Cultured Proteins: An Analysis of the Policy and Regulatory Environment in Selected Geographies

October 2019

PATH

Acknowledgments

This report was developed as part of a series of interrelated assessments regarding alternative proteins. The development of this report was led by PATH in collaboration with Duke University, the International Food Policy Research Institute, and The Nature Conservancy through the Bridge Collaborative.

PATH gratefully acknowledges the input and feedback of the many technical experts who reviewed and contributed to this report. We would like to thank the stakeholders who participated in interviews for their time and insights. We would also like to thank Kaleab Baye, Isha Datar, Cyril Engmann, Bruce Friedrich, Deepti Kulkarni, Varun Deshpande, Elizabeth Derbes, Danie Shajie, and Karin Verzijden for reviewing this report. Finally, we would like to thank Shawn Kavon for graphic design and Teri Gilleland Scott and Rica Asuncion-Reed for proofreading. The development of this report was made possible with funding from The Rockefeller Foundation.

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Suggested citation: PATH. *Cultured Proteins: An Analysis of the Policy and Regulatory Environment in Selected Geographies.* Seattle: PATH; 2019.

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October 2019

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Abbreviations

CDSCO	Central Drugs Standard Control Organization (India)
CFT	confined field trial
EC	European Commission
EFDA	Ethiopian Food and Drug Authority
EFSA	European Food Safety Authority
ESA	Ethiopian Standards Agency
ETA	Enzyme Technical Association
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	US Food and Drug Administration
FSSAI	Food Safety and Standards Authority of India
GDP	gross domestic product
GEAC	Genetic Engineering Appraisal Committee (Ministry of Environment and Forests, India)
GM	genetically modified
GMO	genetically modified organism
GRAS	Generally Regarded as Safe
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LMICs	low- and lower-middle income countries
MOA&L	Ministry of Agriculture and Livestock Resources (Ethiopia)
MoTI	Ministry of Trade and Industry (Ethiopia)
PAFF Committee	Standing Committee on Plants, Animals, Food and Feed (European Commission)
PPP	purchasing power parity
RCGM	Review Committee on Genetic Manipulation (Ministry of Science and Technology, Department of Biotechnology, India)
US	United States
USDA	US Department of Agriculture
WHO	World Health Organization

Key terms

Alternative proteins	A broad term that refers to any proteins intended to replace animal-source proteins derived from traditional livestock. These might include proteins derived from plants, microorganisms, or animal cell culture.
Bioengineered food	Defined by the US Department of Agriculture as "detectable genetic material that has been modified through in vitro recombinant deoxyribonucleic acid (rDNA) techniques and for which the modification could not otherwise be obtained through conventional breeding or found in nature; provided that such a food does not contain modified genetic material if the genetic material is not detectable."[1]
Cellular agriculture	Cellular agriculture is the manufacture of animal products from cells rather than from traditional animal farming methods of breeding, rearing, and slaughter.[2] The two main types of cellular agriculture are fermentation-based and tissue engineering–based processes.[3]
Cultured proteins	Also known as "synthetic," "lab-grown," "fermentation-derived," and "flora-based" proteins, cultured proteins are produced through fermentation wherein unicellular organisms (e.g., microflora such as fungi and yeast) express a desired organic molecule end product during the fermentation process.[4]
Cell-based meat	Also known as "clean," "lab-grown," "cultivated," "cultured," and "in vitro" meat, cell-based meat is the product of a cellular agriculture process that utilizes a cell or tissue line from a living animal to grow and culture a desired product in a laboratory.[3]
Genetically modified (GM) food	Defined by the World Health Organization as "foods derived from organisms whose genetic material (DNA) has been modified in a way that does not occur naturally (e.g., through the introduction of a gene from a different organism)."[5]
Genetically modified organism (GMO)	Defined by the World Health Organization as "organisms (i.e., plants, animals or microorganisms) in which the genetic material (DNA) has been altered in a way that does not occur naturally by mating and/or natural recombination. The technology is often called 'modern biotechnology', or 'gene technology', sometimes also 'recombinant DNA technology', or 'genetic engineering.'"[6]
Living modified organism	Defined by the Cartagena Protocol on Biosafety to the Convention on Biological Diversity as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology."[7]
Microflora	A group of microorganisms, including algae, fungi, and bacteria, that live in a particular habitat (e.g., intestines).[8]
Novel food	Broadly, the term novel food refers to a food that does not have a significant history of human consumption or is produced in a new way. This designation is often used in policies and regulations, and different countries and geographies adopt specific definitions for novel foods. For example, the European Commission defines a novel food as a food that was not consumed significantly in Europe prior to May of 1997.[9] According to the European definition, novel foods include new foods, foods from new sources, new substances or ingredients used in food, and new production technologies and methodologies for foods and ingredients.[10]

Executive summary

The global burden of malnutrition is unacceptably high. Animal-source foods are important components of diverse diets and provide high-quality proteins and other essential nutrients that promote optimal growth and development. The global demand for animal-source foods is projected to increase substantially, particularly in many low- and lower-middle income countries (LMICs). However, cost is a significant barrier to access and meeting this growing demand through livestock production will be highly resource intensive. As such, sustainable, high-quality alternatives to protein from livestock have the potential for significant transformative impact for both people and the planet.

Through a process known as fermentation-based cellular agriculture, animal proteins found in milk and eggs can be produced without animals. According to this method, a gene encoded with an animal protein is introduced into a starter culture of microflora (e.g., fungi or yeast). This culture is grown in controlled fermentation tanks, where it expresses the desired protein. Finally, the protein is separated from the microflora, generally producing a purified protein powder. These resulting "cultured" proteins are designed to be identical to the corresponding animal-source proteins produced through traditional livestock farming and can be used as ingredients in existing or new food products. Although there are many potential sustainability and nutrition-related benefits of these innovations, they also face several challenges to commercialization and market uptake.

This report assesses the current policy and regulatory environment for cultured proteins and their potential applicability in LMIC settings. Specifically, this report focuses on geographies where cultured proteins may be produced, procured, and/or consumed: the United States, the European Union, and two select LMICs (Ethiopia and India).

To inform this paper, we conducted a literature review and held interviews with key stakeholders (N = 25) with knowledge of the food industry and/or cultured proteins, including cultured milk and egg protein manufacturers, academia, donors, multinational food corporations, potential buyers/procurers of cultured proteins, representatives of professional societies/nonprofit organizations, and other regulatory experts. We also reviewed international food standards and guidelines and dietary classifications that may influence the policy and regulatory environments for cultured milk and egg proteins within specific cultural or geographic contexts. Due to the general lack of available information regarding the regulation of this emerging class of products, where applicable, the policy and regulatory environment for microbial food enzymes—which are widely consumed and produced through similar technologies—is used as a comparator.

Findings from this research demonstrate that, at present, the United States has the most clearly defined regulatory pathway for cultured milk and egg proteins, among the countries included in this analysis. In the United States, cultured proteins will likely follow the GRAS (Generally Recognized as Safe) regulatory framework under the purview of the US Food and Drug Administration, or other similar premarket regulatory process. In contrast, although the European Union has clearly defined and well-established food safety regulatory institutions and frameworks, our review did not identify a clear determination as to how cultured milk and egg proteins may be interpreted within the context of existing regulations. Finally, for Ethiopia and India, where food safety institutions and regulations have been established more recently, we also identified multiple potential regulatory pathways. In these cases, it is likely that the regulatory approaches in high-income settings will pave the way in informing other countries' regulation of these emerging products. Table 1 presents a summary of key institutions and relevant regulatory pathways/regulations that were identified as being potentially applicable to cultured proteins in focal geographies.

From a global perspective, international standards and guidelines that apply to foods, such as the Codex Alimentarius, may also impact the policy and regulatory environments of cultured proteins at the national level. The Codex Alimentarius is a joint commission of the Food and Agriculture Organization of the United Nations and the World Health Organization Food Standards Programme. It was established to protect consumer health and promote fair practices in food trade through a collection of voluntary food guidelines, standards, and codes. Although cultured milk and egg proteins are not currently addressed in any Codex guidelines, standards, or codes, these products may be classified as food additives or processing aids, similar to food enzymes, or as foods derived from modern biotechnology.

One key learning is that the microflora used as a starter culture in the production of cultured milk and egg proteins is often genetically modified. Although these genetically modified organisms (GMOs) are removed from the final purified protein powder product, their role in this production process will likely have important implications for the policy and regulatory environments for cultured milk and egg proteins across various geographic settings. National and international policies and guidelines have adopted different definitions of GMO and may therefore each interpret the role of GMOs in the production of cultured milk and egg proteins differently. For example, at a global level, it is likely neither cultured milk nor egg protein would be classified as a "living

TABLE 1. **Summary of key institutions and regulatory pathways for cultured milk and egg proteins in select geographies.**

Geography	Key institution(s)	Relevant pathways/regulation
The United States	US Food and Drug Administration	GRAS pathway or a similar premarket regulatory process Food additive approval
The European Union	European Commission Council of the European Union European Parliament European Food Safety Authority	Novel foods framework Regulations EC 1331 and 1332/2008: approval procedures for food additives, enzymes, and flavorings GMO Directive 2001/18, GMO Regulation 1829/2003, and GMO Regulation 1830/2003
Ethiopia	Ethiopian Food and Drug Administration	Food, Medicine and Health Care Administration and Control Proclamation 661/2009 Biosafety Proclamation 655/2009
India	Food Safety and Standards Authority of India	Food Safety and Standards Act (2006) Regulations for Approval of Non-Specified Food and Food Ingredients (2017) Biopharmaceutical regulatory pathway: Drugs and Cosmetics Act (1940), Drugs and Cosmetic Rules (1945), Environment Protection Act (1986)

Abbreviations: EC, European Commission; GMO, genetically modified organism; GRAS, Generally Recognized as Safe.

modified organism," as defined by the Cartagena Protocol, as there are no GMOs present in the end product.

Finally, dietary classifications (e.g., halal, kosher, vegan, vegetarian) play an important role in consumer choices and behaviors and may impact the policy and regulatory environment for cultured milk and egg proteins within specific geographic and cultural contexts. Halal and kosher foods are typically certified through third-party nongovernmental organizations. Cultured milk and egg proteins (and/or products containing these proteins) may be classified and certified as halal and/or kosher if the products meet required criteria and manufacturers follow the relevant certification procedures. In contrast, there are no established certification agencies for vegetarian and vegan foods, and classification determinations are generally made by individual consumers. Of note, if cultured milk and egg proteins are incorporated as ingredients into food products, dietary classification guidelines would also apply to all of the ingredients in those products.

Overall, lessons learned from the experiences of the microbial food enzyme industry and other relevant case studies highlight the importance of clear and transparent communication with both consumers and regulatory agencies, coordination among manufacturers, and obtaining and sharing rigorous and robust safety data. Many cultured milk and egg protein manufacturers are anticipating near-term product launches, and several manufacturers reported ongoing discussions and consultations with regulatory bodies.

In summary, although many outstanding questions remain about how cultured milk and egg proteins will be classified and regulated in the four geographies included in this paper, we highlight several potential pathways, as well as relevant lessons learned from the experiences of the microbial food enzyme industry and other case studies. Given the growing global demand for animal-source proteins coupled with the substantial environmental impact of livestock, food innovations such as cultured milk and egg proteins could play an important role in the future of food and supporting global nutrition by enabling access to affordable, nutritious, and high-quality protein for vulnerable populations. However, future scientific inquiry in multiple domains (e.g., safety, nutritional profile, consumer acceptance, and impact modeling) and across multiple country contexts is warranted to further grow the evidence base underpinning these food innovations and inform their appropriate introduction, regulation, and commercialization.

Background

Introduction

The global burden of malnutrition is unacceptably high.[11] Worldwide, an estimated 22 percent of children under the age of five were stunted and 8 percent were wasted in 2018.[12] Low-quality diets lacking in essential vitamins, minerals, proteins, and other nutrients are a key contributor to this burden.[13] Animal-source foods—such as meat, poultry, fish, eggs, and dairy—are important components of a diverse diet and provide high-quality proteins and other essential nutrients that promote optimal growth and development.[14-18] As populations and incomes grow, the global demand for animal-source foods is projected to increase substantially, particularly in many low- and lower-middle income countries (LMICs).[19,20]

However, cost is currently a significant barrier to animal-source food consumption. In addition, meeting this growing demand for animal-source foods will require rapid increases in livestock production, which has significant environmental impacts, requiring considerable land, water, chemical, and energy inputs.[11,18,19] Global food production is responsible for roughly one-quarter of all greenhouse gas emissions, most of which (up to 80 percent) are related to livestock.[21,22] Livestock production is also a contributor to water pollution, deforestation, land degradation, overfishing, and antimicrobial resistance.[21,23,24]

Given these challenges, this report aims to assess the current policy and regulatory environment for potentially more sustainable, high-quality alternatives to protein from livestock ("cultured" proteins) and their applicability in LMIC settings.

Cellular agriculture

The term "cellular agriculture" broadly refers to the manufacture of animal products from cell cultures under controlled conditions, as opposed to traditional animal farming methods.[4] According to Stephens et al. (2018), cellular agriculture can be broadly categorized into two main groupings: fermentation based and tissue engineering based.[3,25] Tissue engineering–based cellular agriculture produces cell-based meat (also known as "clean," "lab-grown," "cultivated," "cultured," and "in vitro" meat) and uses a cell or tissue line from a living animal. Stem cells are extracted from the tissue to grow and culture the desired product.[3]

Fermentation-based cellular agriculture—the focus of this paper—uses microflora (e.g., fungi or yeast) to express a desired organic molecule end product (such as protein) during fermentation.[4] Through this process, which bears resemblance to brewing beer, many of the same animal proteins found in milk and eggs can be produced without animals.[4] The process uses a gene encoded with the animal protein, which is introduced into the DNA of a starter culture of microflora. This culture is then fed on a substrate (e.g., sugars) in controlled fermentation tanks, where it expresses the desired protein(s).[4] In most cases, the proteins are separated from the microflora and purified into a powder. The resulting "cultured" proteins—also known as "synthetic," "lab-grown," "fermentation-derived," and "flora-based" proteins—are theoretically identical to the corresponding animal-source protein with respect to structural, organoleptic, and nutritional properties.[a,4]

a. For the remainder of this paper, we will refer to proteins derived according to this approach as cultured proteins.

Cultured proteins could therefore be substituted for animal-source proteins as an ingredient in existing or new food products, such as milk or egg substitute products. They might also be used to improve the nutritional content of products that do not currently contain milk or egg protein. However, cultured milk and egg proteins produced through this technique are not equivalent to whole animal-source foods (e.g., powdered whole milk or powdered whole eggs) because they do not contain other nutrients such as carbohydrates, fats, or other bioactive compounds. Several emerging biotechnology companies are creating cultured milk and egg proteins for use in food products, with the earliest commercial products expected on the market in 2020.

