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Abstract

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Keywords

biomanufacturing; food ingredient; novel food; gene editing; synthetic biology; marketing

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Regulation and Guidance for Marketing of Food Ingredients from Biomanufacturing and Policy Suggestions for China

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Abstract: The tightening policy of market regulation for food ingredients and novel foods produced by genetically modified microorganisms has hindered the development of the bio-economy. Here, the comparative studies have been conducted on the market regulations of food ingredients and novel foods produced by biomanufacturing in EU, US, Japan, and China. These countries are all very concerned about the regulation of food ingredients and novel foods from biomanufacturing. However, they adopt quite different policies. EU is cautious, US is positive, and Japan is less cautious. Over the past decades, China has been tightening the approval of food ingredients and novel foods produced by genetically modified microorganisms. At present, the whole world is actively responding to the supervision and access of new food ingredients and foods produced by new technologies. It is suggested that a positive application and approval path should be established, unified, and simplified for promoting the marketing of new products in China. **DOI:** 10.16418/j.issn.1000-3045.20200405001-en

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Green development is one of the five major concepts of social development in China in the new era. Biomanufacturing, an important way to implement green development, is listed as a national strategic emerging industry, which has been booming. The analysis of six developed countries in Europe and America by the Organization for Economic Co-operation and Development (OECD) shows that application of biomanufacturing technologies has the potential to reduce energy consumption by 15%–80%, raw material consumption by 35%–75%, air pollution by 50%–90%, water pollution by 33%–80%, and operating costs by 9%–90% in industrial processes. It is estimated that, by 2030, 35% of chemicals and related industrial products will be produced by biomanufacturing, reducing CO_2 emissions by 1–2.5 billion tons per year [1].

In the food industry, biomanufacturing products or technologies based on enzymes and microorganisms have been widely used to improve the quality of food ingredients, optimize traditional processing techniques, and reduce pollutant emissions, which have improved the mode of food manufacturing. In recent years, the emergence of biotechnologies represented by recombinant DNA, gene editing, and synthetic biology has laid a solid foundation for the revolution of food industry [2]. Globally, probiotics [3], low-calorie sweeteners [4], nutritional chemicals, synthesized milk [5], lab-grown meat [5], and degradable packaging materials for food have been modified or produced with novel biotechnologies, and some have been applied in industrial production.

With the support of major national research projects such as National High-tech R&D Program (863 Program), National Basic Research Program of China (973 Program), and National Key R&D Program of China, extensive studies have been performed on the application of biotechnology in the manufacturing of food ingredients. However, some advanced achievements have been shelved because of inaccessibility to market and approval. The tightening policy is detrimental to the development of biomanufacturing in China. As manufacturers have no new technology that can be used in international competition, the industrialization and manufacturing technology/performance of products in China have lagged behind those in foreign countries, which seriously hinders the development of bio-economy in China.

We compared the market regulations of food ingredients and novel foods produced by biomanufacturing in the EU, US, Japan, and China, and put forward suggestions for the access of biomanufacturing in the food industry in China.

For ease of understanding, food ingredients or novel foods manufactured by microorganisms without genetic modification are referred to as traditional food ingredients (TFIs), and those manufactured by genetically modified microorganisms (GMMs) are referred to genetically modified food ingredients

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(GMFIs). This study aims to help accelerate the marketing of food ingredients from biomanufacturing and boost their healthy development in China.

1 Market regulation of biomanufactured food ingredients in the EU

The EU attaches great importance to the market regulation of biomanufactured food ingredients and has established a comprehensive management system after years of development. The European Food Safety Authority (EFSA) supervises and assesses the safety of biomanufactured products as food additives [6]. The EU adopts different regulation strategies for microorganisms as production tools or raw materials, providing a clear path for the development and application of new technologies.

1.1 Market regulation of TFIs in EU

In 2003, the EFSA introduced the qualified presumption of safety (QPS) approach [7], which requires microorganisms to pass QPS before being used as production tools. In 2007, the EFSA issued the first QPS list and then released QPS Panel Statement every six months and new QPS list every three years.

