

# **Good Manufacturing Practices (GMPs) for Infant Formula**

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## Good Manufacturing Practices (GMPs) for Infant Formula

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## 0.1 Introduction

These Good Manufacturing Practices (GMPs) establish general requirements for effective control of ingredients, formulations, processes, facilities and equipment used for production of infant formula products.

Effective implementation of GMPs is essential to assure consistent quality, safety and nutritional adequacy of infant formula products. Infant formula may constitute the sole source of nutrition of an infant for up to a year after birth. This is a period of rapid growth and brain development which affects key aspects of a child's long term health status and well-being. Infant formula fabricators and manufacturers are responsible to ensure that effective GMPs are maintained for all products distributed in Canada.

Canadian manufacturers and/or importers are responsible to ensure that infant formula products imported from foreign manufacturing facilities for distribution in Canada are manufactured in accordance with these GMPs. Objective evidence of GMP conformance should be available in Canada. These GMPs will also be used to evaluate technical and quality aspects of premarket notification submissions for new or changed infant formulas.

In recent years, the HACCP (Hazard Analysis Critical Control Point) model for prevention of contamination has been widely accepted and applied in Canada and internationally. The HACCP system is a mandatory regulatory requirement in some food industry sectors and has been embedded in food regulations based on international HACCP Guidelines issued by the Codex Alimentarius Commission (see section 0.4 below).

The ISO 9000 model provides an internationally recognized approach for quality management systems used to establish and maintain effective management processes for all activities affecting quality. ISO 9000 closely parallels GMP requirements. In the food industry, such management controls are often referred to as "prerequisite programs". These programs should be implemented prior to HACCP.

Formal HACCP and ISO 9000 programs are not mandatory for infant formula establishments at this time unless required by regulation. However, all infant formula fabricators and manufacturers are required to have in place effective GMPs and related quality control procedures which provide equivalent results, and which satisfy all applicable regulatory requirements. This GMP standard

encourages the application of HACCP and ISO 9000 principles and programs in infant formula establishments as a means to identify and control critical control points, to prevent contamination and failure incidents, and to continuously improve products and processes.

## **0.2 Purpose**

The purpose of this document is to establish and document the current Good Manufacturing Practices for production and quality control of infant formula products made for distribution in Canada. Health Canada uses the GMPs as a basis on which to assess the manufacturing information received in premarket notifications for new or changed infant formulas. The GMP in turn will be used by the Canadian Food Inspection Agency (CFIA) to assist in assessing Canadian manufacturers and fabricators on their ability to ensure domestic and imported infant formula meet Canadian legislation.

## **0.3 Scope**

The Good Manufacturing Practices described in this document apply to the production of all Human Milk Substitutes (Infant Formulas) as prescribed in Division 25 of the Food and Drug Regulations, whether the product is produced domestically or imported for distribution in Canada.

These GMPs also apply to new or changed infant formulas, and to third party facilities subcontracted to manufacture or package infant formula products.

## **0.4 Reference Documents and Codes of Practice**

It is intended that this GMP document be used in conjunction with the following international Codex Codes of Practice and guidelines or their national equivalents to ensure the production of safe and nutritionally adequate products in accordance with the Food and Drugs Act and Regulations.

1. Recommended International Code of Practice - General Principles of Food Hygiene (Codex Alimentarius Commission CAC/RCP 1-1969, Rev 4, 2003);
2. Hazard Analysis and Critical Control Point (HACCP) System and Guidelines for its Application (annex to Codex Alimentarius)

Commission CAC/RCP 1-1969, Rev 3, 1997);

3. Recommended International Code of Hygienic Practice for Foods for Infants and Children (Codex Alimentarius Commission CAC/RCP 21-1979);
4. Recommended International Code of Hygienic Practice for Low-Acid and Acidified Low Acid Canned Foods (Codex Alimentarius Commission CAC/RCP 23-1979, Rev 2, 1993);
5. Code of Hygienic Practice for Aseptically Processed and Packaged Low-Acid Foods (Codex Alimentarius Commission CAC/RCP 40-1993).
6. Canadian Food Inspection Agency Code of Practice, General Principles of Food Hygiene, Composition and Labelling (Canadian Food Inspection Agency, April 2006)
7. Canadian Food Inspection Agency Good Importing Practices for Food (Canadian Food Inspection Agency, March 2006)
8. 2003 Guide to Food Labelling and Advertising (Canadian Food Inspection Agency, 2003)

Infant formula manufacturers should have ready access to current versions of these international codes and guidelines or their national equivalents, and refer to them for technical guidance as appropriate.

## 0.5 Definitions

For the purpose of these GMPs, the following expressions have the meaning stated:

**Batch** - a specific quantity of infant formula intended to have uniform character and quality within specified limits, which is produced according to a single manufacturing order and which may constitute the whole or a part of a lot.

**Contamination** - an introduction or occurrence of a contaminant in food or food environment.

**Corrective action** - any action to be taken when a nonconformance is encountered at any point in the process including designated critical control points.

**Critical control point (CCP)** - a step in the process at which control can be applied and is essential to prevent or eliminate a food safety hazard or to reduce it to an acceptable level.

**Critical Limit** - a criterion which separates acceptability from unacceptability.

**Deviation** - failure to meet the critical limits or other specified requirements for a critical factor.

**Establishment** - any building or area in which infant formula or its components are handled, and the surroundings under the control of the same management.

**Expiration date** - means, in respect of an infant formula, the date

- (a) after which the manufacturer does not recommend that it be consumed, and
- (b) up to which it maintains its microbiological and physical stability and the nutrient content declared on the label; (Division 25 of the Food and Drug Regulations)

**Fabricator** - a person who manufactures and / or processes and packages an infant formula.

**Failure incidents** - deviations on critical limits and other incidents of nonconformance.

**HACCP system** (Hazard Analysis Critical Control Point) - a system which identifies, evaluates, and controls hazards which are significant for food safety.

**Human milk substitute or infant formula** - any food that is represented (a) for use as a partial or total replacement for human milk and intended for consumption by infants [with normal or special dietary needs], or (b) for use as an ingredient in a human milk substitute (Division 25 of the Food and Drug Regulations).

**Indicator nutrient** - a nutrient whose concentration is measured during the manufacture of an infant formula to confirm complete addition of a premix or other raw ingredients of which the indicator nutrient is a part.

**Lot** - quantity of infant formula produced under identical conditions, all packages of which bear a lot number that identifies the production during a particular time interval from a particular "line" or other critical processing unit.

**Major change** - means, in respect to an infant formula, any change of an ingredient, the amount of an ingredient or the processing or packaging of the infant formula where the manufacturer's or fabricator's experience or generally accepted theory would predict an adverse effect on the levels or availability of nutrients in, or the microbiological or chemical safety of, the human milk substitute (Division 25 of the Food and Drug Regulations).

