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

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1 Scope of this document

1.1 This document aims to provide food businesses with a better understanding of SFA's requirements regarding the safety assessment for novel foods and novel food ingredients.

2 What are novel foods?

2.1 Novel food means the following, but does not include any food that is, consists of or has as an ingredient an insect-like species in any form:

- A substance (which may consist of, be isolated from or produced from, cell culture or tissue culture derived from animals, plants, bacteria or yeast, fungi, algae or other micro-organism) that has not been used to a significant degree as food for a period of at least 20 years, whether within or outside Singapore;
- A food that has been manufactured, prepared or preserved by a process that has not been previously used in food production for a period of at least 20 years, whether within or outside Singapore;
- A food consisting of, isolated from or produced from material of mineral origin that has not been previously used in food production for a period of at least 20 years, whether within or outside Singapore; or
- A food that contains or consists of engineered nanomaterials.

3 Regulatory requirement for novel foods

3.1 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:

- Have received pre-market approval from SFA; and
- Meet the specifications and are produced in accordance with the manufacturing process declared in the safety assessment submitted to SFA

3.2 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 is not limited to):

- The length of consumption/use of the ingredient (i.e. how many years the ingredient has been consumed as food or used in food).
- Extent of use of the ingredient (i.e. whether the ingredient is consumed or used by the general population, sub-population, certain tribes, etc).
- Quantity (i.e. the level of the ingredient consumed as food or used in food).
- Purpose/context of use (i.e. whether the ingredient is used for ceremonial purposes such as weddings, during famines, etc).
- Evidence demonstrating lack of adverse effects to human health attributed to the substance during the specific period of use as food.

3.3 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.

3.4 History of use as medicine or 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.

3.5 Novel food products intended for sale in Singapore must comply with the requirements, including regulatory limits, under the relevant legislation, which includes the Food Safety and Security Act, Sale of Food Act, Wholesome Meat and Fish Act and their subsidiary legislation.

3.6 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 approval from SFA should not be supplied.

3.7 Please refer to the latest guidance document before submitting an application to SFA for review.

4 Administrative requirements and information on novel food application

4.1 Companies may submit novel food applications through a safety assessment dossier to SFA, either directly or through service providers such as regulatory consultants or law firms to Authorisation@sfa.gov.sg. The information in the application should be submitted in a format which is available for SFA to download as a copy. In the event of a malfunction or failure of the above email address or other exceptional circumstances, applications may then be submitted by post to SFA at the National Centre for Food Science, 7 International Business Park, Singapore 609919. Companies should retain copies of all information and materials submitted to SFA. Where a safety assessment dossier and/or supporting information is submitted by post, applicants should make their own arrangements to ensure the secure delivery of the physical media to SFA. Physical media received by SFA will be retained upon receipt.

4.2 SFA does not require novel food applications to be submitted only from companies that are incorporated in Singapore. However, companies based outside of Singapore will need to have either:

- an address in Singapore at which notices, and other documents may be served; or
- the name and address of one or more persons in Singapore authorised by the applicant to accept on the applicant's behalf service of notices and other documents.

4.3 Where the person(s) authorised by the company to accept service of notices and documents in Singapore are not employees of the company, a Letter of Authorisation (LOA) must be provided to confirm that they are willing to act as the company's local representative. The LOA should be an official document signed by both the authorised person(s) and a representative of the company.

4.4 Companies wishing to submit applications for novel foods produced through precision fermentation, biomass fermentation or through cell-based processes, including cultivated meat, seafood, and other products derived from animal cells intended for human consumption must first fill in the respective self-assessment checklist for novel food application. This checklist should be completed electronically by the applicant and submitted in Microsoft Word format (.doc or .docx), together with the safety assessment dossier. The self-assessment checklists can be found here:

- Self-assessment checklist for novel food application – fermentation-derived products
- Self-assessment checklist for novel food application – cell-based products

4.5 SFA charges an application fee of SGD 1,750 to evaluate novel food applications. This fee is payable once all sufficient information has been submitted to initiate scientific evaluation. SFA then takes approximately 9-12 months to complete the scientific evaluation. If SFA requires additional information during this period, the evaluation timeline is paused until the company provides the requested information.

