FOOD STANDARDS Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

12 December 2024
321-24

Supporting document 4

Production and processing requirements – Application A1269

Cultured quail as a novel food

Executive summary

During Application A1269, Food Standards Australia New Zealand (FSANZ) assessed the safety of both the product (cell biomass of quail cell line 221523-Fib-Quail) and its production process (bioreactor production of a potentially hazardous food).

This document focuses on managing potential microbiological hazards identified in the safety assessment (refer to Supporting document 1 (SD1)). It considers the application of production and processing requirements in Chapters 3 and 4 of the Australia New Zealand Food Standards Code (the Code) to cell-cultured quail and the adequacy of current requirements.

Microbiological safety: ensuring safe production

The production and processing stages of culturing quail cells includes selection of cells, development of cell lines and cell expansion in a bioreactor. Cells are then harvested for further manufacturing. The assessment of A1269 was up to the harvested cell stage; further processing steps were not considered.

The microbiological safety assessment examined potential microbiological hazards associated with the production of quail cell biomass from cell line 221523-Fib-Quail, developed from a Japanese quail embryo. The FSANZ safety assessment (SD1 to the 1st call for submissions (CFS)) concluded:

- The cell line is genetically stable and microbiological hazards associated with cell line sourcing are very low.
- The greatest risk of introducing microbiological hazards occurs when cells leave the 'closed' production system during harvesting.
- The cell biomass is a potentially hazardous food and no risk mitigation step (e.g. cooking) has been assessed. The applicant advises further processing includes a cooking step.
- Through-chain controls from initial cell sourcing and subsequent development stages through to bioreactor production is required to prevent contamination. A hazard analysis

critical control point (HACCP)-based production system supported by good practices is critical to managing microbiological risks.

- Standards 3.2.2 and 3.2.3 alone would not be sufficient to adequately identify hazards and manage them through-chain. Current standards were not developed to manage this type of food production.
- Cell culturing food uses techniques and equipment new to food production and its regulation. It is also a food production system still in development with limited data compared to other foods about its safe production.

Existing requirements in the Code

Neither Chapter 3 – Food safety standards or Chapter 4 – Primary production and processing standards were developed for this food type or to provide fully for its safe production and processing. However, current food safety and hygiene requirements provide a strong basis and when supplemented by measures unique to cell-cultured food production, would manage risks with cell-cultured food production and processing.

FSANZ's proposed regulatory approach for production of cell-cultured food is premised on cells, cell lines and the cell biomass each being declared to be a *food* for the purposes of the Code and food laws that apply the Code. FSANZ's understanding is this would provide the certainty required for regulation.

Finalising food safety measures

Cell-cultured food production is closer to food processing in operation than it is to primary production. FSANZ proposed measures that better align with Chapter 3 standards.

FSANZ considered four options to ensure relevant food safety measures apply to each stage of production and processing. As explained in the covering CFS, the preferred option is to introduce a new standard in Chapter 3 applicable to all cell-cultured food: Standard 3.4.1 – Food safety requirements for processing of cell-cultured food. A HACCP-based approach to ensure safe production and processing of cell-cultured food is achieved through mandating a food safety program in line with Standard 3.2.1.

The regulatory framework considers feedback in submissions to the 1st CFS. It involves:

- amending Standard 1.1.1 to provide that a food for sale must not be, or have as an ingredient or a component, a cell-cultured food unless expressly permitted by the Code
- amending subsection 1.1.2—2(3) to include a new definition for 'cell-cultured food' for this purpose
- updating Schedule 27 to include microbiological limits for cell-cultured food for *Listeria monocytogenes* and *Salmonella* spp.
- amending the definition of a 'food business' in Standard 3.1.1 to include a 'cell line supplier' and a 'cell culturing food business' as defined by proposed Standard 3.4.1
- introducing Standard 3.4.1 – Food safety requirements for processing of cell-cultured food.

This framework provides certainty cell-cultured foods and the businesses producing them are subject to food safety production and processing requirements set by Chapter 3. Measures apply to both cell line suppliers and cell culturing food businesses whose product is cell-

cultured food. It captures all stages of cell-cultured food production, starting with the sourcing of cells through to further processed product for retail sale.

FSANZ proposes to work with the jurisdictions to develop guidance to support implementation of the new measures. Microbiological criteria for monitoring purposes will also be developed and published in the *Compendium of Microbiological Criteria for Food.*

The intent of the proposed amendments is to continue to protect public health and safety while providing certainty for regulators and industry about requirements and regulatory capture. Establishing this framework provides certainty of requirements for cell-cultured quail assessed in A1269 as well as future cell-cultured foods, supporting industry innovation.

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1 Introduction

At the 1st call for submissions (CFS), FSANZ sought comment on regulating cultured quail cell production under a documented food safety program in line with Standard 3.2.1 supported by good practices. FSANZ considered through-chain processing requirements were necessary to manage microbiological risks during production and processing of cell-cultured quail, to ensure safe quail cell biomass production. The Australia New Zealand Food Standards Code (the Code) would require amendment for Standard 3.2.1 to apply. This proposed amendment provided for the HACCP-based approach identified as critical in the safety assessment.

FSANZ now also proposes a standard that would apply broadly to the production and processing of all cell-cultured foods. The purpose of this standard is to provide clear requirements for the safe production and processing of cell-cultured foods.

1.1 Reasons for preparing a production and processing standard

FSANZ developed proposed Standard 3.4.1 – Food safety requirements for processing of cell-cultured food, as current standards applying to food production and processing did not clearly or adequately capture cell-cultured foods.

FSANZ considered processing of cell-cultured foods is more in line with food processing than primary production, noting requirements unique to cell-cultured foods would need some prescription. The safety assessment identified the need to apply through-chain controls to address potential risks: some risks were consistent with those faced in typical food processing environments and others would be unique to cell-cultured foods.

