphorus	Method 986.24 or 984.27
11. Vitamin A	Method 992.06/992.04
12. Vitamin D	Method 992.26 or 995.05
13. Vitamin E	Method 992.03
14. Vitamin K	Method 992.27
15. Folic Acid	Method 992.05
16. Pantothenic Acid	Method 992.07
17. Calcium, Copper Iron, Magnesium, Manganese, Potassium, Sodium, and Zinc	Method 985.35 or 984.27
18. Fat	Method 996.01
19. EFA (Linoleic acid)	Method 996.01 or 992.25

Note: Do not use 996.01 to measure cis- or Trans-fatty acids

FDA IFC Collaborative Study Methods

20. Biotin Proc. Soc. Explt. Biol. Med. 56, p. 95, 1944 c (modified) - Extraction - IN H_2SO_4

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

4. Criteria for Forwarding Analytical Results

Medical food nutrient samples which are classified as class 2 or class 3 will be evaluated by HFP to determine if regulatory follow-up is warranted. ACNA should use the following criteria to determine when analytical results should be forwarded to HFP for evaluation.

a) Lab Class 2 – if a nutrient is found to be below 90% of the label declaration.

b) Lab Class 3 – if a nutrient is found to be below 80% of the label declaration, or the product is found to contain a nutrient that is labeled as absent for medical reasons.

Note: Lab should contact HFP medical food CP monitor when excess nutrients are found to determine the regulatory significance and whether a check analysis should be performed.

HFP will evaluate inspection and analytical findings to determine appropriate charges and regulatory follow-up.

5. Microbiological Analysis

Use the methodology, special instructions or sample preparation cited in this compliance program and/or the FDA's electronic Bacteriological Analytical Manual (eBAM).

NOTE: For any commodities NOT included in the eBAM or this compliance program, reach out to the designated HFP OLOAS Contact to determine the best way to analyze that commodity.

NOTE: Before proceeding with the following bacteriological analyses, prepare **four** composites from the 30 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. Repeat using the same subs 1-15 for preparation composite 2; 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 3. Repeat using the same subs 16-30 for preparation of composite 4.

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

Next, randomly select 20 of the 30 subsamples for preparation of four composites for Listeria analysis as follows:

d) Remove 50 mL or g from each of 5 subsamples for a total 250 mL or g for composite 1; then

e) Repeat the above procedure using different subsamples (5 subsamples) to prepare a total of 4 composites each consisting of 250 mL or g.

f) Remove 25 mL or g from each of these four composites for Listeria analysis as instructed below.

All remaining bacteriological analyses are to be done on an individual subsample basis.

Listeria monocytogenes

Refer to eBAM Chapter 10, Detection of Listeria monocytogenes in Foods and Environmental Samples, and Enumeration of Listeria monocytogenes in Foods.

1. Rapids test kit methods validated as AOAC OMA methods can be used.

2. If L. monocytogenes is detected in the sample, enumeration is required when reserve remains.

3. Compositing: Listeria: Refer to the eBAM Chapter 10; only approved for Buffered Listeria Enrichment Broth (BLEB)

SAFETY PRECAUTIONS: Media Preparation for *L. monocytogenes* directs the use of cycloheximide which is an **extremely toxic chemical** and acriflavine which is a powerful mutagen (**use caution**).

Since the *L. monocytogenes* method gives the option of using a -naphthol, **DO NOT** use a - Naphthylamine. All analysts should take **extreme safety precautions** when handling these chemicals; e.g., weigh in a containment hood free of drafts; wear gloves and face mask. Those laboratories with pesticide capabilities should take additional precautions against possible contamination as cycloheximide is a fungicide.

Enumeration

If the "processed finished product" was found to be positive for *L. monocytogenes* and growth was observed at 24 and/or 48 hrs of the enrichment, then enumerate using the MPN method contained in the BAM, Chapter 10, *L.* monocytogenes. Contact HFP OLOAS for information about the use of one of the new chromogenic agars in place of the Oxford agar or if there are any other questions.

