CHAPTER 21 – FOOD COMPOSITION, STANDARDS, LABELING AND ECONOMICS

SUBJECT:	**IMPLEMENTATION DATE**
MEDICAL FOODS PROGRAM – IMPORT AND DOMESTIC (FY 06/07/08) ***This program has completed a Good Guidance Practices clearance by CFSAN's ORP and OC/DFP/CPB in July 2006.***	August 24, 2006 **COMPLETION DATE** September 30, 2008

DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Industry Code 41G (Use appropriate product code)	21002

Note: Material that is not releasable under the Freedom of Information Act (FOIA) has been redacted/deleted from this electronic version of the program. Deletions are marked as follows: (#) denotes one or more words were deleted; (&) denotes one or more paragraphs were deleted; and (%) denotes an entire attachment was deleted.

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. Districts are requested to complete 100% of the operations planned in the ORA Field Workplan for this program.

FIELD REPORTING REQUIREMENTS
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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 hardcopy reports to headquarters are to be sent to the following address and the appropriate office identified below:

Food and Drug Administration
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740-3835

a) Forward a copy of the complete EIR for each domestic inspection to the Medical Foods Program Contact (HFS-636), within 30 days after completion of the inspection. If CFSAN has requested that specific information be collected and documented during the inspection, that information must also be submitted along with the EIR.

b) Submit 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 submitted to CFSAN. If CFSAN 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) The original, complete EIR for each foreign inspection must be sent to the Chief, Imports Branch (HFS-606), upon completion with a copy also forwarded to: Rebecca Hackett, ORA/ORO/Division of Field Investigations (HFC-130).

d) As districts learn of new medical food firms within their district, provide as many details as possible (FEI, name, address, products, and establishment type) in an e-mail to Brenda.Aloi@fda.hhs.gov.

NOTE: Because of the unique nature of medical foods and their compositional complexities, CFSAN will continue to review inspection reports and the analytical results for all medical food samples classified as lab class "2" or "3". Where warning letters are warranted based on inspectional observations and/or analytical results, the Center will prepare the letters for subsequent issuance by the Compliance Branch of the collecting district or home district if they are not the same district.
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2. Analytical

a) Forward a copy of the complete analytical worksheet for all samples classified as lab class "2" or "3" immediately upon completion to the Medical Foods Program Manager. *Refer to Part IV for criteria for determining when to forward analytical worksheets to CFSAN for further evaluation.*

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 SRL/ACNA (HFR-SE680) or SRL/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.

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, CFSAN/Office of Compliance/Division of Field Programs (DFP) (HFS-636) will provide the Office of Regulatory Affairs, Division of Field Investigations (ORA/DFI) a list of all foreign firms known to manufacture medical foods. ORA/DFI will work with individual districts to schedule an inspection at each of these firms.

PART II - IMPLEMENTATION

1. Objectives

   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 district is no longer printed as part of this compliance program. CFSAN's Office of Compliance, Division of Field Programs will issue the schedule to all districts in a separate memorandum prior to the start of each fiscal year. # The inspections and sample collections are also entered into FACTS.*

In order for the Southeast Regional Laboratory to receive a steady flow of samples, it is imperative that this schedule be followed. Contact the Medical Foods Program Manager if difficulties in implementation are encountered.

If a district 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 Brenda.Aloi@fda.hhs.gov. Include the FEI number, name, address, products, and establishment type.

ORA/DFI will be contacting individual districts 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) Domestic Acidified and Low-Acid Canned Foods, CP 7303.803A;

b) Import Acidified and Low-Acid Canned Foods, CP 7303.003;

c) Infant Formula Program, CP 7321.006; or

d) Domestic Food Safety, CP 7303.803.

PART III - INSPECTIONAL

1. 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 sent to HFS-636.

Note: The asterisked material below was modified slightly for clarity by ORA/DFI after initial program issuance.

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Unless product problems have been identified through complaints or unless directed by CFSAN, 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.

Only food regulations apply to medical foods. In addition to 21 CFR Part 110, refer to 21 CFR Parts 108, 113 and 114 for coverage of medical foods that are low acid canned foods (LACF) or acidified foods (AF). However, inspections should cover all aspects of the manufacturing and quality assurance procedures employed by the firm.

See the Guide to Inspections of Manufacturers of Miscellaneous Food Products, Volume II, Section 4—Infant Formula (excluding Infant Formula Act references or authority), September 1996 (hereinafter referred to as the DFI inspection guide) for general instructions on conducting medical foods inspections.

If a form FDA-483 is issued, only food GMP deviations should be included, but the significance of all observations concerning weaknesses in production/control should be discussed with management.

Inspections should document deviations from food GMPs (including LACF or acidified foods if applicable) or other specific conditions that may render medical foods adulterated under section 402 of the Act, or misbranded under section 403 of the Act.

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

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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 CFSAN has provided the district 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.** Forward one (1) original of each new or revised product label, promotional literature, brochure or physician letter to CFSAN along with the EIR as instructed on Page 1 of this compliance program.