Foods with microorganisms as raw materials are regulated in the EU under the Regulation (EU) on novel foods. The Regulation (EU) 2015/2283 [8] was released by the European Commission on December 11, 2015 and came into force on January 1, 2018.

A microorganism can be used to apply for QPS, or its fermentation products or biomass can be used to apply for novel foods. For example, *Yarrowia lipolytica* is on QPS list (only for production purpose) [9], and the food made from it has been approved as a novel food [10].

1.2 Market regulation of GMFIs in the EU

The EU has a strict definition of GMMs, and the microorganisms produced by DNA recombination with vectors or techniques involving direct introduction of genetic materials are recognized as GMMs (presence of exogenous DNA), while those with DNA modification by transduction, conjugation, polyploid induction, cell fusion, or mutagenesis by exposure to specific environment are recognized as non-GMMs (absence of exogenous DNA or genes). The regulation of technologies is shown in Table 1.

example, amino acids (category I) produced by GMMs may be exempted from assessment against the above criteria if the product is refined or purified to contain single component without microbial cells, DNA, and RNA. One representative example of category II GMFIs is food enzyme. Currently, the EFSA is assessing 216 products [15], and a large number of them will be marketed in the future.

Table 1 Regulation of common genetic modification technologies in the EU, US, and Japan [11]

Genetic modification technologies	Genetic changes	Risk control	Whether identified as a genetically modified microorganism		
			EU	US	Japan
Heterologous expression	Stable introduction of exogenous genes	Genetically modified genes or organisms carrying exogenous genes can be transmitted in the environment and food chain	Yes	Yes	Yes
Homologous expression	Genes from the same or a similar species	Genetically modified genes or organisms can be transmitted in the environment and food chain	Yes	No	No
Artificial chromosome	Artificial chromosome with stable inheritance	Artificial chromosomes or organisms with genetically modified genes can be transmitted in the environment	Yes	Yes	Yes
Chemical, UV, or radiation-induced mutations	Changes in single nucleotides, gene deletion, usually changes in endogenous genes	No integration of exogenous or artificial genes; only changes in endogenous DNA, but usually multiple genetic mutations in the genome; genetic changes can alter phenotype, including relative growth rate and survival rate	No	No	No
Changes driven by recombinase or integrase	Partial deletion, inversion, duplication, rearrangement, or insertion, recombinase or integrase with stable or transient expression	No exogenous gene introduction when recombinase or integrase are transiently expressed: endogenous gene modification; risk of spread of recombinase or integrase, risk of transmission of modified organisms	Yes	No	Yes
Gene editing: changes driven by genetic modification (stable or transient)	Minor changes in endogenous genes: driven by stable genetic modification = conventional genetic modification; transient genetic modification: driven by DNA or RNA = genetic modification without integration	No transient expression of nuclease for the editing of exogenous gene, risk of transmission of modified gene or organisms; it is the change of self-gene	Yes	No [12,13]	Yes
Gene editing: changes driven by ribonucleoprotein	Precise mutations in endogenous genes (some target mutations are measurable but very small)	No risk of transmission of foreign genes and modified organisms, more accurate than chemical, radiation, or ultraviolet mutagenesis	Yes	No [12,13]	Yes

Genetically modified microbial strains that are originally included in QPS list can be included again if they pass the safety assessment of EFSA [16,17].

The EU stipulates that all GMFIs on the market should be labeled regardless of whether DNA or protein from GMMs is detected in the final products. Moreover, common foods containing > 0.9% GMFIs should also be labeled. In the case of exemption, labeling is not mandatory if the food contains or consists of < 0.9% GMFIs, or if the producer provides sufficient evidence to the authority indicating the presence of a single GMFI whose presence is adventitious or technically unavoidable [22].

