Food and Agriculture Organization of the United Nations

PRECISION FERMENTATION

WITH A FOCUS ON FOOD SAFETY

PRECISION FERMENTATION
WITH A FOCUS ON FOOD SAFETY

By
Mark Sturme, Jan Pieter van der Berg and Gijs Kleter
Wageningen Food Safety Research, the Netherlands

Food and Agriculture Organization of the United Nations
Rome, 2025

Sturme, M., van der Berg J.P., and Kleter, G., 2025. *Precision fermentation – With a focus on food safety*. Rome, FAO. https://doi.org/10.4060/cd4448en

ISBN: 978-92-5-139643-8

CONTENTS

Figures

Tables

ACKNOWLEDGEMENTS

The Food and Agriculture Organization of the United Nations (FAO) would like to express its appreciation to the many people who provided advice and guidance during the preparation of this document. It was prepared for FAO as a technical background for the relevant expert consultations, and authored by Mark Sturme, Jan Pieter van der Berg and Gijs Kleter, Wageningen Food Safety Research, Kingdom of the Netherlands. The development process of the document was coordinated by Masami Takeuchi (FAO) under the overall guidance of Markus Lipp (FAO). Technical reviews were conducted by various international experts, namely Marija Banovic (Denmark), Kris Blanchard (Chile), Arnout Fischer (Kingdom of the Netherlands), Olivier Fortin (Canada), Andrea Germini (European Food Safety Authority, EFSA), Chee-Seng Hee (China), Stephanie Hice (United States of America), Lisa Kelly (Australia), Teng Yong Low (Singapore), Fei Luo (Canada), Li Ning (Belgium), Estefania Noriega Fernandez (EFSA), Katie Overbey (United States of America), Gabriela Precup (EFSA), Neil Strand (Canada) and Kevin Verstrepen (Belgium). For chapter 5, members from the FAO's informal Technical Working Group (TWG) have contributed valuable information from respective countries and jurisdictions, and their inputs are herewith gratefully acknowledged. Technical and editorial inputs were provided by various FAO colleagues including Vittorio Fattori, William Hallman, Phillis Ochieng and Raffaella Tavelli and technical editing was provided by Agnieszka Gratza.

ABBREVIATIONS

AFPs	antifreeze proteins
BLG	bovine beta-lactoglobulin
CABI	Centre for Agriculture and Biosciences International
CFIA	Canadian Food Inspection Agency
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization of the United Nations
FSANZ	Food Standards Australia New Zealand
GM	genetically modified
GMO	genetically modified organisms
GRAS	generally regarded as safe
HiMOs	human-identical milk oligosaccharides
LegH	leghemoglobin
LNnT	lacto-N-neotetraose
NGTs	new genomic techniques
OECD	Organisation for Economic Co-operation and Development
PTM	post-translational modification
PF	precision fermentation
PBFs	plant-based food
QPS	qualified presumption of safety
SFA	Singapore Food Agency
TWG	Technical Working Group
USDA	United States Department of Agriculture
US FDA	United States Food and Drug Administration
WOAH	World Organisation for Animal Health
WoS	Web of Science
WHO	World Health Organization

EXECUTIVE SUMMARY

The term “precision fermentation” is often used to describe specific fermentation processes for a targeted and efficient production of food ingredients. The term is increasingly used for the production of compounds traditionally sourced from animals. While such processes have been around for a while, the term precision fermentation is relatively new. However, there is no internationally agreed definition, and this may hamper communication among those wishing to discuss the processes of precision fermentation, particularly the food safety competent authorities.

A wide variety of food ingredients can be produced through precision fermentation. Identifying the general characteristics of precision fermentation production processes and the potential associated hazards can be a first useful step for competent authorities to initiate regulatory actions. To this end, precision fermentation production processes have been studied through an in-depth literature synthesis and existing regulatory frameworks applicable to precision fermentation derived food products were collected from various jurisdictions.

Although the definitions vary, the study revealed that precision fermentation can be well explained by a generic production process. It was also understood that many countries have been taking a similar regulatory approach to ensure the food safety of products derived from precision fermentation. The document can serve as a reference point for countries that would like to consider adopting relevant food safety regulatory approaches for precision fermentation derived food products, from reflecting on the appropriate definitions to identifying the needs for food safety assessments and other necessary regulatory actions.

Keywords: precision fermentation, food safety, terminology, definition, standard, technology, innovation, assessment, production process, risk analysis, risk management, regulatory frameworks

1. INTRODUCTION

1.1 Background

1.1.1 Overview

In the pursuit of more sustainable and cost-effective ways of producing food and food ingredients, there has been a gained interest over the last years in the use of fermentation-based technologies (Carter *et al*., 2022). Fermentation-based technologies utilize various types of microorganisms, including bacteria, yeasts, filamentous fungi and microalgae, to convert organic substrates into food products (Terefe, 2021). These products may be either consumed as such or used as food ingredients or additives. Fermentation has been employed for millennia in the production of various foods and beverages, such as fermented dairy, vegetables, meat products, alcoholic beverages and bread. Specific examples include yoghurt, cheese, kefir, miso, kimchi, beer and vinegar. In traditional fermentation processes, fermentation occurs through microorganisms either by the addition of starter cultures or microorganisms naturally present in the substrate, food product or the production environment (Cuamatzin-García *et al*., 2022; Tamang, Watanabe and Holzapfel, 2016).

Fermentation is now increasingly applied for producing large quantities of microbial biomass that can be used as a whole, as a food product or further processed to isolate specific compounds that serve as food ingredients such as lipids, proteins and pigments. The production of microbial protein, sometimes referred to as single cell protein, from biomass fermentation is a particularly fast-growing area (Nyyssölä *et al*., 2022). Recent developments in this field include gas fermentation, where microorganisms are cultured on gaseous substrates, often from flue gases (Woern and Grossmann, 2023).

Recently, there has been a significant increase in the application of fermentation technologies for the targeted production of compounds that are traditionally sourced from animals (Teng *et al*., 2021) and plants (Perrot *et al*., 2024). These include animal-derived proteins, such as egg white protein (ovalbumin), milk proteins (whey, caseins, lactoferrin, beta-lactoglobulin), muscle proteins (collagen and gelatin), human-identical milk oligosaccharides (HiMOs), animal fa and bio-identical honey (Carter *et al*., 2022). The production of non-animal derived biological substances, to be used as media components for cell-based food production, especially growth factors, is another application of this type of fermentation, one that is expected to experience growth in the future (Singh *et al*., 2022, Wood *et al*., 2023).

1.1.2 Nomenclature issues

While it is uncertain when the term “precision fermentation” was coined, it appears to have featured in a scientific article as early as 2015 (Barton *et al*., 2015) and a specific definition has been provided by RethinkX, a Silicon Valley- and London-based global think tank (Tubb and Seba, 2019). However, this is not an internationally harmonized term and other terminologies are also being used to describe similar types of fermentation technologies. Although the term “precision fermentation” may be relatively new, the process itself has been used since the 1980s. For example, the technologies have been employed for decades to produce protein hormones such as insulin and erythropoietin (Zhang, Sun and Ma, 2017) or food-processing enzymes such as chymosin (rennin) in *Escherichia coli* (Flamm, 1991).

The perception of novelty that precision fermentation brings may stem from the idea of using the latest genetic tools targeting at an efficient production of food products, ingredients and additives. It has generated new prospect for future food production systems that will not need to heavily rely on current and conventional agricultural practices, such as slaughtering animals. In this context, precision fermentation contributes to a larger development, often referred to as cellular agriculture, which focuses on the cell-based production of food and food ingredients (FAO and WHO, 2023). Within the scope of cellular agriculture, precision fermentation is expected to play an important role in future agrifood systems, particularly in contributing to sustainable food security in the context of climate change or in regions where agricultural land use is limited (Soice and Johnston, 2021).

A multitude of start-up companies has emerged in the area of precision fermentation, focusing on various food ingredients such as milk and egg proteins (Carter *et al*., 2022). Other functional ingredients to increasingly attract interest include HiMOs for infant nutrition, heme compounds and lipids to enhance flavours in meat analogues and replacers. In the United States of America and in Hong Kong, whey protein (beta-lactoglobulin) produced through precision fermentation has already been commercialized for use in products like ice creams and baked products. Similarly, India, Israel and Singapore have approved the use of milk proteins derived from precision fermentation as food ingredients (Carter *et al*., 2022; Lyubomirova, 2023). In addition, soy leghemoglobin derived from precision fermentation has been commercialized in Australia, Canada, New Zealand, Singapore and the United States of America, as a meat flavour additive (Reyes *et al*., 2023).

1.1.3 Production process

The perception of novelty with the term “precision fermentation” may lead various regulatory authorities to question if existing regulatory frameworks are adequate for assuring food safety aspects of food products derived through precision fermentation, if there are any new aspects of the precision fermentation processes and products that require adaptation of existing regulations or if development of specific regulations for precision fermentation derived products is needed. These questions can be carefully addressed through a comprehensive risk analysis paradigm. The formal risk assessment begins with the hazard identification process, which presupposes a full understanding of the complete production process that precision fermentation derived products undergo. Precision fermentation, in general, makes use of established fermentation processes, however, the use of various production hosts, scale of production, processing modes and type of food applications can differ from established food fermentation processes.

1.1.4 Regulatory frameworks

Since precision fermentation-derived food products have been commercialized and marketed in some countries, regulatory authorities in other countries may benefit from the experience that these countries have gained through their regulatory processes. For example, in some countries and jurisdictions, pre-market approval of precision fermentation derived foods, including a food safety assessment, is required. In some countries, relevant labelling requirements apply, for the purpose of distinguishing the precision fermentation derived products, or for the purpose of allergen indications.

1.2 Scope

It is important for food safety competent authorities to use appropriate, clear and consistent terminology. However, there is currently no internationally agreed definition for the term "precision fermentation". Drawing on a fact-finding study, **chapter 3** illustrates the diversity in terminologies and definitions for precision fermentation in use within different sectors (research/academia, private sector/industry, public sector/government and media). A systematic inventory was conducted based on the available scientific literature as well as non-scientific reports and public communications to identify and describe issues associated with the use of specific terms. The discussions are specifically scoped into food applications of precision fermentation.

The study rests on a systematic review and the document does not include any authors' opinions. The aim of the paper is not to officially define the relevant terms, but to collect existing terms and definitions along with the attributed analyses, so that the subject-matter experts and/or policy makers can use the synthesis as a reference to help them make informed decisions.

Taking the context and the potential needs of food safety competent authorities into account, **chapter 4** focuses on identifying and explaining the generic model of precision fermentation production processes. For the competent authorities, it is important to have a clear understanding of such generic production processes in order to identify associated potential hazards. The available scientific literature and publicly available documents were analysed to illustrate the generic production processes in precision fermentation and the potential associated food safety hazards and possible consumer concerns.

Chapter 5 describes the current status, as of April 2024, on regulations and regulatory activities that apply to precision fermentation-derived food products in different countries worldwide, as well as ongoing developments for adapting these regulations. The chapter was developed based on the analysis conducted on the relevant regulatory frameworks and requirements for food safety assessments, marketing and labelling that apply to precision fermentation-derived food products in different countries and jurisdictions. The document aims to share practical experiences, good practices and lessons learned from various experienced countries so that other food safety competent authorities, particularly those in low- and middle-income countries (LMICs), are able to refer to it when implementing or adapting relevant regulatory activities to ensure the safety of precision fermentation derived food products within their regulatory frameworks.

2. METHODOLOGIES

2.1 Systematic literature reviews

A systematic literature search strategy for the collection of data was defined, focusing on search strings related to nomenclature issues, production processes and regulatory frameworks relevant to precision fermentation, in combination with search strings related to precision fermentation. The strategy covers the collection of data from both scientific literature and from “grey” sources. The latter include national, supernational and regional competent authorities, international organizations, the private sector, academia, research institutions, civil societies and non-governmental organizations, among other stakeholders. Information from grey sources was collected from publicly available websites, white papers, reports, reviews and guidelines, as well as Google Advanced Search. Data from scientific literature were collected through the databases including Web of Science, Scopus and Centre for Agriculture and Bioscience International (CABI), as well as Google Scholar. Abstracts and records retrieved from databases were screened for relevance in an initial evaluation before the retrieval of full references and an in-depth screening. Further details of the strategy can be found in **Annex 1**. The literature search for sources was concluded on 5 October 2023.

2.2 Consultations with regulators

In addition to the systematic reviews, the content of **chapter 4** was informed by online consultations with regulatory authorities from different countries around the world conducted in the context of FAO’s informal Technical Working Group (TWG) on cell-based foods and precision fermentation. These consultations aimed to prepare an inventory of the regulatory frameworks in those countries that apply to precision fermentation derived food products, and to enquire whether precision fermentation-specific regulations exist or are being developed.

3. NOMENCLATURE ISSUES

3.1 Precision fermentation definitions

An overview of definitions of precision fermentation, as retrieved from scientific and grey literature, indicates a diverse array of descriptions for precision fermentation, yet it is possible to identify several key common denominators (**Table 1**). An important element of precision fermentation mentioned in many articles is the use of genetic tools, including genetic modification (GM) via recombinant DNA methods and gene editing for the specific production of the non-native target molecules, which is also referred to as heterologous production.

Box 1. Case study – Definition and regulatory approaches: An insight from Canada

Although the production of non-native molecules can potentially provide an important element for defining "precision fermentation", integrating the concept of genetic modification as a component of its definition may result in differing regulatory approaches to nearly identical products and it may make the product classification meaningless. For example, two nearly identical products may be classified differently based solely on their respective production processes.

- Overexpression of native *Trichoderma reesei*'s xylanase by introduction of additional gene copies in the native host *Trichoderma reesei*.
- Expression of native *Trichoderma reesei*'s xylanase in the non-native (heterologous) host *Bacillus subtilis*.

Policymakers at the national level may wish to take this aspect into consideration when developing definitions about products derived from precision fermentation.

Another main characteristic is the use of microorganisms as production hosts, also named (microbial) cell factories, and their controlled cultivation, often in bioreactors. These can be prokaryotic microorganisms (bacteria) or eukaryotic microorganisms (yeast, filamentous fungi, microalgae). Fermentation using natural microbial isolates or strains is often referred to as traditional fermentation, although the production process may have been scaled up to industrial size. While the vast majority of precision fermentation applications use genetic tools, "precision fermentation" to some may simply mean the production of specific and "precise" compounds through fermentation, which does not necessarily imply the use of any particular genetic tools, such as genetic modifications and gene editing. In fact, some companies active in the field of precision fermentation specifically do not employ genetic modification techniques. While the described precision fermentation developments make use of a microbial production host, non-microbial cells such as mammalian cell lines or insect cells might also be used for the production of specific food components (Markova, Shaw and Reynolds, 2022).

The specific applications or end-products that precision fermentation technologies are used for are rather diverse, but a shared focus in most articles is on the production of foods, food additives and food ingredients. However, it is worth noting that the production of non-food compounds (e.g. insulin) is also mentioned in a limited number of products derived from precision fermentation. The term precision fermentation is commonly used to describe two production processes.

(1) The production of specific proteins that are normally derived from animals. Examples of these are collagen, milk proteins, egg proteins, as well as enzymes such as rennin (chymosin) to make cheese. Precision fermentation is therefore often described as an "animal-free" production system for animal-specific molecules.

(2) The production of a wider range of products, including vitamins, pigments, lipids (fatty acids) and carbohydrates (oligosaccharides). Most of these products were traditionally derived from animals or plants, but they can now be produced using microorganisms.

These precision fermentation-derived products are often purified from the fermentation broth or fractionated from the microbial biomass, for further use as food additives or ingredients. The final degree of purity may differ depending on the food applications, but the final products would be free of microbial cells and, in most cases, also free of recombinant DNA.

Box 2. Case study – Precision fermentation described in plain language in Canada

In Canada, "genetic modification" means "to change the heritable traits of a plant, animal or microorganism by means of intentional manipulation" (Health Canada, 2023). As per this legal definition, adaptative laboratory evolution, protoplast fusion and mutagenesis are considered genetic modifications. As precision fermentation uses a wide range of existing and well-established technologies to generate food ingredients, products derived from precision fermentation can be described in Canada as "substances derived from genetically modified microorganisms obtained through means of biotechnologies". This simple terminology with the plain language definition considers the products listed in the **Table 1** and **Table 2**, and it does not consider how the production organism was developed.

Box 3. Case study – Need for a regulatory definition raised by stakeholders at the meeting organized by the European Food Safety Authority (EFSA)

There is no legal definition for precision fermentation in the European Union. Therefore, for the purpose of discussing food safety aspects related to precision fermentation at EFSA's Scientific Colloquium 27 on "Cell culture-derived foods and food ingredients", precision fermentation was referred as to "the use of engineered microbial cell factories in the production of food ingredients" (European Food Safety Authority *et al*., 2024). However, stakeholders at the colloquium suggested that the technology might go beyond the use of engineered microorganisms to include "precisely designed bioprocesses" and they emphasized the need for a regulatory definition of precision fermentation.

Source: EFSA (European Food Safety Authority), Afonso, A.L., Gelbmann, W., Germini, A., Fernández, E.N., Parrino, L., Precup, G. and Ververis, E. 2024. EFSA Scientific Colloquium 27: Cell Culture-Derived Foods and Food Ingredients. *EFSA Supporting Publications*, 21(3): 8664E. https://doi.org/10.2903/sp.efsa.2024.EN-8664

In general, descriptions of precision fermentation used by the industry and advocacy groups include similar elements to those found in scientific articles (**Table 2**). However, some descriptions of precision fermentation mention not only microorganisms as production hosts but also insect or plant cells or emphasize the production of true-to-nature ingredients. Aside from the production of food ingredients, the production of textile materials (e.g. silk) using precision fermentation is also mentioned.

Box 4. Case study – Commercial definition of precision fermentation

The definition of precision fermentation used by RethinkX is: "fermentation plus precision biology – a process that allows us to program microorganisms to produce almost any complex organic molecule." Herein, precision biology they define as: "the coming together of modern information technologies like artificial intelligence (AI), machine learning, and the cloud, with modern biotechnologies like genetic engineering, synthetic biology, metabolic engineering, systems biology, bioinformatics, and computational biology" (Tubb and Seba, 2019). This definition of precision fermentation is broader than what other scientific literature currently indicates. In addition, it mentions several other technologies, including AI and machine learning, that are not solely focused on the biological and molecular aspects of precision fermentation.