**Manufacturer or distributor** - means a person, including an association or partnership, who under their own name, or under a trade-, design or word mark, trade name or other name, word or mark controlled by them, sells a food or drug; (Part A, Food and Drug Regulations)

**Manufacturing order** - Instructions outlining in detail the materials and procedures required to manufacture a single batch or lot of infant formula.

**Master manufacturing documents** - a set of reference documents detailing the identity and exact quantity of all ingredients, the approved procedures for processing and packaging, and the in-process and finished product testing requirements and specifications for a batch of infant formula at a specified facility.

**Monitoring** - a planned sequence of observations or measurements to assess whether a CCP (or other activity) is under control.

**New human milk substitute or infant formula** - means a human milk substitute that is (a) manufactured for the first time, (b) sold in Canada for the first time, or (c) manufactured by a person who manufactures it for the first time (Division 25 of the Food and Drug Regulations).

**Nonconformance** - a failure to meet an established requirement.

**Premix** - a combination of ingredients containing two or more nutrients as specified on the label, which is compounded in a manufacturing operation distinct from the processing of the final product.

**Quarantine** - the removal of an ingredient, material, or product lot from availability for use or sale. Quarantine may be achieved by physical segregation of the affected lot, or by a procedural material control system which effectively prevents use or sale of the item.

**Raw ingredient, raw material** - any substance used in the manufacture of infant formula.

**Technically qualified person** - a person who has had technical training relevant to his responsibilities or who is qualified by relevant practical experience.

**Verification** - examination of the accuracy, correctness or effectiveness of validated process or process controls through testing, investigation or comparison with a standard.

## 0.6 GMP Update and Revision Process

Infant formula products, manufacturing processes, packaging systems, and related practices change and evolve on an on-going basis in response to scientific, technical, regulatory and marketing developments.

In order to ensure that this GMP standard continues to reflect current practices and requirements, it will be reviewed within 5 years of its issue date and updated if necessary to reflect on-going developments.

Infant formula fabricators, manufacturers, importers and other interested parties were consulted for input during this review and revision process.

### GMP Requirements

- Notes:**
1. References to Annexes and/or Codex Codes of Practice are included where relevant and useful.
  2. The term "shall" indicates a mandatory GMP requirement. It does not necessarily refer to a regulatory requirement. The term "should"

indicates a recommended practice for which the fabricator or manufacturer, as the case may be, is expected to establish appropriate controls which provide equivalent results.

3. General requirements apply as per the Codex Recommended International Code of Practice - General Principles of Food Hygiene and Recommended International Code of Hygienic Practice for Foods for Infants and Children.

## **1.0 Premises and Equipment**

- 1.1 Infant formula manufacturing, storage and distribution facilities shall be designed, constructed and maintained in a manner which permits operations to be conducted under safe, clean, sanitary and orderly conditions to prevent contamination with harmful substances.

Infant formula processing facilities shall satisfy the applicable design, layout and operational requirements of regulatory agencies responsible for establishment registration and/or inspection.

- 1.2 Facilities shall be located in an area, and operated in a manner which minimizes the risk of environmental contaminants of all types from internal and external sources.
- 1.3 Surfaces of walls, floors, ceilings and equipment used where materials or products are exposed shall be designed and maintained in a sanitary condition to prevent contamination of materials and products.
- 1.4 Production areas where products and materials are exposed shall be effectively segregated from storage areas, lunchrooms, washrooms and other service areas.
- 1.5 Equipment shall be designed, operated and maintained in a manner to prevent contamination and to enhance the safety and quality of the product.
- 1.6 Management shall ensure that adequate resources ( i.e., personnel, supervision, time, materials, equipment, tooling, computers, support services, etc.) are provided to ensure effective operation and maintenance of facilities, equipment and processes.

## **2.0 Qualifications, Training and Health of Personnel**

- 2.1 Management responsibilities, authority and reporting relationships shall be clearly defined and documented, and communicated to all affected personnel.
- 2.2 Employees of all departments involved in the design, production, testing, storage and distribution of infant formula shall be adequately qualified by training and experience to competently conduct the responsibilities with which they are charged.
- 2.3 Management should identify the on-going training needs of all personnel including new employees and ensure that these are met.
- 2.4 Management should prepare and periodically update a written annual Training Plan indicating what training will be provided.

The Training Plan should include identification of training requirements including new or updated skills and knowledge necessary for effective operation of new technologies and/or equipment introduced to the establishment (eg., automated production and test equipment, HACCP system and the importance of allergen concerns and their associated critical control factors).

- 2.5 Employees required to perform Internal Quality Audits shall be adequately trained on auditing techniques and procedures.
- 2.6 Training records shall be maintained for all employees involved in the development, production and testing of infant formula products.
- 2.7 Procedures should detail the requirements for health screening for new employees, and on-going monitoring of current employees.
- 2.8 Employees with open wounds or communicable diseases shall not be permitted to work in areas where materials or products are exposed.

### 3.0 Document and Data Approval and Change Control

- 3.1 Written procedures shall be implemented for effective control of approval, distribution and revision of all critical controlled documents and data including:
- Ingredient, premix and packaging material specifications;
  - In-process and finished product specifications;
  - Master manufacturing documents;
  - Product and premix master formulations, including identification of specific ingredients to control composition and allow identification of all possible food allergens;
  - Manufacturing processes and instructions;
  - Test, inspection and calibration methods;
  - Company policies related to manufacturing, quality assurance and distribution;
  - Standard operating procedures, work instructions and related forms;
  - Authorized test protocols and plans (eg., validation protocols, stability plans);
  - Relevant electronic files and databases;
  - Other pertinent documents and data affecting quality.
- 3.2 Controlled documents shall be approved by authorized personnel, and identified by a unique document number, revision number/code, and/or issue date.
- 3.3 Procedures shall be specified for documentation and approval of temporary revisions of controlled documents when necessary, including authorization by qualified personnel.

Temporary changes shall not be implemented without proper authorization including consideration of related documents, processes and validation requirements.

- 3.4 All affected users should be notified promptly of changes in controlled documents.

Additional training should be provided to users if necessary to ensure effective implementation of approved changes.

- 3.5 All obsolete documents shall be promptly removed from distribution. Any copies maintained for reference for legal, business or technical purposes should be stored separately from current documents and clearly marked as obsolete or superseded.

#### **4.0 Hygiene, Sanitation and Contamination Control**

**Note:** General Codex requirements apply as per Recommended International Code of Practice General Principles of Food Hygiene, including the Annex Hazard Analysis and Critical Control Point (HACCP) System and Guidelines for its Application.