2 Market regulation of biomanufactured food ingredients in the US

The Food and Drug Administration (FDA) is responsible for the safety management of microorganisms and their products used in foods. The US adopts a positive attitude towards the use of GMMs in food industry, and does not clearly define or distinct between TFIs and GMFIs. Risk assessment is based on the product itself or the use of the product rather than the manufacturing process.

FDA established a list of generally recognized as safe (GRAS) products to regulate food additives. In the US, GRAS can be determined by (1) FDA approval, which has not been in practice since 1997 and only exists in the Act; or (2) self-confirmation, for which FDA has developed a specific procedure and checklist of materials [23,24]. In the USP/FCC ① Appendix XV of *US Pharmacopeia* (USP) updated in 2012, official description of the general and special requirements of food microorganisms, including probiotics, is provided as a standard reference for enterprises to apply for GRAS approval by FDA [25,26]. Usually less than six months are required from application to a GRAS approval by FDA. In addition to the GRAS list, some biomanufactured products as food additives are reviewed and approved by FDA's Office of Food Additive Safety based on the assessment of consumer safety, chemistry, and toxicology.

Products in the four categories of GMFIs have been approved as GRAS or as food additives for marketing in the US (Table 3).

In terms of labeling products on the market, the US passed the Bioengineered Food Disclosure Law in 2016, which was enacted on January 1, 2020 and will be enforced on January 1, 2022. The law requires labeling of foods containing GMFIs, but with two exemptions: (1) foods containing known GMFIs, provided that the total amount of all GMFIs used in the product is ≤ 5% of the total weight of the product; and (2) foods served only in restaurants or similar retail food stores.

Table 2 Category and relevant laws or guidelines of genetically modified food ingredients (GMFIs) [18]

Category	Definition	Classification	Laws and/or guidelines for characterization and safety assessment
Category I	Chemically defined purified compounds and their mixtures, in which both genetically modified organisms (GMMs) and introduced genes have been removed (e.g., amino acids, vitamins)	Food additives	Regulation (EC) No 1333/2008 Regulation (EC) No 1331/2008 Guidelines for evaluation of food additives [18,19]
		Food flavors	Regulation (EC) No 1334/2008 Regulation (EC) No 1331/2008 Evaluation guidelines [18,20]
Category II	Complex products in which both GMMs and introduced genes are no longer present (e.g., cell extracts, most enzyme preparations)	Food enzymes	Regulation (EC) No 1332/2008 Regulation (EC) No 1331/2008 Evaluation guidelines [18,21]
		Food additives	Regulation (EC) No 1333/2008 Regulation (EC) No 1331/2008 Evaluation guidelines [18,19]
		Food flavors	Regulation (EC) No 1334/2008 Regulation (EC) No 1331/2008 Evaluation guidelines [18,20]
Category III	Products derived from GMMs, in which GMMs capable of multiplication or of transferring genes are not present while introduced genes are still present (e.g. heat-inactivated starter cultures)		Regulation (EC) No 1829/2003 Evaluation guidelines [18]
Category IV	Products consisting of or containing GMMs capable of multiplication or of transferring genes (e.g., live starter cultures for fermented foods and feed)		Regulation (EC) No 1829/2003 Evaluation guidelines [18]

① FFC, *Food Chemical Codex*

Table 3 Typical cases of food ingredients produced by genetically modified microorganisms and approved as generally recognized as safe or food additives in the US

