

Requirements for the Safety Assessment of Novel Foods and Novel Food Ingredients

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1 What are novel foods?

- 1.1 SFA considers novel foods to be foods and food ingredients that do not have a history of safe use. Substances with a history of safe use are those that have been consumed as an ongoing part of the diet by a significant human population (e.g. the population of a country), for a period of at least 20 years and without reported adverse human health effects. Food and food ingredients which are shown to have history of safe use will not be considered novel foods. Novel foods may also include compounds that are chemically identical to naturally occurring substances but produced through advances in technology (e.g. production of functional ingredients through precision fermentation).
- 1.2 The production/manufacture, import, distribution, and sale of the following are not permitted in Singapore:
 - 1.2.1 Foods that lack a history of safe use and have not received pre-market regulatory approval from SFA; and
 - 1.2.2 Food products containing one or more novel food ingredients which lacks a history of safe use and have not received pre-market regulatory approval from SFA.
- 1.3 It is the responsibility of the company to ensure that:
 - 1.3.1 Documents justifying that a food or food ingredient has a history of safe use are available for inspection upon SFA's request.
 - 1.3.2 SFA's pre-market approval has been obtained before any novel food or food ingredients are produced/manufactured, imported, distributed, or sold.
- 1.4 Therefore, companies should consult SFA when in doubt on whether a food or food ingredient is a novel food to discuss the available evidence on the history of safe use that they have compiled. This information can include (but not limited to):
 - 1.4.1 The length of consumption/use of the ingredient (i.e. how many years the ingredient has been consumed as food or used in food).
 - 1.4.2 Extent of use of the ingredient (i.e. whether the ingredient is consumed or used by the general population, sub-population, certain tribes, etc).
 - 1.4.3 Quantity (i.e. the level of the ingredient consumed as food or used in food).
 - 1.4.4 Purpose/context of use (i.e. whether the ingredient is used for ceremonial purposes such as weddings, during famines, etc).
 - 1.4.5 Evidence demonstrating lack of adverse effects to human health attributed to the substance during the specific period of use as food.
- 1.5 History of use as medicine/ alternative medicine, or short-term exposure (e.g. for ceremonial use, during famines, etc.) is insufficient evidence to demonstrate history of safe use as food.

- 1.6 Information sources that could be considered include scientific/non-scientific publications, books (e.g. cookbooks, books on the history of food culture), patents, affidavits from two or more independent, reputable authorities, etc.

2 Scope of this document

- 2.1 This document aims to provide food businesses with a better understanding on SFA's requirements regarding the safety assessment for novel foods and novel food ingredients.
- 2.2 Businesses that intend to produce/manufacture, import, distribute and/or sell novel food or food products containing novel food ingredients in Singapore are required to ensure that the novel food or novel food ingredients:
 - 2.2.1 Have received pre-market regulatory approval from SFA; and
 - 2.2.2 Meet the specifications and are produced in accordance with the manufacturing process declared in the safety assessment submitted to SFA; and
 - 2.2.3 Are only used in the food categories specified in SFA's pre-market regulatory approval, and in accordance with the proposed use levels for each food category described.
- 2.3 Novel food products intended for sale in Singapore must comply with the requirements, including regulatory limits, under the relevant legislation, which includes the Sale of Food Act, Wholesome Meat and Fish Act and their subsidiary legislation.
- 2.4 No approval from SFA is required for research on novel food and novel food ingredients. Novel food and novel food ingredients that are under research and have not received pre-market regulatory approval from SFA should not be made available for sale.
- 2.5 As novel food is a rapidly evolving area, SFA will periodically update and revise this document to facilitate safety assessments by the industry.
- 2.6 The terms 'novel foods' and 'novel food ingredients' may be used interchangeably in this document.

3 General information on the safety assessment criteria for novel foods and food ingredients

- 3.1 Substances that do not have a history of safe use are considered novel foods. Food businesses that intend to produce/manufacture, import, distribute and/or sell novel food or food products containing novel food ingredients in Singapore are required to first seek SFA's pre-market regulatory approval before novel foods can be sold in Singapore.

- 3.2 Safety assessments for novel foods must clearly indicate any food processing substances used during production/manufacture which are not intended to be an ingredient of the final product. If any of these substances is a potential human health hazard, it must be shown that its presence in the final product is at levels that will not cause significant food safety concern, under the proposed intended uses and conditions of consumption.
- 3.3 There is no one-size-fits-all approach to the testing of novel foods and companies should adopt effective testing strategies based on their understanding of the hazards that may be present in their novel foods. Where possible, companies should ensure that that testing is conducted in accordance with principles of Good Laboratory Practices (GLP). The methodologies should also be validated to international standard such as ISO/IEC 17025 or its equivalent and published in the scientific literature, and applicant should therefore include references to these methods.
- 3.4 Useful resources include, but are not limited to, the official testing methods for chemical and microbiological hazards listed under the Official Methods of Analysis published by the Association of Official Agricultural Chemists (AOAC)¹, Pharmacopoeia methods (e.g. British Pharmacopoeia², European Pharmacopoeia³), and international guidelines such as those published by the Organisation for Economic Co-operation and Development (OECD).
- 3.5 Companies that require the use of in-house testing methods will need to send details of the testing method, accreditation status of testing method (if available) and the validation results to SFA, for evaluation of the scientific robustness, accuracy, precision, and sensitivity of the method.
- 3.6 Applicants should provide the following information in a safety assessment for SFA's review, unless otherwise scientifically justified. Please note that it is the responsibility of the applicant to provide all available proprietary, confidential, or published scientific data (including both data in favour and not in favour) that are pertinent to the safety of the novel food. Potential food safety concerns, including but not limited to chemical, microbiological hazards and allergenicity need to be addressed by relevant analytical and/or toxicity testing.
- 3.6.1 Information on the identity and source of the novel food, including percentages of major components present and an indication of whether the figures were determined on a dry or wet mass basis. This can be usually achieved by providing a specification list (e.g. Water content, Protein, Fat, Carbohydrate, Fibres, Vitamins, Minerals, Ash) of the novel food.
- 3.6.2 Information on the purity of the novel food, and the levels and identities of impurities that are expected to be present (e.g. contaminants, toxins, residual solvents, by-products, or metabolites).

- 3.6.3 Information of tests conducted. Please note that tests should be conducted by an accredited laboratory using established testing protocols (e.g. OECD) supported by scientific publications and method references. The limit of detection (LOD) and limit of quantification (LOQ) must be specified.
- 3.6.4 Background information, characterisation, and information on the specifications, purity and safety of all inputs used for novel food production, as well as any potential metabolites whether intended or unintended. Input refers to all food processing materials and food contact articles not intended to be the ingredient of the final novel food product. Companies should indicate whether the substances used are intended as an ingredient of the novel food product, as well as whether their purities comply with specifications listed in the Food Regulations, or if not provided, conform to specifications recommended by the British Pharmacopoeia², European Pharmacopoeia³, Joint FAO/WHO Expert Committee on Food Additives (JECFA)⁴ or Food Chemical Codex⁵.
- 3.6.5 Any safety assessment reports conducted for and/or by overseas food safety authorities, especially in jurisdictions such as Australia, Canada, New Zealand, Japan, the European Union, and the United States of America.
- 3.6.6 The intended use, proposed use levels and anticipated intake amounts of the novel food/novel food ingredients (i.e. exposure data)^{a1}. Intakes are estimated based on proposed use levels and data on actual food consumption. Novel foods which are intended for consumption by specific population groups should be indicated.
- 3.6.7 Information to demonstrate that hazards introduced from the inputs, manufacturing process and any known side reactions do not constitute a food safety risk.
- 3.6.7.1 This can be achieved by either:
- 3.6.7.1.1 Demonstrating that the hazard is not present in the novel food or food ingredient at the appropriate limit of detection (LOD), and that the chronic and acute dietary exposure, assuming the presence of the hazard at the appropriate limit of quantitation (LOQ), is within published health-based guidance values; or
- 3.6.7.1.2 Characterising the hazards that are present in the novel food or food ingredient and performing a risk assessment to show that these hazards do not pose a food safety concern to human health. This could include calculations to show that the chronic and acute dietary exposure is within published health-based guidance values; or
- 3.6.7.1.3 In cases where the novel food or food ingredient is intended to replace a traditional food or food ingredient, demonstrating that the dietary exposure levels to the hazards in the novel food or food ingredient are comparable to that in the traditional food or food ingredient.