Potential benefits and challenges

Benefits

Cultured milk and egg protein production techniques and resulting products have the potential to benefit the environment, agriculture, and health, including for malnourished populations in LMICs. Relative to the same proteins from animal sources, it is possible that cultured proteins will contain the same high nutritional value; have a lower environmental footprint and produce fewer associated greenhouse gas emissions; require fewer agricultural inputs (e.g., land, water, chemicals, energy); require no animal breeding or slaughter; contain fewer or no hormones, antibiotics, or foodborne pathogens; have an extended shelf life (may not require cold storage); have the same taste, texture, and chemical structure; and eventually be lower cost and/or be subject to fewer price fluctuations. Due to these potential benefits and our growing understanding of the role of animal-source foods in promoting nutrition, particularly among young children,[14–18] cultured milk and egg proteins may have a role in sustainably supporting improved diets and nutritional outcomes in LMICs.

Challenges

At the same time, cultured proteins may also face or present commercialization challenges. Potential challenges associated with cultured proteins include displacement of other foods in the food system, difficulty in ensuring equitable access to products, the potentially high cost of these products when they first launch, negative livelihood impacts for farmers, and other possible unintended consequences.

Furthermore, the microflora (e.g., yeast) used as a starter culture in the production of cultured milk and egg proteins is often genetically modified (GM). Genetically modified organisms (GMOs) are defined by the World Health Organization (WHO) as "organisms (i.e., plants, animals or microorganisms) in which the genetic material (DNA) has been altered in a way that does not occur naturally by mating and/or natural recombination."[5,6] Foods that are produced from or with GMOs are often referred to as GM foods.[5] The technology used to alter the genetic material of an organism is often referred to as "genetic engineering."[6] However, in the case of cultured milk and egg protein production, it is important to note that, in most cases, the GM microflora is removed from the final product, meaning that the resulting purified protein powder does not contain GMOs. Although the use of genetically engineered microbial strains in food production is not a new phenomenon, nuances in the details of the role of GMOs in the production of cultured proteins, as well as various country/institutional classification guidelines for GMOs and GM products, may add a layer of complexity to their regulation within various contexts. As such, these considerations will be discussed throughout the paper.

Fermentation-derived products

Many other commercial products are made using technologies similar to those used to produce cultured proteins. These include probiotics, natural flavors, insulin, and food enzymes, among others.[26] These products are manufactured using the same production processes to obtain the desired molecule through safe gene transfer and large-scale fermentation using a microorganism.[27]

Microbial food enzymes (a type of protein) play a vital role in food technology and production. In 2018, the global industry was estimated at US$2.26 billion.[28,29] Microbial food enzymes are derived from microbial sources through fermentation and used to enhance food processing in various food industries.[30] Food enzymes have been used for centuries in age-old processes for food preparation.[31] Some of the earliest applications include brewing beer, baking bread, and making cheese and wine.[25,32] Today, one of the most common microbial food enzymes is rennet, which is used to make most types of cheese. Rennet is composed of two enzymes, chymosin and pepsin. Traditionally, these enzymes were obtained from the stomachs of cows; however, they are now largely manufactured through fermentation-based production techniques involving genetically engineered microbial strains.[25,33] Microbial enzymes are used in food and feed processing. They are efficient biocatalysts that obtain a desired end product with few by-products, low energy requirements, and high efficiency.[27,33] Microbial food enzymes can also be produced at large scale, in a variety of different environmental conditions, and in a limited space.[28] Novozymes, the largest global enzyme manufacturer, reports that more than 5 billion consumers used or ate a product with a Novozymes' enzyme at least once a week in 2018.[34]

Given the emerging nature of the cultured milk and egg protein industry, clear policy and regulatory frameworks have not yet been established in many settings. Microbial food enzymes serve as a relevant comparator to cultured milk and egg proteins because of their widespread global

availability and comparable production processes. For these reasons, this paper will highlight the policy and regulatory environment for microbial food enzymes, when applicable, to identify potential regulatory pathways and lessons learned.

Key objectives of this analysis

The purpose of this paper is to investigate the policy and regulatory environment for cultured milk and egg proteins within various geographic contexts. Specifically, this paper will focus on geographies where the products may be produced, procured, and/or consumed, including both high-income (the United States and the European Union [EU]) and LMIC (Ethiopia and India) settings. This paper also describes how various policy and regulatory environments for these products may influence their use in LMIC settings. Because such products are not yet widely available, the policy and regulatory environments for food enzymes in focal geographies will be examined, when applicable, as a comparator.

Research methodology

In this paper, we examine the policy and regulatory environments for cultured proteins in the United States, the EU, and two LMICs: Ethiopia and India. The United States and the EU were selected for this analysis because several cultured protein manufacturers are currently based in these locations, and these products may first become commercially available there. In contrast, Ethiopia and India were chosen as LMIC case studies based on factors related to their markets (including market size and country readiness), health and nutrition needs (including rates of stunting and wasting, and minimum diet diversity), and agricultural/environmental challenges (including water withdrawals and carbon dioxide/greenhouse gas emissions). Data for multiple indicators under each of these categories were gathered and used to narrow down the list of 81 LMICs to approximately 20 higher-priority countries for further due diligence. From this list, four high-interest countries (Ethiopia, India, Senegal, and Vietnam) were selected based on their rankings within each category, further secondary research, and internal and external feedback. Of these, we selected Ethiopia and India as the final two case study countries to include in this report given their large potential market size, and to provide geographical representation across both Africa and Asia.

We conducted a literature review and interviews with key stakeholders to inform this paper. Our literature review included 285 articles, reports, and other publications that were identified by searching the following databases: PubMed, Scopus, Google Scholar, Web of Science, US Federal Register, Global Agriculture Information Network, Food and Agriculture Organization of the United Nations (FAO) database, EU resource library and archives, Food and Agricultural Import Regulations and Standards reports, and archives of *The Gazette of India*.

To obtain a broad set of perspectives, a variety of stakeholder types were recruited for interviews. Stakeholders were identified through previous work in the field, industry conferences, desk research, and referrals. In the first quarter of 2019, we reviewed existing industry market landscapes to compile a list of all cultured protein manufacturers and larger cell-based meat manufacturers. Additional companies were added from articles, online searches, white papers, and word-of-mouth referrals. Approximately 40 companies were identified. From this list, we chose a subset as priority companies to target for stakeholder interviews. These included all companies producing cultured milk or egg protein products, as well as cell-based meat manufacturers that were farther along in product development and companies developing other alternative protein products.

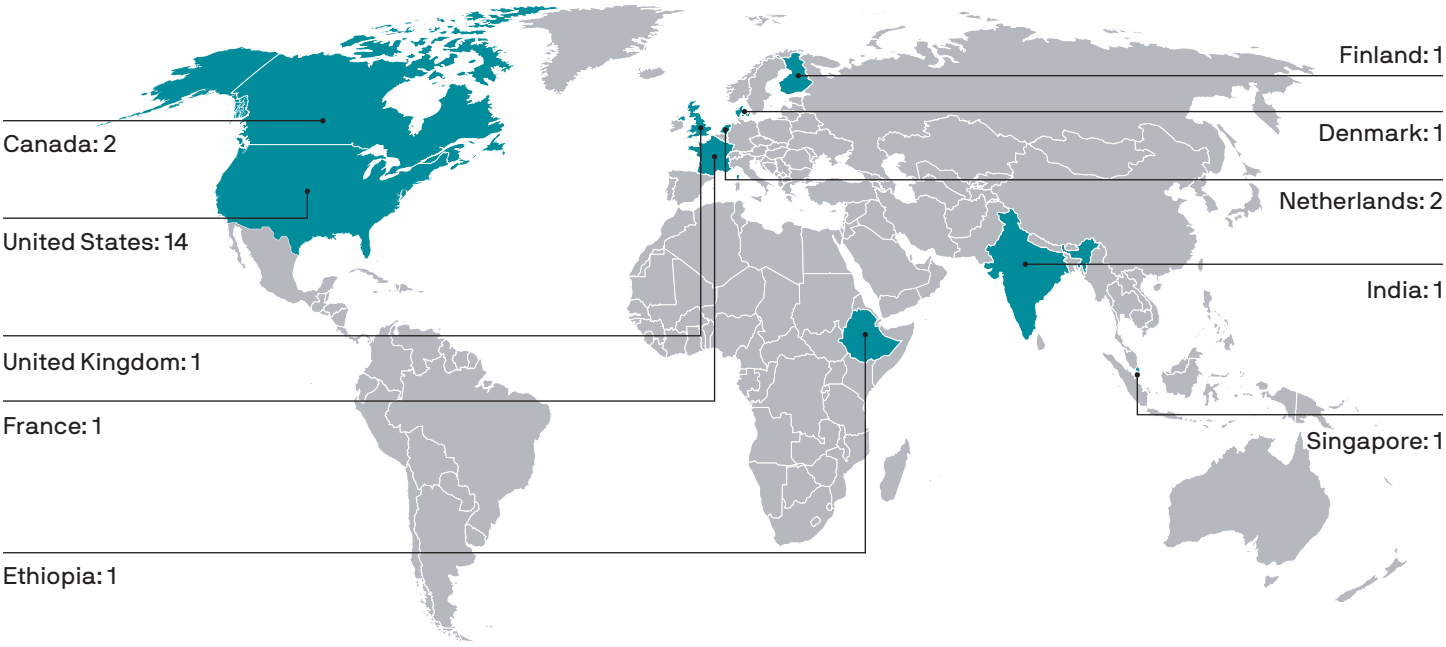
In addition to the priority manufacturers, we targeted a number of organizations and companies for stakeholder interviews. Groups including academia, donors, multinational food companies, potential buyers/procurement organizations, professional societies/nonprofit organizations, and other key experts were identified. Some of these groups are known for their work in cultured proteins, while others are large players in the broader food or food aid industry or experts in the regulatory environments for innovative foods.

In total, 50 people from 43 organizations were invited to participate in an interview. Of those, we interviewed 25 people from 24 organizations, located in ten countries. While 56 percent of respondents are based in the United States, the majority of non-manufacturer respondents have direct experience working in LMICs. See Table 2 for a summary of the stakeholders interviewed and Figure 1 for a map of stakeholders' locations.

TABLE 2. **Number of stakeholders interviewed by type.**

Type of organization	Number of stakeholders interviewed	Organizations included
Manufacturer (cultured protein)	5	BioscienZ, Clara Foods, New Culture, Perfect Day, Solar Foods
Manufacturer (other alternative protein)	5	*Cell-based meat:* Higher Steaks, Memphis Meats, Shiok Meats *Plant-based protein:* Impossible *Multiple:* JUST
Food aid organization (donor, supplier, procurer, or distributor)	6	Arla Foods Ingredients, Catholic Relief Services, Nutriset, US Agency for International Development, World Food Programme, World Vision
Non-profit organization (research, advocacy, or professional group)	4	Cellular Agriculture Society, Good Food Institute (x2), New Harvest
Other	5	*Academia:* Stanford University *Donor/incubator:* IndieBio Government agency: Ethiopia Agriculture Transformation Agency *Other:* Independent experts (x2)

FIGURE 1. **Map of stakeholder locations.**



Note: While 56 percent of respondents are based in the United States, the majority of non-manufacturer respondents have direct experience working in LMICs.

In order to conduct the interviews, the team generated a modular, semi-structured discussion guide that included both qualitative and quantitative questions. All interviews were designed to last approximately one hour. The discussion guide and research approach received a non-research determination from PATH's Office of Research Ethics, and each stakeholder consented to the interview. We asked manufacturers a series of questions about the products they are creating, the regulatory processes they are navigating or anticipating, production and scale-up capabilities, prioritized market segments for introduction and scale, and industry partnerships. Market-related information is summarized in a separate report.

We asked non-manufacturer stakeholders about a series of topics based on their expertise. Each participant was emailed a concept card describing cultured proteins to review before the interview (Appendix A). During the interview, we asked the participants questions related to their prior knowledge of cultured proteins, their perceptions on expected key benefits and potential challenges to market uptake, and their views on the utility of cultured proteins. When relevant, we asked stakeholders about their knowledge of the regulatory environment in various regions, specifically for innovative foods, GMOs, or cultured proteins. Procurement organizations or organizations working in global food aid were asked additional questions about current procurement of animal-source proteins, levels of awareness about cultured proteins in their industry, data that should be presented on cultured proteins, and thoughts on the launch of these products. We compiled data from all interviews for analysis.

International food standards

Key messages

- International standards and guidelines that apply to foods, including the Codex Alimentarius and the Cartagena Protocol, may influence the policy and regulatory environments for cultured milk and egg proteins.
- The Codex Alimentarius, a joint commission of the FAO and WHO's Food Standards Programme, was established to protect consumer health and promote fair practices in food trade through a collection of voluntary guidelines, standards, and codes. Cultured milk and egg proteins may be classified by the Codex as a food additive or processing aid, similar to food enzymes, or classified as a food derived from modern biotechnology, and follow the respective Codex regulatory frameworks for these classifications.
- The Cartagena Protocol on Biosafety to the Convention on Biological Diversity is an international agreement adopted in 2000 that focuses on the safe handling, transport, and use of living modified organisms that result from modern biotechnology practices. According to the Cartagena Protocol's definition of a living modified organism, cultured milk and egg proteins will likely not be impacted if modified genetic material is not considered to be present in the final product.

International food standards exist for the purposes of protecting consumer health and promoting fair food trade practices in the global food system. Although not currently included explicitly in international standards, it is important to consider how cultured milk and egg proteins may be incorporated, as international standards often influence the policy and regulatory frameworks in specific countries—particularly countries with less robust policy and regulatory frameworks and institutions.[35]

Codex Alimentarius

The Codex Alimentarius is a collection of guidelines, standards, and codes adopted by the Codex Alimentarius Commission, a joint commission of the FAO and WHO Food Standards Programme established in 1962 to protect consumer health and promote fair practices in food trade.[36] In total, the commission consists of 189 members (188 countries and the EU), and the application of its principles by countries is voluntary.[37] Importantly, the guidelines, standards, and codes of the Codex are not intended to serve as a substitute for national-level regulation.[35] However, the World Trade Organization encourages governing bodies to harmonize their national regulations with the Codex Alimentarius.[38]

Although cultured milk and egg proteins have yet to be classified by the Codex, it contains several guidelines, standards, and codes that may be relevant for these products. As such, this paper will highlight the status of microbial food enzymes under the Codex, as well as the Codex's provisions related to biotechnology and GMOs.

