Front. Agr. Sci. Eng. 2020, **7**(2): 204–210
https://doi.org/10.15302/J-FASE-2019301
Available online at http://journal.hep.com.cn/fase

REVIEW

Brazilian biosafety law and the new breeding technologies

Alexandre Lima NEPOMUCENO (✉)[1,9], Renata FUGANTI-PAGLIARINI[1], Maria Sueli Soares FELIPE[2,9], Hugo Bruno Correa MOLINARI[3,9], Edivaldo Domingues VELINI[4,9], Eduardo Romano de Campos PINTO[5,9], Maria Lucia Zaidan DAGLI[6,9], Galdino ANDRADE FILHO[7,9], Patrícia Machado Bueno FERNANDES[8,9]

1 Embrapa Soybean, Londrina 86001970, Brazil
2 Catholic University of Brasilia, Brasília 70790160, Brazil
3 Embrapa Agroenergy, Biological Station Park, Brasília 70770901, Brazil
4 Paulista State University Julio de Mesquita Filho, Botucatu Faculty of Agronomic Sciences, Botucatu 18610307, Brazil
5 Embrapa Biotechnology and Genetic Resources—Biological Station Park, Brasília 70770900, Brazil
6 São Paulo University, Veterinary Faculty, São Paulo 05508900, Brazil
7 Londrina State University, Microbiology Department, University Campus, Londrina 86051990, Brazil
8 Espírito Santo Federal University, Biotechnology Post Graduation, Vitória 29040090, Brazil
9 CTNBio (National Biosafety Technical Commission), Brasília 70610200, Brazil

Abstract Globally, the area of land cultivated with genetically modified (GM) crops has increased a thousand-fold over the last two decades. Although this technology has become important for food production, the regulatory frameworks that underpin these outcomes are based on a list of requirements for a risk assessment that differ from country to country. In recent years, policy-makers have had the opportunity to learn from the controversies over transgenics to create effective regulatory milestones for emerging technologies, allowing them to reach their potential for a more sustainable agriculture, ensuring food security. In Brazil, Law No. 11.105 of 24 March 2005 established a framework with four main organizations responsible for risk assessment and management. However, most of new breeding technologies did not exist at that time and were not considered in this law. In 2016, Normative Resolution No. 16 of the National Biosafety Technical Commission (CTNBio) was established to address this gap based on the evaluation of the products obtained through these techniques (termed Innovative Precision Improvement Techniques in the resolution), in a case-by-case consultation system. Briefly, if the product is designated to be a GM, the developer will have to go through the biosafety requirements and will be approved only after CTNBio risk assessment. If the product is designated not to be GM (for the purposes of the legislation), then it can be registered using the existing procedures. Currently, 152 GM products are commercially approved in Brazil. In 2018, CTNBio assessed the first consultation on commercial release of plants generated using the new breeding technologies and has subsequently approved six products. It is expected that many institutions would be able to participate in Brazilian and world markets, developing and introducing new biotechnological solutions and products through a more sustainable approach and without facing public disapproval, a common issue for GM crops.

Keywords Brazilian legislation, CTNBio, genetically modified crops

1 Introduction

The total area cultivated with genetically modified (GM) crops has increased a thousand-fold over the last two decades, from a few thousand hectares in 1996 to more than 190 Mha in 2017[1]. Among the countries producing GM crops, Brazil has the second largest crop area, with more than 53 Mha, surpassed only by the USA with 75 Mha. In the 2018/2019 harvest season, Brazil had more than 95% of its soybean fields planted with GM cultivars; for maize it was more than 88% (first and second harvests), and for cotton it reached more than 84% of the total area[1].