Most stakeholders reaffirmed support for FSANZ's approach to capture cell culturing as food handling under Chapter 3, mandate food safety programs and detail requirements on unique aspects of safe cell culturing processes. However some regulators did not support the mechanism proposed for mandating food safety programs under Schedule 25 – conditions of use (refer to Appendix 1 of the 2nd CFS).

Further, jurisdictions raised the need to establish baseline food safety requirements or a specific processing and production standard for cell-cultured food products to support their safe production and certain regulatory status. Such a standard should include measures similar to those in primary production and processing (PPP) standards.

1.2 Objectives

In developing Standard 3.4.1 and each of the other proposed regulatory measures, FSANZ had regard to each of the assessment criteria prescribed by the *Food Standards Australia New Zealand Act 1991* (FSANZ Act). In addition, the following regulatory objectives were considered:

- **Using best available evidence**

  Noting this application identified both a new food type and food production process, measures are based on best available scientific information available from several sources including the FAO/WHO (2023) guidance on safety assessments of cell-cultured food.

- **Clear and proportionate regulatory measures**

  The regulatory approach provides clarity on when and to whom regulatory measures apply, by defining production stages unique to cell-cultured food and businesses involved in their production; avoids uncertainty as to when food regulation applies.

  Measures are proportionate to identified risks and consistent with regulatory approaches to other foods with similar risk profiles.

  Measures align with known and relevant best practices, supporting food industry innovation and establishing a framework for emerging cell-cultured foods.

- **National consistency**

  Regulatory measures are clear, understandable and enforceable, supporting nationally consistent implementation, particularly on skills and knowledge for cell-cultured food and its production.

  All businesses understand when they are captured by the requirements and what they need to demonstrate to produce cell-cultured foods safely.

1.3 Scope

This supporting document considers whether existing food safety and hygiene requirements and standards in the Code apply to and adequately manage the safety of cell-cultured food including cell-cultured quail during production and processing.

Cell-cultured food is currently regulated through the novel food standard. The approach to novel food regulation has typically been more of a product-based assessment and not a production process assessment.

Noting the considerations above (section 1.2) and considering submissions, FSANZ supports the current overarching framework of standards is appropriate. However, within this framework, specific regulatory measures were necessary to manage risks associated with the production process for cell-cultured foods to ensure their safety. FSANZ considers it important to establish generic requirements for producing cell-cultured foods.

FSANZ does not consider the proposed standalone production and processing standard changes the overall policy approach to cell-cultured foods. This work builds on and nuances existing definitions and measures to ensure production methods result in safe food and avoid doubt of regulatory capture. If approved and listed in the Code, each cell-cultured food still requires case-by-case approval and ongoing safety is delivered through clear and consistent production and processing requirements. FSANZ notes to date, the safety of only one cell-cultured food has been assessed; other cell lines or unique processes may pose other hazards or risks.

Being outcomes based, the proposed standalone standard provides both requirements and flexibility for businesses to manage hazards and risks within their production system, once the unique cell line has been assessed.

1.4 Food safety and hygiene standards

The food safety and hygiene standards in the Code date back to the early 2000s: Chapter 3 – Food safety standards was introduced in 2000 and Chapter 4 – Primary production and processing standards commenced in 2003.

Standard 1.1.1 identifies the Code applies to all food sold, processed, handled or imported into Australia or New Zealand. In Australia, state and territory food acts give the Code force

of law. Standard 1.1.1—14 of the Code requires food businesses in Australia to comply with Chapter 3 – Food safety standards. These standards cover general food safety requirements for people, premises, equipment and processes. Some food business may also be required to develop and implement a food safety program as required under Standard 3.2.1, to demonstrate how they will manage food safety risks.

Standard 3.1.1 – Interpretation and application contains provisions that apply in other Chapter 3 standards, including key definitions explicitly identifying entities (i.e. people and businesses) and activities (i.e. food handling) captured by the standards (refer to Annex 1). It also defines what is primary production and that a business involved in primary production is not a food business.

These definitions hinge on a particular product meeting the definition of *food* for the purposes of the Code and the food laws that apply the Code. As explained, regulation of the production of cell-cultured food is premised on cells, cell lines and cell biomass being declared to be a *food* for these purposes.

Chapter 4 standards apply to *primary producers and processors* who are conducting *primary production and processing* activities (refer to Annex 1). General provisions for all primary producers are in Standard 4.1.1. However unlike Chapter 3 in which Standards 3.1.1, 3.2.2, 3.2.3 and 3.3.1 apply to all food businesses under that standard, general primary production and processing requirements don't apply until there is a commodity-specific standard. There are nine commodity standards (seafood, poultry meat, meat, dairy, eggs, sprouts, berries, leafy vegetables and melons).

For Chapter 3 to apply to cell-cultured foods, the activities involved in its production and processing would need to meet the definition of *food handling* and the businesses to be *food businesses*. Similarly, for Chapter 4 to apply to cell-cultured foods, the activities would need to meet the definition of *primary production and processing* and the business be a *primary producer* or *primary processor*.

1.5 Consultation

At 1st CFS, FSANZ sought comment on regulating cultured quail cell production under a documented food safety program in line with Standard 3.2.1 supported by good practices, to ensure safe cell biomass production. The Code would require amending for Standard 3.2.1 to apply.

Submitters' issues on this approach included sourcing and safety of the cell line, safe production inputs, microbiological safety of the harvested cells and food safety processing requirements (refer to Appendix 1 of the 2nd CFS). Jurisdictional feedback was that as cell-cultured food is a new food type not well known to food regulators, more detail about production risks and controls was needed in the Code. While strongly supportive of production under a HACCP-based approach, they requested clarity on how to mandate Standard 3.2.1. The proposal in the 1st CFS to mandate Standard 3.2.1 under Schedule 25 was not considered enforceable as Schedule 25 contains conditions for use, not production.