According to the Codex, food enzymes are categorized as food additives or processing aids.[39-41] However, the Joint FAO/WHO Expert Committee on Food Additives (JECFA), an independent committee of international experts responsible for assessing the safety of food enzymes, does not distinguish between these categories. The JECFA conducts risk assessments for food enzymes and shares the results with the Codex Committee on Food Additives, which uses these findings to establish levels for maximum use of additives in food and beverages. At the national level, regulatory bodies can use JECFA assessments and/or national safety assessments as the basis for authorizing the use of food additives.[39] Of note, only food additives/processing aids that have been assessed and approved by JECFA and the Codex Alimentarius Commission can be traded internationally.[42]

Further, the Codex defines biotechnology as the application of "in vitro nucleic acid techniques including recombinant DNA and direct injection of nucleic acids into cells or organelles" or "fusion of cells beyond the taxonomic family."[42] The Codex recommends that food products derived from modern biotechnology undergo an analysis including a safety and nutritional risk assessment to determine whether there are any associated hazards and, if present, describe the nature and severity of these safety concerns. This biotechnology safety assessment involves a comparison of the food product derived from modern biotechnological processes and the same food produced using conventional processes.[43] The Codex also includes the Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms, which includes a:[42,44]

1. Description of recombinant DNA microorganisms.
2. Description of the recipient microorganism and its use in food production.
3. Description of the donor organism.
4. Description of the genetic modification, including vector and construct.
5. Characterization of the genetic modification.
6. Safety assessment of potential toxicity and other safety and nutritional concerns.

Of note, this guideline does not apply to microbial food enzymes even though they are often produced using recombinant microflora.

Cartagena Protocol

The Cartagena Protocol on Biosafety to the Convention on Biological Diversity is an international agreement adopted in 2000 that focuses on the safe handling, transport, and use of living modified organisms that result from modern biotechnology practices.[7] The Cartagena Protocol consists of international standards that aim to prevent risks to human health and adverse effects to biological diversity.[7] Under the Cartagena Protocol, a living modified organism is defined as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology."[7] Currently, 171 countries have signed and ratified the Protocol, including the EU, Ethiopia, and India. The United States is one of only a few countries that has not signed onto the Protocol.[45]

Although cultured milk and egg proteins are produced through modern biotechnology practices, they will likely not be impacted by the Cartagena Protocol since no living modified organisms (e.g., GM microflora such as yeast or fungi) are included in the end product.[3]

Policy and regulatory environment: United States

Key messages

- In the United States, cultured milk and egg proteins will likely follow the GRAS (Generally Recognized as Safe) pathway or a similar premarket approval process.
- The National Bioengineered Food Disclosure Standard Law, passed in 2016, requires mandatory disclosures for bioengineered foods and ingredients. Although this regulation may have implications for cultured milk and egg proteins, they are unlikely to be considered "bioengineered" if no modified genetic material is present in the end product.

Several cultured milk and egg protein manufacturers are currently based in the United States and are targeting high-income consumer markets for introduction of their products. For these reasons, we begin our country-specific analyses with a review of the potential policy and regulatory environment for cultured milk and egg proteins in the United States.

In the United States, the two primary federal food safety regulatory agencies are the Food and Drug Administration (FDA) and the US Department of Agriculture (USDA).[46] In general, the FDA regulates most food products, except meat, poultry, processed egg products, and catfish, which are regulated by the USDA.[46] Implementation of the FDA Food Safety Modernization Act in 2011 enabled the two agencies to collaborate more closely to develop a more effective and efficient food safety system, specifically focusing on preventative approaches to food-related illness and harm.[46,47]

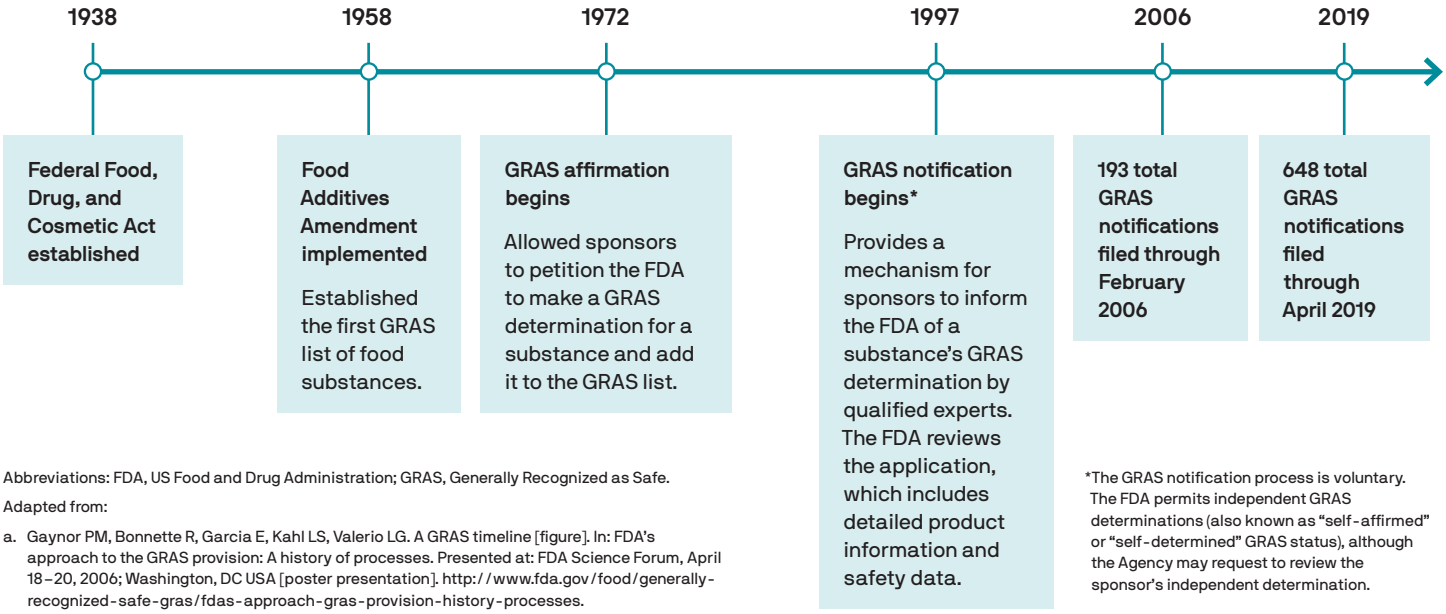
As of the writing of this paper, our findings suggest that the regulation of cultured milk and egg proteins in the United States will likely follow the GRAS (Generally Recognized as Safe) pathway, under the purview of the FDA.[48,49] However, these proteins could also follow the food additive pathway for premarket approval. Below, we describe these regulatory frameworks and their current application to microbial food enzymes.

Food additive regulation and the GRAS regulatory pathway

In the United States, microbial food enzymes historically have followed the GRAS regulatory process, which is overseen by the FDA's Center for Food Safety and Applied Nutrition's Office of Food Additive Safety. A timeline of the history of this program is shown in Figure 2.

In the United States, the Food Additives Amendment of 1958—an amendment of the Federal Food, Drug, and Cosmetic Act of 1938—aimed to prevent the use of unsafe

FIGURE 2. **GRAS framework timeline.**



Abbreviations: FDA, US Food and Drug Administration; GRAS, Generally Recognized as Safe.

Adapted from:

a. Gaynor PM, Bonnette R, Garcia E, Kahl LS, Valerio LG. A GRAS timeline [figure]. In: FDA's approach to the GRAS provision: A history of processes. Presented at: FDA Science Forum, April 18–20, 2006; Washington, DC USA [poster presentation]. http://www.fda.gov/food/generally-recognized-safe-gras/fdas-approach-gras-provision-history-processes.

b. US Food and Drug Administration website. GRAS notices page. https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&sort=FDA_s_Letter&order=ASC&showAll=true&type=basic&search=FDA%20has%20no%20questions. Accessed August 14, 2019.

*The GRAS notification process is voluntary. The FDA permits independent GRAS determinations (also known as "self-affirmed" or "self-determined" GRAS status), although the Agency may request to review the sponsor's independent determination.

food additives through a mandatory premarket FDA review of any new additives introduced into food.[50-52] This amendment defines a food additive in relevant part as "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, either in their becoming a component of food or otherwise affecting the characteristics of food."[50,53] Under this Act, new food additives (or food additives with new intended uses) are subject to premarket approval by the FDA. To obtain premarket approval for a food additive, manufacturers/sponsors must petition the FDA and demonstrate the safety of the substance.[54]

However, some ingredients are exempted from this premarket regulatory process under the Food Additives Amendment. Substances that are generally recognized as safe follow a different regulatory pathway.[50] Substances are deemed to have GRAS status when (1) scientific data and information about the use of the substance are widely known and there is consensus among qualified experts that the information and data establish the substance's safety under the conditions for its intended use; or (2) the safety of the substance has been established by a long history of use in food prior to 1958 (when this amendment took effect).[50,55] Following the passage of the Food Additives Amendment, the FDA published "the GRAS list," a list of ingredients with GRAS status, in the US Code of Federal Regulations.

In 1972, the FDA created the GRAS affirmation process, which allowed sponsors to petition the FDA to make a GRAS determination for a substance and add it to the GRAS list.[50] However, due to the administrative burden of this process, in 1997 the FDA published a proposed rule that established the GRAS notification process as a replacement for the affirmation process.[56] This rule was finalized in 2015 after an Interim Pilot Program (1998 to 2015). The voluntary notification process provides a mechanism for individuals to inform the FDA of a substance's GRAS determination. GRAS notifications submitted to the FDA include information about the identity of the substance, its intended use, anticipated exposure, and any other data or information (e.g., safety data) to support the substance's GRAS status determination. The FDA then reviews the submitted notice and evaluates whether there is sufficient basis for a GRAS determination. The GRAS notification process allows the FDA a 180-day review period with the potential for a 90-day extension. However, in practice, the review period can extend beyond this time frame, if the FDA has questions regarding the submission. Following review, the FDA responds to the notice with a letter outlining one of three possible outcomes:[56]

1. No Questions: The FDA has no questions upon completing the review. This response indicates that the FDA has affirmed the substance's GRAS status.
2. No Basis: The FDA determines that the GRAS notification does not provide sufficient basis for a GRAS determination.
3. Withdrawn: The FDA has ceased to review the GRAS notification at the notifier's request.

Case study: The Impossible Burger

In the United States, the regulatory experience of the Impossible Burger presents a relevant case study for cultured milk and egg proteins. The Impossible Burger includes an ingredient (soy leghemoglobin) that is produced through a process similar to that for cultured milk and egg proteins.[51,60] Soy leghemoglobin is a plant-based heme protein product found in the nodules on the roots of soybean plants, which contributes to the meaty texture, color, and taste of this plant-based burger.[61] It is produced by genetically engineering yeast with the gene for soy leghemoglobin. First, yeast is grown through fermentation, and then the expressed protein is isolated from the yeast and added to the burger. The timeline and details of this product's regulatory approval process in the United States are outlined below.

- **September 2014: Impossible Foods submitted a GRAS notification to the FDA for the protein soybean leghemoglobin.[62]**
- **August 2015: The FDA requested additional safety information from Impossible Foods.[61,62] Impossible Foods withdrew their GRAS notification.**
- **October 2017: After conducting additional safety testing, Impossible Foods submitted a second GRAS notification to the FDA.[62,63] From October 2017 to July 2018, Impossible Foods submitted six different amendments to their GRAS notification to clarify the intended use of the protein and inform the FDA of updates to scientific evidence for the ingredient's safety.[61]**
- **July 2018: Impossible Foods was granted GRAS status for soybean leghemoglobin through the receipt of a "No Questions" response letter from the FDA.[60]**

The FDA maintains an online inventory of GRAS notices and FDA response letters.[57] For each GRAS notification, the FDA posts the name of the substance; the GRAS notification number; the FDA letter sent in response to the GRAS notification, including redactions as needed; the name and address of the notifier; the substance's intended conditions of use; and the basis of determination (either by history of use prior to 1958 or by scientific process and evidence).[56–58] From 1998 to 2015, more than 600 GRAS notices were filed with the FDA, and during that time the average number of GRAS notifications filed from non-US companies doubled.[51,56] More than 63 percent of the first 600 GRAS notifications filed were resolved within 180 days and the FDA consistently issued a majority "No Questions" response (72 to 84 per group of 100 GRAS notifications).[56]

The GRAS notification process is voluntary, and the FDA permits independent GRAS determinations without the Agency's involvement. However, it is typically advisable for companies to seek a "No Questions" letter from the FDA through the formal GRAS notification process, particularly when the food ingredient at issue involves a new technology.[50,55]

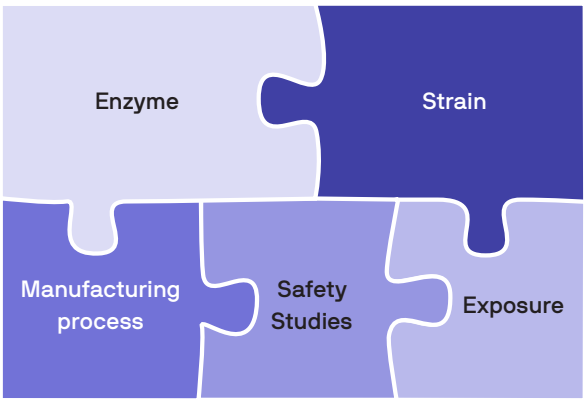
Food enzymes are one of the most common types of substances that undergo the GRAS notification process.[56] Microbial food enzymes have a long history of safe use in food processing.[51] Enzymes became more common in modern food production in the 1960s, coinciding with the timing of the development of this regulatory framework.[33] There is a substantial body of safety evidence for microbial food enzymes, as well as established safety evaluation procedures and methodologies. These include a safety assessment of the production host, the materials and methods of the genetic transformation, the enzyme for its intended use, the manufacturing process, and consideration of dietary exposure (Figure 3).[51] The FDA has issued specific guidance on the submission of technical data in food additive petitions and GRAS notifications for enzyme preparations.[59] As of 2015, 12 percent of filed GRAS notifications were for enzymes, 97 percent of which (67 of 70) received "No Questions" letters from the FDA. The review times for food enzymes are typically shorter (an average of 168 days), compared to other food types. In all, 37 percent of the first 600 GRAS notifications filed took longer for the FDA to process than the 180-day review period.[56]

Potential applications of the GRAS framework to cultured milk and egg proteins

Due to the technical similarities between the production processes for microbial food enzymes and cultured proteins, our review and consultations with manufacturers and other stakeholders suggest that it is likely cultured milk and egg proteins will follow the FDA's GRAS regulatory framework in the United States. Although it is important to note that cultured milk and egg proteins will very likely be present in foods in higher concentrations than food enzymes, the safety of the manufacturing process (protein production via fermentation) is well established.[64] However, if it is difficult to establish general recognition of the safety of cultured proteins, they could also follow the US premarket regulatory pathway for food additives in the United States.[65,66]

The cultured milk and egg protein industry—as well as the broader industrial biotechnology community—can learn from the regulatory experiences of the food enzyme industry.[67] For example, the enzyme industry engaged closely with the FDA during the development of the GRAS program and took a proactive and transparent approach to dialogue with key stakeholders—including experts, regulators, and consumers.[56,67] The experience of food enzyme regulation in the United States also highlights the importance of collecting robust safety and toxicological data when needed to satisfy any regulatory concerns.[51] Moving forward, the cellular

FIGURE 3. **Elements of a safety evaluation for enzyme GRAS determination.**



Source: Sewalt V, Shanahan D, Gregg L, La Marta J, Carrillo R. The Generally Recognized as Safe (GRAS) process for industrial microbial enzymes, Figure 2. *Industrial Biotechnology.* 2016;12(5):295–302. doi:10.1089/ind.2016.0011.

agriculture industry can draw from these lessons and similarly aim to promote the establishment and maintenance of science-based, risk-focused regulatory frameworks that do not inhibit innovation.