4.6 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.

4.7 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.

4.8 SFA currently does not prescribe a specified format for safety assessment. Companies are required to submit an organised dossier containing the safety narratives based on SFA's requirements in a single PDF document. Supporting documents, such as Certificates of Analysis (CoAs), analysis reports, and large data sets, can be sent in separate files. If applicants have submitted safety assessments to other overseas regulatory agencies that are conducted in accordance with the following reference documents, they are also required to use the self-assessment checklists to ensure that the safety assessments meet the requirements of a complete dossier or submission to SFA. The following resources can provide useful reference on foundational principles, methodologies, and references for assessing hazards:

- US FDA Guidance for Industry and Other Stakeholders: Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients
- US FDA Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Food
- EFSA Guidance for submission for food additive evaluations
- FAO/WHO Environmental Health Criteria 240 - Principles and Methods for the Risk Assessment of Chemicals in Food

  EFSA Guidance on the preparation and submission of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283

4.9 SFA conducts Novel Food Virtual Clinics every two months, 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.

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

5.1 Safety assessments for novel foods must clearly indicate any food processing substances used during production/manufacture including those 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.

5.2 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. For example, where the species used or the production process indicates a plausible hazard, testing should address the relevant hazard, such as fumonisins produced by certain *Fusarium* species, as applicable. Applicants should also consider relevant scientific literature and risk assessments published by overseas food safety authorities on emerging or re-emerging food safety hazards, particularly where new food matrices, production methods, or intended use scenarios may affect hazard relevance. Where possible, companies should ensure that testing is conducted in accordance with principles of Good Laboratory Practices (GLP). The methodologies should also be validated to international standards such as ISO/IEC 17025 or its equivalent and published in the scientific literature, and applicants should therefore include references to these methods.

5.3 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), Pharmacopoeia methods (e.g. British Pharmacopoeia, European Pharmacopoeia), and international guidelines such as those published by the Organisation for Economic Co-operation and Development (OECD).

5.4 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.

5.5 Companies are required to provide data from 3 to 5 batches of the novel food. Based on these results, companies should determine and propose an appropriate batch testing frequency as a critical control point, justified by the variability observed in their testing results, for SFA's assessment. Companies should note that the approved monitoring level will be expected to be maintained as part of their post-approval production controls.

5.6 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.

5.6.1 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 usually be achieved by providing a specification list (e.g. Water content, Protein, Fat, Carbohydrate, Fibres, Vitamins, Minerals, Ash) of the novel food.

5.6.2 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).

5.6.3 Information on 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.

5.6.4 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 Singapore Food Regulations, or if not provided, conform to specifications recommended by the British Pharmacopoeia, European Pharmacopoeia, Joint FAO/WHO Expert Committee on Food Additives (JECFA) or Food Chemical Codex.

5.6.5 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.

5.6.6 The intended use, proposed use levels and anticipated intake amounts of the novel food/novel food ingredients (i.e. exposure data)[1]. 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.

[1] Example: Up to 10% (w/w) in yeast-leavened breads and specialty breads and up to 7% (w/w) in cakes, cookies, and pies.

5.6.7 Information to demonstrate that hazards introduced from the inputs, manufacturing process and any known side reactions do not constitute a food safety risk. This can be achieved by, but is not limited to the following:

5.6.7.1 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

5.6.7.2 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

5.6.7.3 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.

5.6.7.4 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 Food

5.6.8 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.

5.6.8.1 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[2] and tiered toxicity testing[3] approach would be applicable for toxicological assessment.

5.6.8.2 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).

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

- 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.
- Predictive screening tools such as quantitative structure-activity relationship (QSAR) analysis[4] and the threshold of toxicological concern (TTC) approach[5], for the purposes of priority setting for risk assessment. Please note that these tools should not replace actual safety testing unless otherwise deemed appropriate.

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[2] 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] 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.

[4] 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.

[5] 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.