This is the first consultation on a standalone production and processing standard for cell-cultured food and related amendments to the Code.

2 Assessment summary

2.1 Risk assessment

The safety assessment (refer to SD1) concludes microbiological hazards associated with the first stage of sourcing cell line 221523-Fib-Quail are very low. FSANZ notes other cell lines may pose other risks.

In the next stages of cell handling, cell selection, immortalisation and multiple rounds of seeding and culture expansion, these all occur under aseptic conditions. If appropriate handling measures are in place, presence of microorganisms during cell proliferation and biomass production stages should therefore be close to nil at harvest. The greatest risk of introduction of microbiological hazards occurs at post-harvest, where the harvested cells are exposed to the food production environment and any foodborne pathogens therein. The risk with all stages will be managed if control measures prevent contamination entering the production process and reduce microbial hazards if present.

There is no step in the production of cultured quail cells to eliminate or reduce microbiological contaminants. Use of a HACCP-based approach with good practices is essential to maintain 'sterility'; i.e. in this case, only the cultured quail cells are present. This is critical given the extracted quail cell biomass is a potentially hazardous food (i.e. supports the growth of microorganisms and requires temperature control).

Food safety controls must be applied in a whole-of-chain management approach; starting with initial cell sourcing from a donor animal/source, expansion stage, harvest and freezing of the harvested quail cells and producing the product used as an ingredient in a food for sale. Specific points during production where microbial hazards could occur and appropriate control points to minimise food safety risks must be identified, using a HACCP-based system. Good practices should be in place (i.e. good cell culturing practice (GCCP), good manufacturing practice (GMP) and good hygienic practice (GHP)), as well as validation of processes and shelf-life.

The assessment recommended using a systematic approach to manage the potential for:

1. contamination of the acquired cells from source animal, reagents, or environment
2. contamination from manual handling
3. contamination from inputs during production and cell expansion and differentiation
4. facility environmental contamination, especially of the extracted/harvested cell biomass and
5. inadequate cleaning and sterilisation of equipment.

Many other foods of animal origin have an established history of consumption and safe production and processing systems, with decades of data underpinning the effectiveness of controls for known hazards. Safe use of bioreactor production technology provides insights on controls and appropriate monitoring (e.g. a long history of therapeutic goods production, precision fermentation and HACCP-based production systems of other potentially hazardous foods). FSANZ considered the key hazards in cell-cultured quail relate more to potential contamination once cells are exposed to the environment, in particular *Salmonella* spp. and *Listeria monocytogenes*.

FSANZ notes the applicant has implemented a through-chain HACCP-based approach supported by good practices for producing cultured quail cells. A recognised mitigation step before consumption (e.g. cooking) would further reduce the risk of foodborne pathogens if

done properly. FSANZ notes the applicant intends for the product to be cooked before consumption, which should mitigate microbiological risk. Further processing of the biomass was not assessed as part of this application.

FSANZ notes the likelihood of microbiological hazards entering the cell biomass has been assessed at the current scale of production and this could change if production is scaled up. The HACCP-based approach makes the business responsible for ensuring changes to processing are validated as effective and subject to ongoing verification.

2.2 Risk management

The FSANZ risk assessment concluded through-chain controls developed using a HACCP-based approach were essential for safe production and processing of cell-cultured food. Standards 3.2.2 and 3.2.3 alone would not be sufficient to adequately identify hazards and manage them through-chain. Standards in Chapter 4 were not developed to manage this type of food production. FSANZ considers cell-cultured food production is more akin to food processing than primary production and has proposed measures that would align with Chapter 3 standards.

This principle of requiring a HACCP-based approach is retained in this 2nd CFS. That is, under draft Standard 3.4.1 – Food safety requirements for processing of cell-cultured food, FSANZ proposes mandating a food safety program in line with Standard 3.2.1 (see sections 3.4.1—4 and 3.4.1—7) which must address cell-cultured food specific items (see sub-sections 3.4.1—4(2) and 3.4.1—7(2)). It will also be supported by good practices as contained in Standards 3.2.2 and 3.2.3, which apply to all food businesses. Together, these standards will address the food safety issues raised in the microbiological safety assessment, supporting safe cell biomass production.

3 Safely culturing cells as food

Application of current standards and at each stage of culturing cells for food use depends on whether they *are* food: i.e. the cells, cell lines and cell biomass meet the definition of food in the FSANZ Act, model food provisions and jurisdictional food legislation. As explained, regulation of the production of cell-cultured food is premised on the latter being declared to be a *food* for the purposes of regulation.

3.1 Capturing cells, cell lines and cell biomass as foods

The definition of food in the FSANZ Act and jurisdictional food legislation, was not developed with cell-cultured foods in mind.

FSANZ considers it important the Code applies to each stage of production, as the risk assessment concluded cell-cultured foods should be produced under a HACCP-based approach with controls at each stage of production and processing to manage risk. Providing regulatory clarity and certainty is essential.

3.2 Food handling or primary production and processing?

To ensure safe production and processing, current requirements under Chapters 3 and/or 4 and their application to cell-cultured foods were reviewed. Noting jurisdictional feedback supporting capture of cell-cultured foods under Chapter 3 and requirements be prescriptive, FSANZ reviewed current Chapter 3 requirements in detail.

The definitions of *food handling*, *food business* and *primary production and processing* may apply to cell-cultured food. Further some commonly used terms occur in one or both chapters such as grow, collect, harvest, produce, process (refer to Annex I for relevant definitions and their location). As neither chapter was developed to cover cell-cultured foods, they do not provide a clear regulatory framework for safe production and processing.

