# A Guide for the Preparation of Submissions on Food Additives

## *Including Information on Irradiated Food Submissions and on Requests for Opinions on Substances Not Regulated as Food Additives*

**Bureau of Chemical Safety**
**Food Directorate**
**Health Products and Food Branch**

*December 27, 2007*

Canada

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## ABBREVIATIONS

| | |
|---|---|
| **ADI** | Acceptable Daily Intake |
| **BCS** | Bureau of Chemical Safety |
| **CAS** | Chemical Abstract Service |
| **CEPA** | Canadian Environmental Protection Act |
| **CFIA** | Canadian Food Inspection Agency |
| **CHHAD** | Chemical Health Hazard Assessment Division |
| **CI** | Colour Index |
| **DSL** | Domestic Substances List |
| **E.C.** | Enzyme Commission |
| **EC** | Environment Canada |
| **FAO** | Food and Agriculture Organization of the United Nations |
| ***F&DA*** | *Food and Drugs Act* |
| ***F&DR*** | *Food and Drugs Regulations* |
| **FCC** | Food Chemicals Codex |
| **FD** | Food Directorate |
| **FRC** | Food Rulings Committee |
| **GSFA** | (Codex) General Standard on Food Additives |
| **HC** | Health Canada |
| **IMA(s)** | Interim Marketing Authorization(s) |
| **INS** | International Numbering System |
| **I.U.P.A.C.** | International Union of Pure and Applied Chemistry |
| **JECFA** | Joint FAO/WHO Expert Committee on Food Additives |
| **NSN** | New Substances Notification |
| **NSNR** | New Substances Notification Regulations and the New Substances Notification Regulations |
| **OECD** | Organization for Economic Co-operation and Development |
| **SNAc** | Significant New Activity |
| **TMA** | Temporary Marketing Authorization |
| **TMDI** | Theoretical Maximum Daily Intake |
| **TOC** | (when selected, links directly to the) Table of Contents |
| **TOS** | Total Organic Solids |
| **VDD** | Veterinary Drugs Directorate |
| **WHO** | World Health Organization |

## INTRODUCTION AND PURPOSE OF THE GUIDE

The purpose of this Guide is to assist food manufacturers and distributors in the preparation of food additive submissions. Information is also provided on irradiated food submissions and on requests for opinions on substances not regulated as food additives. This Guide has been compiled by the staff of the Bureau of Chemical Safety (BCS), with the input of various other bureaus in the Food Directorate (FD), in accordance with their experience in evaluating submissions supplied by manufacturers, food sellers, and other petitioners.

Section 1.0 of the Guide provides relevant definitions and describes the regulatory context within which food additive submissions are considered.

Sections 2.0 and 5.0 of the Guide are most directly relevant to the preparation of a food additive submission. Section 2.0 of the Guide describes the administrative aspects as well as the technical components of a food additive submission. Section 5.0 of the Guide describes Interim Marketing Authorizations (IMAs), which are especially relevant to requests to extend the use of already-permitted food additives.

Section 3.0, describing environmental assessment requirements for food additives that may possibly also be considered "new substances" in the context of environmental regulations, should be considered by those preparing new food additive submissions.

Section 4.0 describes the procedure that is followed by Health Canada (HC) after a food additive submission has been evaluated and considered acceptable by the BCS. This procedure begins with presentation of the submission by the BCS to a senior management committee for approval and ends when the regulatory amendments enabling the use of the food additive in the prescribed manner have been made.

Information pertaining to submissions on irradiated food is found in Section 7.0.

Section 8.0 should be considered by those wishing to obtain an opinion from HC on the acceptability of a particular product that will be used in the manufacture of food or sold in or as a food but which would not be regulated as a food additive in Canada.

It must be emphasized that the material supplied in the present Guide, unlike that appearing in the *Food and Drugs Act (F&DA)* and *the Food and Drug Regulations (F&DR)*, is not legally binding but merely

represents an interpretation and elaboration of the provisions of section B.16.002 of the *F&DR*.

If a reader of this Guide has any further questions, please contact us; the Food Additives and Contaminants Section in the Chemical Health Hazard Assessment Division (CHHAD), BCS, would be pleased to offer any additional advice or clarification.

## PUBLIC ACCESS TO THE CANADIAN *FOOD AND DRUGS ACT* AND THE *FOOD AND DRUG REGULATIONS*

The Department of Justice's website hosts the most current *Food and Drugs Act* and *Regulations*. In addition, a consolidated, departmental version is available on the HC website.

Provisions dealing with food additives appear in Division 16, Part B of the *F&DR*. Section B.16.001 refers to adequate food additive labelling. Section B.16.002 in particular lists the criteria that must be met in support of a submission for a new food additive. The Food Additive Tables, which list approved food additives and the foods in which they may be used, are found in section B.16.100.

Regulatory standards of identity and composition for various foods appear throughout Part B of the *F&DR* (as explained in Section 1.9 of this Guide). In addition, Division 6, Part B of the *F&DR* provides requirements for specifications of certain food colours.

Food additive submissions that have undergone full scientific review and which have been made subject to an IMA may be viewed on the IMA webpage (Section 5.0 of this Guide). Food additives that are approved for use through the issuance of an IMA do not yet appear in the Food Additive Tables of Division 16 of the *F&DR*.

# 1.0 DEFINITIONS, AUTHORITIES, AND REGULATORY STRUCTURE

## *1.1 Food*

Section 2 of the *F&DA* (an Act Respecting Food, Drugs, Cosmetics, and Therapeutic Devices) defines "food" as follows:

> *"food" includes any article manufactured, sold or represented for use as food or drink for human beings, chewing gum, and any ingredient that may be mixed with food for any purpose whatever.*

This is broader than the dictionary definition because it includes any article manufactured, sold or represented for use as food or drink for human being. It does *not* include articles manufactured, sold or represented for use as food or drink for animals, whether domestic or wild. Also, any ingredient or substance that may be intentionally mixed with food for any purpose becomes, by definition, a food.

## *1.2 Authority to make Regulations*

Section 30 of the *F&DA* identifies the Governor-in-Council as having the authority to make regulations that bring the *F&DA* into effect.

> *"...the sale and the conditions of sale of any food, drug, cosmetic or device, and ... the use of any substance as an ingredient in any food, drug, cosmetic or device, to prevent the purchaser or consumer thereof from being deceived or misled in respect of the design, construction, performance, intended use, quantity, character, value, composition, merit or safety thereof, or to prevent injury to the health of the- purchaser or consumer."*

## *1.3 Food Additive*

Section B.01.001 of Division 1, Part B (Foods) of the *F&DR* defines "food additive" as follows:

> *"Food additive means any substance the use of which results, or may reasonably be expected to result, in it or its by-products becoming a part of or affecting the characteristics of a food, but does not include*
>
> *(a) any nutritive material that is used, recognized or commonly sold as an article or ingredient of food,*
> *(b) vitamins, mineral nutrients and amino acids, other than those listed in the tables to Division 16,*

*(c) spices, seasonings, flavouring preparation, essential oils, oleoresins and natural extractives,*
*(d) agricultural chemicals, other than those listed in the tables to Division 16,*
*(e) food packaging materials and components thereof, and*
*(f) drugs recommended for administration to animals that may be consumed as food."*

It will be noted from an examination of the above definition that a substance that is not even present in the final food but which has affected the characteristics of that food would be regulated as a food additive.

Substances which fulfill a technological role during the manufacturing process and which do not remain in the finished food product (and therefore are not functional therein) are not considered to be food additives because they do not meet the definition of a food additive. They are considered to be "processing aids." The use of a processing aid does not require a submission like a food additive but a petitioner may seek a so-called "Letter of Opinion" from the BCS of HC's FD, confirming that, under its conditions of use, the substance in question is indeed considered to be a processing aid and is acceptable for use. Letters of Opinion are described under Section 8.0 of the present Guide. In this regard, a Letter of Opinion expresses only an opinion of the BCS about the acceptability of a product. It is not an approval of the substance in the legal sense and it does not relieve the food manufacturer from the ultimate responsibility for the safety of the product under section 4 of the *F&DA* which states:

*"No person shall sell an article of food that*

*(a) has in or on it any poisonous or harmful substance;*
*(b) is unfit for human consumption;*
*(c) consists in whole or in part of any filthy, putrid, disgusting, rotten, decomposed or diseased animal or vegetable substance;*
*(d) is adulterated; or*
*(e) was manufactured, prepared, preserved, packaged or stored under unsanitary conditions."*

While not officially endorsing use of a particular substance, a Letter of Opinion offers some assurance to a user industry about safety of use as intended.

Nutritive or energy-providing materials, commonly sold as articles or ingredients of food, e.g. sugar, starch, glucose, corn syrup, casein, etc., are specifically exempted from the definition of a food

additive. Even though these substances become a part of or affect the characteristics of a food, they add materially to the nutritive or energy-providing properties of the food. They are considered to be food ingredients or foods in themselves. Where substances with nutritive properties such as gelatin, pectin, lecithin or polyalcohols are added to foods as gelling agents, emulsifying agents, sweeteners, etc., these are considered to fall within the definition of a food additive and have been listed in the Food Additive Tables of section B.16.100. When a question arises as to whether or not a substance is considered to be a food additive, the food manufacturer should contact the Chief of the CHHAD, BCS, FD, HC for an opinion prior to introducing such a substance into food (see Section 2.1.5 of this Guide for full contact information). In submitting such enquiries, the manufacturer should provide information on the composition and specifications, the amount to be used, the area and purpose of use of the substance in question, the amount of substance remaining in ready-to-consume food, and any additional pertinent information.