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2. Import Investigations

Shipments of medical foods listed on I.A. #41-03 should be handled in accordance with the instructions outlined in that import alert. http://www.fda.gov/ora/fiars/ora_import_ia4103.html

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 Import Alert #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.

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3. Sample Collection

General Guidance

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 CFSAN, 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.

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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 *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 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.

Foreign Inspection Samples

Import medical foods (see Attachment A) will be sampled during the inspection conducted at each foreign manufacturer. The general guidance provided above and the sample sizes below apply equally to import samples. Sample only those products and lots intended for exportation to the United States. Verify the U.S. exportation by reviewing the firm's records and/or by discussions with firm management. Obtain the additional information on product exportation listed above under 1. Inspectional.

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 product 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 district investigator’s U.S. address*.

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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 CONTACT INSERT INVESTIGATOR'S SUPERVISOR NAME AND PHONE NUMBER UPON RECEIPT OF THIS SHIPMENT".**
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The sampling district should notify ORA/DFI if any product sampled in the foreign firm is not received in the district 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.

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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.
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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 1 sample of finished product and 1 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

Samples for nutrient analysis and/or microbiological analysis

Send samples to:

DHHS/Food and Drug Administration
Southeast Regional Laboratory
60 Eighth Street, NE
Atlanta, Georgia 30309

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

Notify SRL 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 SRL 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.

5. Data and Hardcopy Reporting

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.

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All hardcopy reports to headquarters are to be sent to the following address and the appropriate office identified below:

Food and Drug Administration
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740-3835

a) Forward a copy of the complete EIR for each inspection to the Medical Foods Program Contact(HFS-636), within 30 days after completion of the inspection. If CFSAN has requested that specific information be collected and documented during the inspection, that information must also be submitted along with the Summary of Findings.

b) Note: The original, complete EIR for each foreign inspection must be forwarded to this same address but be directed to the Chief, Imports Branch (HFS-606). A copy of each foreign EIR should also be forwarded to Rebecca Hackett, ORA/ORO/DFI (HFC-130).

e) Submit an original product label, promotional pamphlet or brochure that is new or has been revised since the last inspection along with each domestic EIR submitted to CFSAN. If CFSAN provided comments on any of the firm's product labels during the previous inspection, verify in the EIR that the firm was advised of the labeling deficiencies.

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PART IV - ANALYTICAL

1. Analyzing Laboratories

For nutrient analysis and label review:

SRL/Atlanta Center for Nutrient Analysis (ACNA), HFR-SE680

For microbiological analysis and label review:

SRL/Microbiology Branch, HFR-SE670

2. Label review

Review all labels for compliance with the general labeling requirements contained in 21 CFR Part 101.

> **NOTE**: According to Section 403(q)(5)(A)(iv) of the Federal 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)(5)(A) of the Act.*

3. Nutrient Analysis

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

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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.
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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).

If the number or types of analyses for a given sample are in doubt, contact Dr. Jeanne Rader (HFS-840) at *(301) 436-1786* for guidance.

Use factor 6.25 to convert nitrogen content to protein.

NOTE: There may be occasions where a more specific factor could be used. If there are questions, contact Dr. Rader.

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

Perform analyses for nutrients as follows:

NOTE: ACNA MUST USE THE METHODS LISTED BELOW OR METHODS AGREED TO IN ADVANCE BY THE CFSAN 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. Exptl. 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.

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4. Criteria for Forwarding Analytical Results to CFSAN

Medical food nutrient samples which are classified as class 2 or class 3 will be evaluated by CFSAN to determine if regulatory follow-up is warranted. ACNA should use the following criteria to determine when analytical results should be forwarded to CFSAN 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: ACNA should contact CFSAN/ONPLDS/Food Labeling and Standards Branch at 301-436-2371 when excess nutrients are found to determine the regulatory significance and whether a check analysis should be performed.

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

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5. Microbiological Analysis

SRL must refer to the guidance contained in the ORA/DFS Standard Operating Procedure dated August 6, 2001 for routine subtyping of all isolates positive for *Salmonella* spp., *Listeria monocytogenes,* and *E. coli* 0157:H7. Do not delay the sample classification or pursuit of additional regulatory action and/or follow-up pending the results of these additional tests.

All references to the BAM refer to the Bacteriological Analytical Manual current edition available online on CFSAN's website http://www.cfsan.fda.gov/~ebam/bam-toc.html (referred to as e-BAM).

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 the July 9, 1998 supplement to the "Guidance for the Use of Rapid Methods for Food Microbiology" issued April 24, 1998.

Analyze according to the e-BAM, Chapter 10 and 11. Analyze on a composite basis only. For products subject to this compliance program, analyze four composites per sample.

> **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

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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 Anthony.Hitchins@fda.hhs.gov 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 "Guidance for the Use of Rapid Methods for Food Microbiology" issued April 24, 1998.

> **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
> Attn: Doris Farmer

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.