However, there are some existing food safety and hygiene measures applicable in managing risks at certain stages of cell-cultured food production. These existing food handling requirements, supplemented by measures unique to cell-cultured food production, would adequately address the risks identified in the safety assessment.

FSANZ considered new measures were necessary to manage risks associated with cell-cultured quail during its production and processing.

4 Regulatory approach: production and processing

Cell culturing for food use is a new application of an existing technology to food production, producing a new food. However, there is a long history of safe use of bioreactor-based production systems; the nature of the end products of cell culturing and their safety; final processed products and how they are handled and consumed; any gaps in managing food safety using existing requirements; and comparable requirements for managing potentially hazardous food (i.e. food that supports microbial growth).

FSANZ referenced food safety approaches being used internationally at the World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO), and in other countries (Singapore, United States of America, Canada, New Zealand and United Kingdom). No Codex texts exist on cell-cultured food production, though some countries are seeking international approaches be rapidly developed to support innovation in food production.

All information sources to date agree production should occur using a HACCP-based approach. In the Australian context, this would mean mandating Standard 3.2.1.

FSANZ considered four management options to address food safety risks identified in the microbiological safety assessment:

Option 1 – Retaining the status-quo, i.e. application of Standards 3.2.2 and 3.2.3

Option 2 – Mandating Standard 3.2.1 for the production of cell-cultured food

Option 3 – Introducing new regulatory food safety measures in Chapter 3 unique to cell-cultured food

Option 4 – Introducing new regulatory measures in Chapter 4 unique to cell-cultured food.

Each option was assessed against the objectives and criteria set out in sections 18 and 29 of the FSANZ Act.

4.1 Rationale for Option 3 as the preferred option

FSANZ determined the preferred approach is a new Chapter 3 standard for the production and processing of cell-cultured foods (option 3) and revised definitions to ensure its application to activities and businesses. The key reasons are:

- The food type and production system are both new, without long-established data of safe history of production and consumption. A cautionary approach is warranted to protect

public health and safety.

- The standard applies existing food safety measures in Chapter 3 (Standards 3.2.1, 3.2.2 and 3.2.3) and adds measures unique to cell-cultured food. It takes a whole-of-chain approach, applying from when cells are collected from a donor animal through to producing the product used as an ingredient in a food for sale. It is consistent with other outcome-based management measures for safe food production and processing.
- The standard would apply to all relevant businesses defined in the standard, delivering nationally consistent requirements and certainty for industry. It reinforces the importance of, and processes for, safe cell-cultured food production and processing.
- It manages risks and supports industry in using well-known effective food safety measures, which may be new to cell culturing food businesses. The outcomes-based approach affords businesses some flexibility as systems, knowledge and data grow.
- It provides a future-ready framework for cell-cultured food production and processing. A standalone processing standard provides clarity and transparency on the requirements now and into the future. It supports a clear regulatory framework for production of cell-cultured foods providing confidence the food can be safely produced.

Option 1

The status quo (option 1) was not a preferred option, as the safety assessment concluded a HACCP-based production system supported by good practices is necessary to manage microbiological risks. FSANZ assesses Standards 3.2.2 and 3.2.3 alone (akin to good hygienic practices and good manufacturing practices) would not be sufficient to manage the food safety risks through-chain and protect public health and safety.

The current food safety standards (and relevant definitions) were developed prior to and without consideration of this food type or production method. Option 1 does not provide regulatory certainty cell-cultured food is *food* (cells, cell lines and cell biomass), its production (i.e. cell selection and culturing) is *food handling* and the businesses are *food businesses*.

Option 2

Option 2 was not a preferred option as it only partially addressed concerns. Mandating food safety programs would require businesses to document their hazard/safety assessments and controls, reinforcing a systems-based approach. This is consistent with managing production of foods that support microbial growth. However, the mechanism for mandating Standard 3.2.1 remained unclear.

Given the novel nature of the food and its production technology, FSANZ considered it important to detail measures unique to cell-cultured food, such as safe sourcing of cells and bioreactor-based production of a potentially hazardous food. Option 2 would not provide for this detail.

Option 4

Option 4 was not a preferred option as primary production and processing standards were aimed at, among other matters, minimising exposure to microbiological contamination which is often from animal faecal matter or the farming environment. Apart from the initial cell sourcing stage, there would be no further contact with animals or farming environments requiring measures specific to primary production management. Cell sourcing via biopsy is likely to be a single event under highly controlled conditions that minimise contamination. The biopsy activity is highly unlikely to present the same risks as ongoing production of an animal or horticultural product that has repeat exposure to contamination sources.

Cell culturing occurs in premises more aligned with food businesses in design, construction and operation; Chapter 3 has more direct application. If Chapter 4 were applied to cell-cultured foods, many requirements would not be relevant given the lack of risks often associated with animals and faecal contamination and/or on-farm activities.

4.2 Establishing processing and production requirements

When considering appropriate management measures for cell-cultured quail, FSANZ concluded the measures would also be applicable to other cell-cultured foods and provide an approach for safe production and processing of cell-cultured foods generally. The similarity of bioreactor food production settings, use of media, and establishing cell line phases would likely pose many of the same risks. Proposed Standard 3.4.1 sets generic production and processing requirements for cell-cultured foods in Australia, including cell-cultured quail (221523-Fib-Quail). The requirement for a food safety program includes measures specific to cell culturing foods, identified in the proposed standard.

Effective control measures in the use of bioreactor production technology are known in the production of therapeutic goods, precision fermentation and HACCP-based production systems of other potentially hazardous foods. Relevant aspects of good cell culturing practice were considered, noting this particular activity would be new to food production and food regulators.