Vitamins, mineral nutrients and amino acids added to foods are excluded from the food additive definition. They are not added to a food for the purpose of exerting a technical effect. These substances are governed by other regulations.
*(Note, however, that some of these substances can be added to foods for two purposes. For example, Vitamin C and ascorbic acid are the same chemical. Vitamin C is controlled by the Regulations in Part D whereas ascorbic acid used as an antioxidant is controlled by the Regulations as a food additive in Division 16, Part B.)*

Spices, seasonings, flavouring preparations, essential oils, or oleoresins are not considered as food additives. Their use is governed either by specific Regulations (Divisions 7 and 10 respectively, Part B of the *F&DR*) or under the general terms of section 4 of the Act as described above.

The use of substances to control pests in pre-harvest crops (pesticides) is controlled by the Pest Management Regulatory Agency under the authority of the *Pest Control Products Act and Regulations*.

Food contact or packaging materials have been excluded from the food additive requirements. Food contact or packaging materials are controlled separately under Division 23, Part B of the *F&DR.*

The use of veterinary drugs in food-producing animals, where there is a possibility of residues of such drugs remaining in the edible tissues of treated animals, is not governed by the food additive regulations of Division 16 but by Maximum Residue Limits appearing in Division 15 of the *F&DR* and by Administrative Maximum Residue Limits, established by the Veterinary Drugs Directorate (VDD).

VDD evaluates and monitors the safety, quality and effectiveness, sets standards, and promotes the prudent use of veterinary drugs administered to food-producing and companion animals.

### *1.4 Manufacturer*

Section A.01.010, Part A (Administration), of the *F&DR* defines "manufacturer" as follows:

> *""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."*

The *F&DR* require that the labels of food additives bear the name and address of the manufacturer, i.e., the person taking the responsibility for production and/or distribution of a food (food additives *are* foods). The definition of manufacturer implicitly includes packers, distributors, and wholesalers.

### *1.5 Sell*

Section 2 of the *F&DA* defines "sell" as follows:

> *""Sell" includes offer for sale, expose for sale, have in possession for sale, and distribute, whether or not the distribution is made for consideration;"*

One of the requirements (section B.16.100, Part B) of the *F&DR* is the prohibition of sale of food additives unless certain conditions have been met. These requirements will be discussed below. It is worth pointing out here that "sell" as defined in the Act does not necessarily require the exchange of money for a commodity. The distribution of free samples or the presentation of a shipment at a port of entry for importation into Canada may be considered as tantamount to offering the commodity for sale.

### *1.6 Food Additive Tables*

Section B.16.100 of the *F&DR* states:

> *"No person shall sell any substance as a food additive unless the food additive is listed in one or more of the following Tables*."

Division 16, Part B of the *F&DR* comprises regulations and a series of tables of permitted food additives classified according to their technological role. There are fifteen major Food Additive Tables, organized by major functional categories:

I) **Anti-caking agents** (reduce adhesion of particles and allow the maintenance of an appropriate food texture)

II) **Bleaching, maturing and dough conditioning agents** (improve the baking quality and colour of dough; added to flour or dough)

III) **Colouring agents** (are used to add or restore colour to foods)

IV) **Emulsifiers, gelling, stabilizing and thickening agents** (form or maintain a uniform emulsion of two or more phases in foods; impart a particular food texture through the formation of a gel; maintain a uniform dispersion of two or more components or modify the viscosity of foods)

V) **Food enzymes** (have various technological functions in foods)

VI) **Firming agents** (make or keep fruit or vegetable tissue firm and crisp; or interact with gelling agents to produce or strengthen a gel)

VII) **Glazing and polishing agents** (when applied to the external surface of a food, impart a shiny appearance or provide a protective coating)

VIII) **Miscellaneous additives** (chemicals with technological functions other than those described in this listing)

IX) **Sweeteners** (impart a sweet taste to foods; do not include mono- or disaccharide sugars commonly found in foods)

X) **pH adjusting agents, acid reacting materials and water correcting agents** (these alter or control the acidity or alkalinity of foods and may also prevent food from drying out)

XI) **Preservatives (Classes I-IV)** (prolong the shelf-life of foods by protecting against deterioration caused by microorganisms or oxidation: Class I - curing preservatives; Class II - antibacterial; Class III - antifungal and antimycotic; Class IV - antioxidants)

XII) **Sequestering agents** (control the availability of metal cations making them inactive as ions)

XIII) **Starch modifiers** (used in the manufacture of modified starches)

XIV) **Yeast foods** (used as yeast nutrients, which are used specifically for yeast growth)

XV) **Carrier or extraction solvents** (used to dissolve, dilute, extract, disperse, deliver or otherwise physically modify a food additive or nutrient without exerting any technological effect on its own).

The Tables show the name of each food additive, its permitted area of use in food and its maximum permitted use level. The *F&DR* make it an offence to sell a substance as a food additive unless the substance is listed in one or more of the Food Additive Tables.

In some instances, the commercial use of a food additive may be enabled by an IMA prior to publication of the proposed amendments in *Canada Gazette* Part II. IMA's are described in detail in Section 5.0 of this Guide.

The requirements respecting a request for the addition of a new food additive to the Tables or for a change in the listing of an existing food additive in the Tables will be discussed further in this Guide under the appropriate subsections of Section 2.0, describing the organization and content of a food additive submission.

### *1.7 Good Manufacturing Practice*

Section B.01.044, Part B of the *F&DR* defines "good manufacturing practice" as follows:

> *"Where the limit prescribed for a food additive in a Table to section B.16.100 is stated to be 'Good Manufacturing Practice', the amount of the food additive added to a food in manufacturing and processing shall not exceed the amount required to accomplish the purpose for which that additive is permitted to be added to that food."*

In a number of instances in the Food Additive Tables, a finite maximum level of use is not given but the maximum use level is stated as "good manufacturing practice". In other instances, for the same food additive, the maximum level of use permitted may be stated as a finite value in some foods. The level of use in the latter situation must not exceed the maximum permitted level indicated in the Tables although "good manufacturing practice" principles should also apply. When "good manufacturing practice" is specified, the amount employed should not exceed the minimum amount required to accomplish the technical purpose for which the additive is used. In most instances in which a good manufacturing practice limit is prescribed, the amount used is self-limiting.

### *1.8 Label Declaration of Ingredients*

The *F&DR* require that most prepackaged foods carry a label and that their ingredients, including food additives, appear in a declared list in decreasing order. These general labelling requirements are set out in several sections of Division 1, Part B of the *F&DR*. For example, the *F&DR* (section B.01.009) do not require components (that is, ingredients of ingredients) of certain foods and products, such as flavourings, seasonings, spices and vinegar, to be listed on food labels. However, HC is finalizing proposed regulatory amendments that would require priority allergens, gluten sources, and sulphites

(the latter of which are regulated as food additives) to be identified on the labels of prepackaged foods even if they are added as ingredients or components of ingredients to foods. Additional information on this proposal is available through the following HC webpage.

As the Canadian Food Inspection Agency (CFIA) is responsible for enforcing both health and non-health-based labelling requirements, the CFIA should be consulted to ensure compliance of prepackaged food ingredient labels with any requirements (CFIA contact information and labelling information, for example, Guide to Food Labelling and Advertising, are available on the CFIA website).

As for prepackaged foods, there are requirements respecting the labelling of food additive preparations. Section B.16.001 of the *F&DR* sets out the following specific requirements respecting the label declaration of ingredients in food additive preparations:

> *"A quantitative statement of the amount of each additive present or directions for use that, if followed, will produce a food that will not contain such additives in excess of the maximum levels of use prescribed by these Regulations shall be shown, grouped together with the list of ingredients, of any substance or mixture of substances for use as a food additive*."

It is the responsibility of the manufacturer or distributor of a food additive preparation to label such products with a quantitative statement of the amount of each additive present or to provide a complete listing of the food additives by name, in descending order of their proportions, accompanied by Directions for Use in order that a user can comply with any constraints on levels of use imposed by the *F&DR*. It is the purpose of these requirements to provide the user with the necessary information such that the use of the preparation in foods will not be in violation of the requirements set out in the Tables of the *F&DR*.

"Coined names" or product numbers may be used on labels of food additive preparations but in addition, the label must carry the common name or names of component additives or ingredients. Since food additives are foods (see definition above for "food"), manufacturers of food additive preparations should also take cognizance of general labelling requirements set out in several sections of Division 1, Part B of the *F&DR*.

## *1.9 Food Additives in Foods Subject to Standards of Composition and in Foods without a Compositional Standard*

Foods subject to a standard of composition and/or identity in the *F&DR* are commonly referred to as "standardized" foods. In the *F&DR*, provisions setting out a standard for a food are designated with the bold letter "**[S]**". These provisions generally also prescribe a common name for the product, printing the name of the food in boldface type. Only products meeting the requirements of the standard can carry the prescribed common name. For example, to carry the name milk or whole milk the product must meet the requirements set out in section "B.08.003. [S] Milk or Whole Milk" of the *F&DR*. Foods that do not have a prescribed compositional standard or do not meet the prescribed standard are considered to be "unstandardized" foods.