^a Example: Up to 10% (w/w) in yeast-leavened breads and specialty breads and up to 7% (w/w) in cakes, cookies, and pies

3.6.7.2 Consumption data used for exposure assessments should accurately reflect the groups of consumers in Singapore that would be expected to consume the novel food or food ingredient. As consumption data for novel food or food ingredients are not usually available, references can be made to data on the conventional food analogue. This data can be obtained from the National Nutrition Survey conducted by the Health Promotion Board. The following publication by the US FDA may serve as a useful reference to determine the approach taken for estimating consumption data:

- US FDA Guidance for Industry: Estimating Dietary Intake of Substances in Food⁶

3.6.8 Information to demonstrate absence of toxicity. The information should cover systemic (acute, sub-chronic and chronic) toxicity studies, carcinogenicity studies, mutagenicity studies, reproductive toxicity studies, developmental toxicity studies, genotoxicity, and other toxicity studies.

3.6.8.1 The decision on whether toxicity testing is required, and which toxicity studies are necessary should be based on the available information on the novel food. A weight-of-evidence^{b2} and tiered toxicity testing approach^c would be applicable for toxicological assessment.^{7,8}

3.6.8.2 When toxicity testing is deemed to be necessary, toxicological studies should be carried out with the novel food as intended to be sold. However, due to the complexity of composition of the novel food, it may be necessary to focus on specific key constituents of the novel food (to be determined on a case-by-case basis).

3.6.8.3 The following would be considered by SFA to be relevant for toxicological evaluation if required:

3.6.8.3.1 A review and compilation of all relevant information on the novel food, its constituents (e.g. degradation products, metabolites), as well as the inputs into the production process (e.g. fermentation media, scaffolds). This information can include but is not limited to: Chemical structure; composition and properties; information on previous human consumption of the novel food and its source; anticipated intake and exposure levels; available toxicokinetic and toxicity data (*in-silico*/computational, *in-vitro*, *in-vivo*). Where there is insufficient data to define with certainty the toxicological profile of the product/ingredient/chemical/molecule under evaluation, toxicity testing is necessary to demonstrate its safety.

3.6.8.3.2 Predictive screening tools such as quantitative structure-activity relationship (QSAR) analysis^{d3} and the threshold of toxicological concern (TTC) approach^{e4}, for the purposes of priority setting for risk assessment. Please note that these tools should not replace actual safety testing unless otherwise deemed appropriate.

^b Weight of evidence assessment is defined as a process in which evidence is integrated to determine the relative support for possible answers to a question. The assessment consists of: (1) assembling the evidence into lines of evidence of similar type, (2) weighing the evidence, (3) integrating the evidence.

3.6.8.3.3 Toxicity studies⁹, examples of which include:

<p>Genotoxicity</p>	<ol style="list-style-type: none"> 1. Bacterial Reverse Mutation Test, Ames Test (OECD TG 471) 2. In Vitro Mammalian Chromosomal Aberration Test (OECD TG 473) 3. Mammalian Erythrocyte Micronucleus Test (OECD TG 474) 4. Genetic Toxicology, Mouse Heritable Translocation Assay (OECD TG 485) 5. <i>In Vitro</i> Mammalian Cell Gene Mutation Test using the Thymine Kinase Gene (OECD TG 490) 6. <i>In vitro</i> Micronucleus test (OECD TG 487)
<p>General systemic toxicity and other toxicity studies</p>	<ol style="list-style-type: none"> 1. Repeated Dose 28-Day Oral Toxicology Study in Rodents (OECD TG 407) 2. Repeated Dose 90-Day Oral Toxicology Study in Rodents (OECD TG 408) 3. Repeated Dose 90-Day Oral Toxicology Study in Non-Rodents (OECD TG 409) <p>Note: The 90-Day studies can be modified to include assessment of additional parameters in the 28-Day study (e.g. endocrine-related endpoints). Nevertheless, sub-chronic toxicity studies (at least 90 days) are typically considered.</p>
<p>Chronic toxicity/carcinogenicity/mutagenicity (if critical findings were reported in the genotoxicity and sub-chronic/acute toxicity studies)</p>	<ol style="list-style-type: none"> 1. Chronic Toxicity Studies (OECD TG 452) 2. Combined Chronic Toxicity/Carcinogenicity Studies (OECD TG 453)
<p>Reproductive and developmental toxicity</p>	<ol style="list-style-type: none"> 1. Two-generation Reproduction Toxicity Study (OECD TG 416) 2. Extended one-generation Reproductive Toxicology Study (OECD TG 443) 3. One-generation Reproductive Toxicity Study (OECD TG 415) 4. Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay (OECD TG 488)

^c In the tiered toxicity approach, a base set of toxicity studies are conducted, and results from these studies trigger specific additional tests that would be needed to adequately characterize a substance's hazard potential.

^d For compounds with limited or no chemical-specific toxicity data and having low exposure levels, QSAR analysis can be undertaken to identify the presence of structural alerts associated with key toxicity endpoints.

^e The TTC approach can be undertaken where chemical substances are classified into different Cramer classes based on its chemical structure, for which an exposure below the TTC value of the assigned Cramer class indicates a low probability of causing adverse health effects.

3.6.8.4 Assessment of genotoxic potential is the core of toxicity assessment, and it should cover all the different genotoxic endpoints i.e. induction of gene mutations, structural and numerical chromosomal aberrations. The following publications by the US FDA and EFSA may serve as useful references to determine the approach taken for toxicity testing:

- US FDA Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Food¹⁰
- US FDA Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions¹¹
- EFSA Guidance for submission for food additive evaluations¹²

3.6.8.5 As it may be challenging to relate the toxicity test results of a whole food product to individual substances present in the product, companies should consider prioritising testing for substances of concern that are present in the final food (e.g. as impurities), or single ingredients, where human exposure is found to be non-negligible. A risk assessment can then be performed based on the results of the test(s) and the estimated human exposure level.

3.6.9 Metabolism or toxicokinetic studies, where relevant. These include absorption, distribution, metabolism, and excretion (ADME) studies using animal models, or relevant information in the scientific literature. Data on the bioaccessibility of the novel food component(s) during digestion should be included where relevant, to address the potential food safety concerns arising from the release such component(s) during digestion.

3.6.10 Information on allergenicity and/or allergen profiling, including cross-allergenicity, if present.

3.6.10.1 A weight-of-evidence approach would be applicable to determine allergenicity risks. In the context of allergenicity, this means that the source of the protein (IgE or non-IgE), amino acid sequence comparison, and in-vitro degradation studies are considered in an integrated manner during allergenicity assessments, with specific serum screening and cell-based/in-vivo assays also included on a case-by-case basis.¹³

3.6.10.2 The most appropriate approach taken would depend on the nature of the novel food or food ingredient. For complex mixtures of proteins, it would generally be more informative to focus the assessment on identifying potential allergenicity concerns arising from the production organism rather than on every single protein in the mixture.

For purified proteins	(i) Searches for sequence homology and structural similarities to known allergens (ii) Pepsin resistance tests and <i>in vitro</i> digestibility tests (iii) Specific serum screening, including IgE binding tests, if homologous sequences or structural similarities to known allergens are found
For production organisms	(iv) Phylogenetic relationships to other organisms for known evidence of allergenicity

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3.6.10.3 In addition to the available scientific literature, the databases below would be considered by SFA to be relevant for allergenicity assessment if required:¹³⁻²⁰

- Allergen online databases hosted under the Food Allergy Research and Resource Program (FARRP)
- National Centre for Biotechnology Information (NCBI) database
- WHO/IUIS Allergen Nomenclature database
- The Allergome database
- The Protein family (Pfam) database
- The AllFam database
- The Structural Database of Allergenic Proteins (SDAP)
- The SWISS-PROT database

3.6.10.4 Where allergens are known to be present, labelling of these allergens may be required.

3.6.11 A clear description of the manufacturing process. Applicants must provide all relevant information pertaining to the food safety management systems in place. Accepted documentation include: Hazard Analysis Critical Control Point (HACCP) plans conforming to ISO standards, Good Manufacturing Practices (GMP), and Good Cell Culture Practices (GCCP). The documentation must include a clear description of the risk monitoring and mitigation steps that have been established, including physical parameters and critical control points. A production flow chart should also be provided. Process controls should be included to address any potential concerns of sensitization effects due to food handling.

3.6.12 Training plans and records of staff members in food safety/food handling/food hygiene courses, as well as in aseptic techniques or cleanroom training (where appropriate).

3.7 Any potential health hazards that have been identified based on the composition, toxicological or other data, should be discussed and adequately addressed in the proposed conditions of use to ensure that the consumption of the novel food/food ingredients is safe for the target population.

3.8 The mode of sale is not a consideration during SFA's safety assessment process and is purely a commercial decision to be made by companies.

Use of genetic modification (GM) organisms to produce novel foods

3.9 Genetically modified foods are foods derived from organisms whose genetic material has been modified in a way that does not occur naturally (e.g. through the introduction of a gene from a different organism).