Table 1. Definitions of precision fermentation retrieved from scientific literature

Technology and application descriptions are paraphrased sentences from articles and key elements are shown in **bold**. Quotes are shown in quotation marks

Name and definition	Application/products	Synonyms mentioned	Substantiation for GM use	Reference
Precision fermentation **Engineered (recombinant)** food grade **microorganisms and fermentation technologies**	…for production of **specific organic molecules such as food proteins**	Cellular agriculture	"…using **engineered (recombinant)** food grade microorganisms"	(Aro *et al.*, 2023)
Precision fermentation **Synthetic biology methods used to program microbes** which are used **as cell factories…**	…to produce **ingredients for the food and pharmaceutical industries**	Bio-manufacturing, recombinant protein production	"The choice of the **recombinant host microorganism** and strain engineering present the initial challenge that determines the possibilities for constructing microbes to express and produce the target molecules…"	(Augustin *et al.*, 2023)
Precision fermentation Using **genetically engineered microorganisms** to produce a variety of food ingredients **via fermentation** …It is a transition from a traditional fermentation technology (for preservation of primary produce) to a **more sophisticated precision fermentation technology (for sustainable production of food ingredients at the industry scale)**	Production of a variety of **food ingredients** via fermentation **that are otherwise conventionally sourced from animals and plants**	N/A	"It uses **genetically engineered** microorganisms to produce…"	(Banovic and Grunert, 2023)

Table 1. (continued)

Name and definition	Application/products	Synonyms mentioned	Substantiation for GM use	Reference
Cellular agriculture (also referred to as precision fermentation) Cellular agriculture is a **field in bio-based economy** that focuses on the production of agriculture products, proteins, fats and meat tissue **from cell cultures using a combination of molecular biology and biotechnology.**	Production of **agriculture products, proteins, fats and meat tissue** from cell cultures	Microbial production	"Although the term cellular agriculture is relatively new, the concept of using **genetically engineered microbes** to produce food is not new."	(Behm *et al*., 2022)
Precision fermentation The use of **microorganisms grown in fermenters** to produce proteins. In recent years, this technology – **also known as recombinant protein technology** – has been used to produce animal-identical food proteins…	Production of **animal-identical food proteins** (e.g., gelatin, milk proteins or egg proteins).	Recombinant protein technology	"…**modified genes (recombinant DNA)** are inserted into fast-growing host organisms such as bacteria, fungi or yeasts so that the desired proteins are produced by these organisms."	(Bijl and Keppler, 2023)
Precision fermentation **Advanced fermentation system** due to the **precise** production of specific molecules under **very controlled manufacturing processes to maximize the yield** of desired products and **minimize cost.**	Precise production of **specific molecules**	N/A	"With the debate around the use of **genetically modified microorganisms (GMO)** still ongoing, we discuss **gene editing** which is likely to assuage some of those safety concerns."	(Boukid *et al*., 2023a)
Precision fermentation **Metabolic engineering tools to serve as** a factory of ingredients such as protein, pigments, vitamins, and fats **to upgrade the quality of plant-based alternatives.**	Production of **ingredients such as protein, pigments, vitamins, and fats**	N/A	"However, its main challenges include consumer perception of **genetically engineered products**, scalability, and ethical and regulatory concerns."	(Boukid *et al*., 2023b)
Precision fermentation **Microorganisms (such as yeast) can be genetically** programmed to express specific proteins, then mixed with nutrients and sugars in a **bioreactor** until those proteins are produced.	Express **specific proteins**	Cellular agriculture	"The production of this animal-free dairy is an extension of well-established processes of precision fermentation that have been used to **create products such as synthetic insulin** for diabetic treatment and **genetically engineered rennet** for mainstream cheese production"	(Broad *et al*., 2022)

Table 1. (continued)

Name and definition	Application/products	Synonyms mentioned	Substantiation for GM use	Reference
Precision fermentation	Production of **recombinant (food) proteins with improved functionality**	N/A	Cysteine (or possibly other amino acid) exchanges can be used as a suitable tool to achieve these structural characteristics, making more efficient use of the **recombinant protein** as a food ingredient.	(Brune *et al.*, 2023)
Precision fermentation	Production of **high-value functional food ingredients**, e.g. enzymes, lipids, carbohydrates, vitamins, flavouring, colourants, antioxidants, and preservatives	Metabolic engineering	"…'precision fermentation' is practically synonymous with **metabolic engineering**, which involves **genetic manipulation** of microbial chassis, often towards non-native products."	(Chai *et al.*, 2022)
Precision fermentation	Production of **desired products, e.g. higher-value chemicals, such as vitamin B12 and acetoin**	Synthetic food production	"Substantial progress in the **biotechnology** industry has been made in recent years toward using acetate as a platform microbial substrate. Many companies have already successfully brought fermentation-derived proteins to market using sugar and starch feedstocks…"	(Crandall *et al.*, 2023)
Precision fermentation	Synthesize **animal-free dairy proteins to create milk**	Cultured animal products	[From supplementary data] "Cow's milk has also been created using a fermentation process similar to the production of beer or soy sauce. **DNA is extracted from cow's milk and inserted into yeast cells,** the yeast is fed sugar and converts into milk"	(Crawshaw and Piazza, 2023)
Precision fermentation	**Focus on measuring metabolites,** either from recombinant protein production or the production of industrially relevant chemicals	Recombinant protein production	"…we provide examples mainly from E. coli and CHO cell cultivations used for **recombinant protein** production as these systems are the most studied"	(Dodia *et al.*, 2023)
Precision cellular agriculture	**Recombinant protein** expression (such as **enzyme**)	Recombinant protein expression	"This review will focus on **recombinant proteins** used in dairy and egg products, meat-associated proteins used in scaffolding cultured meat, high-value antifreeze proteins (AFPs), and sweet proteins"	(Dupuis *et al.*, 2023)

Table 1. (continued)

Name and definition	Application/products	Synonyms mentioned	Substantiation for GM use	Reference
Precision fermentation	Production of **target ingredients or safe food biomaterials**	Cell factories	"Precision fermentation is strongly related to **genetically modified organisms (GMO)** in creating optimized cell factories able to produce specific molecules."	(Hassoun *et al.*, 2022)
Precision fermentation	**modified β-lactoglobulin**	N/A	"…mutations can be induced in **recombinant food proteins** through precision fermentation to increase their tendency to form nanofibrils (possibly under less extreme conditions). In turn, this would lead to more efficient use of costly **recombinant proteins** as a food ingredient."	(Hoppenreijs *et al.*, 2023)
Precision fermentation	Production of **food components such as bioactives, proteins, peptides, fats, color compounds, and carbohydrates**	Synthetic biology	"Precision fermentation through **synthetic biology** will emerge for industrially tailored animal biomolecule or cell-based meat production."	(Juliano and Reyes-De-Corcuera, 2021)
Precision fermentation	Production of **flavonoids for potential use in the food and pharmaceutical industries**	Heterologous production	Via **metabolic engineering** of suitable host microbes	(Lee *et al.*, 2023)
Precision fermentation	*Rhizomucor miehei* **lipase** (RML) production	Heterologous expression system	"However, the rapid development of **synthetic biology** tools and **metabolic engineering** strategies allows the construction of engineered **heterologous expression** systems including *Pichia pastoris* and *Aspergillus oryzae* for improved RML production."	(Li, C *et al.*, 2022)
Precision fermentation	**Medicinal herbs for antimicrobial properties, as animal feed supplement**	N/A	Not GM – precise traditional fermentation	(Liang *et al.*, 2023)
Precision fermentation	**Recombinant food proteins (generally of animal origin)**	Heterologous protein production	"The term 'precision fermentation' was recently coined to specifically describe the **heterologous production** of organic molecules (including **recombinant proteins**) from **transgenic** microorganisms."	(Linder, 2023)

Table 1. (continued)

Name and definition	Application/products	Synonyms mentioned	Substantiation for GM use	Reference
Precision fermentation	Production of **molecules with precise properties** …to substitute **animal-based food** production	Cellular food production	"Thus, the **recombinant proteins** may differ in the physiochemical and functional properties."	(Lübeck and Lübeck, 2022)
Precision fermentation	**Functional protein ingredients that are natural replica of animal proteins (such as collagen and gelatin)**	N/A	"Using **engineering biology, we transform microorganisms with genes** that are responsible for producing animal proteins such as collagen and gelatin."	(Luo *et al.*, 2022)
Precision fermentation	Produce **proteins and other food ingredients …for a wide range of technical or functional uses, including for flavor, color, texture, and nutrient purposes.**	Synthetic biology	**genetically engineered** microorganisms used.	(Marden *et al.*, 2022)
Precision fermentation	produce **desired complex organic molecules, will allow the production of protein** …for consumers (=food)	N/A	"Precision fermentation, through **programming of microorganisms** to produce desired complex organic molecules…"	(Nastasijevic, Veskovic and Milijasevic, 2020)
Precision fermentation	**Alternative proteins**	N/A	"…produced **heterologously by microorganisms,** to which the gene coding for the protein of interest has been inserted."	(Sales Flores, 2023)
Precision fermentation	produce **specific proteins or molecules**	Cell factories	"…[Companies] are also using precision fermentation to produce various growth media ingredients. **Recombinant proteins,** growth factors and inhibitory factors for different animal species and cell types (e.g., fibroblast, muscle, cartilage) appears to be the main product focus of these companies."	(Singh *et al.*, 2022)
Precision fermentation	**recombinant molecules** to yield **new food ingredients** …produce **newer protein sources** with desirable textural and taste characteristics for increased consumer acceptance	N/A	"Most consumers view PF as an unnatural and **synthetic process** that is directly linked to **genetically engineered/ modified (GM)** foods which are seen by some consumers as a threat to human health"	(Tachie, Nwachukwu and Aryee, 2023)

Table 1. (continued)

Name and definition	Application/products	Synonyms mentioned	Substantiation for GM use	Reference
Precision fermentation	produce **non-microbial products** that have been extensively used by the **food industry.** and **protein industry,** where **engineered microbes** now produce **substances that originally came from animals,** such as whey, rennet or casein. Another example is soy leghemoglobin produced by an engineered yeast ..to give its plant-based burger the **flavour and colour** of animal meat. …future food production systems in which fermentation takes a central role to generate a **wide range of food ingredients.**	Targeted fermentation, synthetic biology	"Many start-up companies are now developing **engineered microorganisms** to manufacture a wide range of food compounds."	(Teng *et al.*, 2021)
Precision fermentation	production of **target molecules…variety of food ingredients** that were **conventionally sourced from animals and plants**	Synthetic biology	"Precision fermentation per se is not new and **genetically engineered microorganisms (recombinant DNA technology)** have been used since the 1970s for fermentative production of enzymes and other biomolecules for various applications"	(Terefe, 2021)
Precision fermentation	optimising the expression of the **proteins** that these genes code for… **synthesise compounds that would otherwise be expensive and complicated to acquire.**	N/A	"…the process of **inserting specific genes into the DNA backbone** of single-cell organisms…"	(Thomas and Bryant, 2021)
Precision fermentation	produce **complex organic molecule**	Food-as-Software, Precision biology	"PF is a proven technology that has been used commercially since the 1980s–scientists have been using **genetic engineering to modify microorganisms** for producing human insulin and growth hormone, enzymes such as rennet (chymosin), and various other biologics."	(Tubb and Seba, 2021)

Table 1. (continued)

Name and definition	Application/products	Synonyms mentioned	Substantiation for GM use	Reference
Precision fermentation	**customised (recombinant) molecules** that can serve as **new food ingredients**	Synthetic biology	"…PF relies on **reprogramming microbes** to produce specific, customised **(recombinant)** molecules…"	(Vanhercke and Colgrave, 2022)
Precision fermentation	**Medicines, cosmetics, and other materials.** Recently, this technique has been used in **food manufacture…**	N/A	"…the process begins with **extracting the genes** that encode for soy leghemoglobin protein from soybean roots and **inserting them into a specific yeast created by genetic engineering"**	(William, 2021)
Precision fermentation	…produce the required **protein**	Cellular agriculture	"…the process of **engineering the gene sequence** for a specific protein **into a bacterium or yeast strain…"**	(Wood *et al.*, 2023)
Precision fermentation	produce **highly valuable functional food components such as enzymes, lipids, vitamins, carbohydrates, sweeteners, antioxidants, colorants, and preservatives**	Cellular agriculture, Industry 4.0, Metabolic engineering	"In the synthesis of specific functional food components in precision fermentation, **microorganisms designed using recombinant DNA technologies and synthetic biology techniques** are used."	(Yamaner, 2023)
Precision fermentation	**…individual components of animal products, such as milk or egg proteins…**	Cellular agriculture	"After the **alteration of single-celled organisms' DNA,** PF is conducted in brewery-like facilities to produce specific compounds, either modelled on those found in nature, or entirely novel compounds."	(Zollman Thomas *et al.*, 2023)

Source: See References.

Table 2. **List of definitions of precision fermentation by industry and advocacy groups**

Descriptions are paraphrased, key elements are shown in **bold**.

Definition technology	Application/products	Synonyms mentioned	GMO use?	Reference
…use bioengineering techniques to program microorganisms …to produce a compound of interest when fermented under precise conditions. …exact copy of animal DNA sequence, however it requires no animal involvement in the process... molecularly identical ingredient, made by microorganisms, instead of animals.	…make **medicines** and **food ingredients** including **insulin, rennet in cheese, natural flavors, citric acid, amino acids, and numerous vitamins** commonly found in foods… **molecularly identical ingredient,**	Not mentioned	Yes	(Precision Fermentation Alliance, 2023)
…specialized brewing that uses microbes as "cell factories" for producing specific functional ingredients. Capable of producing proteins, vitamins, enzymes, natural pigments, and fats, …to create high-value ingredients that improve the sensory characteristics and functional attributes of plant-based products or cultivated meat. Precision fermentation can be used to make products like egg proteins, dairy proteins, pepsin, animal-free meat proteins including heme, and fats. …develop products that more closely resemble conventional ones.	…producing **specific functional ingredients.** …producing **proteins, vitamins, enzymes, natural pigments, and fats, …create high-value ingredients** …make **products like egg proteins, dairy proteins, pepsin, animal-free meat proteins including heme, and fats.**	Specific case: animal-free dairy	Not mentioned	(Carter *et al.*, 2022) – The Good Food Institute
Rather than using animals, precision fermentation uses yeast and other micro-organisms that are enhanced through science to convert minerals or plant matter into ingredients such as proteins and sweeteners. Precision fermentation doesn't seek simply to provide analogues to animal-based foods; rather, it produces true-to-nature ingredients, indistinguishable in taste, texture, and nutrition …it uses genetically engineered microflora to produce these ingredients, …such as non-animal rennet for cheese-making, sweeteners, flavors, and many vitamins.	**…ingredients such as proteins and sweeteners.** …provide **analogues to animal-based foods;** rather, it produces **true-to-nature ingredients** …products, such as **non-animal rennet for cheese-making, sweeteners, flavors, and many vitamins.**	Not mentioned	Yes	(Hartman Group, 2023)
…cells, such as yeast, can be grown in microbrewery-like tanks to produce large quantities of the desired product that they would not normally be able to produce (e.g. egg white protein), without the use of animals…., whereby microorganisms are programmed to produce specific proteins. The cells or "biological chassis" for precision fermentation include bacteria, fungi and yeasts, algae, insect and plant cells.	produce **e.g. egg white protein,** whereby microorganisms are programmed to **produce specific proteins.** Several other cellular agriculture companies are focusing on **textiles** using precision fermentation, including **Spiber's silk,**	Not mentioned	Yes	(Ontario Genomics and Agriculture and Agri-Food Canada (AAFC), 2023)

Source: See References.

3.2 Synonyms for precision fermentation and related terminologies

A review of both scientific and grey literature has revealed that many related terms exist for precision fermentation, of which some are used as synonyms (**Table 3**). Some of these terms align closely with the main characteristics of precision fermentation outlined in section 3.1. Examples include "heterologous (protein) production", "recombinant protein production" and "microbial cell factories". Other terms, such as "cellular agriculture" and "cellular food production" encompass broader concepts, which besides covering precision fermentation also include developments of cell-based food products (FAO and WHO, 2023).

Table 3. Terminologies related to precision fermentation retrieved from the scientific and grey literature

Name
bacterial fermentation
biomanufacturing
cell factories
cell-based fermentation
cellular agriculture
cellular food production
foreign protein fermentation
heterologous (protein) production
indigenous protein fermentation
Industry 4.0
lab-grown food
metabolic engineering
microbial cell factories
microbial fermentation
microbial precision fermentation
precision biology
precision cellular agriculture
precision fermentation
protein farming
recombinant protein production/technology
synthetic biology
synthetic food production
targeted fermentation

Source: Author's own elaboration.

The terms "synthetic biology" and "metabolic engineering" are sometimes mentioned as broad terms covering precision fermentation and many characteristics are often overlapping. However, "synthetic biology" cannot be considered a valid synonym to precision fermentation, since it is typically used as the name of a scientific discipline (rather than a tool) that employs its engineering principles to biological entities. "Metabolic engineering" is also a broader term that does not necessarily involve any specific technology but that potentially includes many genetic approaches used in the production of native or non-native molecules. Other terms such as "lab-grown food", "synthetic food production" or "Industry 4.0" are not specific and more commonly used in popular language; or to refer to broader developments in biotechnology.

Terms like "protein farming" suggest a focus on protein production, yet they do not specify whether these proteins are intended for food or pharmaceutical applications. Furthermore, these proteins could be produced using animal or plant cell lines, which is sometimes referred to as "molecular farming". "Biomanufacturing" is potentially an overarching term, encompassing a range of manufacturing technologies that utilize biological systems (e.g. living microorganisms, animal cells, plant cells, enzymes, *in vitro* synthetic [enzymatic] systems or tissues) to produce biomolecules for commercial use in the agricultural, food, material, energy and pharmaceutical industries (Zhang, Sun and Ma, 2017).

"Traditional fermentation" and "biomass fermentation" are sometimes used ambiguously in non-scientific articles possibly discussing precision fermentation. In general, "traditional fermentation" uses naturally present microbes or starter cultures to alter properties of other primary food ingredients (e.g. fermented dairy, meat or vegetable products, or alcoholic beverages) while "biomass fermentation" involves culturing non-genetically modified microbial strains in large quantities, where the entire microbial biomass or fractions thereof are used as the final food product or predominant ingredient. The use of the term "precise" in this context to identify specifically tailored fermentation processes (Liang *et al*., 2023) may lead to potential confusion for the public.

Several efforts in research and development exist that also make use of the term "precision", such as "precision biology", "precision breeding", "precision agriculture" or "precision medicine". "Precision medicine" can indicate, for instance, the optimized and tailored (personalized) use of medicines, while "precision agriculture" often means "a management strategy that gathers, processes and analyses temporal, spatial and individual plant and animal data and combines it with other information to support management decisions according to estimated variability for improved resource use efficiency, productivity, quality, profitability and sustainability of agricultural production" (ISPA, 2021). "Precision breeding" can be a specific term for the applications of some of the new genomic techniques (NGTs), including whole genome sequencing, marker-assisted breeding and genome editing, in plant and animal breeding (Chen *et al*., 2019). "Precision biology" can indicate a broader development that focuses on the use of big data and omics technologies for elucidating the biological effects of genes, proteins and other biomolecules through the analysis of their intricate interactions (Chen *et al*., 2023). It has evolved from the field of "precision" medicine but extends beyond the realm of human biology. These terminologies using "precision" in their developments do not have the same scope as the present topic of this literature synthesis; therefore, they are not to be confused with "precision fermentation".

3.3 Use of precision fermentation terminologies by the media

Using the News on the Web (NOW) corpus (Davies, 2016), a collection of texts (corpora) was searched (**Figure 1**) for the frequency with which "precision fermentation" was mentioned in the media between 2010 and 2023 (**Figure 2**). This indicated that the media coverage of "precision fermentation" developed around 2019 and gained more attention in the following years, peaking in 2022, with 347 occurrences in a total of 198 sources. Other more general concepts such as "biomanufacturing", "cellular agriculture", "cell factories", "animal-free" and "cell-cultivated" followed a similar trend (data not shown). This might be correlated to the steady increase in research and development during this period. Since then, this term has gained a foothold in various sectors, although the term is often defined in different ways.