The following requirements are set out in the *F&DR* respecting the use of food additives in foods:

*(I)* *B.16.007 - "No person shall sell a food containing a food additive other than a food additive provided for in sections B.01.042, B.01.043, and B.25.062."*

*(II)* *B.01.042 - "Where a standard for a food is prescribed in this Part:*

- *(a) the food shall contain only the ingredients included in the standard for the food;*
- *(b) each ingredient shall be incorporated in the food in a quantity within any limits prescribed for that ingredient; and*
- *(c) if the standard includes an ingredient to be used as a food additive for a specified purpose, that ingredient shall be a food additive set out in one of the Tables to section B.16.100 for use as an additive to that food for that purpose".*

*(III)* *B.01.043 - "Subject to section B.25.062, where a standard for a food is not prescribed in this Part:*

- *(a) the food shall not contain any food additives except food additives set out in a Table to section B.16.100 for use as additives to that food for the purpose set out in that Table; and*
- *(b) each such food additive shall be incorporated in the food in a quantity within any limits prescribed for that food and food additive in that Table.*

*(IV)* *B.25.062. (1) - Subject to subsection (2), no person shall sell a food that is labelled or advertised for consumption by infants if the food contains a food additive.*

*(2) - Subsection (1) does not apply to*

- *(a) bakery products that are labelled or advertised for consumption by infants;*
- *(b) ascorbic acid used in cereals containing banana and fruit purées that are labelled or advertised for consumption by infants;*

*(c) soyabean lecithin used in rice cereal labelled or advertised for consumption by infants;*

*(d) citric acid used in foods that are labelled or advertised for consumption by infants;*

*(e) infant formula that contains the food additives set out in Tables IV and X to section B.16.100 for use in infant formula; or*

*(f) infant formula that contains ingredients manufactured with food additives set out in Table V to section B.16.100.*

Section B.25.062 of the *F&DR* includes a general prohibition on the use of food additives in infant foods including infant formula. This prohibition applies to food additives added directly to infant foods, as well as to food additives that are components of ingredients of infant foods.

There are some exceptions to the general prohibition. A limited number of food additives allowed for use in infant formula is specified in Tables IV and X (and in future, Table XI, which is currently being amended) to section B.16.100 of the *F&DR*. Requests for the use of new food additives in infant formulas should be directed to the BCS in HC's FD (see Section 2.1.5 of the Guide) whereas pre-market notifications for new infant formulas or for major changes to existing infant formulas are required to be sent to the Assistant Deputy Minister, Health Products and Food Branch (sections B.25.046 and B.25.048 of the *F&DR).*

Food additives are not permitted in standardized foods unless provision is made within the standard either for a specific named food additive or for a particular class of food additives. In the latter instance, one must refer to the Food Additive Tables of Division 16 to obtain details on the actual additives within a class that are permitted and their maximum levels of use.

In unstandardized foods only those food additives for which provision has been made in the Tables either for that food specifically or for "unstandardized foods" in general may be used.

# 2.0 GENERAL REQUIREMENTS FOR SUBMISSIONS ON FOOD ADDITIVES

## *2.1 Administrative Considerations*

### 2.1.1 When is a Submission required?

A submission for a food additive is required if a petitioner is seeking approval for use in Canada of a new food additive not currently regulated in the *F&DR*. A petitioner is also required to present a submission for an extension of use of an existing food additive; for example, the use of an existing food additive in a different food or the use of a food additive at a higher Maximum Level of Use. In these latter cases, there may not be a need to re-submit data already available at Health Canada.

### 2.1.2 Administrative Information and Number of Copies

The submission should be dated and provided under cover of a letter that provides the petitioner's name, title, full address and other means of communication (telephone and fax numbers, e-mail address, etc.). A summary of technical information pertaining to the subject of the submission is also requested although this may be done by providing a completed Food Additive Submission Checklist (see Section 2.1.4 of this Guide). Consultants, lawyers or third parties other than food or food additive manufacturers or distributors should provide clear information indicating their rights to act on behalf of the petitioner. Appropriate contact information is required for third parties acting on behalf of a petitioner.

Hard copies of the submission should be filed in triplicate, accompanied by a covering letter signed by a responsible manager of the firm, preferably the person with whom subsequent correspondence will be carried out. A hardcopy of the Food Additive Submission Checklist (see Section 2.1.4 of this Guide) should be included as well. One electronic copy (e.g. CD-ROM or DVD) of the submission should also be provided for archival purposes, if possible.

### 2.1.3 Language and Translation

All data and information in the submission should be provided in English or French. Material in other languages must be translated into English or French before it can be considered.

### 2.1.4 Food Additive Submission Checklist

A submission checklist has been developed to assist petitioners as they assemble the components of a typical food additive submission. The checklist includes space for entering administrative information, that is, name, title, full address and other means of communication (telephone and fax numbers, e-mail address, etc.)

It should be emphasized that this electronically-available checklist does not replace the cover letter or any other required documents pertaining to the submission. It is an additional document summarizing both administrative and scientific/technical information that is meant to assist both the petitioner in the preparation of a submission as well as the Scientific Evaluator in verifying that the required information has been submitted. Although not a statutory requirement, it is requested that completed checklists be submitted with the submission and cover letter.

### 2.1.5 Mailing Directions and Contact Information

The parcel containing the submission documents, including a dated covering letter and the submission checklist (see Section 2.1.4 above) should be addressed to:

Submission Management and Information Unit
Food Directorate
Health Products and Food Branch, Health Canada
251 Sir Frederick Banting Driveway
Postal Locator 2202E
Ottawa, Ontario, Canada, K1A 0K9

Submissions of less than 20 pages may be sent electronically by e-mail to the following address: smiu-ugdi@hc-sc.gc.ca. Please use the words “Food Additive Submission” in the subject line.

### 2.1.6 Acknowledgement of Submissions

On receipt of the food additive submission, it is pre-screened to determine if essential information as required by the *F&DR* has been supplied. If such is the case, the submission will be accepted for review and given a file identification number. A letter of acknowledgement (not a letter of acceptance) is sent to the petitioner indicating that the submission has been received, has been assigned a file number, and has entered the evaluation process.

If, however, during preliminary screening the original information and materials are found to be

incomplete (e.g., a type of information that is normally required is missing with no explanation for its omission), the material submitted is acknowledged and the petitioner is advised as to the material required to complete the submission.

The petitioner will be required to submit all of the requested information and materials identified in the initial acknowledgment letter or in subsequent correspondence (which may be in the form of a deficiency letter). The screening "clock" stops when the request for additional information is sent and starts again upon receipt of the data. After receipt of the information requested, a new screening period commences, and the requested materials and information will be again screened for completeness. The original information and materials will be considered a submission and acknowledged when all requested information is found to be acceptable for full scientific evaluation.

### 2.1.7 Evaluation of Submissions

Following acknowledgement of the submission, it is assigned to a Scientific Evaluator in the CHHAD who will be responsible for coordinating the evaluation of the submission against the requirements of section B.16.002 (discussed further below) of the *F&DR*. The coordinating Evaluator will evaluate the exposure and chemical aspects of the submission and will pass any toxicological, microbiological or nutritional data to the respective disciplinary areas for evaluation. The potential environmental impact of the additive may also need to be assessed (see Section 3.0 of this Guide).

During the screening or review of the submission, the BCS in HC's FD may seek clarification of specific information in the submission. Requests will be solicited by the coordinating evaluator in the form of deficiency letters and responses should be returned to that individual using the same submission identification number appearing in the acknowledgment letter. Depending on the volume of information to be provided, information may be transmitted through electronic correspondence. The purpose of such requests is to seek clarification of existing information or to seek missing or additional information. A response is considered complete if all deficiencies or questions identified in the request are addressed. Should a petitioner feel that it is not necessary to develop or file the requested information, a sound scientific rationale for this position must be presented.

Consultation may be required with appropriate stakeholders who will be affected by any proposed regulatory changes arising as a result of an acceptable food additive submission. Other government bodies, for example the CFIA, Environment Canada (EC) or other provincial/territorial authorities, the

medical community, trade associations, industry, consumer associations or others may be consulted in order to allow major stakeholders' concerns to be addressed before any amendments are brought forward for consideration, especially those that have a significant public impact or which affect or involve the *F&DR* standards.

Every effort is made to deal with submissions as promptly as possible. However, given the fact that several Sections, Divisions, Bureaus or even Branches within HC and/or other government bodies may be involved in a particular evaluation, a longer-than-expected time period may be required before the full evaluation is complete. Factors pertaining to the quality of the submission, that is, its completeness, and to the timeliness of petitioner responses to requests for clarification equally contribute to the overall time to complete the evaluation of the submission.

### 2.1.8 Completeness of Data and Information

Every effort should be made to keep submissions short yet complete. Fragmentary data and information that is not clearly related to the submission should be avoided in food additive submissions. In the case of submissions on new food additives (those which do not appear anywhere in the Food Additives Tables of the *F&DR*, detailed data and scientific information meeting the requirements of section B.16.002 of the *F&DR* are required in order to support the development of specifications and verify conformity of the additive with those specifications, develop and verify methods of analysis, establish claims of efficacy, demonstrate residue levels or reaction products, determine human exposure to a food additive in any given application, and demonstrate the absence of any negative health effects of the food additive when used in the prescribed manner.

### 2.1.9 Incomplete or Inconclusive Submissions

If, in pre-screening the submission, the submitted material is found to be obviously deficient (e.g., a section required by the *Regulations* is missing and no explanation is given for the omission), the material submitted will not be acknowledged as a submission but the petitioner will be advised as to the material required to complete the submission. Once the required information has been provided, the submission will be accepted for review and will be assigned a file number. The electronically-available food additive submission checklist (Section 2.1.4 of this Guide) should be helpful in ensuring that the required information is enclosed in the submission.