Formal HACCP implementation is not mandatory unless mandated by other applicable food regulations, but is encouraged for infant formula establishments.

- 4.1 Adequate facilities, suitably designated, should be provided for cleaning utensils and equipment. Such facilities should have an adequate supply of hot and cold potable water where appropriate.
- 4.2 The fabricator shall implement a written sanitation program which includes cleaning procedures for premises and equipment as well as instructions on the sanitary handling of all materials and equipment used in production.
- 4.3 Employee health and hygiene requirements shall be documented and effectively implemented. The hygiene program shall clearly define clothing requirements and hygiene procedures for company personnel and visitors.
- 4.4 The fabricator shall establish and implement a documented pest control program including approval and control of designated pesticide products and pest control contractors.
- 4.5 All materials, ingredients, and products shall be clearly identified and stored under sanitary conditions which prevent contamination and/or quality deterioration.

Materials of different types (e.g., liquid chemicals, bagged raw materials, premixes, packaging materials, etc.) should be stored in different areas of the warehouse in order to prevent contamination or mix-ups.

- 4.6 Written procedures shall be implemented for cleaning and storage of processing equipment in order to prevent microbiological contamination, chemical contamination and accidental carry-over of a food allergen from previous production runs.

Automated cleaning systems such as Clean-In-Place (CIP) systems shall be validated by suitable methods to ensure their effectiveness in achieving cleaning and sanitation objectives and in preventing contamination.

- 4.7 Written procedures shall be implemented for approval, storage and use of approved cleaning chemicals and pesticides. Chemical products shall not be used unless approved for the specified applications by a technically qualified person.

Cleaning chemicals, pesticides and other non-ingredient chemicals shall be stored in a designated area segregated from the areas used for storage of raw materials and products.

All approved non-food chemicals used are listed in the "Reference Listing of Accepted Construction Materials, Packaging Materials, and Non-Food Chemical Products" published by the Canadian Food Inspection Agency (CFIA), or the fabricator and/or manufacturer has a "letter of no objection" from Health Canada.

- 4.8 Critical control points should be identified by the fabricator for each stage of the manufacturing process (preferably in the master manufacturing documents).
- 4.9 Written procedures should be implemented for periodic monitoring of environmental quality in processing and storage areas, and for prevention of environmental contamination.
- 4.10 Records of cleaning and sanitation, environmental monitoring and pest control shall be maintained at the manufacturing establishment for a minimum one year after the expiry date on the label or container.

## **5.0 Quality Assurance, Quality Control and Laboratory Operations**

**Note:** General guidelines on validation of test methods are included in Annex 2.

- 5.1 The fabricator and/or manufacturer shall have a Quality Assurance/Quality

Control (QA/QC) department under the direction of a technically qualified person who reports directly to a unit other than production.

- 5.2 The scope, responsibilities and operations of QA and QC activities including laboratory operations shall be documented in approved, controlled procedures and test and inspection methods. These procedures and methods shall include handling and secure storage of production and test records and related data including electronic data acquisition, storage and back-ups where used.
- 5.3 The fabricator and/or manufacturer shall maintain, or have access to, suitably equipped laboratories to control the production and acceptance of raw ingredients, packaging materials, in-process and finished products including method and process validation and stability capabilities where required.

Chemical, microbiological and physical test facilities shall be designed, equipped, staffed and operated to facilitate generation of reliable quality control test results.

In-house laboratories, particularly those conducting microbiological analysis, require procedures to minimize the risk of contaminating the processing facilities

- 5.4 Analytical and test methods shall be valid for their intended purpose. Methods used to evaluate materials and products should be sufficiently specific, accurate and precise to provide reliable data on which to base an assessment of product quality.

Test methods should either be standard published methods (eg., AOAC, USP, FCC, etc.), or give results comparable to standard methods.

Chemical, microbiological and physical analysis/test methods shall be documented in sufficient detail that a trained analyst or technician can perform the method correctly and consistently, and can produce reliable test results within the known capability of the method.

Method validation studies should be planned, conducted and documented to demonstrate equivalence of new or revised methods to standard methods. Retrospective validation and/or trend analysis may be useful in some situations.

Results of method validation studies should be reviewed and approved by authorized QA/QC personnel prior to routine application of the method to assess product quality.

- 5.5 Third party contract laboratories and test facilities shall be selected, approved and used under control of the QA/QC department based on their test capability including effective operating controls and procedures.
- 5.6 Manufacturing processes shall be monitored at appropriate in-process stages to ensure that activities are conducted according to established procedures and specifications. Special attention should be focussed on critical control points.
- 5.7 Sampling at any stage (ie., incoming, in-process, or finished product) shall be conducted according to the fabricator and/or manufacturer's predetermined sampling plan designed to provide a valid basis for acceptance or rejection of materials and products.
- 5.8 Procedures for identification, handling and storage of samples shall be clearly documented, including instructions for preparation of composite samples where relevant.
- 5.9 Laboratory instruments and apparatus shall be calibrated prior to first use and at defined intervals in accordance with a written calibration program, approved calibration methods, and valid calibration standards.

Calibration records shall be maintained for a minimum of one year after the expiry date on the label or container.

## **6.0 Receiving and Storage**

- 6.1 The establishment should have one or more designated receiving areas with adequate space for temporary handling of incoming materials.

Receiving areas shall be designed and operated in a manner which prevents transfer of contaminants into the facilities.

- 6.2 Approved procedures should clearly describe suitable handling methods for non-product chemicals (eg., insecticides, lubricants). Non-product chemicals should not be co-mingled with product ingredients in the receiving area.

6.3 Procedures for material identification and status control should be documented and effectively implemented to prevent mix-ups, including an effective means of lot control for all incoming materials.

6.4 Suitable facilities, equipment and documented procedures shall be used for sampling of incoming materials to prevent contamination of materials and test samples, and to ensure correct identification and storage of samples.

Sampling should be conducted in a controlled environment where practical.

6.5 Storage areas and material handling equipment shall be operated and maintained in a safe, orderly manner which prevents damage, mix-ups and accidental addition of undeclared food allergens.

Spills shall be cleaned up without delay.

6.6 Any material or product which is held for rework, reprocessing or reinspection shall be identified, segregated, and effectively restricted from inadvertent use or shipment until planned activities have been completed.

6.7 Rejected material and product shall be quarantined, identified as "rejected", and securely stored until its disposal by approved means.

All disposals of rejected material and product shall be clearly documented.

6.8 Waste materials should be physically segregated from incoming materials and disposed of by approved, safe and effective means.

