Guidance Document on the Submission of an Application for the Approval as "Novel Food" of "Novel Proteins" (Alternative Proteins) Derived from Cell Culture Originating in Animals, Plants, or Microorganisms

[Reference: Article 8.3.2b in the Procedure for Registration of Novel Food (No. 004-08)]

Food Risk Management Department

Dr. Ziva Hamama, Dr. Jonatan Darr, Yogev Magen

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Food Control Service
Ministry of Health
236 Yaffo St., Jerusalem
9438317 (Daniel building)
Call.habriut@moh.health.gov.il
Tel *5400 **Fax**: 02-5655969

קול הבריאות *5400

National Food Service
Ministry of Health
236 Jaffa St., Jerusalem
(Daniel Building) 9438317
Call.habriut@moh.health.gov.il
:Tel*5400 **:Fax**02-5655969

A. NOVEL FOOD - OVERVIEW

1. Legal Basis

The Novel Food Registration Procedure (Procedure No. 004-08) (hereinafter "the Procedure"), which has been in effect since 19.02.06, has received the status of a secondary legislation in accordance with Article 321(d) of the Public Health Protection Law (Food), 2015-5776 (hereinafter "the Law"), and is anchored in Item 6 of the Appendix to the Public Health Protection (Food) Order (Extension of the Validity Period of Guidelines and Procedural Instructions), 2020-5780.

1.1 Purpose of the Guide

In accordance with the Procedure, novel food is registered by the Director of the National Food Service (NFS) following a recommendation of the Novel Food Committee (NFC). Among other requirements, and in accordance with the Procedure, two approvals from two competent authorities should be presented (as detailed in section 6.7 of the Procedure). **However, in the absence of two such approvals, the submission, review and approval of a novel food petition shall not be prevented.**

When two such approvals are not presented, a "Novel Food" for which a registration petition has been submitted in accordance with the Procedure, will be reviewed by the Food Risk Management Department (FRMD) of the NFS. The FRMD will then advice the NFC whether to approve or reject the petition. The NFC will discuss the advice of the FRMD and pass its recommendations to the Director of the NFS.

Given the innovative nature of the "novel protein" (alternative protein) field, and specifically of "novel proteins" that are composed, isolated or produced from cell cultures derived from animals, plants or microorganisms, and given the variety of products and technologies and the ever-evolving means of production, the NFS sees fit to publish this guide in order to support and streamline the approval process of these novel foods. This guide is intended to outline the essential requirements and provisions that must be fulfilled in the framework of a petition to register "novel proteins" as a novel food, so that the FRMD of the NFS will draw its recommendation to the committee.

1.2 Scope

Section 2 of the Food Law, defines "novel food" as a food or food component, which is not a food supplement nor a food supplement component, neither a food additive, a flavoring substance nor a manufacturing aid that has one of the following characteristics:

1. It has a new primary molecular structure (e.g. new sugar), or has undergone a deliberate change in the primary molecular structure, and for which little to no history of safe human consumption exists in Israel prior to February 2006;
2. It contains a genetically modified organism or part of it;
3. It contains a plant, animal, microorganism, fungus or algae or is isolated from them, for which there is little to no history of safe human consumption in Israel, with the exception of enzymes;
4. It was produced in a manufacturing process, with the exception of a cleaning and sterilization processes, which is not used in Israel for the particular food or food component, and the process has caused a significant change in the composition, in the structure or in the components of the food, or has affected the nutritional

values, or its properties with respect of physiological metabolism, or the level of unwanted substances in the food;

According to the Procedure, food that meets the aforementioned definition of "novel food", requires an assessment and approval from the NFS prior to marketing and/or import to Israel. This approval is obtained after the NFC discussed the petition and forwarded its recommendation to the Director of the NFS. The procedure details the petition review process and the mechanism for the registration of novel foods imported to or developed in Israel that have received such an approval.
Foods that include "novel proteins" (alternative proteins) produced through precision fermentation, and "cell-based foods" such as "cultured meat" produced using cell cultures **(hereinafter – "novel proteins" – the subject of this guide),** meet the definition of novel food in Israel and must comply with the requirements of the procedure and its appendices.