As with many other plant breeding techniques, the use of genetically modified organisms (GMOs) in agriculture has become important for the production of food and vegetable by-products, but unlike other technologies, the regulatory frameworks that underpin these outputs are based on a broad list of requirements for a risk assessment that differ from country to country. These requirements are primarily to protect human and animal health and the environment from potential adverse effects of the GMO, but in many

Received August 24, 2019; accepted October 8, 2019

Correspondence: alexandre.nepomuceno@embrapa.br

cases the requirements are not proportional to the risks resulting in costly and time-consuming regulatory approval processes. An unintended consequence is that only a few large multinational corporations (currently BASF, Bayer, Corteva and Syngenta) have adequate resources to have new GM crops approved, while publicly funded research laboratories and small and medium-sized institutions/companies and universities usually are unable to develop a product that can obtain regulatory authorization to reach the market. Such public laboratories are often obliged to provide technologies beneficial to society that may not reach the financial thresholds of the large multinational corporations, even though they may benefit a broader range of stakeholders, particularly in impoverished regions. As a result, many socially beneficial technologies have languished in the regulatory limbo.

In recent years, however, after more than two decades of experience, policymakers have had the opportunity to learn from the controversies over transgenics how to create effective regulatory milestones for emerging technologies, such as gene editing and RNA interference, allowing them to reach their potential for a more sustainable agriculture ensuring food security. In Brazil, Law No. 11.105 came into force on 24 March 2005 and was important in establishing the guidelines for the safe use of genetic engineering technologies in research and development, keeping Brazil as an important contributor in the areas of agriculture, industry and human/animal welfare. Discussed below are some of the landmarks of this legislation and some of its outcomes, including the recent publication of the legal framework for products developed using new breeding technologies.

2 Brazilian legislation on GMOs

Brazilian Law No. 11.105 of 24 March 2005 approved by the National Congress is known as the Biosafety Law and put an end to the legislative controversy surrounding GMOs in the country. This law, regulated by the Decree No. 5.591 of 22 November 2005, was a comprehensive and a complemented revision of a previous biosafety law of 1995 that allowed the first commercial planting of GM soybean resistant to glyphosate herbicide, in 1998. In addition to determining the general rules for research and commercial activities with GMOs, Law No. 11.105 regulated constitutional principles and established safety standards and mechanisms for the monitoring of activities involving GMOs and their by-products. The principles used to elaborate this law were to encourage scientific advances in the areas of biosafety and biotechnology, protection of life, human health, animal and plant health and compliance with the precautionary principle for protection of the environment. Law No. 11.105 also established the National Biosafety Council (CNBS), restructured the National Biosafety Technical Commission (CTNBio) and proposed the Brazilian Biosafety Policy. Its purpose and scope were to provide safety standards and inspection mechanisms for the construction, culture, production, handling, transportation, transfer, import, export, storage, research, environmental release, unloading and commercialization of GMOs and their by-products. The law covers research activities and commercial uses for products developed for use in agriculture, human and animal health, the environment and fisheries. This law requires that any individual who is interested in conducting an activity covered by the law should request permission from the CTNBio, which will respond within the deadline stipulated by the CTNBio resolutions. The legislation requests that all public and private organizations, national or foreign, that conduct activities or projects in Brazil, under the description of Law No. 11.105, require a Biosafety Quality Certificate issued by CTNBio before starting any activity. CTNBio through its Normative Resolutions is responsible for establishing the biosafety guidelines for subjects of its competencies. Among its prerogatives, the law mandates the CTNBio to evaluate how new technologies can impact the environment, and human and animal health in the country and then, if necessary, authorizes the commission to propose regulations for these new technologies.

3 New breeding technologies regulation in Brazil

For any new technology it is essential to ensure its safety, but any safety requirements must be commensurate with the risk of the product in order to enable technological advancement. When law No. 11.105 was drafted, most of the Innovative Precision Improvement Techniques (INIT), also known as new breeding technologies, were in their infancy and at the time were not considered in this law. Thus, in 2015, CTNBio established a working group of specialists among its members to better analyze and understand the products of the new breeding techniques and how these products would be framed under the definitions of Law No. 11.105, with the aim of proposing more up-to-date regulations. The techniques analyzed by the work group included gene editing, early flowering, reverse breeding, RNA interference and oligonucleotide-directed mutation, among others. For most of the products considered by the working group, the use of INIT can accelerate the introduction of characteristics of interest in elite genotypes in breeding programs, where in many situations the final product could be designated not to be GM (for the purposes of the legislation). In fact, several products obtained by gene editing result in genetic modification that could be obtained by established mutation techniques, such as radiation and chemical mutagenesis. Since Brazilian Biosafety Law considers organisms obtained by established methods of mutagenesis