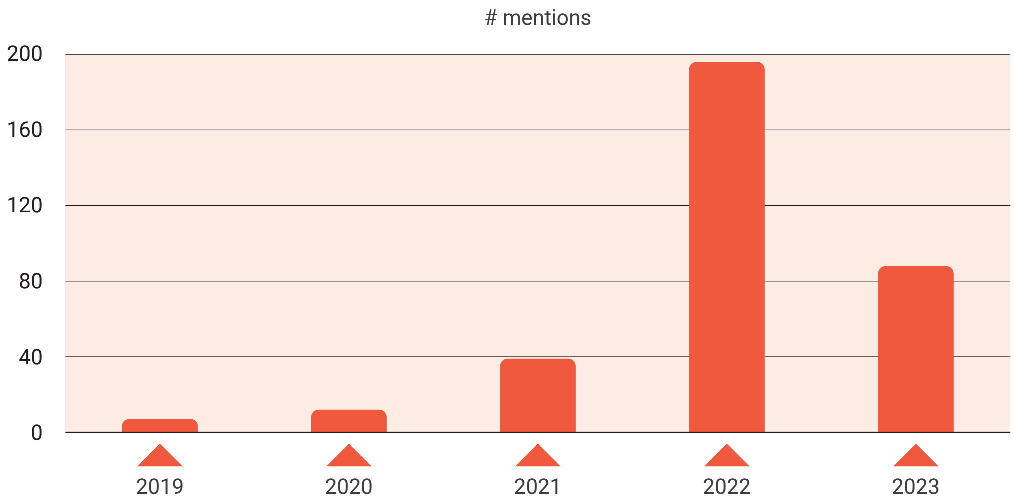
A closer look at the context in which the term "precision fermentation" was cited in the texts retrieved through the NOW corpus, showed that the following words were particularly abundant in these texts and mentioned in close vicinity:

- **Technology-related:** breweries/brewing, bioengineering, biomanufacturing, biotechnology, cell-based, cell-cultivated, cellular agriculture, cultivated meat
- **Product-related:** animal-free, casein, cheese, cow, dairy, insulin, lactoferrin, milk, mycoprotein, protein, rennet, seafood, whey
- **Producer organisms:** algae, bacteria, fungi, microbes, yeast

Notably, product-related terms referring to meat and eggs were somewhat less frequently mentioned in this context. This may point to a superiority of dairy substitutes as an example of precision fermentation products being developed for the alternative protein market.

Figure 1. Occurrence of the term "precision fermentation" in the English corpus of News on the Web (18.0 billion words in total)

Chronology of media occurrences between 2019 and 18 December 2023.



Source: Author's own elaboration.

3.4 Discussion

Analysis of the literature shows that a wide array of descriptions for precision fermentation exist. However, based on characteristics that are frequently mentioned, a general description can be potentially developed by using common elements analysed in **Table 1** of this report.

The absence of an internationally harmonized definition of precision fermentation may create a challenge for various regulatory authorities who may face a need for implementing specific rules (e.g. food safety assessment, product labelling, trade-related certifications) on precision fermentation-derived food products. In addition, depending on applicable regulations, microorganisms used in precision fermentation processes may not be allowed to remain in the final products, and thus authorities may need to apply or adapt additional regulations for food products derived from precision fermentation.

Besides the different definitions, it was found that various synonyms for precision fermentation are also often used in various literature as well as media. However, in many cases they encompass technologies that are not consistent across various synonyms. They, for example, either only describe a subset of technologies used in precision fermentation or indicate larger umbrella terms that may include precision fermentation. When communicating on precision fermentation this aspect should also be taken into account.

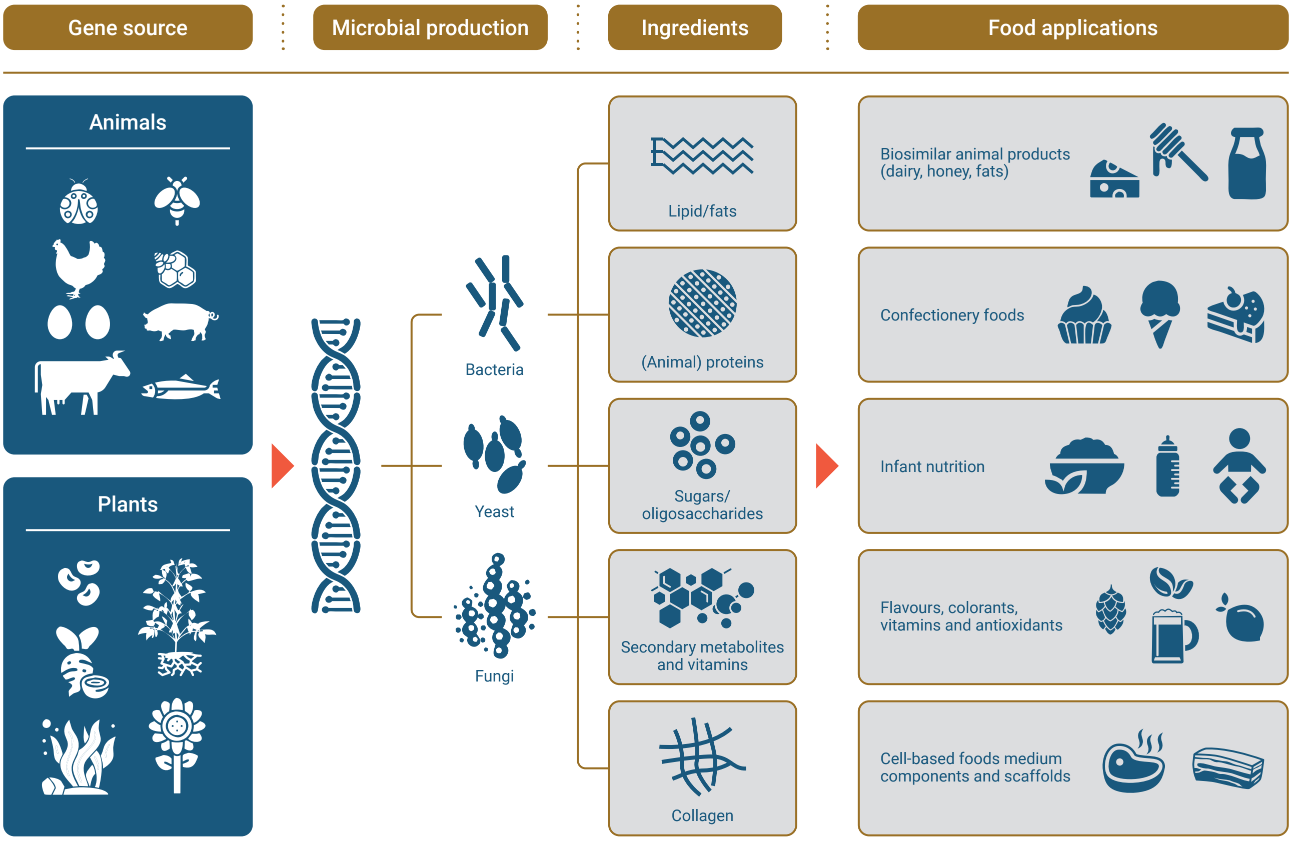
As was the case with the terminology-related recommendations for cell-based food (FAO and WHO, 2023), having a clear and consistent definition for precision fermentation is important for various regulatory aspects. In the case of food items produced through new food production systems, the name of the relevant products is expected to convey their method of production to provide clarity (Hallman, W., Hallman, W. and Hallman, E., 2023). As there is no internationally agreed-upon definition for precision fermentation, the way forward for the competent authorities is to review how the term "precision fermentation" is used within their regulatory context. If that is the case, the competent authorities may also wish to consider the term to be defined within their national contexts to mitigate potential miscommunications.

4. PRODUCTION PROCESSES

4.1 Overview

Despite the fact that precision fermentation can be used to produce a wide variety of food ingredients, the systematic literature review revealed that their generic production processes are highly similar (**Figure 1**). The production phase where differences are likely to be observed is for the downstream processing, which is often dictated by the type of microbial production host (e.g. bacteria, yeast or filamentous fungi or microalgae) or product (e.g. proteins, lipids, oligosaccharides). At the same time, the requirements for formulation in an end-product play a role for the downstream processing steps to be applied. Food additives derived from precision fermentation, such as vitamins, pigments and flavouring or fragrance molecules, and human-identical milk oligosaccharides (HiMO) are, in general, highly purified with little or no non-target or undesired compounds. In contrast, proteins derived from precision fermentation may have a lower purity than specialty (bio)chemicals and might contain some level of non-target proteins, genetic material, or exopolysaccharides from the microbial production host or growth medium. These differences in the level of purity are often related to the intended final use of the precision fermentation-derived product, which for proteins is often as an ingredient or macronutrient supplement, while specific substances like vitamins are often used as additives.

Figure 2. General characteristics of precision fermentation



Note: All the different items and elements that appear in Figure 2 show examples. This is not an exhaustive list of characteristics of precision fermentation.
Source: Author's own elaboration.

4.2 Precision fermentation products and applications

4.2.1 Microbial production hosts in precision fermentation for food products

A variety of microbial production hosts are used in precision fermentation (Augustin et al., 2023; Chai *et al*., 2022; Dupuis *et al*., 2023). Yeast are commonly used as hosts, among which, *Saccharomyces cerevisiae* (bakers' yeast) and *Komagataella phaffii* (previously known as *Pichia pastoris*) are often used. For filamentous fungi, *Trichoderma reesei, Aspergillus oryzae* and *Aspergillus niger* are frequently used production hosts. Among bacteria, *Escherichia coli, Bacillus subtilis* and *Corynebacterium glutamicum* are commonly used and often considered highly productive hosts. These production hosts each have their specific physiological and technical requirements for cultivation, with both intracellular and extracellular metabolites being targeted. Moreover, they differ in the basic biochemical capacities to produce or modify components such as proteins, lipids or oligosaccharides (Anyaogu and Mortensen, 2015).

4.2.2 Precision fermentation products and food applications

Diverse types of food ingredients can be produced using precision fermentation, such as proteins, lipids or oligosaccharides that are traditionally sourced from animals (animal-specific), but also (novel) flavouring agents or colourants (pigments) derived from plants or (micro)algae. Relevant applications, microbial production hosts and production processes are described in more detail in the following sections.

4.2.2.1 Production of animal-specific food ingredients

The production of animal-specific components is a fast-expanding application of precision fermentation that can provide nutritious food ingredients in a potentially sustainable way (Carter *et al*., 2022; Waltz, 2022). One important application is the production of animal-specific proteins such as milk proteins (e.g. caseins, beta-lactoglobulin, lactoferrin), structural/muscle proteins (e.g. collagen, myoglobin) or egg white proteins (e.g. ovalbumin, ovomucoid). Some products, such as beta-lactoglobulin (which is the major whey protein), are already approved for marketing in some countries. These milk proteins are mainly produced using the fungus *Trichoderma reesei* or the yeast *Komagataella phaffii* (Deng *et al*., 2023 Nielsen, Meyer and Arnau, 2023). Myoglobin is a heme-containing component that can be used as a flavouring and colouring agent in, for example, meat replacers, while collagen and egg white proteins are mainly used for the structuring of food products. Another relevant application is the production of animal- or human-specific oligosaccharides, in particular human-identical milk oligosaccharides (HiMOs) that are used in, among other, infant nutrition. These complex oligosaccharides are produced using engineered *Escherichia coli* and are typically purified to a relatively high degree (Augustin *et al*., 2023; Bych *et al*., 2019; Zhu *et al*., 2022). Other animal-specific components of interest for precision fermentation are animal-type "designer" fats that can be used as flavouring agents to add meat-like flavours to meat replacers (Carter *et al*., 2022).

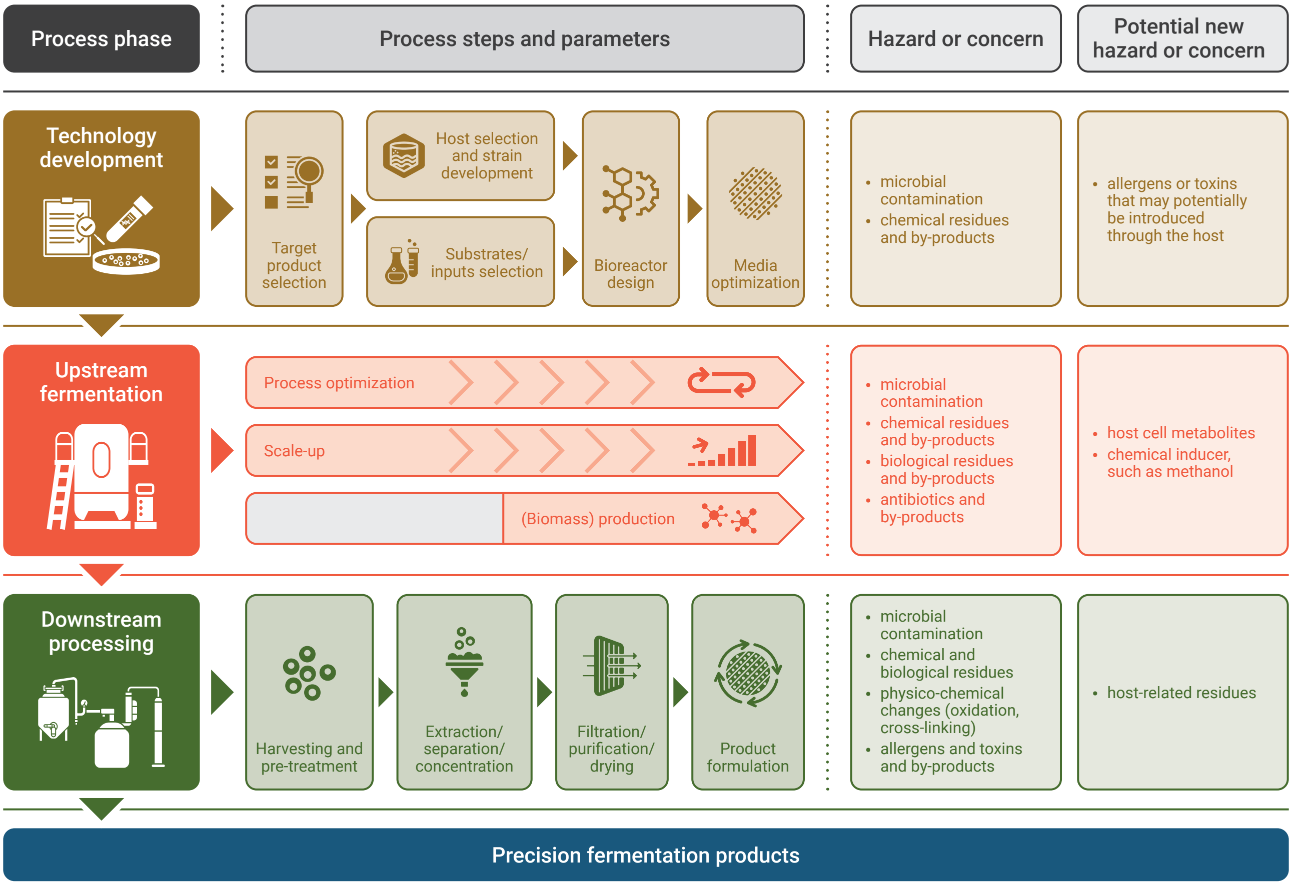
4.2.2.2 Production of flavouring and colouring food ingredients

Flavour compounds and colourants (pigments) for food products are traditionally extracted from plants but they can nowadays in many cases also be produced using precision fermentation. These include flavour compounds like limonene (citrus flavour), vanillin or humulone (hop flavour), and pigments such as carotenoids (lycopene, β-carotene) or the red-colour pigment carminic acid that is normally obtained from scale insects (Dusséaux, Forman and, 2024; Hilgendorf *et al*., 2024 Seo and Jin, 2022). Novel plant-derived flavouring agents are also being sourced and produced by precision fermentation. Soy leghemoglobin, a heme-containing protein from soybean is an example of both a novel flavour compound and colourant that is produced by *Komagataella phaffii* (*Pichia pastoris*) and already commercialized as a food ingredient in a number of countries to add a meat-like flavour and colour to meat replacers (Fraser *et al*., 2018). Also, plant-derived sweet proteins like thaumatin, brazzein and monellin can be produced using precision fermentation. Such novel food ingredients could potentially replace artificial sweeteners like aspartame or low-caloric alcohol sugar sweeteners (polyols) like xylitol, sorbitol, and mannitol (Bilal *et al*., 2022).

4.2.3 Precision fermentation production processes

A generic production process (Figure 2), including a technology development phase, an upstream fermentation phase and a downstream processing phase, can be used to describe common processing steps involved in the production of most food products derived from precision fermentation. The **technology development phase** can start with selection of the target molecule (final product), followed by selection of the microbial production host and strain development. In parallel, selection of substrates and other essential input materials can be done, and the overall production equipment and bioreactor can be designed and set up. During this phase, the fermentation medium composition is also optimized. The **upstream fermentation phase** is where the biomass of the production strain is produced. In this phase, the production would usually be scaled up. The fermentation process might still be optimized throughout the process and between the different scales and bioreactors. This optimization can focus on various process parameters such as pH, temperature and aeration, as well as medium composition. Finally, in the **downstream processing phase**, depending on whether the target compound is intracellular or excreted to the medium, microbial cells are harvested from the bioreactor or the fermentation broth is separated from microbial cells. This is followed by further downstream processing steps such as cell disruption, precipitation of cell extracts, or fractionation (separation) of cell or fermentation broth components. Further concentration and purification steps can be included in this process to obtain the target molecule at the desired purity (e.g. using chromatography and filtration methods). Ultimately, the target molecule might not be delivered as a solution but rather dried as a powder by means of freeze-drying or spray-drying. The formulation of the end product might then be needed for different food applications. Food applications can be as an ingredient for common food products, but also in specialized nutrition.

Figure 3. Generic production process in precision fermentation and associated potential food safety hazards



Source: Author's own elaboration.

4.3 Case studies for precision fermentation production processes

While precision fermentation processes in general share many common production steps, key differences may be found in the cultivation conditions for the microbial production strain used (bacteria, yeast or fungus), whether a product is intracellular or secreted to the medium or the required purity of the product. The following three examples illustrate some of these differences.

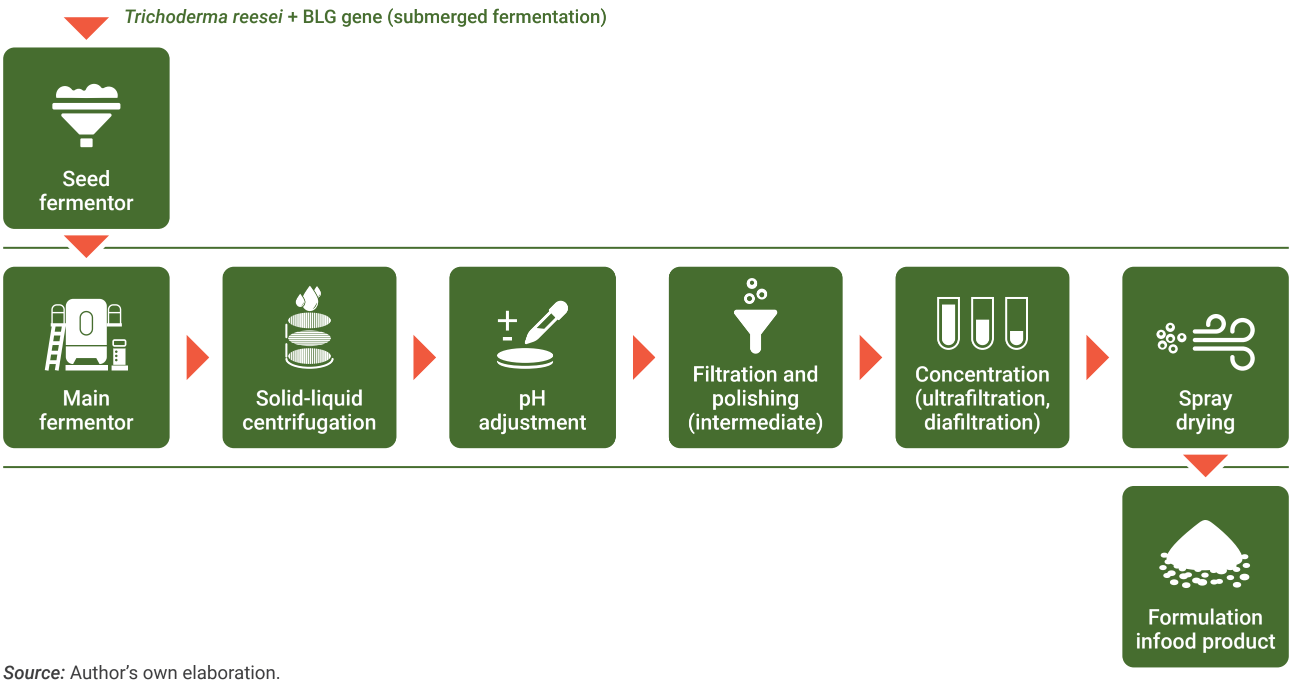
- **Case 1: Animal-specific protein:** bovine milk protein beta-lactoglobulin (whey protein)
- **Case 2: Specialty ingredient:** human-identical milk oligosaccharide (HiMO) – 2’-fucosyllactose (2’-FL)
- **Case 3: Flavour compound:** leghemoglobin from soybean.