Without derogation from the requirements of the Procedure, **the emphasis in this guide is on "novel proteins" and its aim is to incorporate the requirements of the procedure, add to them and elaborate on them, and to clarify and refine them with regard to these specific foods, so as to support the formulation of the FRMD recommendations to the aforementioned NFC.**

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Ministry of Health
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9438317 (Daniel building)
Call.habriut@moh.health.gov.il
Tel *5400 **Fax**: 02-5655969

שרות המזון הארצי
משרד הבריאות
רח' יפו 236, ירושלים
9438317 (בניין דניאל)
Call.habriut@moh.health.gov.il
טל: 5400 * **פקס:** 02-5655969

2. Novel Food Registration Petition

Any person, company or organization may petition to register a novel food. A petition for the registration of a novel food can be submitted in Hebrew or English on the designated website in the Application Form for Novel Food Registration. Documents in any other language must be submitted together with a notarized translation.

According to the procedure, in addition to the details required in the application for novel food registration form, the petitioner must attach a thorough safety dossier that will serve as the basis for the safety assessment of the food and of the production process. Upon completion of the submission of the application form and the attachment of the safety dossier in the website, the petitioner will receive an approval of the receipt of the petition along with a confirmation number identifying it. After receiving the petition, it is reviewed by the FRMD of the NFS and later by the members of the NFC of the Ministry of Health (MOH). Petitions are discussed in accordance with their submission order as registered in the system and in accordance with the timetables set in the Procedure.

3. Safety Dossier Review

The review includes a safety assessment of the food and its production process, starting with the raw materials, including various aspects related to the reproducibility of the production process, the composition of the food, anticipated intake levels, the consumption manner of the food, allergenicity potential, levels of potential contaminants and more. The safety assessment is carried out on the basis of the data submitted to the FRMD, which is the proficient department responsible for receiving novel food registration petitions, and for their scientific review, prior to their discussion within the NFC.

The review of a safety dossier is in every respect a scientific review, which requires relevant data and references to substantiate the claims on the safety of the novel food in question for human consumption in Israel. Therefore, every claim presented throughout the dossier is examined in light of the relevant data and/or the supporting scientific references contained within the dossier.

In addition, the manner in which the various safety tests are carried out and the rationale for choosing said tests so as to provide a comprehensive safety assessment relevant to the final consumer are examined.

Furthermore, the manner in which raw data is collected and processed, and the selection of statistical tests and computational analyses are also reviewed to confirm the conclusions regarding the safety of the product. Thus, it is recommended to:

1. Specify, for all the submitted experiments and tests, the rationale for their selection, the manner in which collected data was analyzed, and the way conclusions were drawn to provide a comprehensive assessment of the safety of the food and the production process. It is also recommended to indicate throughout the dossier how data is collected and stored, and to specify monitoring measures implemented throughout the production process, if any;
2. Include details on compliance with standards, regulations and legislations relevant to the petition, whether Israeli, national, or international standards relevant to the body of the petition;
3. Specify, for each analysis attached in the dossier indicate the name of the laboratory, its certification and the scope of its accreditation;

In light of the variety of technologies, food ingredients and novel foods submitted for approval, the nature of the data required to identify and address safety aspects is varied, and unique questions may arise for specific petitions. Each petition is examined on its own merits, on a case-by-case basis, and therefore critical aspects to consider in the safety assessment of a novel food submitted for approval, depend to a large extent on the nature of the food in question. In light of this, the petitioner might be required to submit additional information required to establish the safety of the product or of the manufacturing process.

This guide is intended to provide information on the submission process and on all the information that should be included in the safety dossier of a "novel protein" obtained from cell culture and that originates from an animal, plant or microorganism, as detailed above, so as to formulate the position of the FRMD to be presented to the NFC.

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9438317 (Daniel building)
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Tel *5400 **Fax**: 02-5655969

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4. Processing of a Petition

Generally, after reviewing the safety dossier, a petition for the registration of a novel food is discussed by the members of the NFC, following which the FRMD sends a reply with the conclusions of the committee directly to the petitioner.