## **7.0 Ingredient and Packaging Material Control**

7.1 Each raw ingredient, packaging-material and nutrient premix shall be covered by approved written specifications which specify applicable physical, chemical, microbiological and identification test requirements and other pertinent details. All material specifications shall be maintained under effective document control.

Specifications for ingredients and packaging materials shall include applicable packaging requirements and storage conditions. All product-contact materials shall be composed of substances that are safe, suitable, and authorized for use by the responsible regulatory authority. Specifications should clearly identify approved product contact/barrier layer composition (if any).

Specifications should include expiry dates and retest criteria (if permitted) to ensure quality and potency of labile properties. The fabricator and/or manufacturer shall maintain records of retest and/or disposition of any material which exceeds its approved usage period.

- 7.2 Water used in products shall meet potable water standards as a minimum, and shall be tested on a sufficient frequency to ensure consistent, acceptable quality.

**Note:** Refer to requirements for potable water in Canada, described in Canadian Drinking Water Guidelines, issued by Health Canada.

- 7.3 Steam, ice, nitrogen, compressed air, process water and other manufacturing aids which come into direct contact with materials or products shall have approved specifications and shall be tested on a sufficient frequency to ensure their quality.

- 7.4 Written procedures shall be implemented for selection, approval and control of suppliers of ingredients and packaging materials. There should be an ongoing program to ensure the continuing reliability of each vendor.

- 7.5 Each receipt of raw ingredient, packaging material or premix shall be assigned a lot number, and held in quarantine pending its testing and release by QA/QC.

Controls include but are not limited to product composition, nutrition profile and safety including microbiological, chemical concerns and control of the presence of undeclared food allergens.

- 7.6 Each lot of incoming material shall be sampled and tested by approved methods to confirm compliance with specifications unless the fabricator has records to show that the material is consistently within specifications.

- 7.7 As a minimum, each lot of raw material shall be tested for identity after receipt by the fabricator.

- 7.8 Criteria for reduced testing of purchased materials shall be documented and approved if used. Reduced or skip-lot testing may be authorized by QA/QC after accumulation of sufficient historical data (eg., typically 3-5 lots of a material) to establish the vendor's reliability and consistency.

7.9 Raw ingredients that are accepted without a supplier's certification, but are relied upon to provide required nutrients in the infant formula, shall be sampled and analyzed for each relied-upon nutrient unless the fabricator has records to show that each nutrient is consistently within specifications.

## 8.0 Process Validation, Qualification and Control

**Note:** Internationally published Codex requirements apply as per the referenced documents listed in section 0.4 above. In particular, the technical and equipment requirements specified in the Recommended International Code of Hygienic Practice for Low and Acidified Low Acid Canned Foods and the Code of Hygienic Practice for Aseptically Processed and Packaged Low Acid Foods are useful reference documents regarding of these GMP requirements.

The fabricator's technically qualified personnel responsible for processing and QA/QC should be familiar with and implement effective controls based on applicable Codex Codes of Practice or their national equivalents for manufacturing processes.

General guidelines on process validation are included in Annex 2.

## 8.1 General Requirements

**Note:** The manufacturer should have a letter from Health Canada verifying the pre-market notification for each infant formula product marketed in Canada. Any major change including changes in ingredients, processing, or packaging require a pre-market notification.

8.1.1 The production of each batch of infant formula shall be conducted according to the approved master manufacturing documents.

8.1.2 Relevant processing procedures and instructions shall be readily available for easy reference by process operators.

8.1.3 Records shall be completed during the production of each batch documenting the actual lot number and quantity of each ingredient added, the completion of each step of the manufacturing procedure, and the actual results of all in-process measurements.

Batch records should be filled out as the process is completed to the greatest extent possible without compromising critical processing operations.

- 8.1.4 Critical stages of the manufacturing process shall be monitored in such a way as to ensure that no unexpected nutrient losses occur during processing.

Process deviations from scheduled processes for sterile products, or from specified action limits for critical control points, and any resulting corrective actions, shall be documented, evaluated and approved by qualified persons.

- 8.1.5 Suitable methods shall be used to evaluate and verify product homogeneity or uniformity after mixing and blending operations, the consistency in composition and the absence of undeclared allergens.

- 8.1.6 The performance of automated/computer controlled equipment shall be controlled and monitored by appropriate methods to ensure on-going reliable operation.

Access to automated and computerized settings shall be restricted to personnel who are qualified and authorized to adjust settings when necessary.

- 8.1.7 Approval of temporary changes or deviations from established processing conditions shall be authorized in writing by a qualified technical person based on appropriate consideration of their potential affects on product quality and safety.

Samples of the product produced under modified conditions should be included in the stability program when there could be potential affects on product shelf-life.

- 8.1.8 Process operators shall be given adequate training under close supervision before they are required to work independently with new technologies and/or new work processes introduced to processing areas.

- 8.1.9 Any in-process product transferred to another establishment for further processing or packaging shall be effectively identified, controlled and documented to prevent inadvertent mix-ups.

## **8.2 Process Validation (see Annex 2)**

- 8.2.1 Prior to the first commercial release of any new infant formula, process qualification studies shall be planned and conducted by technically qualified persons. These studies may include concurrent validation studies when appropriate, and should demonstrate that defined processing procedures and instructions, using the specified ingredients, materials and equipment, consistently yield a product which meets the required specifications. Validation batches may be released for sale subject to meeting all quality, stability and regulatory requirements.
- 8.2.2 Significant changes in blending and mixing operations, including premix blending, shall be validated and approved based on appropriate validation protocols. Special attention should be given to validation of uniform distribution of minor and trace components.
- 8.2.3 Significant changes in the function of automated and computer controlled equipment shall be validated by appropriate methods to ensure capability, reliability, consistency, and freedom from drift over time.
- 8.2.4 Any process changes which could significantly affect product quality or safety shall be validated by the fabricator and/or manufacturer prior to release of the product for distribution.
- 8.2.5 Records of process validation studies shall be approved by technically qualified persons and stored on the fabricator and/or manufacturer's premises for a minimum of 3 years.

## **8.3 Premix Control**

- 8.3.1 Each nutrient premix shall be manufactured according to approved master manufacturing documents and shall be analyzed for each nutrient. Premix specifications shall refer to test methods and limits for each nutrient.
- 8.3.2 Each premix batch should be sampled and analyzed for one or more indicator nutrients to confirm homogeneous distribution of minor components.
- 8.3.3 Process controls and testing/release responsibilities shall be clearly defined for each premix purchased from a third party premix fabricator.

The premix fabricator shall supply a complete certificate of analysis unless the infant formula fabricator completes full retesting.

