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Genetically modified foods in China and the United States: A primer of regulation and intellectual property protection

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Abstract

Food is a basic and personal necessity to human. Safety of food is a prime factor to consider apart from nutrition, quality and cost. Genetically modified (GM) foods first came on the market in 1994. Yet safety, transparency and traceability of GM foods are still under hot debate. Nonetheless, the market of GM foods is huge and attractive. Regulatory affairs and intellectual property (IP) are two critical factors affecting the development and commercial success of a food product. This article will take a look at the GM food technology and regulatory framework for GM foods in China and the United States. This article will also discuss the unique patent issues and non-patent IP tools for safeguarding the technology in these two countries.

1. Introduction

Genetically modified organisms (GMOs), also known as genetically engineered or transgenic organisms, for use as human foods or animal feeds are commonplace nowadays. On November 19, 2015, the Food and Drug Administration (FDA) of the United States approved the first-ever genetically modified animal for human consumption [1]. This approval not only marked a new milestone for GM foods but also re-evoked the public call for safety assessment and transparency of GM foods.

The advances in recombinant DNA technology in the 1980s have led to the creation of GM foods. FlavrSavr® tomato, the first GM food approved for human consumption in the world, entered the U.S. market in 1994 as fresh tomato and reached the United Kingdom in 1996 in the form of tomato paste [2]. Since then, the market of GM foods has grown rapidly and keeps expanding. Many food products currently on our shelves are derived from GM organisms or contain GM ingredients. Most GM foods are produced from plants, but GM microorganisms or GM animals have also been used to produce food products such as yogurt and cheese [3]. GM crops are now widely cultivated throughout the world. In 2014, approximately 18 million farmers in 28 countries planted GM crops in more than 181 million hectares, corresponding to 13% of the world's arable surface [4,5]. Globally, GM soybeans accounted for about 82% of the total soybean area, while GM cotton, maize and oilseed rape occupied 68%, 30% and 25% of the total crops area respectively [4].

Approximately 70%–90% of GM crops are used as feeds for food-producing animals [4]. Foods produced from these GM food-fed animals are not regulated or labeled as GM foods in most if not all countries [6]. Therefore, consumers may unknowingly consume GM ingredients even if they actively avoid GM foods.

As of October 2014, 65 countries have granted regulatory approvals to GM crops for use as foods, feeds or for environmental release, encompassing a total of 27 types of GM crop

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and 357 GM events [5]. Most countries permit the production and marketing of GM organisms except a few such as Russia, Norway, Netherland and Israel, but require an official approval in advance. Among those permissive countries, China, France, New Zealand and South Korea appear to be more restrictive as these countries so far have issued no or few permits to GM crops for commercial cultivation [6].

While for GM foods, production and marketing are generally permitted; many countries do not mandate a labeling of GM foods [6]. The European Union (EU) imposes stricter approval and labeling requirements for GM foods, demanding a risk assessment for all new GM foods and feeds before marketing and a compulsory labeling of GM foods. Following the EU law, many European countries such as the United Kingdom, Sweden, Norway and Germany now require foods containing or produced from GMOs, or containing ingredients produced from GMOs be clearly labeled. However, foods produced with GM technology such as recombinant enzymes, or from animals fed with GM foods are exempted [6].

Available scientific findings seem to be in favor of the safety of GM organisms. Remarkably, a few U.S. scientific organizations have concluded that there is no evidence showing GM organisms are risker than, or present unique safety risks than the conventional organisms [6]. However, the public has not built sufficient confidence in GM foods and generally desires that GM foods be adequately labeled. It is postulated that the lack of objective information about the risks and benefits of GM foods may account for the consumers' skeptical attitude to GM foods [4]. For instance in the U.S., a survey interviewed 2002 adults and 3748 scientists from the American Association for the Advancement of Science (AAAS) revealed that 88% of the scientists think that GM foods are safe for eating compared with only 37% of the general public [7]. The public even thinks that scientists do not have a clear understanding of the health effects of GM foods [4].

There are mounting evidences supporting GM foods are safe. In 2013, Nicolia et al. published a study which systematically reviewed a total of 1783 scientific papers on the safety of GM crops published from 2002 to October 2012. This report concluded that there is no evidence showing the use of GM crops has posed significant hazards to the environment and human [8]. Verma discussed some common public concerns over GM foods such as risks to health, spread of transgene and negative impacts on ecosystem, concluding that many of these concerns are hypothetical and not substantiated by scientific grounds [9]. Bawa et al. reviewed a number of safety assessment reports on common commercial GM crops such as tomato, soybean and maize. The authors noted a few findings indicated that there are differences in terms of protein production and morphological observations between animals fed with GM varieties and animals fed with conventional varieties, but pointed out that in these studies the methodology was not properly designed or the data could not sufficiently support the finding that transgenic species are more toxic than the conventional species [10].

On the other hand, focusing on long-term rat feeding studies of GM crops that are no less than 90 days of duration, Zdziarski et al. reviewed 21 published articles investigating the effects of GM crops containing one or more of three common foreign traits on the gastrointestinal tract of rats. The authors found that many of these studies did not provide sufficient details of their methodology, results or any definition of toxicity or signs of pathology, and concluded that all these studies are significantly inadequate or flawed to demonstrate the toxicity and safety of the tested GM crops for human and animal consumption [11]. Nonetheless, the above reviewers concurred that case-by-case, rigorous and detailed scientific studies assessing the risks of GM foods to human and animals are essential to provide objective scientific information for consumers to thoroughly understand GM foods and to minimize the adverse impacts from GM foods.

United States and China are two large markets of GM foods. In 2014, the U.S. grew the largest area of GM crops, followed by Brazil and Argentina [4]. GM soybean, maize and cotton are extensively adopted, respectively accounting for 94%, 93% and 96% of the total crops area in 2014 [4]. China is the biggest grain consumer, taking up one-third of the global soybean production. The country ranked the sixth in terms of the cultivation area of GM crops in 2014 [4]. It was estimated that nearly 95% of all imported maize and over 90% of the imported soybean of China are genetically modified [4].

Legislation and regulation for GM organisms and foods in the U.S. and China are on the horizon. Recently in July 2015, the U.S. government announced its plan to revise its 30-year-old regulatory system over GM crops and some other biotechnology products [12]. While in China, the Ministry of Agriculture (MOA) intends to strengthen research on the technology of agricultural GMOs as well as the safety assessment, regulation and management of agricultural GMOs [13].

While regulatory affairs are important to the development and commercialization of GM food products, intellectual property (IP) is another key factor for paving the way to success. IP serves a fundamental role in protecting innovators' interest by preserving the exclusive right in their inventions, meanwhile can be monetarized through various transactions such as investment, licensing, technology transfer to foster future research and development. This article will provide an overview of the current regulatory framework concerning GM foods in China and the United States. We will also take a look at the patent landscape and non-patent options in these two countries as a guide to IP protection for the GM food technology.

2. Genetic engineering and food

Thanks to the advancements in recombinant DNA technology, we can now modify the genetic makeup of organisms. Recombinant organisms were created in 1970s and have been widely applied in the agricultural and pharmaceutical industries, producing GM foods and therapeutic proteins such as growth hormones, vaccines and antibodies.

Defined by the World Health Organization (WHO), genetically modified (GM) or genetically engineered (GE) foods are foods derived from organisms in which genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination [3]. Transgenic organisms are usually created by inserting a foreign gene into the genome or cells of an organism using virus, gene gun or direct injection into the nucleus. Technologies such as intragenesis and cisgenesis are available to transfer a gene from the same or close species [14]. It is also possible to modify genetic sequences without inserting foreign materials into the organism for example using the Clustered Regularly-Interspaced Short Palindromic Repeats (CRISPR) system.

With limited natural resources such as land, water and energy, food security is not limited to developing countries but a global issue. The Food and Agriculture Organization of the United Nations (FAO) issued a report in 2011, estimated that almost one-third of food produced for human consumption (about 1.3 billion tons per year) was either lost or wasted [15]. Minimizing food loss is a must, while having a sustainable food production is another way to satisfy the global food demand. Food crops occupy a substantial portion in human and animal diet. Extreme weather, pests, weeds and crop diseases could impose detrimental effects to crops and significantly reduce their yields. Pesticides, herbicides and chemical fertilizers have long been used to enhance the production, however, drawbacks such as discharges of noxious or polluting ingredients and weakened effectiveness upon prolong use undermine their long-term use.