FSANZ considered stakeholder feedback that safety must be assured, the framework provide clarity for this and future cell-cultured foods and measures support industry innovation. The proposed approach aims to deliver a future-ready approach maintaining food safety and supporting industry innovation.

As each stage of cell-cultured food production is considered to have a different risk profile, FSANZ considered production and processing measures for cell lines separate to the cell biomass. Each food (cell line or cell biomass) and each business (cell line supplier and cell culturing food business) are defined and would be subject to the proposed standard. Businesses will be ‘food businesses’ under Chapter 3.

Consequential amendments to definitions in Standard 3.1.1 for *food business* and *food handling* provide certainty Chapter 3 standards apply to this processing activity and the *businesses* producing cell-cultured food.

The individual measures proposed are:

- amending the definition of a food business in Standard 3.1.1 to include a *cell line supplier* and *cell culturing food business*
- a new processing standard, Standard 3.4.1, requiring businesses to have a food safety program complying with Standard 3.2.1 and other requirements

- updating Schedule 27 to include microbiological criteria for cell-cultured food for *Salmonella* spp. and *L. monocytogenes* (detailed further in section 4.3 below).

4.2.1 Regulatory measures under Standard 3.4.1: cell line supplier

A cell line supplier is defined as a business, enterprise or activity that involves both of the following:

(a) sourcing cells for use in creating a cell line that will be used to produce cell-cultured food

(b) creating a cell line for use in cell-cultured food production.

Food safety program

A cell line supplier must have a food safety program covering activities associated with sourcing of cells, development of cell lines and cell banking. These activities are *food handling*. Their system must ensure adequate calibration, cleaning and sterilisation of equipment used for cell culturing.

This measure manages the risk microbiological hazards may contaminate cells if taken from diseased animals, or during the isolation and subsequent processes to develop a cell line and the resulting cell bank. The processes in a food safety program must include handling of cells, adding media components, expanding cell numbers and harvesting for cell banking (with addition of components such as cryoprotectants for freezing and storage of cell lines).

Inputs management

A cell line supplier must ensure inputs do not make cell-cultured food unsafe or unsuitable.

Inputs such as anti-microbials, media and cryoprotectants are used in the development and storage of cell lines. The microbiological safety assessment concluded these inputs must be assessed for food safety, as inputs such as antibiotics or animal-derived media can be a source of contamination of cell banks and the resulting cell-cultured food.

Traceability

A cell line supplier must have a traceability system that can identify cells and trace them back to the donor animal source, and can trace forward to identify to whom that cell line was sold or supplied.

This enables trace back through the supply chain to the donor animal/source if a food safety issue was identified in a cell-cultured food. It supports identifying the cause and taking preventative measures to avoid a re-occurrence of sourcing contaminated cells.

4.2.2 Regulatory measures under Standard 3.4.1: cell culturing food business

A cell culturing food business is defined as a business, enterprise or activity that undertakes cell proliferation to produce a cell-cultured food.

Food safety program

A cell culturing food business must have a food safety program covering processes for culturing cells for food use.

The microbiological safety assessment concluded there is a risk of microbiological contamination at each step of cell proliferation, which involves a series of steps increasing cell density/volume moving from flasks to seeding of bioreactors. Cell harvest (extraction

from bioreactor) and subsequent handling of the cell biomass poses the greatest risk of microbial contamination.

Contamination may be detected by changes in pH, turbidity, carbon dioxide concentration or other parameters in the bioreactor. These parameters and any corrective actions to be taken when they indicate loss of process control should be documented in the food safety program. This aspect of food production may be new to food businesses and regulators. To date there is limited data published to support establishing clear indicators of hygiene control. For these reasons, FSANZ is explicit a food safety program must address these unique aspects of cell culturing.

Inputs management

A cell culturing food business must ensure inputs do not make cell-cultured foods unsafe or unsuitable.

Inputs include basal media, media additives, growth factors, cryoprotectant and cleaning agents. The microbiological safety assessment concluded inputs must be assessed for food safety (and allergenicity) risks as they are a potential source of contamination of the cell biomass.

FSANZ-assessed cell line

A cell culturing food business must only use a cell line assessed by FSANZ.

As this is an emerging sector and new food with only one cell line assessed to date (quail cell line, 221523-Fib-Quail under A1269), FSANZ will continue to assess each line on a case-by-case basis.

Cell lines can be a source of contamination affecting the safety of the final cell-cultured food. Only assessed cell lines will have been evaluated for the potential for allergenicity or microbiological contamination. This will support preventing the presence of allergens and viruses and *Mycoplasma* spp. infections at cell expansion stage.

The cell line is also an identity marker for what cell-cultured food was assessed and considered safe for entry into the human food supply.

Cell culturing food business – temperature control

A cell culturing food business must ensure temperature control of the extracted cell biomass consistent with it being a potentially hazardous food under Standard 3.2.2.

The microbiological safety assessment concluded nutrient and water availability and neutral pH of the residual growth medium will support growth of most bacterial species if present in the cell biomass post-harvest. Temperature control of the biomass once harvested will be the key limiting factor for most foodborne bacterial pathogens.

Cell culturing food business – traceability

A cell culturing food business must have a traceability system that can identify cells and trace them back to the cell line supplier and can trace forward to identify to whom that cell-cultured food (or cell biomass) was sold or supplied.

This enables trace back through the supply chain to the donor animal/source if a food safety issue was identified in a cell-cultured food. It supports identifying the cause and taking preventative measures to avoid a re-occurrence of sourcing contaminated cells.