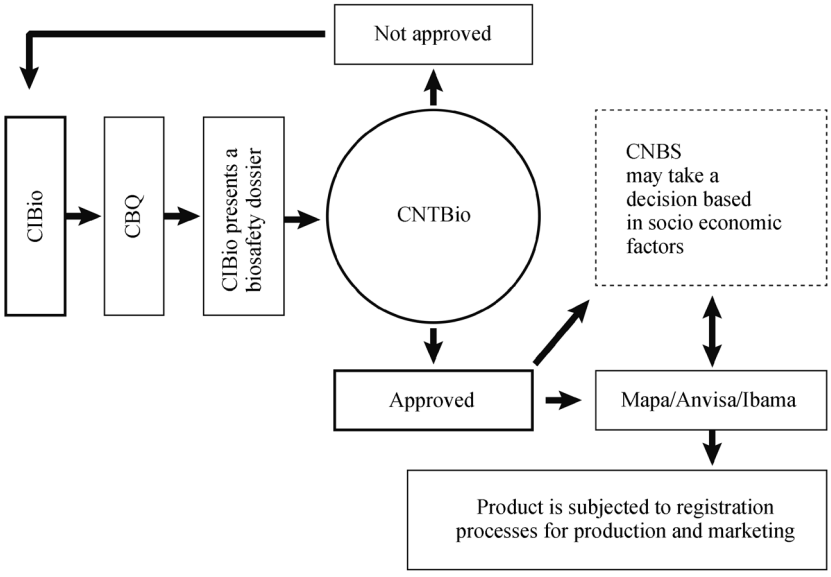

Fig. 1 General procedure for a case-by-case consultation at CTNBio for a product generated by INIT, according to Normative Resolution No. 16. If the product is designated to be GM, the developer will have to go through all the biosafety requirements and will be approved only after the CTNBio risk assessment. If the product is designated as not GM (for the purposes of the legislation), it can be registered using the existing procedures.

as not GM, the working group considered that some products could be excluded from the scope of the GMO legislation, after a case-by-case analysis submitted to CTNBio.

The CTNBio Normative Resolution No. 16, which proposed this update, was unanimously approved by the members of CTNBio and by the Legal Adviser of the Ministry of Science, Technology, Innovation and Communication, and it was published in the Official Gazette on 15 January 2018. The Normative Resolution No. 16 was developed based on the report of the working group and the regulations and experiences from other countries.

In general terms, the principle of this resolution is the determination, through a case-by-case consultation system, whether a product generated by INIT should be designated as GM by the CTNBio (Fig. 1). For this consultation the developer institution provides information about the original organism and the product, including the methods used to generate it and the molecular analysis of the product. The trigger for a product to be designated as not GM (for the purposes of the legislation) is based on the following criteria: (1) absence of recombinant DNA/RNA, (2) presence of genetic elements that could be obtained by crossbreeding, (3) presence of induced mutations that could also be obtained by established techniques, such as radiation or chemical exposure, and (4) presence of mutations that could occur naturally. In practical terms, products obtained either by site-directed random mutation involving the joining of non-homologous ends (SDN1 mutation), or site-directed homologous repair involving one or few nucleotides (SDN2 mutation) meets the conditions established in Normative Resolution No. 16 to be designated as not GM in a case-by-case analysis. In contrast, site-directed transgene insertions (SDN3 mutation) are designated GM according to the provisions of the resolution. If the product is designated as GM the developer will have to go through all the biosafety requirements and will be approved only after the CTNBio risk assessment. If the product is designated not GM, it can be registered trough the existing procedures.

The CTNBio Normative Resolution No. 16 is applicable to all types of organisms, including plants, animals and microorganisms, and is considered at the stage of commercial release. If during the product development a GMO is used the requirements for contained use and experimental release according to Law No. 11.105 are still valid.