Category of GMFIs in EU	Product with market access	Approval	Genetic modification
Category I	Rebaudioside M	GRAS	*Saccharomyces cerevisiae* CEN.PK113-7D expresses enzyme for stevioside production, and pure product is obtained by fermentation and purification
		GRAS	*Pichia pastoris* strain A expresses uridine-5'-diphospho-glucosyltransferase that catalyzes the conversion of stevioside to rebaudioside E; *P. pastoris* strain B expresses UDP-glucosyltransferase and sucrose synthetase to catalyze the conversion of rebaudioside E to rebaudioside M and the conversion of UDP to UDP-glucose, respectively, and the pure product is obtained by fermentation and purification
Category II	Bovine chymosin [27]	GRAS	*Escherichia coli* K-12 expresses bovine chymosin
	Peroxidase	GRAS	*Aspergillus niger* MOX-54 expresses the peroxidase gene of Marasmius scorodonius
Category III	*Saccharomyces cerevisiae* [28]	GRAS	A malate permease gene from *Schizosaccharomyces* pombe and a malic enzyme from *Oenococcus* oeni are integrated into the constitutive promoter of 3-phosphoglycerate kinase in *S. cerevisiae* for the conversion of malate into ethanol
Category IV	Soy leghemoglobin	GRAS	Soy leghemoglobin gene is transformed into *P. pastoris* for the development of lab-grown meat
		Food additives	Soy leghemoglobin gene is transformed into *P. pastoris* for the development of lab-grown meat
	Agaricus bisporus [29]	Cultivated with USDA license	Absence of polyphenol oxidase gene (1–14 bp)
	Bacillus subtilis [3]	GRAS	Integration of aldehyde dehydrogenase gene to facilitate in vivo ethanol degradation

3 Market regulation of biomanufactured food ingredients in Japan

In Japan, most microorganisms used to produce food additives and common foods, along with their products, are managed through the food additive system. While some probiotic strains mainly used in the production of specific health foods are managed through a specific health food system. In Japan, the Ministry of Health, Labour and Welfare is responsible for the management of food additives and the safety approval of genetically modified foods.

3.1 Market regulation of TFIs in Japan

In 1948, the Food Sanitation Law, the first comprehensive law on food safety/sanitation was enacted in Japan, which established a positive list system for food additives, and only food additives designated as safe by the Ministry of Health, Labour and Welfare can be used. In 1995, the positive list was expanded from chemically synthesized food additives to the majority of additives used in foods.

The Food Sanitation Law stipulates that novel food additives apply for approval of marketing by the Ministry of Health, Labour and Welfare. The Ministry of Health, Labour and Welfare submit the application materials to the Pharmaceutical Affairs and Food Sanitation Council, which examines the process necessity and function of the additive, and sets quality specifications and standards for the food additive based on assessment of impact on health. The Food Safety Commission in the Cabinet Office of Japan is primarily responsible for risk assessment and establishment of allowable daily intake. A special investigation team conducts a scientific risk assessment on the food additive, seeks public comments, and feeds the results back to the Ministry of Health, Labour and Welfare [30].

3.2 Market regulation of GMFIs in Japan

In Japan, the Guidelines for the Safety Assessment of Foods and Food Additives Produced with DNA Recombination Techniques was established as early as in 1991 to restrain the safety review guidelines for genetically modified foods and food additives, followed by the Inspection Methods for Foods Produced with DNA Recombination Techniques (March 27, 2001) and the Law Concerning Standardization and Proper Labeling of Agricultural and Forestry Products (April 1, 2001).

On March 25, 2004, the Food Safety Commission of Japan

declared the Standards for Safety Assessments of Food Additives from Genetically Modified Microorganisms, in which DNA recombination technology is defined as that used to recombine DNA molecules by enzymes or other methods and to transfer them into living cells for multiplication. Genetically modified additives shall be covered by the additives approved by the Food Sanitation Law. In principle, if an exogenous gene is derived from the DNA of a microorganism belonging to the same taxonomic group as the host, or if a modified microorganism has the same genetic structure as a microorganism that already exists in the nature, they are not recognized as DNA recombination technologies. However, if the dose-dependent effect of an additive on human health is unclear, the effect should be examined as required. In addition, the final products with residual microbial cells are required to meet the safety assessment criteria for genetically modified foods (microorganisms) (Table 1). Meanwhile, the criteria suggest that the safety assessment of GMFIs should take into account the level of additive refinement, the way of use, and the amount of residue in the food. In the Appendix revised in April 2005, GMMs-produced non-protein additives with highly refined end products (i.e., amino acids and vitamins) are recognized as safe, and safety assessment based on these criteria is unnecessary. Therefore, high-purity food additives (i.e., vitamins, amino acids, and nucleotides) produced with GMMs are equivalent to non-genetically modified food additives in Japan.