When a petition is approved, a directive, signed by the Director of the NFS will be published on the NFS website. This directive will include the conditions of the approval. From the moment a complete safety dossier is submitted in accordance with the Procedure, the allocated duration to reply is up to 6 months for novel foods approved by two recognized foreign authorities (section 8.3.2a.5), and up to 12 months for novel foods that have not been approved by two foreign authorities (section 8.3.2b.3).

More details about the processing of a petition can be found on the NFS website.

5. Amending an Approved Novel Food Directive

Since "novel food" is in practice an evolving field, the characteristics of an approved novel food product may change with its continued development and continued assimilation of new production technologies. Generally, if a petitioner seeks to amend a published novel food directive, the petitioner must submit as part of the amendment petition all the relevant and updated data pertaining to the safety dossier.

It should be emphasized that even in the event that changes and/or modifications are made in the production process or in any additional aspect that served as a justification for granting the approval at the time the initial safety dossier was submitted, the petitioner must notify the FRMD of such modifications even when no amendment to the published directive is sought.

Amendments to the safety dossier of a newly approved food product should be submitted with attention to any differences in production methods and/or product specifications. In submitting a petition for an amendment, it is necessary to specify the differences in the specifications/production process in relation to the data submitted within the reviewed and approved safety dossier. In so far as the petitioner's position is that the data submitted prior to the amendment are still relevant following the modifications, it is necessary to explain how this data is relevant. Accordingly, all supporting data and conclusions submitted in the amendment petition will be reviewed alongside the entirety of the previously reviewed safety dossier.

This is also the case with "novel proteins" for which the technological developments and changes are even more accelerated.

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B. SAFETY DOSSIER - CONTENTS

In order to streamline an application process, it is **recommended** to include the following information detailed in sections 1-8 below in a safety dossier submitted for approval of a "novel protein":

1. Identity, Origin and Characterization of Cell Lines

1.1 Full taxonomic identification of all organisms which constitute, or parts of them constitute, or products derived from them constitute the novel food ingredient or novel food submitted for approval. Or of those organisms that participate in the production process of the novel food ingredient (for genetically engineered microorganisms, details should be provided regarding the donor organism, host, and producer organisms).

The following information should be detailed:

1.1.1 Full taxonomic identification including scientific name and synonyms;

1.1.2 Common morphological characteristics;

1.1.3 Procurement process, method of shipping and import of the cells relevant to the petition, along with any verification steps of their identity made by the petitioner, and any measures taken to ensure full traceability of the cells from the moment they were isolated until their use in the production of the final product;

1.1.4 Methods for cell isolation, characterization, and selection in culture;

1.1.5 Phenotypic and genetic stability of the relevant cell lines, **throughout the production process**. The criteria and methods for establishing stability should be described, along with the rationale behind their selection. Raw and/or processed results supporting the conclusion on stability throughout the production stages and relevance of the tested

generations to commercial production should be provided. If genetic instability is observed during production, it should be specifically addressed in the safety assessment. It is recommended to examine stability on more than one production batch;

1.1.6 Methods for ensuring culture purity during cell line establishment stages, including; exclusion of relevant pathogens, method of assessing relevant pathogens and analytical methods to exclude their presence in the initial culture;

1.2 For cells of animal origin, in addition to article 1.1, information about the following should be included:

1.2.1 Genus, species and breed of animals, the organs and tissues from which the cells were taken, the stage at which the cells were isolated;

1.2.2 Potential presence of prions;

1.2.3 Comparison between the gene expression patterns along the production process, to gene expression patterns in comparable cellular processes in-situ. An explanation should be attached as to the rationale for the choice of a comparable cellular processes and as to the genes discussed in this section;

1.2.4 Potential changes in metabolic pathways of the cells that form a part of the product, compared to comparable cells in-situ. A detailed reference to the potential formation of metabolites that do not exist or whose level is different compared to comparable cells in-situ, or that may be formed as a result of the production process;

In case differences in hormone levels / growth factors / metabolites are observed, a risk assessment should be performed to determine whether these differences pose a food safety risk, in accordance with section 8 of this document;