4 Brazilian regulatory framework

Law No. 11.105 of 24 March 2005 established a framework with four main organizations responsible for risk assessment and management (Fig. 2): (1) National Biosafety Council (CNBS), (2) National Biosafety Technical Commission (CTNBio), (3) Internal Biosafety Commission (CIBio), and (4) Organizations and Entities of Registration and Inspection (OERF), which are the Ministry of Agriculture, Livestock and Food Production (MAPA); the Ministry of Health, the Ministry of Environment and Ministry of Aquaculture and Fisheries.

As a general procedure, any demand for a commercial activity with a GMO is submitted for CTNBio evaluation by the CIBio president of the concerned institution, which

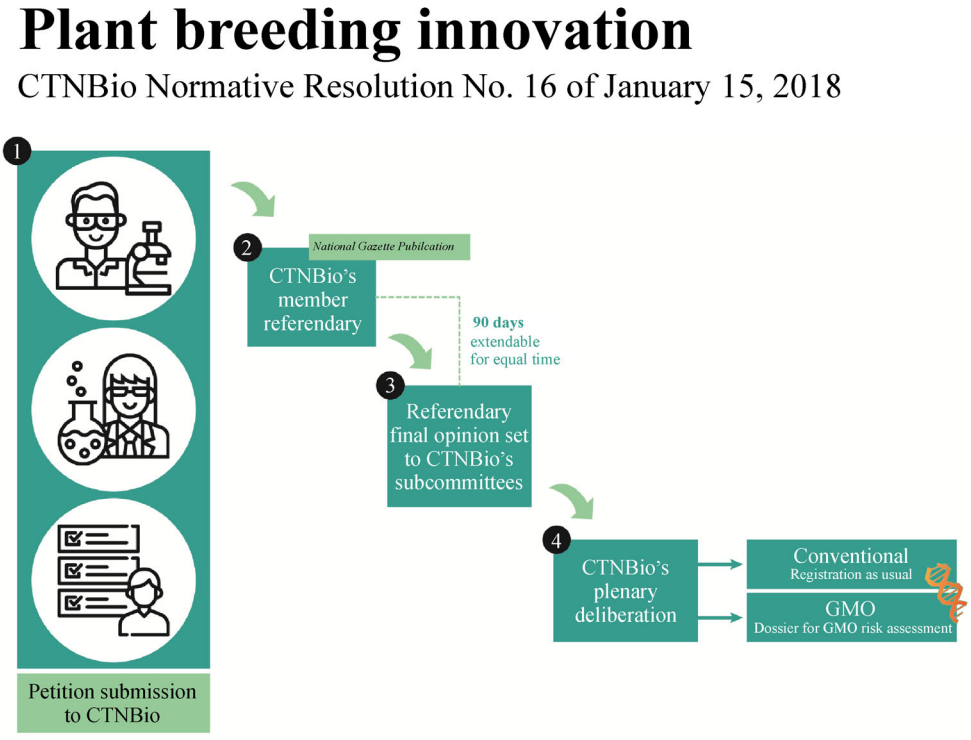

Fig. 2 Workflow representing the approval process of GMOs for commercial release according to the Brazilian Biosafety Law No. 11.105/2005 and its Normative Resolutions.

must have an approved Certificate of Quality in Biosafety. The certificate is issued after CTNBio analysis authorizing the research institution to handle GMOs in their facility considering that the required safety levels are met by the institution. A complete and detailed dossier containing the biosafety risk assessments is also delivered with the commercial release application process. The guidelines for the risk assessment are established in a specific Normative Resolution No. 5, which provides for standards rules for commercial release of GMOs and their derivatives. The CTNBio will assess the risk and elaborate a technical report. If it is approved for a commercial release, it is forwarded to the OERF responsible for the GMO registration for production and marketing.

4.1 National Biosafety Council (CNBS)

CNBS is a collegiate organ consisting of 11 ministers of state. Furthermore, the CNBS includes the Minister of State of the Civil House, who presides over it, the Minister of Justice, the Minister of Science and Technology, the Minister of Agrarian Development, the Minister of Agriculture, Livestock and Supply; Minister of Health, the Minister of the Environment, the Ministry of Development, Industry and Foreign Trade, the Minister for Foreign Affairs, the Minister of Defense and the Secretary of Aquaculture and Fisheries.