New variety of crops endowed with desired properties can be created through genetic engineering. For instance, with the new traits, crops could survive better in extreme climate such as drought and cold, or become more tolerant to pathogen-borne diseases or to pest, insect or weed killers. Accordingly, crops can be produced at higher yields and even be marketed at lower prices [3]. Crops can also be modified to synthesize pesticides in their body so that farmers can reduce their use of pesticides. According to a meta-analysis reviewed 147 GM crop studies released from 1995 to March 2014, the adoption of GM technology in crop cultivation has reduced the use of chemical pesticides by 37%, increased crop yields by 22%, and increased farmer profits by 68% on average [16]. Beyond profitability, farmers also save time and labor in weed control and have more flexibility in planning the cultivation [4]. Nutritional value, flavor and shelf life can also be improved by genetic engineering.

3. Examples of GM crops

3.1. Biopesticides

Bacillus thuringiensis (Bt) is a soil bacterium that has been widely used as a natural pesticide in agriculture since 1920s. Bt produces Crystal (Cry) proteins which can paralyze the pest's digestive system by inducing pores in cell membrane of the gut epithelial cells and in turn kill the pests, whilst remain safe to human because human does not have the equivalent receptor in the gut. Cry proteins are traditionally sprayed on crops but are susceptible to degradation under sunlight. Also, since Cry protein sprays could not reach underground and internal parts of the plants, the sprays are ineffective in eradicating pests living in those regions. To confer a long-term and thorough protection against pests, crops are engineered with Bt gene so that they can express the Bt toxins themselves for killing the pests [17]. GM potato and corn expressing Cry proteins were first approved for commercial production in 1995–1996 in the U.S. and are now planted worldwide [18,19].

3.2. Glyphosate-resistant crops

Glyphosate, a common ingredient found in herbicides, is able to kill weeds effectively by halting the shikimate pathway responsible for the biosynthesis of aromatic amino acids. Glyphosate blocks the shikimate pathway by binding to and inhibiting one of the catalyzing enzymes called 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, and eventually kills the organism from the deficiency of essential aromatic amino acids [20]. Roundup® is one representative glyphosate-based herbicide developed by Monsanto. The company discovered that a strain of *Agrobacterium tumefaciens CP4* could survive in a glyphosate production facility by producing a glyphosate-insensitive variant of EPSP synthase. The discovery led to the development of glyphosate-resistant Roundup Ready® crops which are modified with the gene encoding the glyphosate-insensitive variant of EPSP synthase. It is also possible to create glyphosate-resistant crops using a glyphosate-degrading enzyme encoding gene [20,21]. Roundup Ready® seeds including soybean, cotton, canola and corn seeds have been widely distributed. Notably in March 2015, the WHO's International Agency for Research on Cancer (IARC) classified glyphosate in Category 2A (meaning that glyphosate is probably carcinogenic to human). The agency opines that there are convincing evidence showing glyphosate can cause cancer in laboratory animals, and glyphosate has been reported to cause DNA and chromosomal damage in human cells [22]. However later in November 2015, the European Food Safety Authority (EFSA) concluded that glyphosate is unlikely to pose a carcinogenic hazard to human [23]. One possible reason for the different conclusions is that the EFSA evaluation was conducted based on a large body of evidence including a number of studies that were not assessed by the IARC [23].

4. Safety and risks of GM organisms and foods

As discussed in the introductory session, scientific evidence is inclined to conclude that GM foods are safe for consumption. Safety, risks and concerns over GM foods and crops have been discussed in many reviews [4,8–11]. Without going into details, the following sessions serve a brief summary of these aspects.

4.1. Human health

Whether or not GM foods are safe for human consumption is the leading subject of public controversies. Consumers desire to know about the transient and long-term effects to human health upon consumption; among them, allergenicity, toxicity and spread of transgene are commonly concerned.

The unpredictable and hidden effects of foreign genes to the GM organisms and consumers may be one underlying reason for the public disquiet. First at the gene level, it is unpredictable whether the new genetic material will be exclusivity and precisely incorporated into the target site, and whether the genetic material will interfere with the recipient's biological system and produce any effects beyond expectation. It has been demonstrated that DNA fragments from high-copy number genes can pass across through the gastrointestinal tract and go to internal organs, tissues and blood of different animals [8], implicating a chance of incorporating foreign DNA into the consumers' cells. However, the incidence that the DNA absorbed through the gut could integrate into the host organism is believed to be really low, given that the DNA intake from diet is as low as about 0.1–1 g per day and the consumed DNA is digested and diluted in the consumer body. So far there is no evidence showing the foreign gene absorbed from the gut can integrate into consumer's cells and lead to a germ line transfer [8].

At the protein level, the modifications may lead to new allergens or toxins that cannot be identified by current methodologies that screen for known toxins and allergens, and could put human health at risks. So far two GM crops have been reported on the potential allergenicity of transgenic protein. The first one is a soybean introduced with the gene encoding methionine-rich 2S albumin from the Brazil nut for improving the methionine content of the soybean. Subjects that were allergic to Brazil nuts developed positive reactions to extracts of transgenic soybean but negative reactions to extracts of non-GM soybean in skin-prick tests [24]. The second case is the StarLink corn engineered with a Bt protein Cry9C. StarLink was only approved for animal feed in the U.S. in 1998 but was later discovered in tacos and tortillas in September 2000. The FDA received 51 reports of adverse reaction to these corn products and among them 28 individuals appeared to develop allergic reactions. However, the U.S. Centers for Disease Control (CDC) found no conclusive evidence of hypersensitivity to the Cry9C protein in these subjects [25]. Nonetheless, the developer Aventis voluntarily withdrew the registration for StarLink corn in October 2000.

There are also animal studies reporting that consumption of GM foods may lead to disruption to kidneys and livers, higher rates of infant mortality and infertility problems [26,27], but more tests are needed for verification.

4.2. Wild life and environment

Impacts and risks of GM organisms to the environment may be more apparent than to human health. Some common environmental concerns include a reduction of biodiversity, contamination of wild species, threats to non-target species, outbreak of antibiotic resistant bacterial strains and super-weeds, and deterioration of soil and water pollution.

First, it is concerned that the GM technology promotes large scale monocultures and may reduce the biodiversity [9]. Farmers likely prefer to grow one or few GM varieties having desired traits, hence GM varieties may become dominant while traditional varieties may be gradually lost. Reliance on limited varieties may also reduce the emergence of new variety because the genetic makeup becomes more uniform. However, it should be noted that the loss of biodiversity can also be attributed by other selective breeding non-GM technologies [9,28]. Monoculture of one single crop variety may also increase the vulnerability of crops to diseases and other environmental challenges [28].

Adoption of GM crops may endanger non-target species in the environment. For example, Bt protein was reported to be toxic to non-target insect such as monarch butterflies [28]. However, the review by Nicolia et al. concluded that there is no consolidated scientific evidence showing the negative impacts of GM crops on the biodiversity of non-target species such as birds, snakes and soil macro and micro fauna [8].

Genetic drift is another key concern as genes may migrate out of the GM organism to wild species and even to largely unrelated species. Outcrossing of transgenes to conventional species may happen and contaminate the wild-type species [9,28]. GM commingling and contamination during post-harvest handling are common and severely impact the organic farmers [21]. Setting aside the crop quality, organic farmers who have their seeds or crops contaminated with patented GM varieties may be liable for patent infringement. Notably, after the report of GM contamination of conventional corn and rice, a few countries such as Japan and Europe banned or strictly limited the importation of corn and rice from the U.S., causing a significant loss to the farmers and the industry [29]. On the other hand, antibiotic resistance genes that serve as selectable marker genes for selecting transgenic cells may pass to bacteria present in the environment or in the consumers' gut [3,8,9], although the occurrence is unlikely given the extremely low frequency of uptaking exogenous DNA by bacteria (10^{-4} to 10^{-8}) [8].

Lastly, it is postulated that the prevalent use of herbicide-resistant crops would further encourage the use of herbicides and promote the development of super weeds [9]. Many GM crops are modified to be glyphosate-resistant, farmers are now less reluctant to use glyphosate-containing herbicides on their crops. The repetitive and high-volume use of herbicides has created a vicious cycle worsening the pollution and making weed control more difficult. Glyphosate resistant weeds and Bt-toxin resistant pests have been reported [8].

5. Regulation in China

5.1. Adoption of GM crops in China

Nurturing nearly one-fifth of the world population but possessing only 6% of fresh water and 7% arable land, food security is a critical issue to China [30]. China consumes the greatest portion of grains and is the largest rice producer and consumer [31]. Currently papaya is the only edible GM plant allowed for commercial production in China.

China's agriculture biotechnology is world-leading and is one of the major areas that the Chinese government has been pledging to actively promote. By 2011, it was estimated that over 70% of the total agricultural biotechnology invention patent were filed by domestic sectors [31]. As early as 1992, China is the first country permitting the commercialization of GM crop, but the approved virus resistant tobacco was revoked from cultivation a few years later because of strong pressure from other regions [32]. To this point, China has only approved the commercial planting of two GM crops which are a Bt cotton (in 1996) and a virus resistant papaya (in 2006) [6,33]. The two GM crops are now planted with an adoption rate of around 93%–94% [34,35].