1.3 For a genetically modified organism (and if several strains are involved in the production process, refer to all of them), include at least the following information:

1.3.1 Full and detailed description of the history of safe use of the host organism strain in the food industry (if this exists);

1.3.2 The purpose of any genetic modification;

1.3.3 A detailed description of the genetic modification process, including: A description of the sequences of the various vectors used, including the size, origin and function of all the different genetic components (open reading frames (ORFs), genetic vectors, regulatory elements, restriction sites, selection markers with specific references to any antibiotic resistance, origin of replication and etc.);

1.3.4 Full molecular characterization of the genetic change and expression patterns in the production organism, including:

1.3.4.1 Identification of the new genetic material, reference to genetic reorganization, identification of all integration sites and number of copies in each integration site, analysis of the integration sites for the presence of new ORFs;

1.3.4.2 Desired changes derived from the genetic engineering process, such as: silencing and induction of gene expression, change in protein expression levels, expression of proteins that are not naturally expressed, expression of proteins that do not exist in

nature, molecular modifications of protein for functional purpose (e.g., imparting thermal stability, reducing allergenic potential, etc.), changes in metabolic pathways for the expression of molecules that are meant to serve as a novel food component. Reference should be made to the validation measures of the desired changes;

1.3.4.3 Undesirable changes following the genetic engineering process, such as: the presence of new ORFs at integration sites, unintended changes in gene expression levels, undesirable changes in metabolite levels, any potential for the presence of new allergens or metabolites, etc;

1.3.4.4 Reference to the toxigenic potential of all the microorganisms involved in the process;

For all mentioned genetic elements, refer to the history of safe use in food (if it exists) along with the literary references. It is recommended to summarize the information in tables and include among other things, information about the source of the genetic sequence, the genetic modifications made to it, the history of safe consumption in food, and the relevant literary references. Detailed vector maps of all genetic components in the various vectors used should be attached.

All desirable and undesirable changes described in this section should be considered in the overall safety assessment of the product submitted for approval as food, in accordance with section 8 of this document.

1.4 It is recommended to deposit new microorganisms, in particularly genetically modified microorganisms, in a repository recognized as an international repository, and to indicate the unique identifier of the organism in the submission.

2. Raw Materials and Processing Aids

2.1 Include a description of all raw materials, food improvement agents and processing aids used throughout the production process from initial cell procurement up to the finished product. It is advised to summarize this information in a table with reference to the following points:

2.1.1 The stage during the production process in which the material is used;

2.1.2 The technological function of the material (e.g. nutrient, acidity regulator, anti-foam, flavoring, etc.);

2.1.3 Quality grade, with an emphasis on food grade;

2.1.4 Purity;

2.1.5 The concentration of the substance in the various stages of production in which it is used;

2.1.6 Potential for residues in the final product (based on initial concentration, dilution, adsorption, etc.);

2.1.7 History of safe consumption in food, with references;

2.1.8 For each material, indicate whether its purity matches the specification recommended by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), British Pharmacopoeia, European Pharmacopoeia, or Food Chemical Codex. Indicate whether the material is used in conventional food industry as is, including processing aids used

throughout the process, and materials used in cleaning/concentration processes, etc.;

2.1.9 If relevant, all information related to any "scaffold" materials. If these materials are used, indicate the identity of the material, its consumption history, specifications, and so on. Describe all the processes that the scaffold undergoes from the beginning of the production process to the end (sterilization, washing, etc.), and indicate its relative part in the final product;

2.1.10 All information related to the composition of the growth medium. If different growth media or solutions are used at different stages throughout the process, indicate their composition at each stage;

2.1.11 If components or raw materials are reused, a full and detailed description of the recycling process must be provided;

2.1.12 Include specific references to organic solvents, growth factors, recombinant factors, and materials for which there is no history of safe use in food. For all these materials, in addition to the details in the sections above, add information regarding:

2.1.12.1 Their concentration along various stages of the production process;

2.1.12.2 Measured residual levels in or on the novel food. Indicate the maximum safe residual concentration for use and the relevant source for this from scientific literature or attached safety tests;

2.2 Assessment of consumer exposure to residues of raw materials and processing aids in the product in relation to relevant health reference values.