Classification and labeling: GMOs

In July 2016, Congress passed the National Bioengineered Food Disclosure Standard Law, which requires mandatory disclosures for bioengineered foods and ingredients.[1] The USDA finalized the regulations in December 2018, and the rules went into effect in February 2019, with a general compliance date of January 2020.[1] Under these regulations, food manufacturers, importers, and other entities that label foods for retail sale must disclose information on bioengineered food and/or ingredients.[1] A bioengineered food is defined as containing "detectable genetic material that has been modified through in vitro recombinant deoxyribonucleic acid (rDNA) techniques and for which the modification could not otherwise be obtained through conventional breeding or found in nature; provided that such a food does not contain modified genetic material if the genetic material is not detectable."[1] Under this regulation, a textual, symbol, or electronic disclosure is required on all foods[b] in the United States that are considered "bioengineered" by the USDA (Figure 4). Further, voluntary disclosure guidelines are provided for foods that do not contain any modified genetic material but that have been *derived* from bioengineered foods or ingredients.[1]

Case Study: Cell-based meat regulation in the United States

In the United States, cultured milk and egg proteins will likely follow a different regulatory pathway than cell-based meat products. Producing cell-based meat involves a highly complex production process that includes harvesting cells directly from animals, as well as contamination and safety risks that are not relevant for cultured milk and egg proteins.[68] However, as both cultured proteins and cell-based meats are approaching commercial launches, it is important to highlight the key differences between the two product categories and their anticipated regulatory processes.

In November of 2018, the US government announced that cell-based meat would be jointly regulated by the USDA and the FDA.[48] Prior to this announcement, several cell-based meat manufacturers and stakeholders were engaged in a consultation process with both the USDA and the FDA. According to the formal agreement between these agencies (released in March 2019), the FDA will regulate cell collection, cell banks, and cell growth and differentiation. A transition from FDA to USDA oversight will occur during the cell harvest stage of the process, and the USDA will regulate the production and labeling of human food products developed from animal cell cultures.[48] This joint scheme of regulation may be expected to capitalize on the strengths of both agencies in their capacities as regulators.

FIGURE 4. **Mandatory symbol disclosure for "bioengineered" foods/ingredients and voluntary symbol disclosure for foods/ingredients "derived from bioengineering" in the United States.**

Source: US Department of Agriculture, Agricultural Marketing Service website. BE labeling & disclosure page. https://www.ams.usda.gov/rules-regulations-terms/gmo-labeling-disclosure. Accessed August 21, 2019.

b. Exceptions to this rule include most meat, poultry, and egg products, animal feed, and food served in restaurants.

Importantly, this regulation specifies that "incidental additives" that are present in foods at insignificant levels and do not "have any technical or functional effect in the food" are not considered to be bioengineered.[1] The USDA specifically addresses microbial strains and yeast developed using bioengineering, stating that "those substances may not be subject to bioengineering disclosure if they qualify as an incidental additive that is not required to be labeled or if the modified genetic material in those products is undetectable."[1]

These mandatory labeling requirements in the United States may inform the labeling of cultured proteins and associated products.[1] Based on the definitions provided above, it is unlikely that cultured proteins will be considered "bioengineered" foods or ingredients under this regulation, as they do not contain any GM material. However, depending on the status of the inputs used to produce these proteins, it is possible they might be considered to be *derived from* bioengineering.[1]

Non-GMO

The federal government's National Bioengineered Food Disclosure Standard does not define "non-GMO." However, the standard does specify that foods certified as organic by the Organic Foods Protection Act of 1990 can be labeled as "non-GMO," "not bioengineered," or other similar claims.[1] The USDA's Process Verified Program verifies such claims, and companies can voluntarily submit a product application for review.[69]

In addition, nongovernment entities provide voluntary third-party certifications for "non-GMO" foods in the United States. For example, the Non-GMO Project is one of the largest and leading third-party verifiers of non-GMO products in the United States. According to the Non-GMO Project, a GMO is defined as "a plant, animal, microorganism or other organism whose genetic makeup has been modified in a laboratory using genetic engineering or transgenic technology."[70] In order to be verified by the Non-GMO Project, the inputs and ingredients of a product must meet the requirements outlined in the organization's standard, which contains many nuances for specific products, inputs, and ingredients.[70] According to this standard, all inputs into and ingredients in food products are classified as either "major," "minor," or "micro," based on their weight percentage in the finished product. Of note, the standard specifies that when microorganisms—or inputs or ingredients derived from microorganisms—are considered to be products, major ingredients, or minor ingredients, both the microorganism and the growth media must comply with Non-GMO Project requirements.[70]

For example, the Non-GMO Project considers food enzymes to be GMO products if they are made with a genetically modified microorganism (Figure 5).[64,70] In January of 2016, the Enzyme Technical Association (ETA) sent a letter to the Non-GMO Project to submit comments on their standard of labeling enzymes made from GM microflora as GMO products.[71] In the letter, the ETA stated that all enzymes—regardless of whether they were produced with GM microflora—should not be considered GMO because "enzymes are proteins. As such, they are not organisms, and thus, by their very nature, they cannot be GMO."[71] Despite the ETA's efforts, the Non-GMO Project has not provided non-GMO certification for these types of enzymes. Due to similarities in the production processes between food enzymes and cultured milk and egg proteins, it is plausible these products will face similar challenges in securing a non-GMO certification in the United States through this third-party verification body.

FIGURE 5. **Non-GMO Project certification.**

Source: Non-GMO Project website. Product verification page. Our seal of approval: independent study by Consumer Reports link. https://www.nongmoproject.org/product-verification/. Accessed October 19, 2019.

Policy and regulatory framework: European Union

Key messages

- As of the writing of this paper, the specific pathway for cultured milk and egg protein regulation in the EU has yet to be clarified. More information is needed on the business case and product formulation for forthcoming cultured protein products to inform this determination.
- If cultured milk or egg products are determined to contain, consist of, or have been produced from GMOs, these products will most likely have to obtain premarket approval under the EU's GMO regulatory framework. However, in the EU food products produced with GMOs (e.g., as processing aids) are not subject to this regulation, provided that DNA from GMOs cannot be retrieved in the end product.
- If these products do not require premarket approval under the EU's GMO regulatory framework, the novel food framework and the food enzyme regulatory pathway may be relevant for these types of products.

As one of the world's largest exporters and importers of food—including emergency relief food products—the EU's policy and regulatory environment presents a relevant case study for the emerging cellular agriculture industry.[72] In addition, several emerging cellular agriculture companies, including developers of cell-based meat and cultured protein products (e.g., BioscienZ, Higher Steaks), are also based in the EU.

The primary institutions involved in food policy and regulation in the EU are the European Commission, the Council of the European Union, and the European Parliament.[73] The European Commission is responsible for drafting and introducing policy proposals for the EU and individual member countries, which are implemented by EU institutions and the EU member countries. The Council of the European Union and the European Parliament are responsible for considering proposals and proposing amendments.[74] In addition, the European Council is responsible for bringing together member country government leaders to ultimately provide political direction and determine strategies for future EU policies. Finally, the Court of Justice is involved in the implementation of policies and navigates policy implementation disputes between member countries.[74] The courts of the EU countries can request a preliminary ruling from the Court of Justice if and when they need guidance on the interpretation of Community law.

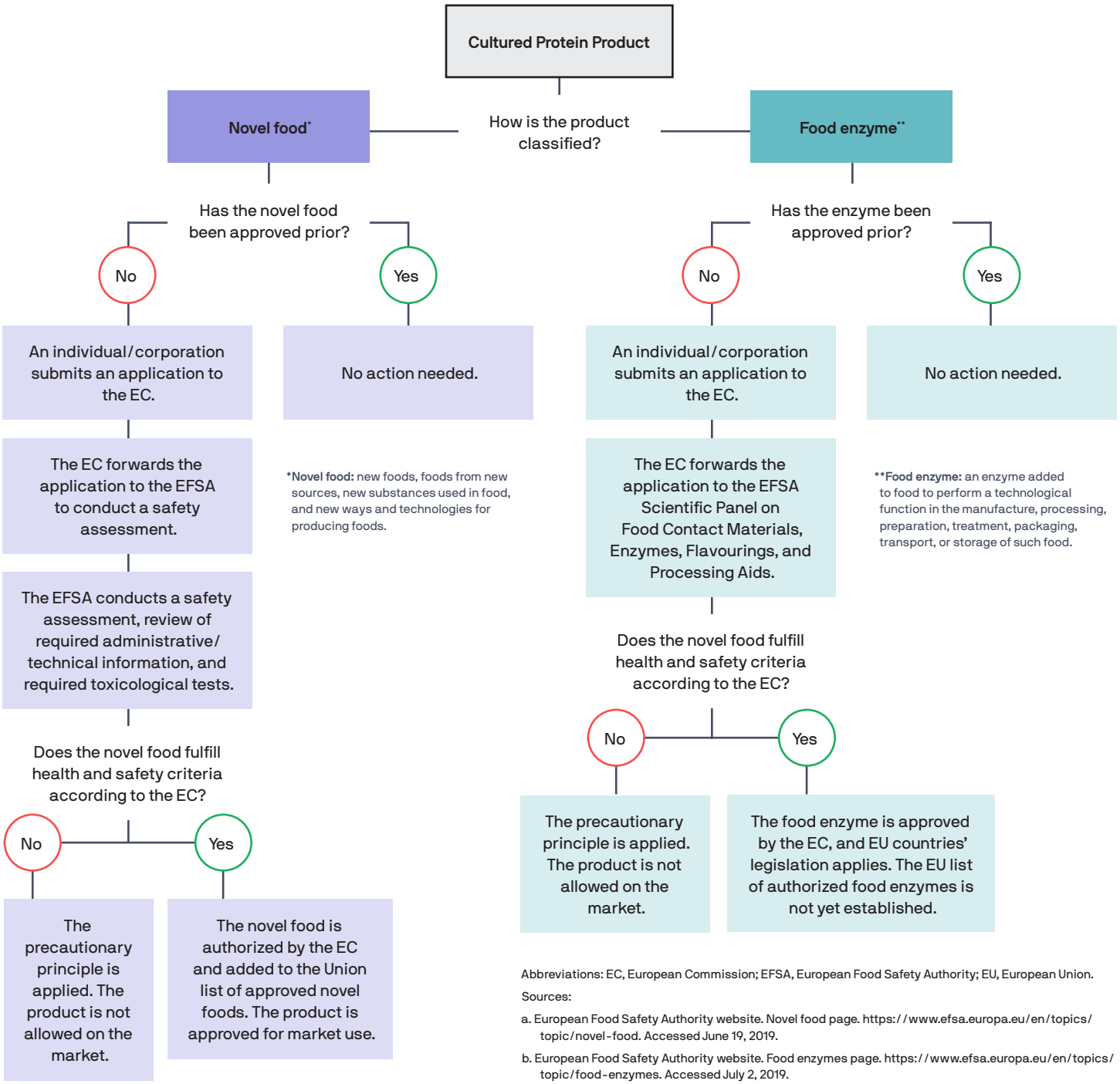
In the early 1990s, a series of food safety incidents led to a call for heightened food safety regulation in the EU. In response, in 2002 the European Parliament and Council of the European Union adopted General Food Law Regulation (EC) No. 178/2002, which serves as the foundation for all food and feed policies and legal measures within the EU. This regulation also established the European Food Safety Authority (EFSA), an independent agency responsible for conducting food safety risk assessments and providing scientific advice and support to decision-making related to risks along the food value chain.[75-78] The EFSA is also responsible for clearly communicating information about risks associated with the food chain to partners, stakeholders, and the public.[78] Although the EFSA conducts food-related risk assessments, it is not responsible for risk management and therefore does not make decisions related to product sale or use in the EU. The European Commission,

independent member countries, and the European Parliament are responsible for risk management, which includes food safety legislation and decision-making in the EU.[78,79] Each EU member country subsequently enforces the applicable legislation within its own territory.

In contrast to the US system, the EU upholds the "precautionary" principle, which carries implications for the regulation of new food products in the EU.[75,80,81]

As of the writing of this paper, the specific pathway for cultured milk and egg protein regulation in the EU has yet to be clarified. We describe two potential regulatory pathways (Figure 6)—the novel food framework and the food enzyme regulatory pathway—which may be relevant for these types of products.

FIGURE 6. **Food enzyme and novel food regulatory pathways in the EU.**



Abbreviations: EC, European Commission; EFSA, European Food Safety Authority; EU, European Union.

Sources:

a. European Food Safety Authority website. Novel food page. https://www.efsa.europa.eu/en/topics/topic/novel-food. Accessed June 19, 2019.

b. European Food Safety Authority website. Food enzymes page. https://www.efsa.europa.eu/en/topics/topic/food-enzymes. Accessed July 2, 2019.