3.10 The following information should be submitted for safety assessment if GM organisms are used for novel food production:

3.10.1 Detailed procedures of the genetic modification process.

3.10.2 An evaluation of whether genetic modification would give rise to any significant changes resulting in additional food safety hazards (e.g. presence of toxins or allergens) that need to be addressed. This includes the genetic stability of the production strain.

3.10.3 Risk assessment and risk management measures to address food safety hazards present or introduced due to Section 3.10.

3.10.4 Safety information of the host/recipient strain (e.g. Whole Genome Sequencing and proteomics data to investigate whether genes are known to produce toxins, any toxins produced).

3.10.5 Genome characterization to determine the absence of virulence-related genes, antibiotic resistances and their potential horizontal transfer, and other potentially adverse metabolic features such as toxin production.

3.10.6 Any documented history of use with absence of adverse effects to human health.

3.10.7 The following Codex documents may serve as useful references to when using recombinant DNA microorganisms and animals:

- Guideline for the conduct of food safety assessment of foods produced using recombinant DNA microorganisms (CAC/GL 46-2003)²¹
- Guideline for the conduct of food safety assessment of foods produced using recombinant DNA animals (CAC/GL 68-2008)²²

4 Information on the safety assessment criteria for specific types of novel foods

4.1 Companies should provide the following information if their product falls within the respective categories of novel foods below.

Novel foods which are ingredients produced through precision fermentation

4.2 Such ingredients are considered novel foods that are chemically identical to naturally occurring substances but produced by unconventional processes. For these ingredients, a full safety assessment involving submission of the full set of toxicity studies would not be required. The key aspects of the safety assessment for these ingredients should cover the product composition and characterisation, accounting for all major and minor components, as well as volatiles/non-volatiles.

4.3 For these ingredients, the following information are to be submitted for safety assessment:

4.3.1 Information to demonstrate that the ingredient is chemically identical to its naturally occurring counterpart. Appropriate techniques from the following list, as well as any other appropriate approaches, would be considered by SFA to be relevant:

- Amino acid sequences for ingredients of a proteinaceous nature

- Liquid chromatography (LC), gas chromatography (GC), mass spectrometry (MS), tandem mass spectrometry (MS/MS)
 - Nuclear magnetic resonance spectroscopy (NMR)
 - Infra-red spectroscopy (IR)
 - Ultra-violet spectroscopy (UV)
 - X-ray crystallography
- 4.3.2 Information listed in Section 3.6, as well as in Section 3.10 if GM organisms/microorganisms are used. It is not necessary to provide the information listed in Section 3.6.1, 3.6.8, 3.6.9 and 3.6.10 unless they are relevant for the application.
- 4.3.3 Under Section 3.6.4, the inputs should cover the following (Note that the list is non-exhaustive):
- Microorganisms (e.g. bacterial or fungal strains)
 - Growth media used for fermentation processes
 - Enzymes and/or processing aids
 - Solvents
- 4.3.4 The information in Section 3.6.11 should also include any aseptic processing steps established to ensure that the fermentation media is free from infectious agents (e.g. viruses, pathogenic bacteria, pathogenic fungi) throughout the entire production process.
- 4.3.5 Information related to the microorganism(s) used, including:
- 4.3.5.1 Background information, identity (an unambiguous taxonomic classification at species level), and source of the microorganism(s).
- 4.3.5.2 Description of any modifications and adaptations made to the microorganism(s), and how these relate to the expression of substances that may result in food safety risk.
- 4.3.5.3 Complete strain characterization by fully assembled and validated whole-genome sequence analysis, including assessment for presence of virulence-related genes, antibiotic resistances and their potential horizontal transfer, and other potentially adverse metabolic features such as genes encoding for toxin production.
- 4.3.5.4 Viability of the microorganism(s) in the novel food/food ingredient to address potential concerns of infectivity.
- 4.3.6 Information related to the fermentation media used, including:
- 4.3.6.1 Composition of media, including identities and purity of all added substances, as well as unintended metabolites that could be potentially produced.
- 4.3.6.2 Risk assessments or tests to determine the residue levels for all non-food grade components and potential unintended metabolites present in the fermentation media.
- 4.3.6.3 Information demonstrating the removal of fermentation media and/or added substances (if these are removed completely)
- 4.3.6.4 Information on whether the anti-microbials, if used, would contribute to anti-microbial resistance (AMR).

Novel foods produced by biomass fermentation

- 4.4 Biomass fermentation produces intact or minimally processed cells, which contain a high level of protein. The biomass produced could itself be consumed or used as a food ingredient. Novel foods under this category include single-cell proteins, mycelial biomass from fungal species etc.
- 4.5 For such novel foods, the following information should be submitted for safety assessment:
- 4.5.1 Information listed in Section 3.6, as well as in Section 3.11 if GM organisms/microorganisms are used.
- 4.5.2 Under Section 3.6.4, the inputs could cover the following, but are not limited to:
- Microorganisms (e.g. bacterial or fungal strains)
 - Growth media used for fermentation processes
 - Enzymes and/or processing aids
 - Solvents
- 4.5.3 Information related to the fermentation media used, including:
- 4.5.3.1 Composition of media, including identities and purity of all added substances, as well as unintended metabolites that could be potentially produced.
- 4.5.3.2 Risk assessments or tests to determine the residue levels for all non-food grade components and potential unintended metabolites present in the fermentation media.
- 4.5.3.3 Information demonstrating the removal of fermentation media and/or added substances (if these are removed completely).
- 4.5.3.4 Information on whether the anti-microbials, if used, would contribute to anti-microbial resistance (AMR).
- 4.5.4 A risk assessment based on the available toxicity data of the non-food grade components and unintended metabolites, as well as the dietary exposure levels arising from the biomass product, or a comparison of the levels present to that of the same compound found naturally in conventional analogue (if these remain in the finished biomass product).
- 4.5.5 Safety assessment covering food safety hazards that are at high risk of occurrence based on the nature of the microorganism(s) used to produce the novel food, and the measures proposed to mitigate the potential food safety concerns. For example, mycotoxins are commonly found in novel foods produced by biomass fermentation.
- 4.5.6 The information listed in Section 3.6.11 should also include any aseptic processing steps established to ensure that the fermentation media is free from infectious agents (e.g. viruses, pathogenic bacteria, pathogenic fungi) throughout the entire production process.
- 4.5.7 Information related to the microorganism(s) used, including:
- 4.5.7.1 Background information, identity (an unambiguous taxonomic classification at species level), and source of the microorganism(s).

- 4.5.7.2 Description of any modifications and adaptations made to the microorganism(s), and how these relate to the expression of substances that may result in food safety risk.
- 4.5.7.3 Complete strain characterization by fully assembled and validated whole-genome sequence analysis, including assessment for presence of virulence-related genes, antibiotic resistances and their potential horizontal transfer, and other potentially adverse metabolic features such as genes encoding for toxin production.
- 4.5.7.4 Viability of the microorganism(s) in the novel food / food ingredient to address potential concerns of infectivity.