Salmonella

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

NOTE: The serovar of *Salmonella* that has been identified in the contamination of some dried infant formula samples is *S. tennessee*, a member of *Salmonella* Group C_1. Recent isolates of this serovar from dried products have been **lactose positive**. Keep this in mind when analyzing medical food samples.

Preparation of composites - BAM, Chapter 1. The minimum number of sample composites to be analyzed is four.

Isolation and Identification - BAM, Chapter 5.

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

Food and Drug Administration
Arkansas Regional Laboratory (HFR-SW500)
3900 NCTR Road
Jefferson, AR 72079-9502
870-543-4071

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

Perform the following additional analyses on each sample. Analyze individual subsamples (no compositing) as directed in the referenced chapters of the e-BAM.

Staphylococcus sp.

Direct microscopic examination using e-BAM, Chapter 2.

Refer to eBAM Chapter 12, Staphylococcus aureus and Appendix 2.

Identification, enumeration, coagulase, ancillary tests, and viable count (MPN dilutions) will be performed using e-BAM, Chapter 12. Analyze 5 subsamples per sample.

Staphyloccoccal Enterotoxin Determination

If viable *Staphylococcus sp.* colonies are observed by either:

- most probable number (MPN) result is >11,000; or
- direct plate count indicates a level of 10,000

then determine the enterotoxigenicity of isolates as per the most current version e-BAM, Chapter 13B, Staphylococcal Enterotoxins Detection Methods

Follow the methodology outlined in Chapter 13. The laboratory will individually test each sub-sample using the TECRA™ ELISA kit with proper procedures followed accordingly.

NOTE: Under no circumstances should positive TECRA™ ELISA results be conveyed to a regulated firm or consumer without confirmation. The TECRA™ ELISA kit is intended as a screening technique only, and positive results are considered as presumptive.

When the TECRA™ ELISA kit is used and renders a:

- Negative result – the laboratory need not conduct further analysis for enterotoxin. The sample is considered "negative" and no other regulatory or follow-up action is warranted.

- Positive result – to confirm the positive result, the laboratory must analyze the original sample using e-BAM, Chapter 13, "Microslide Gel Double Diffusion or perform the VIDAS.

If the TECRA™ ELISA kit **and** the VIDAS test are **positive**, the division may proceed with regulatory consideration. However, the results must be re-confirmed by HFP.

If the result of the TECRA™ ELISA kit is positive and the VIDAS test is negative then the sample must be confirmed positive or negative by HFP.

Bacillus cereus

Refer to e-BAM, Chapter 14. Analyze 10 sub-samples per sample. Reach out to HFP OLOAS Contact if a sample is found to be positive for *B. cereus*, send isolate slants together with the reserve portion of each of the ten sub-samples representing the sample.

Aerobic Plate Count: Chapter 3. Analyze 5 subsamples per sample.

Coliform and *Escherichia coli*: See Chapter 4 e-BAM—Enumeration of *Escherichia coli* and the Coliform Bacteria. Section I.C. MPN – presumptive test for coliforms, fecal coliforms and *E. coli*.

Analyze 5 subsamples per sample.

If any of the LST tubes are gas positive, subculture a loopful to BGLB to obtain confirmed results for coliforms and another loopful to EC broth for fecal coliform and *E. coli* determination.

If *E. coli* are isolated, **perform serological testing for 0157 and H7** as described in Chapter 4a. Diarrheagenic *E. coli*, e-BAM, Section Q. If less than 10 colonies of *E. coli* are found, test all isolates. If more than 10 colonies are found, randomly test 10 isolates.

If *E. coli* are present at levels of 10^4/g or higher, **perform ETEC analysis** using the DNA probe for ST and LT described in e-BAM Chapter 24.

Consult HFP OLOAS Contact if needed, for final identification.

4. **Reporting**

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

Salmonella: presence

Listeria monocytogenes: presence

Escherichia coli 0157:H7: presence

Staphylococcal enterotoxin: presence

Bacillus cereus: If any subsample exceeds 1000 organisms/gram

Aerobic Plate Count: If any subsample exceeds 10,000 organisms/gram, or if three or more subsamples exceed 1,000 organisms/gram.