Novel foods framework

The most recent regulation on novel foods in the EU came into effect in January 2018: Regulation (EU) 2015/2283.[83,86] Under this regulation, the European Commission is responsible for authorizing novel foods, and a centralized assessment and authorization procedure was introduced to streamline the process.[86,87] To receive authorization as a novel food, an individual or corporation must submit an application to the European Commission that includes the name and description of the novel food, a description of the production process, a detailed description of the food's composition, scientific evidence that shows the food does not pose risks to human health, and a proposal for the conditions of intended use and labeling requirements.[9,88]

As part of this process, the European Commission can then request that the EFSA conduct a scientific risk assessment of the product's safety.[9] During this safety assessment, information on the history and safety of the novel food in countries outside of the EU are taken into consideration, among other data.[88] As such, it can be helpful if a food has already obtained GRAS status in the United States. However, such data are not a decisive factor in establishing prior safety, as this will need to be established by data relating to any food use in the EU. Once the EFSA has completed its risk assessment, the European Commission and individual member countries via the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee) are responsible for deciding whether the novel food should be authorized for sale on the market.[83,89] If there is uncertainty regarding the food's safety, the precautionary principle is applied and the product is not allowed on the market until future assessments are able to confirm its safety.[83] The European Commission grants premarket authorization for novel foods if they are safe, properly labeled such that consumers are not misled, and not nutritionally disadvantageous for the consumer if intended to replace another food.[83]

If a novel food is deemed to be safe by the EFSA and the European Commission, it is added to the EU's list of novel foods and can be placed on the EU market.[83] Once authorized, additional labeling requirements may apply for novel foods in order to ensure that consumers are properly informed about the products and their contents.[83]

What is a novel food?

In Europe, a "novel" food is defined as a food that was not consumed significantly in Europe prior to May of 1997, when the first regulation on novel foods came into effect.[9] Novel foods include new foods, foods from new sources, new substances or ingredients used in food, and new production technologies and methodologies for foods and ingredients.[10] Fermented soybean extract; pasteurized fruit-based preparations produced using high-pressure treatment; and ultraviolet-treated bread, milk, mushrooms, and yeast are all examples of novel foods.[9,82] Of note, foods "consisting of, isolated from or produced from microorganisms, fungi, or algae" and foods "consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, microorganisms, fungi or algae" are considered to be novel in the EU.[82] However, despite the fact that many food enzymes are produced with microorganisms, the EU's regulation on novel foods does not apply to food enzymes, food additives,[c] food flavorings, extraction solvents used in food production, or GMOs for food or feed, which are covered within the scope of other European regulations.[83–85] The European Commission maintains a list of all authorized novel foods in the EU ("the Union list").[85]

European Union regulatory pathway for food enzymes

In the EU, food enzymes are not considered to be novel foods and therefore follow a different regulatory pathway. In 2008, the EU adopted Regulation EC 1331/2008, which introduced a formal approval procedure for food additives, enzymes, and flavorings, and EC 1332/2008, which established a harmonized regulatory framework and safety approval process for food enzymes.[82,85,90,91] Prior to the introduction of this legislation, which became fully applicable in January 2010, food enzymes were generally not regulated at the EU level or were regulated inconsistently by member countries.[92,93] According to this regulation, the safety of all currently marketed and new food enzymes in the EU must be evaluated by the EFSA, prior to approval by the European Commission.[92] Ultimately, this legislation aims to establish a list of approved enzymes for the EU; however, this process is still ongoing.[93]

In order to gain approval for a food enzyme in the EU, an application must be submitted to the European Commission, which includes information on the identity of the source materials, the manufacturing process, an assessment of dietary exposure, and toxicological data.[92] Similar to novel foods, food enzyme safety then is assessed by the EFSA—specifically the EFSA's Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids. From September of 2011 to March of 2015, 300 applications for existing food enzymes were submitted to the European Commission for evaluation and authorization.[93] Due to the large number of applications filed and the rigorous evaluation and authorization process for each application, it may take years to establish

c. Food additives are defined as "substances that are not normally consumed as food itself but are added to food intentionally for a technological purpose . . . such as the preservation of food." Additionally, substances are not considered food additives if they are "used for the purpose of imparting flavour and/or taste or for nutritional purposes, such as salt replacers, vitamins and minerals" and "foods which may be used for a technological function, such as sodium chloride or saffron for coloring and food enzymes."[84]

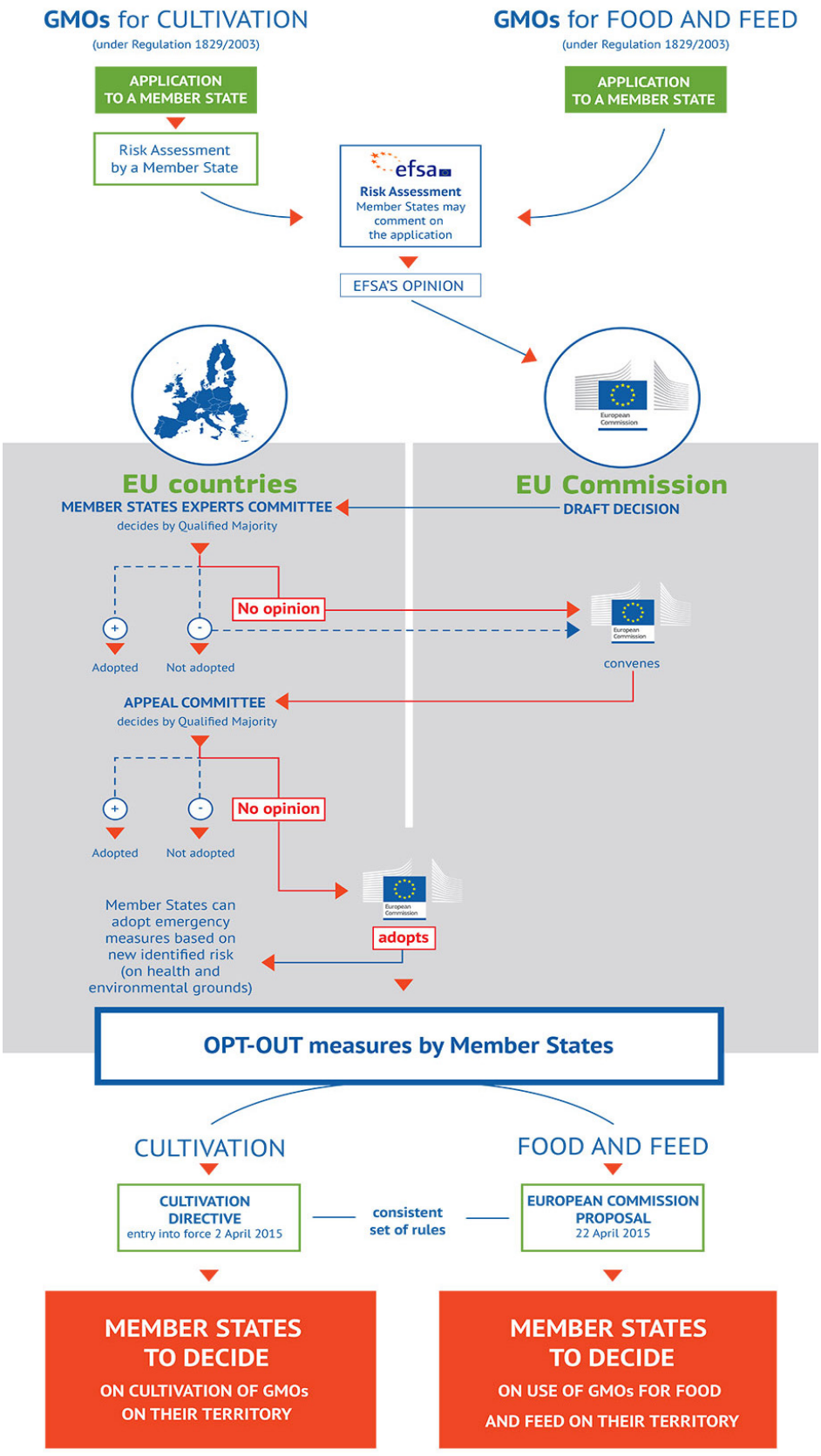
the EU list of approved food enzymes.[93] Until the EU list is established, national regulation on food enzyme marketing and use will continue to apply in member countries.[92]

Classification and labeling: GMOs

The EU takes a precautionary and relatively stringent approach to the regulation of GMOs, requiring premarket authorization for any GMO to be sold on the market, as well as post-market environmental monitoring for any authorized GMO.[94] The EU defines a genetically modified organism (GMO) as "an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination."[95] The European Commission defines genetically modified food as "food containing, consisting of or produced from GMOs."[96] Of note, the European Commission distinguishes food products (1) containing or consisting of, (2) produced *from* GMOs, and (3) and produced *with* GMOs.[80,97]

Food products produced *with* GMOs (e.g., as processing aids) do not contain any GMOs in the final product, whereas foods containing or consisting of GMOs, as well as foods produced *from* GMOs, have GMOs (or their residues) in the end products.[80,98] Based on this definition, proteins produced via fermentation of GM yeast or other microflora would be considered to be produced *with* GMOs, provided the DNA of the GMO compound can no longer be retrieved in the end product.[64] In the EU, food products containing or consisting of GMOS as well as those made *from* GMOs are subject to the regulatory approval process described under Regulation 1829/2003 (Figure 7). In contrast, food products made *with* GMOs are not subject to this regulation, subject to the provisions stated above.

FIGURE 7. **Genetically modified organisms: European Union decision-making process explained.**



Source: European Commission website. Plants page. https://ec.europa.eu/food/plant/gmo/authorisation/decision_making_process_en. Accessed October 19, 2019.

In the EU, the centralized procedure for GMO authorization is outlined in Regulation No. 1829/2003 and Directive 2001/18/EC, which regulates the intentional release of GMOs into the environment with a "zero tolerance" policy for unauthorized GMOs on the market (Figure 7).[99,100] These regulations, which aim to protect both human health and the environment, apply to GM food and feed, GMO imports, and the release of GMOs into the environment.[97]

According to the process outlined in Regulation No. 1829/2003 (Figure 7), manufacturers first submit an application to a member country. Then, at the EU level, GMO risk assessments are conducted by the EFSA's Panel on Genetically Modified Organisms, in close collaboration with the scientific bodies of member countries.[97] Once the opinion of the EFSA is received, the European Commission prepares a draft decision either granting or denying authorization. Just like the novel food authorization trajectory, this procedure includes a vote by the PAFF Committee. Ultimately, if authorization for a GMO is granted by the European Commission, it is applicable for a period of ten years, after which time the product must be reassessed.[96] A food product containing GMOs is authorized and approved by the European Commission if it does not cause any adverse effects to human, animal, or environmental health; does not mislead consumers; and does not replace a food that is nutritionally advantageous to the GMO food product.[80] If a product cannot be determined to be safe, the EU takes a precautionary approach and does not authorize it for sale or use.[101]

As of 2015, 67 GMOs are authorized for food and feed use in the EU, which are found in the EU register of authorized GMOs.[102] In 2015, the Commission proposed an amendment to Regulation No. 1829/2003 to allow member countries to opt out of the use of GM food or feed in part or all of their territory for reasons other than risks to human, animal, or environmental health, since these risks are already assessed by the EFSA.[80,130]

Policy and regulatory framework: Select low- and lower-middle income countries

Case study: Ethiopia

Key messages

- Multiple government agencies and ministries regulate different aspects of food safety in Ethiopia, including the Ethiopian Standards Agency, the Ethiopian Food and Drug Authority, the Ministry of Agriculture and Livestock Resources, and the Ministry of Trade and Industry.
- The regulatory framework for cultured milk and egg proteins is unclear in Ethiopia, and no information specific to microbial food enzyme regulation was identified.
- There have been recent developments to establish a biotechnology policy framework for GMOs.

With a population exceeding 100 million, Ethiopia is one of the most populated countries on the African continent. By 2050, the country is projected to become one of the most populous in the world, with an estimated 190.9 million people.[104,105] Ethiopia remains one of the poorest African countries with a gross domestic product per capita of $2,018.6 in 2018, and it is among the largest recipients of food aid (Table 3).[106] As of 2015, more than a quarter (27 percent) of the population lived below the poverty line.[d,107]

Despite these statistics, Ethiopia has a fast-growing economy with agricultural, services, and manufacturing sectors playing vital roles.[109] The agricultural sector alone accounts for 40 percent of the country's gross domestic product, and the majority (75 percent) of the population is engaged in agriculture, with cattle production being one of the main industries.[110,111] Milk production exceeds 3.8 billion liters per year and is valued at $2.5 billion.[112] Despite this substantial output, only half (54 percent) of households in Ethiopia regularly consume animal-source foods, and consumption largely depends on income.[112,113] Only one-third (30 percent) of the poorest households in Ethiopia consume milk and consumption quantities within the lowest quintile are less than half those of the highest income quintiles (Table 4).[112]

In recent years, the prevalence of malnutrition has decreased, but Ethiopia continues to experience high rates of stunting (38 percent), wasting (10 percent), and underweight (24 percent) among children under five years of age (Table 3).[114] Malnutrition rates vary significantly by region, with children in rural areas more likely to be malnourished than children in urban areas.[108] In 2016, less than one in five (14 percent) children aged 6 to 23 months met the minimum dietary diversity requirements.[108] Ethiopia's Ministry of Health has demonstrated a commitment to improving nutrition among its population by implementing interventions associated with the Scaling Up Nutrition movement, and several other national policies, strategies, and initiatives.[115,116]

d Defined as living on $1.90 per day or less.

TABLE 3. **Ethiopia demographic and nutrition indicators.**

Indicator	Value	Year	Source**
Total population	105,000,000	2017	[a]
Gross domestic product (GDP) per capita by PPP	$2,018.6	2018	[a]
Total expenditure on health as percentage of GDP	4.9%	2014	[b]
Population below the international poverty line	27.3%	2015	[a]
Prevalence of stunting among children under five	38.4%	2016	[c]
Prevalence of wasting among children under five	10.0 %	2016	[c]
Prevalence of underweight among children under five	23.6%	2016	[c]
Prevalence of overweight among children under five	2.9%	2016	[c]
Global Hunger Index ranking	32.3 (Serious)	2017	[d]
Under five mortality rate (number of deaths per 1,000 live births)	58	2016	[b]
Prevalence of undernourishment among the total population	20.6%	2018	[e]
Kilograms of eggs per capita available for human consumption per year	0.36	2013	[e]
Kilograms of milk (excluding butter) per capita available for human consumption per year	44.1	2013	[e]
Minimum Dietary Diversity among children 6 to 23 months*	13.8%	2016	[c]

Abbreviations: GDP, gross domestic product; PPP, purchasing power parity.

* Minimum dietary diversity: Children receive foods from four or more of the following food groups: (1) infant formula, milk other than breast milk, cheese or yogurt or other milk products; (2) foods made from grains, roots, and tubers, including porridge and fortified baby food from grains; (3) vitamin A–rich fruits and vegetables; (4) other fruits and vegetables; (5) eggs; (6) meat, poultry, fish, and shellfish (and organ meats); (7) legumes and nuts.[108]

** Sources:

a. World Bank website. Poverty & equity data portal: Ethiopia page. http://povertydata.worldbank.org/poverty/country/ETH. Accessed September 4, 2019.
b. World Health Organization website. Ethiopia page [Global Health Observatory data]. http://www.who.int/countries/eth/en/. Accessed July 11, 2019.
c. Central Statistical Agency (CSA) Ethiopia, ICF. *Ethiopia Demographic and Health Survey 2016*. Addis Ababa, Ethiopia, and Rockville, Maryland USA: CSA and ICF; 2016. https://dhsprogram.com publications/publication-FR328-DHS-Final-Reports.cfm.
d. Global Hunger Index website. Ethiopia page. https://www.globalhungerindex.org/ethiopia.html. Accessed September 5, 2019.
e. Food and Agriculture Organization of the United Nations website. FAOSTAT: Food supply – Livestock and fish primary equivalent page. http://www.fao.org/faostat/en/#data/CL/visualize. Accessed July 11, 2019.