Cultured meat

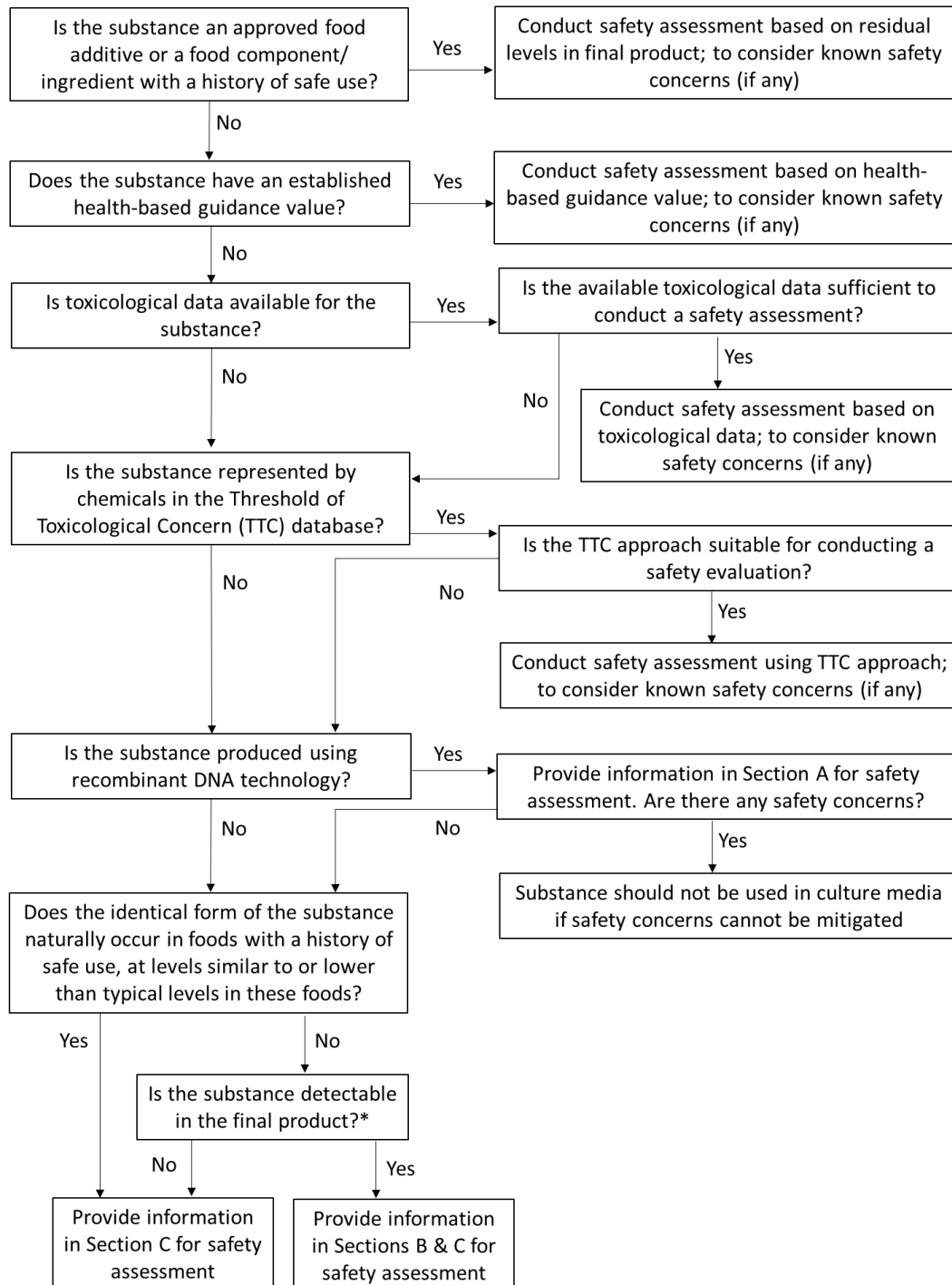
- 4.6 Cultured meat refers to meat developed from animal cell culture. The process to produce cultured meat involves growing the selected cell lines (or stem cells) in a bioreactor. The cells are grown in a suitable growth media and may subsequently be assembled on a “scaffold” to produce products resembling meat muscle.
- 4.7 SFA notes that the science for producing cultured meat is still at an early stage. SFA currently requires the following information to be submitted for the safety assessment of cultured meat. Information required may change based on the developments on the science of producing cultured meat.
- 4.7.1 Information listed in Section 3.6, as well as in Section 3.11 if GM organisms/microorganisms are used.
- 4.7.2 The information provided in Section 3.6.1 should also cover a characterisation of the cultured meat product, including nutritional composition, and comparison of residual anti-microbials, growth promoters and/or modulating factors against levels in published literature.
- 4.7.3 The information provided in Section 3.6.4 should cover the following inputs, but is not limited to:
- Cell lines or stem cells, and chemicals used for their induction
 - Culture media, growth promoters, modulating factors and anti-microbials
 - Scaffolding materials, solvents, enzymes, and processing aids
- 4.7.4 The information in Section 3.6.11 should also include aseptic processing steps established to ensure that the culture media and cell lines are free from infectious agents (e.g. viruses, bacteria, fungi, prions) throughout cell line selection, cell adaptation, cell proliferation, scaffolding, extraction, concentration and washing.
- 4.7.5 Information related to the cell lines used, including:
- 4.7.5.1 Background information, identity, and source of cell lines.
- 4.7.5.2 Description of methods used for selection and screening of cells.
- 4.7.5.3 Information on how the cell lines are prepared and banked following their extraction from animals.
- 4.7.5.4 Risk assessments on any chemicals used for induction.
- 4.7.5.5 Information (e.g. biological tests) to show that the cell lines are free from infectious agents (e.g. viruses, bacteria, fungi, prions) where relevant.
- 4.7.5.6 Description of any modifications and adaptations made to the cell lines, and how these relate to the expression of substances that may result in food safety risk.
- 4.7.5.7 Information to demonstrate that biopsies comply with Singapore’s animal health and food safety requirements and are free from animal disease. (If biopsies are taken from food animals).

- 4.7.6 Information related to the culture media used, including:
- 4.7.6.1 Composition of media, including identities and purity of all added substances (e.g. anti-microbials, growth promoters and modulating factors), as well as unintended metabolites that could be potentially produced.
 - 4.7.6.2 Risk assessments or tests to determine the residue levels for all non-food grade components and potential unintended metabolites present in the culture media.
 - 4.7.6.3 Safety assessments of biological substances used as media components during production. The safety assessments should be performed according to the approach described in Section 5.
 - 4.7.6.4 Information demonstrating the removal of culture media and/or added substances (if these are removed completely).
 - 4.7.6.5 A risk assessment based on the available toxicity data of the non-food grade components and unintended metabolites, as well as dietary exposure levels arising from the cultured meat product, or a comparison of the levels present to that of the same compound found naturally in conventionally grown meat (if these remain in the finished cultured meat product).
 - 4.7.6.6 Information on whether the anti-microbials, at the levels of exposure anticipated, would contribute to anti-microbial resistance (AMR).
 - 4.7.7 Information to reasonably demonstrate that genome instability and genetic drift would not result in the production of undesirable substances in the end-product at levels that can pose a food safety hazard. To this end, SFA will allow applicants the flexibility to identify potential substances for targeted safety analysis in the end-product cells through a combination of strategy (1) **AND** strategy (2) or (3):
 - (1) By conducting a systematic scientific literature review to identify all known undesirable substances of food safety concern associated with the animal species of the cell culture and establish a list of such substances for subsequent targeted analysis.
 - (2) By performing an in-silico genome screen against relevant databases highlighted in Section 3.6.10.3 to establish a list of potential toxins/allergens for subsequent targeted analysis.
 - (3) By carrying out quantitative comparison of the end-product cells against the starter cells through methodologies such as transcriptomics, proteomics or metabolomics so that a list of differentially expressed undesirable substances of food safety concern can be established for subsequent targeted analysis.

- 4.7.8 Information to demonstrate that good cell culture practices (GCCP) have been applied for ensuring reproducibility and consistency of the cellular products. This can involve assessments of genetic stability (e.g. karyotyping) and close monitoring for variations in growth rates, nutrient usage and/or biomass composition in the end-product cells.
- 4.7.9 Safety assessment covering food safety hazards that are at high risk of occurrence based on the nature of the cell line used to produce cultured meat, and the measures proposed to mitigate the potential food safety concerns. For example, certain species of shellfish are known to be of a higher risk of containing marine biotoxins. Companies utilising cell-lines related to these species should include genomic, transcriptomic, or proteomic analyses, measures that could be implemented to mitigate these risks, and/or any other information to address this potential safety concern.

5 Safety assessment approach for biological substances used in media for cultured meat/seafood production

5.1 Biological substances used in media for the production for cultured meat/seafood should be assessed for their safety according to the information in Sections A to C as indicated in the flowchart below:



**The detection methodology and limit of detection must be comparable to scientifically established detection methodologies for the substance*

Section A

- i. Scientific name of the recipient strain/host plant
- ii. A detailed description of the genetic modification process, listing the genetic elements that have been introduced into the host organism. The presence of any DNA from the vector and/or donor organism not intended to be inserted into the genetically modified organism should be highlighted. Genes coding for known toxins or anti-nutrients present in the donor organism should not be transferred to the recipient strain.
- iii. For recombinant proteins, information on the primary sequence of the recombinant protein, which should be characterized by established analytical methodologies to be equivalent, or almost equivalent, to the protein from the native source. If protein purification tags or other small sequence modifications are introduced, companies should address potential allergenicity and toxicity concerns using a bioinformatics approach.
- iv. For substances derived from recombinant DNA plants, an assessment of the safety of the host plant, including any known toxicity and allergenicity.
- v. For substances derived from recombinant DNA microorganisms, an assessment of the safety and pathogenicity of the recombinant host. Reference may be made to the organisms covered in the EFSA Qualified Presumption of Safety list, or other established sources in the scientific literature. The absence of virulence-related genes and other potentially adverse metabolic features such as toxin production should be demonstrated. Details on the potential for horizontal transfer of antibiotic resistance genes from the host to another organism should be provided.
- vi. Information on whether the host organism has been used to produce other recombinant substances that have been safely used in humans.
- vii. Chemical purity of substance, including information on the impurities present. Protein purity should also be specified if substance is a recombinant protein.
- viii. Information on whether genetically modified cells and recombinant DNA are removed from the substance.
- ix. An evaluation of whether the genetic modification may give rise to any additional food safety hazards not described above (e.g., allergenicity concerns that may arise from using transgenes obtained from known allergenic sources).