Identification, enumeration, coagulase, ancillary tests, and viable count (MPN) 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 13.

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.

NOTE: If the District or Regional laboratory cannot perform the VIDAS, then contact Reginald Bennett at (301) 436-2009 to arrange for shipment of portions of the actual sub-samples to CFSAN for confirmation.

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

NOTE: Send the extract used for the TECRA™ ELISA kit and the reserve portion of all the original sub-samples to:

Mr. Reginald Bennett (HFS-516)
CFSAN/Microbiology Methods Research Branch
5100 Paint Branch Parkway, Rm. 3E019
College Park, MD 20740
Phone: 301-436-2009
Contact Mr. Bennett prior to shipment

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 CFSAN. Send the extract used for the TECRA™ ELISA kit and the reserve portion for all of the original sub-samples to Mr. Bennett at the above address as expeditiously as possible.
*

Bacillus cereus

e-BAM, Chapter 14. Analyze 10 sub-samples per sample. 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 to CFSAN/Microbiology Methods Research Branch for enterotoxigenicity testing.

Include a copy of the collection report and the analyst worksheet and ship according to the Federal Standards for Etiological Agents to:

Mr. Reginald Bennett (HFS-516)
CFSAN/Microbiology Methods Research Branch
*5100 Paint Parkway
College Park, MD 20740
(301) 436-2009*

Contact Mr. Bennett prior to shipment.

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 Dr. Peter Feng (HFS-516) at 301-436-1650 if needed, for final identification.
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6. Reporting of Results to CFSAN and the Home District

SRL/Microbiology Branch will immediately contact the CFSAN Regulatory/Compliance Contact and the CFSAN Regulatory/Policy Contact listed in Part VI, as well as the home district when samples with the following microbiological results are found:

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

7. 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 Medical Foods Program Manager at the address listed on page 1 of this compliance program.

8. 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

CFSAN 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". Because the EIR and analytical packages come directly to CFSAN, the home district does not need to send a formal recommendation to CFSAN. When violations are clearly supported by the evidence, the Center will prepare a warning letter for subsequent issuance by the home district. #

CFSAN 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 CFSAN when conditions observed during the inspection or analytical results warrant regulatory follow-up. In addition, CFSAN will forward to DIOP 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 & PROGRAM CONTACTS

1. References

ORA/DFI "Guide to Inspection of Manufacturers of Miscellaneous Food Products, Volume II", Section 4.
(http://www.fda.gov/ora/inspect_ref/igs/foodsp2.html)

Code of Federal Regulations, Title 21, Parts 101, 110, and 113 Food Labeling, CGMPs for Human Foods, and Thermally Processed Low-Acid Canned Foods Packaged in Hermetically Sealed Containers, respectively.
(http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfrv2_01.html)

2. Attachments

Attachment A--List of known foreign medical foods manufacturers/shippers and their products **(Not for Public Distribution)**
*Attachment B--List of exempt infant formulas **(Not for Public Distribution)***

3. Contacts

General Program Guidance Contact - Brenda Aloi, HFS-636, CFSAN/OC/Division of Field Programs (301) 436-2065, FAX (301) 436-2657

Regulatory/Compliance Contacts—Domestic: CFSAN/OC/Division of Enforcement, Domestic Branch, Nutritional Products, Labeling, and Dietary Supplements Team, HFS-607: Leader--Jennifer Thomas (301) 436-2094
Regulatory/Compliance Contact—Imports: CFSAN/OC/Division of Enforcement, Imports Branch, HFS-606; Sal Evola (301) 436-2164
Regulatory/Policy Contact (including questions on the classification of a product as a medical food) - Domestic and Import – CFSAN/ONPLDS, Division of Food Labeling and Standards, Compliance and Enforcement Branch, HFS-820 (301) 436-2371.

CFSAN Methods Contacts

For methodology other than metals/ minerals:

Dr. Jeanne Radar, HFS-840 at (301) 436-1786

For methodology involving metals/minerals:

Primary contact - William Mindak, HFS-338, (301) 436-2005
Backup - Stephen Capar, HFS-338, (301) 436-2003

ORA/ORO Methods Contacts

Marsha Hayden (Microbiology) ORA/DFS (HFC-140), (301) 827-1039

George Salem (nutrients) ORA/DFS (HFC-140), (301) 827-1031

ORA/ORO Inspection/Investigation Contacts

Domestic Investigations Contact - Barbara Marcelletti, ORA/DFI (HFC-132), (301) 827-5635

Imports Contact - Ted Poplawski ORA/DIOP (HFC-170), (301) 443-6553

PART VII - CENTER RESPONSIBILITIES

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The Director, Office of Nutritional Products, Labeling, and Dietary Supplements, is responsible for submitting an annual evaluation of this program. The evaluation should be submitted to the Chief, Compliance Programs Branch by April 1. The Division of Field Programs will provide accomplishment data to the Office of Nutritional products, Labeling, and Dietary Supplements when requested to aid in the program evaluation.
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