Case 1: Animal-specific protein: Bovine milk whey protein beta-lactoglobulin

The efficient and sustainable production of animal-specific proteins is an application area that interests many food companies. In particular, the production of milk proteins using precision fermentation has already reached the stage of marketed products for at least several years in some countries. The first milk protein to have been commercialized was bovine beta-lactoglobulin (BLG), which was produced using the genetically engineered fungus, *Trichoderma reesei* (FDA, 2019). The BLG derived from precision fermentation has already been used as an ingredient in ice cream, melting cheese on pizzas and sport drinks.

Companies explain that the BLG production process is aligned with good manufacturing practices (GMP) and the product meets all the relevant food-grade specifications. The production starts by growing the fungus in a seed fermenter for each batch, which is subsequently used as the starting culture to inoculate a large fermenter. In this case, BLG is produced by submerged fermentation, and the BLG protein is secreted from the fungal cell into the cultivation medium. The first downstream processing step is therefore the separation of the BLG-containing medium from the fungal biomass and other solids using centrifugation. The BLG protein is concentrated using pH adjustment of the medium, and then further purified using filtration (e.g. ultrafiltration and diafiltration) and polishing steps (removal of remaining traces of impurities and closely related substances such as aggregates). The purified protein fraction is then spray dried to a powder, after which it is ready for use as a food (macro) ingredient. The purity of the end product is set as ≥90 percent BLG (of the total protein), with >85 percent w/w total protein on a dry weight basis in the end product (FDA, 2019).

Figure 4. Production of bovine milk whey protein beta-lactoglobulin by *Trichoderma reesei*

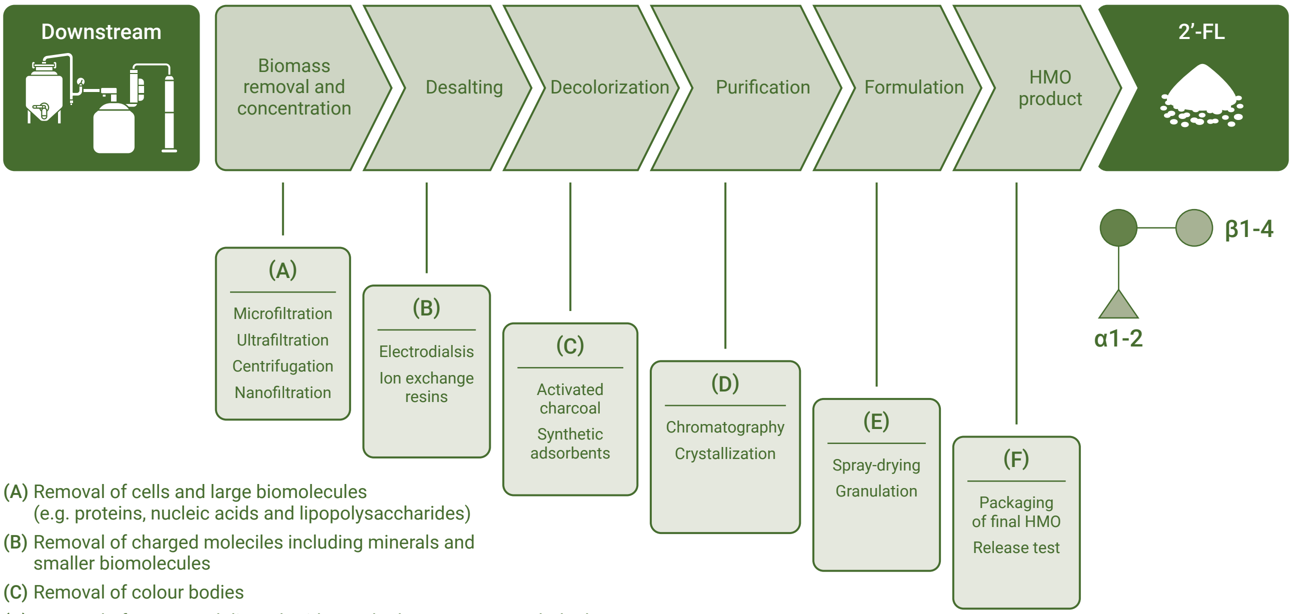


Source: Author’s own elaboration.

Case 2: Specialty ingredient: Human-identical milk oligosaccharide

Human milk oligosaccharides (HiMOs) make up a large fraction of the solid components present in human milk and play an important role in infant health. Originally, they were isolated from human milk for addition to infant formula but, more recently, HiMOs have been efficiently produced through precision fermentation (e.g. using *Escherichia coli* and *Corynebacterium glutamicum*). Commercial production has been achieved for example for the HiMOs 2'-fucosyllactose (2'-FL) and lacto-N-neotetraose (LNnT), with production facilities of over 200 m^3 (Bych *et al*., 2019). These HiMOs require high purity for use in infant formula, with complete removal of the cells of the production strain and all biomolecules, including proteins, lipopolysaccharides and nucleic acids. The downstream processing for purification of 2'-FL (≥90–94 percent purity) is described in Figure 5, outlining a number of alternative methods that are available for each step in the process (Bych *et al*., 2019).

Figure 5. Downstream processing steps for the purification of the HiMO 2'-fucosyllactose



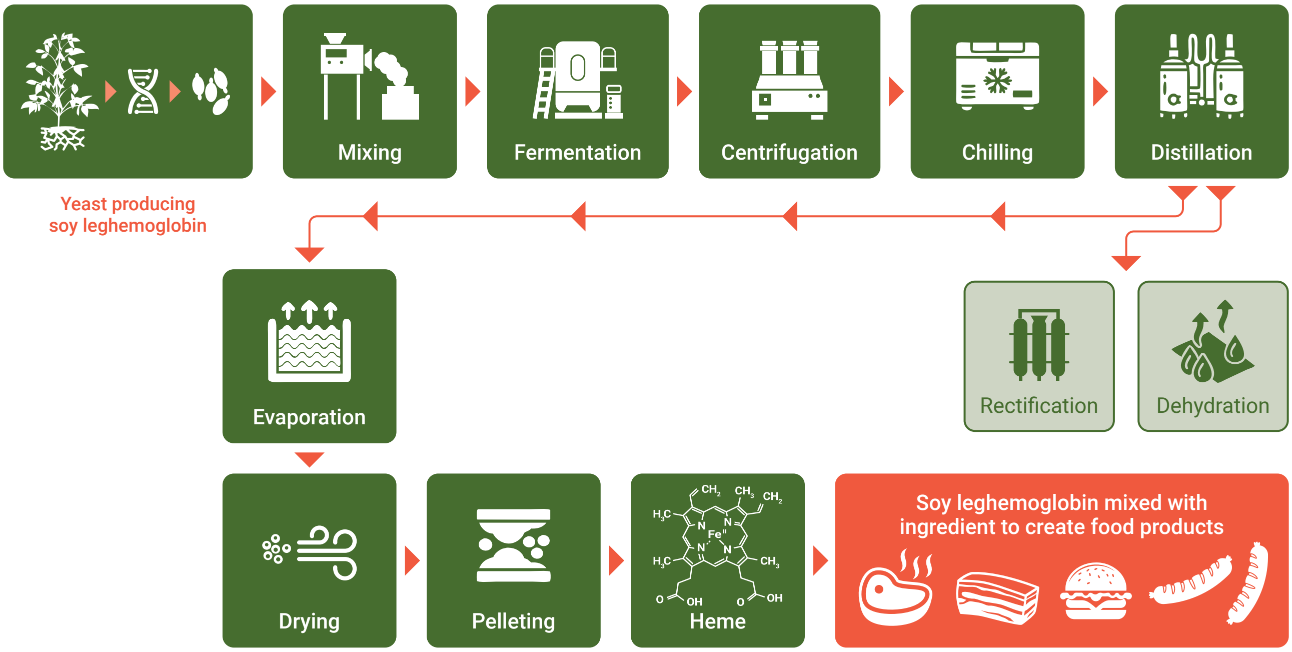
(A) Removal of cells and large biomolecules (e.g. proteins, nucleic acids and lipopolysaccharides)
(B) Removal of charged moleciles including minerals and smaller biomolecules
(C) Removal of colour bodies
(D) Removal of mono- and disaccharides and other non-HMO carbohydrates
(E) Removal of water; Residual solvent; Elaborating powder properties
(F) Final HMO analyzed vsl specification

Source: Adapted from Bych, K., Mikš, M.H., Johanson, T., Hederos, M.J., Vigsnæs, L.K. and Becker, P. 2019. Production of HMOs using microbial hosts – From cell engineering to large scale production. *Current Opinion in Biotechnology*, 56: 130-137. doi.org/10.1016/j.copbio.2018.11.003

Case 3: Flavour compound: Soy leghemoglobin

One of the potential applications of certain flavouring and colouring agents produced through precision fermentation is their use as meat-like flavours in plant-based and other alternative meat replacers. Soy leghemoglobin (LegH) is a plant-derived heme-containing protein that can add a meat-like flavour and a blood-like colour to food products. It has been commercialized for these purposes in the United States of America (FDA, 2018). Leghemoglobin is currently produced using the yeast *Komagataella phaffii*. After fermentation, the yeast cells are lysed using high-pressure homogenization or mechanical shearing (e.g. bead milling) to recover LegH, which is an intracellular product. Cell lysates are cleared of insoluble particles by high-speed centrifugation and microfiltration (**Figure 6**). Leghemoglobin is then concentrated using such technologies as ultrafiltration. Stabilizers, such as sodium chloride and sodium ascorbate, are added to the concentrated sample, which can then be stored as a frozen liquid.

Figure 6. Production of soy leghemoglobin produced by *Komagataella phaffii*



Source: Adapted from Ahmad M.I., Farooq S., Alhamoud Y., Li C. and Zhang H. 2023. Soy Leghemoglobin: A review of its structure, production, safety aspects, and food applications. *Trends in Food Science and Technology*, 141: 104119. doi.org/10.1016/j.tifs.2023.104199

4.4 Potential food safety hazards and concerns of precision fermentation

4.4.1 Technology development phase

4.4.1.1 Potential hazards related to the microbial production host

In theory, a wide variety of microbial production hosts can be suitable for precision fermentation applications; in practice, however, a limited set of "model"[1] hosts is currently used (Chai *et al*., 2022; Dupuis *et al*., 2023; Li, Huo and Guo, 2022). These include bacteria, yeasts, filamentous fungi and microalgae. Some countries and jurisdictions have established regulatory tools, such as the qualified presumption of safety (QPS) status in the European Union for safe use in food production (EFSA Panel on Biological Hazards *et al*., 2024) and the generally regarded as safe (GRAS) status for food applications involving specific production hosts for the United States of America (FDA, 2016).

Although used in food production, filamentous fungi can potentially have traits for mycotoxin production. Similarly, some bacterial production hosts like streptomycetes, *Enterococcus faecium, Escherichia coli* and *Clostridium butyricum* can potentially produce toxins (EFSA Panel on Biological Hazards *et al*., 2024). For the production of food ingredients (e.g., additives, enzymes) commonly used yeasts are *Saccharomyces cerevisiae* (bakers' yeast), *Komagataella phaffii* (previously described as *Pichia pastoris*) and *Kluyveromyces* spp., while for filamentous fungi, *Trichoderma reesei* and *Aspergillus* spp. (A. niger and A. oryzae) are considered suitable production hosts. For bacteria, *Escherichia coli* and *Bacillus spp*. are common production hosts (Augustin *et al*., 2023; Dupuis *et al*., 2023).

The food industry may need to explore new microbial species with more diverse and versatile metabolic capacities to produce desirable substances and satisfy the increasing protein demand driven by population growth and environmental challenges. Consequently, "non-model" microbial species (i.e. microorganisms with no history of safe use as cell factories) are selected as candidates for the production of both novel and non-novel food ingredients. However, since their genetics, metabolisms and physiology sometimes are yet to be fully understood, various genetic tools are developed to unlock their full potential as cell factories (Fatma *et al*., 2020; Li, Huo and Guo, 2022; Riley *et al*., 2021).

1 Model microorganisms refer to well-studied microbial species that have been used by the food industry in the long term with well-characterized metabolisms and toward which a large genetic tool box is available. Despite the deep knowledge gathered toward model microorganisms, they often lack certain traits desirable for the development of innovative microbial cell factories, such as flexibility to use different carbon sources and stress tolerance.

4.4.1.2 Regulatory requirements for the use of genetic modification techniques

Application of modern biotechnology, such as genetic modification techniques, to develop production hosts would likely call for regulatory considerations in many countries with relevant frameworks in place. However, all potential consumer concerns on food safety issues related to genetic modification should be addressed at the stage of developing the genetically modified microorganisms, prior to their use in fermentation and the downstream processing phase. This is to prevent those safety issues from being transferred or leach into the final product. It may, in some jurisdictions, create some additional regulatory requirements, such as food labelling, to indicate that the product may contain such microorganisms at the level above regulatory thresholds.

As to the need for additional regulatory requirements to ensure the food safety of genetically modified microorganisms, in nearly all countries and jurisdictions, companies are expected to provide a detailed description and characterization of all introduced genetic elements. These are essential to understand the production strain development and to address safety issues related to the genetic modification(s). An adequate molecular characterization of the production strain is essential to ensure that the genomic modification(s) have occurred as designed and that the production microorganism exhibits only the trait(s) associated with the intended modification(s). A deep understanding of the intrinsic risks related to the different genetic modification techniques is essential for the development of a safe genetically modified microorganism.

4.4.1.3 Potential allergenicity of the newly expressed proteins

When precision fermentation is used to produce proteins that are similar or identical to known conventionally existing proteins, one should consider that the allergenic potential in newly expressed proteins may be similar to that of the respective known proteins. Moreover, microbial production hosts vary in their ability to carry out the post-translational modification (PTM) of proteins, such as glycosylation or phosphorylation. When proteins are produced using microbial hosts, these differences can influence the protein modification patterns, thereby resulting in newly expressed proteins that are not fully identical to their conventional counterparts (Anyaogu and Mortensen, 2015). Yeasts and filamentous fungi can perform complex PTMs (glycosylation especially), making the proteins they produce more closely resemble known animal/plant-specific proteins, which also undergo similar modifications. However, bacteria in general have more limited capacities to perform PTMs. Proteins produced in bacterial systems typically lack the complexity of known animal/plant proteins and are therefore less similar. Such differences in PTMs, as compared to conventional animal/plant proteins, might affect the allergenicity of the newly expressed proteins.

4.4.2 Upstream fermentation phase

4.4.2.1 Microbial and chemical contaminants and by-products

Microbial contamination from the production environment is possible, especially at the start of the fermentation phase when cell densities are still low and the production host might be outcompeted by a microbiological contaminant, but it can also happen in the scale-up phase when the biomass or fermentation broth is transferred from small-scale to large bioreactors. Microbial contamination should therefore be minimized and monitored, particularly in the case of heat-resistant and spore-forming microorganisms. Antibiotics might be added to the medium to supress the growth of microbial contaminants and to preserve specific genetic features in the microbial production host. These antibiotics are considered a hazard and should be removed in the downstream processing phase. The production strain might also produce undesired metabolites or fermentation by-products might be formed if fermentation conditions are not controlled well. Recombinant production by a genetically engineered micro-organism sometimes relies on the use of so-called inducer chemicals, that trigger gene expression for production of the compound. A well-known example of this is the frequent use of methanol as inducer for gene expression in the yeast *Komagataella phaffii* (*Pichia pastoris*) (Pan *et al*., 2022). Methanol is a toxic compound, which is only required in low concentrations, and it should be removed during the downstream processing phase.

4.4.3 Downstream processing

4.4.3.1 Processing contaminants and unwanted by-products

At the end of the fermentation phase, the harvesting and downstream processing of microbial cells or the fermentation broth are used to extract, separate and purify the desired target component. Microbial contamination from the production environment is also possible at the processing stage, and should therefore be minimized and monitored. Many unwanted components may be efficiently removed, although this will depend on the downstream processing methods used. In some cases, however, certain components from the production host or the fermentation broth can remain present in the end-product. These may include host cell proteins (HCPs), lipopolysaccharides (LPS, endotoxin) in Gram-negative bacteria, antimicrobial compounds produced by the host or undesired secondary metabolites.

In some instances, it may be important to sufficiently reduce the content of nucleic acid in microbial biomass (normally via a heat treatment procedure), as high purine levels are toxic to humans, particularly for individuals suffering from gout. This is especially relevant when using lower-purity, non-heated protein fractions in food applications (Linder, 2023).

Chemical contamination is also possible, for example when solvents are used during lipid extraction, or chemicals and salts used in some protein extraction methods. Heating steps, alone or in combination with pH adjustment, can also lead to the formation of unwanted chemical by-products, via denaturation and degradation or chemical reactions of the target molecule with other cell or medium components. In particular Maillard-type reactions (cross-linking of sugars and proteins) are well known for animal proteins, which can lead to a further breakdown into toxic components or a reduced protein digestibility (Aljahdali and Carbonero, 2019; Grossmann and McClements, 2023; Mondaca-Navarro *et al*., 2019). The oxidation of lipids can also result in unwanted products with potentially adverse effects on food quality and human health (Wang *et al*., 2023).

4.5 General quality assurance and control systems in precision fermentation

The majority of the potential food safety hazards in the precision fermentation production process, such as microbiological and chemical hazards, are not new. For these common food safety hazards, there are many risk-mitigating tools available, such as good practices (GHP, GMP, GCCP and HACCP), hygienic design of manufacturing equipment, production areas and general principles, guidelines and methodologies for the whole food safety assessment of end-products, according to the Codex Alimentarius.

As for the production strains, they must meet specific quality standards to ensure safe production and constant product quality. Important requirements in this respect are ensuring strain identity and purity as well as maintaining the genetic stability of the strain and avoiding the genetic drift during prolonged cultivation. Measures that can be implemented to ensure this include: 1) centralized in-house strain banking; 2) storage of reference stocks below −80 °C to minimize genetic or physiological changes to the strain during long-term storage; 3) a traceability system in place; 4) a database recording of all the reference stocks, where all changes to the basic strain data record are saved in log files; 5) the lowest number of generations from the reference stock to the final product to minimize genetic changes in the reference stock to the final industrial scale batch of the strain; 6) DNA fingerprint and basic phenotypic characterization for a specific microorganism carried out for each inoculation material batch of the microorganism and compared to the reference material to ensure a stable performance (Laulund *et al*., 2017). Genotyping and genotypic stability testing should be part of the standard quality assurance and quality control (QA/QC) practice for inoculation batches of the GM production strains, as it is for non-GM production strains. Considering the relatively small genomes of microorganisms, whole genome sequencing (WGS) might be used to screen for purity of the cultures, genetic drift or unwanted genetic changes in newly developed production strains.

4.6 Discussion

By studying various precision fermentation production processes, several common steps have been identified to illustrate a generic production system for precision fermentation as shown in **Figure 2**. Depending on the desired end-product these steps may be conducted in different ways or they may contain specific differences. For example, different optimized production hosts may be used for certain end-products or fermentation reactions may be tailored to optimize production yields. More specifically, during the downstream phase, there can be wide variations among different production processes. Such variations can be explained by differences in such aspects as the properties of the end-product or intended purity, which may be related to the requirements for the application. Specialized nutrition products (e.g. infant formula), for instance, may require high quality standards for safety and nutritional adequacy.