A submission cannot be considered further if the submitted material is unsatisfactory. If the results of

the evaluation of a submission indicate that it is not satisfactory with respect to content or that the supporting data are inconclusive, the petitioner is so advised in writing by an officer of the BCS of the FD. The deficiencies and additional data and information required to complete the submission are outlined in the correspondence. No further action on the submission is taken until the petitioner responds to the request for missing data and supplies the necessary information. The requested information will be screened for its acceptability. It should be accompanied by a copy of the letter requesting the additional data and the responses should be submitted in a question and answer format and cross-referenced to existing or replacement volumes, where appropriate.

Prior to filing a submission, the petitioner should ensure full and complete disclosure of all the relevant data and information in support of the request. This will help to facilitate the evaluation of the submission in as timely a manner as possible.

### 2.1.10 Submissions from Foreign Countries

Delays have occasionally been encountered in evaluating submissions filed by Canadian petitioners associated with firms operating outside of Canada. Although submission requirements are not described in detail in the *Regulations* with respect to the amount and type of supporting data, it is expected that some of the efficacy data and information will be procured in institutions in Canada under Canadian food manufacturing industry practices and trade conditions. At the least, the petitioner should ensure that the data is relevant to Canadian manufacturing conditions and practices.

The Canadian distributor should recognize that a food additive submission compiled by a foreign associate or principal, while meeting regulatory pre-clearance requirements in that country, may fail to comply with the Canadian pre-clearance requirements. Although other countries may have similar general pre-clearance requirements as Canada, there may be differences in specific requirements. Therefore, it is essential that the foreign manufacturer, or the Canadian distributor or the third party preparing the submission on its behalf, become fully familiar with the Canadian requirements for food additive submissions, to ensure that the form and content of such submissions meet the requirements of section B.16.002 of the *F&DR* (see Section 2.2 below).

In the event that any of the required information cannot be provided, a rationale for that omission should be presented.

### 2.1.11 Compilation of Data Pertaining to a Submission

The evaluator's assessment can be facilitated by the form, manner, appearance and substance of the submission presented. In this regard, the following points are offered as a guide:

- For submissions involving large amounts of information, wherever possible the data and information should be contained in appropriately organized binders. The contents of any binders should be described on the cover and index tabs used to indicate different sections of the submission within each binder.
- The material must be legible.
- The data and information provided with the submission should be organized in sections corresponding to the respective requirements of section B.16.002 of the *F&DR* (see Section 2.2 of this Guide) and any additional non-statutory requirements (see Section 2.3 of this Guide).
- Tables of contents, indices and page numbers of the respective sections of large submissions are very helpful in locating data and information. These simplify the task of evaluators in referring to material during any discussions with the petitioner and in correspondence, and are useful in the cross-referencing of data and information.

## *2.2 Statutory Requirements for Submissions on Food Additives*

The following requirements are set out in the *F&DR* respecting the filing of food additive submissions:

> *B.16.002. "A request that a food additive be added to or a change made in the Tables following section B.16.100 shall be accompanied by a submission to the Minister in a form, manner and content satisfactory to him and shall include:*
>
> *(a) a description of the food additive, including its chemical name and the name under which it is proposed to be sold, its method of manufacture, its chemical and physical properties, its composition and its specifications and, where that information is not available, a detailed explanation;*
> *(b) a statement of the amount of the food additive proposed for use, and the purpose for which it is proposed, together with all directions, recommendations and suggestions for use;*
> *(c) where necessary, in the opinion of the Director, an acceptable method of analysis suitable for regulatory purposes that will determine the amount of the food additive and of any substance resulting from the use of the food additive in the finished food;*
> *(d) data establishing that the food additive will have the intended physical or other*

*technical effect;*

*(e) detailed reports of tests made to establish the safety of the food additive under the conditions of use recommended;*

*(f) data to indicate the residues that may remain in or upon the finished food when the food additive is used in accordance with good manufacturing practice;*

*(g) a proposed maximum limit for residues of the food additive in or upon the finished food;*

*(h) specimens of the labelling proposed for the food additive; and*

*(i) a sample of the food additive in the form in which it is proposed to be used in foods, a sample of the active ingredient, and, on request a sample of food containing the food additive.*

*B.16.003. The Minister shall, within ninety days after the filing of a submission in accordance with section B.16.002, notify the person filing the submission whether or not it is his intention to recommend to the Governor-in-Council that the said food additive be so listed and the detail of any listing to be recommended.*"

The requirements pursuant to section B.16.002 of the *F&DR a*re also listed on the electronically-available submission checklist (see Section 2.1.4 of this Guide).

The information required in a food additive submission will depend on a number of factors such as the nature of the additive, the intended use, whether it has previously been permitted for use in other foods, etc. The types of studies designed to collect the data and information to support the basic requirements of a food additive submission are not static, but change with advancements in scientific knowledge. This Guide must be used in conjunction with present knowledge available in the scientific literature and from research and development studies conducted by the manufacturer using the best techniques available at the time. Thus, the explanations and interpretations indicated below are subject to change as additional knowledge and experience are gained in evaluating data and information supplied in food additive submissions. Every effort will be made by the BCS of HC's FD to keep the Guide up-to-date and to advise manufacturers and distributors of revisions and changes.

### 2.2.1 Description of the Food Additive – Name, Chemical Properties, Specifications, etc.

*[Section B.16.002 (a) of the F&DR]*

#### Identity of the Food Additive

A comprehensive monograph on the food additive should be supplied. This should include the recognized common or non-proprietary name of the substance; e.g. names appearing in the Food Chemicals Codex (FCC)

and names used by the Joint Food and Agriculture Organization of the United Nations / World Health Organization Expert Committee on Food Additives (JECFA), the U.S. and British Pharmacopoeia, the National Formulary, etc. Where applicable, the chemical name, following the International Union of Pure and Applied Chemistry (I.U.P.A.C.) rules of nomenclature, should be supplied. Also, the Chemical Abstract Service (CAS) registry, the International Numbering System (INS) number, the Colour Index (CI) number in the case of colours and/or the Enzyme Commission (E.C.) number in the case of enzymes should be indicated, as well as any trade or brand names assigned to the additive.

The empirical formula, structural formula, molecular formula and molecular weight of the additive should be supplied where applicable. When there is no structural formula applicable to the additive, a means of identification to characterize the composition of the additive should be provided.

### Method of Manufacture

In the case of new food additives not previously listed anywhere in the Food Additive Tables, the method of manufacture of the additive, along with the sequence of reactions or flow chart of the synthesis, should be supplied. If the additive is obtained from natural sources, a description and a step-by-step outline of the manufacturing procedures should be provided. Particular attention should be given to supplying information on reactants and solvents used and possible contaminants or intermediates resulting from the synthesis, isolation or extraction during manufacture of the particular food additive. In the case of requests for extensions of use or changes to maximum levels of use of food additives already appearing in the Food Additive Tables, petitioners are not asked to provide the method of manufacture as part of the food additive submission, but should be prepared to provide such information if requested.

### Chemical and Physical Properties

A description of the food additive, including its chemical, organoleptic, physical and biological properties, should be supplied. The quantitative composition of the commercial additive preparation as used, including any carriers, solvents, coatings or other ingredients employed to aid in its functionality, should be identified in the submission.

Studies on the chemical and physical stability of the food additive as such and as used in food should be provided in submissions. These studies should be designed to determine the effect of temperature, humidity, light, particle size and other physical characteristics, on the stability of the additive. Foods containing particular food additives may need to be stored or transported under certain conditions of temperature, pH or time constraints and information about such conditions should be provided in a submission. The methods and tests used in the stability studies should be capable of identifying and determining the additive as such and not only its functional groups. Specificity in methodology is most important in determining and defining the stability of an

additive.

Data and information to show the fate of the food additive in the food(s) for which it is intended should be supplied. In the case of an additive remaining in the food, evidence should be presented to show whether it is unchanged, converted, or partially converted to other substances due to oxidation, reduction, degradation or reaction with food constituents. Methods and procedures should be devised to determine breakdown products in order to enable an assessment of the hazards associated with those by-products.

Accelerated studies are often useful in evaluating stability under abuse conditions. It is most important that data and information be supplied to show to what extent degradation products may contribute to the overall toxicity of the additive and its conversion products in food. Conditions should be stipulated under which minimum degradation of the additive occurs. The results of stability studies should be tabulated and presented in a manner to support any recommended expiry date for the additive or for foods containing the additive.

### Specifications

The Food Additives Tables do not generally set out specifications and standards of quality of food additives. Where specific standards of quality for a given food additive are prescribed in relevant sections of the *F&DR* (e.g. certain colours in Division 6), these take priority over other official compendia. Where specifications for a given substance do not exist under the *F&DR*, the specifications and standards of quality set out in the most recent edition (or its supplements) of the *FCC* (available from U.S. Pharmacopeia) are employed (section B.01.045 of the *F&DR)*. In the absence of a specification in either the *F&DR* or the FCC, the most recent specifications appearing in the JECFA *Compendium of Food-grade Specifications* are accepted as official standards in meeting the intent of the requirements. In demonstrating that a food additive meets its specifications for identity and purity, the results of analysis of a suitable number of representative batches, showing the range and variability of impurities, heavy metal content, reaction by-products, etc., should be provided. Detailed procedures used to test conformity of the food additive with its specifications must be supplied.