- Toxicity studies, examples of which include:

Genotoxicity	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. *In vitro* Mammalian Cell Gene Mutation Test using the Thymidine Kinase Gene (OECD TG 490) 6. *In vitro* Micronucleus test (OECD TG 487)
General systemic toxicity and other toxicity studies	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) 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.
Chronic toxicity/ carcinogenicity/ mutagenicity (if critical findings were reported in the genotoxicity and sub-chronic/acute toxicity studies)	1. Chronic Toxicity Studies (OECD TG 452) 2. Combined Chronic Toxicity/Carcinogenicity Studies (OECD TG 453)
Reproductive and developmental toxicity	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)

5.6.8.4 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 Food
- US FDA Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions
- EFSA Guidance for submission for food additive evaluations

5.6.8.5 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.

5.6.9 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 bio-accessibility of the novel food component(s) during digestion should be included where relevant, to address the potential food safety concerns arising from the release of such component(s) during digestion.

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

5.6.10.1 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.

5.6.10.2 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 *in vitro* 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

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

- 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

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

5.6.11 A clear description of the manufacturing process. Applicants must provide all relevant information pertaining to the food safety management systems in place. Accepted documentation includes 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.

5.7 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.

5.8 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

5.9 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).

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

5.10.1 Detailed procedures of the genetic modification process.

5.10.2 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.

5.10.3 Risk assessment and risk management measures to address food safety hazards present or introduced due to the genetic modification process

5.10.4 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).

5.10.5 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.

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

5.10.7 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)
- Guideline for the conduct of food safety assessment of foods produced using recombinant DNA animals (CAC/GL 68-2008)

6 Information on the safety assessment criteria for novel foods which are ingredients produced through precision fermentation

6.1 This section should be read in conjunction with Section 5.

6.2 Ingredients derived from precision fermentation that are chemically identical to naturally occurring substances but produced by unconventional processes are considered novel food. 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.

6.3 For these ingredients, the following information is to be submitted for safety assessment:

6.3.1 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

6.3.2 Information listed in Section 5.6, as well as in Section 5.9 if GM organisms/microorganisms are used. It is not necessary to provide the information listed in Section 5.6.1, 5.6.8, 5.6.9, 5.6.10 unless they are relevant for the application.

6.3.3 Under Section 5.6.4, 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

6.3.4 The information in Section 5.6.11 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.

6.3.5 Information related to the microorganism(s) used, including:

- Background information, identity (an unambiguous taxonomic classification at species level), and source of the microorganism(s).
- 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.
- 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.
- Viability of the microorganism(s) in the novel food/food ingredient to address potential concerns of infectivity.

6.3.6 Information related to the fermentation media used, including:

- Composition of media, including identities and purity of all added substances, as well as unintended metabolites that could be potentially produced.
- Risk assessments or tests to determine the residue levels for all non-food grade components and potential unintended metabolites present in the fermentation media.
- Information demonstrating the removal of fermentation media and/or added substances (if these are removed completely).
- Information on whether the anti-microbials, if used, would contribute to anti-microbial resistance (AMR).

7 Information on the safety assessment criteria for novel foods produced by biomass fermentation

7.1 This section should be read in conjunction with Section 5.

7.2 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.

7.3 For such novel foods, the following information should be submitted for safety assessment:

7.3.1 Information listed in Section 5.6, as well as in Section 5.10 if GM organisms/microorganisms are used.

7.3.2 Under Section 5.6.4, 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

7.3.3 Information related to the fermentation media used, including:

- Composition of media, including identities and purity of all added substances, as well as unintended metabolites that could be potentially produced.
- Risk assessments or tests to determine the residue levels for all non-food grade components and potential unintended metabolites present in the fermentation media.
- Information demonstrating the removal of fermentation media and/or added substances (if these are removed completely).
- Information on whether the anti-microbials, if used, would contribute to anti-microbial resistance (AMR).

7.3.4 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).

7.3.5 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.

7.3.6 The information in Section 5.6.11 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.

7.3.7 Information related to the microorganism(s) used, including:

- Background information, identity (an unambiguous taxonomic classification at species level), and source of the microorganism(s).
- 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.
- 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.
- Viability of the microorganism(s) in the novel food / food ingredient to address potential concerns of infectivity.

8 Information on the safety assessment criteria for cultivated meat

8.1 This section should be read in conjunction with Section 5.

8.2 Cultivated meat refers to meat developed from animal cell culture. The process to produce cultivated 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.