Five types of transgenic crops soybean, corn, cotton, canola and sugar beet have been permitted for import into China either for cultivation or as raw materials for processing [6,33]. Besides, a transgenic poplar was approved for commercial plantation in 2003 by the State Ministry of Forestry and is the only transgenic forest tree approved so far [34].

5.2. Legislation

China has not enacted any national law specific for GMOs or GM foods but regulations overseeing agricultural GMOs are available. The Ministry of Agriculture (MOA) and the General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ) are the two agencies responsible for policing agricultural GMOs and GM foods.

In the 12th Five-Year Plan on National Economic and Social Development for 2011–2015, the Chinese government expressed its ambition to speed up the innovation and application of biotech breeding in agriculture and to foster a large and strong modern seed industry [36]. Despite the State's highly permissive policy and plentiful research funding, commercial prospects of GM crops are not too promising. The less receptive attitude of the Chinese population may be one reason for the government's hesitation in permitting the commercialization of transgenic crops [30]. According to an online survey interviewing 50,000 people in 2010, about 84% of the respondents would not choose GM foods for safety reasons [30].

In early 2015, the Central Committee of the Communist Party of China and State Council provided 32 concrete suggestions on how to foster the development of modern agriculture and rural community and how to increase farmers' income [37]. The authorities emphasize the significance of food security and the vital role of agriculture in national socioeconomic development, while acknowledging the necessity to enhance food safety and the quality of agricultural products. Among these suggestions, one is to reinforce the research on agricultural GMOs, and their safety management and the general public education about them. The above reflect the Chinese government's desire to develop agricultural GM technology in full force and more importantly the substantive initiative to look into the public concern over GM foods.

5.3. Agency regulations

5.3.1. Ministry of Agriculture (MOA)

Promulgated by the State Council in 2002, the GMOs Regulations or formally known as "Regulations on Administration of Agricultural Genetically Modified Organisms Safety" outline the regulatory framework for research, testing, production, processing, marketing, import and export of agricultural GMOs [38]. The MOA issued four administrative measures regarding the safety evaluation [39], processing [40], safety control for import [41] and labeling [42] of agricultural GMOs to implement the GMOs Regulations.

These provisions define that agricultural GMOs are animals, plants or microorganisms of which genomic structures have been modified by genetic engineering technologies (and their products) which are used in agricultural production or processing. GM foods are subject to these provisions absent any specific rules [6], given that the prior two GM food rules implemented by the Ministry of Health (MOH) were abolished in 2007 and 2013 respectively.

Each step of testing, production, processing, import and marketing of agricultural GMOs must seek an approval from the MOA. Production and marketing GMOs or GMO products require special licenses, and a biosafety certificate is a prerequisite for applying the licenses. For instance, at least four permits are required for commercial cultivation and marketing a transgenic crop, namely a biosafety certificate as a proof of safety to human and the environment, a crop variety certificate as a successful registration of the new crop variety, a production license for producing the transgenic crop and a marketing license for marketing the transgenic crop.

5.3.1.1. Biosafety certificate. Biosafety certificate evidences that an agricultural GMO has passed the safety assessment conducted by the GMO Biosafety Committee. Under the GMOs Regulations, a biosafety certificate is compulsory for the following basket of transgenic organisms and products: transgenic planting seeds, livestock and poultry breeds and aquatic fry, and planting seeds, livestock and poultry breeds, aquatic fry, pesticides, veterinary drugs, fertilizers, additives and others produced using agricultural GMOs or containing agricultural GMOs ingredients.

There are five stages for obtaining a biosafety certification of a new agricultural GMO, namely (i) laboratory research; (ii) restricted field trials; (iii) environmental release field trials; (iv) preproduction testing; and (v) application for a biosafety certificate. Agricultural GMOs are classified by the MOA into Class I, II, III or IV according to the extent of their risks to human, animals, plants, microorganisms and the ecological environment. Notification to the MOA must be made before commencement of research involving Class III or IV GMOs [38].

After laboratory research, the developer may proceed with the three testing stages successively. The developer needs to report to the MOA before starting any restricted field trials, and must provide data and information to the MOA for approval for moving to the next stage. In short, the developer has to furnish a test report issued by a competent inspection organization in the field of agricultural GM technology, safety management and precautionary measures, and report of the previous testing stage. The MOA will grant a permit for proceeding with the next stage only if the GMO passes the safety assessment. Upon completion of all the three testing stages, the developer can apply for a biosafety certificate with a summary report of the preproduction testing. The MOA will make a decision within 20 days after receiving the safety assessment report form the Biosafety Committee [38].

The biosafety certificate is valid for five years and requires renewal 1 year before the expiration date. From 2002 to 2012, the MOA has approved 2775 applications for restricted field trials of GM plants, 459 for environmental release field trials and 317 for preproduction testing, and issued 1830 biosafety certificates to seven types of crops [35]. However, until now only cotton and papaya can be commercially produced and marketed in China.

5.3.1.2. Production and marketing license. To commercially produce or market an agricultural GMO or product, one or more licenses from the MOA are required depending on the purpose.

5.3.1.2.1. Production and processing. By law, all new variety of planting seeds, livestock breeds, poultry breeds and aquatic fry must be evaluated and approved by the Variety Approval Committee under the competent administrative department of the MOA before popularization. For crops, all new variety of rice, wheat, corn, cotton, soybean, canola, and potatoes must be evaluated by the Crop Variety Approval Committee under the National Seed Law. The application requires a two-year variety comparison study comprising field trials and production trials. Upon approval, the MOA will issue a crop variety approval certificate which the developer would need for getting a production license from the competent agricultural administrative department. Individuals or companies engaged in the production or processing of agricultural GMOs also need a permit from the MOA or the provincial agricultural administrative department. For farmers who cultivate or breed the GMOs, sellers of the transgenic seeds or breeds should apply for the permit on behalf of the farmers.

5.3.1.2.2. Marketing and advertising. Similarly, a marketing license issued by the competent administrative department of the MOA is essential for marketing transgenic planting seeds, livestock breeds, poultry breeds and aquatic fry. Advertising of GMOs requires prior approval from the MOA [38].

5.3.1.3. Import into China. Import of agricultural GMOs and products into China can be subdivided into four types (i) import for research; (ii) import for testing; (iii) import for production; and (iv) import as raw materials for processing [41]. Cotton is the only GMO that can be imported to China for production at present, while transgenic soybeans, corn, canola and sugar beets are imported as raw materials for processing and cannot be used otherwise [35,43].

For research purpose, approval from the MOA is needed for all Classes I-IV of agricultural GMOs. For testing, similar to the domestic route, the applicant has to apply for restricted fields trials, environmental release and preproduction product testing in succession. Both research and testing applications require documents evidencing corresponding research or testing have been conducted outside China [41].

Types (iii) and (iv) would require a biosafety certificate for import. For importing the basket of transgenic GMOs and products for production, the foreign company needs to seek approval at the beginning and complete all the three testing phases to apply for a biosafety certificate. The application also requires documents which indicate the exporting country or region has permitted the marketing of the GMOs for the same intended uses, and has determined that the GMOs are safe through scientific experiments [41].

While for introducing GMOs as raw materials for processing or directly as consumer goods, procedures for applying a biosafety certificate are similar to type (iii) except that testing in China is not required. MOA will appoint a competent inspection organization to assess the safety of the subject GMO and issue a certificate upon approval by the GMO Biosafety Committee [41]. For each batch of product imported into China, merchant needs to separately apply for a biosafety certificate and furnish the GMO developer's biosafety certificate (for import) as a proof [44].

5.3.1.4. Labeling. China does not mandate labeling of GM foods except certain classes of GM organisms and products listed in the MOA's GMO-catalog [42,44]. Presently cotton seeds, soybean, corn, canola, tomato and their seeds, and a few products derived from these crops such as soybean oil, corn flour and tomato paste are on the list [42]. All items listed in the GMO-catalog that are for sale in China must be clearly labeled if they contain GM ingredient(s). For transgenic organisms and their products, or seeds, livestock and poultry breeds, aquatic fry, pesticides, veterinary drugs, fertilizers and additives containing these GMOs or GMOs ingredients, a direct label such as "transgenic soybean" should be used. While for processed products directly derived from agricultural transgenic products, the label must indicate the name of the main raw materials containing GM ingredients, for example, "soybean oil – transgenic soybean as raw material". Moreover, labeling is needed even if the GM ingredient is no longer detectable in the final processed product; the label should indicate that the product is manufactured using transgenic raw materials but no longer contains the GM ingredient [42].