2.3 Details on water sources and the tests performed to ensure their purity and quality during production.

2.4 Detailed description of the methods employed to ensure the quality, safety, and reproducibility of the cell banks held by the petitioner, that are used as raw material in the production process. This description should include references to the following points:

2.4.1 Types of cell banks held by the petitioner;

2.4.2 Standards under which these cell banks are kept;

2.4.3 Genetic stability of the cell banks;

2.4.4 Methods for maintaining the purity of cell banks;

2.4.5 Any additional quality controls on the identity of cells in banks;

2.4.6 Method of thawing banks;

2.4.7 Method of cell bank renewal (if applicable);

3. Production Processes

3.1 Full and detailed description of the product's production process and of a representative batch, beginning with the raw materials, through the production technology, and up to packaging and storage prior to marketing. It is advised to add flow charts for a schematic description of the production process. For various stages along the production process, relevant Standard Operating Procedures (SOPs) may be required in order to establish the reproducibility and safety of the production process and examine its compliance with relevant legal provisions.

Throughout the submission, distinguish between the research and development stages of the product to the final production process of the product in question. For data collected during the research and development stages, clarify the relevance to the final product and attach, as far as possible, data substantiating this relevance.

3.2 The safety of the product submitted for approval, as well as the reproducibility of the production process, must be demonstrated with at least 3 representative batches (preferably non-continuous) produced in the final production process. The description of the production processes will include a detailed reference to the following points:

3.2.1 Initial cell extraction process;

3.2.2 Main biological processes such as genetic engineering, selection, proliferation and differentiation;

3.2.3 Thawing method along with the quality control of cell banks. Refer also to their renewal if applicable;

3.2.4 Recovery and recycling processes of raw materials, buffers and media;

3.2.5 Changes in the composition of buffers and growth media;

3.2.6 Main physical and chemical processes (precipitation, crystallization, extraction, drying, etc.);

3.2.7 Any washing, cleaning, concentrating, extrusion or thermal treatment steps of food (when applicable);

3.2.8 Details on quality control processes designed to negate the presence of the production organism in the final food product intended for marketing;

3.2.9 Process controls (electronic and otherwise) employed throughout the production process;

3.2.10 Reference to the suitability of the various equipment for use in the food industry;

3.2.11 Description of the equipment cleaning processes during production;

3.2.12 Reference to the documentation systems;

3.2.13 Description of the storage conditions;

It is advised to add an illustration describing the stages of the production process, along with essential variables in the process (such as temperature, pressure, time, etc.) and critical control points (in ac accordance with the Hazard analysis and critical control points (HACCP) program).

3.3 In describing the production process, care should be taken to include information regarding:

3.3.1 Key process factors such as: Cell division rate, Population Doubling Levels (PDL) relevant to the production process, extraction, concentration, drying and dilution factors;

3.3.2 Batch definition of the food product or food component under consideration, indicating for instance whether batches are continuously produced or not. It is advisable to specify the production scale of each batch;

3.4 Conducting a Life Cycle Assessment (LCA) study to assess the sustainability of the production process is recommended. If any claims regarding sustainability are made, supporting data should be attached in support of their credibility.

4. Specifications

4.1 Complete specifications describing the product submitted for approval must be attached. Along with the specifications, analysis certificates demonstrating the compliance of 3-5 (preferably non-consecutive) batches should be attached along with a description of the analytical methods used.

The specification should faithfully represent the product described in the safety dossier. If this is not the case, a rational should be provided for the reason the petition includes specifications that differ from the specifications of the product intended for marketing.

It should be emphasized that it is mandatory to demonstrate the reproducibility of the production process using representative specifications of at least three batches (preferably non-consecutive, if possible), and attach analytical certificates demonstrating compliance with these specification.