In the case of new substances not already listed in the *F&DR*, nor in the *FCC* or in the *Compendium of Food-grade Specifications* published by the JECFA, particular attention should be given to establishing appropriate food-grade specifications, which characterize and define the identity, purity and strength of the additive. A suitable number of characterizing properties for the additive should be provided as specifications, such as physical, chemical and physico-chemical parameters, i.e. melting point; solubility; optical rotation; loss on drying; residue on ignition; specific gravity; heavy metal content (arsenic, lead, cadmium, mercury, or others as appropriate); paper, thin-layer, or gas chromatograms; infrared and ultraviolet absorption spectra, pH characteristics; microbiological specifications, etc. Where applicable, copies of spectra and chromatograms

should be included in the submission.

The results of analysis of a suitable number of representative batches should be provided. These analyses will serve as useful background material and can be used to provide a rationale for deciding upon values for individual specifications.

### 2.2.2 Purpose and Level of Use, Efficacy, Residue Data and Proposed Maximum Level of Use

*[Sections B.16.002 (b), (d), (f) and (g) of the F&DR]*

Although the level, directions for use and the intended physical or technical effects of a food additive will vary with the additive under consideration, the following points are submitted as guidelines in supplying and organizing the supporting data and information.

#### Purpose

The submission should contain a clear statement of the purpose or the function for which the food additive is intended. In general, this statement should use the terms employed in the headings used in the Food Additive Tables of Division 16 of the *F&DR*.

#### Directions for Use

In accordance with the purpose and manner in which the additive is to be used, adequate Directions for Use should be submitted. These should include information on what amounts of the active and inactive ingredients of a food additive preparation are to be used, in which units the amounts are determined (by volume, by weight, metric measures, etc.), how the preparation should be added to obtain homogeneity in the food, and at which processing stage and under which conditions the preparation should be added to ensure its efficacious use.

#### Efficacy Data Demonstrating the Technical Effect

Evidence from well-designed experiments are required to be submitted to support the purpose for which the additive is intended and to demonstrate that the additive indeed fulfils the intended effect. Where possible, these experiments should be carried out using graded levels of the additive in the food and the effects should be noted. The effects should be compared with controls containing no additive. Appropriate statistical treatment of the results should be undertaken, including application of tests of significance. These data should be used not only to demonstrate efficacy, but also to establish the minimum efficacious use level. Presentation of the results in tabular and graphical form is desirable and is appreciated by evaluators as it helps to facilitate the interpretation of the results.

For example, a graphical representation of effects at various food additive use levels allows quick visualization of minimum and maximum levels of efficacious use of a food additive.

### Residue Data

Data must be provided showing the typical levels of residues of the food additive or its conversion products in or upon the finished food(s) as sold when used in the proposed manner and in accordance with good manufacturing practice.

### Proposed Maximum Level of Use

The submission must also propose a maximum level of use that would appear in the Food Additive Tables of Division 16 of the *F&DR* and that would serve as a maximum limit for residues of the food additive in or upon the finished food as sold. This proposed maximum residue limit and its units should be clearly expressed, e.g. parts per million (ppm, mg/kg) or a percentage by weight (w/w), in or upon the finished food(s).

The maximum level of use of an additive is the highest concentration of the additive determined to be functionally effective in a food or food category and agreed to be safe by HC. In practice, the maximum level may not necessarily always correspond to the optimum, recommended, or typical level of use. Under Good Manufacturing Practice, the optimum, recommended, or typical use level may be lower than the maximum level of use. Among different foods, the amount of additive required to achieve the desired technical effect will be a function of the type of raw material, food processing and post-manufacturing storage, transport and handling by distributors, retailers and consumers. As a result, the maximum levels of use of a particular food additive will differ depending on the food.

## 2.2.3 Analytical Method

*[Section B.16.002 (c) of the F&DR]*

For new food additives not previously listed anywhere in the Food Additive Tables of section B.16.100 of the *F&DR*, analytical methods for determining both the residual amount of the additive and, if applicable, its conversion products remaining in the food, should be developed. A complete report on the development of the analytical methods should be documented, as well as a description of the final method intended for use. The method should be practical for control purposes and applicable to the food(s) for which the additive is intended. Wherever possible, the method should be subjected to collaborative study, with data and information supplied on variations within and between laboratories. Details pertaining to the precision, accuracy, variability (reproducibility), and specificity of the method should be supplied.

In the case of requests for extensions of use or changes to maximum levels of use of food additives already appearing in the Food Additive Tables of Division 16 of the *F&DR*, petitioners are not asked to

provide an analytical method as part of the food additive submission, but they should be prepared to provide such information if requested.

### 2.2.4 Food Additive Safety Data

*[Section B.16.002 (e) of the Food and Drug Regulations]*

Note: The submission of food additive safety data [as per section B.16.002 (e) of the *F&DR* is most important for submissions for the use of a new food additive, that is, a food additive that does not appear anywhere in the Food Additives Tables of section B.16.100 of the *F&DR*. Submissions requesting "extensions of use" or changes to maximum levels of use of food additives that have previously been approved for use in certain foods in Canada may require much less safety data since the food additive will have already been assessed for safety and will also have a history of safe use in Canada.

#### *2.2.4.1 Consideration of Food Intake Data*

An overall assessment of the intake resulting from a proposed new use of a food additive should be provided, if possible. Information about the amount of the food additive that would typically be ingested is useful to the evaluation of the safety of the proposed food additive use. In this regard, consideration should be made of the maximum level of use of the additive and the dietary intake of the food in question.

If an evaluation of the potential food additive intake is provided as part of a submission, the evaluation should be based on the most recent Canadian food intake data available. The two major types of food consumption data originate from (1) per capita disappearance of particular foodstuffs for the general population; and (2) survey data based on the actual amounts of foods consumed by individuals or households.

Per capita disappearance data, which is available from Statistics Canada, is a measure of the apparent disappearance of food on a per person (per capita) basis. The values are averaged over the entire population, which includes individuals who may never eat some of the foods (so-called "non-eaters"). Therefore, per capita disappearance data can tend to underestimate actual consumption and do not provide an indication of the possibly higher consumption rates of "eaters" of a particular commodity.

Food intake data based on surveys include those collected during dietary recall surveys (e.g. the

Canadian Community Health Survey; and various surveys conducted by the United States Department of Agriculture). The data in such studies is collected in a manner that allows extraction of information on food consumption by specified age groups, by "eaters" of certain food commodities, by "all persons" (which encompasses both eaters and non-eaters), by vulnerable sub-populations, etc. The data also allows extraction of "point" estimates of food intake (e.g. mean, median, upper percentiles). The type of data based on such dietary surveys is preferred and can provide closer estimates of true consumption by the group of interest.

For health and safety reasons, in performing intake calculations, it is important to ensure that any assumptions are sufficiently conservative; i.e. employ maximum levels of use and assume that all of a particular food commodity contains a given food additive. Calculations should be performed using not only mean general population intakes, but also intakes by the "eaters only" population. Depending on the additive, exposure estimations at upper percentile intakes (e.g. 90$^{th}$ percentile) among the "eaters only" population may also be required. It may also be necessary to estimate exposure for potentially sensitive segments of the population (e.g., children, people with particular physiological conditions, lactating and pregnant women, people who are diabetic, sick, elderly, etc.).

Intake data based on market share or penetration by a food commodity containing a food additive are not useful because of expected changes in use patterns once an additive is approved. Such an approach also tends to underestimate consumption by consumers of the food commodity, thereby resulting in potentially misleading results.

There are preliminary screening methods that can be employed to assess intake and to determine whether further, more intensive, intake methodology needs to be employed. The reader is referred to the so-called "Budget Method," details of which may be found in Annex A (Guidelines for the development of maximum levels for the use of food additives with numerical acceptable daily intakes) of the Codex General Standard for Food Additives (GSFA, Codex Stan 192-1995, last revised in 2007). The Budget Method relies on an assumption regarding human physiological requirements for energy and liquid and on the energy density of food, rather than on food consumption surveys. The method assumes that an individual can absorb daily a given maximum amount of solid and liquid food. On this basis, the theoretical maximum daily intake (TMDI) is calculated by assuming that all foods contributing to energy intake, and all beverages contributing to liquid intake, will contain the additive at maximum permitted use levels. An additive is said to "pass" the Budget Method screen based on a

comparison of the TMDI to the additive's corresponding Acceptable Daily Intake (ADI).

Estimates of food additive intake can be further refined if necessary using more detailed relevant data, i.e. food consumption data (as described previously), portion sizes, consumer characteristics, percentages (and percentiles) of various consumer categories, frequency of consumption, analytical data describing residues of the food additive and/or food additive by-products in foods, etc. There are numerous sources of information on how to conduct so-called deterministic and probabilistic food additive intake assessments and, as a start, the reader is referred to "Guidelines for Simple Evaluation of Food Additive Intake (CAC/GL 03-1989)" published by the Codex Alimentarius Commission.

Irrespective of the methodology used, the ultimate goal of all of these types of calculations is to determine whether the requested levels of food additive use are effective technologically and, more importantly, do not pose an unacceptable health risk to the human population.