Products synthesized by means of precision fermentation are often perceived to have positive characteristics for developers and producers with a high production yield of final products that have a history of safe use in food. At the same time, just as in other conventional food production systems, there are always food safety hazards, such as microbiological and chemical contaminants. Such food safety hazards can be controlled by following good practices and systematic food safety assurance plans. In the literature, there are few mentions of potential new hazards in the process of precision fermentation and they mostly on the concern that input materials for the fermentation process might remain in the final products.

Another key consideration is the potential allergenicity and hypersensitivity of products derived from precision fermentation. Different precision fermentation systems may or may not increase or decrease the allergenicity of known conventional proteins (EFSA *et al*., 2024), thus continuous studies for relevant risk assessments are useful.

In conclusion, precision fermentation provides additional means to produce food ingredients and additives in a way that may potentially reduce reliance on intensive livestock agriculture. However, as is the case with any other type of food production system, it is important for food safety competent authorities to have a basic understanding of the production processes so that relevant risk assessment and risk management activities can be appropriately conducted to ensure the safety of food products derived from precision fermentation.

5. REGULATORY FRAMEWORKS

5.1 Regulatory frameworks for precision fermentation-derived food products

5.1.1 Overview

To obtain the global snapshot of the current state of precision fermentation related regulatory frameworks from various countries and jurisdictions, two online sessions of regulatory consultations were held with food safety competent authorities in March 2024. A total of 35 countries and jurisdictions have participated in the consultation and contributed to the collection of relevant information, namely Argentina, Australia, Bangladesh, Brazil, Canada, Chile, China, European Union, Estonia, France, Germany, Greece, Guatemala, Hungary, Indonesia, Islamic Republic of Iran, Israel, Italy, Japan, New Zealand, North Macedonia, Oman, Qatar, Republic of Korea, Saudi Arabia, Singapore, Spain, Sudan, Switzerland, Thailand, United Arab Emirates, United Kingdom of Great Britain and Northern Ireland, Uruguay, United States of America and Yemen. Additional information on regulations was collected from publicly available literature. Among them, 22 countries and the European Union provided a written summary of their regulatory frameworks. The full results and the original input from them can be found in Annex 2 of this document and in Table 4, presenting a summary of the results.

Table 4. Regulatory overview for precision fermentation (PF) products in the country contexts (as of 8 July 2024)

Country/jurisdiction	PF definition	PF-specific regulations	Other applicable regulations	Premarket food safety assessment	Food safety assessment guidelines	Presubmission consultation	Categorization of PF products (e.g. additives, ingredients)	Labelling requirements specific to PF	PF- derived products on the market
Argentina	No	No	Yes	Required	Not mentioned	Available	Depends on the intended use	Not specific to PF	Yes
Australia	No	No	Yes	Required	Yes	Available	Depends on the intended use	Not specific to PF	Yes
Brazil	No	No	Yes	Required	Yes	Available	Depends on the intended use	Not specific to PF	Yes
Canada	No	No	Yes	Required	Yes	Available	Depends on the intended use	Yes	Yes
Chile	No	No	Not mentioned	Required	Internal guidelines exist	No	Depends on the intended use	Not specific to PF	No
China	No	No	Yes	Required	Yes	No	Depends on the intended use	Not specific to PF	Yes
European Union	No but a working definition exists	No	Yes	Required	Yes	Available	Depends on the intended use	Not specific to PF	Yes
Guatemala	No	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Indonesia	No	No	Yes	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Islamic Republic of Iran	No	No	Yes	Required	Yes but not specific to PF	No	Depends on the intended use	Not specific to PF	Yes
Israel	No	No	Yes	Required	Yes	Available	Depends on the intended use	Not specific to PF	Yes

Source: Author's own elaboration.

Table 4. (continued)

Country/jurisdiction	PF definition	PF-specific regulations	Other applicable regulations	Premarket food safety assessment	Food safety assessment guidelines	Presubmission consultation	Categorization of PF products (e.g. additives, ingredients)	Labelling requirements specific to PF	PF- derived products on the market
Japan	No	No	Yes	Required if GMO is used	Yes but for GMO only	Available	Depends on the intended use	Not specific to PF	Yes
New Zealand	No	No	Yes	Required	Yes but not specific to PF	Strongly advised	Depends on the intended use	Not specific to PF	Yes
North Macedonia	No	No	Yes	Not mentioned	No	Available	Depends on the intended use	Not specific to PF	Yes
Qatar	No	No	Yes	Required	Yes	No	Depends on the intended use	Not specific to PF	No
Republic of Korea	No	No	Yes	Required	Yes	Available	Depends on the intended use	Not specific to PF	Yes
Saudi Arabia	No	No	Yes	Required	Not mentioned	Not mentioned	Not mentioned	Not specific to PF	No
Singapore	No but a working definition exists	No	Yes	Required	Yes	Encouraged	Depends on the intended use	Not specific to PF	Yes
Switzerland	No	No	Yes	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Thailand	No	No	Yes	Required	Not mentioned	Not mentioned	Not mentioned	Not specific to PF	Not mentioned
United Arab Emirates	No	No	Yes	Required	Yes	No	Depends on the intended use	Not specific to PF	Yes
United Kingdom of Great Britain and Northern Ireland	No	No	Yes	Required	Yes	Encouraged	Depends on the intended use	Not specific to PF	Yes
United States of America	No	No	Yes	Voluntary but strongly encouraged	Yes	Strongly encouraged	Depends on the intended use	Not specific to PF	Yes

Source: Author's own elaboration.

5.1.2 Definition of "precision fermentation"

No country or jurisdiction has an official or legal definition of the term "precision fermentation", although many of them have informally been using the term, even in regulatory contexts. The European Food Safety Authority (EFSA) and the Singapore Food Agency (SFA) reported that internal working definitions do exist, and gave the following information:

- **European Union:** In the absence of a legal definition and for the purpose of EFSA's Scientific Colloquium 27 on "Cell culture-derived foods and food ingredients", EFSA defined precision fermentation as "the use of engineered microbial cell factories in the production of food ingredients" (EFSA *et al.*, 2024).
- **Singapore:** While there is no official definition, SFA has set a working definition of precision fermentation as "ingredients that are chemically identical to naturally occurring substances but produced by unconventional processes".

5.1.3 Precision fermentation-derived products on the market

Precision fermentation-derived products are already marketed in many of the countries consulted, and some of those products have been commercialized for many years. They include food additives such as vitamin and colourants, food enzymes and processing aids. A well-known product is chymosin, an enzyme used in cheese-making. Other newer precision fermentation-derived products that have been marketed more recently include the following:

- human-identical milk oligosaccharides (HiMOs or HMOs) in Australia, Brazil, China, the European Union, Israel, New Zealand, the Republic of Korea and the United Kingdom of Great Britain and Northern Ireland;
- soy leghemoglobin as a nutritive substance and for food flavouring in Australia, Canada, New Zealand and the United States of America;
- beta-lactoglobulin (or whey protein) as a food ingredient in Canada, Israel, Singapore and the United States of America;
- steviol glycosides as sweeteners in Australia and New Zealand.

5.1.4 Specific regulations and guidelines

The phenomenon that countries use the term precision fermentation without its definition can possibly be due to the fact that the technology itself is not new while the term has relatively recently emerged (Tubb and Seba, 2021). This implies that the legislative provisions for the regulation and commercial approval of precision fermentation-derived food products may already be in place in some countries, without using the term "precision fermentation". However, during the consultations, many countries indicated that the decisions as to what legislation or regulations may be applied to precision fermentation-derived food products would depend on the nature of the product and its application, and that having a clear definition to work with could be useful.

Areas of regulatory frameworks that may be affected by certain definitions of precision fermentation include:

- "Novel" or conventional: Some countries or jurisdictions may consider precision fermentation-derived food products as "novel" and, depending on whether thethe existence of relevant regulations, such products may be regulated according to the regulations.
- GMO or not: while not all, many precision fermentation processes may employ the use of genetically modified (GM) microorganisms. In almost all the cases of precision fermentation, such GM microorganisms are, in theory, not to be remaining in the final products, however, the use of them in food production processes may still require regulatory compliance, countries or jurisdictions that have specific regulations regarding the use of GM microorganisms in the process.
- Additives or ingredients: Many countries and jurisdictions have regulatory categories for additives, enzymes, flavouring agents, processing aids, vitamins, infant nutrition and so forth, separated from other food ingredient category. Thus some precision fermentation-derived products that can be used as additives may require complying to the relevant categorical regulations. Here are some examples of products already commercialized in some countries and jurisdictions:
    - ice-structuring protein for use as an ingredient in ice cream;
    - steviol glycosides for use as a flavouring agent (sweetener);
    - soy leghemoglobin for use as a colourant, a flavouring agent or an ingredient for meat substitutes; and
    - bovine beta-lactoglobulin for use as an ingredient (dairy protein substitutes).
- Labelling issues, including allergenicity and hypersensitivity: Currently there is no country or jurisdiction that has precision fermentation specific labelling requirements. However, while the production processes can be different, precision fermentation-derived food products would be expected to have the same level of allergenicity and hypersensitivity in the foods produced through conventional production process.

As of July 2024, none of the countries or jurisdictions had any specific regulations in place for food products derived from precision fermentation. The food safety assessment for premarket approval is required in some countries or jurisdictions according to the relevant regulations, such as novel food regulations (Canada, the European Union). While there are no specific regulations for precision fermentation-derived food products, some countries indicated that new policy, legislation or regulations had been considered to be developed (Japan); or that at least the current regulatory framework would be amenable to changes (Australia, New Zealand). Several countries with premarket approval requirements indicated that there is a possibility for producers and developers to consult relevant regulatory authorities (e.g. presubmission consultation sessions) to discuss the regulatory pathway and food safety dossier requirements for their product. The Singapore Food Agency has issued a self-assessment checklist for companies producing precision fermentation-derived food products, so that they can submit a self-assessment of their food product for consultation, before submitting a full safety assessment dossier.

5.2 Food safety assessment

As in all other conventional food processing, the production process of precision fermentation would need to have a proper food safety assurance in all countries and jurisdictions. In the countries where premarket approval is required, submission and approval of the product's food safety assessment is one of the essential elements in the process. Various countries indicated they have either developed guidelines on safety considerations for the broader category of "cell-based foods", including not only microbial but also animal cells, or are in the process of doing so (Singapore, United States of America, Thailand). For many specific categories of products or processes (vitamins, enzymes, genetically modified organisms and so on), guidelines and procedures have already been elaborated in most of the countries that took part in the consultation.

Moreover, the FAO/WHO Codex Alimentarius has published internationally harmonized guidelines for the food safety assessment of microorganisms obtained through recombinant DNA techniques, excluding that of some substances produced by such microorganisms, namely processing aids and additives, such as enzymes (CXG 46-2003 – Guideline for the conduct of food safety assessment of foods produced using recombinant-DNA microorganisms). These guidelines recommend a comparative approach, assessing the genetically modified microbe (or derived foodstuff) against a conventional counterpart with a presumed history of safe use. Differences between them may arise from both intended and unintended effects of the modification. Depending on the identified differences, the focus will often be on assessing the safety of the recombinant microorganism itself or the substances it produces that are used in food. Items commonly considered during a safety assessment include, in brief (CXG 46-2003 – Guideline for the conduct of food safety assessment of foods produced using recombinant-DNA microorganisms):

- information concerning the safety of the gene donor organism and of the recipient host microorganism, together with the known function and safety of the gene product being transferred;[2]
- molecular characteristics of the DNA introduced into the recipient and any other changes to the host's DNA caused by the modification;
- characteristics of the newly expressed gene products (proteins, metabolites), their potential toxicity and role in pathogenicity;
- composition of foods produced by the recombinant microorganism as compared to conventional ones;
- potential allergenic and other immunological impacts of newly expressed proteins and metabolites, as well as potential interaction of the microorganism with the host's gastrointestinal immune system;
- viability of the microorganisms (if still present in the food) and their potential for residence in the gastrointestinal tract;
- presence of antibiotic resistance genes, and whether these are chromosomal or located on transmissible elements; avoidance of the use antibiotic resistance marker genes is discouraged, particularly if their transfer to other gastrointestinal microorganisms would result in a selective advantage; and
- nutritional modifications and to what extent these will affect the nutrient status of the population, particularly consumer groups at risk.

2 **Note:** In the European Union, the microbial production host used for food production will often belong to species or families that have been assessed by EFSA as having no history of pathogenicity or safety issues. These hosts thus have a qualified presumption of safety (QPS) status and do not require safety assessments for food applications. However, this is not the case for some microorganisms used in food production, such as filamentous fungi that, as a result of their possibly harmful traits, including the potential production of mycotoxins, always need to undergo a full safety assessment for each new food application {EFSA Panel on Biological Hazards *et al*., 2024). In the United States of America this evaluation is covered by the generally regarded as safe (GRAS) status of the food application involving the specific production host (FDA, 2016)

Given that all known food allergens are proteins, the question of whether a protein produced by genetically modified microorganisms could be an allergen deserves consideration. The annex to the guidelines describes, in more detail, the various aspects that an allergenicity assessment of a newly expressed protein should include (CXG 46-2003 – Guideline for the conduct of food safety assessment of foods produced using recombinant-DNA microorganisms). This follows a "weight of evidence" approach that includes:

- information on the source of the gene encoding the protein, including any reasonable proof of allergenicity via immunoglobulin E (IgE)-mediated reactions, be it through food, skin or inhalation;
- use of bioinformatics algorithms, the amino acid sequence of the newly expressed proteins can be compared to the sequences of proteins known to provoke allergic reactions;
- resistance to *in vitro* digestibility, for example by the stomach protease pepsin; and
- serum-binding tests: any relevant similarity with a known allergenic protein could warrant follow-up investigations into potential cross-reactivity in patients with that particular allergy. One way to do that would be through IgE sera testing.

An EFSA scientific colloquium on cell-culture-derived foods and food ingredients examined whether emerging safety concerns or methodological considerations related to the risk assessment of precision fermentation products could affect EFSA's current risk assessment procedures (EFSA *et al*., 2024). The EFSA colloquium concluded that most potential process- and product-related hazards (chemical and biological) were generally accounted for in existing risk assessment procedures. For food safety assessments focusing on product-related potential hazards, the following aspects were identified for consideration: the possible presence of (microbial) toxins, the presence and safety of secondary metabolites, potential allergenicity, the integrity of the product, protein function and the relative similarity or dissimilarity of the newly expressed proteins to known proteins. New, complex food matrices or whole foods such as cheese, produced through a combination of different precision fermentation-derived components, or proteins with unusual amino acids, may call for a closer attention for a specific safety assessment. A review on regulatory frameworks for novel foods further indicated that additional information on (i) microorganisms (e.g. modifications, antibiotic resistance, metabolic features including toxins); (ii) fermentation media (e.g. added substances, use of antimicrobial compounds); (iii) other materials used (e.g. enzymes, processing aids, solvents) and final product characteristics (e.g. analogy with traditional counterpart, viability of microbes in novel food product) might be useful for a comprehensive food safety assessment (Samarasiri, Chai and Chen, 2023).

A variety of safety assessment requirements acrossfrom various sectoral regulatory bodies in different countries would be likely to pose a significant challenge for developers/producers to comply with them. Having a set of internationally recognizable practical safety guidelines for production, input material selection and safety assessment can be useful for further development and commercialization of precision fermentation-derived food products. Some countries are leading efforts to collaborate with multiple regulatory agencies to align requirements for cell-based food safety assessment, including developing standardized medium compositions and a whitelist of food-grade input materials.

As regards the data sharing between authorities, there is a requirement for signatories to the international convention on biological diversity to notify other countries of the "living modified organisms" (LMOs) that may be traded or moved internationally. This is done via the Biosafety Clearing-House portal, established as per article 20 of the Cartagena Protocol on Biosafety. Information includes but is not limited to summaries of risk assessments and environmental reviews, final decisions and applicable national laws (Secretariat of the Convention on Biological Diversity, 2000). Besides this required sharing of data, nations may also voluntarily share data on genetically modified organisms through other international organizations' platforms, such as the OECD's BioTrack Product Database and FAO's GM Foods Platform, yet so far these have contained data on GM plants only. The OECD Working Party on the Safety of Novel Foods and Feeds has issued a consensus document detailing the various scenarios under which authorities from different nations can share and jointly assess dossier data on GM plants (OECD, 2023). The document lists the potential benefits and challenges of the different modes of collaboration, including peer-review of another agency's assessment, joint/parallel assessments, data sharing, risk assessment sharing, recognition of another agency's assessment, or the citation of other agencies' assessment in their own. It also highlights the role of such collaboration in capacity building and international harmonization. These collaborative practices could potentially extend to data on microorganisms.

5.3 Labelling, product names, authenticity and traceability

None of the countries or jurisdictions that participated in the consultation sessions reported that there is a labelling provision specifically set for precision fermentation. However, many of them indicated that there are labelling provisions for specific product categories (e.g. additives, ingredients), and reference was frequently made to the labelling of allergens, genetically modified organisms or compliance with religious standards (e.g. halal, kosher). A study on the specific regulatory frameworks applicable for dairy products obtained from precision fermentation in the European Union yielded similar outcomes (Ronchetti, Springer and Purnhagen, 2024). This study further indicated that product labelling regulations play an important role in premarket authorization. This relates to product naming, as well as claims regarding health, nutrition and dietary claims such as "vegan". Dairy products derived from precision fermentation may partly address the issue with specific legal names (e.g. milk or milk product). There is no clarity yet as to how milk-identical or similar components derived from precision fermentation can be named in many countries and jurisdictions. Similar issues may apply for other compounds produced by means of precision fermentation, such as collagen (meat protein) or ovalbumin (egg protein).

The authenticity and traceability of precision fermentation-derived products are also important issues for regulatory authorities, as it is in view of cellular agriculture developments at large (Camin *et al*., 2019; Defra, 2023; Mariano *et al*., 2023). In particular, the use of animal-specific compounds in food products produced through precision fermentation may face food fraud cases. Marketing claims such as "vegan" or "animal-free" or "sustainability" on the labelling are often linked to higher product prices and/or a positive product image, raising concerns about potential fraud, where cheaper conventional animal-derived ingredients might be included in food products making such claims. Strengthening the scientific capacity to detect such frauds may benefit competent authorities handle these situations more effectively in the future. Ensuring food authenticity might also be achieved by using technology-assisted traceability tools, such as blockchain.

5.4 Discussion

The study found that current regulatory frameworks in many countries cover the safety assurance of food products derived from precision fermentation, with more similarities than differences found across regulatory frameworks. It was highlighted that there are potentially significant varieties in labelling regulations and requirements, thus the topic may benefit from larger discussions among competent authorities at the international level. The relevant committees of the Codex Alimentarius, such as the Codex Committee on Food Labelling (CCFL), may provide a good forum for such discussions.

The regulatory snapshot presented in the document reflects the status as of July 2024 and may evolve as the industry grows and research and development progress. The regulatory practices presented in this document are real-case examples, and do not imply that FAO is endorsing any specific approach to regulating or managing the products derived through precision fermentation. This document is intended to support countries preparing for relevant regulatory activities, helping them to learn from the experience of other countries and identify approaches best suited to their needs and country contexts.