Coliforms: If any subsample exceeds 3 organisms/gram

Reporting of Results to HFP and OII CFC Team

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

Data Reporting

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

Nutrient Analysis	= PAF "NIS"
Microbiological Analysis	= PAF "MIC" (APC, Coliform, *B. cereus*, *Listeria, Salmonella*, *S. aureus*, Staphyloccoccal Toxin, *E. Coli*, ETEC & EHEC)
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

HFP will review all domestic EIRs (including those inspections where no sample was collected), and the analytical packages for all samples classified as class "2" or "3". When violations are clearly supported by the evidence, the HFP will prepare a warning letter for subsequent issuance by the home division.

HFP will review EIRs and analytical worksheets resulting from foreign inspections as well as the analytical worksheets for imported samples collected outside of the foreign inspections. Warning Letters will be prepared by HFP when conditions observed during the inspection or analytical results warrant regulatory follow-up. In addition, HFP will forward to OIO a recommendation that the firm or product be placed on I.A. #41-03.

Actions taken under this program will be based on the adulteration provisions in section 402 of the Act and labeling provisions in section 403 of the Act.

According to Section 403(q)(5)(A)(iv) of the Food Drug, and Cosmetic Act (as amended by the Nutrition Labeling and Education Act of 1990), medical foods are exempt from nutrition labeling. Medical foods are also exempt from the requirements for nutrient content claims and health claims under section 403(r) of the Act.

PART VI REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

1. **References**

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

Code of Federal Regulations, Title 21, Part 101, "FOOD LABELING"
eCFR – 21 CFR Part 101 – Food Labeling

Code of Federal Regulations, Title 21, Part 110—"CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKING, OR HOLDING HUMAN FOOD"
eCFR – 21 CFR Part 110 – Current Good Manufacturing Practice in manufacturing, Packing, or Holding Human Food

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

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

Inspection for Compliance with CGMP and Preventive Controls for Human Food Requirements in 21 CFR Part 117

2. **Attachments**

Attachment A--List of known foreign medical foods manufacturers/shippers and their products

Attachment B--List of exempt infant formulas

3. **Program Contacts**

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

HFP Regulatory/Compliance Contacts

Marjorie Davis, HFP/OCE/OE/DCFDSE/Critical Foods and Labeling Enforcement Branch,

Email: Marjorie.Davis@fda.hhs.gov, Phone: (240) 402-6672

Darren Morgan, HFP/OCE/OE/DCFDSE/Critical Foods and Labeling Enforcement Branch,
Email: Darren.Morgan@fda.hhs.gov, Phone: 313-393-8149

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

HFP Office of Critical Foods Contact:

Shawne Suggs-Anderson, HFP/NCE/OCF/IFPMRS,
Email: Shawne.Suggs-Anderson@fda.hhs.gov, Phone: 240-402-1783

HFP Office of Lab Operations and Applied Science Contacts

Microbiological Analysis

Yi Chen, HFP/ OLOAS/OAMT/DFES/MMDB,
Email: Yi.Chen@fda.hhs.gov, Phone: (240) 402-2783

Rachel Binet, HFP/ OLOAS/OAMT/DFES/MMDB,
Email: Rachel.Binet@fda.hhs.gov, Phone: (240) 402-2468

Jeremi Mullins, HFP/OLOAS/ORTS/DSPC/MB,
Email: Jeremi.Mullins@fda.hhs.gov, Phone: (404) 575-1582

Julia Manetas, HFP/OLOAS/ORTS/DSPC/MB,
Email: Julia.Manetas@fda.hhs.gov, Phone: (718) 340-7034

Nutrients, Metals Analysis

Shaun MacMahon, HFP/OLOAS/OSCCS/SSAS,
Email: Shaun.MacMahon@fda.hhs.gov, Phone: (240) 402-1998