5.3.2. General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ)

AQSIQ is responsible for the inspection and quarantine of import and export of agricultural GMO products under the AQSIQ regulation [44]. Upon entry into China, the product's owner or the owner's agents should declare to AQSIQ whether or not the importing product is transgenic and provide a copy of biosafety certificate or relevant documents as proof [44]. AQSIQ verifies all products declared to be transgenic using genetic tests. Whereas for non-transgenic products, AQSIQ conducts genetic tests on a random sampling basis. AQSIQ may also test products not listed in the GMO-catalog. Products will be withdrawn or destroyed if they are found to contain GM ingredients different from those declared.

For GMOs in transit, prior application with the AQSIQ and official proof evidencing the approval of research or marketing of the products issued by the exported country or region are required.

5.4. Bt rice in China

Vast effort and resources from the Chinese government and scientists have been invested on rice – the essential staple to Chinese. Among the many locally developed transgenic rice, two varieties named "Bt Shanyou 63" and "Huahui No. 1" received a biosafety certificate for commercial plantation within Hubei province in 2009. Research demonstrated that Bt rice could benefit farmers by a higher yield and decreased use of pesticides, thus could provide more food to feed the public, improve farmers' health and reduce the pollution arose from crop cultivations [4,31]. Up to date, no transgenic rice variety has obtained a crop variety certificate and therefore no GM rice is available to the public [31,35]. However, GM rice has been detected in both the local and exported markets. In Europe, after detecting GM contamination of rice from China time after time, the European Union has implemented emergency measures since 2012 to impose stricter inspection on rice products from China. In 2013, the EU reported 25 incidences of GM contamination in the rice imported from China mostly concerning "Bt Shanyou 63" [45].

Regulatory agencies do not perform genetic testing on rice because the test is not required under the current national rice standard. Therefore stakeholders such as sellers, exporters and consumers would not be able to know whether the rice contains GM ingredient [46]. In 2014, the local media China Central Television (CCTV) sampled five bags of rice from supermarket in Wuhan city of Hubei province for genetic testing, revealed that three out of the five samples contained transgenic ingredient "Bt Shanyo 63" [46]. The developer of "Bt Shanyo 63" speculated that the GM seeds have probably leaked out during the preproduction testing. In the same year, illegal large-scaled planting of transgenic rice and corn in four provinces were reported. Illegal environment release testing, preproduction testing or production may account for the emergence of these unauthorized GM crops [47].

6. Regulation in the U.S.

6.1. Adoption of GM crops

United States is the country that grew the largest area of transgenic crops since 2010 [5]. The country alone grew 73.1 million hectares of transgenic crops accounting for 40% of the global contributions in 2014. Adoption rate of transgenic crops is very high in the U.S. and keeps elevating, for example from 2013 to 2014, the adoption rate of soybean rose from 93% to 94%, maize from 90% to 93%, and cotton from 90% to 96% [5]. Among the 357 GM events approved in the world as of October 2014, the U.S. has approved 171 events (excluding stacking events), slightly fewer than the first ranking country Japan which has granted 201 events. Currently, GM alfalfa, canola, corn, cotton, papaya, soybean, sugar beets and squash are commercially cultivated in the U.S. [5]. Many of these crops are used to produce processed foods and strikingly more than 95% of food-producing animals are fed with GM foods [4]. With such a high adoption rate and coverage, it is not surprising that over 75% of processed foods in the supermarkets contain GM ingredients [48].

6.2. Legislation

Similar to China, there is no federal law specific for GMOs or GM foods. GM organisms and foods are regulated by legislations enacted for conventional products [6]. The U.S. is much more lenient to GMOs and GM foods than China and many other countries, probably because of the FDA's premise that GM foods do not significantly differ from non-GM foods and hence, without a contrary evidence, GM foods are safe and do not require particular safety assessment and labeling [4].

The U.S. adopts a voluntary labeling system for GM foods although labeling is a top public concern. In a poll conducted in 2013, 93% of respondents supported a mandatory labeling of GM foods [49]. Under the U.S. legal system, a state could exercise its discretion to pass their own law to regulate GM foods absent conflict with the federal law [6]. Many states have already proposed bills to require GM food labeling. Among the 50 states, currently only three of them, Connecticut, Maine and Vermont passed their own legislation mandating GM food labeling during 2013–2014 [4]. The first two states require at least four neighboring states to pass similar laws before actual implementation of the labeling law. As of July 1, 2016, Vermont will be the very first state to institute compulsory labeling of foods produced with or partially produced with genetic engineering.

At the federal level, both anti-labeling and pro-labeling bills have been proposed and discussed for years. In 2015, two labeling bills "Safe and Accurate Food Labeling Act of 2015" and "Genetically Engineered Food Right-to-Know Act" were introduced. The former prohibits states from demanding GM food labeling and does not require food producers to declare use of genetic engineering solely because the food was developed with GE technology. This bill was passed in House on July 23, 2015 [50]; if enacted, this would preempt all existing state's GM food labeling laws such as the Vermont Act 120. On the contrary, the latter bill requires whole or processed foods produced with GE or containing GE ingredients be labeled, and prohibits the use of "natural" or similar words to advertise or label foods containing GE ingredients [51]. How the battle over GM food labeling is going is largely unpredictable for now, but definitely would bring a huge impact to the public regardless of the outcome.

Some counties such as Maui County of Hawaii and Jackson and Josephine Counties of Oregon managed to restrict GM crops cultivation. However, Maui's ban was invalidated by the federal district court because the court ruled that the prohibition is conflicted with the state law. While in Oregon, since Jackson is exempted from the state "right to farm" law which gives the state sole discretion in regulating seeds, Jackson's ban is not preempted by the state law and hence enforceable, whereas Josephine's ban is likely to be challenged at the court [52].

Call for a tighter control over GM foods remains across the country. On July 20, 2015, the U.S. government announced that the government has recognized the need to review its regulatory framework over GM crops in view of the advances in the technology and change of product landscape, and admitted that its 30-year-old system is unclear and did not foster public confidence [12]. A special task force will be set up for this mission and the first year focus would be to clarify the products or product areas responsible for each agency.

6.3. Agency regulations

Three federal bodies, namely the U.S. Department of Agriculture (USDA), the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) are in charge of overseeing GMOs and GM food products.

6.3.1. USDA – safe to grow?

The USDA takes the role of protecting the environment and plants from agricultural pests, weeds and diseases. Introduction of a GM plant to the U.S. is subject to prior approval from the USDA. The subsidiary agency, Animal and Plant Health Inspection Service (APHIS), is responsible for approving and monitoring biotech crops under the Plant Protection Act [53] and regulations set forth in Title 7 of Code of Federal Regulations, Part 340 (7 C.F.R. §340) [54].

Under statutory definition, GM organisms that are plant pests (or potentially plant pests) and products containing these GMOs are "regulated articles" subject to APHIS regulations. Hence, APHIS has the authority to approve and police field testing, planting, import and interstate movement of most GM crops.

Three routes are available to introduce a regulated article to the U.S.– (i) notification procedure, (ii) permit application and (iii) determination of nonregulated status [54].

(i) Notification procedure

As its name implies, this procedure notifies the APHIS about the introduction of a GM crop without a permit. Notification must be made 10 days before the interstate movement, or 30 days before the importation or environmental release. The APHIS will either acknowledge or deny the notification within 10 days after receiving the application for interstate movement, or 30 days for application for importation or environmental release. If the APHIS denies the notification, applicant may apply for a permit.

The regulated article must meet six requirements to be eligible for the notification procedure (7 C.F.R §340.3). Generally GM plant that is not listed as a noxious weed under the PPA can opt for the notification procedure, provided that the expression of the introduced genetic material does not result in any plant diseases, toxicity or virus. Information about the nature of GM plant and the introduced gene, destination facilities for movement or the field site location for environmental release, size of the introduction is required for the application.

If the introduction is an environmental release, field trials must be conducted to show the GM plant would not harm the plants, non-target organisms and the environment. Field test reports must be submitted within six months after the field test terminates. Acknowledgment to notification for environmental release is valid for one year from the date of introduction and can be renewed annually by submitting additional notification to the APHIS.

(ii) Permit application

GM plants not meeting the criteria for a notification procedure must apply for a permit. The permit procedure is more rigorous requiring details about, among others, the expression of the altered genetic material, the molecular biology of the system (e.g. donor–recipient–vector) for producing the GM plant, procedures and safeguards for preventing contamination, release and dissemination in the production of the GM plant including the donor and recipient organisms and vectors, as well as procedures and safeguards for preventing the escape and dissemination of plant at each of the intended destinations, and final disposition of the GM plant (7 C.F.R §340.4).