4.2.3 Regulatory measures – conclusions

The proposed approach was designed to be the minimal regulation needed to achieve appropriate food safety outcomes for processing cell-cultured food. The importance of maintaining a sterile environment from cell selection through to harvesting the cell biomass from a bioreactor has been reinforced in FAO/WHO guidance; without it, growth of microorganisms would readily occur. The only means of minimising this risk is for businesses producing cell-cultured foods to implement HACCP-based systems supported by pre-requisite programs such as GMP, GHP and, unique to this food type, GCCP. FSANZ notes GCCP is widely used to safely produce therapeutic products in bioreactors.

In developing a general standard applying to all businesses culturing cells for food, FSANZ considers this supports the production and supply of safe food. It also provides regulatory clarity and certainty for this emerging sector by permitting the sale of cell-cultured foods.

Cell line suppliers already exist, having previously supplied cell lines for non-food purposes. As many cell bank collection facilities already operate under GCCP and the proposed standard incorporates relevant parts of GCCP within a food safety program, minor changes may be needed to amend their system if supplying cell lines for food production purposes.

Cell-cultured food is a newly emerging food type, with only a few countries approving it for human consumption. Given the lack of consumption history in Australia and the limited scientific data available, FSANZ will continue to require pre-market assessment.

4.3 Microbiological criteria

The applicant proposed several microbiological criteria which, under a novel food application, would normally be included as specifications in Schedule 3 (refer to SD1). FSANZ's proposed regulatory measures do not include the applicant's microbiological specifications in Schedule 3. Instead, FSANZ considers it is more appropriate to include *food safety* microbiological criteria in Schedule 27 and *indicators* of hygiene control in the *Compendium of Microbiological Criteria for Food*.

While Schedule 27 criteria are mandatory, criteria in the Compendium are guidance. It is up to a food business to identify which hygiene indicators are relevant to monitor their operations based on each process-product combination.

4.3.1 Setting microbiological criteria

Setting microbiological criteria in different parts of the Code or in supporting guidance is based on delivering different outcomes:

- *Schedule 3 specifications* are identity and purity parameters. They apply at one point in time and typically to the final product/ingredient (i.e. an end-product). To date, criteria in Schedule 3 have typically been for foods that are highly purified, well characterised, single compound and shelf-stable ingredients used in small amounts in a final food. In the context of this application, the end product is the quail cell biomass.

  FSANZ considers end product specifications in Schedule 3 for a cell-cultured food would not provide for adequate management of microbiological hazards as best practice is to manage microbial hazards using a systems-based approach.

- *Schedule 27 microbiological criteria* are focussed on pathogens in a food not further treated (i.e. ready-to-eat) and if present, would cause illness to the consumer. Criteria include: minimum number of samples of food to be tested (n); number (c) permitted to

exceed minimum permitted detections (m); and maximum detection limit (M) (e.g. minimum sample size (n) of 5, c = 0 with a maximum limit of not detected in 25 g).

Consistent with the International Committee on Microbiological Specifications for Foods (e.g. ICMSF 2011 Microorganisms in Foods 8), this 'follows a risk-based approach to verify food lot acceptance, using sampling plans related to the 15 cases for proportional management stringency'. The criteria provide for statistical robustness for confidence in the safety of a food lot that takes into consideration heterogeneous distribution of contamination and that an unsafe lot will be rejected with 95% probability.

- The FSANZ *Compendium of Microbiological Criteria for Food* contains criteria typically used to monitor quality and hygiene control rather than safety *per se*. Such criteria include those for *E. coli*, Enterobacteriaceae, coliforms, SPC and coagulase-positive staphylococci. As indicators of process control, they are typically identified in guidance material such as the Compendium rather than in the Code. The Compendium contains a chapter on environmental monitoring, with a specific section on *L. monocytogenes*.

  A food business should identify which hygiene indicators are important for monitoring their operations based on each process-product combination.

4.3.2 The applicant's proposed microbiological specifications

The applicant's specifications in Table 5 of SD1, section 4.4.1, included both food safety and hygiene microbiological criteria: for *Salmonella* spp., standard plate count, *E. coli* and Enterobacteriaceae.

FSANZ agrees with including a *food safety* criteria for *Salmonella* spp. and also identified *L. monocytogenes* as a post-harvest hazard in cell-cultured food. *Listeria* spp. are known to occur in food processing environments and can contaminate food through contact. The other specifications were for microorganisms typically used as hygiene criteria to check process control. FSANZ agrees they are appropriate for verifying the process is under control and to trigger corrective action where results indicate a problem.

FSANZ notes the applicant has a HACCP-based approach which includes their monitoring program. The applicant advised their environmental monitoring program includes *L. monocytogenes* and coagulase-positive staphylococci.

FSANZ considers it important to identify in Schedule 27 criteria for the two pathogens as, if present (and food is consumed as is), the food is unsafe for human consumption. This is not a monitoring criteria *per se* but a safety criteria for a lot of food.

FSANZ also proposes the applicant include monitoring for two additional process hygiene parameters: for coagulase-positive staphylococci and for yeasts and mould. These are not mandatory specifications; like other indicators of hygiene and quality control, they are guidance.

4.3.3 Microbiological criteria for cell-cultured food

In setting criteria, FSANZ considered which microbial hazards could occur during processing of cell-cultured food, including from the food (cell line and cells), inputs, environment and food handlers.

Food safety criteria – standards

Cell-cultured quail is a new food with limited history of commercial food production or human consumption, with no assessed risk mitigation step and it readily supports microbial growth. FSANZ's conclusion is to include criteria for cell-cultured food in Schedule 27 for *Salmonella* spp. and *L. monocytogenes* (Table 1).

This amendment to Schedule 27 means all cell culturing food businesses, including the applicant, must ensure a harvested cell biomass complies with these criteria.