Christine Parker, HFP/OLOAS/OCT/DBC,
Email: Christine.Parker@fda.hhs.gov, Phone: (240) 402-2019

Yanxuan (Tina) Cai, HFP/OLOAS/ORTS/DSPC/CB
Email: Yanxuan.Cai@fda.hhs.gov, Phone: (240) 402-1369

Aubrey Shahriari, HFP/OLOAS/ORTS/ATLHAFL/ANAB
Email: Aubrey.Shariari@fda.hhs.gov, Phone: (404) 253-2345

OII CFC Team Inspectional Inquiries

Elizabeth Mayer, OII/OHFI/OGSHFI/HFNES,
Email: Elizabeth.Mayer@fda.hhs.gov, Phone: (612) 834-4830

Andrea Charles-Julien, OII/OHFI/OGSHFI/DCSF/CFIB,
Email: Andrea.Charles@fda.hhs.gov, Phone: (561) 416-1065 x 1110

HFP Import Contact

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

OII Office of Import Operations (OIO) Contacts

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

PART VII - CENTER RESPONSIBILITIES

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

ATTACHMENT A

NOT FOR PUBLIC DISTRIBUTION

MEDICAL FOODS - IMPORT AND DOMESTIC

The following list consists of foreign manufacturers of medical foods, and the specific products each firm handles.

FIRM	PRODUCTS
Scientific Hospital Supplies (Liverpool, U.K.) FEI 3002809433	XP Maximaid XP Maximum MSUD Maximaid MSUD Maximum XMET Maximaid XMET Maximum XLYS, TRY Maximaid XLYS, TRY Maximum XLEU Maximaid XPHEN, TYR Maximaid XMET, THRE, VAL, ISOLEU Maximaid Super Soluble Duocal XP Maximaid Bar Duobar Code 196 PKU Aid MSUD Aid Methionaid Elemental 028 Lorenzo's Oil Glycerol Trierucate Oil Super Soluble Maxijul Enteral 400 Dialamine Pepdite 0-2 (infant product) MCT Pepdite 0-2 (infant product) Super Soluble Maxipro MCT Pepdite 2+ Pepdite 2+ Generaid PK Aid III Maxisorb Range

	Albumaid XP Hepatamine Vipro

NOT FOR PUBLIC DISTRIBUTION

MEDICAL FOODS - IMPORT AND DOMESTIC

FIRM	PRODUCTS
Milupa A.G., Friedricksdorf (Federal Republic of Germany) FEI 3002809505	Milupa PKU 2 Milupa PKU 3 MSUD 2 HOM 2 TYR 2 LYS 2 HIST 2 OS 2 UCD 2