This council provides higher advisory assistance to the Brazilian Republic President in formulating and implementing the National Biosafety Policy, establishing principles and guidelines that consider socioeconomic and political conveniences and opportunities related to the national interest involved in the commercial use of GMOs and related products. CNBS technical advice regarding a final decision on the release of a GMO for commercial use will be requested only if any strategic socioeconomic and/or political decision needs to be taken. CTNBio makes the technical judgment on the biosafety of a commercially used GMO. However, the CNBS has 30 days to refute the commercial approval of that GMO after CTNBio has released their official opinion. If refutation does not occur in 30 days, the product is automatically authorized for commercialization.

4.2 National Biosafety Technical Commission (CTNBio)

CTNBio is linked to the Ministry of Science, Technology, Innovation and Communication (MCTIC), which is a consultative and deliberative multidisciplinary collegiate that provides assistance and technical support to the federal government to formulate, update and implement the National Biosafety Policy for the development of GM products or biotechnology products, which in some phase might generate a GMO. It also establishes safety technical

norms regarding the authorization of research-related activities and the commercial release of GMOs.

CTNBio is also the organization responsible for assessing the zoosanitary, phytosanitary, human health and environmental risk of GMOs and to establish risk management measures. Other competencies of CTNBio include the authorization to import GMOs for research, to provide technical assistance to the registration and inspection organizations and entities and to monitor the development and technical-scientific progress attained in biosafety, biotechnology, bioethics and related areas, aiming to increase the capacity to protect human, animal and plant health and the environment.

CTNBio is organized into plant, animal, human health and environmental sub-commissions. The Minister of MCTIC nominates one of its members to serve as the CTNBio President for a two-year term, extendable for the same period. It also has a permanent executive secretariat that provides technical and administrative assistance to CTNBio members and organizes the monthly meetings (except in January and July). This commission is composed of 27 titular members and their substitutes, who are indicated by the same minister after receiving nominations from other ministries. All members serve a two-year term, which is extendable for two additional consecutive periods. They must be Brazilian citizens with acknowledged technical competence and recognized for distinguished participation in the scientific community. All members must have a PhD and be professionally active in the areas of biosafety, biotechnology, biology, microbiology, plant and human/animal health and environment or in closely related areas. Twelve members from the scientific community are directly nominated by the MCTIC, while the others are nominated by one of the following: Ministry of Agriculture, Livestock and Supply, Ministry of Health; Ministry of Environment, Ministry of Agrarian Development, Ministry of Development, Industry and Foreign Trade, Ministry of Defense, Ministry of Aquaculture and Fisheries, Ministry of International Affairs, and Minister of Justice. The full list of CTNBio members can be found at CTNBio's website (in Portuguese).

CTNBio meetings can be held with the minimum quorum of 14 members (half plus one), including at least one representative from each of the four sub-commissions. If necessary, representatives from the scientific community, the public sector and civil society entities with expertise in a particular field can be invited to attend meetings but they do not have voting rights. Any decisions made by CTNBio must have the approval by nominal vote of at least 14 members. To provide greater transparency in the process, all decisions are published in the official gazette for comments and are opened for public comments within 30 days and all CTNBio meetings are open to citizens, who can consult the meeting agendas and all documents produced by the commission on the CTNBio website.

4.3 Internal Biosafety Commission (CIBio)

Any public or private institution that uses genetic engineering techniques and methods to develop biotechnological products, which in some development phase might generate a GMO, must have a CIBio, composed of individuals with proper training and education in the areas of biotechnology, genetic engineering, biosafety or other related fields. A Certificate of Quality in Biosafety, an essential document required for CIBio to work under governmental control is also issued by CTNBio to the concerned institution.