Japan is also facing the emergence of new technologies with a positive attitude. For example, an expert advisory committee in Japan recommended approval of gene-edited foods to be sold to consumers without safety assessment, provided that the technologies involved meet certain criteria. The final report for the implementation of this recommendation has not been published, while an initial draft was posted on the website of the Ministry of Health, Labour and Welfare of Japan on March 18, 2019 for public comment [31].

Table 4 presents the typical cases of category I, II, and III GMFIs approved for marketing in Japan. It is believed that there will be gene-edited category IV GMFIs approved for marketing with a positive attitude toward gene editing in Japan.

In terms of labeling products on the market in Japan, specific labeling methods have been established for foods with safety certificate of genetic modification and foods with residual recombinant DNA or its encoded protein after processing, by the Law Concerning Standardization and Proper Labeling of Agricultural and Forestry Products, and the terminology used on the labels for foods with TFIs has been standardized. With the emergence of gene editing technology, the Consumer Affairs Agency of Japan announced on September 19, 2019 that producers and sellers of most foods produced by gene editing are not obliged to label them as gene-edited foods. The eventual implementation of this guideline may be related to the aforementioned safety approval of gene editing technology.

4 Market regulation of biomanufactured food ingredients in China

According to Article 37 of the Food Safety Law of the People's Republic of China, production of foods with novel ingredients, production of novel food additives, and production of novel food-related products require submission of safety assessment documents of the product to the health administrative department of the State Council. The Ministry of Health, the National Health and Family Planning Commission (NHFPC), and the National Health Commission (NHC) have been successively in charge of the review, approval, and supervision of biomanufactured food ingredients, mainly involving novel food ingredients, food additives, and the List of Microorganisms for Food Production. GMFI is not defined and differentially managed in China.

Table 4 Typical cases of genetically modified food ingredients (GMFIs) approved for marketing in Japan

Category of GMFIs in EU	Products with market access	Genetic modification	Evaluation results
Category I	*L*-Histidine	Prepared by fermentation with *Escherichia coli* HIS-No.2 constructed by introducing *L*-histidine synthesis genes derived from *E. coli* K-12 with a mutant of *E. coli*K-12 as host	Safe, safety evaluation is unnecessary according to the Standards for Safety Assessments of Food Additives Produced by Genetically Modified Microorganisms
Category II	Allulose isomerase	Prepared by fermentation with genetically modified *E. coli* K-12 W3110 (pWKLP)	Safe, evaluation shows no effect on human health
Category III	*Saccharomyces* sake FAS2-1250s	Yeast modified by self-cloning [32]	Safe
Category IV			

4.1 Market regulation of TFIs in China

The products manufactured by microorganisms and microorganisms as products are mainly regulated in China according to the laws and regulations of novel food ingredients and additives. For novel food ingredients, the NHFPC issued in 2013 the Measures for Administration of Safety Review of Novel Food ingredients, the Regulations on the Application and Acceptance of Novel Food ingredients, and the Procedures for Safety Review of Novel Food ingredients. From 2008 to 2019, a total of 130 novel food ingredients were approved, including 23 novel microbial strains. Food additives are listed in the National Standards of Food Safety: Use of Food Additives (GB 2760-2014), the National Standard of Food Safety: Use of Food Nutrient Fortifiers (GB 14880-2012), and the announcements of national health administration departments. From 2014 to 2019, a total of 180 novel food additives, 11 novel nutrient fortifiers, and 20 nutrient fortifiers with expanded usage and dosage were approved.

For the microorganisms used for food production, the Ministry of Health issued the List of Microorganisms for Food Production in 2010 and the List of Microorganisms for Infant Food Production in 2011. Microorganisms traditionally used in food production and processing can be used without approval, while novel strains out of the lists should be approved in accordance with the Measures for Administration of New Source Food (from December 1, 2007 to October 1, 2013) and the Measures for Administration of Safety Review of Novel Food Ingredients (after October 1, 2013).