Section B

- i. A description of the purpose of adding the substance to culture media.
- ii. Characterization and specification data of the substance added to culture media.
- iii. Information on the level of the substance present in cultured meat, and how this differs from the levels of the substance found in its conventionally produced equivalent.
- iv. Information on whether the substance naturally occurs in other foods with a history safe use, as well as typical levels in these foods.
- v. Any other safety concerns related to the substance or its preparation (e.g., potential presence of viruses or prions, risk of allergenicity attributed to the substance or impurities, potential toxicity concerns)

Section C

- i. Synthesis and the mode of action of the substance in the human body.
- ii. An assessment of how the level and/or biological activity of the substances in food may be impacted by food processing (e.g. denaturation during cooking).
- iii. If the substance is absorbed, companies should evaluate, based on scientific information available, whether the expected levels absorbed presents a safety concern.
- iv. Information on the links between the consumption of food containing the substance and/or other dietary factors, and the blood concentrations of the substance, where available. (E.g. Whether increased consumption of dairy products, which are known to contain insulin-like growth factor 1, is linked to increase blood concentrations of the substance)
- v. Information on the mechanisms responsible for any links found in (iv).

6 Information related to the testing of novel foods

- 6.1 SFA does not prescribe a specific requirement for the number of batches to be tested. Applications will be considered if the companies have demonstrated that the study design is statistically sound. Nevertheless, SFA has observed that companies typically provide data from 3 or 5 non-consecutive batches of the novel food product as an indication of reproducibility.
- 6.2 Currently, SFA does not require novel food companies to include stability data (i.e. shelf-life testing data) to be submitted at the point of novel food application, however as with any other food, the data should be made available on demand to SFA once the novel food has been reviewed and allowed for sale in Singapore.
- 6.3 Applicants may wish to engage the testing services of SFA's recognised laboratories under the Lab Recognition Program (LRP) to meet their food testing needs. The list of LRP-recognised laboratories is available [here](#).

7 Information related to the format of safety assessments

- SFA currently does not have a specified format for safety assessment. If applicants have submitted safety assessments to other overseas regulatory agencies that are conducted in accordance with the following reference documents, they are encouraged to use the self-assessment checklists ([Section 8.3](#)) to ensure that the safety assessments meet the requirements of a complete dossier or submission to SFA.
- US FDA [Guidance for Industry and Other Stakeholders: Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients](#)²³
- US FDA [Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Food](#)¹⁰
- EFSA [Guidance for submission for food additive evaluations](#)¹²
- FAO/WHO [Environmental Health Criteria 240 - Principles and Methods for the Risk Assessment of Chemicals in Food](#)²⁴
- EFSA [Guidance on the preparation and submission of an application for authorisation of a novel food in the context of Regulation \(EU\) 2015/2283](#)²⁵

8 Information related to the application process for novel foods

- 8.1 SFA does not require novel food applications to be submitted only from companies that are incorporated in Singapore, and SFA will also review submissions made by companies based outside of Singapore. Novel foods that have received pre-market regulatory approval by SFA and are produced/manufactured outside of Singapore are subject to requirements for the import, distribution, and sale of food in Singapore.

- 8.2 Companies should submit their applications for the use of novel foods to [SFA- NovelFoods@sfa.gov.sg](mailto:NovelFoods@sfa.gov.sg). The information in the application should be submitted in a format which is available for SFA to download as a copy.
- 8.3 Companies wishing to submit applications for novel foods derived from precision fermentation, biomass fermentation or for cultured meat/seafood must fill in the respective self-assessment checklist and attach the acknowledgement upon submission to the application. The self-assessment checklists can be found here:
- [Self-assessment checklist for precision and biomass fermentation](#)
 - [Self-assessment checklist for cultured meat/seafood](#)
- 8.4 Confidential information and trade secrets submitted by companies will be kept confidential and not shared outside of SFA without companies' consent. Please note that SFA does not sign non-disclosure agreements (NDA) with applicants for the purposes of evaluating the safety information submitted, as SFA employees are bound to the preservation of secrecy under [Section 34 of the Singapore Food Agency Act 2019](#).
- 8.5 In the event where information is required to be shared with external parties (for example to address media queries or to seek external scientific expertise), SFA will first seek companies' consent for the information to be shared. SFA encourages novel food companies to think from an early stage on which aspects of their safety assessment dossier would need to be kept confidential, as well as to make available non commercially sensitive information publicly wherever possible as this would help to build consumer trust in their products.
- 8.6 SFA does not charge any fees for the evaluation of applications for the use of novel foods. SFA estimates a timeline of about 9-12 months to complete an evaluation of a novel food, upon receipt of complete information required for the evaluation. To avoid delays, food businesses are encouraged to consult SFA early in their product development process to understand the information that would be required to be submitted to substantiate the safety of their novel food.

9 Information related to novel food applications after SFA has issued a decision

- 9.1 If changes are made to the manufacturing process of novel foods which have received pre-market regulatory approval by SFA that may affect the validity of the original safety assessment submitted, novel food companies are required to seek approval from SFA before the products made using the updated manufacturing process are imported into, distributed, or sold in Singapore. An example of such a change would be modifications in input materials (e.g. cell-lines or culture media components) in the production of cultured meat.
- 9.2 Similarly, companies that intend to expand the scope of intended use of their novel food to other food categories are required to seek prior approval from SFA, to ensure that the expanded exposure to the novel food is safe for consumers.
- 9.3 The outcomes of novel food safety assessments are not applicable to similar novel foods produced by other companies. This is because novel food safety assessments are specific to the materials and manufacturing processes described within application. Different companies could be using completely different materials and processes in the production of their novel foods, and should conduct their own safety assessments, even if they may be producing a similar novel food.
- 9.4 Currently, SFA does not publish approvals to the public domain. Companies wishing to make SFA's approval public and mention SFA in the accompanying press release or materials are encouraged to send SFA a draft for our review before releasing them to the public.
- 9.5 Companies selling pre-packed alternative proteins (including cultured meat) are required to label the product packaging with suitable qualifying terms such as "cultured" or "cell-based" to indicate their true nature. Similarly, food establishments selling non prepacked foods are required to clearly communicate to their customers on the true nature of their food sold. For example, misrepresenting cultured meat as conventionally produced meat will not be allowed.

10 Information on the sensory evaluation and tasting of unassessed novel foods

10.1 Both sensory evaluations and tastings of unassessed novel foods will be referred to as 'tasting' in this section.

10.2 Novel foods that have yet to undergo safety assessment should not be offered for consumption for the purpose of advertisement or in furtherance of any trade or business. Companies that are found to have offered unassessed novel foods for consumption for the purpose of advertisement or in furtherance of any trade or business may be subject to enforcement actions under the Sale of Food Act.

10.3 SFA recognises that companies/researcher(s) may want to conduct tastings of novel food such as:

- Sensory evaluation studies as part of the novel food R&D process; and
- Demonstration that the novel foods meet the requirements of potential clients and investors.

Application for administrative exemption

10.4 Companies are required to seek an administrative exemption from SFA for tastings of novel foods that have not completed the safety assessment process, The following self-assessment checklist should be completed, and the acknowledgement should be attached together with the application for administrative exemption. The self-assessment checklist can be found [here](#).

10.5 Companies should submit applications with complete set of information for administrative exemption **eight (8) weeks** prior to the planned date of the tasting session.