- 8.3.4 As a minimum, each premix lot shall be sampled after receipt by the infant formula fabricator and tested to confirm its correct identity and uniformity.
- 8.3.5 Premixes shall be stored in approved packaging under controlled conditions which ensure preservation of quality and potency until the designated expiry or retest date.

A premix shall not be used after its expiry date unless it has been re-approved by QC/QA with an extended expiry date.

- 8.3.6 The fabricator should ensure that appropriate stability studies have been conducted to verify the assigned expiry date of premixes containing labile nutrients.

#### **8.4 Reprocessing or Rework of Infant Formula**

- 8.4.1 Any proposed rework, reprocessing, sorting, and/or reinspection instructions shall be documented and approved by authorized QA/QC personnel prior to undertaking the activity.
- 8.4.2 Rework, reprocessing or reinspection of an infant formula product shall be conducted under carefully controlled conditions to prevent contamination or deterioration of the product. Carryover of nutrients in rework should be considered and nutrient addition adjusted accordingly. Completion of such activities shall be supervised, documented and approved by qualified personnel.

Rework should be controlled to avoid the presence of undeclared allergens, by only reworking the same product back into a batch.

- 8.4.3 Results of such activities, including related test and inspection results, shall be documented and approved by the designated QA/QC authority prior to product release or rejection.

8.4.4 Consideration should be given to including reworked lots in the stability program to monitor for possible long-term adverse impacts on product quality.

## **8.5 Calibration and Maintenance of Manufacturing and Test Equipment**

8.5.1 Written procedures shall be available for calibration of critical inspection, test and measuring devices including computerized and/or automated equipment and dispensing devices.

There should be a master schedule of required calibration activities including calibration frequency, methods, and required accuracy or performance criteria.

8.5.2 A planned preventive maintenance program and procedures shall be documented and implemented for critical processing equipment, and for support facilities and equipment essential for maintenance of effective control of critical manufacturing processes.

8.5.3 The fabricator shall establish and implement procedures for reactive maintenance, and provide adequate maintenance capacity and capability to ensure process reliability.

8.5.4 Planned calibration and maintenance activities shall be completed on schedule.

Related critical calibration and maintenance records shall be retained on-site for a minimum of one year after the expiry date.

8.5.5 Processing equipment and inspection, test and measurement devices which no longer function correctly shall be promptly removed from service and repaired or replaced.

When defective processing equipment or inspection, test and measuring devices have been detected, appropriate action shall be taken to prevent use or distribution of non-conforming products. Potentially affected products, including released lots in distribution, shall be quarantined or held if necessary pending completion of a retrospective investigation to determine if product quality has been adversely affected.

## 9.0 Finished Product Control

- 9.1 Each lot of finished infant formula product shall be sampled according to an approved sampling plan and held in quarantine until it has been evaluated and released for sale by the QA/QC department.
- 9.2 Each lot shall be tested for compliance with its chemical, microbiological, physical and packaging specifications.
- 9.3 Each lot of Infant Formula Products should meet, as a minimum, the microbiological criteria seen in the Table below:

**Note:** Link to The Compendium of Analytical Methods Volumes 2 and 3  
[http://www.hc-sc.gc.ca/fn-an/res-rech/analy-meth/microbio/index\\_e.html](http://www.hc-sc.gc.ca/fn-an/res-rech/analy-meth/microbio/index_e.html)

Method	Guideline	Sampling Plan Parameters			
		n	c	m	M
MFHPB-18	ACC	5	2	10 <sup>3</sup>	10 <sup>4</sup>
MFHPB-19	<i>E. coli</i>	10	1	<1.8	10 <sup>1</sup>
MFHPB-20	Salmonella	20	0	0	0
MFHPB-21	<i>S. aureus</i>	10	1	10 <sup>1</sup>	10 <sup>2</sup>
MFLH-42	<i>Bacillus cereus</i>	10	1	10 <sup>2</sup>	10 <sup>4</sup>
MFHPB-23	<i>Clostridium perfringens</i>	10	1	10 <sup>2</sup>	10 <sup>3</sup>

**Important Note Regarding Microbiological Monitoring and Testing for *Enterobacter sakazakii* and *Salmonella* spp.** In light of the emergence of *Enterobacter sakazakii* as a recognized opportunistic pathogen, it is important to ensure control over this pathogen, as well as *Salmonella* spp. The presence of these pathogens constitutes a considerable risk if conditions after reconstitution permit multiplication. More specifically, control over these pathogens is important for those products developed specifically for highly sensitive populations such as infants less than 6 months, with a subgroup of this population being at greatest risk, i.e., neonates of less than 28 days, particularly pre-term infants, low-birth weight infants and immunocompromised infants. One way this could be accomplished is through monitoring and testing for the Enterobacteriaceae in both the manufacturing environment and finished product. Although microbiological criteria for *E. sakazakii* have not been agreed upon as yet at the international level, the proposed EU approach where products intended for infants under 6 months of age are first tested for Enterobacteriaceae, and then if positive, lots are examined further for both *E. sakazakii* and *Salmonella* spp., should be the approach followed.

- 9.4 Finished product specifications and test results shall confirm correct addition of each nutrient required or quantified on the label. Suitable indicator nutrients may be tested to confirm correct addition and distribution of nutrient premixes (generally 1 or more nutrients should be tested per premix).

Each nutrient required or quantified on the label and added individually to the batch shall be tested at some point to confirm its correct addition.

Specifications should include appropriate tests to confirm uniform distribution of representative nutrients throughout the batch, especially for labile or trace components. Uniformity testing may be reduced when confirmed by suitable process validation studies, in-process controls and process history.

- 9.5 Production, packaging and QA/QC test records shall be reviewed and approved by a technically qualified person of the QA/QC department prior to release of the lot.
- 9.6 Finished product shall not be shipped from the manufacturing site prior to release unless the fabricator and/or manufacturer maintains effective control of the warehouse facility to which it is shipped.
- 9.7 Subsequent to reviews as part of premarket notification, there are procedures in place to ensure that labels continue to be in compliance with the *Food and Drugs Act and Regulations* and the *Consumer Packaging and Labelling Regulations* and that all labelling information is accurate.
- 9.8 All pamphlets, posters, handouts, and other Canadian advertising materials, developed and/or distributed are reviewed and verified for accuracy and compliance with Canadian legislation (see Chapter 3 of the *2003 Guide to Food Labelling and Advertising*).

## **10.0 Contract Manufacturing and Packaging**

- 10.1 Written procedures shall be implemented for selection, approval and control of third party production and packaging establishments. Selection shall be based on the contract fabricator's ability to comply with these infant formula GMPs and applicable regulations, in addition to other business criteria.
- 10.2 Controls and responsibilities shall be documented for each contract manufacturing establishment including provisions for: ingredient and product

handling; storage; processing; accurate labelling; packaging; supervision of processing activities; QC/QA responsibilities; product test methods; GMP and regulatory compliance.