Table 1: Proposed mandatory food safety criteria for harvested cell biomass (Schedule 27)

Parameter tested	Proposed microbiological criteria[1]
Salmonella	n=5, c=0, m = not detected in 25g
Listeria monocytogenes	n=5, c=0, m = not detected in 25g

[1] n=number of sample units; c= number of sample units permitted to exceed m; m = the acceptable microbiological limit

The reasons for establishing these criteria are:

- The safety assessment concluded *L. monocytogenes* and *Salmonella* spp. in food and the food production environment to be significant hazards for cell-cultured food, particularly during cell harvest and onwards through post-harvest processing; this is consistent for many food business producing potentially hazardous foods.
- There is limited history of use and thus evidence on the persistence of foodborne pathogens, viral or bacterial, in cell-cultured foods. No data could be found in literature on microbiological growth potential in or the stability of cell-cultured food. However by its very nature, a cell culture is designed for growing cells, including microbial cells.
- Microbiological data on the shelf-life of harvested cells (which is confidential commercial information) identified the biomass to be a potentially hazardous food; that is, it supported microbial growth. As more cell-cultured foods are developed there will be more data, which may support revising the criteria.
- Microbiological specifications for cell-cultured food should be part of a food safety management system, with controls of hazards occurring at each relevant step. A specification in Schedule 3 may place undue focus on end-product testing, which would not provide confidence microbial risks have been managed through-chain or in the cell biomass.
- A treatment step has not been assessed as part of this application (i.e. cooking/further processing). FSANZ was unable to consider downstream risk mitigation. For instance, further processing and cooking would mitigate many of the microbiological risks with cell-cultured food.

The *Compendium of Microbiological Criteria for Food* recommends that food businesses implement a *L. monocytogenes* environmental monitoring program for presence of this food pathogen, to assist with managing this hazard in their processing environment.

Food hygiene criteria – guidance

To support application of the processing standard and provide guidance on monitoring of process hygiene and control of cell-cultured food production, FSANZ will amend the *Compendium of Microbiological Criteria for Food* to include guideline limits as per Table 2. This information will be available to all cell culturing food businesses. These limits take into account knowledge of effective hygiene monitoring and controls in other established food

production systems, as well as the applicant's proposed microbiological specifications for the harvested cell biomass.

These limits are established to support decision making about a food or process, with different consequences to those included in Schedule 27 if the limits are not met.

Table 2: FSANZ proposed process hygiene guideline limits for harvested cell biomass *(Compendium of microbiological criteria for food*)

Parameter tested	Proposed process hygiene guideline limit
Standard plate count	$<10^4$ (cfu/g)
Escherichia coli	<3 (MPN/g)
Enterobacteriaceae	<100 (cfu/g)
Yeasts and moulds	<10 (cfu/g)
Coagulase-positive staphylococci	<100(cfu/g)

As indicated above, including these limits in Schedule 3 is not considered the best approach to managing safety of a potentially hazardous food. Assurance of safety is via a HACCP-based approach that identifies and manages hazards through-chain and verifies effective controls with support of an appropriate monitoring regime.

Submitter feedback

Several submitters considered the applicant's microbiological specifications (Table 5 of SD1 of the 1st CFS) were not sufficient to provide adequate safety assurance of the harvested cell biomass, given its high moisture content and potential to support growth of pathogens. They suggested specifications for *L. monocytogenes* and coagulase-positive staphylococci be included in biomass testing by the applicant. This feedback has been addressed by including a Schedule 27 criteria for *L. monocytogenes* and developing guidance for indicator organisms.

One submitter supported including *L. monocytogenes* testing of the final retail food product. Further processing of the harvested cell biomass into the final food product is not within scope of this application. The microbial hazard assessment was to the point of freezing the harvested cell biomass. Any business further processing the cell biomass would be subject to the food safety standards in Chapter 3 (Standards 3.2.2 and 3.2.3), including validating and verifying the safety of the final food. Additionally, if the final retail food product is a ready-to-eat food, it would need to comply with Standard 1.6.1 and relevant microbiological criteria in Schedule 27, which includes criteria for *L. monocytogenes*.

4.3.4 Specifications conclusion

FSANZ's regulatory measures do not include amending Schedule 3 to include the applicant's proposed microbiological specifications. Instead, FSANZ considers *food safety* microbiological criteria be included in Schedule 27 and *indicators* of hygiene control be added to the *Compendium of Microbiological Criteria for Food*.

Schedule 27 will be amended to include *Salmonella* spp. and *L. monocytogenes* as, if present (and food is consumed as is), the food is unsafe for human consumption. These mandatory criteria apply to all cell-cultured foods including the applicant's cultured quail cells.

Microbiological criteria should be part of a sampling and testing program designed to monitor for hygienic production and safe food, captured within a HACCP plan or food safety system. Every business should establish specifications for their products. However, while these are

useful tools to verify process control they should not be used in isolation to demonstrate food safety.

5 Proposed regulatory framework

FSANZ prepared Standard 3.4.1 on safe production and processing requirements for cell-cultured foods. Several consequential amendments were also prepared to support the new standard.

To implement the proposed regulatory approach:

- Subsection 1.1.2—2(3) would include a new definition ‘for cell-cultured food’.
- Schedule 27 would include microbiological criteria for cell-cultured food for *L. monocytogenes* and *Salmonella* spp.
- Standard 3.1.1 would include an amendment to the definition of a ‘food business’ to include a ‘cell line supplier’ and a ‘cell culturing food business’ as defined by proposed Standard 3.4.1.
- The proposed new Standard 3.4.1 – Food safety requirements for processing of cell-cultured food would be introduced.

As explained this regulatory approach is premised on cells, cell lines and cell biomass when used for food being declared to be a *food* for regulatory purposes.