REFERENCES

Ahmad, M. I., Farooq S., Alhamoud Y., Li C., Zhang H. 2023. Soy leghemoglobin: A review of its structure, production, safety aspects, and food applications. *Trends in Food Science and Technology*, 141: 104199. https://doi.org/10.1016/j.tifs.2023.104199

Aljahdali, N. and Carbonero, F. 2019. Impact of Maillard reaction products on nutrition and health: Current knowledge and need to understand their fate in the human digestive system. *Critical Reviews in Food Science and Nutrition*, 59(3): 474–487. https://doi.org/10.1080/10408398.2017.1378865

Anyaogu, D. C. and Mortensen, U. H. 2015. Manipulating the glycosylation pathway in bacterial and lower eukaryotes for production of therapeutic proteins. *Current Opinion in Biotechnology*, 36: 122–128. https://doi.org/10.1016/j.copbio.2015.08.012

Barton, N.R., Burgard, A.P., Burk, M.J., Crater, J.S., Osterhout, R.E., Pharkya, P., Steer, B.A., Sun, J., Trawick, J.D., Van Dien, S.J., Yang, T.H. and Yim, H. 2015. An integrated biotechnology platform for developing sustainable chemical processes. *Journal of Industrial Microbiology and Biotechnology*, 42(3): 349–360. https://doi.org/10.1007/s10295-014-1541-1

Bilal, M., Ji, L., Xu, S., Zhang, Y., Iqbal, H.M.N. and Cheng, H. 2022. Bioprospecting and biotechnological insights into sweet-tasting proteins by microbial hosts-a review. Bioengineered, 13(4): 9815–9828. https://doi.org/10.1080/21655979.2022.2061147

Bych, K., Mikš, M.H., Johanson, T., Hederos, M.J., Vigsnæs, L.K. and Becker, P. 2019. Production of HMOs using microbial hosts — From cell engineering to large scale production. *Current Opinion in Biotechnology*, 56: 130–137. https://doi.org/10.1016/j.copbio.2018.11.003

Camin, F., Bontempo, L., Ziller, L., Franceschi, P., Molteni, A., Corbella, R. and Verga, I. 2019. Assessing the authenticity of animal rennet using δ15N analysis of chymosin. *Food Chemistry*, 293: 545–549. https://doi.org/10.1016/j.foodchem.2019.04.106

Chen, K., Wang, Y., Zhang, R., Zhang, H. and Gao, C. 2019. CRISPR/Cas Genome Editing and Precision Plant Breeding in Agriculture. *Annual Review of Plant Biology*, 70(1): 667–697. https://doi.org/10.1146/annurev-arplant-050718-100049

Chen, M., Liu, X., Liu, Q., Shi, D. and Li, H. 2023. 3D genomics and its applications in precision medicine. *Cellular and Molecular Biology Letters*, 28(1): 19. https://doi.org/10.1186/s11658-023-00428-x

Cuamatzin-García, L., Rodríguez-Rugarcía, P., El-Kassis, E. G., Galicia, G., Meza-Jiménez, M. d.L., Baños-Lara, M.d.R., Zaragoza-Maldonado, D.S. and Pérez-Armendáriz, B. 2022. Traditional fermented foods and beverages from around the world and their tealth benefits. *Microorganisms*, 10(6): 1151. https://doi.org/10.3390/microorganisms10061151

Davies, M. 2016. Corpus of News on the Web (NOW). https://www.english-corpora.org/now/

Defra. 2023. Implications of emerging novel proteins for food authenticity and labelling. Defra, FAO197. [Accessed 29 October 2024]. https://randd.defra.gov.uk/ProjectDetails?ProjectId=21140

Deng, M., Lv, X., Liu, L., Li, J., Du, G., Chen, J. and Liu, Y. 2023. Cell factory-based milk protein biomanufacturing: Advances and perspectives. *International Journal of Biological Macromolecules*, 244: 125335. https://doi.org/10.1016/j.ijbiomac.2023.125335

Dusséaux, S., Forman, V. and Kampranis, S. C. 2024. Precision fermentation to make non-alcoholic beer taste great. *Trends in Biotechnology*, 42(2): 253–254. https://doi.org/10.1016/j.tibtech.2023.10.016

EFSA (European Food Safety Authority), Afonso, A.L., Gelbmann, W., Germini, A., Fernández, E.N., Parrino, L., Precup, G. and Ververis, E. 2024. EFSA Scientific Colloquium 27: Cell Culture-Derived Foods and Food Ingredients. *EFSA Supporting Publications*, 21(3): 8664E. https://doi.org/10.2903/sp.efsa.2024.EN-8664

EFSA Panel on Biological Hazards, Koutsoumanis, K., Allende, A., Alvarez-Ordóñez, A., Bolton, D., Bover-Cid, S., Chemaly, M., De Cesare, A., Hilbert, F., Lindqvist, R., Nauta, M., Nonno, R., Peixe, L., Ru, G., Simmons, M., Skandamis, P., Suffredini, E., Cocconcelli, P.S., Fernández Escámez, P.S., Prieto Maradona, M., Querol, A., Sijtsma, L., Suarez, J. E., Sundh, I., Barizzone, F., Correia, S. and Herman, L. 2024. Update of the list of qualified presumption of safety (QPS) recommended microbiological agents intentionally added to food or feed as notified to EFSA 19: Suitability of taxonomic units notified to EFSA until September 2023. *EFSA Journal*, 22(1): e8517. https://doi.org/10.2903/j.efsa.2024.8517

Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO). 2023. Food safety aspects of cell-based food. Rome. https://doi.org/10.4060/cc4855en

Fatma, Z., Schultz, J.C. and Zhao, H. 2020. Recent advances in domesticating non-model microorganisms. *Biotechnology Progress*, 36(5): e3008. https://doi.org/10.1002/btpr.3008

FDA (Food and Drug Administration). 2016. Eligibility for classification as generally recognized as safe (GRAS). In: Food and Drug Administration, Department of Health and Human Services, ed. 21 CFR 570.30. https://www.ecfr.gov/current/title-21/part-570/section-570.3

FDA. 2018. Soy leghemoglobin protein preparation derived from *Pichia pastoris*. GRAS Notices, No. 737 [Accessed 30 October 2024]. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=737

FDA. 2019. β-lactoglobulin produced by *Trichoderma reesei*. GRAS Notices, No. 863. [Accessed 30 October 2024]. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=863

Flamm, E.L. 1991. How FDA approved chymosin: A case history. *Bio/Technology*, 9(4): 349–351. https://doi.org./10.1038/nbt0491-349

Fraser, R.Z., Shitut, M., Agrawal, P., Mendes, O. and Klapholz, S. 2018. Safety evaluation of soy leghemoglobin protein preparation derived from *Pichia pastoris*, intended for use as a flavor catalyst in plant-based meat. *International Journal of Toxicology*, 37(3): 241–262. https://doi.org./10.1177/1091581818766318

Grossmann, L. and McClements, D.J. 2023. Current insights into protein solubility: A review of its importance for alternative proteins. *Food Hydrocolloids*, 137: 108416. https://doi.org/10.1016/j.foodhyd.2022.108416

Hallman, W.K., Hallman, W.K. and Hallman, E.E. 2023. Cell-based, cell-cultured, cell-cultivated, cultured, or cultivated. What is the best name for meat, poultry, and seafood made directly from the cells of animals? *npj Science of Food*, 7(1): 62. https://doi.org/10.1038/s41538-023-00234-x

Health Canada. 2023. Food and Drug Regulations. C.R.C., c. 870, section B.28.001 https://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/section-B.28.001.html

Hilgendorf, K., Wang, Y., Miller, M.J. and Jin, Y.-S. 2024. Precision fermentation for improving the quality, flavor, safety, and sustainability of foods. *Current Opinion in Biotechnology*, 86: 103084. https://doi.org/10.1016/j.copbio.2024.103084

ISPA (International Society of Precision Agriculture). 2021. Precision Ag definition. In: *International Society of Precision Agriculture*. [Accessed 30 October 2024]. https://www.ispag.org/about/definition

Laulund, S., Wind, A., Derkx, P. M. F. and Zuliani, V. 2017. Regulatory and Safety Requirements for Food Cultures. *Microorganisms*, 5(2): 28. https://doi.org/10.3390/microorganisms5020028

Li, M., Huo, Y.X. and Guo, S., 2022. CRISPR-mediated base editing: From precise point mutation to genome-wide engineering in nonmodel microbes. *Biology*, 11(4): 571. https://doi.org/10.3390/biology11040571

Lyubomirova, T. 2023. 'A defining moment': Remilk's cow-free milk protein secures Israeli approval. *FoodNavigator-USA*. [Cited 31 October]. https://www.foodnavigator-usa.com/Article/2023/04/28/a-defining-moment-remilk-s-cow-free-milk-protein-secures-israeli-approval

Mariano, E., Lee, D.Y., Yun, S.H., Lee, J., Lee, S.Y. and Hur, S.J. 2023. Checkmeat: A review on the applicability of conventional meat authentication techniques to cultured meat. *Food Science of Animal Resources*, 43(6): 1055–1066. https://doi.org/10.5851/kosfa.2023.e48

Markova, E.A., Shaw, R.E. and Reynolds, C.R. 2022. Prediction of strain engineerings that amplify recombinant protein secretion through the machine learning approach MaLPHAS. *Engineering Biology*, 6(4): 82–90. https://doi.org/10.1049/enb2.12025

Mondaca-Navarro, B.A., Ramírez, R.R., Villa Lerma, A.G., Villa, L.A.A. and Pardo, G.D. 2019. Glycation of animal proteins via Maillard reaction and their bioactivity. In A.R. Marc, A.V. Díaz and G.D. Posada Izquierda, eds. *Food Processing*. Rijeka, IntechOpen. https://doi.org/10.5772/intechopen.90373

Nielsen, M.B., Meyer, A.S. and Arnau, J. 2023. The next food revolution is here: Recombinant microbial production of milk and egg proteins by precision ermentation. *Annual Review of Food Science and Technology*, 15: 173–187. https://doi.org/10.1146/annurev-food-072023-034256

Nyyssölä, A., Suhonen, A., Ritala, A. and Oksman-Caldentey, K.-M. 2022. The role of single cell protein in cellular agriculture. *Current Opinion in Biotechnology*, 75: 102686. https://doi.org/10.1016/j.copbio.2022.102686

Organisation for Economic Co-operation and Development (OECD). 2023. Considerations for collaborative work on the safety assessments of foods and feeds derived from rDNA plants – Consensus document. Series on the Safety of Novel Foods and Feeds No. 3. https://one.oecd.org/document/ENV/CBC/MONO%282023%2937/en/pdf

Pan, Y., Yang, J., Wu, J., Yang, L. and Fang, H. 2022. Current advances of *Pichia pastoris* as cell factories for production of recombinant proteins. *Frontiers in Microbiology*, 13: 1–14. https://doi.org/10.3389/fmicb.2022.1059777

Perrot, T., Marc, J., Lezin, E., Papon, N., Besseau, S. and Courdavault, V. 2024. Emerging trends in production of plant natural products and new-to-nature biopharmaceuticals in yeast. *Current Opinion in Biotechnology*, 87: 103098. https://doi.org/10.1016/j.copbio.2024.103098

Reyes, T.F., Agrawal, P., Chan, T., Green, R. and Matulka, R.A. 2023. The safety of soy leghemoglobin protein preparation derived from *Pichia pastoris* expressing a soy leghemoglobin gene from *Glycine max:* In vitro and in vivo studies. *Journal of Toxicology*, 2023: 7398724. https://doi.org/10.1155/2023/7398724

Riley, L.A.; Guss, A.M. 2021. Approaches to genetic tool development for rapid domestication of non-model microorganisms. *Biotechnology for Biofuels and Bioproducts*, 14: 1–17. https://doi.org/10.1186/s13068-020-01872-z

Ronchetti, F., Springer, L. and Purnhagen, K. P. 2024. *The Regulatory Landscape in the EU for Dairy Products Derived from Precision Fermentation*. Springer Cham2024].

Samarasiri, M., Chai, K.F. and Chen, W.N. 2023. Forward-looking risk assessment framework for novel foods. *Food and Humanity*, 1: 500–513. https://doi.org/10.1016/j.foohum.2023.06.020

Secretariat of the Convention on Biological Diversity. 2000. Cartagena Protocol on Biosafety to the Convention on Biological Diversity: Text and Annexes. Montreal, Canada, Secretariat of the Convention on Biological Diversity. [Cited 31 October 2024]. https://bch.cbd.int/protocol/default.shtml

Seo, S.-O. and Jin, Y.-S. 2022. Next-generation genetic and fermentation technologies for safe and sustainable production of food ingredients: Colors and flavorings. *Annual Review of Food Science and Technology*, 13: 463–488. https://doi.org/10.1146/annurev-food-052720-012228

Soice, E. and Johnston, J. 2021. How cellular agriculture systems can promote food security. *Frontiers in Sustainable Food Systems*, 5. https://doi.org/10.3389/fsufs.2021.753996

Tamang, J.P., Watanabe, K. and Holzapfel, W.H. 2016. Review: Diversity of microorganisms in global fermented foods and beverages. *Frontiers in Microbiology*, 7. https://doi.org/10.3389/fmicb.2016.00377

Tubb, C. and Seba, T. 2021. Rethinking food and agriculture 2020–2030: The second domestication of plants and animals, the disruption of the cow, and the collapse of industrial livestock farming. *Industrial Biotechnology*, 17(2): 57–72. https://doi.org/10.1089/ind.2021.29240.ctu

Waltz, E. 2022. Cow-less milk: The rising tide of animal-free dairy attracts big players. *Nature Biotechnology*, 40(11): 1534–1536. https://doi.org/10.1038/s41587-022-01548-z

Wang, D., Huaming, X., Xin, L., Hong, C. and Fang, W. 2023. Lipid oxidation in food science and nutritional health: A comprehensive review. *Oil Crop Science*, 8(1): 35–44. https://doi.org/10.1016/j.ocsci.2023.02.002

William, R. A. 2021. Opportunities and challenges for the introduction of new food proteins. *Annual Review of Food Science and Technology*, 12: 75–91. https://doi.org/10.1146/annurev-food-061220-012838

Woern, C. and Grossmann, L. 2023. Microbial gas fermentation technology for sustainable food protein production. *Biotechnology Advances*, 69: 108240. https://doi.org/10.1016/j.biotechadv.2023.108240

Wood, P., Thorrez, L., Hocquette, J.F., Troy, D. and Gagaoua, M. 2023. "Cellular agriculture": Current gaps between facts and claims regarding "cell-based meat". *Animal Frontiers*, 13(2): 68–74. https://doi.org/10.1093/af/vfac092

Zhang, Y.-H. P., Sun, J. and Ma, Y. 2017. Biomanufacturing: history and perspective. *Journal of Industrial Microbiology and Biotechnology*, 44(4–5): 773–784. https://doi.org/10.1007/s10295-016-1863-2

Zhu, Y., Cao, H., Wang, H. and Mu, W. 2022. Biosynthesis of human milk oligosaccharides via metabolic engineering approaches: Current advances and challenges. *Current Opinion in Biotechnology*, 78: 102841. https://doi.org/10.1016/j.copbio.2022.102841

Table 1

Aro, N., Ercili-Cura, D., Andberg, M., Silventoinen, P., Lille, M., Hosia, W., Nordlund, E. and Landowski, C. P. 2023. Production of bovine beta-lactoglobulin and hen egg ovalbumin by *Trichoderma reesei* using precision fermentation technology and testing of their techno-functional properties. *Food Research International*, 163(50): 112131. https://doi.org/10.1016/j.foodres.2022.112131

Augustin, M. A., Hartley, C. J., Maloney, G. and Tyndall, S. 2023. Innovation in precision fermentation for food ingredients. *Critical Reviews in Food Science and Nutrition*, 64(18): 6218–6238. https://doi.org/10.1080/10408398.2023.2166014

Banovic, M. and Grunert, K. G. 2023. Consumer acceptance of precision fermentation technology: A cross-cultural study. (Special issue on advances in food science and technology towards a healthy, safe, diverse, sustainable, efficient and resilient food chain.). *Innovative Food Science and Emerging Technologies*, 88: 103435. https://doi.org/10.1016/j.ifset.2023.103435

Behm, K., Nappa, M., Aro, N., Welman, A., Ledgard, S., Suomalainen, M. and Hill, J. 2022. Comparison of carbon footprint and water scarcity footprint of milk protein produced by cellular agriculture and the dairy industry. *International Journal of Life Cycle Assessment*, 27(8): 1017–1034. https://doi.org/10.1007/s11367-022-02087-0

Bijl, E. and Keppler, J. K. 2023. Lab-grown food? The precision fermentation approach. In: S. Pyett, W. Jenkins, B. van Mierlo, L.M. Trindade, D. Welch and H. van Zanten, eds. *Our future proteins: A diversity of perspectives*. Amsterdam, VU University Press.

Boukid, F., Ganeshan, S., Wang, Y., Tulbek, M. C. and Nickerson, M. T. 2023a. Bioengineered enzymes and precision fermentation in the food industry. *International Journal of Molecular Sciences*, 24(12): 10156. https://doi.org/10.3390/ijms241210156

Boukid, F., Hassoun, A., Zouari, A., Tülbek, M.C., Mefleh, M., Aït-Kaddour, A. & Castellari, M. 2023b. Fermentation for designing innovative plant-based meat and dairy alternatives. *Foods*, 12(5): 1005. https://doi.org/10.3390/foods12051005

Broad, G.M., Thomas, O.Z., Dillard, C., Bowman, D. and Le Roy, B. 2022. Framing the futures of animal-free dairy: Using focus groups to explore early-adopter perceptions of the precision fermentation process. *Frontiers in Nutrition*, 9, 1–14. https://doi.org/10.3389/fnut.2022.997632

Brune, S.E., Hoppenreijs, L.J.G., Kühl, T., Lautenbach, V., Walter, J., Peukert, W., Schwarz, K., Imhof, D., Boom, R.M., Krull, R., Keppler, J.K. and Biedendieck, R. 2023. Precision fermentation as a route to modify β-lactoglobulin structure through substitution of specific cysteine residues. *International Dairy Journal*, 147: 105772. https://doi.org/10.1016/j.idairyj.2023.105772

Chai, K. F., Ng, K. R., Samarasiri, M. and Chen, W. N. 2022. Precision fermentation to advance fungal food fermentations. *Current Opinion in Food Science*, 47(55): 100881. https://doi.org/10.1016/j.cofs.2022.100881

Crandall, B. S., Overa, S., Shin, H. and Jiao, F. 2023. Turning carbon dioxide into sustainable food and chemicals: How electrosynthesized acetate is paving the way for fermentation innovation. *Accounts of Chemical Research*, 56(12): 1505–1516. https://10.1021/acs.accounts.3c00098

Crawshaw, C. and Piazza, J. 2023. Livestock farmers' attitudes towards alternative proteins. *Sustainability*, 15(12): 9253. https://doi.org/10.3390/su15129253

Dodia, H., Sunder, A. V., Borkar, Y. and Wangikar, P.P. 2023. Precision fermentation with mass spectrometry-based spent media analysis. *Biotechnology and Bioengineering*, 120(10): 2809–2826. https://doi.org/10.1002/bit.28450

Dupuis, J.H., Cheung, L.K.Y., Newman, L., Dee, D.R. and Yada, R.Y. 2023. Precision cellular agriculture: The future role of recombinantly expressed protein as food. *Comprehensive Reviews in Food Science and Food Safety*, 22(2): 882–912. https://doi.org/10.1111/1541-4337.13094

Hassoun, A., Bekhit, A.E.D., Jambrak, A.R., Regenstein, J.M., Chemat, F., Morton, J.D., Gudjónsdóttir, M., Carpena, M., Prieto, M.A., Varela, P., Arshad, R.N., Aadil, R. M., Bhat, Z. and Ueland, O. 2022. The fourth industrial revolution in the food industry-part II: Emerging food trends. *Critical Reviews in Food Science and Nutrition*, 64(2): 407–437. https://doi.org/10.1080/10408398.2022.2106472

Hoppenreijs, L.J.G., Overbeck, A., Brune, S.E., Biedendieck, R., Kwade, A., Krull, R., Boom, R.M. and Keppler, J.K. 2023. Amyloid-like aggregation of recombinant β-lactoglobulin at pH 3.5 and 7.0: Is disulfide bond removal the key to fibrillation? *International Journal of Biological Macromolecules*, 242(2): 124855. https://doi.org/10.1016/j.ijbiomac.2023.124855

Juliano, P. and Reyes-De-Corcuera, J.I. 2021. Food engineering innovations across the food supply chain: Debrief and learnings from the ICEF13 congress and the future of food engineering. *Food Engineering Innovations Across the Food Supply Chain*, pp. 431–476. https://doi.org/10.1016/B978-0-12-821292-9.00027-3

Lee, J.J.L., Ng, K.R., Liang, J., Cui, X., Li, A. and Chen, W.N. 2023. Engineering the phenylpropanoid pathway in *Rhodosporidium toruloides* for naringenin production from tyrosine by leveraging on its native PAL gene. *ACS Food Science and Technology*, 3(1): 92–99. https://doi.org/10.1021/acsfoodscitech.2c00301

Li, C., Xu, D., Xiong, Z.Y., Yang, Y.M., Tian, G.W., Wu, X.Z., Wang, Y.H., Zhuang, Y.P., Chu, J. and Tian, X.W. 2022. Optimization of the fermentative production of *Rhizomucor miehei* Lipase in Aspergillus oryzae by controlling morphology. *Bioengineering-Basel*, 9(11): 610. https://doi.org/10.3390/bioengineering9110610

Liang, X., Du, J., Zhai, Z., Wang, R., Cao, Y., Niu, K. and Wu, X. 2023. Reclamation of the Lianhua-Qingwen residue as functional feed additives processed by a designed precise fermentation. *Waste and Biomass Valorization*, 15: 2121–2132. https://doi.org/10.1007/s12649-023-02262-w

Linder, T. 2023. Beyond agriculture – How microorganisms can revolutionize global food production. *ACS Food Science and Technology*, 3(7): 1144–1152. https://doi.org/10.1021/acsfoodscitech.3c00099

Lübeck, M. and Lübeck, P.S. 2022. Fungal cell factories for efficient and sustainable production of proteins and peptides. *Microorganisms*, 10(4): 753. https://doi.org/10.3390/microorganisms10040753

Luo, F., Halgas, O., Gawand, P. and Lahiri, S. 2022. Animal-free protein production using precision fermentation. *Journal of The American Oil Chemists Society*, 99: 148–149.