- 10.6 The application should demonstrate that the tasting is conducted under the following controlled conditions:
- 10.6.1 Tasting is only for selected individual(s) identified by company/researcher(s) in writing to SFA before the event, and the tasting must not be made available to the general public. Each tasting session must not exceed thirty (30) participants.
- 10.6.2 Companies or researcher(s) conducting the tasting should ensure that the tasting would be safe even though there is no approval for the novel food. The companies or researcher(s) should demonstrate a minimum threshold of food safety i.e., that the one-time consumption of the yet-to-be-approved novel food will not cause adverse impacts or foodborne illnesses. To demonstrate this, companies/researcher(s) should declare a Statement of Compliance with SFA's conditions for the tasting of unapproved novel food with supporting evidence such as:
- 10.6.2.1 Certificate(s) of analyses or mass balance estimations of all inputs used in the production of the novel food.
- 10.6.2.2 Certificate(s) of analysis indicating that the novel food meets food safety specifications which have been established by the company/researcher(s).
- 10.6.2.3 Acute risk assessments (including exposure calculations) for one-time consumption of the novel food. The risk assessments should cover potential food safety hazards, including but not limited to microbiological agents, contaminants, toxins and allergens.
- 10.6.2.4 If in-house analytical methods are used to determine the levels of microbiological and chemical hazards in the unassessed novel food, details of methods used, including the accredited or scientifically accepted reference method on which the in-house method is based on, method validation report, limit of detection (LOD) and/or limit of quantification (LOQ) must be provided for evaluating the scientific robustness, accuracy, precision, and sensitivity of the method.
- 10.6.2.5 Companies may perform hazard analysis and risk assessment based on the serving size of the novel food ingredient intended for one-time consumption at the sensory evaluation / tasting session.
- 10.6.2.6 Description of measures established to minimize microbial and chemical contamination during storage, production, and post-production.
- 10.6.2.7 Documentation to show that the companies/researcher(s) have complied with their respective internal Institutional Review Board (IRB) requirements (where available).
- 10.6.3 The person(s) involved in the tasting must note in writing to acknowledge the following, and a template of the form issued to person(s) involved in the tasting will need to be submitted to SFA.
- They are participating on voluntary basis;
 - They have been informed that the product is unapproved and hence aware of potential risks;
 - They can withdraw from the tasting anytime without penalty or reason; and

- They agree to waive SFA of liabilities resulting from the consumption of the unapproved novel food.

10.6.4 Companies conducting the tasting should ensure traceability (e.g. keep records of the participants) in the event.

10.6.5 The tasting should be conducted in a non-food service facility designed for sensory evaluation R&D (e.g. test kitchens, IHLs, RIs), or at a test kitchen facility in an SFA-licensed restaurant, as long as:

- The controlled conditions mentioned in the existing sensory evaluation and tasting policy are maintained;
- The venue is closed to the general public during the tasting or able to demonstrate segregation of facilities for preparation and serving of unassessed novel foods; and
- The facility is thoroughly cleaned after the event to avoid cross contamination.

10.6.6 Companies or organisers of the tasting event are required to prepare for medical contingencies in the event of unforeseen allergic reactions as well as to inform Singapore Food Agency of any detected or reported adverse events occurring within two (2) weeks.

11 Further guidance for novel food companies

11.1 SFA conducts Novel Food Virtual Clinics on a bimonthly basis, which serves as a platform for novel food companies in their early stages of R&D to engage with SFA, as well as for SFA to share more details on our novel food regulatory framework. Please book your attendance at our Virtual Clinics using the registration form [here](#).

11.2 Companies may submit novel food applications to SFA either directly or through service providers such as regulatory consultants or law firms. Regulatory consultancy is also available for novel food companies at the Future Ready Food Safety Hub (FRESH), a tri-partite joint initiative by the Singapore Food Agency (SFA), Nanyang Technological University (NTU) and Agency for Science, Technology and Research (A*STAR). The company's profile and core capabilities can be found at <https://www.ntu.edu.sg/fresh>.

- 11.3 FRESH can provide the following consultancy services to assist companies in ascertaining and substantiating the safety of their novel food, and with their novel food safety dossier for regulatory submission to SFA for pre-market approval.
- 11.3.1 Map out a regulatory road map for company's submission and advise action plan for safety assessment.
- 11.3.2 Review company's safety data on the novel food, assess the level of readiness of safety data, identify data gaps (if any) and advise on corrective action.
- 11.3.3 Perform a risk assessment on the novel food by undertaking a structured safety review process: systematic literature review and annotated bibliography; predictive safety assessment using *in-silico*/ computational tools; *in-vitro* and/or *in-vivo* safety testing based on current and newly developed risk assessment protocols. Please note that depending on the type of testing, FRESH can either perform it in-house or partner/outsourcing to contract labs.
- 11.3.4 Structure safety dossier outline with company in preparation for submission to SFA.
- 11.4 For more information, visit the company's website or contact the team at FRESH@ntu.edu.sg.
- 11.5 A list of scientific literature related to novel foods is provided below, which may be useful references for novel food companies:
- Hadi, J.; Brightwell, G. Safety of Alternative Proteins: Technological, Environmental and Regulatory Aspects of Cultured Meat, Plant-Based Meat, Insect Protein and Single-Cell Protein. *Foods* **2021**, 10, 1226. <https://doi.org/10.3390/foods10061226>
 - Ververis, E.; Ackerl, R.; Azzollini, D.; Colombo, P.A.; Sesmaisons, A.; Dumas, C.; Fernandez-Dumont, A.; Ferreira da Costa, L.; Germini, A.; Goumperis, T.; Kouloura, E.; Matijevic, L.; Precup, G.; Roldan-Torres, R.; Rossi, A.; Svejstil, R.; Turla, E.; Gelbmann, W. Novel foods in the European Union: Scientific requirements and challenges of the risk assessment process by the European Food Safety Authority. *Food Research International*, **2020**, 137,109515: <https://doi.org/10.1016/j.foodres.2020.109515>
 - EFSA Guidance on the use of Threshold of Toxicological Concern approach in food safety assessment. <https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2019.5708>
 - EFSA statement on the requirements for whole genome sequence analysis of microorganisms intentionally used in the food chain. <https://www.efsa.europa.eu/en/efsajournal/pub/6506>
- 11.6 Further FAQs on novel foods can be found in Annex A and a Glossary of Terms can be found in Annex B.

12 Contact information

National Centre for Food Science
Singapore Food Agency
52 Jurong Gateway Road, #14-01,
Singapore 608550

For clarifications, please submit enquiries electronically via the online feedback form:
<https://csp.sfa.gov.sg/feedback>

13 Revision History

- 22 November 2019 – First version
- 23 November 2020 – Updated language for clarity
- 13 December 2021 – Updated the format and included further guidance. Please note that the regulatory framework remains unchanged.
- 22 April 2022 – Updated information on the sensory evaluation of unassessed novel foods
- 26 September 2022 – Updated information on revised policy, regulatory positions, safety assessment approaches, self-assessment checklists and online registration links.
- 20 July 2023 – Updated information on the tasting and sensory evaluation of unassessed novel foods

Annex A: FAQs for Novel Food companies

Version: 20 July 2023

Overview

Novel food companies are encouraged to engage with SFA to share information on their product and processes even at an early stage, as this will facilitate their regulatory pathway when they eventually submit their safety assessments for approval.

This set of FAQs, together with the main document, thus serves as a basis for further discussions between companies and SFA prior to the submission of safety assessments. The FAQs have been categorised in various sections for ease of reference:

1. Questions related to the submission process for novel food applications
2. Questions related to novel food safety assessments
3. Questions related to research on novel foods
4. Questions related to processes after approvals have been granted
5. Questions related to labelling
6. Questions related to tasting/sensory events
7. Questions related to manufacturing novel foods in Singapore
8. Other questions related to novel foods

1. Questions related to the submission process for novel food applications

Q1.1: Is the dossier and safety information shared with SFA kept confidential?

Confidential information submitted by companies will be kept confidential and will not be shared outside of SFA. SFA employees are bound to the preservation of secrecy under [Section 34 of the Singapore Food Agency Act 2019](#). In any event where information is required to be shared with external parties (for example to address media queries or to seek external scientific expertise), SFA will first seek companies' consent for the information to be shared. SFA encourages novel food companies to think from an early stage on which aspects of their safety assessment dossier would need to be kept confidential, as well as to make available non commercially sensitive information publicly wherever possible as this would help to build consumer trust in their products.

Q1.2: Does a company need to be incorporated in Singapore to submit a novel food application?

SFA does not require novel food applications to be submitted only from companies that are incorporated in Singapore, and we can also review submissions made by companies based outside of Singapore. Overseas novel food companies should note that novel foods that are manufactured outside of Singapore and which have been successfully undergone the review process and allowed for sale in Singapore would be subject to requirements for the import of food into Singapore. Traders who import food products into Singapore are required to obtain a relevant trader's licence or register with SFA and must be registered with the Accounting and

Corporate Regulatory Authority (ACRA). More information on the Licensing and Registration of Traders is available at the following [website](#).

Q1.3: Can a company make a novel food application directly or should it be done through a regulatory consultant or law firm?

Companies may submit novel food applications to SFA either directly or through service providers such as regulatory consultants or law firms.

Q1.4: Is there a specific format for the safety assessment?

SFA currently does not have a specified format for safety assessment. If applicants have submitted safety assessments to other overseas regulatory agencies that are conducted in accordance with the following reference documents, they are encouraged to use the self-assessment checklists ([Section 8.3](#)) to ensure that the safety assessments meet the requirements of a complete dossier or submission to SFA.