As a mandatory procedure, a principal investigator must be indicated as responsible for each specific project using such technologies at the institution. Furthermore, each CIBio is legally responsible for ensuring the biosafety conditions of the entity facilities, performing regular audits on its facilities and sending an annual report of its activities and projects to the CTNBio. CTNBio currently oversees 480 private and public institutions in Brazil.

4.4 Organizations and Entities of Registration and Inspection (OERF)

OERF include Ministry of Agriculture, Livestock and Food Production; the Ministry of Health and the Ministry of Environment and the Ministry of Aquaculture and Fisheries.

Under Law No. 11.105 and within their field of competence, in compliance with CTNBio technical resolutions and technical opinions, the OERF are responsible for monitoring GMOs and their by-products. Their responsibilities include: (1) to inspect research activities, (2) to register and inspect the commercial use of GMOs, (3) to grant authorization for importing products for research and commercial use, (4) to keep updated information regarding institutions and principal investigators that carry out activities and projects, (5) to assist CTNBio in defining biosafety assessment parameters, (6) to disclose to the public, grant registrations and authorizations for the commercial use of GMOs, and (7) to enforce the law and to apply the established penalties when noncompliance is identified.

5 Overview of the status of use of biotechnology in Brazilian agriculture

Brazil is one of the major food and agriculture related goods producers in the world and one of the few countries that could considerably increase its production in the next decades, without compromising areas of environmental protection and the Amazon rainforest. Among the world producers, Brazil also has great potential to become the leading biofuels supplier. Furthermore, unlike most developed countries where agroenergy production could

compete with food production, Brazil can cultivate more than 30 Mha without destroying native and preserved environments or invading food production areas[2]. Brazil uses about 12% of the world's fresh water for drinking and for agriculture. Additionally, Brazil contains between 15% and 20% of global biodiversity, which has a huge potential as a source of new products for agriculture, medicine and industry.

Therefore, Brazilian agriculture (from small to large farmers) and the entire agribusiness related to it possess all the conditions to increase agricultural development to similar levels that are occurring in other emergent economies and, consequently, help to improve economic and social progress in the country and at the same time aid to feed the growing world population. The flow of crops and livestock production to the Cerrado areas in the 1970s revealed how agribusiness can enhance economic and social development. For example, it is noteworthy that some cities in the Midwest currently have the highest human development indexes in Brazil, showing that the importance of agribusiness to the economy is effective and undeniable.

Many of the important achievements in Brazilian agriculture over recent decades came from the combined application of biotechnological and breeding approaches (Fig. 3). Also, in the near future, the combination of these methodologies will be crucial in order to secure sustainable food production, in a scenario involving multiple challenges arising from global warming, the consequent climatic extremes and an increasing world population. Thus, to maintain productivity, it is fundamental to be alert, informed and acquainted with new technologies that could change production and consumption concepts, standards and paradigms. Consequently, the incorporation of a genetic engineering toolbox in agriculture to confront the challenges ahead is a strategic action, not only for Brazil, but also for the world.

In December 2018, the CTNBio evaluated, within the scope of CTNBio Normative Resolution No. 16, the first consultation on commercial release of plants generated using new breeding technologies in Brazil. A genotype of maize in which the metabolic pathway for amylose production was inactivated by CRISPR/Cas9 was designated as not GM. After analysis, CTNBio concluded that the introduced mutation could have been obtained by crossbreeding methods, or induced by other mutagens, such as ionizing radiations or ethyl methane sulfonate. In this specific case, the reduction in amylose production resulted in a near doubling of amylopectin content, which is beneficial for some industrial uses of corn starch. In another CTNBio consultation, also in 2018, a *Saccharomyces cerevisiae* strain received mutations in four genes from another strain of *S. cerevisiae* using CRISPR/Cas9, with only the mutations remaining at the end of the process. The edited organism increased the production of alcohol from sugarcane and was designated a non-GM yeast, since these mutations could have been introduced by other methods of mutagenesis, but with less precision. So far, CTNBio has approved the following products developed using INIT as non-GM: four different lineages of