#### *2.2.4.2 Types of Toxicological Tests Employed to Establish Safety of a New Food Additive*

The requirement for safety data in the submission implies a need for the results of toxicological tests for any food additive under consideration. It is generally recognized that the safety of a food additive can be predicted through pharmacokinetic studies (absorption, distribution, metabolism, and excretion studies), toxicological testing in animals and clinical studies in humans. The goal of this testing is to assist in the determination of the greatest level of exposure to a food additive that does not present a health risk to a consumer even if ingested daily over the lifetime. For a given food additive, the ADI is an expression of this level. In the event of very low toxicity, toxicological limitations on daily intakes of an additive may be unnecessary (i.e., an ADI "Not Limited" could be supported). However, even if an additive has an ADI "Not Limited" or "Not Specified," it should be used only at the minimal level that achieves its intended technological effect (i.e., a level consistent with "Good Manufacturing Practice").

A summary of toxicological studies used to establish safety for a food additive is presented below. However, depending on the knowledge available on the food additive's chemical structure and properties, its disposition, toxicity and exposure, all or only some of the studies listed may be required. For food additives that have a long-established record of safe use in foods, the provision of detailed toxicological data may not be required, e.g. in the case of requests to extend the permitted uses of an existing food additive. In specific cases, mechanistic studies may be required to further assure safety.

In other cases additional toxicological testing may be required to assess the metabolite(s) or degradation product(s) of the food additive. All studies should be conducted according to high testing standards (e.g., Organization for Economic Co-operation and Development (OECD) Guidelines for Testing of Chemicals; Good Laboratory Practices) to produce valid results, which must be reported in sufficient detail and clarity so the evaluator may have confidence in the findings.

Food additives are ingested and therefore in order to extrapolate the findings from toxicity studies in animals to the human situation, studies should be conducted using the oral route of exposure (as opposed to inhalation, dermal or injection routes).

### Acute Toxicity Studies

The purpose of these studies is to determine the adverse effects occurring within a short time of oral administration of a single dose of a food additive or multiple doses given within 24 hours to the test species (the rat is most commonly used).

### Short-term Toxicity Studies

The purpose of these studies is to determine the adverse effects occurring after daily oral administration of a food additive for 28 or 90 days in rodents or dogs, or for 1 year in dogs. The results of these tests in rodents are used to determine oral dosages used in long-term toxicity studies. These tests can also be used as an indication of significant toxicological effects, defining target organs and assessing the potential for accumulation of the test material. The more extended of these short-term studies (i.e. 90 day study in rodents and 1 year study in dogs) can be used for more detailed evaluation of toxicity of the food additive (e.g. measurements of hematology and clinical chemistry parameters).

### Long-term Toxicity Studies

The purpose of these studies is to determine the adverse effects occurring after daily oral administration of a food additive for a period of time that represents the major portion of the lifespan of the test animal (e.g. one year in rats). The results of these tests are used to assess the potential of the food additive to cause toxicity and include detailed evaluations of signs of clinical toxicity, behavioural effects, hematology, clinical chemistry, urinalysis, gross and microscopic pathology. With the extension of the study to two years duration, the studies can also be used to assess the potential oncogenicity of the food additive.

### Oncogenicity Toxicity Studies

The purpose of these studies is to determine the adverse effects occurring after daily oral administration of a food additive for two years in rodents. The results of these tests are used to assess the potential oncogenicity of the food additive. The tests are often combined with studies of long-term toxicity.

### Neurotoxicity Studies

The purpose of these studies is to determine the adverse neurological effects occurring after daily oral administration of a food additive over an acute period, short-term or long-term. The tests are often conducted in rodents. The results of these tests are used to assess the potential of the food additive to cause neurotoxicity. Observations related to neurotoxic endpoints are often included in standard acute, short-term and long-term studies.

### Genotoxicity Tests

The purpose of these studies is to determine the potential of a food additive to adversely affect the DNA in germ and somatic cells. Tests are conducted in microbes and mammalian cell lines in *in vitro* systems, as well as, in mammalian *in vivo* systems. Endpoints for these tests may include evidence of mutation or clastogenicity.

### Developmental Toxicity Studies

The purpose of these studies is to determine the adverse effects in the newborn, after daily oral administration of a food additive to the pregnant mother during that part of the gestation period when major organ development is ongoing. The tests are conducted in at least one rodent and one non-rodent species (often rabbit). The results of these tests are used to assess the potential of the food additive to cause maternal effects, as well as, developmental abnormalities in the offspring.

### Reproductive Toxicity Studies

The purpose of these studies is to determine the adverse effects on the reproductive capacity of parental animals and the adverse postnatal effects in their offspring occurring after daily oral administration of a food additive during premating, mating, gestation and lactation periods of reproduction. The tests are conducted in rodent species. The results of these tests are used to assess the potential of the food additive to impair reproduction in the parental animals. Studies are often combined with developmental toxicity studies.

## *2.2.4.3 Other Types of Tests Employed to Establish Safety of a New Food Additive*

### Pharmacokinetic Studies

The purpose of these studies is to characterize the fate of the food additive following consumption (i.e. the absorption, distribution, metabolism and excretion of the food additive after ingestion), to assist in the selection of the most appropriate species for toxicity testing and the dose levels to be used in toxicity tests, and to understand potential species differences.

### Human Clinical Studies

The purpose of these studies is to determine the tolerance to the food additive after its ingestion by humans.

Generally these tests are conducted after preclinical studies (animal toxicity studies) have been conducted, or when sufficient preliminary evidence is already gathered on the safety of the food additive in humans. The results of these tests are used to confirm the safety of the food additive in the general population and to assess the tolerance to the food additive in a subpopulation within the general population (e.g. a subpopulation with a medical condition).

#### *2.2.4.4 Nutritional Safety Considerations*

There may also be a need to submit data attesting to the nutritional safety of a food additive. The petitioner should consider and present information on direct and indirect effects of the food additive on nutritional quality and safety. The purpose of the nutritional safety assessment is to verify and ensure that the presence of an additive at the proposed level in the proposed foods would not have an adverse effect on nutritional quality and safety of the food. The implications of the additive on nutritional quality and safety, on the population as a whole and/or for specific groups should be determined. Population subgroups may be more vulnerable for different reasons: e.g. young children, pregnant and lactating women, those with particular metabolic characteristics, adolescents and others who may consume large amounts of a particular food.

In some cases, introduction of an additive could have a broader impact on nutrition. Food additives may include compounds that are nutrients (e.g., ascorbic acid) or contain elements that are mineral nutrients and in other instances, the food additive may affect the availability of other nutrients in the food in which it is added. The potential contribution to dietary intake of these food additives will require greater scrutiny. In some cases the impact on nutrition may be difficult to predict. The need for and feasibility of projections or of post-market follow up is assessed on a case-by-case basis.

#### *2.2.4.5 Microbiological Considerations*

Finally, there may be a need to submit data pertaining to the microbiological safety of a food additive (e.g., data relating to strain history, potential pathogenicity, and information on toxin levels of a microorganism that produces an enzyme). A summary of microbiological requirements are presented below.

##### A. Food Additives derived from Microbial Sources

It is recommended that the following information be included for assessing the acceptability of microorganisms and their products that are intended for use as food additives. These information requirements are not intended to define explicitly all the data that might be required in the course of a safety assessment. Further data

requirements may be identified on a case-by-case basis during the safety assessment process.

*a) Strain Identification*

The accurate identification of a strain will provide important information for the safety assessment of a microorganism and/or its products. A microbial strain should have an appropriate taxonomic designation following international codes of nomenclature and standard taxonomic references. The taxonomic designation should be provided to a level that distinguishes the microorganism from pathogenic species of the same genus. In the event that the identification is not conclusive, additional data may be required to address the safety of the microorganism.

In general, the methods used to identify an organism should be consistent with methods currently used for microbial classification. A taxonomic designation should be accompanied by a list of the tests used to arrive at the designation, with the results and any other information used to make the designation. A brief description of the type of tests used, or references, should be provided.

*b) Pathogenicity*

The potential for a viable microorganism in a food product to have adverse effects on human health must be considered. Adverse effects would include, but are not limited to infection, disease, adverse immunologic reactions and toxicosis. While information from a review of the scientific literature is sufficient to satisfy this information requirement, petitioners should search various sources for information on the human health effects of the microorganism (databases, regulatory authorities, etc.). The search should provide information that would give a complete and thorough overview of any known involvement of the microorganism in an adverse health effect or the lack of any documented adverse health effects caused by the microorganism. In some cases, further testing may be required to address the pathogenic potential of the organism.

*c) Antimicrobial Production*

Information should be provided on the production of antimicrobial compounds by the microorganism or its close relatives. These include classical antibiotics and other antimicrobials such as bacteriocins. The significance of these compounds in relation to clinically important antimicrobials will be considered.

*d) Antimicrobial Resistance*

The presence of antimicrobial resistance factors, especially resistance to clinically important antibiotics, must be assessed if the microorganism is present in the food additive itself or in the final food to which the additive is added. Data on the susceptibility of the microorganism to various antibiotics must be provided if the microorganism can survive or colonize the gastrointestinal tract (e.g. a new starter culture/probiotic strain used in yoghourt).

*e) Production/Specifications*

Microbial specifications for assuring microbial safety and data demonstrating compliance with these specifications should be provided for a number of production batches. The identification and levels of microbial contaminants must be reported. A food grade fermentation would be expected to yield a pure culture without microbiological contamination prior to down stream processing. Certificates of analysis for appropriate indicator organisms should be provided to demonstrate microbial safety. Documentation on the quality control of the manufacturing process should be provided, including a description of the manufacturing process and control measures that are applied to ensure quality and prevent microbial contamination.