Food regulation

Over the past decade, Ethiopia has invested substantially in updating its food safety regulations and systems.[117] Jurisdiction over food regulation is distributed across multiple government agencies and ministries, including the Ethiopian Standards Agency (ESA), the Ethiopian Food and Drug Authority (EFDA), the Ministry of Agriculture and Livestock Resources (MOA&L), and the Ministry of Trade and Industry (MoTI).[118] The ESA was established in 1970 as Ethiopia's first standardization body for food, water, and other commodities.[117,119] Although the institution's title and role has shifted since its inception, the ESA's overall objective is to represent the country's interests with regard to international and national standardization.[106] The ESA is a participating member of the Codex Alimentarius Commission and established a National Codex Committee in 2003 to provide guidance to the government on national implementation of the Codex.[106] In addition, the EFDA—formerly known as the Food, Medicine and Health Care Administration and Control Authority—was founded in 2010 to ensure the quality, safety, and/or efficacy of medicines,

TABLE 4. **Household milk consumption in Ethiopia, by income group.**

Income group	Percentage of households consuming dairy	Consumption per capita per week (grams)	Share of own production in consumption
Poorest quintile	30%	324	71%
Moderately poor quintile	34%	427	72%
Middle quintile	45%	592	62%
Moderately rich quintile	44%	714	53%
Richest quintile	57%	779	31%

Source: Food and Agriculture Organization of the United Nations (FAO). *Africa Sustainable Livestock 2050: Livestock and Livelihoods Spotlight – Ethiopia Cattle Sector*. Rome, Italy: FAO; 2018. http://www.fao.org/3/I8676EN/i8676en.pdf.

food, cosmetics, and medical devices in Ethiopia. The EFDA, which sits under Ethiopia's Ministry of Health, is mandated by Food, Medicine and Health Care Administration and Control Proclamation 661/2009.[108,117,120–123] The EFDA works in collaboration with the MOA&L to regulate the importation of products of plants, plant materials, livestock, and livestock genetic products.[124] Finally, the MoTI is responsible for quality control of food imports and exports.[106]

At present, information specific to microbial food enzyme regulation in Ethiopia has not been identified. As such, the information presented here is limited to a discussion of Ethiopia's regulation of GM crops, foods, and other products produced through modern biotechnology.

Biotechnology regulatory framework

In 2009, Ethiopia enacted Biosafety Proclamation No. 655/2009 with the objective of "protect[ing] human and animal health, biological diversity and in general, the environment, local communities and the country at large by preventing or at least managing down to levels of insignificance the adverse effects of modified organisms."[125] Ethiopia's Ministry of Environment, Forest and Climate Change is responsible for implementing this law.[126] The provisions outlined in the regulation are strict and precautionary, exceeding those of the Cartagena Protocol.[127] For example, Ethiopia's Biosafety Proclamation adopts a broader definition of a "modified organism" as "any biological entity which has been artificially synthesized, or in which the genetic material or the expression of any of its traits has been changed by the introduction of any foreign gene or any other chemical whether taken from another organism, from a fossil organism or artificially synthesized."[125,127] In contrast, the Cartagena Protocol defines a "living modified organism" as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology."[7]

Under the framework of the Biosafety Proclamation, there are strict regulations that must be followed with regard to food products in Ethiopia.[125] This law requires that an advanced informed agreement and rigorous risk evaluation be obtained before any modified organism may enter or be used/made available in Ethiopia, including for use in food or feed.[125,126] It also requires that all "modified organisms" are labeled.[125] Applications for advanced informed agreements are submitted to Ethiopia's Environmental Protection Authority. The applicant must also use a qualified expert to conduct a risk assessment of the product and submit the application to the Environmental Protection Authority, along with a detailed technical analysis and a document summarizing the report in nontechnical terms.[125] Since Ethiopia is one of the largest

Genetically modified crops in Ethiopia

In 2018, the government of Ethiopia granted its first approval for the cultivation of a GM crop: Bt cotton.[111] The government was motivated to increase cotton production to support the rapidly growing textile industry. In July 2016, the MOA&L and the Ethiopia Institute of Agricultural Research planted the first confined field trials (CFTs) for Bt cotton.[130] They completed the second round of CFTs 2017.[111] The Bioaffairs Directorate of the Ministry of Environment, Forest and Climate Change, the Environment, Forest and Climate Change Commission, and biosafety technical working team supervise the CFTs.[111]

This approval of the first GM crop in Ethiopia illustrates a breakthrough in the government's strict regulatory framework. Furthermore, the Environment, Forest and Climate Change Commission and biosafety technical working team authorized CFTs for GM maize in 2018 as part of the Water Efficient Maize for Africa project, with the goal of approving the use of drought-resistant GM maize in Ethiopia.[111]

recipients of US food aid, processed foods, specifically with corn-soya blends that are made from GM products, are allowed into the country with a waiver.[111] The prohibitive nature of this regulation has received criticism for hindering the advancement of biotechnology research, development, and innovation in the country.[126,127] However, despite these restrictions, Ethiopia has a more advanced biotechnology policy regulatory framework relative to those of many other African countries (Figure 8).

In response to increasing demand for biotechnology research and development, Ethiopia's Biosafety Proclamation was amended in 2015 to allow the Ethiopian government to approve genetically modified Bt cotton, a specific GMO strain, for cultivation.[128] Ethiopia is the fourth country in Africa to approve a GM crop for commercialization; however, it is important to note that this crop is not intended for human consumption. With this amendment, the Proclamation now defines modern biotechnology as the application of "a) in vitro nucleic techniques, including recombinant deoxyribonucleic acid and direct injection of nucleic acid into cells or organelles; b) fusion of cells beyond the taxonomic family; that overcome natural physiological, reproductive or recombination barriers and that are not techniques used in traditional breeding and selection."[129]

Case study: India

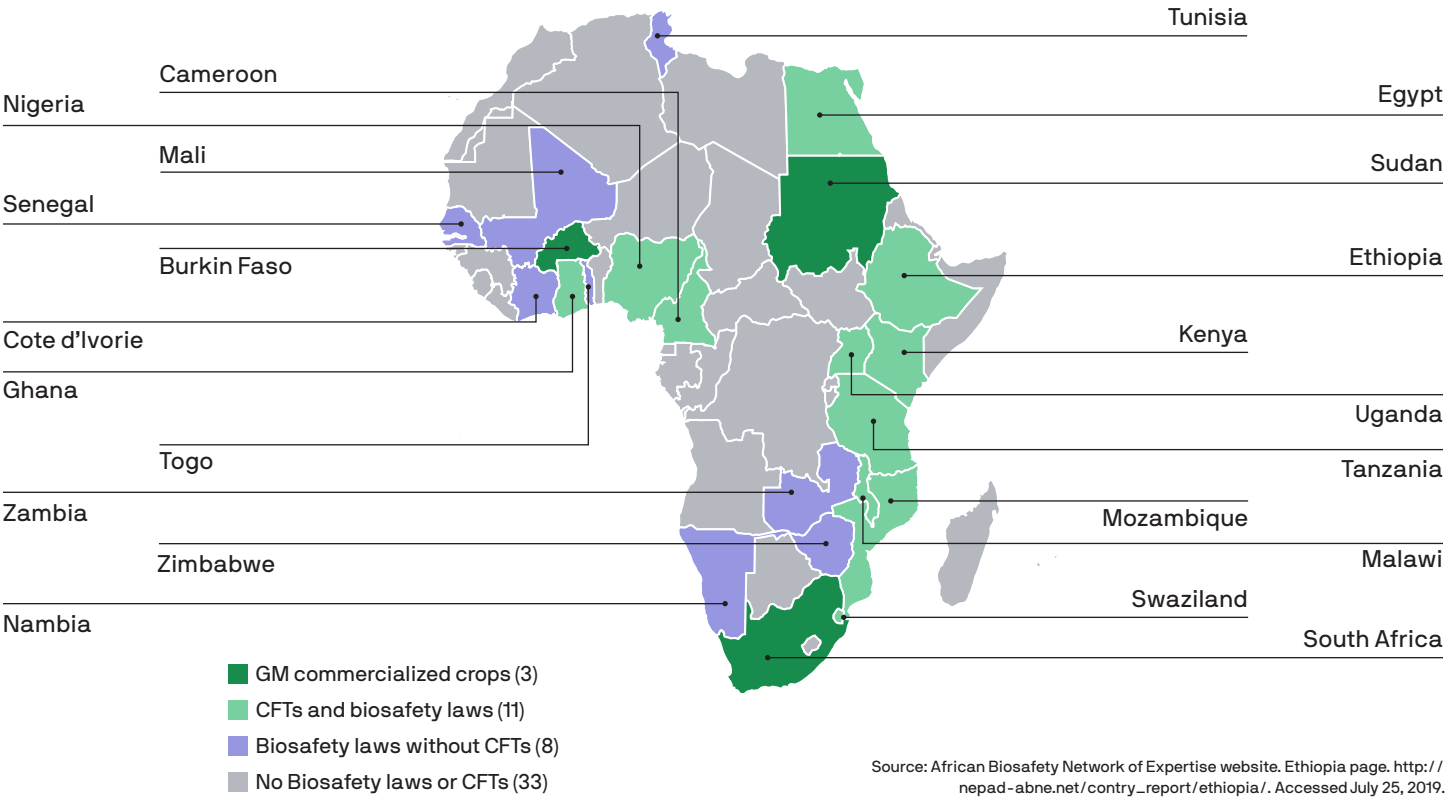
India is the second most populated country in the world (1.34 billion).[131] One-fifth (21 percent) of the country lived below the poverty line[e] in 2011, but India is classified as a lower-middle

e. Defined as living on $1.90 per day or less.

Key messages

- The Food Safety and Standards Authority of India, Ministry of Agriculture, Ministry of Food Processing Industries, Ministry of Health and Family Welfare, and Ministry of Commerce and Industry play important roles in food regulation in India.
- In India, no clear determination has been made regarding the regulatory framework for cultured milk and egg proteins to date. However, three potential regulatory pathways for these proteins include the (1) food product and food additive framework; (2) non-specified food framework; and (3) regulatory pathway for pharmaceutical products.

FIGURE 8. **Status of African biotechnology regulations for GM crops.**



Source: African Biosafety Network of Expertise website. Ethiopia page. http://nepad-abne.net/contry_report/ethiopia/. Accessed July 25, 2019.

income country due to its gross domestic product per capita of $7,761.[105,132,133] The Indian economy relies heavily on the agricultural sector. Half (50 percent) of the workforce works in agriculture.[134–136] As of 2017, the country was no longer reliant on food aid and is now a net food exporter.[137] India is the world's largest producer and consumer of milk, with the majority of production coming from water buffalo as well as cattle.[136,138,139] Over the past two decades (2000 to 2017), Indian milk production increased by 4.2 percent annually.[136] In 2016, the government launched several programs to double farmers' income by 2022 in order to remove barriers (e.g., uneven wealth distribution) to greater agricultural productivity.[135]

Despite this, India experiences a high burden of malnutrition, and accounts for almost one-third (31 percent) of the global burden of stunting. Among children under five years of age, 38 percent are stunted, 21 percent are wasted, and 36 percent are underweight (Table 5).[140] Rates of stunting vary greatly from region to region; children in rural areas are more likely to be stunted (41 percent) compared to children in urban areas (31

Table 5: India demographic and nutrition indicators.

Indicator	Value	Year	Source**
Total population	1,339,200,000	2017	[a]
Gross domestic product (GDP) per capita by PPP	$7,761	2018	[a]
Total expenditure on health as percentage of GDP	4.7%	2014	[b]
Population below the international poverty line	21.2%	2011	[a]
Prevalence of stunting among children under five	37.9%	2016	[c]
Prevalence of wasting among children under five	20.8 %	2016	[c]
Prevalence of underweight among children under five	36.3%	2016	[c]
Prevalence of overweight among children under five	2.4%	2016	[c]
Global Hunger Index ranking	31.4 (Serious)	2017	[d]
Under five mortality rate (number of deaths per 1,000 live births)	50	2016	[b]
Prevalence of undernourishment among the total population	14.5%	2018	[e]
Kilograms of eggs per capita available for human consumption per year	2.6	2013	[e]
Kilograms of milk (excluding butter) per capita available for human consumption per year	84.5	2013	[e]
Minimum Dietary Diversity among children 6 to 23 months*	22.0%	2016	[c]

Abbreviations: GDP, gross domestic product; PPP, purchasing power parity.

* Minimum dietary diversity: Children receive foods from four or more of the following food groups: (1) infant formula, milk other than breast milk, cheese or yogurt or other milk products; (2) foods made from grains, roots, and tubers, including porridge and fortified baby food from grains; (3) vitamin A–rich fruits and vegetables; (4) other fruits and vegetables; (5) eggs; (6) meat, poultry, fish, and shellfish (and organ meats); (7) legumes and nuts.