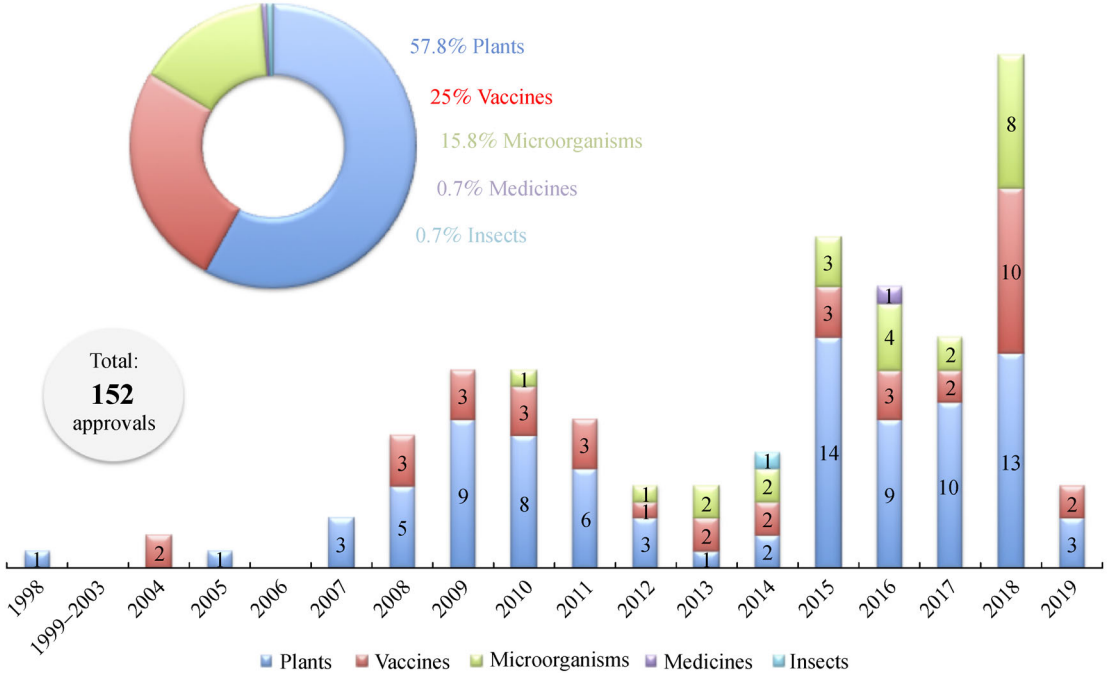

Fig. 3 GM products approved in Brazil from 1998 to 2019, including plants, vaccines, microorganisms, medicines and insects. Data from Biotechnology Information Board[3].

S. cerevisiae for bioethanol production; hornless cattle (although the application for commercial authorization was withdrawn at the request of the applicant) and waxy maize. INIT development, evaluated along with modern regulations that protects the human and animal health, and the environment, will allow the democratization of biotechnology use in Brazilian agribusiness. Within this context, it is expected that small, medium and large national/international institutions would be able to participate in the Brazilian and world market, developing and introducing new biotechnological solutions and products through a more sustainable approach and without facing public disapproval, a common issue for GM crops.

Compliance with ethics guidelines Alexandre Lima Nepomuceno, Renata Fuganti-Pagliarini, Maria Sueli Soares Felipe, Hugo Bruno Correa Molinari, Edivaldo Domingues Velini, Eduardo Romano de Campos Pinto, Maria Lucia Zaidan Dagli, Galdino Andrade Filho, and Patrícia Machado Bueno Fernandes declare that they have no conflicts of interest or financial conflicts to disclose.

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Global Status of Commercialized Biotech/GM Crops in 2017: Biotech Crop Adoption Surges as Economic Benefits Accumulate in 22 Years. ISAAA, 2019, 53. Available at ISAAA website on October 8, 2019 (in Portuguese)
2. Malingreau J P, Eva H D, de Miranda E E. Brazilian Amazon: a significant five year drop in deforestation rates but figures are on the rise again. *Ambio*, 2012, **41**(3): 309–314
3. Biotechnology Information Board, 2019. Available at CIB website on October 8, 2019 (in Portuguese)