8.3 Information listed in Section 5.6, as well as in Section 5.10 if GM organisms/microorganisms are used

8.4 The information provided in Section 5.6.1 should also cover a characterisation of the cultivated meat product, including nutritional composition, and comparison of residual anti-microbials, growth promoters and/or modulating factors against levels in published literature.

8.5 The information provided in Section 5.6.4 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

8.6 The information in Section 5.6.11 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.

8.7 Information related to the cell lines used, including:

- Background information, identity, and source of cell lines.
- Description of methods used for selection and screening of cells.
- Information on how the cell lines are prepared and banked following their extraction from animals.
- Risk assessments on any chemicals used for induction.
- Information (e.g. biological tests) to show that the cell lines are free from infectious agents (e.g. viruses, bacteria, fungi, prions) where relevant.
- 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.
- Information to demonstrate that biopsies comply with Singapore's animal health and food safety requirements and are free from animal diseases. (If biopsies are taken from food animals).

8.8 Information related to the culture media used, including:

- 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.
- Risk assessments or tests to determine the residue levels for all non-food grade components and potential unintended metabolites present in the culture media.
- Safety assessments of biological substances used as media components during production. The safety assessments should be performed according to the approach described in Section 8.12.
- Information demonstrating the removal of culture media and/or added substances (if these are removed completely).
- 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 cultivated 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 cultivated meat product).
- Information on whether the anti-microbials, at the levels of exposure anticipated, would contribute to anti-microbial resistance (AMR).

8.9 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.

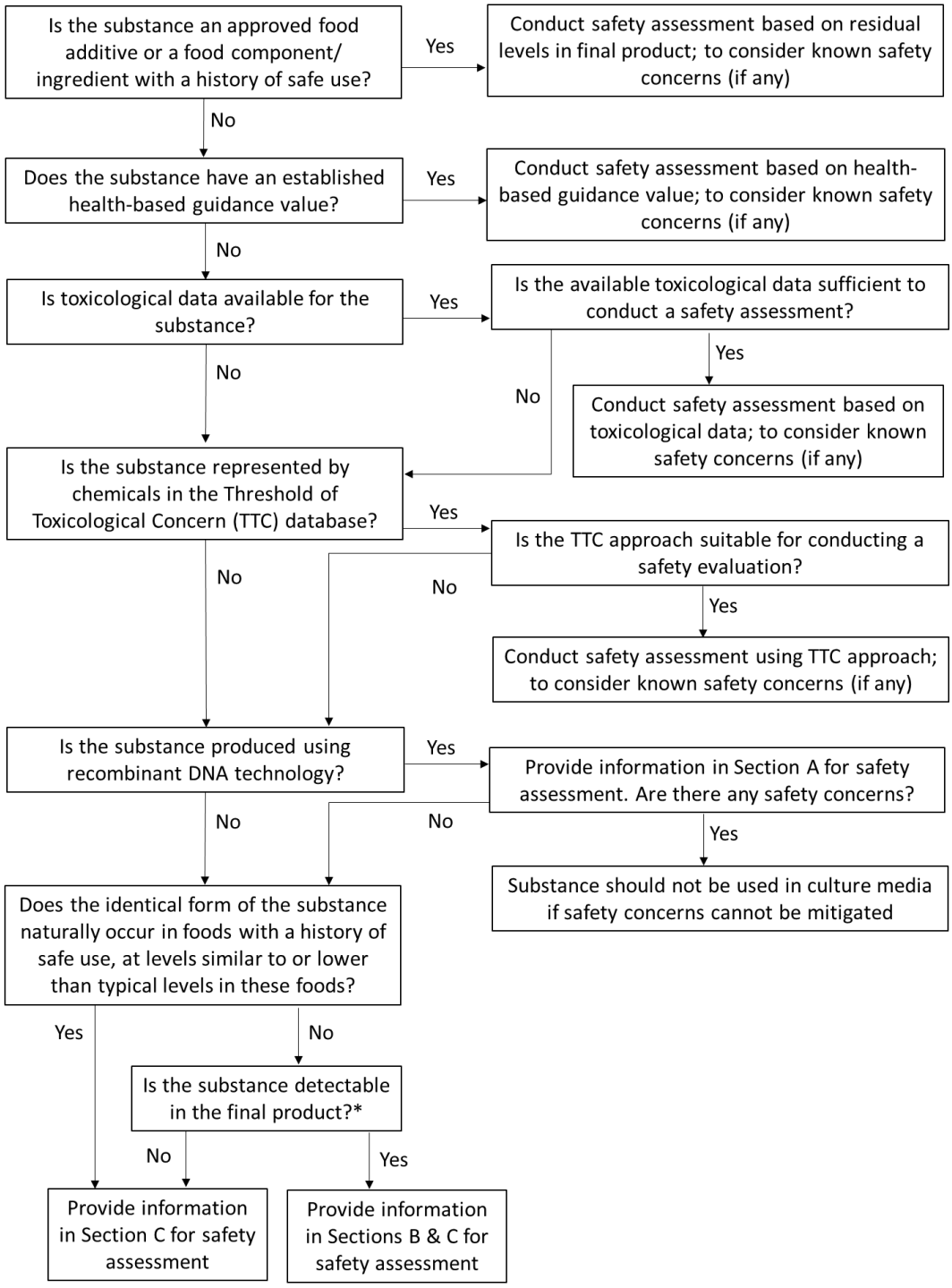
(2) By performing an *in-silico* genome screen against relevant databases highlighted in Section 5.6.10.3 to establish a list of potential toxins/allergens for subsequent targeted analysis.