Application for an environmental release permit has to be submitted 120 days before the proposed release, to which the APHIS will respond within 30 days after receiving the application. While for interstate movement or importation, application 60 days in advance is required and the APHIS will respond within 15 days. Permit for importation has to be applied for each shipment of the article. If interstate movement of multiple GM plants is desired, one may apply for a single limited permit for the multiple regulated articles, and the permit would be valid for movement between specified locations for one year. APHIS will grant a permit if it determines that the regulated article would be properly maintained and disposed to prevent dissemination. If allowed for conducting field tests, submission of test reports is due six months after the end of the test.

(iii) Determination of nonregulated status

After sufficient field testing, GM plants that are proven not to pose a plant pest risk to health and the environment may petition for a nonregulated status with factual grounds why the plant should not be regulated under 7 C.F.R. §340. Field test reports conducted under the permit and notification procedures, and relevant experimental data and literatures to support the request are required (7 C.F.R. §340.6).

APHIS will publish the petition on the Federal Register for public comments for 60 days. The APHIS will either deny the petition, or approve the petition in whole or in part within 180 days after the receipt of the petition. If granted a nonregulated status, the GM plants is no longer considered a regulated article and can be planted and moved without APHIS oversight [55].

The first GM crop approved by the APHIS for commercialization is FlavrSavr® tomato in 1994. As of September 2013, the APHIS has granted more than 17,000 permits and notifications for environmental release of GMOs which are mostly GM plants, while 96 out of 145 petitions for non-regulated status have been granted. Corn is the type of plant mostly approved both for environmental release and nonregulated status [55].

Furthermore, under the National Environmental Policy Act, if the GM plant represents a new species or a new modification, prior to making decisions about permits or nonregulated status, the USDA needs to complete an environmental assessment (EA) to determine whether the new plant release will affect the environment. Environmental impact statement (EIS) may be further required if the USDA finds the new plant significantly impacts the environment [29].

The USDA does not actively monitor the approved GM crops [29] but provides verification programs "Process Verified Program" and "Organic Certification" to food producers for certifying their products with regard to their manufacturing or handling processes.

6.3.2. EPA – safe to the environment?

The EPA is in charge of overseeing the manufacture, sale and use of all pesticides under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) [56]. The EPA also regulates microorganisms for commercial purposes under the Toxic Substances Control Act (TSCA) since "chemical substance" is interpreted to include microorganisms [57], while microorganisms that are plant pests abide by the USDA regulations under the Plant Protection Act.

Not all transgenic plants are subject to EPA regulation unless the plant is pesticidal in nature. Any substance that is intended to control pests and to be produced and used in a living plant (or in the produce of the plant) is identified as a "plant incorporated protectant (PIP)". The FIFRA defines that PIP also includes any genetic material necessary for the production of the pesticide substance or any inert ingredient which is intentionally included in a pesticide product such as a selectable marker [58]. For instance a transgenic Bt crop, both the Bt protein and the gene encoding the Bt protein are subject to EPA pesticidal regulation.

Accordingly, the production of PIP-containing plant is regulated by both the USDA and the EPA. What the EPA concerns is the new pesticidal substances and its risk to human and the environment; while the USDA examines the entire plant and looks into the plant pest risk. The first PIP approved by the EPA is NewLeaf potato in 1995 [29].

6.3.2.1. PIP – tolerance and exemptions. PIPs are subject to additional regulations for their special properties. For pesticides applied to foods and animal feeds, the EPA sets a level of pesticide that is safe for human and animal consumption. Leaning on toxicity data and exposure data, the EPA determines the amount of pesticide that may remain in or on foods that would pose a low probability of risk to human health and the environment; "tolerance" is the maximum permissible level for pesticide residues allowed in or on commodities for human and animal consumption [59].

There are some circumstances that PIPs can be exempted from the formal registration. First, the EPA has absolved certain types of PIP from the tolerance requirements because the agency determined that these PIPs meet the standard of "reasonable certainty of no harm" from dietary exposure to the pesticide residues. Therefore, no registration for a PIP-containing food plant is required if the PIP residue is exempted from the tolerance requirement. Currently a number of Bt proteins as expressed in certain crops or in all type of plants are exempted from the tolerance requirement; nucleic acids that are part of the PIP are also exempted [59]. In addition, formal registration is waived if the genetic material encoding the pesticidal substance is from a plant that is sexually compatible with the recipient plant and is not derived from a sexually incompatible source, or if the PIP is an approved inert ingredient from a sexually compatible plant (40 C.F.R. §174.2). Nonetheless, if exempted, the producer has to report to the EPA any adverse effects within 30 days after the date of awareness of the events.

6.3.2.2. Experimental Use Permit. All new pesticides or registered pesticides for an unregistered use must be registered with the EPA before their sale unless they are otherwise exempted. Field test data is necessary for the registration. Developers may apply for an "Experimental Use Permit" for conducting large scaled field tests so as to accumulate data for the new pesticide or new use. Laboratory and greenhouse tests do not need a permit; while small scaled field tests involving less than 10 acres of land or 1 acre of water only require a notification to the EPA (40 C.F.R. §172.3) [60].

6.3.2.3. Registration. To register a pesticide with the EPA, the applicant needs to submit data demonstrating that the pesticide will not pose any unreasonable risk to human health or the environment when used according to label directions [58]. As for food plants containing PIPs, the level of pesticide residue must comply with the EPA tolerance standards. Basically, the applicant needs to establish the tolerance of pesticide residue, and submits data of field testing, insect resistant management plan and a draft labeling. Apart from risks to human health, non-target organisms and the environment, the EPA also looks into the potential of gene flow to other plants and the need for insect resistance management plans to prevent the development of resistant pests [58]. A permit will be issued if the EPA finds the foreign gene or protein is safe; however, if there is a chance of gene flow as in the case of a Bt cotton, the EPA will restrict the planting of the GM plant to reduce the risk. The EPA has so far approved 12 PIPs and 8 GM microbial pesticides [58].

6.3.3. FDA – safe to eat?

6.3.3.1. Food safety. The FDA regulates all food products (except meat, poultry and processed egg products which are governed by the USDA), biological products and drugs [61] under the Federal Food, Drug and Cosmetic Act (FFDCA) [62]. Transgenic plants and transgenic animals are regulated distinctly because transgenic animals are interpreted as veterinary drugs and hence subject to the drug provisions [6]. How the FDA polices transgenic animals will be discussed shortly.

The FDA primarily monitors food safety by fighting against food adulteration and overseeing food additives (21 U.S.C. §342(a)(1)). Food containing any poisonous or deleterious substance that may render it deleterious to health is regarded as adulterated and is prohibited from the introduction, delivery and sale in the country. Generally, a pre-market approval of whole food or food products is unnecessary unless a food additive exists.

Any substance that is intentionally added to food can be classified as either a food additive or a "Generally Recognized as Safe (GRAS)" substance. A GRAS substance is a substance considered safe by experts and thus does not require a pre-market review. In contrast, any food containing a food additive is regarded as unsafe and adulterated and cannot be marketed without the FDA approval. Accordingly, a pre-market approval is mandatory only if the food contains a non-GRAS substance or a food additive. Notably, the FDA is not responsible for validating the GRAS status [63]. Instead, the agency establishes a voluntary GRAS notification program such that the food producer may claim the added substance is GRAS and supplement information supporting the GRAS assertion [29]. Unless there is any issue that leads the FDA to question whether the use of the substance is GRAS, such substance is exempted from the food additive approval process and can be marketed without the FDA oversight. Hence, it is up to the food producer to market the GM foods directly, submit a GRAS notification to the FDA, or opt for the food additive route. So far only one GM crop, FlavrSavr® tomato, was reviewed and approved as a food additive [29].

As early as 1992, the FDA stated clearly that is it not necessary to specially regulate GM foods, noting that foods produced by bioengineering do not present any different or greater safety concern than foods developed by traditional plant breeding [64]. The FDA added that the agency "has rarely had occasion to review the GRAS status of foods derived from new plant varieties because these foods have been widely recognized and accepted as safe". The FDA reasoned that regulatory status of a food is irrespective of its developing method'; instead is dependent upon objective characteristics of the food and the intended use of the food. Since "substances added to the food as a result of genetic modification of the plant will be the same as or substantially similar to substances commonly found in food" and these substances are subject to regulation as food additives if they are not GRAS, the FDA concluded that a premarket approval and labeling of GM foods are not needed.

Accordingly, absent contrary evidence showing the expressed product of a GM food is significantly different from the conventional counterpart in terms of structure, function or compositions (hence subject to regulation as food additives), GM food can be marketed without referencing it is produced by GE technology [64]. For instance a soybean expressing a peanut protein may have significant allergenic difference from the natural counterparts, therefore may require a pre-market approval.