- 10.3 Raw materials and packaging materials received directly from the supplier at the contract fabricator's facility shall be subject to the same incoming testing, identification and release requirements as if they were received by the primary fabricator or manufacturer.
- 10.4 Materials and products transferred to/from a contract fabricator or packager shall be effectively identified, controlled and documented to prevent inadvertent mix-ups.
- 10.5 Any significant quality problems and/or processing deviations experienced by the contract fabricator shall be documented and communicated to representatives of the primary fabricator and/or manufacturer, and shall become part of the quality records.
- 10.6 Copies of the contract fabricator or packager's processing and quality control records shall be forwarded to, and reviewed by, the primary fabricator and/or manufacturer's QA/QC personnel prior to product release unless other arrangements and responsibilities have been clearly defined.

The manufacturer remains ultimately responsible for product release, and for compliance of the contract fabricator/packager with Infant Formula GMPs.

- 10.7 There should be an ongoing program to ensure the continuing reliability of each contract fabricator.
- 10.8 The primary fabricator's and/or manufacturer's QA/QC personnel (or authorized designate) shall conduct periodic quality audits of each contract manufacturing facility at an adequate frequency to ensure GMP compliance.
- 10.9 Nonconformance and corrective actions arising from quality audits and on-going operations of a contract fabricator shall be reviewed by the primary fabricator's or manufacturer's QA/QC personnel, and shall be addressed and corrected in a timely manner.

## 11.0 Stability Program and Expiry Date Control

- 11.1 The fabricator or manufacturer shall establish and maintain a documented stability program or procedure for all infant formula products and packaging container variations in order to monitor product quality over shelf-life and to support the authorized expiry dates. Responsibility and authority for interpretation of stability test results and for setting and revising product expiry dates shall be defined. This is normally a QA/QC responsibility.

The stability program should specify the stability sample requirements, test schedule and required physical, chemical and microbiological test requirements for each product or product family.

The stability program shall monitor product quality of a sufficient number of batches of each product over the labelled shelf-life to support overall conclusions regarding the stability of labile ingredients and physical properties, and the expiry date.

The stability program should specify the number of batches per year for each product depending on production volumes (eg., one batch per quarter). The number of batches and frequency of stability testing may be reduced once a sufficient database has been developed, but should not be less than one batch per year per product.

The stability program should include provisions for special stability studies to be initiated on products which have been reprocessed or reworked, and on processing/formulation trial batches. In special cases, it may be appropriate to evaluate the stability of returned or expired goods.

- 11.2 Product samples for stability studies shall be stored under controlled conditions which reflect normal shelf-life storage and, in special cases, well defined, accelerated stress conditions which may occur in distribution (e.g., freeze/thaw cycles or elevated temperature).
- 11.3 For each infant formula product, the fabricator or manufacturer shall conduct stability analysis for selected nutrients with sufficient frequency to substantiate the maintenance of nutrient content up to the expiration date of the product when subjected to normal conditions of storage and distribution.

- 11.4 A product-specific stability protocol shall be documented by responsible personnel for each new or significantly changed infant formula product and/or packaging format.
- 11.5 Stability data and records should be stored in a manner which facilitates their retrieval for review, analysis and summary reporting.
- 11.6 Responsible QA/QC personnel shall be notified promptly when stability tests indicate a possible concern with nutrient content or physical stability. The situation shall be investigated, communicated and appropriate action initiated if concerns are verified.

## **12.0 Control of Imported Infant Formula Products**

- 12.1 The manufacturer and/or importer of an infant formula shall ensure that each imported product is produced under quality and GMP standards and conditions consistent with the requirements of these Infant Formula GMPs for products manufactured in Canada.
- 12.2 The manufacturer and/or importer shall designate a technically qualified person in Canada to oversee and approve relevant quality, GMP, technical and regulatory matters.

This designated person(s) shall oversee effective control systems for product release, handling and investigation of complaints, review and approval of stability studies and expiry dates, and maintenance of product master documents and internal audit reports.

- 12.3 The manufacturer and/or importer shall retain on-site in Canada current copies of the master manufacturing documents under which an imported product has been manufactured. Detailed manufacturing procedures and actual processing and quality control records need not be maintained in Canada for each imported lot, but shall be available on request.

The manufacturer and/or importer should have access to a letter from Health Canada verifying the pre-market notification for each product intended for marketing in Canada. Any major change including changes in ingredients, processing, labelling require a pre-market notification.

- 12.4 Subsequent to reviews as part of premarket notification, there are procedures in place to ensure that labels are in compliance with the *Food and Drugs Act and Regulations* and the *Consumer Packaging and Labelling Regulations* and that all labelling information is accurate.
- 12.5 All pamphlets, posters, handouts, and other Canadian advertising materials, developed and/or distributed are reviewed and verified for accuracy and compliance with Canadian legislation (see Chapter 3 of the *2003 Guide to Food Labelling and Advertising*).
- 12.6 An imported lot of infant formula shall not be released for sale until the manufacturer and/or importer's designated technically qualified person has reviewed and approved the supplier's certificate of analysis and related documentation.
- 12.7 When an imported product is procured from an unrelated company, a technically qualified representative of the manufacturer and/or importer shall conduct an on-site GMP audit of the manufacturing facility prior to importation, and at least once in each 2-year period to ensure compliance with these Infant Formula GMP requirements.
- 12.8 When an imported product is sourced from a related company controlled and operated under the same corporate standards as those of the Canadian manufacturer or importer, the manufacturer and/or importer may rely on internal audits conducted by qualified corporate staff. Such internal audits should be completed at least once in each 2-year period.
- 12.9 Documentation regarding audit reports and related corrective actions shall be readily available for review and follow-up by the manufacturer and/or importer's designated person.
- 12.10 A stability program shall be maintained in Canada on each imported product unless comprehensive stability data are available from the source facility or corporate stability program.
- 12.11 Representative samples of each imported lot shall be retained under normal storage conditions in Canada for a minimum of one year after the product's expiry date.

### **13.0 Nonconformance Reporting and Corrective/Preventive Action**

- 13.1 The fabricator and manufacturer shall implement and maintain a system for documenting problems, Nonconformance, and the results of related investigations, decisions and corrective or preventive actions.
- 13.2 Disposition of all nonconforming materials and products shall be subject to review and approval by the fabricator and/or manufacturer's QA/QC department.
- 13.3 The fabricator and manufacturer should conduct a periodic review of historical nonconformance and complaints in order to identify and initiate appropriate corrective or preventive actions on adverse performance trends and/or recurring problems.