4.2 Market regulation of GMFIs in China

There is currently no approval of category I, III, and IV GMFIs in China (Table 2). For category II GMFIs, novel food enzyme preparations derived from GMFIs were applied as novel food additives in China before 2009 and included in GB2760 after approval. There are currently 56 GMFI-derived enzyme preparations used in food industry. In 2009, the Food Safety Law of the People's Republic of China transformed the approval of novel food additives into administrative licensing, and only one and 13 novel enzyme preparations in food industry were licensed in 2019 and 2020, respectively.

4.3 Comparison of market regulations of biomanufactured food ingredients in the US, EU, Japan, and China

By comparison, the EU implements full-process supervision of biomanufactured food ingredients and takes a cautious attitude towards biotechnology, though a large number of category I products have been approved for marketing after safety assessment. The US mainly controls the end products and has a positive attitude towards biotechnology. Japan has adopted a moderate attitude balancing those of EU and US. China is currently cautious about marketing of biotechnology products, tightening the approval of GMFIs for many years, with only a few category II products approved before and after 2019 (Figure 1).

With the emergence of new biotechnologies, the EU, US, and Japan have approved many biomanufactured food ingredients for marketing. Highly-productive chassis cells as well as optimized functional gene elements and metabolic pathways confer biological production and the products have high yield, low pollution, and simple production process, which have greatly impacted traditional industries. In sharp contrast, some world-leading biomanufacturing technologies of food ingredients in China have been shelved due to the absence of market access approval, such as salidroside, lycopene, high value-added products manufactured by genetically engineered enzymes (e.g., allulose, chitosan oligosaccharide, stevioside RA/RD/RM), glycyrrhizic acid, glucosamine, and amino acids. Some of these products (e.g., sialic acid and rebaudioside M) have been instead submitted to the US FDA for GRAS.

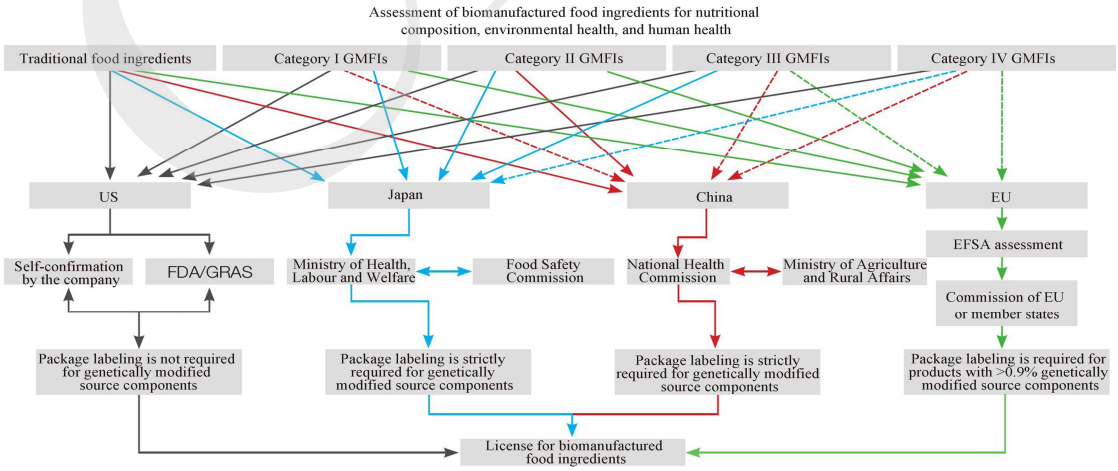

Figure 1 Comparison of market regulations of biomanufactured food ingredients in the US, EU, Japan, and China

Dashed lines: inaccessible; solid lines: accessible.