(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.

8.10 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.

8.11 Safety assessment covering food safety hazards that are at high risk of occurrence based on the nature of the cell line used to produce cultivated 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.

8.12 Biological substances used in media for the production of cultivated meat or 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 - Required Information for Recombinantly Produced Substances

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 - Required Information for Substances Detectable in the Final Product

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 cultivated 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 of 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 - Required Information on Human Exposure and Physiological Effects

- **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 present 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 increased blood concentrations of the substance)
- **v.** Information on the mechanisms responsible for any links found in (iv).

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

9.1 The pre-market approval granted by SFA is specific to the manufacturing process and intended use declared in the application. If changes are made to the manufacturing process of novel foods which have received pre-market approval by SFA that may affect the validity of the original safety assessment submitted, the holder of the pre-market approval should contact SFA to discuss whether such changes require a modification to the existing approval 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 to input materials (e.g. cell-lines or culture media components) in the production of cultivated meat.

9.2 Similarly, if changes are made to the finished product such that it represents an expansion in the intended use where it may fall outside the approved scope, the holder of the pre-market approval should contact SFA to discuss whether this new intended use requires a modification to the existing approval, to ensure that the expanded exposure to the novel food is safe for consumers.

9.3 Companies should note that SFA may cancel the pre-market approval where SFA assesses it to be necessary (e.g. where a material change has been made to information provided in connection with the original application). A cancellation of pre-market approval would render the novel food a defined food, and its supply in Singapore without a new pre-market approval would constitute an offence under the Food Safety and Security Act 2025.

9.4 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.

9.5 SFA maintains a list of novel foods that have received pre-market approval for import and sale in Singapore. Prior to publication, SFA will liaise with the holder of the pre-market approval regarding the information to be published on the list. As the list is periodically updated, please refer to SFA's website for the latest version.

9.6 Companies selling pre-packed alternative proteins (including cultivated meat) are required to label the product packaging with suitable qualifying terms such as “cultivated” 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 cultivated meat as conventionally produced meat will not be allowed.

10 Information on Singapore Food Agency's policy for the tasting of unapproved novel foods

10.1 Novel foods that have not been granted pre-market approval under the Food Safety and Security Act ("unapproved novel foods") should not be supplied for consumption. Companies that are found to have supplied defined food for consumption, including unapproved novel foods, may be subject to enforcement actions under the Food Safety and Security Act.

10.2 For the purposes of this section, "tasting" refers to an event involving the consumption of unapproved novel food, conducted within a continuous period not exceeding 24 hours. Tastings may include, but are not limited to:

- Tastings for potential business partnerships, such as targeted tasting events, networking events, exhibitions, and competitions, conducted with investors, commercial partners, or food industry professionals;
- Product research and development tastings conducted with food industry professionals, with the aim of improving product characteristics or identifying potential use cases; and
- Market research tastings conducted to assess commercial viability or consumer taste preferences, which may include potential consumers as participants.