The specifications should include data on the following characteristics of the product in question:

4.1.1 Nutritional values;

4.1.2 Maximal levels of contaminants such as heavy metals and endotoxins;

4.1.3 Maximal levels of microbial contaminants;

4.1.4 Residues of processing aids;

4.1.5 Residues of substances not permitted/used in traditional food industry;

4.1.6 Residues of growth factors and recombinant components;

4.1.7 Undesirable by-products and residual metabolites resulting from the production process itself;

4.1.8 Residual levels of the producing organism (DNA, residual proteins, viable cells, etc.);

4.2 For "cell-based" food products, in addition to the details specified in article 4.1, the specifications should also include details on:

4.2.1. The Identification of the cells;

4.2.2. The relative percentage of cell mass in the product;

4.3 For all the characteristics listed in the specifications, and more broadly, for all the characteristics that establish the safety of the product for human consumption, details should be included on the quantification methods, test standards used for quantification and their purity levels, as well as factors that may impair quantification in the method of choice.

4.4 It is advisable to attach a table to summarize all the analytical methods used to characterize the product, and on which the specifications and safety assessment are based. The table should contain the following details:

4.4.1 Measured parameter;

4.4.2 Measurement method;

4.4.3 Relevant test standards;

4.4.4 LOQ and LOD;

4.4.5 Name of the laboratory performing the test;

4.4.6 Accreditation status of the laboratory ;

4.5 For analytical methods developed in-house, in addition to the data mentioned above, reports detailing the validation processes for reproducibility and accuracy of the methods, and an explanation of the choice of the method over alternative methods should be provided as well.

5. GMP and HACCP

Production of novel food requires manufacturing under GMP conditions:

5.1 Clarify compliance with GMP requirements (whether Israeli or international standards, in accordance with the production site);

5.2 Elaborate on the product quality control and assurance methods implemented throughout the production process and of the final product;

5.3 Specify the critical control points along the production process and explain how they were selected;

5.4 Describe all the processes implemented to maintain the purity of the cell culture and all quality control measures of the final product;

5.5 Describe the frequency of contaminant tests, including (but not limited to) microbiological and chemical contaminants;

5.6 Clarify whether the methods are validated and accredited according to an accepted standard, and by whom;

5.7 Explain the selection of stages in which the various tests are performed (according to the HACCP program);

5.8 Describe the monitoring plan for the implementation of the HACCP program;

5.9 Include reference to corrective actions in cases of deviations;

6. Product Description

6.1 The product description should include reference to the following points:

6.1.1 Whether the novel food or food ingredient is intended to replace a conventional food or food ingredient, and which one;

6.1.2 Nutritional values of the food in its ready-to-eat form and the degree of nutritional equivalence to a comparable "conventional" product, if any. If the product is expected to mimic or replace a "conventional" product, add a table comparing the specifications of the new product with a representative conventional product in terms of ingredients and nutritional values;

6.1.3 Reference to the bioavailability of nutrients in the product;

6.1.4 Shelf life stability tests (to be performed on 3-5 preferably non-consecutive batches);

6.1.5 Instructions regarding storage conditions;

6.1.6 Product marketing strategy (to the final consumer, to restaurants, as a raw material for the food industry, etc.);

6.1.7 Description of the suggested labeling, including the proposed product/ingredient name, consumer instructions, allergens, and various additional claims such as ones related to environmental benefit and more;

6.1.8 Specific analytical methods allowing for the authentication and quantification of the novel food product or its breakdown products. Elaborate on the identification method, and explain the rationale for choosing this method. Address whether this method is relevant to the final food product as well;

6.2 In the case of a novel food ingredient, cellular or otherwise, which is intended to be used as an ingredient in food products, the following points should be addressed:

6.2.1 The purpose achieved in the addition of the ingredient to foods;

6.2.2 Reference to the self-limiting levels of use of the ingredient in the final product;

6.2.3 Proposed maximum level for use of the ingredient in each food category for which the approval is requested and the classification of the food category according to the food classification system;

7. Exposure Assessment

7.1 Exposure assessment should be carried out according to the nature of the novel food product or ingredient and the described marketing strategy. The exposure assessment may be derived from food consumption data retrieved from national nutrition surveys, relevant analytical surveys, or other validated sources.