Therefore, promotion of the marketing approval of biomanufactured food ingredients will greatly advance the commercialization of biomanufacturing R&D achievements in China, promote the development of biomanufacturing industry, and help Chinese enterprises take the lead in the new round of international competition. This is of strategic significance for national security, economic growth, and regional development.

5 Debates on the access of new technologies in synthetic biology

Synthetic biology is an emerging technology with rapid growth and a promising prospect. It helps scientists design organisms different from those existing in the nature and redesign existing organisms for enhanced or novel properties [33]. Synthetic biotechnology modifies target organisms by mutating one or a few nucleotides, editing a large DNA fragment, or introducing exogenous genes. Mutation or deletion of a limited number of nucleotides has similar effects while increased precision compared with conventional mutagenesis. Crops modified in this way have been grown directly with no need for regulation all over the world [29], and the same management practice should apply to microorganisms genetically edited in the same way. However, these microorganisms are still under strict regulation in China and EU, which brings great uncertainty for the development of novel technologies and products.

Crops with genetic modification of large DNA fragments should be managed differently from those developed with common breeding techniques. The EU has required strict approval of plants modified by synthetic biotechnology to minimize the risks posed by cultivation of these plants in open fields [34]. However, since microbial production is generally conducted in industrial reactors, the environmental impact on GMMs can be effectively controlled through standardized management. Therefore, the review and approval of microorganisms modified by synthetic biotechnology should be different from those of genetically modified plants.

Synthetic biotechnology provides revolutionary product solutions for food industry, such as lab-grown meat and synthesized milk. Since 2011, Impossible Foods in the US has introduced lab-grown pork and sausage based on plant proteins and heme produced by yeast fermentation [35]. While celebrating the approval of marketing lab-grown meat, supervision of these novel foods should be well prepared. For lab-grown meat, the traditional supervision of meat processing by USDA (with focus on slaughter and processing hygiene) does not apply, neither does the supervision of food additives by FDA, because lab-grown meat is a complete food. With the rapid development of technology, an increasing number of novel foods incompatible with existing management systems will emerge. The future development of synthetic biology requires revision of existing laws or establishment of new laws, and identification of the weak points of current risk assessment methods. In addition, it is essential to think creatively about the potential unforeseen events that may occur.

6 Suggestions on promoting the marketing of biomanufactured food ingredients in China

China has currently approved some category II GMFIs, which is temporary and achieved by administrative coordination, because the requirements and processes of technical review remain at the level of consensus within the ministries and commissions, and clear institutionalized regulations are still lacking. There is no application timeline and successful cases are very limited. Legislation and institutionalization have seriously lagged behind the development of science and technology. Based on the above problems, we put forward the following three suggestions.

(1) Accelerating legislation. We should promote the enactment of Biosafety Law and relevant regulations as soon as possible, clarify the management requirements for new technologies and their applications, and define the management responsibilities from the perspective of safety. We should establish the criteria for R&D, production, and application of biomanufactured products with a positive attitude, clarify the application and review procedures of novel products, unify market access criteria and review systems, and simplify review processes to promote the marketing of novel products, especially the biosafety assessment and marketing approval of category I novel products.

(2) Managing by categorisation. We should learn from the successful experience of other countries and manage biomanufactured products separately based on whether exogenous genes are introduced, distinguish the GMMs for industrial use from those for agricultural application, and introduce the concept of closed use and management of GMMs. It is recommended that the common practices in the US and EU should be taken as reference for establishing assessment criteria, which adopt a simplified process for chassis microorganisms that have been reviewed and approved, and create a list of safe chassis microorganisms.

(3) Establishing safety assessment criteria. By introducing global advanced management experience (such as GRAS notification system) and carrying out biosafety research, we should establish scientific safety assessment criteria for products manufactured by different GMMs. For example, the successful biosafety management experience in other countries for category I and II GMFIs can be actively introduced to China. There are also some cases for category III and IV products, which should be actively investigated to push China's biomanufacturing industry to the top of the world. Moreover, it is suggested that category V GMFIs should be notified and exempted.

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