- US FDA [Guidance for Industry and Other Stakeholders, Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients](#)²³ US FDA [Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Food](#)¹⁰
- EFSA [Guidance for submission for food additive evaluations](#)¹²
- FAO/WHO [Environmental Health Criteria 240 - Principles and Methods for the Risk Assessment of Chemicals in Food](#)²⁴
- EFSA [Guidance on the preparation and submission of an application for authorisation of a novel food in the context of Regulation \(EU\) 2015/2283](#)²⁵

Q1.5: How long does it take for SFA to issue a decision?

SFA estimates that the review of safety assessment dossiers submitted by companies will take about 9-12 months. However, this timeline assumes that the safety assessment dossier is complete with no further need for questions or clarifications from SFA. As this is generally not the case, it is important for companies to engage in pre-submission consultations with SFA. As part of these pre-submission consultations, SFA encourages companies to provide parts of their safety assessment dossier in phases for early discussion and opportunity to seek clarifications.

2. [Questions related to novel food safety assessments](#)

Q2.1: Can SFA share what requirements are needed for testing of novel foods?

There is no one-size-fits-all approach to the testing novel foods and companies should adopt effective testing strategies based on their understanding of the hazards that may be present in their novel foods. Where possible, companies should ensure that that testing is conducted in accordance with principles of Good Laboratory Practices (GLP). The methodologies should also be validated to international standard such as ISO/IEC 17025 or its equivalent and published in the scientific literature, and

applicant should therefore include references to these methods. Useful resources include but are not limited to the official testing methods for chemical and microbiological hazards listed under the Official Methods of Analysis published by the Association of Official Agricultural Chemists (AOAC)¹, Pharmacopoeia methods (e.g. British Pharmacopoeia², European Pharmacopoeia³), and international guidelines such as those published by the Organisation for Economic Co-operation and Development (OECD).

Companies that require the use of in-house/novel testing methods will need to send details of the testing method, accreditation status of testing method (if available) and the validation results to SFA, for evaluation of the scientific robustness, accuracy, precision, and sensitivity of the method.

Q2.2: How many batches are required to be tested to generate the data needed to provide product specifications?

SFA does not prescribe a specific requirement for the number of batches to be tested. Applications will be considered if the companies have demonstrated that the study design is statistically sound. Nevertheless, we observe that companies typically provide data from 3 or 5 non-consecutive batches of the end-product as an indication of reproducibility.

The end-product for which data is generated on should be produced at a scale that is representative of the eventual manufacturing scale. If significant changes to the inputs and/or processes are required during scaling up, it may affect the validity of the original safety assessment submitted to SFA.

Q2.3: Do companies need to provide data to justify proposed shelf-life in the safety dossier?

SFA currently does not require novel food companies to include stability data to be submitted at the point of novel food application, however as with any other food, the data should be made available on demand to SFA once the novel food has been reviewed and allowed for sale in Singapore.

Q2.4: Is the mode of sale a consideration in SFA's approval process?

No, the mode of sale is a commercial decision to be made by the companies. SFA requires novel food companies to fully describe the intended use and proposed use levels of the novel food.

Q2.5: When would SFA expect that a company provide an update to their original safety assessment if there are changes made to the manufacturing process of a novel food that has been assessed and allowed for sale?

Novel food companies should inform and seek SFA's agreement if changes are made to the manufacturing process of novel foods that may affect the validity of the original safety assessment submitted to SFA. For example, for cultured meat companies, changes in input materials such as cell-lines or culture media components

should be notified to SFA before products made using the updated manufacturing process are sold on the market. Similarly, companies that intend to expand the scope of intended use of their novel food should seek SFA's agreement to ensure that the expanded exposure to the novel food is safe for consumers.

Q2.6: Are the outcomes of novel food safety assessments applicable for similar novel foods produced by other companies?

No, the outcomes of novel food safety assessments are specific to the materials and manufacturing processes described within each safety assessment. Different companies could be using completely different materials and processes in the production of their novel foods, and should conduct their own safety assessments, even if they may be producing a similar novel food.

Q2.7: What is SFA's stance on the use of genetically modified cells to produce novel foods (including cultured meat)?

GM foods which are approved by SFA following a safety assessment process may be sold in Singapore. Therefore, it is possible for applicants to make use of GM organisms to produce novel foods and SFA has already assessed and approved some examples of such food for sale. When assessing such novel foods produced from GM microorganisms, SFA takes reference from the Codex guidelines on conduct of food safety assessment of foods produced using recombinant DNA microorganisms (CAC/GL 46-2003)²¹ or DNA animals (CAC/GL 68-2008)²². If the GM organism is present in the finished food product, the food itself would be subject to review of Genetic Modification Advisory Committee of Singapore (GMAC).

The following information should be submitted for safety assessment if GM organisms/microorganisms are used for novel food production:

- (i) Detailed procedures of the genetic modification process.
- (ii) An evaluation of whether genetic modification would give rise to any significant changes resulting in additional food safety hazards (e.g. presence of toxins or allergens) that need to be addressed. This includes the genetic stability of the production strain.
- (iii) Risk assessment and risk management measures to address food safety hazards present or introduced due to (i).
- (iv) Safety information of the host/recipient strain (e.g. Whole Genome Sequencing and proteomics data to investigate whether genes are known to produce toxins, any toxins produced).
- (v) Genome characterization to determine the absence of virulence-related genes, antibiotic resistances and their potential horizontal transfer, and other potentially adverse metabolic features such as toxin production.
- (vi) Any documented history of use with absence of adverse effects to human health.

Q2.8: What safety information would SFA require in a safety assessment for cultured meat?

SFA has published the information that would be required in a safety assessment for cultured meats on [SFA's website](#). In general, the safety assessment should include information on the identity and genetic stability and purity of the cell culture during the manufacturing process, information on the identity and purity of all inputs used (such as culture media components and scaffolding materials), as well as possible hazards arising from the manufacturing process.

Q2.9: What are SFA's considerations on establishing the safety of cell-lines?

SFA requires companies to be able to provide information on the identity and source of their cell-lines as well as to describe the modifications and adaptations made to the cell lines, and how these relate to the expression of substances that may result in food safety risk.

For example, certain species of fungi and shellfish are known to be of a higher risk of containing mycotoxins and marine biotoxins respectively. Companies using cell-lines derived from these species should include information to demonstrate that the respective potential food safety hazards do not cause food safety concerns in their novel food product. This information may include (but are not limited to) genomic, transcriptomic, or proteomic analyses. Companies should also inform SFA of any measures that could be implemented to mitigate these risks.

Q2.10: Does SFA have any guidance on biopsy collection - should companies be following regulations that apply to meat from slaughterhouses?

Whether or not biopsies are taken to establish the cell-line, SFA requires companies to be able to provide information on the identity and source of their cell lines as well as to describe the modifications and adaptations made to the cell lines, and how these relate to the expression of substances that may result in food safety risk. If biopsies are taken from food animals, SFA would require companies to demonstrate that they comply with Singapore's animal health and food safety requirements.

Q2.11: What are SFA's considerations on establishing the safety of culture media components?

SFA requires companies to provide the identities and purity information on individual components in culture media used, and whether these culture media components are expected to remain in the finished cultured meat product or will be removed completely. Where possible, culture media components used should conform with purity specifications recommended by the [British Pharmacopoeia](#)², [European Pharmacopoeia](#)³, [Joint FAO/WHO Expert Committee on Food Additives \(JECFA\)](#)⁴ or [Food Chemical Codex](#)⁵. Companies can establish the safety of culture media components that are not known to be used in food by: (1) demonstrating that no residue or the culture media component remained in the cultured meat; (2) comparing levels of the culture media component in cultured meat to levels of the same compound where naturally found in conventionally grown meat; and (3) by comparing levels of the culture media component in cultured meat to available toxicity data for the same compound, taking into consideration the intended use levels of the cultured meat.

Q2.12: What is SFA's stance on requiring cultured meat companies to have in place food safety management systems (e.g. HACCP)? Are current GMP according to US regulations adequate, and is the implementation of Good Cell Culture Practice (GCCP) recommended/required?

Food safety management systems are important because they help companies to prioritise and control potential food safety hazards which could be introduced during food production. Hence, SFA expects cultured meat companies to put in place food safety management systems such as Hazard Analysis Critical Control Point (HACCP) plans to identify and document the possible food safety hazards and their corresponding mitigation steps for the manufacture of their cultured meat products. SFA does not specify requirements for companies to adopt specific types of food safety management systems.

Some possible critical control points which companies may consider include:

- Maintaining physical parameters (e.g. Temperature, Pressure, Humidity) in the bioreactor during cultured meat production to reduce the risks of unintended side reactions.
- Ensuring aseptic conditions during cell proliferation, scaffolding and extraction stages of cultured meat production to prevent potential microbiological contamination.
- End-point testing and/or risk assessment of the novel food product for chemical, microbiological, and physical food safety hazards.