** Sources:

a. World Bank website. Poverty & equity data portal: India page. http://povertydata.worldbank.org/poverty/country/IND. Accessed September 4, 2019.
b. World Health Organization website. India page [Global Health Observatory data]. http://www.who.int/countries/ind/en/. Accessed July 11, 2019.
c. International Institute for Population Sciences (IIPS) India, ICF. *India National Family Health Survey (NFHS) 4 2015-16*. Mumbai, India: IIPS and ICF; 2017. http://dhsprogram.com/pubs/pdf/FR339/FR339.pdf.
d. Global Hunger Index website. India page. https://www.globalhungerindex.org/india.html. Accessed September 5, 2019.
e. Food and Agriculture Organization of the United Nations website. FAOSTAT: Food supply – Livestock and fish primary equivalent page. http://www.fao.org/faostat/en/#data/CL/visualize. Accessed July 11, 2019.

percent).[140] Only 22 percent of Indian children 6 to 23 months consume a diet that meets the minimum dietary diversity requirements.[140] Dietary patterns vary significantly between regions, yet many are vegetarian, with staple diets including fruits, vegetables, dal, and pulses.[141] The government of India has demonstrated commitment to improving nutrition through the Scaling Up Nutrition movement, as well as by enacting several national policies and programs designed and implemented to improve the population's nutritional status.[135,142]

Food regulation

In 2006, the Indian government passed the Food Safety and Standards Act with the goal of consolidating all previous food safety standards regulations under one unified act.[138,143-145] This legislation established the Food Safety and Standards Authority of India (FSSAI) under the Ministry of Health and Family Welfare. The FSSAI is responsible for establishing food standards and regulating the manufacture, storage, distribution, sale, and import of food in India.[146,147] The FSSAI is a participating member of the Codex Alimentarius Commission and established the National Codex Committee to provide guidance to the government on national implementation of the standards outlined in the Codex.[147] In 2011, the FSSAI published the Food Safety and Standards Rule to establish guidance on how to implement the Food Safety and Standards Act standards. The purpose of this rule is to "consolidate the laws relating to food" and "lay down science based standards for articles of food."[147]

Additional government bodies that participate in Indian food regulation include the Ministry of Food Processing Industries, the Ministry of Health and Welfare, the MOA&L, and the Ministry of Commerce and Industry.[148,149]

At present, no clear determination has been made regarding the regulation process for cultured milk and egg proteins in India. We describe three potential regulatory pathways—the food product and food additive framework, the non-specified food framework, and the regulatory pathway for pharmaceutical products—which may be relevant for these types of products in India, based on findings from our literature review and stakeholder interviews (Figure 9).

Regulatory pathway for food products and food additives

In 2011, the FSSAI published the Food Safety and Standards (Food Products Standards and Food Additives) Regulations.[138,147,150] This set of regulations details standards for the manufacture, storage, distribution, sale, and import of commonly used food products, including commonly used food enzymes, in India.[150] For example, non-animal rennet, a microbial enzyme in cheese and other dairy products widely used in India, is approved for use under this regulation.[150,151] Amendments are continually made to this set of regulations. The FSSAI announced the sixteenth amendment in 2017 to update sub-regulations on specific food products.[152]

Regulatory pathway for non-specified foods

The FSSAI regulates foods (including new additives, processing aids, and enzymes) that are not covered under the Food Safety and Standards (Food Products Standards and Food Additives) Regulations (2011) as "non-specified foods." These include the following types of foods/ingredients:[153,154]

1. Novel foods or novel food ingredients or processed with the use of novel technology.[f]
2. New food additives.
3. New processing aids, including enzymes.
4. Articles of food and food ingredients consisting of or isolated from microorganisms, bacteria, yeast, fungi, or algae.

According to the Food Safety and Standards (Approval for Non-Specified Food and Food Ingredients) Regulations (2017), non-specified foods require FSSAI approval prior to manufacture, storage, sale, distribution, or import.[143] To obtain approval, manufacturers are required to submit an application to the FSSAI along with a fee including information that describes the product, its intended and functional use, the manufacturing process, and safety information. Applications are required to include additional specific information about the food, depending on its type. The FSSAI then conducts a scientific risk assessment and makes a determination as to whether to approve or reject the application.[153]

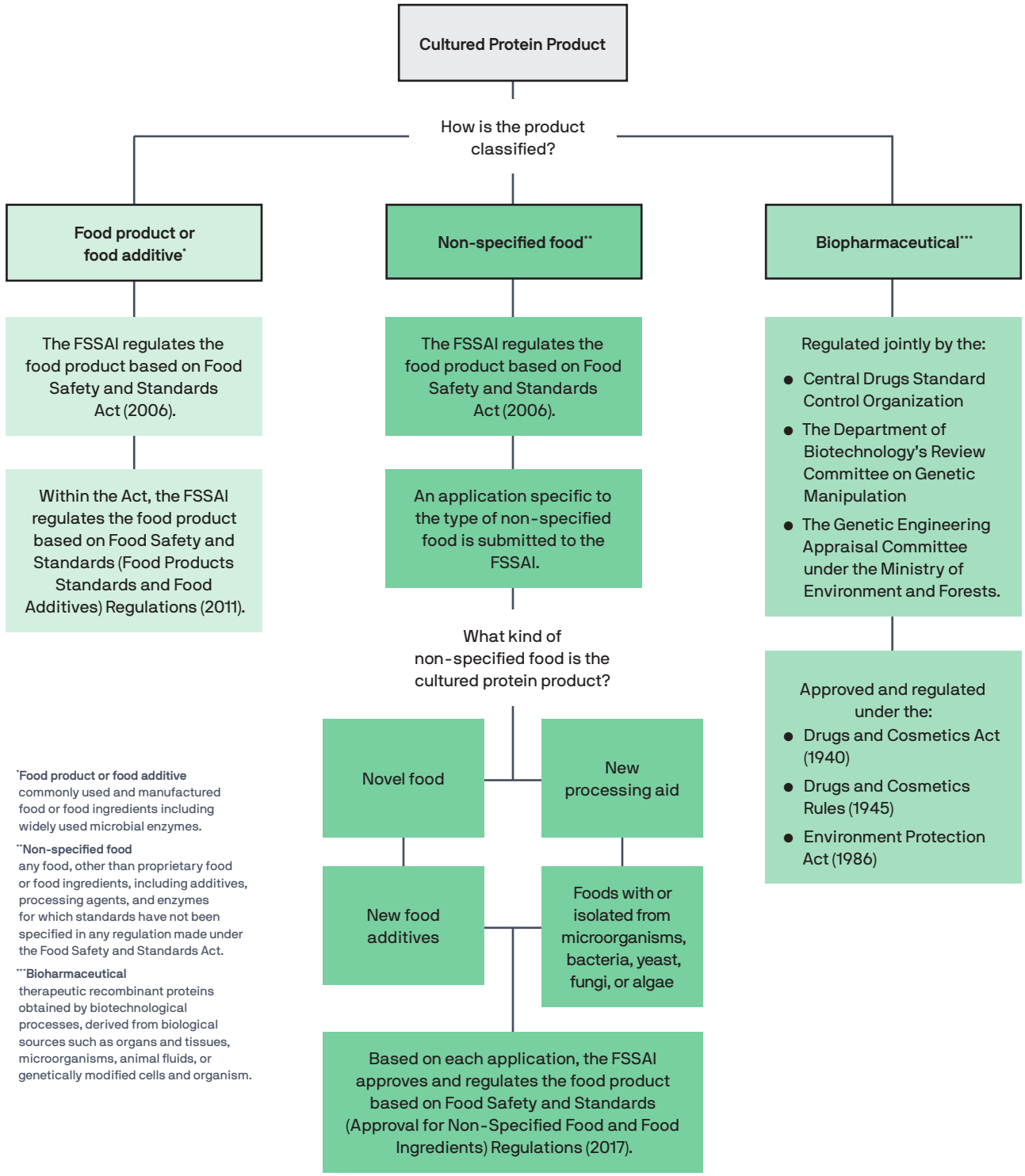
Regulatory pathway for pharmaceutical products

Many biopharmaceuticals—"therapeutic recombinant proteins obtained by biotechnological processes, derived from biological sources such as organs and tissues, microorganisms, animal fluids, or genetically modified cells and organisms"—are produced through similar techniques to cultured proteins, using host organisms (e.g., yeast, bacteria, or cell lines).[155] Insulin is a common example of a biopharmaceutical produced through this type of process.[155,156] Despite similarities in the production processes, biopharmaceuticals typically follow separate and more rigorous regulatory pathways from cultured products intended for human consumption through food (e.g., enzymes).

A large biopharmaceutical industry in India manufactures products for both animal and human use. This industry was valued at $33 billion in 2017 and is expected to reach a value of $55 billion by 2020.[138,157] For example, India is one of the world's top producers of insulin.[150,157] Biopharmaceutical products are regulated under the Drugs and Cosmetics Act (1940); the Drugs and Cosmetics Rules

f. Novel foods are classified as ingredients with no history of human consumption in India or not specified under other regulations under the Food Safety and Standards Act, 2006.[153]

FIGURE 9. **Potential regulatory pathways for cultured protein products in India**



Abbreviation: FSSAI, Food Safety and Standards Authority of India.

Sources:

a. Slette J, Mani R. Draft regulation on product approval published in Indian Gazette. In: *US Department of Agriculture, Foreign Agricultural Services: Global Agricultural Information Network Report*. GAIN Report No. IN7026. February 14, 2017. https://gain.fas.usda.gov/Recent%20GAIN%20Publications/Draft%20Regulation%20on%20Product%20Approval%20Published%20in%20Indian%20Gazette_New%20Delhi_India_2-14-2017.pdf.

b. Ministry of Health and family Welfare, Food Safety and Standards Authority of India. Food Safety and Standards (Food Products Standards and Food Additives) Regulations, 2011. New Delhi, India: Ministry of Health and Family Welfare; August 1, 2011. http://fsdaup.gov.in/writereaddata/images/pdf/act-and-rules/fss-regulation/Food-safety-and-standards-Food-product-standards-and-Food-Additives-regulation-2011.pdf.

c. Meher BR, Balan S, Mohanty RR, Jena M, Das S. Biosimilars in India: current status and future perspectives. *Journal of Pharmacy and Bioallied Sciences*. 2019;11(1):12–15. doi:10.4103/jpbs.JPBS_167_18.

d. Rathore A. Guidelines on similar biologics: regulatory requirements for marketing authorization in India. *Parenteral Drug Association Journal of Pharmaceutical Science and Technology*. 2012;66(5):393. doi:10.5731/pdajpst.2012.00886.

(1945); and the Rules for Manufacture, Use, Import, Export and Storage of Hazardous Microorganisms/Genetically Engineered Organisms or Cells, which was notified under the Environment Protection Act (1986).[158] They are regulated jointly by the Central Drugs Standard Control Organization (CDSCO), the Department of Biotechnology's Review Committee on Genetic Manipulation (RCGM), and the Genetic Engineering Appraisal Committee (GEAC) under the Ministry of Environment and Forests. The CDSCO is responsible for evaluating the safety, efficacy, and quality of drugs in India. The RCGM oversees the development and preclinical evaluation of biopharmaceuticals. Finally, the GEAC reviews and approves activities related to the large-scale use of living modified organisms in research and development, production, and environmental release.[159]

Growing momentum for cellular agriculture in India

In early 2019, The Good Food Institute and the Institute of Chemical Technology, Mumbai announced plans to develop the first cellular agriculture Center of Excellence in Maharashtra to advance research in cell-based meat.[160] Several months later, the government of India's Department of Biotechnology announced a $640,000 grant for cell-based meat research to the Centre for Cellular and Molecular Biology and the National Research Centre on Meat in Hyderabad.[161] These recent developments highlight the rapidly evolving nature of the cellular agriculture industry as well as growing momentum and interest in the space in India and globally.[162]

Classification and labeling: GMOs

The regulatory framework for GM foods in India is still evolving. Regulation of all activities, processes, and products related to GMOs—and products derived from GMOs—falls under the Rules for Manufacture, Use, Import, Export and Storage of Hazardous Microorganisms/Genetically Engineered Organisms or Cells, under the Environmental Protection Act (1986).[163] Although initially regulated by the GEAC under the broad framework of the Environmental Protection Act, GM foods also fall under the purview of the 2006 Food Safety and Standards Act. This Act defines GM food as "food and food ingredients composed of or containing genetically modified or engineered organisms obtained through modern biotechnology, or food and food ingredients produced from but not containing genetically modified or engineered organisms obtained through modern biotechnology."[146]

In mid-2018, the FSSAI initiated development of new regulations for GM foods, which are still in progress, and established a panel on GM organisms and foods.[147] At the time of writing, the only GM food products that are approved for import in India are soybean and canola oil, and the only GM crop approved for cultivation within the country is cotton.[138] Given the role of GMOs in the production process for cultured milk and egg proteins and the evolving nature of India's regulatory framework, it is unclear how cultured milk and egg proteins will be classified with respect to their GM status.[164]

Dietary classifications

Key messages

- Various dietary classifications—such as halal, kosher, vegetarian, and vegan—may play a role in the policy and regulatory environments for cultured milk and egg proteins within different cultural and geographic contexts.
- Halal and kosher foods are certified through third-party nongovernmental agencies. Cultured milk and egg proteins (and/or products containing these proteins) may be classified and certified as halal and/or kosher if the products meet required criteria and manufacturers follow the relevant certification procedures.
- For vegan and vegetarian foods, there are no established certification agencies and classification determinations are made by individual consumers.
- If cultured milk and egg proteins are incorporated as ingredients into food products, all dietary classification guidelines would also apply to all of the ingredients in the product.

Various dietary classifications may play a role in the policy and regulatory environments for cultured milk and egg proteins within different cultural and geographic contexts. Here, we discuss the classification (and certification processes, where applicable) of halal, kosher, vegetarian, and vegan foods. Importantly, if cultured milk and egg proteins are incorporated as ingredients into other food products, the guidelines described below would also apply to all of the ingredients in the product.

Halal

The halal certification process for foods is similar across geographies and is led by Halal Certification Bodies: private, third-party organizations that certify halal food products and provide labels indicating that key requirements for halal dietary law have been upheld in the product.[168] In 1994, the Halal Food Authority was established as the first Halal Certification Body in the United Kingdom.[168] In the United States, the largest halal certification organizations include the Islamic Society of the Washington Area, the Islamic Food and Nutrition Council of America, Islamic Services of America, the Islamic Society of North America's Halal Certification Agency, and Halal Food Council International.[169] Each third-party certification agency has specific requirements for their halal inspectors.

In order to gain halal certification for food products through one of these third-party agencies, the manufacturer must submit an application that considers halal guidelines. There are halal guidelines for egg, milk, and dairy products as well as guidelines on the use of genetically modified microorganisms.[170] Below, we list several relevant criteria for the halal certification of milk, dairy, and egg products:[170]

What is halal?

A halal food is compliant with Muslim dietary rules and is considered to be a permissible and lawful food under Islamic law.[165] Foods that are not halal include alcohol; meat from swine, boars, and carnivorous animals; and meats that do not meet specific conditions for slaughtering methods.[166] For meats to be considered halal, animals should be alive and healthy prior to slaughter, a Muslim should perform the slaughter, the slaughter should follow specific practices specified by Islamic principles, and any flowing blood of the carcass should be completely drained.[167]

1. For yogurt products, gelatin should not be used; if it is used, the gelatin must be from bones and hides of halal-slaughtered animals.
2. Since many types of cheese contain rennet and other enzymes derived from animals, these enzymes need to come from halal-slaughtered animals or from microbial or plant sources.
3. Eggs are halal as long as they do not come into contact with foods that do not follow halal guidelines.

A food is considered to be halal if all of its components are halal. Therefore, food enzymes are considered halal if the source of the enzyme is halal. For example, enzymes made from the DNA of chickens and cows are considered halal, yet enzymes made from the DNA of pigs are not.[170] As such, cultured milk and egg proteins may be classified as halal if the DNA used in the genetically modified yeast originates from a halal source and is approved by certification agencies.