## B. Characterization of a Genetically Modified Microorganism

Where a microorganism has been modified, whether by selection and mutagenesis techniques or by recombinant nucleic acid technology, the relationship of the derived strain with the parent organism(s) should be characterized. In all cases, the degree of exposure to the modified microorganism or its products will be an important factor in determining the extent of the characterization data required for the safety assessment.

The approach of the safety assessment is based on the principle that the safety of novel microorganism is assessed relative to a conventional counterpart having a history of safe use, taking into account both intended and unintended effects. Any significant differences between the novel and the conventional strain are then assessed for potential adverse health effects. Of particular interest to the safety assessment is whether the modification could inadvertently develop or increase the pathogenicity, toxicity, or allergenicity potential of the organism.

In cases where a microorganism has been modified using modern genetic techniques, such as recombinant nucleic acid technology (rDNA), the safety assessment will consider detailed characterization data of a microorganism at the molecular level. In general, the FD considers the following when assessing microorganisms derived from modern genetic techniques:

- Host and donor organisms (i.e. history of safe use)
- Description of the genetic modification process
- Information on genetic material added, inserted, deleted, or modified
- Identification, genetic stability, and expression of the introduced genetic material
- Information on the product(s) (e.g. a protein) encoded by the introduced genetic material

The FD will continue to participate at the international level (FAO/WHO, Codex, OECD, etc.) to ensure that the requirements for the molecular characterization of rDNA derived microorganisms remain consistent with

international standards.

### C. Efficacy of Preservatives - Antimicrobials

The determination of the efficacy of a preservative on the overall spoilage microflora or on specific foodborne pathogens will be assessed on a case-by-case basis, based on the intended effect of the additive. However, overall principles are given here for general guidance. The types of claim(s) and the food(s) to which the additive is added will determine the type of study required, and the target organisms to be studied.

Experiments intended to generate data to demonstrate efficacy of the preservative should be designed and conducted in accordance with sound scientific concepts and principles, as well as, where applicable, Good Laboratory Practice. Primary data should be made available to regulatory authorities upon request. Data should be obtained using sound scientific methods and analyzed using appropriate statistical techniques, when applicable. The sensitivity of all analytical methods should be documented and references to analytical methods made available.

Appropriate target microorganisms to be used in challenge studies are determined by the intended technical effect of the additive, and by the food to which the additive is being added. When the case specific species are proposed for a challenge study, the use of standard and well characterized references strains is recommended. A minimum of five strains, preferably isolated from the food which is the subject of the study, and/or from patients suffering from illness as a result of consuming the studied food at approximately equal populations in a mixed inoculum, is recommended. If only one strain is used as an inoculum, that strain should be evaluated against several other strains to determine if it is the most appropriate for the test conditions. Appropriate methodology should be used to inoculate the food, and to recover and enumerate the microorganisms in the challenged food.

### D. General microbiological considerations

The addition of a food additive may change the physicochemical properties of a food. This could lead to a change in the microbiological safety of the food by altering the pH, water activity or other parameters of the food which may affect microbiological growth. If such parameters are affected by the food additive, the petitioner will need to demonstrate that the addition of the additive will not affect the microbiological safety of the food. The data or information required in the assessment will depend on the physicochemical effect (on a case-by-case basis).

## 2.2.5 Food Additive Label Content

*[Section B.16.002 (h) of the F&DR]*

A draft, in triplicate, of the proposed label of the food additive preparation should be submitted for

review and should provide the following information:

(a) the common name of the active ingredient(s) in accordance with recognized nomenclature, e.g., *CAS* registry, *FCC*, etc.,
(b) the brand name, if one is to be used,
(c) a quantitative statement of the amount of each additive present or a list of the additives present in descending order of their proportions (in accordance with section B.16.001), or
(d) directions for use, such that, when followed, the food will not contain in excess of the maximum level of the additive proposed for use (in accordance with section B.16.001),
(e) precautions to be taken in handling and to ensure preservation of strength or potency,
(f) an expiry date where applicable,
(g) batch or lot number, or any code allowing traceability of the additive,
(h) net contents.

If a product brochure and/or promotional literature are to be used in connection with the distribution and sale of the food additive, a draft copy should be submitted for review. A statement should be included on the trade mark status of the brand name or mark.

#### 2.2.6 Samples of the Food Additive

*[Section B.16.002 (i) of the F&DR]*

Petitioners should be prepared to provide a sample, if requested, of the food additive in the proposed formulation (commercial package unit) and a sample of the active ingredient (sufficient to serve as a reference standard). After reviewing the submission, a request may also be forwarded to the petitioner by the BCS of the FD for a sample of the food containing the food additive in order to conduct methodological studies in the FD Research Laboratories.

### *2.3 Other Requirements (Non-Statutory) for Submissions on Food Additives*

#### 2.3.1 Consumer Benefits and Food Quality Considerations

Although food additives benefit food manufacturers in that they enable production of a wide variety of foods with desirable qualities, the use of a food additive should have some general direct or indirect benefits or advantages to the consumer. The benefits should be documented with supporting data and information. Depending on the purpose or function of the additive, examples of such data include

evidence for an improvement in shelf life, maintenance of nutritional quality, reduction of wastage, or correction for natural variations in colour, flavour, or texture of foods. Improvements in texture and other sensory characteristics of food should be supported by objective tests designed to demonstrate these improvements. These are in keeping with the Codex General Principles on the Use of Food Additives which have been incorporated into the *Preamble* of the Codex GSFA.

HC's FD may not respond favourably to any submission in which there is evidence that the proposed use of an additive could encourage faulty or careless handling and processing, causing a reduction in nutritive quality of the food or making the food appear deceptively better or of greater value than it really is. If the use of the additive does have some adverse effects on nutrient composition, these effects should be quantified (note that any such nutritional effects are assessed as part of the evaluation of safety data, as described in Section 2.2.4.4 of this Guide).

### 2.3.2 Information on Evaluations, Approvals, and Authorisations of other National and International Bodies

In the event that the substance has undergone evaluation by other domestic, foreign or international scientific bodies, their outcomes and possible legal implications should be submitted as a part of the request. In particular, summaries and pertinent details of evaluations conducted by JECFA and/or other national jurisdictions such as the U.S. Food and Drug Administration, the European Union food safety authorities, and Food Standards Australia and New Zealand should be provided. The status of the food additive according to the Codex Alimentarius may also be provided. Such evaluations do not replace the requisite national assessments by Canadian authorities. However, such information is included in the internal documents considered by the Food Rulings Committee (FRC), a senior management committee of the FD and/or the sub-Committee of Cabinet when making decisions regarding the use of the additive in foods offered for sale in Canada (see Section 4.0 of this Guide for more detail in this regard).

## *2.4 Submissions for Enzymes*

Enzymes that are approved for food additives uses are listed in Table V, section B.16.100 of the *F&DR*. In this table, enzymes are referenced by their primary activity and the source from which they are derived (animal, plant or microbial). Enzymes, when added to food or food ingredients to affect their characteristics, are considered food additives, even when present in the deactivated form. All requirements relevant to a submission of a new food additive as laid down in Section 2.0 of this Guide

apply to enzymes as well. Additional specific points for consideration are the following:

a) As an aid to identification, the E.C. number should be provided as well as the CAS registry number if possible.

b) Full specifications should be provided for the parameters set out for "Food Enzymes" in the *Food Chemicals Codex*, Fifth Edition, 2004, The National Academies Press, Washington, D.C., U.S.A or in the *Compendium of Food Additive Specifications*, Addendum 9, Food and Nutrition Paper 52, Rome, Italy, Food and Agricultural Organization of the United Nations, Joint FAO/WHO Expert Committee on Food Additives, 57$^{th}$ Session, June 2001.

c) The Total Organic Solids (TOS) content of an enzyme preparation should be specified. In order to distinguish the proportion of the requested enzyme preparation derived from the source material from that contributed by other additives and ingredients or diluents, individual specifications may require a statement of percentage TOS which is defined as follows:

% TOS = 100 - (A+W+D), where

*A= % ash, W= % water and D=% diluents and/or other additives and ingredients.*

*All components of enzyme preparations should be identified, e.g active components, source materials, preservatives, carriers (liquid or solid) and other additives and ingredients, etc.*

d) In the context of toxicological considerations and intake calculations, the petitioner should specify whether the active or inactive form of the enzyme will be present in the food as sold.

e) As for other food additive submissions, technological justification for the use of the enzyme at its proposed level of use, safety data, and, if possible, an intake assessment of the enzyme as consumed should be provided. Consideration should be given to providing toxicological data on the form of the enzyme (active or inactive) that would actually be consumed.

f) The issue of any allergic effects should be addressed.

g) With respect to environmental assessments, a search of the Domestic Substances List (DSL) can be conducted for enzymes, according to the E.C. or CAS registry numbers, or for microorganisms. Further detail on environmental assessments appears in Section 3.0 of this Guide.

h) In the case of immobilized enzymes that are considered as food additives rather than processing aids (the latter do not require pre-market evaluation under the *F&DR)*, the evaluation of several additional parameters will be required, i.e. the chemicals used for enzyme immobilization, such as carriers, organic or inorganic supports. A petitioner should provide full identification of these chemicals and proof of their safety.

## 3.0 ENVIRONMENTAL ASSESSMENT OF NEW FOOD ADDITIVES

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) is the primary federal legislation respecting the protection of the environment and human health. The goal of CEPA 1999 is to contribute to sustainable development through pollution prevention.