10.3 A person seeking to conduct a tasting that constitutes the supply of unapproved novel food is required to seek an administrative exemption from SFA.

<u>Application for administrative exemption for tasting of unapproved novel foods</u>

10.4 SFA will only accept applications for administrative exemptions from a person who has applied for pre-market approval of the novel food. An application for an administrative exemption should only be submitted after SFA has conducted a preliminary assessment of their safety assessment dossier and assessed that the information is sufficient for evaluation.

10.5 Applications for administrative exemptions should be submitted with the complete set of information at least **ten (10) weeks** prior to the planned date of the tasting. SFA will notify applicants of the outcome at least two (2) weeks prior to the planned date of the tasting.

10.6 In the event where applicants intend to conduct tastings that fall within **two (2) weeks before or after** the annual Singapore International Agri-Food Week (SIAW), applications should be submitted with the complete set of information for administrative exemption at least **twelve (12) weeks** prior to the planned date of the tasting.

10.7 To apply for an administrative exemption, please complete the application and email the acknowledgement page generated upon submission to SFA-NovelFoods@sfa.gov.sg. The application form can be found here.

10.8 The application for an administrative exemption must be accompanied by the following documents:

- Acute risk assessment (including exposure calculations) for one-time consumption of the novel food at the intended serving size. The risk assessment should cover potential food safety hazards, including but not limited to microbiological agents, contaminants, toxins and allergens. The following supporting documents must be submitted together with the risk assessment:
    - Certificate(s) of analysis of all inputs used in the production of the novel food.
    - Certificate(s) of analysis indicating that the novel food meets specifications which have been established by the applicant.
    - If in-house analytical methods are used to determine the levels of microbiological and chemical hazards in the unapproved novel food, details of methods used, including the accredited or scientifically accepted reference method 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.
- Description of measures established to minimise microbial and chemical contamination during storage, production, and post-production of the novel food
- Medical contingency plan to manage unforeseen adverse reactions during the tasting
- Completed and signed “Statement of Compliance with Singapore Food Agency’s Policy for the Tasting of Unapproved Novel Foods”
- Completed and signed “Release, Waiver and Discharge of Liability and Indemnity Form”
- A template of the acknowledgement form to be issued to participants, which requires participants to acknowledge the following:
    - They are participating on a voluntary basis;
    - They have been informed that the product is unapproved and hence aware of potential risks;
    - They may withdraw from the tasting anytime without penalty or reason; and
    - They agree to release SFA from liability resulting from the consumption of the unapproved novel food.

Conditions for the conduct of tastings

10.9 The applicant must ensure that the tasting is conducted under the following conditions:

10.9.1 The tasting must not be made available to the general public.

10.9.2 The tasting must not involve more than **thirty** (**30**) participants.

10.9.3 Prior to the tasting, all participants must sign the acknowledgement form that was submitted to SFA.

10.9.4 The tasting can be conducted in a non-food service facility (e.g. designated areas at events, test kitchens, IHLs, RIs), or in an SFA-licensed restaurant, as long as:

- The venue is closed to the general public during the tasting;
- There is segregation of facilities for preparation and serving of unapproved novel foods; and
- The facility is thoroughly cleaned after the tasting to avoid cross contamination.

10.9.5 Sufficient records, including but not limited to the records of participants and manufacturing batch records, must be maintained for a minimum of two (2) weeks following the tasting, to enable tracing of any adverse event that may arise.

10.9.6 SFA must be notified of any detected or reported adverse events occurring within two (2) weeks of the tasting. In the absence of adverse events, a 'Nil' return must be submitted to SFA after two (2) weeks of the tasting.