Marden, E., Kulkarni, D., McMahon, E.M., Rowand, M.S. and Verzijden, K. 2022. Regulatory frameworks applicable to food products of genome editing and synthetic biology in the United States, Canada, and the European Union. *Genomics and the Global Bioeconomy*, pp. 255–285. https://doi.org/10.1016/B978-0-323-91601-1.00001-8

Nastasijevic, I., Vesković, S. and Milijašević, M. 2020. Meat safety: Risk based assurance systems and novel technologies. *Meat Technology*, 61(2): 97–119. https://doi.org/10.18485/meattech.2020.61.2.1

Singh, S., Yap, W.S., Ge, X.Y., Min, V.L.X. and Choudhury, D. 2022. Cultured meat production fuelled by fermentation. *Trends In Food Science and Technology*, 120: 48–58. https://doi.org/10.1016/j.tifs.2021.12.028

Tachie, C., Nwachukwu, I.D. and Aryee, A.N.A. 2023. Trends and innovations in the formulation of plant-based foods. *Food Production, Processing and Nutrition*, 5(16). https://doi.org/10.1186/s43014-023-00129-0

Teng, T.S., Chin, Y.L., Chai, K.F. and Chen, W.N. 2021. Fermentation for future food systems precision fermentation can complement the scope and applications of traditional fermentation. *EMBO Reports*, 22(5): e52680. https://doi.org/10.15252/embr.202152680

Terefe, N. S. 2021. Recent developments in fermentation technology: Toward the next revolution in food production. *Food Engineering Innovations Across the Food Supply Chain*, pp. 89–106. https://doi.org/10.1016/B978-0-12-821292-9.00026-1

Thomas, O. Z. and Bryant, C. 2021. Don't have a cow, man: Consumer acceptance of animal-free dairy products in five countries. *Frontiers In Sustainable Food Systems*, 5. https://doi.org/10.3389/fsufs.2021.678491

Tubb, C. and Seba, T. 2019. Rethinking Food and Agriculture 2020-2030: The second domestication of plants and animals, the disruption of the cow, and the collapse of industrial livestock farming. In: *RethinkX*. [Cited 31 October 2024]. https://www.rethinkx.com/food-and-agriculture

Vanhercke, T. and Colgrave, M. 2022. What's brewing?: Precision food proteins from fermentation. *Food Australia*, 74(1): 23–25.

Yamaner, C. 2023. Precision cell agriculture and precision fermentation. In M.F. Baran and R. Gezer, eds. *Scope and importance of agricultural studies*, pp. 142. Isparta, Türkiye, Iksad Publishing House. https://iksadyayinevi.com/wp-content/uploads/2023/07/Scope-And-Importance-Of-Agricultural-Studies.pdf

Zollman T.O., Chong, M., Leung, A., Fernandez, T.M. and Ng, S.T. 2023. Not getting laid: Consumer acceptance of precision fermentation made egg. *Frontiers in Sustainable Food Systems*, 7. https://doi.org/10.3389/fsufs.2023.1209533

Table 2

Carter, M., Cohen, M., Eastham, L., Gertner, D., Ignaszewski, E., Leman, A., Murray, S., O'Donnell, M., Pierce, B. and Voss, S. 2022. *State of the industry report. Fermentation: Meat, seafood, eggs, and dairy*. The Good Food Institute. https://gfi.org/wp-content/uploads/2023/01/State-of-the-Industry-Report-Fermentation-2022.pdf

Hartman Group. 2023. Fermenting the future: The growing opportunity for products made with precision fermentation. White Paper. [Accessed 30 October 2024]. https://www.hartman-group.com/documents/2112785198/fermenting-the-future-the-growing-opportunity-for-products-made-with-precision-fermentation

Ontario Genomics and Agriculture and Agri-Food Canada (AAFC). 2023. *Cellular agriculture – Canada's $12.5 billion opportunity in food innovation*. Toronto, Ontario Genomics. https://www.ontariogenomics.ca/wp-content/uploads/2023/10/CELL_AG_REPORT_FULL-FINAL.pdf

Precision Fermentation Alliance. 2023. Frequently asked questions. In: *Precision Fermentation Alliance*. [Cited 31 October 2024]. https://www.pfalliance.org/faq/

Sales Flores, J. 2023. From lab to table: Precision fermentation for sustainable food innovation. Barcelona, Spain, Universitat Autònoma de Barcelona. Bachelor's degree dissertation. [Cited 31 October 2024]. https://ddd.uab.cat/record/277720

ANNEX 1. SEARCH STRATEGY

Introduction

This annex describes a strategy for the collection of data on different terminologies and definitions for precision fermentation. It covers the collection of data from both scientific literature and from "grey" sources. The latter include governmental risk assessment bodies, international associations, research institution reports and funding bodies, among other.

Databases

To ensure a comprehensive coverage of the relevant scientific literature, the following scientific databases were searched:

- **Web of Science (WoS; by Clarivate Analytics):** A collection of scientific citation and bibliographic databases covering more than 11 000 scientific journals. Besides the Web of Science Core Collection (*), the searches also accessed the Current Contents Connect, KCI – Korean Journal Database, Medline, Russian Science Citation Index and SciELO Citation Index databases.
- **CAB Abstracts (CAB International):** An applied life sciences-oriented database drawing on hand-selected references from over 10 000 titles of serials, books and conference proceedings from over 120 countries. CAB Abstracts offers an especially strong coverage of agricultural and food sciences.
- **Scopus (Elsevier):** A database covering more than 24 600 titles, including more than 23 500 journals, besides book series, other books and trade publications, spanning life, health, physical and social sciences.

In addition, the search engine Google Scholar was used for retrieving scientific articles.

Search strings

The search terms used in search strings for the concept "precision fermentation" are listed in **Box A1**.

Box A1. Concept and the linked search terms used for the bibliographic searches

Concept	Search terms#
Precision fermentation	• "precis* NEAR/2 ferment*" (Web of Science) • "precis* W/2 ferment*" (Scopus) • "precis* ADJ2 ferment*" (CAB Abstracts) • "precision fermentation" (Google searches)

Note: # For two words at a distance from each other (for example, "W/2" in Scopus).

Search operators

The proximity operator "NEAR/2" in WoS (equates to "ADJ2" in CAB Abstracts and "W/2" in Scopus) was used to ensure that both concepts would be linked in a significant portion of the retrieved records.

Further limitations

The period of publication was not limited to a specific period, as the term precision fermentation is relatively new. The searches were concluded on 5 October 2023. They were performed for Title, Abstracts and Keywords/Topic/Identifiers (this last term depends on the specific database). The language of the body of the publication was limited to English. Abstracts (e.g. conference proceedings), editorials, opinions, reviews and all other works not representing original work were not included in the core selection, yet some of these may still be retained for use (e.g. reviews).

Benchmark test

A benchmark test was performed to confirm the appropriateness and effectiveness of the search string for the complete retrieval of the relevant literature (i.e. 100 percent recovery of the benchmark).

Retrieval and selection of literature references

Bibliography searches and record retrieval

The bibliographic databases were queried using the selected search string. The records were then downloaded to a specific Endnote library file for each database. The records to be downloaded should contain sufficient bibliographic details (e.g. authors, title, source) and content (abstract, keywords), to the extent that these are available (for example, an abstract may in some cases be lacking). The contents of the separate Endnote file with the downloaded records from WoS, CAB and Scopus were merged, by means of an automatic and subsequently manual deduplication of records, into a single Endnote file. The latter file served as a basis for the screening of relevant content based on title, abstract and full text, followed by the full-text analysis and evidence synthesis.

Consistency checks

At each stage of the selection procedure (title, abstract and full-text levels), a subset of each selection of records was independently screened by two researchers and compared for inconsistencies. These inconsistencies were discussed and reconciled by the researchers to ensure that a consistent and reproducible screening could be performed. Each record of the remainder of the selection was then screened by at least one researcher.

Screening for relevance

The following subsequent steps were undertaken to screen for relevance and select those references that were relevant or for which irrelevance could not be confirmed (i.e. relevance still unclear):

1. **Screening of titles:** The titles were screened for relevance (“yes or unclear”) and those that appeared to be irrelevant (“no”) were discarded.

   While the complete exercise was to be carried out by one operator, a consistency check was to be performed upfront between this operator and another expert. To achieve this, the titles of the same, randomly chosen 10 percent of the records (from the retrieved records) were screened independently by both. Results were compared and inconsistencies resolved in discussions so that there was a common understanding of which titles needed to be retained and which not.

   Subsequently, a screening of the whole set of records was carried out. Selected titles were retained in a dedicated Endnote file, which was used at the next stage.

2. **Screening of abstracts:** For scoring, the operator used an Excel sheet into which the bibliographic data and abstracts of the retained records have been pasted. The records retained after title screening were thus scored for the following attributes:

   a. Abstract present? (Yes/no; if not, stop screening and retain record for next stage);

   b. English language? (Yes and unclear/no; if not, stop screening and discard record);

   c. Precision fermentation? (Yes and unclear/no; if not, stop screening and discard record).

   For the retained records, full references were collected and appended to the records within the Endnote file, so that these can be further used for the screening of full-text references in the next stage.

3. **Screening of the full text:** Similar to point 2, with the differences that full texts were gone over in order to extract information that was filled in into a more extensive manner. These outputs served as input for statistics mapping the features of the references as well as a narrative review summarizing the findings of the screened publications.

Grey literature research

Various sources were checked for relevant information on precision fermentation, as follows:

Category	Sources (examples)	Reference types
Non-original scientific papers	Discarded selection records	Reviews, congress papers, white papers
Regulatory	Risk assessment bodies (e.g. EFSA, US FDA and USDA, Health Canada and CFIA, FSANZ, SFA)	Risk assessments and safety assessment guidelines
Policy	Government institutions (European Commission, national governments) Advisory bodies Science academies Advocacy groups	Policy advice, regulatory impact assessments, research needs analyses, etc.
Food/feed sector media	Library collections, webpages industry, sector magazines (e.g. Food Navigator)	News items and reports from food/feed organisations
Health and food safety	International Organizations (FAO, WOAH, WHO, OECD)	Expert consultations, standards, guidelines and codes
Focus groups	The Good Food Institute, New Harvest	White papers, reviews, market developments, policy advice, research needs analysis

For the media use of precision fermentation terminologies (or common synonyms) by the media, the News on the Web corpus was used (https://www.english-corpora.org/now/), which is a highly searchable collection of texts, for the analysis of the frequency of use of specific terms.

Results

Database	Query	Hits
SCOPUS	TITLE–ABS–KEY(precis* W/2 ferment*)	100
Web of science	TS = (precis* NEAR/2 ferment*)	76
CAB abstracts	(precis* ADJ2 ferment*).ti, ab, id.	26
Google Scholar	intitle: “precision fermentation”	23
References retained (after merging and deduplication)		109
References retained (after title and abstract screening)		55

Database	Query	Hits
Google Advanced Search	"precision fermentation" filetype:pdf	about 2090 results

ANNEX 2. ORIGINAL INFORMATION SHARED

By the informal technical working group

Original regulatory snapshot table on Precision Fermentation (PF) filled by the countries participating in the informal Technical Working Group (As of July 2024)

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
Argentina							
No official definition for precision fermentation	No specific regulation for precision fermentation, regulation for microorganisms is present	Not specific for precision fermentation	Required, but not specific for precision fermentation	Several enzymes are on the market, purified products	Either, depending on the products	No specific requirements for labelling	
Australia							
No official definition for precision fermentation	No specific regulations for precision fermentation products. Precision fermentation products derived from GM microorganisms are regulated as food produced using gene technology under Standard 1.5.2 in the Australia New Zealand Food Standards Code which is developed and maintained by Food Standards Australia New Zealand (FSANZ). Other food standards may also apply, for example if the PF product is intended for use as a food additive, a nutritive substance or a processing aid. The relevant food standards are joint food standards with New Zealand.	Pre-market approval is required for food produced using gene technology, food additives, nutritive substances and processing aids. Pre-application assistance is available by contacting FSANZ directly. Further information available from: https://www.foodstandards.gov.au/food-standards-code/changing-the-code/pre-application-assistance	Guidelines and data requirements for food safety assessment of various substances and food ingredients are set out in the FSANZ Application Handbook.	A number of approved food additives, enzyme processing aids and nutritive substances derived using precision fermentation are likely in foods for sale in Australia, for example various steviol glycoside sweeteners, food enzymes and a number of human identical milk ooligosaccharide substances. FSANZ has also approved soy leghemoglobin as a nutritive substance in meat analogue products such as the Impossible burger.	See previous answers – most of the precision fermentation products approved to date are food additives, enzyme processing aids or nutritive substances.	There are no labelling requirements specifically related to precision fermentation. Standard ingredient labelling requirements apply such as for food additives or nutritive substances. GM labelling may also apply if novel DNA or novel protein is present in the food for sale. The FSANZ assessment will also consider whether additional labelling will also apply, e.g. allergen labelling.	Through pre-application discussions FSANZ is aware of a number of other precision fermentation products that are in the pipeline for submission to FSANZ over the next 12 months.

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
Brazil							
No official definition	There is no specific legislation for precision fermentation. Food ingredients obtained from GMO are regulated under the same resolution for novel foods ingredients – RDC 839/2023 (https://antigo.anvisa.gov.br/documents/10181/6582266/RDC_839_2023_.pdf/a064b871-55dd-44b9-ab40-16ca7672497d) In case of additives, the legal requirement to be met is RDC 778/23 (https://antigo.anvisa.gov.br/documents/10181/6561857/RDC_778_2023_COMP.pdf/1d50d56f-3aa1-4a62-8e19-f56068cc7337) Also, genetically modified organisms (GMOs) are regulated by Brazilian Biosecurity Law 11.105/2005.	A pre-market approval is necessary for any novel food ingredients or additives. For novel foods a consultation is possible (https://consultas.anvisa.gov.br/#/consultadeassuntos/detalhe/4144?codigosAssunto=4144).	Yes, the applicant must follow Guide 23/2019 (https://antigo.anvisa.gov.br/documents/10181/5355698/Guia+23_2019_vers%C3%A3o+1_de+23+07+19.pdf/96bc484d-2bde-4c99-9296-65c9325a033a).	Yes. 2'fucosyllactose, glucosamine, 6'-sialyllactose sodium salt	Food ingredients produced from GMO can be novel foods (nutritive purpose) or additives/processing aids. (technological function)	No specific labelling as precision fermentation derived product.	

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
Canada							
No official definition	Any food ingredient for nutritive purposes produced from an organism genetically modified to change the organism's characteristics meets the definition of Novel Food and is subject to the pre-market provisions under the Food and Drug Regulations B.28 (Novel Food Regulations)	Petitioners preparing a Novel Food pre-market submission are encouraged to request a pre-submission consultation by contacting the Submission Management Information Unit (smiu-ugdi@hc-sc.gc.ca). The consultation meeting is a voluntary service allows petitioners to ask questions about the pre-market process their intended approach for meeting safety end-points.	Yes. See Guidelines for the Safety Assessment of Novel Foods – Canada.ca section 4.2.3 for GM microbes. For products produced using cultured cells other than microbes, please consult SMIU.	Yes. 2'fucosyllactose, soy leghemoglobin, beta-lactoglobulin	Food ingredients produced from GM organism and are for nutritive purposes are Novel Foods. Products for other food uses could be classified as food additives or processing aids. Consultation with Food Directorate is recommended for any questions regarding classification.	Under federal law, all foods sold in Canada, including any approved product of cellular agriculture such as precision fermentation derived products, must be labelled so that they will not be mistaken for another food. The label must have the food's common name that is specific and accurately identifies or describes the food in clear terms to allow a person to make an informed purchasing decision. All label information must be truthful and not misleading, including any health- or environment-related claims. Other food labelling rules may also apply, such as labelling for health and safety (i.e., allergen labelling) and compositional standards of identity. They would apply on a case-by-case basis.	N/A

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
Chile							
No.	No. Chile does not have any specific legislation for precision fermentation.	No relevant legislation.	For any food product that the Chilean health authority does not have history record of safe consumption, the health authority asks food businesses for some additional tests to have the production process approved. These tests depend on the nature of the food products, for example, toxicological tests. There are internal guides established by the central level of the Ministry of Health, so that the local health authority applies these criteria, but there is no specific regulations. Usually these processes take a long time and there are no homologous criteria regarding the requirements to approve the products for consumption.	No, but there are some enterprises in the country that are innovating in this area (and the government is expecting to set up regulatory frameworks accordingly)	No specific regulations.	No specific regulations.	There is a definition of "new food" in the Chilean legislation. ACHIPIA is assisting the Ministry of Health to make a specific regulator framework for new foods with relevant definitions, an approval process and criteria for approval. The current definition is: "New food, ingredient and food material: that food, ingredient and food material obtained through physical-chemical synthesis process or through processes that occur in nature that do not correspond to molecule or compound typical of known human nutrition."

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
China							
No. At present, there is no definition of "precision fermentation" in China's relevant national food safety standards, but for some products of precision fermentation, China is allowed to use. For example, some food additives and nutritional fortifiers produced by genetically modified microorganisms have been approved for use.	No specific one. However, China Food Safety Law asked National Health Commission (NHC) to carry our pre-market approval of following three new food products, novel foods/new food ingredients, new food additives, new food related products. NHC allow to use new technologies, such as precision fermentation to produce the enzymes and ingredient with genetically modified microorganisms. However, at present, for food additives and nutritional fortifiers produced by GMO and synth-biology technology, the safety of the producing strains is first evaluated by the Ministry of Agriculture, mainly based on the relevant management documents of GMO. After issuing the GMO biosafety certificate, NHC take the pre-market approval after the CFSA risk assessment.	Yes. In China, three new food products (novel foods/ New Food Ingredients, new food additives, new food related products) using new technologies, such as precision fermentation, need the pre-market approvals.	Yes. At present, for food additives and nutritional fortifiers produced by genetically modified microorganisms, the safety of the strains produced is mainly based on the relevant management documents of genetically modified microorganisms of the Ministry of Agriculture and Rural Affairs. Now CFSA is studying the classification and management measures for novel foods, novel foods and new food-related products produced by genetically modified microorganisms or precision fermentation, and establishing the related guideline based on classification.	Yes. Some food additives and nutritional fortifiers produced by genetically modified microorganisms have been approved for use. For example: HOMs produced by microbial fermentation. Up to now, China has approved 2-FL and 1 LNnT produced by 4 different strains, which can be used as nutritional fortifiers for children's milk powder, infant formula, etc.	They are usually food additives and nutritional fortifiers. New food ingredients will come soon.	Such substances are managed in accordance with food additives in China, and their labeling should comply with the GB29924 National Food Safety Standards General Principles for the Labeling of Food Additives». If new food ingredients, GB7718 should be comply with National Food safety standards for food labelling.	