ATTACHMENT B

EXEMPT INFANT FORMULAS---REASONS FOR EXEMPTION

Infant Formula Name (Manufacturer)	Type of Infant Formula Reason For Exemption
Cyclinex-1 (Ross)	Metabolic infant formula. Reason for exemption: below CFR levels for protein; inborn errors of metabolism.
Glutarex-1 (Ross)	Metabolic infant formula. Reason for exemption: free of lysine and tryptophan; inborn errors of metabolism.
Hominex-1 (Ross)	Metabolic infant formula. Reason for exemption: free of methionine; inborn errors of metabolism.
I-Valex-1 (Ross)	Metabolic infant formula. Reason for exemption: free of leucine; inborn errors of metabolism.
Ketonex-1 (Ross)	Metabolic infant formula. Reason for exemption: free of branched chain amino acids; inborn errors of metabolism.
Phenex-1 (Ross)	Metabolic infant formula. Reason for exemption: free of phenylalanine; inborn errors of metabolism.
Propimex-1 (Ross)	Metabolic infant formula. Reason for exemption: free of methionine and valine; low in isoleucine and threonine; inborn errors of metab.
Tyrex-1 (Ross)	Metabolic infant formula. Reason for exemption: free of tyrosine and phenylalanine; inborn errors of metabolism
Similac Special Care 20 w/Low Iron (Ross)	Formula for premature infants. Reason for exemption: above CFR levels for vitamins A and D and Ca:P ratio.
Similac Special Care 20 w/Iron (Ross)	Formula for premature infants. Reason for exemption: above CFR levels for vitamins A and D and Ca:P ratio.
Similac Special Care 24 w/Low Iron (Ross)	Formula for premature infants. Reason for exemption: above CFR levels for vitamins A and D and Ca:P ratio; higher calories per ounce.
Similac Special Care 24 w/Iron (Ross)	Formula for premature infants. Reason for exemption: above CFR levels for vitamins A and D and Ca:P ratio; higher calories per ounce.
Alimentum (Ross)	Protein hydrolysate infant formula. Reason for exemption: unusual medical or dietary problems; intolerances or allergies to whole protein and conditions which limit intestinal hydrolysis of protein due to pancreatic insufficiency.
Calcilo XD (Ross)	Miscellaneous* infant formula. Reason for exemption: below CFR level for calcium; contains no vitamin D.
Isomil DF (Ross)	Miscellaneous* infant formula. Reason for exemption: unusual medical or dietary problems; for short-term treatment of diarrhea.
Pro-Phree (Ross)	Miscellaneous* infant formula (energy module). Reason for exemption: below CFR level for protein (contains no protein).
ProViMin (Ross)	Miscellaneous* infant formula (modular†). Reason for exemption: below CFR level for amount of fat and linoleic acid.

Ross Carbohydrate Free Soy Formula w/Iron (Ross)	Miscellaneous* infant formula (formula base). Reason for exemption: unusual medical or dietary problems; contains no carbohydrate.
Similac Powdered Human Milk Fortifier (Ross)	Miscellaneous* (human milk fortifier; modular†). Reason for exemption: above CFR levels for vitamins A and D.

EXEMPT INFANT FORMULAS---REASONS FOR EXEMPTION

Infant Formula Name (Manufacturer)	**Type of Infant Formula Basis For Exemption**
Similac Natural Care Human Milk Fortifier (Ross)	Miscellaneous* (human milk fortifier; modular†). Reason for exemption: above CFR levels for vitamins A and D and Ca:P ratio.
Similac NeoSure (Ross)	Miscellaneous* infant formula (transitional formula for premature infants). Reason for exemption: higher calories per ounce and more nutrients per 100 kcals.
Similac PM 60/40 (Ross)	Miscellaneous* infant formula. Reason for exemption: slightly below CFR lower limit for calcium and phosphorus.
Lofenalac (Mead Johnson)	Metabolic infant formula. Reason for exemption: represented and labeled for use by infants with an inborn error of metabolism, free of phenylalanine; protein source not nutritionally equivalent to casein.
MSUD Diet Powder (Mead Johnson)	Metabolic infant formula. Reason for exemption: free of leucine, isoleucine, valine; protein source not nutritionally equivalent to casein.
Phenyl Free 1 (Mead Johnson)	Metabolic infant formula. Reason for exemption: free of phenylalanine.
Product 3200 AB (Mead Johnson)	Metabolic infant formula. Reason for exemption: free of phenylalaine and protein source not nutritionally equivalent to casein.
Enfamil Premature 20 (Mead Johnson)	Formula for premature infants. Reason for exemption: above CFR levels for vitamins A and D.
Enfamil Premature 20 w/Iron (Mead Johnson)	Formula for premature infants. Reason for exemption: above CFR levels for vitamins A and D.
Enfamil Premature 24 (Mead Johnson)	Formula for premature infants. Reason for exemption: above CFR levels for vitamins A and D, higher calories per ounce.
Enfamil Premature 24 w/Iron (Mead Johnson)	Formula for premature infants. Reason for exemption: above CFR levels for vitamins A and D, higher calories per ounce.
Nutramigen (Mead Johnson)	Protein hydrolysate infant formula. Reason for exemption: unusual medical or dietary problems; for sensitivity to intact proteins.
Pregestimil (Mead Johnson)	Protein hydrolysate infant formula. Reason for exemption: unusual medical or dietary problems; for severe malabsorption disorders.
Pregestimil 24 (Mead Johnson)	Protein hydrolysate infant formula. Reason for exemption: unusual medical or dietary problems, above CFR levels for vitamin D; higher calories per ounce; for severe malabsorption disorders.
Enfamil EnfaCare (Mead Johnson)	Miscellaneous* infant formula (transitional formula for premature infants). Reason for exemption: higher calories per ounce and more nutrients per 100 kcals.
Product 3232A (Mead Johnson)	Miscellaneous* infant formula. Reason for exemption: unusual medical or dietary problems.
Product 80056 (Mead Johnson)	Miscellaneous* infant formula. Reason for exemption: unusual medical or dietary problems, below CFR level for protein (no protein).