### **14.0 Customer Complaints and Resolutions**

Responsibility for recording, investigating and reporting on customer complaints shall be documented in approved procedures.

Responsibilities for medical input, initiating follow-up or corrective action, communicating with regulatory and corporate officials, and responding to the complainant shall be clearly defined.

The complaint handling process shall be capable of quickly escalating critical complaints and problems to senior management and regulatory officials in situations which could involve significant health or safety risks and/or potential recall.

Complaint handling procedures shall be capable of quickly identifying recurring or related complaints on specific products and/or lots of product.

### **15.0 Internal Quality Audits (or Self-Inspections)**

- 15.1 Periodic internal quality audits (or self-inspections) of all activities outlined in this GMP document shall be carried out by qualified personnel according to an established audit plan and schedule.

The purpose of internal audits is to assess conformance with established GMPs and quality requirements, to evaluate overall effectiveness in assuring quality,

safety and nutritional adequacy, and to initiate corrective or preventive actions and/or other improvements where required.

- 15.2 The scope of the internal audit program and activities should include contract fabricators (see section 10.0), foreign fabricators of imported products (see section 12.0), and suppliers of critical raw and packaging materials (see section 7.0).
- 15.3 All activities covered by the Infant Formula GMPs shall be audited at a frequency which reflects their importance, but for all requirements, at a minimum frequency of once per 2 years.

The frequency of internal audits should be increased for critical activities when on-going experience such as performance trends, Nonconformance or complaints indicate potential weaknesses or the need for on-going improvement.

- 15.4 Personnel conducting internal audits shall be trained as quality auditors, and shall be independent of the activities they audit, ie., they shall not audit their own areas of responsibility.
- 15.5 Corrective actions to address audit findings shall be initiated, documented and completed in a timely manner.
- 15.6 The results of internal audits and related corrective actions shall be reported to senior management.
- 15.7 Records of internal audits shall be maintained for a minimum of 3 years.

#### **16.0 Product Distribution, Returned Goods and Recall**

- 16.1 Written procedures shall be implemented and maintained for control of the fabricator's and manufacturer's warehousing, distribution and shipping activities, including proper stock rotation throughout the distribution channels.
- 16.2 Detailed distribution records shall be maintained, for a minimum period of one year after the product's expiry date, for all infant formula including products distributed free of charge to hospitals, doctors' offices, consumers and other customers or facilities.

16.3 Written procedures shall be available for control, evaluation and disposition of returned goods. Effective controls should be in place to ensure that returned goods are not restocked for resale without assurance of their continued safety and quality.

16.4 Written procedures shall be implemented and maintained for recall of infant formula when required.

The recall procedure shall clearly define the fabricator's and manufacturer's company responsibilities for evaluating health risks, making recall decisions, communicating with government officials and other external parties, and for implementing and reporting results of the recall.

16.5 Distribution records shall be readily accessible and should facilitate product recall by permitting traceability of individual lots of infant formula to the retail customer level in the event of a product recall.

The distribution system should be capable of quickly identifying the time period and geographic regions in which any individual lot was distributed (including previous returns of the lot), as well as effectively segregating, quarantining, and restricting distribution of remaining stock and returned goods of the problem lot(s).

16.6 The capability of the distribution system to identify, control, trace and reconcile individual infant formula lots should be tested periodically in a mock recall activity. Any deficiencies shall be corrected.

16.7 During a recall of infant formula, the manufacturer shall track progress of the recall and maintain effective control of all returned and remaining quantities of affected lots.

16.8 On conclusion of the recall, a final report should be prepared including final results of traceability, recovery and disposal of recalled product, related investigations and corrective actions, and communications with regulatory authorities.

16.9 Corrective action shall be taken to effectively prevent similar recalls in the future.

## 17.0 Quality Records and Retained Samples

- 17.1 The fabricator and/or manufacturer shall maintain all required manufacturing and quality control records, results of all analyses carried out, distribution records, and customer complaints for each lot of infant formula for a minimum of one year after the product's expiry date.

Longer storage periods designated for specific records in these GMPs take precedence over the expiration date of individual lots.

- 17.2 Written procedures shall be implemented for secure storage of electronic records for which there is no paper hardcopy. These procedures should include maintenance of backup files, and security provisions to prevent tampering with or inadvertent deletion or loss of electronic files and data.
- 17.3 Laboratory worksheets/books and instrument charts/scans, as well as electronic records, shall be maintained as part of the quality records.
- 17.4 The fabricator and/or manufacturer shall maintain in Canada retained samples of each lot of infant formula for minimum of one year after the product's expiry date.
- 17.5 The fabricator and/or manufacturer shall retain records of method and process validation studies, internal quality audits, and related corrective and preventive actions for a minimum of one year after the product's expiry date.
- 17.6 All required records and retained samples shall be stored in a restricted access area in an orderly fashion which facilitates ease of retrieval and prevents loss, under controlled environmental conditions which prevent avoidable deterioration.

## Annex 1

### HACCP Principles and Implementation Plan (based On Codex Guidelines)

The approach defined by the Codex Alimentarius Commission HACCP Guidelines establishes the following 7 universal principles of the HACCP System:

- Principle 1** Conduct a hazard analysis.
- Principle 2** Determine the Critical Control Points (CCPs).
- Principle 3** Establish critical limits.
- Principle 4** Establish a system to monitor control of the CCPs.
- Principle 5** Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control.
- Principle 6** Establish procedures for verification to confirm that the HACCP system is working effectively.
- Principle 7** Establish documentation concerning all procedures and records appropriate to these principles and their application.

Strictly speaking, implementation of process-focussed HACCP controls is not in itself enough since it does not cover the general policy and procedure framework, responsibilities, or GMP conditions which ensure effective control at all times.

Consequently, an establishment implementing HACCP should develop, document, and implement programs and procedures to control factors that may not be directly related to manufacturing controls but support the HACCP plans. These "prerequisite programs" are universal steps or standard operating procedures that control the operational conditions within a food establishment allowing for environmental conditions that are favourable to the production of safe food.

**Prerequisite programs** are required for the following:

1. Premises: outside property; building; sanitary facilities, water/steam/ice, quality control.
2. Transportation and Storage: food carriers; temperature control, storage of incoming materials, non-food chemicals, and finished product.
3. Equipment: general equipment design; equipment installation; equipment maintenance and calibration.
4. Personnel: training, health and hygiene requirements.
5. Sanitation and Pest Control: sanitation program; pest control program.
6. Recalls: recall procedures; distribution records.

While these prerequisite programs cover many important criteria, they do not address some critical issues for infant formulas such as overages, nutrient contributions, product uniformity, stability requirements, and process and method validation.