The effect of these proposed measures will be as follows:

- The production of cell-cultured food in Australia will be subject to food safety production and processing requirements set by Chapter 3 of the Code, including proposed Standard 3.4.1. These requirements will apply to cell line suppliers and cell culturing food businesses whose product is for food use. Both will be a ‘food business’ for the purposes of Chapter 3 of the Code.
- Production of cell lines and cell biomass must be done under a food safety program.

Food manufacturers who use products supplied by cell culturing food businesses will already be subject to Chapter 3 standards as they are food businesses.

Annex 1

Definitions in food safety and hygiene standards, FSANZ Act and Model food provisions (MFP)

Key definitions	Location
5 Meaning of *food* (1) ***Food*** includes: (a) any substance or thing of a kind used, capable of being used, or represented as being for use, for human consumption (whether it is live, raw, prepared or partly prepared); and (b) any substance or thing of a kind used, capable of being used, or represented as being for use, as an ingredient or additive in a substance or thing referred to in paragraph (a); and (c) any substance used in preparing a substance or thing referred to in paragraph (a); and (d) chewing gum or an ingredient or additive in chewing gum, or any substance used in preparing chewing gum; and (e) any substance or thing declared to be a food under a declaration in force under section 6. (It does not matter whether the substance, thing or chewing gum is in a condition fit for human consumption.) (2) However, ***food*** does not include a therapeutic good within the meaning of the *Therapeutic Goods Act 1989*. (3) To avoid doubt, ***food*** may include live animals and plants.	**FSANZ Act** Clause 5 **MFP**, section 3*
A **food business** means a business, enterprise or activity (other than primary food production) that involves – (a) the handling of food intended for sale; or (b) the sale of food; regardless of whether the business, enterprise or activity concerned is of a commercial, charitable or community nature or whether it involves the handling or sale of food on one occasion only.	**Standard 3.1.1** Clause 1 **MFP**, section 4
handling of food includes the making, manufacturing, producing, collecting, extracting, processing, storing, transporting, delivering, preparing, treating, preserving, packing, cooking, thawing, serving or displaying of food.	**Standard 3.1.1** Clause 1 **MFP**, section 3
handling of food includes the producing (including growing, cultivation, picking, harvesting or catching), collecting, extracting, processing, manufacturing, storing, transporting, delivering, preparing, treating, preserving, packing, cooking, thawing, serving or displaying of food.	**Standard 4.1.1** Clause 1
primary food production means the growing, cultivation, picking, harvesting, collection or catching of food, and includes the following – (a) the transportation or delivery of food on, from or between the premises on which it was grown, cultivated, picked, harvested, collected or caught; (b) the packing, treating (for example, washing) or storing of food on the premises on which it was grown, cultivated, picked, harvested, collected or caught; and	**Standard 3.1.1** Clause 1 **MFP**, section 5

Key definitions	Location
(c) any other food production activity that is regulated by or under an Act prescribed by the regulations for the purposes of this definition. However, primary food production does not include – (d) any process involving the substantial transformation of food (for example, manufacturing or canning), regardless of whether the process is carried out on the premises in which the food was grown, cultivated, picked, harvested, collected or caught; or (e) the sale or service of food directly to the public; or (f) any other food production activity prescribed by the regulations under the Act for the purposes of this definition.	
Primary producer and processor definitions are in commodity standards: • **seafood business** means a business, enterprise or activity that involves the primary production of seafood intended for sale. • **poultry producer** means a business, enterprise or activity that involves – (a) growing; or (b) live transporting; of poultry for human consumption. • **poultry processor** means a business, enterprise or activity that involves the processing or transporting of poultry product for human consumption. • **meat producer** means a business, enterprise or activity that involves the growing, supply or transportation of animals for human consumption. • **producer of ready-to-eat meat** means a food business that engages in the – (a) making, manufacturing, producing, extracting, processing, preparing, treating, preserving, packing, cooking, thawing or handling of ready-to-eat meat; or (b) handling of ready-to-eat meat for retail sale. • **dairy primary production business** means a business, enterprise or activity that involves dairy primary production. • **dairy processing business** means a business, enterprise or activity that involves dairy processing.	**Standard 4.2.1** Clause 2 **Standard 4.2.2** Clause 1 **Standard 4.2.3** Clause 2 Clause 3 **Standard 4.2.4** Clause 1 **Standard 4.2.5** Clause 2

Key definitions	Location
• **egg producer** means a business, enterprise or activity that involves the production of eggs, whether or not the business grades, packs, washes, candles or assesses for cracks, oils, pulps for supply to the processor for pasteurisation or stores or transports eggs or egg pulp. • **egg processor** means a business, enterprise or activity that involves – (a) pulping, separating, grading, packing, washing, candling, assessing for cracks or oiling eggs received from an egg producer; or (b) storing or transporting eggs in association with any of the activities in paragraph (a); or (c) processing egg product under clause 21 of this Standard. • A **sprout processor** means a business, enterprise or activity that involves any or all of the following for producing seed sprouts – (a) decontamination of seed or seed sprouts; (b) soaking of seed; (c) germination or growth of seed; (d) harvest of seed sprouts; or (e) washing, drying or packing of seed sprouts. • **primary horticulture producer** means a business, enterprise or activity that involves the growing and/or harvesting of berries. • **primary horticulture processor** means a business, enterprise or activity that involves one or more of the following activities in relation to berries that have been harvested: (a) washing; (b) trimming; (c) sorting; (d) sanitising; (e) storing; (f) combining harvested berries; (g) packing; and (h) transport between primary processing premises.	**Standard 4.2.6** Clause 4 **Standards 4.2.7, 4.2.8, 4.2.9** Clause 2

* Model food provisions clause 3 (1) (e) differs to the FSANZ Act: any substance or thing declared to be a food under a declaration in force under section 3B of the Australia New Zealand Food Authority Act 1991 of the Commonwealth [and prescribed by the regulations for the purposes of this paragraph]