- For this purpose, an adverse event is considered to have occurred when either of the following applies:
    - At least one food safety complaint has been received from participants, which involves an adverse health effect, and which could be reasonably traced to the tasting; or
    - Information from other studies, sources, sensory evaluations or tasting events which demonstrate that there is a food safety concern associated with the unapproved novel food.
- In the event of a detection or report of an adverse event, the applicant must initiate internal investigations forthwith to determine its cause. SFA will independently investigate into the adverse event and if there is sufficient evidence to point to any non-compliance with our food safety laws, enforcement action may be taken. SFA reserves the right to take any form of action deemed necessary for the protection of public health, including but not limited to, issuing a direction to prohibit the event from continuing. To facilitate SFA's investigations, the applicant must provide the following information upon request:
    - Internal investigation findings;
    - Participant details;
    - Adverse health effect encountered; and

- Any other information deemed necessary for the purpose of SFA's investigations.

11 Contact information

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

12 Revision History

Date of Revision DD-MMM-YYYY	Summary of Revisions
22-Nov-2019	First version of the document
23-Nov-2020	Updated language for clarity
13-Dec-2021	Updated the format and included further guidance Regulatory framework remains unchanged
22-Apr-2022	Updated information on the sensory evaluation of unassessed novel foods.
26-Sep-2022	Updated guidance on: • Revised policy and regulatory positions • Safety assessment approaches • Self-assessment checklists • Online registration links
20-Jul-2023	Updated information on: • Tasting and sensory evaluation of unassessed novel foods
17-Mar-2025	Updated guidance on: • Format and language for clarity • Information on the sensory evaluation and tasting of unassessed novel foods
18-Nov-2025	Updated information on: • Food Safety and Security Act
XX-Xxx-2026	Updated guidance on: • Administrative requirements • Self-assessment checklists • Post-approval changes • Policy for the tasting of unapproved novel foods

Annex A: FAQs for Novel Food companies

Overview

Novel food companies are encouraged to familiarise themselves with SFA's guidance documents and requirements at an early stage of product development. Companies may also engage with SFA to clarify regulatory requirements and application procedures, which can help facilitate the regulatory pathway when they eventually submit their safety assessments for approval. Applicants remain responsible for preparing and submitting a complete safety assessment dossier that demonstrates the safety of their novel food.

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 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. However, companies based outside of Singapore will need to have either:

- an address in Singapore at which notices, and other documents may be served; or
- the name and address of one or more persons in Singapore authorised by the applicant to accept on the applicant's behalf service of notices and other documents

Overseas novel food companies should note that novel foods that are manufactured outside of Singapore and which have 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, they are encouraged to use the self-assessment checklists (Section 4.4) to ensure that the safety assessments meet the requirements of a complete dossier or submission to SFA. This is applicable where safety assessments were conducted in accordance with any of the following reference documents:

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

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. Applicants are encouraged to familiarise themselves with the requirements and guidance documents published by SFA prior to submission. Pre-submission engagements with SFA may be useful for clarifying regulatory requirements and application procedures. However, applicants remain responsible for preparing and submitting a complete dossier that demonstrates the safety of their novel food.

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 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 testing is conducted in accordance with principles of Good Laboratory Practices (GLP). The methodologies should also be validated to international standards such as ISO/IEC 17025 or its equivalent and published in the scientific literature, and applicants 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), Pharmacopoeia methods (e.g. British Pharmacopoeia, European Pharmacopoeia), 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.

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.

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

Companies are required to provide data from 3 to 5 batches of the novel food. Based on these results, companies should determine and propose an appropriate batch testing frequency as a critical control point, justified by the variability observed in their testing results, for SFA's assessment. Companies should note that the approved monitoring level will be expected to be maintained as part of their post-approval production controls.

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 contact SFA if changes are made to the manufacturing process of novel foods that may affect the validity of the original safety assessment submitted to SFA, to discuss whether such changes require a modification to the existing approval. An example of such a change would be modifications to input materials (e.g. cell-lines or culture media components) in the production of cultivated meat. Similarly, companies that intend to expand the scope of intended use of their novel food should contact SFA to discuss whether the new intended use requires a modification to the existing approval, 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 (GM) / genome edited (GEd) cells to produce novel foods (including cultivated meat)?

When assessing novel foods produced from GM/GEd organisms, SFA takes reference from relevant Codex guidelines such as "Guideline for the conduct of food safety assessment of foods produced using recombinant DNA microorganisms" (CAC/GL 46-2003) and "Guideline for the conduct of food safety assessment of foods produced using recombinant DNA animals" (CAC/GL 68-2008). If a GM organism is present in the finished food product, the food itself would be subject to review by the Genetic Modification Advisory Committee of Singapore (GMAC).