Kosher

Kosher certifications communicate to consumers that foods, ingredients, beverages, and/or food service facilities and equipment have been verified as compliant with Jewish dietary laws. Similar to halal, the kosher certification process is managed by third-party certification organizations that provide products, equipment, and/or facilities with kosher approval by a verified rabbinic agency.[171] Globally, there are more than 1,400 kosher certification agencies.[173] The Orthodox Union Kosher Certification Agency is the world's largest kosher certification and supervision agency.[171] Additional agencies include the Kosher Certification Agency, OK Kosher Certification, EarthKosher, and Star-K.[174] Each regulatory agency has a logo or symbol that can be displayed on the packaging of certified products. In order to gain kosher certification for a food product, manufacturers must submit an application to an agency, which is then assessed and approved or denied by a qualified rabbinic field representative, who typically visits the manufacturing facility. As part of this application, manufacturers are required to submit a list of all ingredients and machinery used in the product's production.[171]

Microorganisms, naturally occurring microflora, and microbial food enzymes are considered to be kosher if they are grown using kosher media. Novozymes, one of the largest producers of microbial food enzymes, has modified their production practices to maintain kosher certification. The company undergoes audits and inspections each year.[172] In 2015, 60 percent of Novozymes' enzyme products were kosher certified.[172]

Although the classification of cultured milk and egg proteins under kosher dietary law has not yet been established globally, they could be considered pareve if rabbinic field representatives deem them to be non-dairy.[175,176] For example, Perfect Day Foods, a manufacturer of cultured milk proteins, states on their website that they are currently pursuing kosher certification and have been in contact with rabbis.[176] However, it is important to reiterate that if cultured proteins are used as ingredients in other food products, all other components of that food would also be subject to kosher dietary laws in order for the entire product to be considered kosher.[176]

In July 2019, Perfect Day Foods launched a limited-release ice cream product in the United States that was produced using cultured proteins. Photo: PATH/Patrick McKern.

What is kosher?

A kosher food is a food that satisfies the requirements of Jewish law. Kosher laws are numerous and complex and specify which foods may be consumed as well as guidelines for their production, processing, and preparation.[171,172] Of note, kosher law prohibits the pairing of dairy and meat as well as the consumption of specific types of animals and cuts of meat. Kosher law also provides guidelines for the slaughter and preparation of animals as food.[171] Under Jewish law, a "pareve" food is considered to be a "neutral" food—that is, prepared without meat, dairy, or their derivatives—and therefore can be eaten in combination with these foods. Examples of pareve foods include raw fruits and vegetables, flour, sugar, and eggs.[171]

Vegetarian and vegan

Vegetarians are individuals who do not consume meat of any kind, but may consume animal products, such as dairy and eggs. Veganism refers to a strictly plant-based diet that does not include any type of animal product—including dairy, eggs, and animal-based added fats. There are many different motivations for following a vegetarian or vegan diet, which include health/nutrition, philosophical/ethical, environmental, and religious considerations. Of note, there are no established institutions or third-party agencies that make official determinations as to whether a food is considered to be "vegetarian" or "vegan." Rather, this distinction is typically left up to the individual and falls along a spectrum, with many different variations and interpretations.[177] In general, however, multiple companies assert that their forthcoming cultured milk and egg protein products will be classified as both vegetarian and vegan.[178–180]

Discussion

In this paper, we assessed and described the potential policy environment and regulatory pathways for cultured milk and egg proteins in the United States, the EU, Ethiopia, and India, drawing lessons learned from the experiences of the microbial food enzyme industry and other food innovations. Ultimately, this analysis aims to inform an understanding of how cultured milk and egg protein products and production techniques may be used to sustainably promote nutrition among vulnerable populations in LMICs. However, in order for these populations to have access to such products through commercial or philanthropic market pathways, understanding the policy and regulatory environments for these products among countries that may produce, procure, and consume them is a critical foundation.

Our findings demonstrate that, at present, the United States has the most clearly defined regulatory structure for cultured milk and egg proteins. Findings from both stakeholder interviews as well as our literature review indicate that cultured milk and egg proteins will likely be regulated by the FDA in the United States, according to the GRAS framework. In contrast, although the EU has clearly defined and well-established food safety regulatory institutions and frameworks, our review did not identify a clear determination as to how cultured milk and egg proteins will be interpreted within the context of existing regulations. More information on the formulation and business case for specific cultured protein products will be needed to inform this determination. Finally, for Ethiopia and India, where food safety institutions and regulations have been established more recently, our findings also did not identify a single potential regulatory pathway for these products. In these cases, it is likely that the regulatory approaches in high-income settings, such as the United States and the EU, will play significant roles in informing the global regulation of this emerging class of products.

However, despite this uncertainty, our review highlights a number of lessons learned from the policy and regulatory experiences of microbial food enzymes and other innovative food products derived through similar processes in multiple countries. For example, the regulatory experience of the Impossible Burger's fermentation-derived soybean leghemoglobin under the GRAS framework in the United States highlights the importance of obtaining and sharing rigorous and robust safety data for these products. This has also been an important theme for microbial food enzymes, which have a clearly defined safety evaluation framework in the United States.[31,51]

Additionally, the experiences of the microbial food enzyme industry highlight the importance of organization and communication among manufacturers and stakeholders. Many cultured protein manufacturers anticipate near-term product launches, with the earliest commercial products expected on the market in 2020. In addition, several manufacturers reported ongoing discussions and consultations with regulatory bodies. As emerging cellular agriculture companies grow, evolve, and move further toward product introduction and commercialization in the coming years, industry coordination and transparent communication and consultation with regulatory agencies in multiple countries will be critical for success.[181] This will allow manufacturers to draw from lessons learned from other food innovations and play an active role in advocating for and shaping policy and regulatory environments that promote innovation alongside consumer safety, nutrition, and access.

Finally, our findings highlight a high degree of ambiguity regarding the GMO classification of both cultured proteins as well as microbial food enzymes across multiple country contexts. For GMO classification, nuances in the details of the production process—specifically the potential role of GM microflora in protein production—as well as various countries'/institutions' interpretation of the implications of that role—create complexity. For example, in the United States the National Bioengineered Food Disclosure Standard includes mandatory disclosure requirements for all food classified as "bioengineered" and voluntary disclosure guidelines for foods "derived from bioengineering."[1] Additionally, countries set varying quantity thresholds for the amount of modified genetic material that can be present in the final product for it to be defined as GM.[80] The details of the production processes for cultured proteins will play an important role in the classification of their GMO status across various country contexts. On the part of manufacturers, close engagement with regulators and clear communication with the public about the production processes for these proteins will enable transparency and trust as the industry evolves and products approach commercialization.

Limitations

Our analysis has several limitations. First, the general lack of published and peer-reviewed data related to cultured milk and egg proteins—and cellular agriculture more broadly—was a key limitation of our desk research. Broadly, currently there is a lack of unbiased academic expertise specialized on this topic. Varied terminology for cultured proteins (e.g., "synthetic," "lab-grown," "fermentation-derived," and "flora-based") was also a limitation of our analysis, as selected search terms may not have yielded all relevant sources due to a lack of consistency in this emerging space. Additionally, there are a limited number of case studies from which to learn to inform how cultured proteins will be regulated. Future scientific inquiry in multiple domains (e.g., safety, nutritional profile, consumer acceptance, and impact modeling) and across multiple country contexts is warranted to further grow the evidence base underpinning these food innovations and inform their appropriate introduction and commercialization.

Second, our stakeholder interviews included a relatively small sample (N = 25 individuals), and only a subset of the stakeholders interviewed (n = 18) had expertise in policy and regulatory environments. Additionally, several stakeholders we interviewed were unfamiliar with these products and production processes.

Further, this paper focuses specifically on the policy and regulatory environments for cultured milk and egg proteins themselves and does not include an examination of policies and regulations that relate to the manufacturing processes or inputs used to produce these proteins.

Finally, our analysis represents a snapshot of the policy and regulatory landscape for a rapidly evolving industry at a specific time point and within specific geographies. Several stakeholders mentioned the policy and regulatory environments for geographies outside the scope of this paper. In the past two years alone, multiple new cultured protein manufacturers have emerged and made significant strides toward product introduction and commercialization. The next few years will yield further important developments for this industry and impact the establishment of policy and regulatory environments in different settings.

Conclusion

In summary, although many outstanding questions remain about how cultured milk and egg proteins will be classified and regulated in the four geographies included in this paper, the results highlight several potential pathways, as well as relevant lessons learned from the experiences of the microbial food enzyme industry and manufacturers of other innovative food products produced through similar processes. Given the growing global demand for animal-source proteins coupled with the substantial environmental impact of livestock, food innovations such as cultured milk and egg proteins could play an important role in the future of food and supporting global nutrition by enabling access to affordable, nutritious, and high-quality protein for vulnerable populations. However, in order for this to be realized, an enabling environment that prioritizes both innovation and consumer safety and promotes conditions for global equitable access will be critical.

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Appendix

Concept card: Cultured milk and egg proteins for use in low- and lower-middle income countries

Background

Undernutrition of children and mothers is the leading underlying cause of child morbidity and mortality worldwide,[1] and is a significant health problem in low- and lower-middle income countries (LMICs). Low-quality diets that are lacking in essential proteins, sufficient energy, and essential vitamins and minerals are a key contributor to undernutrition.[2] Studies have shown that increasing consumption of animal-source proteins can combat child malnutrition,[3,4] while other studies have shown the negative agricultural and environmental impacts of raising livestock (including high land/water use requirements and greenhouse gas emissions).[5] The commercialization of cultured proteins (also referred to as synthetic proteins, flora-based proteins, or fermentation-derived proteins) has the potential to increase access to high-quality and affordable proteins, which could sustainably support global nutrition while reducing the environmental and agricultural pressures of producing animal-source proteins.

Cultured proteins, which are identical to their equivalent animal-source proteins, are made through cell cultures in a laboratory setting (Figure A). While this process can create many types of animal-source proteins, this concept card focuses specifically on "cultured" milk and egg proteins. Several emerging biotechnology companies are creating cultured milk and egg proteins for use in food products (Figure B), though none are yet commercially available.

TABLE A. **Characteristics of cultured milk and egg proteins**

Production process	To produce cultured milk or egg proteins, the gene encoding the animal protein is introduced into the DNA of a starter culture of microflora (e.g., yeast or fungi). This culture is fed sugar and grown in controlled fermentation tanks, where it expresses the desired protein. This end protein is then separated from the host cells and purified into a powder (see Figure A). This fermentation process is similar to that of brewing beer or creating probiotics, and the proteins could potentially be manufactured in LMICs.
End product	A purified protein powder that is identical in structural, organoleptic, and nutritional properties to the same protein derived from an animal source. This purified protein can be used as a stand-alone protein powder product or as an ingredient in other products, including animal-source food (e.g., milk or egg) substitutes. The final product is GMO free.
Development stage	Research and development
Time to market	Expected to launch in 2020 (at the earliest) for small scale/limited markets, with large scale/global production possible beginning in 2025.[6]
Target cost	Final product cost will depend on the form of the end-product, and will differ between additive (e.g., purified milk protein powder) or complete (e.g., alternative milk that is ready for consumption) products. Cost will also depend on scale, and will likely decrease as sales and production capacity increase. Once scale is achieved, costs may be on par with or less expensive than animal-source proteins.
Expected key benefits over animal-source proteins	• Contains the same, high nutritional value. • Have a lower environmental footprint and fewer greenhouse gas emissions. • Require less agricultural inputs (e.g., land, water, energy). • Do not require any animal breeding or slaughter (is a vegan product). • Contain no hormones, antibiotics, or food-borne pathogens. • May have an extended shelf-life (may not require cold storage). • Have the same taste, texture, and chemical structure. • May be lower-cost and/or have fewer cost fluctuations.

FIGURE A. **Diagram of the production process for cultured milk and egg proteins.**[7]

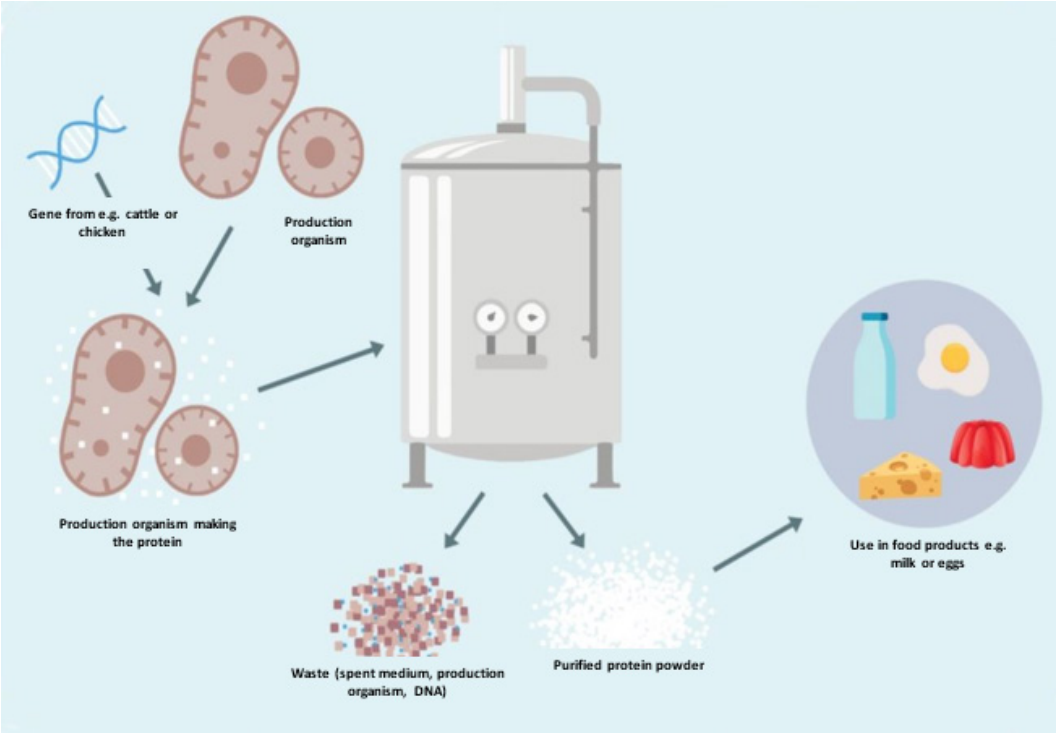

FIGURE B. **Select cultured milk and egg protein manufacturers.**

- BioscienZ
- Clara Foods
- Motif
- New Culture
- Perfect Day

Additional resources and background information.

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