The potential intake of the novel food or food ingredient, along with the intentional and undesirable changes in the nature of the product intended for consumption, will contribute to the overall risk assessment. The following information must be included in a safety dossier submitted for approval in Israel:

7.1.1 The food categories according to the food classification system of the National Food Service (2002), for which the petitioner requests approval to add the food ingredient or the novel food;

7.1.2 The maximum use level of the novel food ingredient sought for each food category or range of levels. The quantity can be specified in different units such as: W/W, W/V, cell density per unit of weight, molar concentration, etc;

7.1.3 Expected consumption levels in Israel, divided into sub-populations as best as possible, with references to average and 95'Th percentile consumption level of the relevant food categories or food ingredient submitted for approval;

7.1.4 Various limitations on the consumption level of the food or food ingredient. Acceptable Daily Intake (ADI), if any, with reference to contaminants and/or residues from the production process or from the raw materials;

7.1.5 If there are any natural dietary sources of the novel food or food ingredient, or for any substance contained within it, include data on existing and expected consumption levels following the introduction of the novel product to the relevant food categories;

7.1.6 If the novel food or food ingredient submitted for approval is already placed on the market in other countries, include the following information, when available:

7.1.6.1 The countries in which it is placed on the market and the duration of use;

7.1.6.2 The food categories that are approved for the novel food or food ingredient;

7.1.6.3 The maximal allowed level of use of the novel food or food ingredient, for each approved food category;

7.1.6.4 Current consumption levels of the novel food or food ingredient, divided into sub-populations as best as possible;

7.1.6.5 Any observed changes in consumption behavior among the consumers in the relevant countries, following the approval of the novel food or food ingredient;

7.1.6.6 Restrictions and / or conditions of use set with regards to the consumption of the novel food or food ingredient;

8. Safety Assessment

8.1 Address potential risks derived from various stages along the entire production process of the novel product submitted for approval, beginning with the acquisition of the cell line and of the raw materials, through the production process and up to the final product, as reflected in the information submitted within the safety dossier and based on the various sections detailed in this guide.

In addition to these potential risks, address the monitoring and control measures implemented to mitigate these risk as they are described throughout the dossier and with reference to the various sections in this guidance document.

The risk assessment will include, among other things, reference to the following information:

8.1.1 Desirable and undesirable changes derived from the genetic modification processes;

8.1.2 Cell lines used in the production process, and any toxigenic or allergenic potential they have;

8.1.3 Novel proteins or metabolites that form a part of the novel food product;

8.1.5 Risks derived from the production process or from the specifications of the product submitted for approval;

8.1.6 Composition of the novel product, including nutritional composition, residues of processing aids, contaminants, in light of exposure assessments, target population, marketing strategy, etc.;

8.1.7 Any effects on the consumer (nutritional, behavioral, etc.);

8.1.8 Reference to possible long-term effects on the consumer following frequent consumption of the product over time;

8.1.9 Any additional information regarding the safety of the product and/or the production process;

8.2 In order to establish the safety of the novel food or food ingredient, the following points must be considered, according to the nature of the product:

8.2.1 History of safe consumption;

8.2.2 Degree of molecular similarity to conventional dietary components;

8.2.3 Genotoxic/mutagenic studies;

8.2.4 Metabolism and Toxicity Studies (ADME-TOX);

8.2.5 Allergenicity assessment;

8.2.6 Safety and tolerability studies in humans;

8.2.7 Exposure assessment;

8.2.8 Safety assessment reports from foreign competent bodies (if such exist);

8.3 Throughout the submission it is advisable to elaborate as much as possible on:

8.3.1 The rationale behind the selection of the various model systems and the experiments performed in order to provide a comprehensive safety assessment. Explanation on the way analytical results were analyzed and how the detailed safety conclusions were drawn;

8.3.2 All assays and tests along with their complete results, including genotoxicity assays, sub-chronic and chronic assays in various models, metabolism and digestion assays, allergenic profile, genetic characteristics, enzymatic induction assays, and more;

8.3.3 Any relevant information on the validation of the method and results, including the experimental protocols, standards, test facility, etc. attesting on the reliability, accuracy and reproducibility of the analytical results used to establish the product safety;