In 2001, HC announced its intent to develop environmental assessment regulations for new substances regulated under the *F&DA.* The proposed substances to be regulated include food additives.

Until such time as the proposed regulations are promulgated, the *New Substances Notification Regulations (Chemicals and Polymers)* and the *New Substances Notification Regulations (Organisms)* (collectively referred to as the NSNR for the remainder of this document) of CEPA 1999 apply to all substances regulated under the F&DA. The NSNR first came into effect for such substances in September 2001. The New Substances Program is jointly administered by EC and HC.

The objective of the NSNR is to preclude introduction into Canada of new substances exhibiting potential toxicity to the environment and its biological diversity. According to CEPA 1999, an assessment of toxicity must consider three components: any harmful effect on the environment or its biological diversity, danger to the environment on which life depends (also referred to as indirect human health impacts), and danger to human life or health.

The DSL is the sole basis for determining whether a substance is new for the purposes of CEPA 1999 and the NSNR. The DSL is a list of substances, including those that were in Canadian commerce between 1984 and 1986, as well as those that have been assessed as not suspected of being toxic under CEPA 1999. Substances that are not on the DSL are considered to be new to Canada and are subject to notification under the NSNR. Substances that are on the DSL do not require notification unless they are listed with an S flag and are proposed for a Significant New Activity (SNAc), or are listed with a P flag and a non-Reduced Regulatory Requirement version of the polymer is proposed.

The submission of a New Substances Notification (NSN) is required for all food additive substances that meet the definition of a new substance under CEPA 1999, prior to import or manufacture beyond regulatory trigger quantities. Notification may also be required for a source organism that is used to obtain a substance added to food (such as an enzyme or a microbial metabolite). Notification and assessment under the NSNR is commonly referred to as an environmental assessment.

A new food additive submission should indicate whether or not the petitioner will be providing an NSN. If an NSN is required, the notification must be provided separately to the New Substances Division at EC, in accordance with the timelines set out in the NSNR. A copy of the NSN does not need to be included in the food additive submission that is provided to the BCS of HC's FD.

If the petitioner does not plan to submit an NSN, a rationale for this decision should be provided with the food additive submission.

Guidance documents on current NSN requirements for all new substances (including substances in products regulated under the F&DA are available on EC's New Substances Program website. There is a guidance document specific to the notification of Chemicals and Polymers, and another specific to the notification of Organisms.

Questions concerning the NSNR for substances in products regulated under the F&DA should be directed to the Environmental Assessment Unit of HC.

## 4.0 ACCEPTANCE OF SUBMISSIONS

After evaluation, if the data and information are found to be satisfactory in form and content, the proposal for amendment of the *F&DR* is presented at the FRC, a FD senior management committee that advises the Director General of HC's FD on regulatory matters. If the Committee does not object to the proposal, acceptance of the submission is indicated by sending the petitioner a letter advising that a recommendation will be made to the Governor-in-Council (practically, a sub-committee of Cabinet which is an advisory body appointed by the Governor General of Canada on the advice of the Prime Minister) for the necessary addition or change to the Food Additive Tables. The recommendations are forwarded to the Governor-in-Council as regulatory amendments project, which, if accepted, will be pre-published for public consultation in Part I of the *Canada Gazette*. The public consultation period which follows the publication is usually 75 days.

At the conclusion of the public consultation period and provided no substantive concerns have been raised, the amendments (revised, if necessary) will again be forwarded to the Governor-in-Council for final consideration. Shortly after, the Schedule of Amendments is published in Part II of the *Canada Gazette*. The amendments come into effect and hence are enforceable the date they are registered and must be published in *Canada Gazette* Part II within 21 days of registration. The petitioner is advised by the FD when the item appears in the *Canada Gazette* Part II. It should be noted that some time may elapse between the initial advice given to a petitioner that the FD intends to recommend a change in the Food Additive Tables to the Governor-in-Council (i.e., after completion of the technical evaluation of the submission) and the moment when the final Order-in-Council is issued and appears in the *Canada Gazette* Part II. During this time, the additive may not be used as requested (unless an IMA, described in Section 5.0 of this Guide, has been issued), since the amendment has not been promulgated into law.

For further information on the making of federal regulations, please visit the Government of Canada Privy Council Office website.

## 5.0 INTERIM MARKETING AUTHORIZATIONS (IMAs)

An IMA, as set out in B.01.056, is a notice published in *Canada Gazette* Part I that allows the immediate sale of foods not in compliance with specific provisions of the *F&DR* while the *Regulations* are being amended. The IMA notice specifies which foods may be sold and allows their sale by all manufacturers. An IMA provides a mechanism for bridging the time between acceptance of a petition and publication of the final regulatory amendments in *Canada Gazette* Part II. Consideration for issuing an IMA can only be given as part of a formal request for specific types of amendments. In the case of food additives, only petitions requesting regulatory amendment to extend the use of a food additive already permitted in other foods into a new food or to the change of a permitted level of use are eligible. An IMA is issued only when the scientific evaluation is complete, the petition to amended the *Regulations* is considered to be acceptable and the formal process to amend the *F&DR* is initiated. Consequently, an IMA may be considered as part of the food additive submission process for eligible submissions but not as means to circumvent this process.

For more information relevant to IMA's, readers are invited to consult the Regulatory Impact Analysis Statement, Schedule 923, available on the HC website. There is also information on proposed regulatory amendments regarding IMAs.

A list of currently active IMAs may be viewed on the HC IMA webpage.

## 6.0 TEMPORARY MARKETING AUTHORIZATIONS (TMAs)

The conditions necessary for issuance of a TMA are set out in sections B.01.054 and B.01.055 of the *F&DR*.

A letter authorizing a TMA may be issued for the sale of a food out of compliance with the current *F&DR* for a limited time, within a designated geographical area for a specified quantity of food. Essentially, it would allow the sale of a particular food, under specified conditions, that does not comply with the *F&DR*. The purpose of a TMA is to generate information in support of an amendment to the *Regulations*, provided the petitioner has supplied adequate data to demonstrate that the use of an additive in the particular food will not be detrimental to the health of the consumer. During the TMA period, a petitioner must provide the requested information pertaining to the submission.

It should be noted that in the case of food additives, TMAs would rarely be issued and only under extraordinary circumstances.

## 7.0 SUBMISSIONS FOR IRRADIATED FOOD

Petitioners seeking to amend the table under Division 26 (Food Irradiation) should complete the electronically-available submission form for irradiated food and convey it with the hard copy of the submission to the CHHAD, BCS, FD, HC (see Section 2.1.5 of this Guide). Like food additives, the use of irradiation in the processing of retail foods requires pre-market clearance. There is an obligation to demonstrate the chemical, toxicological, microbial and nutritional safety of a food which has undergone the process of irradiation. It should be noted that irradiated foods are not eligible for either IMAs or TMAs (described in Section 5.0 and Section 6.0, respectively, of this Guide).

### *7.1 Information Requirements for Submissions on Irradiated Food*

The following information pertaining to the irradiation process that is intended to be applied to a specified food is required: purpose for using irradiation; details of the irradiation process; efficacy data pertaining to the dose applied; dosimeters and dosimetry; safety of the irradiated food; effect of the irradiation or combination processes on the nutrient composition of raw and ready-to-consume irradiation-treated products; chemical/physical/microbiological effects of the irradiation; details of pre- and post-irradiation handling and storage of the food; details of other technological processes applied to food destined for irradiation; and any other information pertaining to the safety of a given irradiated food. An Irradiated Food Submission Checklist summarizing these requirements is available in Annexe B.

Detailed safety data demonstrating a lack of deleterious effects of the irradiation process on the chemical, toxicological, microbial and nutritional characteristics are a crucial component of the submission. Imported retail food that has been irradiated (even at low doses for quarantine purpose) is also subject to the above provisions and safety requirements. Irradiated food should bear an adequate label, pursuant to section B.01.035 of the *F&DR*. The CFIA can provide additional information concerning requirements for labelling of irradiated food.

## 8.0 LETTERS OF OPINION

A Letter of Opinion from the BCS of HC's FD expresses an opinion on the acceptability of a product. A Letter of Opinion can be issued, upon request, for substances not regulated as food additives under the *F&DR* and which therefore are not required to undergo a pre-market evaluation; for example, processing aids, flavouring substances or other categories of substances, such as food contact materials and indirect food additives. The intent of a Letter of Opinion is to indicate, based on the information provided on chemical identity, specifications, and on patterns and levels of use, that the use of the product in the opinion of the Bureau would not lead to a violation of section 4 of the *F&DA* or any applicable regulations. Opinions expressed in a Letter of Opinion may provide assurance to a petitioner about the safety-in-use of a given substance, although the letter neither constitutes an approval of the product in a legal sense, nor does it relieve the food manufacturer or seller from the ultimate responsibility for the product's safety under section 4 of the *F&DA.*

Once the information in support of a request for a Letter of Opinion has been reviewed and found acceptable, an officer of the BCS will inform the petitioner in a form of a Letter of Opinion. Such a letter constitutes proof that a given substance has been evaluated as to its acceptability for its intended use. On condition that the information provided for evaluation of processing aids or flavouring substances is complete, the evaluation and preparation of letters of opinion generally require a shorter time period than the full evaluation of food additives.

If, upon the completion of a review of the request for a Letter of Opinion, the BCS has reservations about the safety-in-use of a given substance, the petitioner will be so advised through issuance of a Letter of Opinion objecting to or expressing concerns about the proposed use. Specific concerns will be described in the letter.