The following information should be included in the safety assessment if GM/GEd organisms 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. introduction 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 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 is not limited to genomic, transcriptomic, or proteomic analyses. Companies should also inform SFA of any measures that could be implemented to mitigate these risks.

Q2.9: 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.

Q2.10: 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 cultivated meat product or will be removed completely. Where possible, culture media components used should conform with purity specifications recommended by the British Pharmacopoeia, European Pharmacopoeia, Joint FAO/WHO Expert Committee on Food Additives (JECFA) or Food Chemical Codex. Companies can establish the safety of culture media components that are not known to be used in food by: (1) demonstrating that no residue of the culture media component remains in the cultivated meat; (2)

comparing levels of the culture media component in cultivated meat to levels of the same compound that are naturally found in conventionally grown meat; and (3) by comparing levels of the culture media component in cultivated meat to available toxicity data for the same compound, taking into consideration the intended use levels of the cultivated meat. Companies should also address whether any anti-microbials used in the culture media, at anticipated exposure levels, would contribute to anti-microbial resistance. For biological substances used as culture media components, the safety assessment should be performed according to the approach described in Section 8.12.

Q2.11: What is SFA's stance on requiring cultivated 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 cultivated 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 cultivated 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 cultivated meat production to reduce the risks of unintended side reactions.
- Ensuring aseptic conditions during cell proliferation, scaffolding and extraction stages of cultivated 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.

Q2.12: What are the steps involved in importing cultivated meat or inputs for production of cultivated meat into Singapore? Are there specific requirements to be met (e.g. testing) at point of import?

Companies intending to import cultivated meat products into Singapore should provide a signed statement or affidavit, together with relevant Certificates of Analysis (COA), demonstrating compliance with the specifications of the approved novel food. The parameters included for testing would depend on the specific hazards identified in the individual safety assessments submitted by companies. The food must also meet the food safety requirements and limits set out in Singapore Food Regulations.

Q2.13 SFA regulates the levels of various mycotoxins (e.g. Aflatoxins, DON, Ochratoxin A, Patulin, Fumonisins 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 refer to any reported NOAEL or health-based guidance values when performing safety assessments for such mycotoxins. Please substantiate in the safety assessment 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.

Q2.14: 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 approval from SFA should not be supplied.

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 should contact SFA regarding changes to their manufacturing processes that may affect the validity of the original safety assessment, to discuss whether such changes require a modification to the existing approval.

5. Questions related to labelling

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

Companies selling pre-packed alternative proteins (including cultivated meat) are required to label the product packaging with suitable qualifying terms such as "cultivated" 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 cultivated meat as conventionally produced meat will not be allowed.

6. Questions related to tastings of unapproved novel foods

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

A separate application for an administrative exemption must be submitted for each tasting event.

Q6.2: Can I apply for an administrative exemption immediately after submitting a novel food application?

An application for an administrative exemption should only be submitted after SFA has conducted a preliminary assessment of the safety assessment dossier and assessed that the information submitted is sufficient for evaluation.

Q6.3: Do I need to apply for an administrative exemption for a new tasting event if I am using the same batch of novel food product as the previous tasting session(s)?

A separate application for an administrative exemption must be submitted for each tasting event, even if the same batch of novel food will be used. The applicant should identify the batch to be used and submit the information required under Section 10 for the proposed tasting 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 (EnterpriseSG) or Economic Development Board (EDB) to explore potential support mechanisms to finance their ventures into the alternative protein sector.

EnterpriseSG: Food Manufacturing & Agritech (foodmfg@enterprisesg.gov.sg).

EDB: Grace Lee (Grace_LEE@edb.gov.sg)

(ii) Technical Support

Start-ups can work with Singapore's institutes of higher learning and research institutes who are conducting research and development to support alternative protein companies, some of whom are supported by the Singapore Food R&D Programme by SFA.

SFA: Singapore Food R&D Programme Office (SFA_RND@sfa.gov.sg)

(iii) 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: Novel Foods Email (SFA-NovelFoods@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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