Q2.13: What are the steps involved in importing cultured meat or inputs for production of cultured meat into Singapore? Are there specific requirements to be met (e.g. testing) at point of import?

SFA recognises that the production of cultured meat is still a nascent industry in most countries. To ensure a high level of assurance of the safety of cultured meat in Singapore, SFA requires cultured meat companies who have successfully undergone the review process and who are allowed to sell cultured meat in Singapore to conduct testing on each consignment of cultured meat shipped to Singapore. The parameters included for testing would depend on the specific hazards identified in the individual safety assessments submitted by companies. The food must meet the food safety requirements and limits set out in Singapore Food Regulations.

Q2.14 SFA regulates the levels of various mycotoxins (e.g. Aflatoxins, DON, Ochratoxin A, Patulin, Fumonisin and Zearalenone). If my company is using filamentous fungi, there could be a lot more mycotoxins of concern, e.g. derivatives, masked mycotoxins. In that case, how should my company decide what to test for? Similarly, can I exclude mycotoxins which are not reported to have been produced by the type of food product I am developing?

Your company should consult the available literature to review the types of mycotoxins reported to be produced by the microorganisms. Your company should also reference to any reported NOAEL or health-based guidance values when performing safety assessments for such mycotoxins. Please substantiate in the safety assessment on why your novel food product is unlikely to produce certain types of mycotoxins to justify its omission from food safety tests. Note that it is the company's

responsibility to ensure that their novel food product complies with the Singapore Food Regulations.

Q2.15: Is it necessary for my company to test for pesticides that are used in growing the raw materials and are reported to be commonly present in the raw materials, which may potentially end up in the fermented food that my company is developing?

It is likely that your company would need to test for such pesticides and perform a risk assessment to demonstrate that they do not pose a safety concern arising from the consumption of the fermented food you are developing.

3. Questions related to research on novel foods

Q3.1: Do companies require regulatory approval at the research stage?

No approval is required from SFA for research on novel foods and novel food ingredients. Novel food and novel food ingredients that are under research and have not received pre-market regulatory approval from SFA should not be made available for sale.

Q3.2: Is tasting of novel food that has yet to undergo safety assessment allowed?

Yes, however, companies need to apply for administrative exemptions from SFA before conducting such tastings. Further information on SFA's policy on this matter can be found in [Section 10](#).

4. Questions related to processes after approvals have been granted

Q4.1: Does SFA require companies to provide periodic updates after a novel food has been allowed for sale as part of food safety assurance?

SFA does not require novel food companies to provide updates on a periodic basis after they have successfully undergone the review process. Food safety assurance is achieved through documentation, attestations, and testing. For higher risk food products, they are subjected to SFA's source accreditation program, which involves visiting the food establishment for checks. If novel food manufacturing activities are performed in Singapore, companies are required to obtain a license from SFA to set up the food manufacturing facilities to do so. The facilities, production processes and novel food products manufactured will be subject to SFA's inspection, sampling, and food safety testing programmes.

Novel food companies that have updated their manufacturing processes are expected to inform SFA of the changes.

Q4.2: Will SFA make approvals of novel foods public?

Currently, SFA does not publish approvals to the public domain. Companies wishing to make SFA's approval public and mention SFA in the accompanying press release or materials are encouraged to send SFA a draft for our review before releasing them to the public.

5. Questions related to labelling

Q5.1: What are the labelling requirements for cultured meat, when retailed in packaged/unpackaged formats?

Companies selling pre-packed alternative proteins (including cultured meat) are required to label the product packaging with suitable qualifying terms such as "cultured" or "cell-based" to indicate their true nature. Similarly, food establishments selling non prepacked foods are required to clearly communicate to their customers on the true nature of their food sold. For example, misrepresenting cultured meat as conventionally produced meat will not be allowed.

6. Questions related to tasting/sensory events

Q6.1: Can I apply for administrative exemptions for multiple tasting/sensory evaluation events in a single application?

This is not possible as companies would need to demonstrate that there have been no adverse events resulting from a prior tasting/sensory evaluation event before they are allowed to conduct another such event.

7. Questions related to manufacturing novel foods in Singapore

Q7.1: What is the process for companies seeking to manufacture novel foods in Singapore?

Companies that intend to manufacture novel foods in Singapore should refer to the application process for Food Process Establishments, which can be found [here](#). Specific guidance may be found below:

- [Guidance on safe use of genetically modified microorganisms \(GMM\) in food processing establishments](#)

8. Other questions related to novel foods

Q8.1: For international companies, how does SFA conduct inspection of the manufacturing site?

At present, SFA does not conduct inspections of novel food manufacturing sites overseas. Companies are therefore required to provide detailed information on their manufacturing processes and controls when submitting their safety assessments for SFA's review. SFA also periodically visits novel food companies that we have been engaging to understand their business and manufacturing operations.

Q8.2: What are the types of support available to novel food companies?

The Singapore Government offers support in various areas for novel food companies. Details of the support and contact information of the respective officers are available below:

(i) Financial support

Start-ups can work with Enterprise Singapore (ESG) or Economic Development Board (EDB) to explore potential support mechanism to finance their ventures into the Alternative protein space.

ESG: Phil Teoh (Phil_TEOH@enterprisesg.gov.sg)

EDB: Lim Hui Yi (lim_hui_yi@edb.gov.sg)

(ii) Regulatory Support

Start-ups can work with Future Ready Food Safety Hub (FRESH), a tri-partite joint initiative by the Singapore Food Agency (SFA), Nanyang Technological University (NTU) and Agency for Science, Technology and Research (A*STAR), to develop and understand the food safety tests required for novel food safety dossiers. The company's profile and core capabilities can be found at <https://www.ntu.edu.sg/fresh>.

To connect with FRESH, please send an email to: FRESH@ntu.edu.sg.

(iii) Technical Support

Start-ups can work with CRISP, a program dedicated to support alternative protein companies, based in A*STAR, Singapore's nation research agency. Start-ups can seek support in a variety of channels from culture development or cell-line selection, to name a few.

CRISP Meats: Michelle Chan (Michelle_chan@bti.a-star.edu.sg)

(iv) Infrastructure Support

For start-ups keen to start a facility in Singapore, whether a lab facility, a pilot scale facility or even a commercial facility, SFA will be able to link you up to the right points of contact, who can offer a range of support mechanisms.

SFA: Charles Tan (charles_tan@sfa.gov.sg)

Annex B: Glossary of Terms

ADME: An abbreviation for "absorption, distribution, metabolism and excretion", the four key processes which describe how drugs and chemicals get into the body, what happens to them while they are there, and how they are eliminated.

Contaminant: Any substance occurring in foodstuffs that was not added intentionally. Contaminants can arise from packaging, food processing and transportation, farming practices or the use of animal medicines. The term does not include contamination from insects or rodents.

Cross reactivity: A situation where an allergic reaction to one substance also leads to an allergic reaction to another substance. This is usually because the allergens (e.g. peanuts and tree nuts) possess similar characteristics which trigger the body's immune defences.

Dietary exposure: For the purposes of risk assessment, measurement of the amount of a substance consumed by a person or animal in their diet that is intentionally added or unintentionally present (e.g. a nutrient, additive or pesticide).

Exposure assessment: The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant.

Food safety hazard: A biological, chemical, or physical agent in, or condition of, food with the potential to cause an adverse health effect.

Hazard identification: The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods.

Hazard characterisation: The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical, and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable.

Health Based Guidance Value: A guidance value on the safe consumption of substances that considers current safety data, uncertainties in these data, and the likely duration of consumption. Examples include:

- **Acceptable daily intake:** An estimate of the amount of a substance in food or drinking water that can be consumed daily over a lifetime without presenting an appreciable risk to health. It is usually expressed as milligrams of the substance per kilogram of body weight and applies to chemical substances such as food additives, pesticide residues and veterinary drugs.

- Tolerable daily intake: An estimate of the amount of a substance in food or drinking water which is not added deliberately (e.g. contaminants) and which can be consumed over a lifetime without presenting an appreciable risk to health.
- Tolerable weekly intake: The maximum intake of substances in food, such as nutrients or contaminants, that can be consumed weekly over a lifetime without risking adverse health effects.

Limit of Detection (LOD): The lowest concentration of a substance that can be detected using standard tests, but which is too small to be measured with certainty.

Limit of Quantitation (LOQ): The lowest concentration of a substance that can be measured with certainty using standard tests.

Risk: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food.

Risk assessment: A scientifically based process consisting of hazard identification, hazard characterization, exposure assessment, and risk characterization.

Risk characterisation: The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.

Weight of evidence: A process in which all the evidence relating to a decision is evaluated based on its strength and quality.

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