6.3.3.1.1. Pre-market "Consultation Procedures" for plants. Regardless of the FDA's preposition that foods from GM plants are safe, the agency established some voluntary "Consultation Procedures" for new plant varieties in 1994 to encourage food developers to consult the FDA on safety assessment and relevant regulatory issues of the plant products. Food developers need to submit a summary of the safety and nutritional assessment of the plant including information about the new genetic trait and its effect, and any known or suspected toxicity and allergenicity of the expressed products. The FDA stated clearly that it would not conduct a comprehensive scientific review of the developer's data, but would consider whether there is any unresolved issue that needs FDA to institute further legal action [65]. If no outstanding regulatory or legal issue is found, the FDA will issue a letter acknowledging that a pre-market review is not required because the developer has concluded that the new plant variety is not materially different from related foods and feeds on the market. On its face, completion of the consultation process does not mean the FDA has verified the safety of GM plant for consumption.

Lately in 2015, the FDA noted that investigation into the scientific proof to ensure safety of foods would go beyond the agency's resources [66]. According to the director of FDA's Centre for Food Safety and Applied Nutrition, no company has marketed GMO products without completing the FDA's consultation program although it is totally voluntary, but cautioned that overseas company may still import GM foods to the U.S. without a pre-market review [67].

6.3.3.2. Transgenic animals. The FDA has historically regulated GM animals under the drug provisions as bound by the statutory definition. To commercially produce a GM animal, developer needs to submit "New Animal Drug Application" (NADA) and provides data to demonstrate the GM animal is safe and effective for its intended use as required by 21 U.S.C. §360b [68,69]. GM animals generally require a pre-market approval via NADA except those qualify for an investigational use such as animals for laboratory research. The FDA may also exercise its discretion to not require a NADA for GM animals of very low risk such as GloFish® which is an aquarium fish genetically engineered to fluoresce in the dark [69].

The unique way of policing transgenic animals as drugs has been criticized. Firstly, information are usually kept confidential in the FDA's drug approval process, therefore creating hurdle to public to fully participate the regulatory process [29]. Another question is that whether it is appropriate to adopt a drug standard to evaluate a GM animal that is consumed as food.

On November 19, 2015, the FDA approved the first GM animal as human food, announced that the fast-growing AquAdvatage salmon produced by AquaBounty Technologies is as safe to eat and nutritious as non-GM Atlantic salmon [1]. The GM salmon is inserted with a growth hormone gene from Chinook salmon under the control of a promoter from ocean pout, and grows faster than non-GM Atlantic salmon [70]. After a rigorous evaluation on the safety and effectiveness of the GM salmon, the FDA concluded that the inserted genes remained stable over all generations of fish, therefore the modification is safe for the fish and the food derived therefrom are safe for human and animal consumption. The agency also believes that the approval would not cause a significant impact to the environment, because the approved GM salmon can only be raised in two specific land-based facilities in Panama and Canada which are guarded with multiple containment measures to prevent the escape of eggs and fish and to make reproduction of the fish in wild extremely difficult [1]. Yet, to bring the GM salmon to the market, the producer further needs an approval from the USDA for slaughter of the fish.

6.4. Labeling

6.4.1. FDA labeling guidance

The FDA also oversees food labeling. Indication of GM ingredients or GM status is wholly voluntary. Not until recently has the FDA finalized its guidance on labeling foods derived from genetically engineered plants [66] and concurrently drafted a guidance on labeling foods derived from the GM salmon [71]. The FDA maintains its stance on voluntary labeling; food producers may indicate whether their food products are derived from GM plants or salmon on their labels, provided that the labeling is truthful and not misleading.

The FDA provides a few examples illustrating that a truthful labeling could be misleading. Like a product made largely of GM corn flour while containing a small amount of oil derived from non-GM soybean, a statement that “does not contain bioengineered soybean oil” could be misleading because the consumer may believe that the entire or a larger portion of the product is free of GM material. Also, the labeling should not contain any statement implying that the non-GM product is safer, more nutritious or has different attributes than other foods because the product was not produced using modern biotechnology [66].

Notably, the FDA interprets that “genetic modification” means any alternation of genetic composition including those achieved through traditional hybridization or breeding techniques, and therefore recommends using “genetically engineered” or “modern biotechnology” rather than “genetically modified” on food labels to indicate the food is developed using recombinant biotechnology [66]. If “genetically modified” is used, conjunction with “genetically engineered” or “modern biotechnology” is recommended. Rather, the FDA recommends using statements such as “not genetically engineered”, “the oil is made from soybeans that were not genetically engineered” and “we do not use Atlantic salmon produced using modern biotechnology” to indicate that the food product is not derived from GMOs.

Moreover, the FDA cautions the use of statement such as “non-GMO” or “GMO free” for two reasons. Firstly, most foods do not contain the entire organism and it is the organism rather than the food being modified. Secondly, absent a regulatory definition, the term “free” means zero or total absence which could render the claim misleading. For example, a statement “none of the ingredients in this food is genetically engineered” is potentially misleading if some ingredients such as salt are not capable of being produced through bioengineering [66].

As for GM foods, the FDA gives examples such as “genetically engineered”, “this product contains cornmeal from corn that was produced using modern biotechnology” and “this salmon patty was made from Atlantic salmon produced using modern biotechnology”. Special labeling is required if the GM plant or salmon derived food is significantly different from the non-GM counterparts in terms of its intended uses, consequences of its uses, nutritional property or allergenicity [66,71].

6.4.2. USDA verification programs

Currently there is no governmental verification explicitly certifies a product as non-GMO. Food producers may request the USDA to certify their products under “Process Verified Program” or “Organic Certification” but neither of them necessarily verifies a GMO-free or non-GM status of the product.

The first one “Process Verified Program” is an auditing service provided by the Agricultural Marketing Services (AMS) for certifying labeling claims about the production, handling or certain characteristics of the products. For example, company can request the AMS to certify their products are non-GMO, or the products were made without antibiotics. Upon approval, companies can use the “USDA Process Verified” shield and/or term on promotional materials for their products [72]. The “USDA Process Verified” shield can be used to certify GMO-unrelated claims hence bearing the shield does not necessary mean the product is GMO-free [73].

The second one “Organic Certification” verifies that the product is in compliance with the USDA organic standards under 7 C.F.R. Part 205. Products produced using GMOs cannot be certified as organic because the use of GMOs is prohibited in organic production and handling. The USDA may test for GM substances if the agency believes GM technology was used to produce or handle the product. However, since GMOs commingling or contamination may occur during processing, an organic certificate does not fully guarantee a GMO-free status; and the inadvertent presence of GMOs in organic products would not result in the loss of organic status if the producers have taken preventive measures to avoid GMO contact. Also, the Organic Certification is not applicable for GMO-free products that were produced or handled by non-organic means [73].

Producers may also consider GMO-specific certification provided by non-governmental organizations such as Non-GMO Project which issues a verified seal bearing a signature butterfly logo. According to Non-GMO Project, many biggest food companies are sourcing non-GMO ingredients, and many major companies voluntarily state their products do not contain any GM ingredients or simply put the butterfly logo on the packaging [74].

6.5. Post-market surveillance

While it is totally voluntary for producers to submit a GRAS notification to the FDA, the safety of GM food could only rely on the post-market surveillance on adulterated foods [29]. Consumers can raise inquires and complaints about the validity of claims for foods to the FDA. The agency will take action to ensure the validity of claims and works with the Federal Trade Commission (FTC) in the case of advertising [63].

7. Intellectual property protection

Intellectual property (IP) is an intangible but valuable asset that, if used strategically, can foster innovation and development of a business. IP protects one’s innovation from unauthorized commercial exploitation and provides a market exclusivity that secures freedom to operate. Innovators can also raise funds using their IP through for example right transfer, licensing and mortgage, or use IP to attract investment and collaboration.

IP can be of various forms. IP can be a right granted by the government such as patent, trademark, industrial design and copyright, a self-operating and self-policing protection like trade secret, and others. Each type of IP is different from each other in term of protectable subject matters, requirements and the scope of protection. Acquiring proper IP rights is very crucial, requiring preparation and action in the early stage of research, and continuous procurement, evaluation and strategic planning during the course of development. Every form of IP tools should be thoroughly considered to strike a comprehensive protection for the creation and marketing advantages.

7.1. Basics of patent

Patent is probably the most fundamental tool to protect a biotech invention. Patent is a right granted by the government to exclude others from making, using, selling, offering for sale, or importing an invention for a fixed period of time. Patent is not an automatic protection and requires individual application in each country or region.