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
European Union							
No legal definition. In the absence of a legal definition and for the purpose of the 27th EFSA's Scientific Colloquium on "Cell culture-derived foods and food ingredients", EFSA defined precision fermentation (PF) as the use of engineered microbial cell factories in the production of food ingredients.	No specific regulation for PF-derived foods. In the EU, food ingredients derived from PF require pre-market authorisation under different regulatory frameworks and are subject to risk assessment by EFSA. • Food additives and flavourings fall under the scope of Regulations (EC) No 1331/2008, 1333/2008 and 1334/2008, • Food enzymes under Regulation (EU) 1332/2008, • Novel foods under Regulation (EU) 2015/2283, • Genetically modified organisms (GMOs) under Regulation (EC) No 1829/2003.	For novel foods a consultation is possible in the case that food business operators would be unsure on whether or not a food which they intend to place on the market within the EU falls within the scope of the Novel Foods Regulation. But it is not specific to precision fermentation products., https://food.ec.europa.eu/safety/novel-food/consultation-process-novel-food-status_en In addition, general pre-submission advice by EFSA is available, together with other dedicated services for potential applicants. https://www.efsa.europa.eu/en/applications/about/services	Yes, EFSA guidance documents for: Novel foods () GMMs: https://www.efsa.europa.eu/en/efsajournal/pub/2193 Food additives: https://www.efsa.europa.eu/en/efsajournal/pub/2760 Food enzymes: https://www.efsa.europa.eu/en/efsajournal/pub/6851 FYI, EFSA is currently developing a horizontal guidance on the risk assessment of microorganism intentionally added to the food chain, in order to harmonise the scientific requirements for the risk assessment across regulatory sectors. This guidance is relevant for precision fermentation derived products.	Yes. This counts e.g. for common food additives (vitamins, colorants) and enzymes from precision fermentation, that are already on the market for a long time. With regards to Novel foods i) Ice-structuring protein (ISP) type III (originally isolated from *Macrozoarces* americanus), produced by precision fermentation, was authorised in 2009. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32009D0344 ii) Several human-identical milk oligosaccharides (HiMOs) produced by precision fermentation are already authorised as novel foods (2'-fucosyl-lactose, 3-fucosyl-lactose, 2'-fucosyl-lactose/difucosyl-lactose mixture, lacto-N-tetraose, lacto-N-neotetraose, 3'-sialyl-lactose sodium salt and 6'-sialyl-lactose sodium salt). In addition, a lacto-N-fucopentaose I/2'-fucosyl-lactose mixture has already been assessed by EFSA with positive outcome.	This depends on nature and use of the product, see column C.	No specific labelling as precision fermentation derived product. If a PF product falls under the GMO legislation (See column C), the GMO labelling provisions apply. Note: general labelling requirements or restrictions may exist. E.g. food additives need to be mentioned as ingredient on a label. Precision fermentation derived dairy products cannot be named as e.g. milk or cheese.	

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
Guatemala							
No specific definition.	No specific regulation for precision fermentation						
Indonesia							
No	No specific regulation, but Food Law 86 of 2019, of the Indonesian Food Authority.	No specific pre-market assessment for these products.	General Food safety assessment is required for new food products entering the market, as well as halal evaluation				
Iran (Islamic Republic of)							
No official definition.	Fermented food products have its own regulation in Iran (Islamic Republic of), no specific regulation for precision fermentation	Pre-market approval is necessary for fermented products	Assessment conform Biosafety Law and regulations for GMOs	Yes. Fermentation derived enzymes and food products		Labelling requirements for fermented products, not specific to precision fermentation	
Israel							
No legal definition.	No specific regulation for -precision fermentation derived foods.	Pre-market approval is needed in case of novel food but not specific to precision fermentation. For novel food consultation is possible but it is not set in the regulation.	General guidelines for novel food are available in Hebrew on the NFS website.	Yes. Food additives and HMO that are derived from precision fermentation are on the market for quite some time.	It depend on the intendent use, there are food additives but also ingredients.	No specific labelling.	
Japan							
No official definition for precision fermentation.	No specific regulations for precision fermentation products. The safety assessment of foods and food additives produced by recombinant DNA techniques (hereafter GM foods) is mandatory under the Food Sanitation Act. Further information available from: https://www.caa.go.jp/en/policy/standards_evaluation/dna_techniques	No specific regulations for precision fermentation products. In the case of GM Foods, pre-market approval is required, and the applicant can request a prior consultation in order to confirm whether such foods, etc. fall under a target of notification or safety assessment.	In the case of GM foods, the following guidelines would apply. See Guideline; https://www.fsc.go.jp/senmon/idensi/gm_kijun_english.pdf https://www.fsc.go.jp/senmon/idensi/index.data/Standards_GM_microorganism.pdf https://www.fsc.go.jp/senmon/idensi/gm_tenkabutukijun_english.pdf https://www.fsc.go.jp/senmon/idensi/gm_hitanpakutenkabutu_kijyun_english.pdf	No official definition for precision fermentation. The GM foods and food additives which completed safety assessment are available to use and distribute on the market.	Depending on the final use of the product, it may be considered as food additive or ingredients.	No official definition for precision fermentation.	

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
New Zealand							
No legal definition for precision fermentation.	No specific regulations have been identified for precision fermentation in NZ, but the food safety framework allows for additional regulation to be developed as identified and needed to address new risks introduced by food processing. Precision processing is seen as a food production process that is subject to regulation. Food safety requirements are risk-based and a processor would need to prove their method produced a safe and suitable/fit for purpose product. Once permission for a novel food has been granted, and a processor applies to make it in NZ, the processor needs to meet food/product processing requirements; including validating product safety and suitable or fitness for purpose. MPI provides guidance: https://www.mpi.govt.nz/food-business/running-a-food-business/risk-management-programmes-rmps/develop-a-risk-management-programme/ And https://www.mpi.govt.nz/food-business/running-a-food-business/food-control-plans/custom-food-control-plans/	The use and sale of food/substances derived from precision fermentation requires pre-market approval by Food Standards Australia and New Zealand (FSANZ). Depending on the nature and intended use, the final product may be approved as food produced using gene technology, food additives, processing aids and/or nutritive substances. Most PF products are regulated in the Australia and New Zealand Food Standards Code (the Code) as foods produced using gene technology. Other regulations relating to food additives and processing aids may also apply. FSANZ strongly advise applicants to arrange a meeting with FSANZ to discuss their application prior to submission.	Guidelines on the pre-market approval process as well as data requirements for different product categories (e.g. food additives, nutritive substances, food produced using gene technology) are available in the 'FSANZ Application handbook': https://www.foodstandards.gov.au/food-standards-code/consultation/applicationshandbook	The FSANZ process has approved: soy-based 'heme' (Soy Leghemoglobin); Lacto-N-neotetraose (LNnT); 2'-Fucosyl-lactose (2'FL) – produced by microbial fermentation using a genetically modified (GM) strain of *Escherichia coli* K-12; Rebaudioside M as a steviol glycoside; Precision fermentation-derived enzymes	To date: Soy Leghemoglobin) approved as a nutritive substance (iron in the form of soy leghemoglobin) for use in meat analogue products; Lacto-N-neotetraose (LNnT) is approved as nutritive substance added to infant formula products; 2'-FL as a nutritive substance for use in infant formula products; Rebaudioside M as a steviol glycoside food additive; Enzymes as processing aids. Precision fermentation products meet the definition of 'food' in NZ legislation, and the system enables them to be categorised according to the food sector they are developed by.	No specific labelling currently for precision fermentation-derived products. In New Zealand, food labelling requirements are set through the Code. A FSANZ assessment would identify any changes needed to the Code for product labelling. Where there is a GM component to substances produced using precision fermentation, and novel DNA or novel protein is present in the food for sale, there is a requirement to label the ingredient as 'genetically modified'	

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
North Macedonia							
No legal definition.	Foods derived by precision fermentation are generally considered novel foods in North Macedonia. Thus, they need to comply with the requirements concerning novel foods provided in the Law on food safety and the Rulebook of specific requirements for safety of novel foods (OG of RNM 173/2020) which is aligned with EU Regulation 2283/2015. Novel foods require pre-market authorization in North Macedonia.	Pre-submission consultation is available for all novel foods in case food business operators are unsure on whether or not a food which they intend to place on the market in North Macedonia falls within the scope of the novel foods. Rulebook on the consultation process for novel foods is planned to be adopted by the end of 2026 but it is not specific to precision fermentation-derived novel foods.	No guidelines are currently available.	Yes, precision fermentation – derived food ingredients considered as novel foods which are authorized by the EU and included in the Union list of novel foods can be placed on the market in North Macedonia as well. These mostly fall in the category of HIMOs, such as 2'-fucosyl-lactose, 3'-fucosyl-lactose, 3'-sialyllactose sodium salt etc.	Depending on the proposed use of the product and in line with the adopted EU authorizations. Generally, they are considered novel foods, but may also be considered food improvement agents (additives, enzymes).	No specific labelling requirements for precision fermentation ingredients other than those specified in the Union list of novel foods (EU Regulation 2470/2017) which is transposed in the national legislation.	
Qatar							
No	Novel food standard GSO 2696:2022	Yes, it must be evaluated by SC regarding its safety and suitability	There is a procedure that must be followed according to the relevant GSO standard 2696:2022	No, any food or ingredients issued from Genetically modified bacteria or microbes are not yet allowed in Qatar	We do not have any official definition for precision fermentation products	Yes, all ingredients should be presented clearly to the consumer	There are some precision fermentation products that are in the process of being evaluated from a food safety perspective
Republic of Korea							
No official definition	New food ingredient derived from precision fermentation is subject to 'Standards for Approval of Temporary Standards and Specifications for Foods, etc.' under Food Sanitation Act (Article 7.2) for safety assessment.	Yes. There is a division called the Pre-submission Consultation Division in MFDS and applicants can receive consultation when applying to that division.	Yes. 'Guideline for safety assessment of new food ingredients' and 'Explanation of safety assessment regulations for genetically modified foods' for in Korean is on the Ministry of Food and Drug Safety website. https://www.mfds.go.kr/brd/m_1060/list.do?multi_itm_seq=0&board_id=data0011&seq=&data_stts_gubun=C9999&srchTp=0&srchWord=%EC%8B%9D%ED%92%88%EC%9B%90%EB%A3%8C	Yes. 2-fucosyl-lactose	Usually considered as food ingredients	No specific labelling as precision fermentation derived product. Basically, the name of ingredient used in foods shall be labelled under Act on Labelling and Advertising of Foods.	

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
Saudi Arabia							
No	There are general technical regulations, standards and guidelines of food product safety, labelling, and additives and others that apply to all food products marketed or sold in Saudi Arabia. In addition, there is a specific technical regulation for Novel Foods: • SFDA.FD 5013 : General Requirements for Novel Foods. and Technical regulations for Genetically Modified Organisms: • SFDA.FD/GSO 2141: General Requirements for Genetically Modified Unprocessed Agricultural Products. • SFDA.FD/GSO 2142: General Requirements for Genetically Modified Processed Food and Feed. • SFDA.FD/GSO 2143: General requirements for risk assessment and traceability for genetically modified products. SFDA.FD/GSO 2371: General requirements for risk assessment and traceability for genetically modified products.	Generally, food products that are considered novel, such as those containing new ingredients or innovative production techniques, may require pre-market approval from the Saudi Food and Drug Authority before they can be imported, manufactured, or sold in Saudi Arabia. In many jurisdictions, including Saudi Arabia, the regulatory framework for novel food products, including those derived from precision fermentation, depends on factors such as their safety, composition, intended use, and similarity to existing food products. Guide to The Approval of Novel Foods – link.	Novel foods are subject to scientific evaluation process to ensure their safety and effectiveness in producing a product suitable for human consumption. This procedure takes place before authorizing the marketing of the novel food product	No		No, but there are general requirements for labelling of prepacked foodstuffs and it depends on the product requirements. SFDA.FD/GSO 9: Labelling Of Prepackaged Food Stuffs.	When it comes to cell-based food products, Saudi Arabia is not only concerned about ensuring the safety of these products for the consumer, but we're also keen to study the religious aspect of such products. Therefore, currently Saudi Arabia is leading the Islamic view file on 2 levels: 1. Islamic member countries under Standards and Metrology Institute for Islamic Countries (SMIIC). 2. Gulf member countries under GCC Standard-ization Organization (GSO).

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
Singapore							
No official definition. Working definition of precision fermentation is ingredients that are chemically identical to naturally occurring substances but produced by unconventional processes.	Product of precision fermentation could be evaluated as novel foods. Novel foods are required to undergo pre-market safety assessment before being allowed for sale. Requirements for safety assessment are detailed in SFA's novel food guidance document. SFA is currently in process of public consultation for the Food Safety and Security Bill (FSSB), which amongst other matters, will seek to formalize the need for companies to seek pre-market approval for novel foods. Where substances derived from precision fermentation are intended to be used as food additives (i.e. their addition is intended to fulfill a specific technological function), companies are required to apply for the inclusion of their food additive into the Singapore Food Regulations.	SFA will direct companies intending to sell novel foods to attend the SFA Novel Food Clinic to better understand SFA's requirements. For companies that are intending to sell food additives produced with precision fermentation, SFA encourages these companies to review SFA's guidance document on food additives and engage with SFA early on their plans.	Novel food companies applying for application of precision fermentation products can refer to the SFA Novel Food guidance document (specifically Section 4.2-4.3) and also fill up the self-assessment checklist for precision/ biomass fermentation processes.	Yes, in the area of food additives, various food enzymes that are derived from precision fermentation have been listed as permitted food additives in the Singapore Food Regulations. In the area of novel foods, Beta-lactoglobulin is an example of a novel food produced by precision fermentation that has been previously assessed and allowed for sale as a novel food ingredient.	This is dependent on the intended use proposed by the developer.	There is currently no specific labelling requirement for a precision fermentation derived product. Labels should be truthful and not misleading, e.g., beverage containing whey protein made using precision fermentation should not be labelled as milk from cows. Allergen labelling is still required for substances that are chemically equivalent to existing allergens.	
Switzerland							
No official definition	No specific regulation, if host is genetically modified then follows GMO regulation, otherwise Novel Foods regulation, which are based on EU regulations and guidance by EFSA						

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
Thailand							
No official definition	There is no specific regulation for cell-based food in Thailand. However, any food manufactured with the novel process such as, in this case, precision fermentation may or may not fall under the Notification Number 376 depending on the output or finished products of the process. Novel Food Registration is enforced by the Notification of Ministry of Public Health No. 376 issued in 2016, which defined Novel food as a substance (both finished product or a single ingredient) or an innovative process to produce food.		For cell-based and precision fermentation, safety assessment of the product shall be evaluated prior to product registration and submission of the label to Food and Drug Administration for approval before use. There is no specific regulations or guidance on labelling for cell-based and precision fermentation.			No specific labelling as precision fermentation derived product. Labeling of novel food shall follow the Notification of the Ministry of Public Health No. 367 regarding labeling of prepackaged foods packaged for both imported and domestically produced food products. Indication of ingredient source shall be expressed on its label to help with the consumer's choice. Information on food labels shall not be false or misleading to consumers.	Thailand is on the process to develop the guideline for cell-based food safety assessment and additional requirements for critical control points in the facilities manufactured these innovative foods to ensure the safety and suitability of the product.
United Arab Emirates							
No official definition	No specific regulation for precision fermentation derived foods. Any food ingredient derived from precision fermentation is considered as a Novel Food. Therefore, it falls under UAE.S 5048:2021: General Requirements for Novel Foods	Yes, Novel Foods undergo a pre-marketing evaluation from the competent authorities with regard to risk analysis and health and safety considerations, including carrying out the necessary laboratory tests prior to handling and marketing.	Yes, There is a general framework for risk assessment and requirements for the novel food are stated in UAE.S 5048:2021: General Requirements for Novel Foods	Yes, Several types of Genetically Modified foods are available in UAE markets.	Depending on the final use of the product it may be considered as ingredient or food additive, other.	Yes, All food labelling in UAE falls under the regulation UAE.S 9: Labelling of Pre-Packed Foods	N/A

Definition	Specific regulations	Pre-market food safety assessment	Safety assessment guidelines	Products on the market	Categorization of the products (additives or ingredients)	Labelling requirements	Additional information
United Kingdom of Great Britain and Northern Ireland							
No official definition	No specific regulation for PF-derived foods. Food ingredients derived from PF likely to require pre-market authorisation where they meet the definition of a novel food, GM or other regulated product. They would be subject to our regulated products service and risk assessment	There is no requirement for pre-submission consultation. Those interested in applying for precision fermentation products are encouraged to engage with the pre-application team to support the development of their application.	For precision fermentation products that are subject to regulated products premarket authorization we continue to use the EFSA guidance. We have also developed a hazard identification for cultured meat which may be useful for informing the development of applications.	Yes, there are a number of products of precision fermentation that were authorized before the UK's exit from the EU. Under the respective regulated products frameworks. We have also authorized a number of products, in particular HMOs for use in the UK market.	The classification of the precision fermented product would depend on the regulatory framework that applied – some are foods, some are additives, and some are GMOs depending on their characteristics, how they are produced and function.	No specific labelling is required for precision fermentation products. Products would be labelled as a GMO or additive where they meet the definition of that regulated product regime. There is the potential to label if there is a risk management need.	
United States of America							
No official definition.	Substances produced from precision fermentation are regulated using the same legal provisions to used to regulate the use of other food ingredients. We have tools available to help developers determine the regulatory status of a food ingredient and guidance that can be used to inform safety assessment and how to make a submission to our programs.	Yes. We strongly encourage firms wishing to engage in our premarket processes to meet with us prior to making a submission. Pre-submission meetings are typically available upon request and are operated virtually.	Yes. We have a wide range of tools available to help developers. We have tools available to help developers determine the regulatory status of a food ingredient and guidance that can be used to inform safety assessment and how to make a submission to our programs. We also recognized that the Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombiant-DNA Microorganisms may have useful information. Because precision fermentation can be used to produce a wide range of products, we strong suggest that developers meet with us before making a premarket submission to our programs. During such meetings we can point developers to the guidance most relevant to their product.	Yes. Such products have arguably been on the market since the 1990's when chymosin was produced in a genetically engineered microbe.	Ordinarily substances derived from precision fermentation (purified substances intended to be added to food for a specific intended use) would be considered ingredients and would be regulated as food additives unless their use is generally recognized as safe. Importantly, however, the fact that a product was or was not produced through precision fermentation is not determinative of its regulatory status.	Whether labeling indicating that a food contains an ingredient that is "bioengineered" may depend on specific aspects of the product and how it is intended to be used. This program is administered by the Department of Agriculture's Agricultural Marketing Service. Res for complying with bioengineered labeling requirements can be found here.	

Agrifood Systems and Food Safety
Economic and Social Development
fao.org/food-safety

Food and Agriculture Organization of the United Nations
Rome, Italy

ISBN 978-92-5-139643-8

9 789251 396438

CD4448EN/1/03.25