### **HACCP's 12 Implementation Steps**

The Codex HACCP System Guidelines establish the following 12 typical steps for implementation of an effective HACCP program.

- Step 1.** Assemble HACCP Team
- Step 2.** Describe product
- Step 3.** Identify intended use
- Step 4.** Construct flow diagram
- Step 5.** On-site confirmation of flow diagram
- Step 6.** List all potential hazards associated with each step, conduct a hazard analysis, and consider any measures to control identified hazards
- Step 7.** Determine critical control points (CCPs)

- Step 8.** Establish critical limits for each CCP
- Step 9.** Establish a monitoring system for each CCP
- Step 10.** Establish corrective actions
- Step 11.** Establish verification procedures
- Step 12.** Establish documentation and record keeping

For additional information on implementation of HACCP, see the Codex HACCP System Guidelines and other published application guides.

## Annex 2

### Validation of Manufacturing Processes and Test Methods

This annex provides general guidelines intended to assist those responsible for validating manufacturing processes and test methods.

Without reliable knowledge of the inherent variation of manufacturing processes and test methods, it is difficult or impossible to make good management decisions based on technical data. Validation studies are used to evaluate and confirm the reliability of technical processes, equipment and methods in the hands of trained operators in order to provide confidence in the resulting data and required decisions based on good science.

When manufacturing processes or test methods are changed, it is useful to conduct controlled validation studies to verify the reliability and consistency of the process or method under normal operating conditions with trained operators. The design of validation studies depends on many factors including the nature of the product, process, equipment, reference methods, specification limits, and other aspects.

#### A. Validation of Manufacturing Processes

The following guidelines should be considered when planning or reviewing validation studies to evaluate and confirm process reliability:

1. A written validation protocol should be prepared and approved describing the objectives, processing conditions, and key variables for the study.
2. The study should be conducted under conditions which represent as closely as possible the current or proposed commercial production scale. Batch size, equipment scale and processing time are critical factors for mixing, blending, heat processing and similar unit processes.
3. Generally, 3 or more batches should be produced under controlled conditions in order to assess the consistency of the process. No conclusions can be made about process reliability and consistency based on a single batch.
4. The type and grade of materials used must be controlled.
5. Test and inspection results must be generated by valid test methods with

known precision and accuracy to be able to draw valid conclusions. (See section B)

6. The Sampling Plan is critically important. For validation of time-dependent blending and mixing operations, the protocol and sampling plan should call for samples from extreme points of the mixing equipment (eg., top, middle, and bottom) over a period of time. This should be repeated over 3 or more lots.
7. Process validation is specific to the equipment used. If different types or sizes of equipment may be used interchangeably for regular production, then each type should be validated individually (eg., different types or sizes of blenders, mixers, heaters, homogenizers, etc.).
8. The validation runs should be carried out by regular, trained operators. It may be necessary to determine how human factors could influence the process.
9. All observations, data and conclusions should be summarized in a formal validation report which is reviewed and approved by technically qualified personnel. If the operating conditions were changed significantly from those in the Validation Protocol, it may be necessary to conduct additional studies.
10. Once the new process is approved, care should be taken to ensure that any newly validated process conditions are accurately transposed into the regular production documents for commercial production.
11. Care must be taken in extrapolating validation results between different products, formulations, materials, and plant facilities. In critical processes, small changes can have significant effects on product quality, safety and/or process efficiency. Validation results obtained in one plant may not reflect process performance in a different facility, even when conditions seem to be equal, because of different environmental, material, equipment and human factors.
12. Retrospective process validation is useful in some cases to evaluate or demonstrate consistency of unit processes based on historical results for similar products and equipment. For example, the variation in losses of labile nutrients, or the homogeneity of trace components, may be strongly supported based on a statistical review of actual results for the previous 20 - 100 batches. This retrospective data may be very useful for determining the normal range of variation of a process under normal operating conditions.

13. Successful commercial scale validation batches may generally be accepted for sale subject to approval by QA/QC if the product complies with all specifications and regulatory requirements.

## **B. Validation of Test Methods**

Chemical, microbiological, and physical test methods must be reliable when used by trained operators in order to generate high quality analytical data to support decisions on product quality. Method reliability is generally demonstrated by completion of controlled method validation studies.

Typically, an analytical method should be validated for precision, accuracy, recovery, linearity and sensitivity by repetitive analyses of samples of known composition. Another acceptable approach is to analyze several samples by the new or proposed method and by a published reference method (eg., USP, AOAC or FCC) which has been proven reliable through inter-laboratory collaborative studies prior to its adoption for publication.

Method validation involves many of the same concerns as process validation. The following factors should be considered when designing a validation protocol or when evaluating the results:

1. Method validation studies should be conducted according to a defined validation protocol or plan with specific objectives.
2. Analyses should be conducted under normal laboratory environmental and operating conditions with normal supplies which reflect standard laboratory practices unless the new method or protocol calls for improved operating conditions to improve method reliability. The validation analyses should be conducted by trained analysts using their normal techniques unless specified otherwise in the method.
3. Since different analysts often use different techniques, it may be necessary to use several analysts over several sessions (or even different laboratories) to get a true measure of the method's repeatability and reproducibility.
4. The type and grade of materials, samples and standards must be well controlled. In some cases, the method of mixing, compositing or dispensing of test samples can have a major affect on test results.

5. A proper study of method precision and accuracy requires generation of several sets of test results on several similar samples. Verification of linearity requires use of standards and known samples over a range of concentrations. Verification of limits of detection requires evaluation of baseline noise and use of samples with very low concentrations of analyte close to the limit of detection.
6. Use of spiked additions in validation studies to evaluate recovery should be used and interpreted with care. Often the added (spiked) analyte is not fully absorbed into the sample matrix. It may be more easily recovered resulting in false conclusions.
7. Method validation is specific to the equipment used. If different types of equipment will be used interchangeably during regular analysis, then each should be validated individually (eg., 2 different types of ICPs, HPLC columns, etc.).
8. All observations, test results and conclusions should be summarized in a formal method validation report which is reviewed and approved by technically qualified personnel.
9. Once the new method is approved, care should be taken to ensure that newly validated test conditions are accurately transposed into the regular laboratory procedures.
10. Care should be taken when extrapolating method validation results between different products, formulations, materials or laboratories. In some cases, small changes can have very significant effects on method performance and reliability.
11. Retrospective method validation is useful in some cases to evaluate or demonstrate consistency of analytical methods based on historical results for similar samples. For example, the recovery of vitamins from a particular type of sample (eg. milk-based, liquid infant formula) may be strongly supported based on a statistical review of actual results for the previous 20 - 100 test or batches.