Infant Formula Name (Manufacturer)	Type of Infant Formula Basis For Exemption
HIST 1 (Milupa AG)/{Mead Johnson (dist)}	Metabolic infant formula. Reason for exemption: inborn errors of metabolism, free of histidine.
HOM 1 (Milupa AG)/{Mead Johnson (dist)}	Metabolic infant formula. Reason for exemption: inborn errors of metabolism, free of methionine.
LYS 1 (Milupa AG)/{Mead Johnson (dist)}	Metabolic infant formula. Reason for exemption: inborn errors of metabolism, free of lysine.
MSUD 1 (Milupa AG)/{Mead Johnson (dist)}	Metabolic infant formula. Reason for exemption: inborn errors of metabolism, free of isoleucine, leucine and valine.
OS 1 (Milupa AG)/{Mead Johnson (dist)}	Metabolic infant formula. Reason for exemption: inborn errors of metabolism, free of isoleucine, methionine, threonine and valine.
PKU 1 (Milupa AG)/{Mead Johnson (dist)}	Metabolic infant formula. Reason for exemption: inborn errors of metabolism, free of phenylalanine.
TYR 1 (Milupa AG)/{Mead Johnson (dist)}	Metabolic infant formula. Reason for exemption: inborn errors of metabolism, free of phenylalanine and tyrosine.
UCD 1 (Milupa AG)/{Mead Johnson (dist)}	Metabolic infant formula. Reason for exemption: inborn errors of metabolism, only contains essential L-amino acids.
MSUD Analog (SHS International Limited)	Metabolic infant formula. Reason for exemption: free of branched-chain amino acids; used for inborn errors of metabolism.
XLeu Analog (SHS International Limited)	Metabolic infant formula. Reason for exemption: free of leucine; used for inborn errors of metabolism.
XLys Analog (SHS International Limited)	Metabolic infant formula. Reason for exemption: free of lysine; used for inborn errors of metabolism.
XLys, Trp Analog (SHS International Limited)	Metabolic infant formula. Reason for exemption: free of lysine and tryptophan; used for inborn errors of metabolism.
XMet Analog (SHS International Limited)	Metabolic infant formula. Reason for exemption: free of methionine; used for inborn errors of metabolism.
XMTVI Analog (SHS International Limited)	Metabolic infant formula. Reason for exemption: free of methionine, threonine, valine and isoleucine; used for inborn errors of metabolism.
XPhe Analog (SHS International Limited)	Metabolic infant formula. Reason for exemption: free of phenylalanine; used for inborn errors of metabolism.
XPhe, XTyr Analog (SHS International Limited)	Metabolic infant formula. Reason for exemption: free of phenylalanine and tyrosine; used for inborn errors of metabolism.
XPTM Analog (SHS International Limited)	Metabolic infant formula. Reason for exemption: free of phenylalanine, tyrosine and methionine; used for inborn errors of metabolism.
Neocate (SHS International Limited)	Amino acid-based infant formula. Reason for exemption: unusual medical or dietary problems; for sensitivity to intact proteins.

*For the purpose of this table, miscellaneous refers to those infant formulas placed in a nonspecific category.

†Modular often refers to products that are added to a base formula or a more complete formula for the purposes of supplementation.