Each jurisdiction has its own patent system and requirements but the "first-to-file" rule is generally adopted. That means a patent is granted to the first one who files a patent application regardless of the date of invention. The term of protection is usually 20 years from the effective date of filing the application. To be entitled a patent, the invention must be a statutory patent-eligible subject matter that is useful, novel and non-obvious. The invention must be fully described and enabled by the specification [63]. Generally patent is eligible for compositions, products (articles of manufacture), methods (processes) and machines, while natural laws and abstract ideas are excluded. For instance, food ingredients, food products, production methods and apparatuses could be the subject of a patent. For GMOs, animal and plant varieties are not patentable in certain jurisdictions such as China and Europe, whilst microorganisms and cell lines other than human embryonic stem cells are typically patentable [75].

This article does not intend to discuss the patentability requirements. Instead, the following sections highlight a few patenting issues unique in China and the U.S. and discuss possible non-patent IP measures for protecting the GM food technology.

7.1.1. Chinese patent landscape

7.1.1.1. Patent-eligible subject matter. Invention patent in China is eligible for products, methods and machines. However, under Article 25 of the Patent Law, animal and plant varieties as well as methods for the diagnosis and treatment of diseases cannot be patented [76]. Although China disallows animal and plant patents, methods for producing or breeding GM animals or plants are patentable (see e.g., CN101494969B and CN1620506B). Furthermore, components and axillary methods for producing GM varieties such as genes, promoters and transformation methods are patentable. Nonetheless, as discussed later, breeders who want to acquire an exclusive right in their plant varieties can apply for a new plant variety certificate from the MOA.

7.1.2. U.S. patent landscape

7.1.2.1. Patent-eligible subject matter. Laws of nature, natural phenomena and abstract ideas have been historically excepted from the U.S. patent protection. The exclusion further extends to natural matters and their uses in light of a few Supreme Court's rulings about patent eligibility of natural matters such as *Myriad* [77]. *Myriad* ruled that an isolated nucleic acid having sequence identical to a breast cancer-related gene is not patentable; whereas a complementary DNA (cDNA) having non-coding introns of the gene removed is patentable because the cDNA is distinct from the natural gene [77]. The decision implies that nucleic acids having identical sequence to natural DNA are not patentable irrespective of its production method. Since then, the U.S. Patent and Trademark Office (USPTO) holds that products such as nucleic acids and chemicals of natural origin, taken alone or in combination, are not patentable unless the products exhibit markedly different characteristics from the natural counterparts in terms of structure, function and/or other properties [78]. Absent a standard for "markedly different characteristics", the USPTO will evaluate the products based on what is recited in the claim on a case-by-case basis. The new examining policy also notes that general uses or applications of natural products are not patentable; for example, a method of treating breast cancer comprising administering to a patient an effective amount of a purified natural compound is deemed eligible because the method practically applies the natural product to treat a particular disease [78].

7.1.2.2. Plant patents vs utility patents. U.S. is one of the few jurisdictions practicing a plant patent system. By law, plant patents protect asexually reproduced plants (cuttings and bunds) excluding tuber propagated plants [79]; while utility patent is eligible for sexually reproduced plants (flowers and seeds) including transgenic varieties. A plant patent is granted to the entire plant. Utility patent is more versatile because it could widely cover traits, transformants, production methods and many other inventions associated with the GM technology. Both plant patent and utility patent are entitled a patent term of 20 years. It is also possible to protect sexually reproduced or tuber propagated plant varieties through a plant variety protection certificate (PVPC) which is independent of plant and utility patent [80].

7.1.2.3. Patent exhaustion of patented GM seeds. Monsanto is a U.S. founded multinational company that is highly devoted in biotech agrochemicals and agriculture. One major success of the company is the invention of the herbicide Roundup® and a plurality of Roundup Ready® GM seeds engineered with Roundup®-resistant trait. The proprietary Roundup technology has brought the company a considerable revenue from global sale. The company holds U.S. patents on the Roundup technology and has actively exercised its patent right by suing farmers for infringement. *Bowman* is a notable case which looked into the issue of patent exhaustion of seed patents [81].

Monsanto sells its GM seeds with licensing agreements restricting the farmers that they can only plant the GM seeds for a single season, and forbidding the farmers to supply the original seeds to others, or to save or sell to others the resulting crops for replanting purposes.

In *Bowman*, Monsanto sued farmer Bowman for infringing its patent on Roundup® technology in 2007. Bowman bought commodity soybeans intended for consumption from a grain elevator in 1999. These commodity soybeans are a mixture of soybeans harvested by other farmers and some of them may have been derived from Monsanto's Roundup Ready® soybeans. Bowman planted the purchased commodity soybeans and sprayed glyphosate during the cultivation. He finally obtained a crop in that season and retained the harvested soybeans. By replanting these harvested soybeans in later seasons, Bowman obtained eight crops in total [81].

It has long been held that a patent right in an item exhausts upon an authorized sale of the item. The so-called "patent exhaustion" or "first-sale doctrine" terminates the patent right in a patented item upon initial authorized sale of the item, and hence the purchaser can freely use or resell that purchased item without bound by the patent [81]. Under the patent exhaustion doctrine, Monsanto has no control over the uses of its patented seed upon sale.

During the court proceedings, Bowman raised the patent exhaustion as a defense, argued that Monsanto's right should have extinguished upon the authorized sale of its soybeans from the local farmers to the grain elevator. Monsanto claimed that the company's restrictive sale prohibited the replanting activity. Therefore, the underlying question is whether the replanting and harvesting activity of Bowman, who purchased soybeans from a vendor other than Monsanto has infringed Monsanto's patents. Both the district court and the appellant court held that Bowman infringed Monsanto's patents, reasoned that patent exhaustion protects the "right to use" a patented article following an authorized sale, but the "right to make" a patented article remains with the patentee [81].

In 2013, the Supreme Court affirmed the appellant court's decision and ruled in favor of Monsanto. According to the court, Bowman may resell the purchased commodity soybeans to others, consumed the soybeans himself or feed them to his animals, but the exhaustion doctrine does not enable Bowman to make additional copies of the patented soybeans without Monsanto's permission. The Court elaborated that other companies or farmers could purchase patented seeds from Monsanto, and then reproduce and sell the seeds; if the exhaustion doctrine protects the right to produce subsequent generations of the crops, this would deprive Monsanto of its monopoly. As in the case of Bowman, Monsanto received no gain from Bowman's annual production and sale of the Roundup Ready® soybeans [81].

The Judge of *Bowman* expressed that the court's decision only addresses the specific case of *Bowman*. While whether *Bowman* would set a precedent for every self-replicating patented product remains to be seen, it nonetheless upheld that patent owners preserve their right in anew copies of the patented item despite the copies are derived from a prior authorized sale. Therefore not just the agricultural industry, other biotech industries which involve self-replicating products should be cautious about the issue of *Bowman* which could be far-reaching and significant to their business and practice.

8. Non-patent IP protection

This section introduces plant breeder's right and trade secret which are two common IP tools that are applicable for the GM technology. Regardless, others such as trademark, design and branding should also be considered.

8.1. Plant breeder's right

Plant breeder's right is a patent-like protection for plant varieties conferred based on the International Union for the Protection of New Varieties of Plants (UPOV) Convention [80].

Plant breeder's right provides a patent independent option for protecting plant species, hence is particularly useful in jurisdictions that bar plant patents. The approval requirements are far less stringent than patent. In brief, developers need to provide information showing the plant variety is new, distinct from other varieties, uniform, and stable. A new variety means the propagating material of the variety has not been sold for more than one year in the country of protection, or more than four years (or six years in the case of trees and vines) outside the country of protection. Essentially, research uses or uses of the protected variety for breeding (i.e., developing) a new variety are exempted from infringement of the plant breeder's right. More importantly, farmers can grow and save seeds of the protected varieties and plant the harvested seeds at a later time in their own farms without prior consent of the certificate holders [80].

In China, the plant breeder's right is managed as a new plant variety certificate issued by the MOA (for agricultural plants) and the Ministry of Forestry (for forest plants). The term of protection is 20 years from the date of issuance of the certificate for vines, forest trees, fruit trees and ornamental plants, and 15 years for the others [82]. Certificate holders are entitled an exclusive right to commercially produce and sell the propagating material of the protected variety, as well as the commercial production of other varieties which involve the use of the propagating material in a repeated manner.

While in the U.S., the Plant Variety Protection Office (PVPO) under the USDA is responsible for issuing the plant variety protection certificate (PVPC). The term of protection is 20 years for most plants except for vines and trees having 25 years. Apart from the right in commercial production and selling of the protected varieties and in uses of the protected varieties in producing other varieties, PVPC holders also enjoy an exclusive right in importing and exporting the protected varieties. Protection could also be extended to essentially derived varieties, indistinct varieties and the harvested materials obtained through the use of propagating material of the protected variety [83]. Given that patent does not provide any research, breeding or farmer exemptions as the plant breeder's right does, it is possible to exploit both patent and PVPC in the U.S. to maximize the protection.

8.2. Trade secret

Trade secret is one form of IP which protects confidential information against theft. Information that are useful in business and possessing economic value can be the subject of trade secret. Unlike patent which encourages sharing of information and mandates disclosure of an invention, secrecy is essential for a trade secret protection. Trade secret owner must make reasonable effort to maintain secrecy of the information. The Coca-Cola® formula is the most famous example of trade secret that has been held for years.

Table 1
Major differences between patents and trade secrets.

		Patents	Trade secrets
1	Exclusive right	Yes. Prevents unauthorized production, use, sale and import of inventions.	No. Only prevents acquisition of trade secrets by improper means.
2	Protectable subject matters	Useful, new and non-obvious compositions, processes, machines and manufactures.	Virtually everything.
3	Disclosure	Full disclosure on how to make and use the invention at the time of filing.	Kept confidential.
4	Effective time for protection	Upon approval of patent which can take >3 years for most biotech inventions.	Immediate protection.
5	Duration	20 years from filing date.	Perpetual term until it is disclosed, reverse engineered, or independently developed.
6	Cost	Filing, prosecution, maintenance and attorney fees.	Costs for maintaining secrecy.
7	Risks	Loss of right if patent is invalidated or held unenforceable. Validity also subject to change in patent law or legal precedents.	Right lost upon disclosure; has no control in reverse engineering and independent development.

Trade secret and patent are frequently regarded as mutually exclusive. Indeed there are many difference between trade secret and patent (Table 1) but in fact they can be used in conjunction to generate synergistic effects [84]. It should be emphasized that trade secret serves to prevent improper acquisition and use of confidential information, and does not represent an exclusive right in using the information. As a general guidance, below explores a host of factors that may affect the choice between patent and trade secret protection.

8.2.1. *Patent vs trade secret*

8.2.1.1. Protectable subject matter. Trade secret does not have to be patentable. Theoretically all forms of invention can be maintained as trade secret. Apart from substantive parts of the technology (e.g. genes, breeding methods and manufacturing methods, devices), knowledge or experience related to the technology ("know-how") or even matters irrelevant to the technology (e.g. customer lists) can be the subject of trade secret.

Trade secret is a good option for protecting subject matters that are not patent-eligible, such as natural products in the U.S. and treatment methods in China. Patentability of the technology and the possible scope of patent protection must be fully evaluated. Inventions that are not novel or inventive may better be protected as trade secret.

8.2.1.2. Disclosure. Patent requires a full disclosure about how to make and use an invention. The information is exposed to the public domain upon publication of the application even if a patent is not ultimately awarded. Disclosure of the technical information may facilitate competitors and hence undermine the competitive advantages.

8.2.1.3. Effective term for protection. Patent right in an invention runs into effect upon issuance of the patent and vanishes on the expiry date of the patent. While for trade secret, protection commences immediately and stands till the information is disclosed or otherwise independently obtained.

8.2.1.4. Costs. Subject to actual circumstance, costs for patent and trade secret can be comparable or highly different. Patent requires a substantial amount of fees for application, maintenance and attorney service. Maintaining a trade secret may, among other things, involve access control over computers and documents, non-disclosure agreements (NDA) with employees and collaborators, guidelines for confidentiality and so on. Costs for trade secret can be very high to set up a high level of confidentiality. While it is worth noting that for a fast-evolving technology which gets outdated quickly and replaced by newer creations, a 20-year patent term to one single invention may not be necessary. Instead, the innovator may put resources in filing new applications for follow-on generations of the invention. It may be more cost-effective for startups or small enterprises to pursue patents for their core and groundbreaking technology while protecting the subsequent modifications as trade secret.

8.2.1.5. Enforcement and risks. Getting a patent does not guarantee a protection for an invention because patent can be invalidated or held unenforceable. Validity of patent is susceptible to change in patent law and regulations. For example, the ever patent-eligible business method and isolated genes are now no longer patentable in the U.S. In common law jurisdictions in which the courts are usually bound to follow decisions of legal precedents, patentability standards could change now and then thus affecting the patent validity and jeopardizing right of the patent owners.

It is not uncommon that potential infringers or stakeholders challenge a patent on the ground of patentability or inequitable conducts through litigations or post-grant proceedings. Some or all of the claims, upon re-examination by the court or the patent office, may be held invalid or unenforceable. On the other hand, determination of infringement is never an easy task and is predominantly based on how the claim language is interpreted. Plainly, every element in the claims of the infringed patent or its substantial equivalent must be found in the accused invention to constitute an infringement.

Not every invention is suitable to be protected as a trade secret. Trade secret does not preclude a third party from obtaining and using the information by fair means. Hence, innovators need to consider how easily their inventions be reversed engineered or developed independently. For instance, a device on public sale may risk reverse-engineering and hence may opt for a patent protection instead. Notwithstanding patent can preserve right in an invention upon independent discovery of the invention, protection could still be ineffective if the invention can be easily designed around.

8.2.1.6. Prior use exemption. Prior use exemption creates a safe harbor to any third party who independently developed and uses a patented invention before a prescribed time by exempting the party from charges of patent infringement. China, U.S., Australia, Canada, Japan, Korea and many other countries provide exemption for prior commercial uses. Generally there are two limitations in the exemption: (1) prior users cannot extend their uses beyond the original scope of the prior commercial use; and (2) the exemption is not transferable unless the transfer is done in connection with the entire, or at least part of the, business (it is freely assignable in Australia) [85].

In the U.S., prior use exemption includes commercial exploitation of patented processes, or commercial uses of patented machines, manufactures or compositions. The prior uses must occur at least one year before the earlier of the effective filing date of the patent application or the date of public disclosure of the invention. Also, the exemption is limited to uses at sites where the invention was initially used. The exemption further encompasses non-commercial uses by non-profit research laboratory or entities, and uses for the purpose of premarket regulatory review. Notably, the prior use defense cannot be used against patents owned by or assigned to universities and their affiliates, meaning that a person could still be liable for infringement if the patent involved is held by a university [86].

In China, practice of a patented method or manufacture of a patented product before the date of patent application is qualified for a prior use exemption. The exemption is also applicable if the users have already made necessary preparations for the use or manufacture. The prior user can continue to use the patented method or make the patented product within the original scope of the prior use. The exemption is also eligible for uses for the purpose of premarket regulatory review or research [76].

Unlike most forms of IP, the prior use exemption cannot be transferred, assigned or licensed to others but it is transferable if the transfer is made together with the entire business (China and U.S.) or the line of the business (U.S.).

8.2.2. Patent or trade secret?

In short, patent and trade secret have their pros and cons and are not mutually exclusive. Patent requires vast effort in formulating strategy, prosecution and policing. Trade secret must institute adequate measures to prevent inadvertent or intentional disclosure because exposure of the information could be fatal to a business.

It is advised to regularly evaluate the relative strength and weakness of patent and trade secret for each invention as the technology evolves. Also, it is not necessary to protect the entire technology using either patent or trade secret. Some aspects such as compositions may be protected by patent while manufacturing methods or know-how could be maintained as trade secret. A hybrid approach could generate synergetic benefits than the sum of the two options.

While the best strategy needs to be determined case-by-case, it is generally recommend to file a patent application for groundbreaking or core technology that is crucial to the business. For subsequent improvements or optimizations, innovator may file a U.S. provisional patent application to secure an earliest filing date while buying time to evaluate the patentability of the invention [63]. A provisional application does not grant any patent right, and a regular application must be filed within a year after the filing date of the provisional application if the innovator decides to protect the invention using patent. On the contrary, if opt for a trade secret protection, the invention will not be disclosed since the provisional application goes abandoned automatically after 12 months and is never published.

9. Conclusion

Use of genetic engineering in food industries is deemed inevitable under the strong wave of biotechnology. Agricultural biotechnology has already achieved a great commercial success. Foods derived from GM crops or GM-crops fed animals are readily available in the market and more GM foods are expected to hit the market. While it may be beyond the government's ability and authority to assure safety of every GM food before its marketing, the public call for GM labeling is rational and deserves attention and actions. The Chinese and U.S. government have promised to revisit their regulations for GM organisms and products. New law or regulation is at sight and could significantly influence the development and commercialization of GM foods. Intellectual property is another factor determinative in the success of the business. Innovators and the industries need to watchfully monitor the regulatory and IP landscapes, adapt to the evolving policy, and work with experienced professionals to map out a realistic strategy for moving the business forward.

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